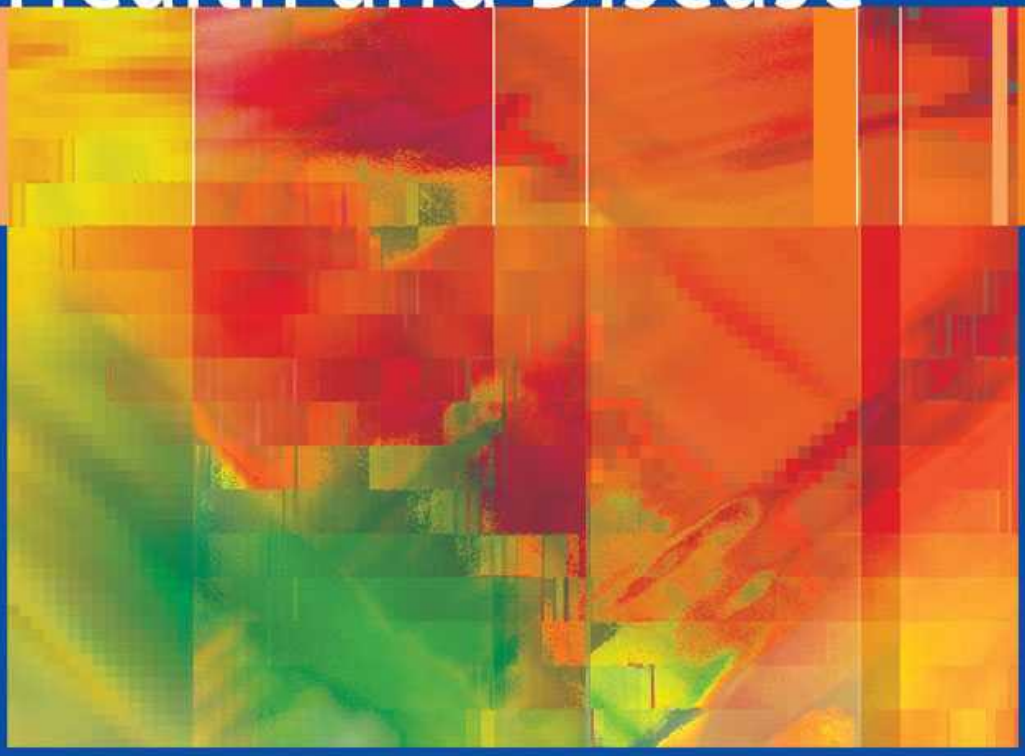
Juan F. Macías Núñez
J. Stewart Cameron
Dimitrios G. Oreopoulos
Editors

The Aging Kidney in Health and Disease



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The Aging Kidney in Health and Disease

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Edited by

Juan F. Macías Núñez, M.D., Ph.D
Profesor Titular de Medicina
Departamento de Medicina
University of Salamanca
Salamanca, Spain

J. Stewart Cameron, M.D., B.Sc., FRCP
Emeritus Professor of Renal Medicine
Guy's, King's, and St. Thomas' School of Medicine
King's College
London, UK

Dimitrios G. Oreopoulos, M.D., Ph.D.
Professor of Medicine
Toronto Western Hospital
Toronto, Ontario
Canada

Springer

Juan F. Macías-Núñez, MD, PhD
Professor Titular de Medicina
Departamento de Medicina
University of Salamanca
Salamanca, Spain

Dimitrios G. Oreopoulos, MD, PhD
Professor of Medicine
Toronto Western Hospital
Toronto, Ontario
Canada

J. Stewart Cameron, MD, BSc, FRCP
Emeritus Professor of Renal Medicine
Guy's, King's, and St. Thomas'
School of Medicine
King's College
London, UK

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To all our elderly patients, our best teachers

Contents

Contributors

Steven Achinger, M.D.
Post-doctoral Fellow
Texas Diabetes Institute
University Center for Community
Health – Dialysis West
San Antonio, Texas
USA

Gerasimos Alivizatos, M.D., Ph.D., FEBU
Associate Professor of Urology
2nd Department of Urology
Athens Medical School
Sismanoglio Hospital
Athens, Greece

Ali Alobaidli, M.D., FRCP
Renal Transplant Fellow
University of Toronto
Toronto, Ontario
Canada

Cristina Alonso Bouzón
Specialist in Geriatrics
University Hospital of Getafe
Madrid, Spain

Joaquin Antonio Alvarez Gregori, M.D.
Research Fellow
Faculty of Medicine
University of Salamanca
Salamanca, Spain

Carmen Ariznavarreta
Professor of Physiology
Department of Physiology, Faculty of Medicine
University Complutense of Madrid
Madrid, Spain

Juan Carlos Ayus, M.D., FACP, FASN
Professor of Medicine
Texas Diabetes Institute
University Center for Community
Health – Dialysis West
San Antonio, Texas
USA

Gustavo Barja Quiroga
Titular Profesor of Physiology
Department of Animal Physiology,
Faculty of Biological Sciences
University Complutense of Madrid
Madrid, Spain

Monica Bonella, M.D.
Centro Di Emodialisi
Anagni, Rome, Italy

Gonzalo Bravo Fernández De Araoz
Specialist in Geriatrics
Ruber Hospital
Madrid, Spain

J. Stewart Cameron, M.D., B.Sc., FRCP
Emeritus Professor of Renal Medicine
Guy's, King's, and St. Thomas'
School of Medicine
King's College
London, UK

Marta Castro Rodriguez, M,D,
Geriatrician Research Fellow
University Hospital of Getafe
Madrid, Spain

Mónica de la Fuente del Rey
Full Professor of Physiology
Department of Animal Physiology
Faculty of Biological Sciences
University Complutense
Madrid, Spain

Nada Dimkovic
Zvezdara University Hospital
Belgrade, Yugoslavia

Ananias Diokno, M,D,
Peter & Florine Ministrelli
Distinguished Chair in Urology

Chairman, Department of Urology
William Beaumont Hospital
Royal Oak, MI 48073
USA

Alfonso Dominguez-Gil Hurlé, Ph.D.
Head of University Hospital Pharmacy
Professor of Pharmacy Department
University of Salamanca
Salamanca, Spain

Tzvi Dwolatzky
Director Department of Geriatrics and Memory Clinic
Mental Health Center, Beersheva
Lecturer Faculty of Health Sciences
Ben-Gurion University of the Negev
Beer Sheva, Israel

Mariam El Assar De La Fuente
Research Fellow
University Hospital of Getafe
Madrid, Spain

Léon Ferder
Departments of Medicine and Physiology
Ponce School of Medicine
Ponce, Puerto Rico

José Carlos Fernandez
Honorary Consultant in Nephrology
Intensive Care Unit
Hospital Militar Central
Buenos Aires, Argentina

M.M. Fernández De Gatta, Ph.D.
Specialist of Drug Analysis
Lecturer of Pharmacy Department
University of Salamanca
Salamanca, Spain

R. H. Fisher, MB, FRCP (Ed) (C
Professor Emeritus
University of Toronto / Sunnybrook
Health Science Centre
Department of Medicine
Toronto, Ontario
Canada

Alessia Fornoni, M.D., Ph.D.
Division of Nephrology and Hypertension
University of Miami Miller School of Medicine
Miami, Florida
USA

Amy L. Friedman, M.D.
Associate Professor of Surgery
Yale University, School of Medicine
New Haven, CT
USA

Eli A. Friedman, M.D.
Distinguished Teaching
Professor of Medicine
Downstate Medical Center
Brooklyn, NY
USA

David Galinsky
Professor of Geriatric Medicine
Faculty of Health Sciences
Ben Gurion University of Negev
Beer Sheva, Israel

M.J. García Sánchez, Ph.D.
Specialist of Hospital Pharmacy
Professor of Pharmacy Department
University of Salamanca
Salamanca, Spain

Jose A. Garcia-Donaire
Nephrologist, Hypertension Unit
Hosital 12 de Octubre
Madrid, Spain

Francisco Guillén Llera
Head of Geriatrics Department
University Hospital of Getafe
Madrid, Spain

Michael Ingber, M.D.
Department of Urology
William Beaumont Hospital
Royal Oak, MI
USA

Sarbjit V. Jassal, MB, FRCP, M.S., M.D.
Assistant Professor
University of Toronto and

Staff Physician, University Health Network
Toronto, Ontario
Canada

David Jayne, M.D., FRCP
Consultant in Nephrology and Vasculitis
Addenbrooke's Hospital
Cambridge CB2 2QQ, UK

Roberto Kaplan, M.D.
Consultant in Geriatrics
Academic Unit: Hospital Italiano de Buenos Aires
Director Postgraduate Fellowship in Geriatric Medicine
Faculty of Medicine, University of Buenos Aires
Buenos Aires, Argentina

Zoltan G. Laszik
Department of Pathology
UC San Francisco School of Medicine
San Francisco, CA
USA

Carlos Leon, M.D.
Division of Nephrology and Hypertension
University of Miam Miller School of Medicine
Miami, FL
USA

José M. López-Novoa
Full Professor of Physiology
Department of Physiology and Pharmacology
Faculty of Medicine
University of Salamanca
Instituto Reina Sofia de Investigación Nefrológica
Salamanca, Spain

Juan-Florencio Macías-Núñez, M.D., Ph.D.
Professor Titular de Medicina
Departamento de Medicina
University of Salamanca
Salamanca, Spain

Manuel Martinez-Maldonado
Executive Vice President for Research
Professor of Medicine and Pharmacology
University of Louisville
Louisville, KY
USA

Michael F. Michelis, M.D.
Director, Division of Nephrology
Lenox Hill Hospital
New York, NY
Clinical Professor of Medicine
New York University School of Medicine
New York, NY
USA

Carlos G. Musso, M.D.
Department of Nephrology
Hospital Italiano
Buenos Aires, Argentina

Pradeep Nagaraju, M.D.
Urology Specialists of Michigan
William Beaumont Hospital
Royal Oak, MI
USA

Lindsay E. Nicolle, M.D., FRCPC
Department of Internal Medicine
University of Manitoba
Health Sciences Centre
Winnipeg, Manitoba
Canada

Dimitrios G. Oreopoulos, M.D., Ph.D.
Professor of Medicine
Toronto Western Hospital
Toronto, Ontario
Canada

Francisco Ortega
Nephrologist, Director of Health Outcomes Research Unit
Hospital Universitario Central de Asturias
Oviedo, Spain
Director of Nephrological Research Institute Reina Sofía
Renal Foundation "Iñigo Álvarez de Toledo"
Spain

Norberto Perico, M.D.
Clinical Research Centre for Rare Diseases "Aldo E Cele Daccó"
Villa Camozzi
Ranica (Bergamo), Italy

Dimitris Petras, M.D.
Department of Nephrology
General Hospital Hypocration
Athens, Greece

Leopoldo Raij, M.D.
Nephrology-Hypertension Section
Veteran Affairs Medical Center
Miami, FL
USA

Pablo Rebollo
Scientific Director
BAP Health Outcomes Research, S.L.
Oviedo, Spain

Giuseppe Remuzzi, M.D., FRCP
Clinical Research Centre for Rare Diseases Aldo e Cele Daccó
Mario Negri Institute for Pharmacological Research
Villa Camozzi, Ranica, Italy
Unit of Nephrology, Azienda Ospedaliera, Ospedali
Riuniti, Bergamo, Italy

José-Manuel Ribera Casado
Professor of Geriatrics
Faculty of Medicine
University Complutense of Madrid
Madrid, Spain

Zaccaria Ricci, M.D.
Centro di Terapia Intensiva
Ospedale Bambin Gesú
Rome, Italy

José Luís Rodicio Díaz
Emeritus Professor of Medicine
Universidad Complutense of Madrid
Madrid, Spain

Leocadio Rodríguez-Mañas, M.D., Ph.D.
Geriatric Research Laboratori
Registrar, Geriatric Unit
University Hospital of Getafe
Madrid, Spain

Claudio Ronco, M.D.
Professor of Nephrology
Department of Nephrology
St. Bortolo Hospital
Vicenza, Italy

Jordan L. Rosenstock, M.D.
Division of Nephrology
Lenox Hill Hospital
New York, NY

Clinical Assistant Professor of Medicine
New York University School of Medicine
New York, NY
USA

Piero Ruggenenti, M.D.
Clinical Research Centre for Rare
Diseases "Aldo e Cele Daccò"
Mario Negri Institute for Pharmacological Research
Villa Camozzi, Ranica, Italy
Unit of Nephrology, Azienda Ospedaliera,
Ospedali Riuniti
Bergamo, Italy

Luis M. Ruilope
Emeritus Professor of Medicine
Universidad Complutense of Madrid
Madrid, Spain

Amparo Sánchez Navarro, Ph.D.
Specialist of Hospital Pharmacy
Lecturer of Pharmacy Department
University of Salamanca
Salamanca, Spain

Sanjib Kumar Sharma, M.D.
Clinical Research Centre for Rare
Diseases "Aldo e Cele Daccò"
Mario Negri Institute for Pharmacological Research
Villa Camozzi, Ranica, Italy
Department of Medicine
BP Koirala Institute of Health Sciences
Dharan, Nepal

Fred G. Silva
U.S. and Canadian Academy of Pathology
Augusta, GA
USA

Andreas Skolarikos
Athens Medical School
2nd Department of Urology
Sismanoglio Hospital
Athens, Greece

Jesus A.F. Tresguerres
Full Professor of Physiology
Department of Physiology, Faculty of Medicine
University Complutense of Madrid
Madrid, Spain

Roser Torra Balcells, M.D., Ph.D.
Inherited Renal Disorders
Nephrology Department
Fundació Puigvert
Barcelona, Spain

Franco Vendemia, M.D.
Geriatric Renal Unit, Department of Nephrology
San Carlo Borromeo Hospital
Milan, Italy

Nereo Zamperetti, M.D.
Department of Intensive Care
St. Bortolo Hospital
Vicenza, Italy

Xin J. Zhou
Department of Pathology
UT Southwestern Medical Center
Dallas, TX
USA

Foreword

It is a great pleasure to respond to the invitation to write a foreword for this book.

With a worldwide increase in an aging population, the practice of medicine is increasingly focused on elderly patients with chronic diseases and episodic acute exacerbations rather than the previous model of acute disease management only.

As nephrologists around the world deal with millions of elderly individuals, many of whom are classified as suffering from chronic kidney disease in stages 2–5, they are, of necessity, practicing geriatrics without specific training or previous exposure in this field.

Therefore, most nephrologists, as well as dealing with new types of clinical presentations, and geriatric evaluation tools, will face the difficulties of reaching the treatment targets specific to geriatric patients.

These geriatric targets include, in addition to the usual diagnosis and medical or surgical treatment for young adults, the recuperation of the ability to perform activities of daily living, which are often partially or totally lost in renal disease.

Apart from these clinical difficulties, physicians will also face enormous ethical challenges. These issues are clearly dealt with by geriatricians and nephrologists.

Improvements in care and advancing clinical knowledge will enable us to delineate more clearly those changes that are due to aging as opposed to those changes due to disease. This book provides an important step in further clarifying and quantifying the differences between an aging and a diseased kidney.

Advances continue not only in the treatment and management of renal disease in the elderly, but also in the primary and secondary prevention of renal disease in this population.

This book is written from a multidisciplinary view, with nephrologists, urologists, geriatricians, pathologists, biologists, and pharmacists working together to provide the reader with a holistic view of geriatric nephrology.

The editors bring a wealth of experience to the subject of renal aging in health and disease, each from his own perspective. They have also assembled a large number of international experts to address a wide range of topics, thus providing comprehensive coverage of all issues relating to renal function in the elderly. These range from the discussion of the anatomical, biological, and physiological changes in the aging kidney to specific pathological processes, noting common problems and treatment advances.

This book will provide important assistance not only for both nephrologists and geriatricians but also for trainees in these two specialties, to whom I would strongly recommend it.

I would like to congratulate the editors as well as the individual chapter authors for the outstanding job they have done.

R.H. Fisher
MB, FRCP(Ed)(C
Professor Emeritus
University of Toronto
Sunnybrook Health Science Centre
Department of Medicine
Toronto, Ontario
Canada

1

Holistic Approach to the Geriatric Patient: Geriatric Evaluation

David Galinsky, Roberto Kaplan, and Tzvi Dwolatzky

Introduction

The latter half of the 20th century was characterized by a significant increase in the number of elderly. This worldwide biological and demographic phenomenon has many implications for a large number of different disciplines, including health, politics, economics, social services, and others.

This introductory chapter will deal with the demography of the aged, will present the concept of frailty in the elderly, and will provide a comprehensive approach to the clinical evaluation of older people. We will emphasize the effect of some of the physiological changes of aging on the clinical evaluation; describe factors that make the assessment of the older patient more complex, especially the nonspecific presentation of disease and the frequent presence of multiple pathology in advanced age; describe the impact of social and economic factors on the health status of the elderly; and, in particular, detail the functional and clinical manifestations resulting from the combination of these phenomena. Finally, the chapter will discuss the provision of home care services designed to meet the needs of the elderly.

Demography

The latter half of the 20th century was associated with a marked increase in life expectancy and in the number of older people, particularly in the developed world. The emergence of global aging is one of the most significant results of the biological revolution taking place in our generation, with consequences affecting most aspects of society, including health, politics, economics, social services, and family structure.

In 2003 the total number of those older than 65 years worldwide was 450 million people, representing some 7% of the world‘s population [1–3]. It is expected that by 2025 this number will almost double and will reach approximately 835 million people, or more than 10% of the global population. The largest number of the elderly will reside in Europe (15% of the population), and by 2025 one-fifth of the population in Europe will be over 65 years old. The oldest countries are expected to be China, India, the United States, Japan, and Russia, with half of the world‘s elderly living in these countries.

At present, the percentage of the elderly in Italy, Japan, and Greece is the highest in the world, being greater than 18%. It is predicted that by 2025 some 25% of Japanese men and 32% of women will be over the age of 65. It is of importance to note that in developed countries there are an increasing number of those over the age of 80 years. In Japan, for example, it is predicted that some 10% of the population will be over 80 years by the year 2025, and in Europe this group of the older-old will constitute approximately 6% of the population. At present, the percentage of people over the age of 75 and 80 in Sweden is the highest in the world (9% and 5%, respectively).

Life expectancy is the highest in Japan, being 78.4 years for men and 85.3 years for women, followed closely by Sweden, Australia, Israel, and Canada [2]. Also, life expectancy in good health is the highest in Japan, being 72 years for men and 78 years for women. With regard to the participation of the elderly in the workforce, there are great differences between countries, with 49% of those older than 65 years still working in Ethiopia, and only 1.3% in France [4]. In Japan, the rate of those over the age of 65 who are still working is 30% for men and 13% for women [4].

In the majority of the developed countries, some 75% of the deaths in men and 80% of deaths in women occur over the age of 65 years. In the developing world, the contribution of this group to mortality rates is much lower. For example, in Ethiopia, 12% of male deaths and 13% of female deaths are in the group over the age of 65 years [5].

These demographic factors suggest that not only is there an increase in life expectancy and in the number of older people in both developed and developing countries, but also that the aging of the population in many countries is associated with significant demands on the economy and on health services.

Geriatric Evaluation

Although the evaluation of the healthy older person may not be significantly different from that of younger adults, those who are biologically older or frail may differ fundamentally in their clinical presentation. This is due to the complex interactions between various intrinsic and extrinsic factors (Table 1.1). Thus, when evaluating the older patient, the physician is frequently faced with a significant challenge in obtaining an adequate history and eliciting physical signs. The clinical presentation of illness, particularly

Table 1.1 Factors Affecting the Clinical Presentation in the Elderly.

1. Intrinsic factors
1.1 Physiological changes of aging
1.2 Atypical presentation of illness
1.3 Nutrition
1.4 Mood
1.5 Cognition
2. Extrinsic factors
2.1 Pharmacological
2.2 Social
2.3 Financial

Table 1.2 The "Geriatric Giants."

- Incontinence
- Immobility
- Instability
- Intellectual impairment

Source: B. Isaacs, *The Challenge of Geriatric Medicine.* Oxford: Oxford University Press, 1992.

in the frail elderly, is often nonspecific or atypical. Significant illness may be present with minimal symptoms and signs. It is thus essential to maintain a high index of suspicion when assessing the elderly patient.

Bernard Isaacs, a leading geriatrician in the UK and one of the pioneers of modern geriatric medicine, described the "giants of geriatrics," comprising incontinence, immobility, instability, and intellectual impairment (Table 1.2) [6]. This important contribution to our understanding of the clinical presentation of disease in the elderly provided us with the realization that many diseases may present by means of a common pathway affecting function, with these "giants" being the most common symptoms (Figure 1.1).

Thus, any change to the previous level of function is frequently one of the first signs of disease in the elderly and should always be carefully evaluated and never ignored. An approach to the management of the "giants" involving treatment and rehabilitation is presented in Figure 1.2.

Physiology of Aging

It is not within the scope of this chapter to describe the multiple physiological changes associated with the aging process, but rather to highlight

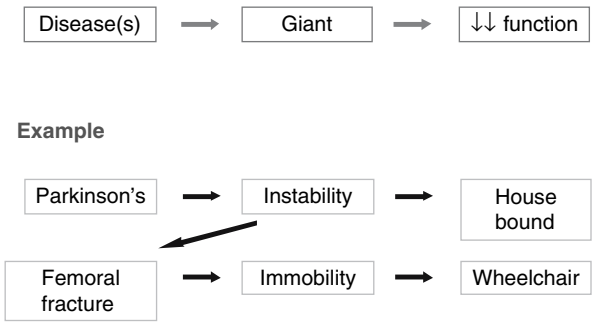

Fig. 1.1 Giants of geriatrics – pathway.

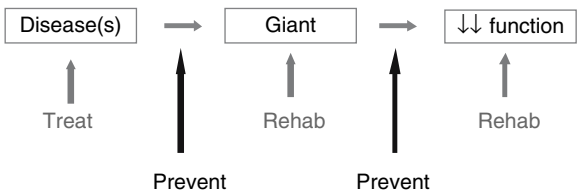

Fig. 1.2 Giants of geriatrics – management.

those changes that may be relevant to the clinical evaluation of the older person. This section will also emphasize the particular changes affecting the functional abilities of the older person, including those of the musculoskeletal and nervous systems.

The aging changes of the skin are particularly prominent in those areas that have been exposed to the sun [7]. The most prominent changes include atrophy and thinning of the skin, with wrinkling due to a loss of collagen. The patient is prone to easy bruising, and there are changes in pigmentation. Pigmented lesions are common and should be carefully assessed for malignant transformation [8]. Baldness is usual in men, and thinning of the hair is not uncommon in women, who may develop a significant growth of facial hair. Graying of the hair is usual, due to a progressive loss of melanocytes from the hair bulb. The outer third of the eyebrows is frequently absent, and this aspect of aging associated with thickening of the skin of the face should not necessarily be assumed to be a clinical manifestation of hypothyroidism [9].

The skin of the elderly is frequently dry, due to an age-associated decrease in the production of sebum and a lower content of water in the tissues. As well, wound healing is poor, which may be related to a decrease in the strength of the skin, a reduction in dermal microvasculature, and an impaired inflammatory response. The nails become thickened and acquire a yellow color.

Many old people are edentulous as a result of the loss of teeth at a younger age, usually due to caries or periodontal disease. The enamel of the teeth that are retained is often of a yellow color. There is recession of the gums, and thus dentures are frequently loose and ill-fitting, leading to problems in nutrition. Advances in the dental care of the elderly over the past decade have improved this situation significantly [10].

Dietary changes and age-related changes in calcium absorption and vitamin D metabolism [as a result of a decrease in the ability of the skin to manufacture vitamin D on exposure to sunlight, a decrease in the level of serum 25 OH vitamin D, and a diminished capacity of the kidney to convert this to 1,25 $(OH)_2$ vitamin D] lead to decreased bone volume and osteoporosis. Skeletal changes occur, with older people developing thoracic kyphoscoliosis, leading to a stooped posture and diminished stature. The neck is shortened with limited extension, making the detection of thyroid masses more difficult. There is often a compensatory lumbar lordosis, and the knees are maintained in a state of flexion in order to maintain balance.

One of the most important changes affecting the musculoskeletal system in the elderly is sarcopenia, an age-related decrease in skeletal muscle mass. The resulting muscle weakness results in difficulty in standing up from a seated position and in climbing stairs. The patient will fatigue easily and be more prone to falls. A decrease in muscle mass will be evident on physical examination.

The eye undergoes a number of changes with important clinical implications. Tear production decreases and the eyes are often dry. Intraocular pressure increases with age, and the development of glaucoma, which is frequently asymptomatic and is a major cause of blindness, should always be suspected in the elderly person with visual impairment. Other age-related conditions resulting in visual impairment include cataract, macular degeneration, and diabetic retinopathy. Laxity of the eyelids often causes ectropion and entropion of the lower eyelid, or ptosis of the upper eyelid.

Hearing impairment is one of the most common aspects of the aging process, with presbycusis causing a predominantly high-frequency sensorineural hearing loss [11]. This may lead to great difficulty in communicating with the older patient, making it difficult in acquiring a history and evaluating cognition. Other common conditions are tinnitus and vestibular dysfunction with dizziness and vertigo.

Although the aging of the nervous system does not lead to a significant decrease in the speed of impulse transmission along peripheral nerves, there is a slowing of response time to external stimuli. This most probably occurs as a result of a delay in the central nervous system's capacity to process stimuli. Atrophy of the aging brain is usual, and may be associated with intellectual decline and a decrease in cognitive function. Aging of the autonomic nervous system frequently results in changes in bowel and bladder function and in impaired thermoregulation. Orthostatic changes in blood pressure may occur and, when present, a possible relationship to the use of vasopressor medications and diuretics should also be considered. Heart rate decreases with age, and there is an increase in both supraventricular and ventricular premature beats in healthy older men and women.

A Comprehensive Approach

The clinical geriatric evaluation comprises a comprehensive multidomain approach designed to cover all of the factors affecting the health and well-being of the older patient (Figure 1.3). A multidisciplinary team approach is employed where financially feasible and may include, apart from the physician, physical therapists, occupational therapists, dieticians, nurses, and social workers.

The components of the geriatric evaluation include an assessment of the following areas:

- Clinical assessment
- Nutritional assessment
- Cognitive and mood assessment
- Functional assessment
- Social assessment

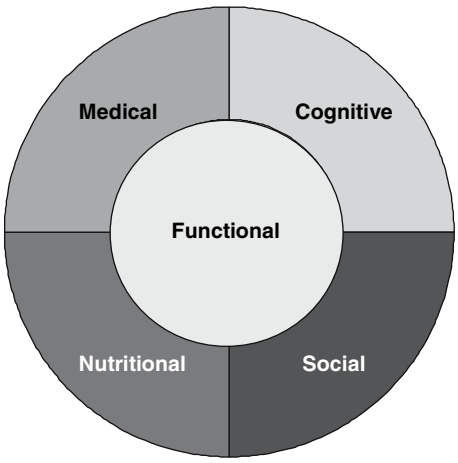

Fig. 1.3 The Geriatric Evaluation -– a multidomain approach.

Clinical Assessment

History A detailed history is essential for the proper assessment of the health status of the older patient. As mentioned previously, the passing of the years often results in the acquisition of a wealth of medical conditions, surgical interventions, traumatic events, infectious diseases, exposure to occupational hazards, and other significant life events. It is often very difficult (for both the patient and the physician) to distinguish between aspects of the history that have relevance to the current medical complaint and those that are interesting but unrelated. This requires that the physician develop skills in history taking from older patients that are frequently attained mainly from experience and communication skills. Emphasis should be placed on what is actually bothering the patient at the current period of time.

The patient is often unable to remember specific particulars related to his symptoms or to past medical history. Communication may be hampered by impaired vision or hearing and language incompatibility. Thus, further information should always be obtained from the patient‘s medical records, as well as from family members and caregivers. That being said, the accuracy of these informant reports should be accepted with some caution, as up to 40% may be inaccurate [12].

Of particular importance is the need to get an accurate description of all drugs that the patient is taking, including prescription drugs, over-the-counter medications, vitamins, and homeopathic and herbal compounds. The patient should bring all his medications with him to the physician, if possible at each visit. A drug review should aim to decrease as much as possible the effect of these medications on cognition. Alcohol and other substance abuse should also be carefully sought and a history of smoking noted.

A history of exposure to occupational hazards should be ascertained, since substances such as asbestos, heavy metals, and radiation, among others, may have significant health implications decades following exposure. The level of education achieved by the patient is significant, both in assessing the results of cognitive testing and as a risk factor for conditions such as Alzheimer‘s disease, where a low level of education places the patient at higher risk for developing the disease [13, 14].

Physical Examination A thorough physical examination should be performed in all patients. Blood pressure should always be measured both supine and standing in order to exclude orthostatic hypotension. Changes in blood vessel elasticity with aging and an increase in peripheral vascular resistance frequently lead to a rise in blood pressure with age. This having been said, it must be emphasized that blood pressure values greater than 160/90 are associated with increased morbidity and mortality even at an advanced age.

Examining the pulse provides a great deal of relevant information in the older patient. The presence of ectopic beats is common and often has no clinical significance. However, arrhythmias such as atrial fibrillation should be sought, and absent pulses or bruits over major arteries documented. The temporal arteries should be palpated, and temporal arteritis should be considered in the appropriate clinical context.

Arcus senilis, manifested by a light blue ring at the outer border of the iris of the eye, is a prominent finding in many older people. Although this finding has no specific effects on the health of the patient, it may reflect the presence of vascular disease. It is important to note the presence of thyroid masses or

lymphadenopathy. Raised jugular venous pressure or other findings of fluid retention may suggest the insidious onset of cardiac failure. Dyspnea and/or tachypnea support the possibility of hypoxia, which may lead to confusion and excess daytime somnolence. Where possible, a pulse oximeter should be used to determine the level of oxygen saturation of the blood.

The presence of muscle weakness and wasting should be noted. It is essential to note the patient's ability to get up from a chair as well as stability and type of gait. A useful test that is recommended in evaluating these abilities is the "timed get up and go" test [15]. Focal neurological signs are often subtle and should be sought. Myoclonus should be noted as should dyskinesias. Bradykinesia, tremor, festination, and postural instability suggest Parkinson's disease, or frequently drug effects. The presence of a positive glabellar tap, a palmar-mental reflex, and other frontal release signs should be noted. Vision and hearing should be assessed, since they are often missed or underestimated. Also, sensory deprivation is an important contributory cause of cognitive decline in the elderly.

The lower extremities should be examined carefully, noting joint deformities, tenderness, and edema. The feet should be inspected for rashes, callouses, and painful spurs, ulcers, thickening of the nails, warmth, and loss of sensation. Ill-fitting shoes is an important cause of gait abnormalities in the older patient.

Laboratory Investigations What comprises normal values for a number of laboratory investigations in the elderly has not been clearly determined. For example, although the presence of anemia is always pathological, the definition of this condition in older people remains controversial. It is generally accepted that normal healthy elderly subjects should have minimal, if any, declines in hemoglobin (Hb) values. The World Health Organization (WHO) criteria for the diagnosis of anemia are less than 13.0 g/dL in men and less than 12.0 g/dL in women. This having been said, a number of community-based epidemiological studies [16, 17] have found a significant age-related decline in Hb from age over 70 years among healthy men, and a less pronounced decline among women, resulting in a high prevalence of anemia at advanced age using standard WHO criteria. Thus, it may be justified to use a lower level of hemoglobin of about 11.5 g/dL in defining anemia in both men and women older than 80 years [16].

Age-associated physiological changes may significantly alter certain laboratory values in the elderly without constituting a pathological process. Laboratory values may appear abnormal in 10% or more of the healthy elderly without necessarily representing a pathological process, such as serum alkaline phosphatase and erythrocyte sedimentation rate. Also, the serum creatinine level may be normal in spite of a markedly decreased creatinine clearance. There is a slight age-related increase in fasting glucose levels and a delayed return to normal of glucose levels following an oral glucose challenge. This may be related in part to a decline in sensitivity to the metabolic effects of insulin with age.

Subclinical hypothyroidism, defined as mildly elevated serum TSH and normal serum thyroxine levels, is the most common thyroid dysfunction in the elderly. In patients with subclinical hypothyroidism, treatment with thyroxine therapy is controversial [18].

To ensure proper assessment of the geriatric patient, the clinician needs to be aware of these age-related changes and possible effects on laboratory values. Thus, more clinical research is needed to establish appropriate reference ranges, especially for those over the age of 75 years [19].

Nutritional Assessment

Since nutritional factors may contribute to the pathogenesis of many conditions affecting the older patient, nutritional assessment is an essential element of the clinical evaluation. A nutritional history should obtain information regarding the patient‘s regular dietary habits and intake (including the ingestion of alcohol), the use of supplements, changes in appetite, and the presence of gastrointestinal symptoms and weight loss. Nutritional screening instruments have been developed and validated for use in the elderly, such as the Mini Nutritional Assessment (MNA) [20].

Weight and height should be measured and the body mass index (BMI) calculated. Additional anthropometric measures that are valuable in the nutritional assessment include the mid-arm circumference and triceps' skinfold thickness. Relevant laboratory investigations are the hemoglobin level, total lymphocyte count, and serum cholesterol, as well as serum albumin. It is of importance to note that serum albumin concentration is an independent predictor of mortality risk in older patients [21].

Attention should be given not only to dietary habits but also to the distribution of meals during the day. Many older people may have their main meal at lunch and then consume only a piece of toast and tea or yogurt for supper. It seems reasonable to postulate that an evening meal of low caloric content or that is eaten in the early evening as the last source of calories for the day may result in low night-time glucose levels and increase the risk of nocturnal falls or confusion.

Cognitive and Mood Assessment

Many older patients complain of failing memory, name-finding difficulty, and poor concentration ability. The nature of the onset and progression of the symptoms should be determined, and the complaints should be confirmed and further described by family members or caregivers.

A clinical assessment of mental status should be performed, some of which will be done during the history. This includes an evaluation of the patient‘s level of consciousness, attention span, and the ability to concentrate. The assessment of memory includes the ability to recall names and past events, recent memory, and learning of new information. Orientation to time and place and language skills should be evaluated. Calculation and praxis are also assessed.

The testing of these cognitive functions is incorporated into validated scales such as the Mini-Mental State Examination (MMSE) [22]. This instrument is short and relatively simple to administer and has been well validated in the community setting [23, 24]. As a screening tool it provides a good indication of cognitive function. However, it is not sensitive to early cognitive changes. It should also be adjusted to the age and education level of the patient [25].

Various other instruments have been developed to assess cognitive function in the community setting [26, 27]. One of the most popular office tests used in the approach to cognitive impairment is the clock-drawing test. The patient is requested to draw a clock, to position all the numbers, and to draw the

hands at a specific time (such as ten past eleven). This test assesses a wide range of cognitive abilities including executive functions, is quick and easy to administer and to score, and offers excellent acceptability to subjects [28]. Although the sensitivity and specificity of the test are reasonable, it is probably less useful in patients with early cognitive changes [29]. There are many scoring systems available in assessing the clock-drawing test, and these are of particular value in following up patients over time [30]. The primary care physician should acquaint himself or herself with one of these systems in order to monitor the progression of the patient.

The gold standard for the assessment of cognitive ability remains comprehensive neuropsychological testing. This will provide the clinician with additional information regarding those cognitive functions already mentioned as well as an assessment of functions such as organizational and planning skills, executive function, word generation, praxis, gnosis, and judgment. However, such testing is not usually available in the primary care setting. It is expensive and usually exists only in tertiary care memory clinics and research centers. A recent development has been the design and validation of computerized neuropsychological batteries [31]. These may soon become widely available through the Internet to primary care physicians in their clinics and may well comprise a major advance in the assessment of cognitive complaints in the community setting.

When the older patient presents with cognitive symptoms, such as failing memory, that are confirmed by objective testing, mild cognitive impairment is likely [32]. However, the presence of more severe symptoms, including difficulty in recalling names, disorientation and confusion, poor concentration, or language difficulties, with an associated decrease in the patient‘s functional ability, is most likely to reflect dementia.

The mood of the patient should be evaluated; a loss of interest in social activities, poor concentration, insomnia, or loss of appetite may suggest depression. This is especially the case in patients who have suffered a recent loss. As stated previously, depression itself may lead to cognitive impairment or may be associated with the early stages of dementia.

Functional Assessment

As was mentioned previously, an assessment of the functional capacity of the patient is essential, since functional decline is often the earliest and most reliable sign of disease in the elderly. An evaluation of instrumental activities of daily living (IADL) will include an assessment of the patient‘s ability to manage household tasks such as cooking, cleaning, doing laundry, and using the telephone. In addition, information is ascertained as to whether the patient can handle banking, shopping, and driving or use public transport. A number of instruments have been developed and validated to assess the level of IADL function [33]. Basic activities of daily living (ADL) such as bathing, dressing, toileting, and the ability to feed oneself are assessed. The patient‘s mobility and transferring are also evaluated. The Barthel index is widely used to assess the ADL of those with a disability [34].

Social Assessment

One of the cornerstones of the geriatric assessment is the evaluation of the social status and support structure of the patient. Many elderly patients live alone and are frequently socially isolated or financially insecure. As a result

they may suffer from depression, nutritional deficiency, inadequate medical supervision, and poor drug compliance. Also, bereavement, retirement, and poverty play a major role in determining the health status of the elderly [35–37]. The social assessment must thus be an integral part of the workup of the older patient and form the basis for the subsequent provision of appropriate services necessary for the patient‘s well-being.

The social evaluation of the patient should include a careful inquiry regarding the family structure and the relationship and degree of contact that is maintained with the members of the family. The major caregiver should be identified, and the ability of this caregiver to fulfill this role should be evaluated. The presence of caregiver stress, a common finding especially in the patient with chronic conditions such as dementia, should be identified.

An evaluation of the patient‘s living conditions will provide a critical insight into his current state of health. Adequate heating, cooking facilities, refrigeration, water, and sewerage should not be taken for granted. An older person residing on an upper floor of a building without an elevator may become socially isolated and suffer physical deconditioning, as well as being unable to purchase supplies of fresh produce. Inadequate light may lead to depression and osteoporosis. Potentially dangerous elements in the patient‘s home should be identified and neutralized, such as exposed electrical wires, leaking gas, poorly fitting carpets, and cluttering of furniture.

An assessment of the patient‘s financial situation will provide an essential insight into such aspects as inadequate nutrition due to an inability to purchase nutritious foodstuffs, poor compliance resulting from not being able to buy prescribed medications, and hypothermia due to inadequate heating. The services that are available to the patient should be determined and utilized.

The problem of abuse of the elderly may take many forms, including physical and financial abuse, and neglect. A high index of suspicion is needed in order to recognize these symptoms of abuse, and the appropriate interventions should be initiated without delay.

Key Concepts in the Geriatric Evaluation

Function and Frailty

The way we function is determined by a complex interaction between our genetic structure, our biological makeup, our ability to overcome disease and traumatic life events, our cognitive abilities and psychological attitudes, and the social support structure and policies of the society within which we live. Every abnormality that occurs to weaken this structure will have some effect on our ability to function. The older person is particularly vulnerable, being prone to major changes in many of these elements. When the older patient becomes unable to overcome these challenges, functional ability deteriorates and frailty ensues (Figure 1.4).

There is as yet no clear definition of frailty. One of the earliest attempts to define this condition referred to a disability caused by chronic diseases and their sequelae, associated with complexity and increased vulnerability [38]. Later, Fried defined frailty as a “physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and even dysregulation, of multiple physiologic systems” [39, 40].

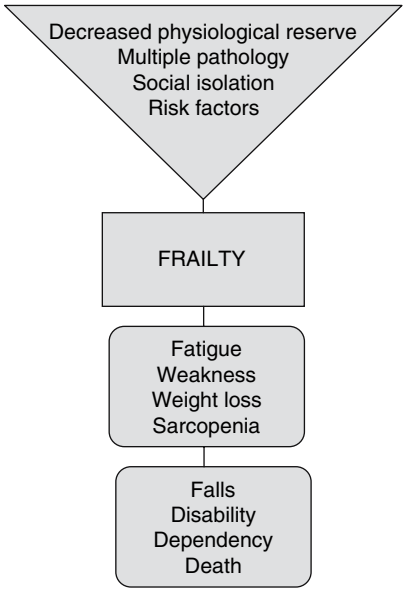

Fig. 1.4 Frailty in the elderly.

The frail patient usually has a decline in physiological function and reserve, making him particularly prone to insults. In addition, the presence of multiple diseases is common, and as a result polypharmacy is usual (see later). The frail patient frequently presents with significant, nonspecific symptoms, such as weakness, fatigue, anorexia and weight loss, and decreased motor activity. A slow, unsteady gait is frequent, with signs of poor nutrition and decreased muscle mass (sarcopenia). As a result, falls are common, frequently resulting in fractures due to associated osteoporosis. Frail patients are more prone to acute illnesses with resulting hospitalizations. Functional loss with disability and dependency is common, and institutionalization may be inevitable.

The approach to frailty should include both prevention and rehabilitation. A number of risk factors for frailty have been identified at different stages across the life span. These include low weight at birth and decreased grip strength in mid-life. Lifestyle factors of importance include physical inactivity, cigarette smoking, heavy drinking, and abnormal body mass index (BMI). Cognitive impairment, depression, social isolation, and more than one chronic condition are also risk factors. Those elements that are amenable to intervention should be identified and managed, where possible.

Once frailty begins to develop, an active approach to rehabilitation should be adopted. The involvement of a number of disciplines is essential. Diseases should be treated, and drug therapy kept simple, giving as few medications as possible at the lowest therapeutic dose preferably once daily. The patient should be carefully evaluated for the presence of depression and treated accordingly. Physical therapy is aimed at increasing muscle mass and stamina; the patient is encouraged to walk as much as possible, with the use of walking aids to maintain balance and function. Occupational therapy is aimed at maintaining function in activities of daily living and encouraging stimulating activities.

Where frailty and poor health status are present, it is important to exclude social factors, such as poverty, social isolation, poor living conditions, and

inadequate heating during the winter months or cooling during the summer. Social intervention should ensure that the patient is adequately supervised, that help is provided when necessary, and that interaction with others is ensured.

Such an integrated approach instigated early on in the development of frailty may be effective in maintaining function and reversing the ravaging consequences of this condition.

Atypical Presentation of Disease

The elderly often present with atypical or nonspecific symptoms. Subsequently, there may be a significant delay in the diagnosis of disease in older patients, resulting in increased morbidity and even mortality. This challenges the diagnostic skills of those caring for the elderly. A high index of suspicion should thus be maintained when an older patient presents with a change in functional status [41].

The most common symptoms presenting atypically in the elderly are listed in Table 1.3. A patient may develop a severe or life-threatening condition and yet have minimal or nonspecific symptoms. For example, a frail older patient with pneumonia may present with drowsiness and confusion, yet no cough or fever. Cardiac failure may present with fatigue, nausea, and abdominal pain. Or urinary infection may present only with the recent development of incontinence. Thus, these symptoms should be recognized and the patient investigated accordingly.

Multiple Pathology and Polypharmacy

One of the hallmarks of geriatric medicine is the presence of multiple pathology in the older patient [42]. Most older patients have developed a number of diseases during the decades of their lifetime, which makes the acquisition of an accurate history time-consuming and complicated.

Diseases such as hypertension, diabetes, and dyslipidemia are common and are frequently risk factors for the development of vascular diseases. A patient may develop various unrelated neoplastic conditions over the years and undergo different modalities of treatment, such as a partial colectomy for carcinoma of the bowel, excision of a malignant skin lesion, and chemotherapy for breast carcinoma. Past infectious diseases, such as tuberculosis, may be of significance. It is thus important to determine which aspect of the medical history is relevant to the patient‘s current clinical state.

Table 1.3 Nonspecific Symptoms of Disease in the Elderly.

• Weakness
• Lethargy
• Somnolence
• Apathy
• Confusion
• Poor attention
• Anorexia
• Dyspnea

The almost inevitable result of patients suffering from a number of diseases is that they are prescribed a number of different medications. This is associated with an increased rate of adverse events and drug–drug interactions. There is also evidence that many older adults receive medications that could potentially cause more harm than good [43]. Finding the right balance between too few and too many drugs will help ensure increased longevity, improved overall health, and enhanced functioning and quality of life for the older patient.

The Provision of Health Services

A Historical Perspective

United States of America

At the beginning of the 20th century, healthcare professionals began investigating aspects of the aging process and the healthcare requirements of older people. Dr. Ignatz Leo Nascher, a pediatrician, was a pioneer in this field, with the term *geriatrics* being attributed to him [44]. The latter half of the 20th century was witness to the creation of professional bodies, such as the *American Geriatrics Society* and the *Gerontological Society of America*, which had a significant influence on public health policy and led to the establishment of government-funded programs for the elderly and to the initiation of professional training in the field of geriatrics.

Nursing homes were established and the provision of long-term care in institutional settings developed, with the determination of clear criteria for funding and supervision. Medical health insurance programs focused initially on acute conditions, but the establishment of *Medicare* and *Medicaid* in the 1960s provided public funding for hospitalization and medical consultation costs (Medicare) and long-term care for the elderly (Medicaid). However, a significant number of individuals remain excluded from health coverage.

The creation of the *National Institutes of Health* in 1974 helped to place the care of the elderly on a strong base, to encourage the education and training of healthcare professionals, and to sponsor a large number of research programs examining the medical, epidemiological, social, and behavioral aspects of aging and its effects on the healthcare system.

United Kingdom

Geriatrics as a specialty providing quality medical services to the elderly originated in the UK, when Marjory Warren, a surgeon, took charge of a residential home for the elderly (*Workhouses*) next to the *West Middlesex Hospital*. This institution had over 800 inpatients, many of them elderly, with a multiplicity of problems. The patients for the most part suffered from chronic conditions, many were disabled, socially deprived individuals, and some were psychiatric patients. Dr. Warren was the first physician to describe many of the characteristics of chronic patients, providing the first classification based on function and contributing significantly to the development of geriatrics [45]. Subsequently, rehabilitation programs focusing not only on the physical recovery of these patients but also on the provision of services allowing them to function in the community were developed.

Marjory Warren also brought the needs of these patients to the attention of the medical community, which until then showed little interest in chronically ill patients. At that time, younger physically disabled patients were

hospitalized in specialized clinics, whereas older patients were hospitalized in institutions for the chronically ill [45].

The implementation in 1948 of the *National Health Service* (NHS), which made health services universally available, was another major turning point in the provision of health services in the UK. Quality medical care was now made accessible to patients, many of them elderly, who had until then been excluded from formal medical care, and who at best had spent the last days of their life in quasi-warehouse institutions. A law that was enacted at that time, the *National Assistant Act,* forced town councils to provide health care to all patients lacking the ability to care for themselves. Thus, the elderly residential homes and many of the old "Workhouses" were frequently managed by the town council, and clinics and healthcare centers were built to provide health care to older and disabled patients.

This universal availability of health services motivated physicians to show a greater interest in this "new kind" of patient. Professionals and academics began to support the field of geriatric medicine, resulting in the formation of the *British Geriatrics Society* in 1945 and subsequently in the publication of a growing number of scientific publications in the field of geriatrics. Research studies led to the realization that chronic disease was not necessarily synonymous with old age and that those suffering from these conditions did not inevitably require permanent institutional care. Also, the "chronically ill patient" was better defined, and the following four types of chronicity were described, laying the foundations for modern-day geriatric medicine:

1. Patients whose disease had become chronic due to a delay in the timely provision of treatment
2. Patients with any type of disease who were in need of hospitalization due to a lack of family support
3. Patients suffering an avoidable disease
4. Chronic patients with the exacerbation of disease that improves during hospitalization but who are then unable to return to their homes due to inadequate community support

At that time, renowned medical associations such as the *British Medical Association* (BMA) began to review the quality of health care provided to the elderly in institutions and to make recommendations to the medical community. Many elderly patients treated in long-term institutions suffered from the consequences of prolonged hospitalization and immobility, including pressure ulcers, contractures, and deformities. It was recommended that geriatric departments be established in general hospitals, including university hospitals, with the development of outpatient clinics, centers for group activities, and psychopathology units.

Home Care

The provision of medical care at home was the accepted form of health care in many societies. The first experience of a formal medical home care program in the United States, the *Boston University Home Medical Service*, was published in the 19th century. Subsequently, the New York Montefiore Hospital implemented another successful hospital-based home care program, with patients being evaluated by medical staff or social workers at home. In

developed countries, with improved transport and communications systems, increased population dispersion, and, in particular, the development of medical technology, the provision of health care became centered around institutions, including hospitals, clinics, and medical offices. Insufficient funding of home care, the need for the medical provider to travel to the home of the patient, and time limitations made home care less popular. Also, little formal training in home care provision was provided to medical professionals, at both an undergraduate and a postgraduate level.

Despite this reality, countries such as the UK made an effort to improve home care services. Within the NHS setting, physicians perform under contract home visits, known as "assessment visits." These visits are useful in evaluating those patients with limitations in mobility or with decrease in function who are no longer able to care for themselves. Home visits provide valuable information regarding living conditions and interpersonal relationships within the family. Also, home visits strengthen the therapeutic bond between the physician and patient.

Home care is currently defined by the American Medical Association as the provision of services and/or equipment to the patient at home with the purpose of restoring and maintaining the highest level of welfare, functioning, and health [46]. It constitutes one of the most rapidly increasing health-related areas within the American health system in recent years, and this growth seems to be taking place in other developed countries as well [47].

This strategy of bringing care to patients at home, without the need for permanent institutionalization or long hospital stays, has emerged as an attractive alternative. The benefit to the patient and the potential improvement in the quality of life should be the primary aim of home care, with the economic advantages being the secondary issue [48, 49]. Clear advantages of home care include a decrease in the rate of rehospitalization, permanent institutionalization, and exposure to resistant hospital-acquired infections. Since organized home medical care programs are able to provide health care at a lower cost than hospitalization, the development of these programs in countries with ever-increasing demands on national health budgets is essential**.** Of note is that medical training programs have recently included training in the field of geriatric home care in the curriculum, particularly in the areas of family and internal medicine [50].

Home care programs for the elderly are particularly beneficial when provided as immediate care following discharge from hospital. This approach has been shown to reduce rehospitalizations, functional deterioration, the risk of placement in nursing homes, and mortality [51]. In order to achieve these results, the use of experienced teams to ensure continuity of care following discharge and the performance of a multidisciplinary comprehensive geriatric assessment are useful. It has yet to be determined whether the provision of supportive or long-term home care, although being increasingly employed in some countries, is of definite benefit [52].

Summary

The clinical evaluation of the older patient is complex and demands both a thorough knowledge of the pathophysiological changes associated with aging as well as patience and clinical expertise in eliciting an adequate history

and examination. A multidomain approach with an emphasis on the patient's function is the key to proper assessment and may help to prevent the decline into frailty and dependency, which increases suffering and is a burden on the family and society. The development of home care programs should contribute both to an improvement in the quality of life of the frail elderly and to a decrease in healthcare expenditure.

References

1. World Population Prospects: The 1998 Revision: The Population Division, Department of Economic and Social Affairs, United Nations Secretariat; 1998.
2. The World Health Report: Working together for health: World Health Organization; 2006.
3. International Data Base. In: US Census Bureau. http://www.census.gov/ipc/www/idbnew.html.
4. Yearbook of Labour Statistics: International Labour Organization; 2006.
5. World Mortality in 2002: World Health Organization; 2002.
6. Isaacs, B. *The Challenge of Geriatric Medicine*. Oxford: Oxford University Press; 1992.
7. Hashizume, H. Skin aging and dry skin. *J. Dermatol.* 2004;31(8):603–609.
8. Ortonne, J.P. Pigmentary changes of the aging skin. *Br. J. Dermatol.* 1990;122(Suppl 35):21–28.
9. Rehman, S.U., Cope, D.W., Senseney, A.D., Brzezinski, W. Thyroid disorders in elderly patients. *South Med. J*. 2005;98(5):543–549.
10. Dolan, T.A., Atchison, K., Huynh, T.N. Access to dental care among older adults in the United States. *J. Dent. Educ*. 2005;69(9):961–974.
11. Gates, G.A., Mills, J.H. Presbycusis. *Lancet* 2005;366(9491):1111–1120.
12. Kemp, N.M., Brodaty, H., Pond, D., Luscombe, G. Diagnosing dementia in primary care: The accuracy of informant reports. *Alzheimer Dis. Assoc. Disord.* 2002;16(3):171–176.
13. Fritsch, T., McClendon, M.J., Smyth, K.A., Ogrocki, P.K. Effects of educational attainment and occupational status on cognitive and functional decline in persons with Alzheimer-type dementia. *Int. Psychogeriatr.* 2002;14(4):347–363.
14. Wilson, R.S., Bennett, D.A., Bienias, J.L., et al. Cognitive activity and incident AD in a population-based sample of older persons. *Neurology* 2002;59(12):1910–1914.
15. Podsiadlo, D., Richardson, S. The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* 1991;39(2):142–148.
16. Nilsson-Ehle, H., Jagenburg, R., Landahl, S., Svanborg, A. Blood haemoglobin declines in the elderly: Implications for reference intervals from age 70 to 88. *Eur. J. Haematol.* 2000;65(5):297–305.
17. Ania, B.J., Suman, V.J., Fairbanks, V.F., Rademacher, D.M., Melton III, L.J. Incidence of anemia in older people: An epidemiologic study in a well defined population. *J. Am. Geriatr. Soc*. 1997;45(7):825–831.
18. Fatourechi, V. Subclinical thyroid disease. *Mayo Clin. Proc*. 2001;76(4):413–6; quiz 6–7.
19. Brigden, M.L., Heathcote, J.C. Problems in interpreting laboratory tests. What do unexpected results mean? *Postgrad. Med*. 2000;107(7):145–146, 51–52, 55–58 passim.
20. Guigoz, Y., Lauque, S., Vellas, B.J. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. *Clin. Geriatr. Med*. 2002;18(4):737–757.
21. Goldwasser, P. Albumin trend and mortality. *Am. J. Kidney Dis,* 1997;30(2):308–309.

22. Folstein, M.F., Folstein, S.E., McHugh, P.R. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res*. 1975;12(3):189–198.
23. O'Connor, D.W., Pollitt, P.A., Hyde, J.B., et al. The reliability and validity of the Mini-Mental State in a British community survey. *J. Psychiatr. Res.* 1989;23(1):87–96.
24. Galasko, D., Klauber, M.R., Hofstetter, C.R., Salmon, D.P., Lasker, B., Thal, L.J. The Mini-Mental State Examination in the early diagnosis of Alzheimer's disease. *Arch. Neurol*. 1990;47(1):49–52.
25. Crum, R.M., Anthony, J.C., Bassett, S.S., Folstein, M.F. Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA* 1993;269(18):2386–2391.
26. Solomon, P.R., Hirschoff, A., Kelly, B., et al. A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. *Arch. Neurol.* 1998;55(3): 349–355.
27. Brodaty, H., Kemp, N.M., Low, L.F. Characteristics of the GPCOG, a screening tool for cognitive impairment. *Int. J. Geriatr. Psychiatry* 2004;19(9):870–874.
28. Shulman, K.I. Clock-drawing: Is it the ideal cognitive screening test? *Int. J. Geriatr. Psychiatry* 2000;15(6):548–561.
29. Kirby, M., Denihan, A., Bruce, I., Coakley, D., Lawlor, B.A. The clock drawing test in primary care: Sensitivity in dementia detection and specificity against normal and depressed elderly. *Int. J. Geriatr. Psychiatry* 2001;16(10):935–940.
30. Richardson, H.E., Glass, J.N. A comparison of scoring protocols on the clock drawing test in relation to ease of use, diagnostic group, and correlations with Mini-Mental State Examination. *J. Am. Geriatr. Soc*. 2002;50(1):169–173.
31. Dwolatzky, T., Whitehead, V., Doniger, G.M., et al. Validity of a novel computerized cognitive battery for mild cognitive impairment. *BMC Geriatr.* 2003;3:4.
32. Petersen, R.C., Morris, J.C. Mild cognitive impairment as a clinical entity and treatment target. *Arch. Neurol*. 2005;62(7):1160–1163.
33. Lawton, M.P., Brody, E.M. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179–186.
34. Mahoney, F.I., Barthel, D.W. Functional evaluation: The Barthel index. *MD State Med. J.* 1965;14:61–65.
35. Biderman, A., Cwikel, J., Fried, A.V., Galinsky, D. Depression and falls among community dwelling elderly people: A search for common risk factors. *J. Epidemiol. Community Health* 2002;56(8):631–636.
36. Biderman, A., Galinsky, D. Preventive geriatric medicine: Reality or fiction? *Isr. Med. Assoc. J*. 2001;3(8):615–617.
37. Guralnik, J.M., Ferrucci, L. Assessing the building blocks of function: Utilizing measures of functional limitation. *Am. J. Prev. Med*. 2003;25(3 Suppl 2):112–121.
38. Hamerman, D. Toward an understanding of frailty. *Ann. Intern. Med*. 1999;130(11):945–950.
39. Fried, L.P., Ferrucci, L., Darer, J., Williamson, J.D., Anderson, G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J. Gerontol. A Biol. Sci. Med. Sci.* 2004;59(3):255–263.
40. Fried, L.P., Tangen, C.M., Walston, J., et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* 2001;56(3):M146–156.
41. Dwolatzky, T., Clarfield, A., Bergman, H. Non-specific presentations of illness. *Oxford Textbook of Primary Medical Care.* Oxford: Oxford University Press; 2004.
42. OldeRikkert, M., Rigaud, A., vanHoeyweghen, R., deGraaf, J. Geriatric syndromes: Medical misnomer or progress in geriatrics. *Neth. J. Med.* 2003;61(3):83–87.
43. Williams, C. Using medications appropriately in older adults. *Am. Fam. Physician* 2002;66(10):1917–1924.

44. Nascher, I.L. A history of geriatrics. *Med. Rev. Rev.* 1926;32:281–284.
45. Warren, M.W. Care of the chronic sick: A case for treating chronic sick in blocks in a general hospital. *BMJ* 1943;2:822–823.
46. Home care in the 1990s. Council on Scientific Affairs. *JAMA* 1990;263(9): 1241–1244.
47. Steel, K., Leff, B., Vaitovas, B. A home care annotated bibliography. *J. Am. Geriatr. Soc.* 1998;46(7):898–909.
48. Clarfield, A.M., Bergman, H. Medical home care services for the housebound elderly.*CMAJ* 1991;144(1):40–45.
49. Kane, R.A. Expanding the home care concept: Blurring distinctions among home care, institutional care, and other long-term-care services. *Milbank Q.* 1995;73(2):161–186.
50. Sullivan, G.M., Boling, P.A., Ritchie, C., Levine, S. Curriculum recommendations for resident training in home care. *J. Am. Geriatr. Soc*. 1998;46(7):910–912.
51. Gitlin, L.N., Winter, L., Dennis, M.P., Corcoran, M., Schinfeld, S., Hauck, W.W. A randomized trial of a multicomponent home intervention to reduce functional difficulties in older adults. *J. Am. Geriatr. Soc*. 2006;54(5):809–816.
52. Gill, T.M., Baker, D.I., Gottschalk, M., Peduzzi, P.N., Allore, H., Byers, A. A program to prevent functional decline in physically frail, elderly persons who live at home. *N. Engl. J. Med.* 2002;347(14):1068–1074.

2

Incidence of Renal Diseases in an Acute Geriatric Unit

Cristina Alonso Bouzón, Gonzalo Bravo Fernández de Araoz and Francisco Guillén Llera

Introduction

In the foreword to the book *Internal Medicine in Old Age* written by Mùller-Denhan in 1942, the author states, "When I took charge of the senile patient clinic, I could realise that my before formation and my longer activity like head of other medical departments were not enough and I had to begin again. It was like, suddenly, I was in front of a children clinic; the difference was so big."

The emergence of geriatrics as a medical specialty in its own right began in the UK in 1945. From there it spread, not without difficulties, to the rest of Europe and to some of North and South America. In Spain, geriatrics has been an official specialty since 1978.

Currently, the medical welfare scene is characterized by a progressively aging population and an increasing life expectancy, more pronounced in the developed countries (Figure 2.1). This has produced a "geriatrization" of medicine, resulting in a continuous rise in the utilization of sanitary and social resources by the elderly.

In this context, the development of systems that cover the specific needs of the elderly has become a challenge to the health services in developed countries. A good geriatric healthcare system should be based upon three main components: primary care, hospital care, and social services in the community (Table 2.1).

Our hospitals´ available beds are increasingly being occupied by elderly patients, in medical as well as certain surgical departments. Figure 2.2 indexes the bed occupation for 65- and 80-year-olds in the Acute Geriatric Unit of the University Hospital of Getafe in Madrid.

Acute Geriatric Unit in General Hospitals

Geriatrics today is understood as different levels of care, which must give a suitable response to the different states of disease presented by the elderly. The mentioned situations range from acute disease to continuous care, with

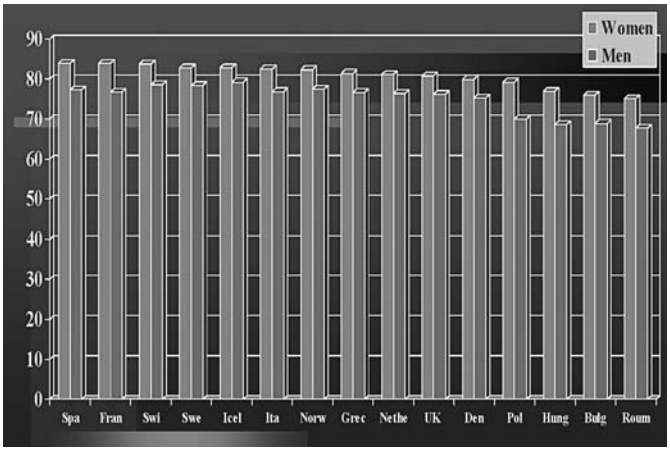

Fig. 2.1 Life expectancy at birth (2004) in several European countries. (*Source:* EUROSTAT, 2006.)

Table 2.1 Geriatric Care Levels.

1. Primary care services
2. Hospital care
• Acute Geriatric Unit
• Geriatric Evaluation Unit
• Functional Recovery Unit
• Day Hospital
• Community Care Unit
• Special units
3. Social services
• Community care
• Domiciliary care
• Nursing home care

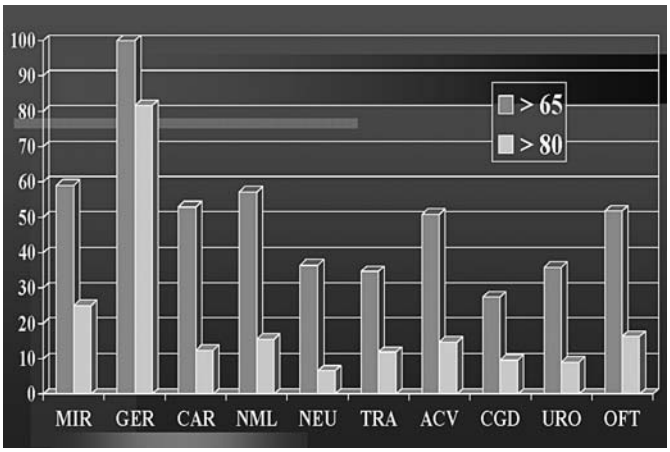

Fig. 2.2 Bed occupation (%) for patients between 65 and 80 years old in different general hospital departments.
(*Source:* Geriatric Department 2005. University Hospital of Getafe.)

a special emphasis placed upon the phases of rehabilitation and functional recovery.

The acute geriatric unit (AGU) is an essential component of progressive geriatric care. Only elderly patients who fulfill the admission criteria are admitted to AGUs. Such patients only account for 10–15% of the elderly inpatients in a general hospital.

Geriatric Practice

Geriatric practice is based on the application of the following tools:

- **Integral evaluation**: It is a multidimensional, multidisciplinary diagnostic process, designed to identify and quantify medical problems, to evaluate functional capacities and psychosocial conditions, to reach a plan of global treatment, to optimize the utilization of resources, and to guarantee the continuity of care.
- **Multidisciplinary approach:** It relies on the integration and coordination of different healthcare professionals working toward a common goal.
- A**vailability of different levels of care** according to the different situations of disease and patient needs.

Table 2.2 shows the methodical performance of the AGU. This way of approaching patient care separates geriatric medicine from the other medical specialities and is at the center of its clinical practice.

Admission Criteria

It is fundamental to know the type of patients admitted to an AGU, since it is only with a specific type of patient (see Table 2.3) that the AGU has demonstrated benefits such as reduced mortality, increased functional recovery, and a reduction in the number of medications, the length of hospital stay, and the institutionalization rate at discharge.

The admission criteria of the emergency department in the AGU of our hospital follow the guidelines shown in Table 2.3. Our AGU is not obliged to fulfill all of these criteria, but it must fulfill at least three of them.

Patient Characteristics

"Geriatric patients" are characterized by very advanced ages, the presence of acute illness with a tendency toward disability or the exacerbation of chronic diseases, a combination of different illnesses, polypharmacy, and physical,

Table 2.2 Acute Geriatric Unit Characteristics.

• Established admission criteria
• Integral geriatric assessment
• List of patient problems
• Established performance guidelines
• Progressive care
• Clinic, functional, mental, and social diagnosis
• Programmed discharges
• Continuous care control

Table 2.3 Admission Criteria for an Acute Geriatric Unit.

1. >80-Year-old patients
   - • Acute medical disease that does not need other specialist unit admission
2. 70–80-Year-old patients
   - ∗ Acute illness with risk of disability
   - ∗ Exacerbation of chronic disease
   - ∗ Combination of several diseases
   - ∗ Intake of >3 medications
   - ∗ Previous functional state
     - √ Barthel index < 60
   - ∗ Previous mental state
     - √ Mini-mental test <24
   - ∗ Social problems previously or at discharge

Source: Geriatric Department, Getafe University Hospital, 2005.

mental, and social components. Actually, the admitted patients in our AGU exceed an average age of 85 years and 65% of the patients are women (Figure 2.3). In recent years, there has been a high proportion of patients with severe previous disability (physical or mental), which limits the possibility of rehabilitation. This situation may be explained by the large percentage of patients admitted from nursing homes (practically 30% in our department) (Figure 2.4).

The administrative management records show an average length of stay of less than 10 days with a mortality rate close to 14%. Readmissions are higher, with 20% of patients readmitted within 90 days after discharge. Four percent of these patients are even readmitted within the first 10 days after discharge (these ones are considered unsuccessful discharges).

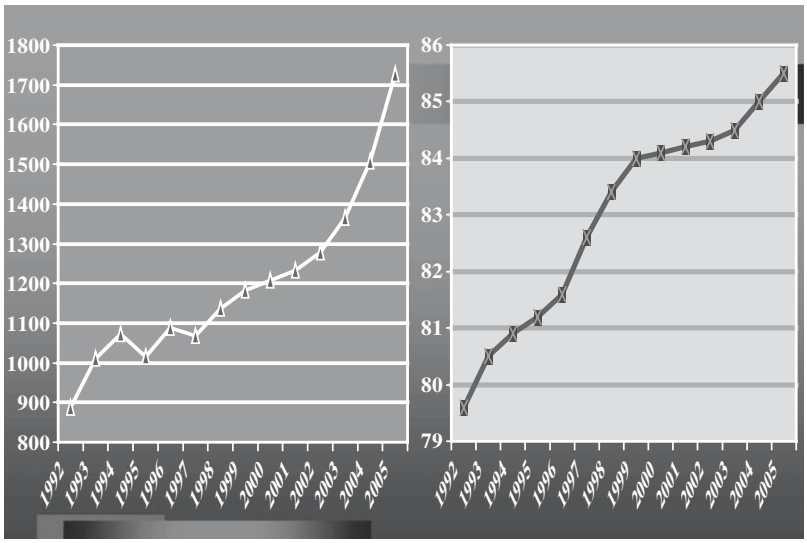

Fig. 2.3 Number of inpatients and their mean age during the last 14 years in an acute geriatric unit (MIR: Internal Medicine; GER: Geriatrics).
(*Source:* 2005 University Hospital of Getafe.)

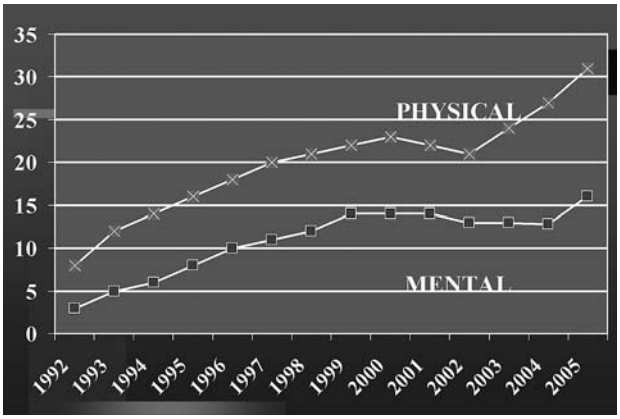

Fig. 2.4 Severe incapacity rate of patients during the last 14 years in an acute geriatric unit.
(*Source:* Geriatric Department 2005. University Hospital of Getafe.)

Common Diseases

The main causes of admission to an AGU are acute diseases and exacerbations of chronic diseases. The most frequent DGR (groups related to the diagnosis) are heart failure, chronic obstructive airways disease, pneumonia, cerebrovascular disease, and urinary tract infection. The most commonly associated diseases are hypertension, rheumatic degenerative processes, diabetes mellitus, hypercholesterolemia, chronic kidney failure, dementia, and residual hip fracture.

The Most Common Renal Pathology in an Acute Geriatric Unit

Renal pathology is very common in acute geriatric units as a principal diagnosis (acute renal failure in 13.4% of the patients) as well as being associated with other illnesses (chronic renal disease in 18.2% of our inpatients). Benign prostatic hyperplasia is diagnosed in 36% of all male patients and urinary tract infection in 20.6% of all patients. Malignant tumors are diagnosed in 5% of inpatients, with prostate and bladder carcinomas being the most frequently diagnosed tumors (Table 2.4). We have included in the following paragraph the main renal diseases and their characteristics in the elderly patients admitted to an AGU.

Acute Renal Failure

Acute renal failure (ARF) is a very common pathology in the elderly. Its incidence varies between 6.8% and 36% according to different studies [1–3]. In 2005, the incidence in our acute geriatric unit was 13.4%.

For diagnosic purposes, creatinine clearance is a better marker of glomerular filtration than blood creatinine levels [4], as the influence of muscle mass on plasma creatinine levels is often reduced in the elderly.

The causes of ARF can be divided into pre-renal (e.g., dehydration, hypotension), renal (e.g., acute tubular necrosis, glomerulonephritis, and

Table 2.4 Renal Disease in an Acute Geriatric Unit(n = 1.726; Average Age 85 Years).

Pathology	Number of Patients	Percentage
Chronic renal disease	315	18.2%
Acute renal disease	233	13.4%
Urinary tract infection	356	20.6%
Benign prostatic hyperplasia (males: 605)	218	36%
Malignant masses	86	4.9%
Prostatic cancer	46	2.6%
Bladder cancer	31	1.8%
Kidney cancer	10	0.5%

Source: Geriatric Department, Getafe University Hospital. 2005.

thrombosis of the renal artery or vein), and postrenal (e.g., increased size of the prostate, calculus). With increasing age, the incidence of pre-renal and postrenal causes increases, while that of acute tubular necrosis falls [5]. The most common causes of ARF in old age are dehydration, sepsis, nephrotoxic drugs, and obstructive abnormalities. In concordance with other studies carried out in our unit, the leading cause was volume depletion, followed by nephrotoxic drugs, obstructive uropathy, shock (sepsis and cardiac), and a combination of several factors (Table 2.5). In the elderly, the combination of several causes is very common, making up about 20–25% of the acute renal failure in this population in some studies [6].

Oliguria [3, 7], the need for dialysis [3], the presence of surgical causes of acute renal failure [3], mechanical respiration [2], decreased level of consciousness [2], and hypotension [2, 5, 7] were associated with poor prognosis. The recovery in elderly patients is less frequent and slower than in younger ones. In a stratified analysis, the relative mortality risk in elderly patients compared with younger ones was not significant [2,3,5]. It is possible that the co-morbidities and the level of independence in carrying out activities of daily living are more important for the outcome than age. The age "per se" should not be a discriminating factor in denying any technical treatment for acute renal failure, such as hemodialysis or kidney transplantation.

In an AGU, acute renal failure raises the mortality rate to 50–60%[3] and worsens the outcome when compared to other pathologies [8]. It is very

Table 2.5 Principal Factors Related with Acute Renal Failure in Geriatric Patients.

1. Volume depletion
   - Dehydration
   - Diarrhea/vomiting
   - Diuretic treatment
   - Hemorrhage
2. Multifactorial origin
3. Previous chronic renal disease
4. Nephrotoxic drugs
5. Cardiogenic shock
6. Obstructive uropathy
7. Septic shock

important not only to quickly reach a diagnosis and initiate treatment, but also to prophylactically avoid nephrotoxic drugs and hypoperfusion situations (for more details, see Chapter 20).

Chronic Renal Failure

Varying by country, 7–55% of the population over the age of 60 presents with chronic renal disease (CRD) [9]; in our study the prevalence was 18.2%. Prevalence is rising more steeply than incidence, mostly due to improved efficiency of treatment [10]. Among patients presenting with CRD, the number of patients developing end-stage renal disease diminishes with age [9], which could be due to increased cardiovascular disease, co-morbidity, or a higher mortality associated with chronic renal failure. Today, it is estimated that 18–20% of patients per year who present with CRD die before entering end-stage renal disease [9]. The main causes of progression from chronic disease to end-stage renal disease in the elderly are hypertension and diabetes [10].

The elderly are in a high-risk group for developing CRD. The increased risk is ascribable to several factors such as living alone, reduced performance in activities of daily living, cognitive impairment, and unfavorable economical and social reasons. Due to these factors, many elderly cannot access regular medical checkups. For this reason, admission to an acute geriatric unit is an excellent opportunity to prevent and detect chronic kidney disease. It is of importance to find underrecognized diabetes mellitus and hypertension and to treat them adequately with medications, which delay the development and progression of kidney failure. It is also important to detect the earlier stages of chronic kidney disease by means of evaluation, classification, and stratification, applying therapeutic interventions to delay progression and reduce associated morbidity and exacerbating factors [11]. On discharge, strong social and medical support is necessary.

For end-stage renal disease, renal replacement therapy is the treatment of choice (continuous ambulatory peritoneal dialysis, hemodialysis, or renal transplantation). It is best for nephrologists to discuss the treatment options with the patient and to carefully consider the previous quality of life, life expectancy, and the existence of concomitant illness.

Urinary Tract Infection

Urinary tract infections (UTI) account for 25% of all community-acquired bacterial infections and for 25–30% of all bacterial infections in institutionalized elderly patients [12, 13]. Among hospitalized patients, UTIs are the most common nosocomial infection, accounting for 35% of all infections [14]. Sixty percent of older women suffer a recurrence after an initial UTI. Women with recurrent UTIs have a higher 10-year mortality rate than women without recurrent UTIs (37 vs. 28%, $p < 0.001$) [15].

This high prevalence in the elderly can be explained by a number of factors: low pH, micturition dysfunction, mechanical obstruction to urine flow, urinary tract abnormalities, and hormonally dependent changes in vaginal pH and its flora [16]. We must also bear in mind predisposing factors such as bladder catheters and their handling and previous incapacity.

For healthy adults, urinary tract infection usually is a mild illness requiring only short-term antimicrobial therapy at home. This is not the

case for elderly patients due to aging-related immune system changes, comorbidities (diabetes mellitus, cancer, chronic renal failure), secondary causes of immune dysfunction (malnutrition, metabolic changes like hyperglycemia), and selected medications such as immunosuppressants [16]. The typical clinical symptoms (dysuria, flank or suprapubic pain, fever, and cloudy urine) are less frequent. Atypical symptoms such as altered mental status, newly developed incontinence, urinary retention, or functional deterioration may be the way of presentation. On the other hand, in frail elderly patients, UTIs can more easily result in bacteremia, decreased functional status, and death. Therefore, elderly patients with UTIs often need systemic antimicrobial therapy and hospitalization (Figure 2.5).

Gram-negative bacilli cause most urinary tract infections. The most common causative single organism is *Escherichia coli*, although *Proteus mirabilis*, *Klebsiella pneumoniae*, *Citrobacter spp*., *Serratia spp*., and *Enterobacter spp*. are also frequently isolated. *Enterococci* and *Staphylococcus spp*. are the most common Gram-positive cocci [17].

The appropriate use of catheters and their good handling could reduce the high incidence of UTIs among hospitalized patients. However, the treatment of asymptomatic bacteriuria with antimicrobial agents has not been shown to result in improved patient outcomes and is currently not recommended.

Table 2.6 portrays the level of physical and mental disability in patients with urinary tract infection compared to the patients in the general group. Although severe physical and/or mental disability is very high in both groups, it is higher in the patients with UTIs (44 vs. 31% and 23 vs. 11%, respectively) (for more details, see Chapter 15).

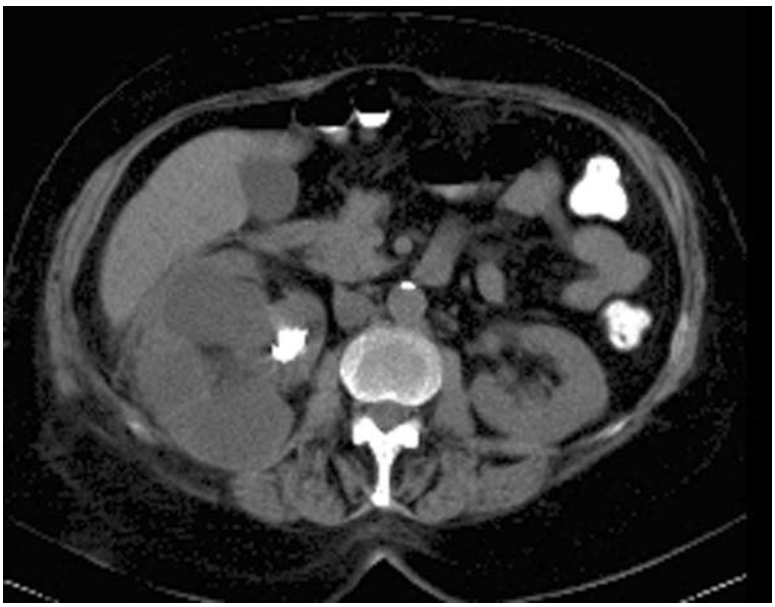

Fig. 2.5 Pyelonephritis.
(*Source:* Geriatric and Radiology Departments 2005. University Hospital of Getafe.)

Table 2.6 Disability, Previous Admission in Urinary Tract Infection, and Total Patients.

Disability Type	% UTI Patients (n = 1.726)	% Total Admissions
Physical		
Without disability	10%	16%
Moderate disability	46%	53%
Severe disability	44%	31%
Mental		
Without disability	40%	53%
Moderate cognitive impairment	36%	26%
Severe cognitive impairment	23%	11%

Source: Geriatric Department, Getafe University Hospital. 2005.

Renal Lithiasis

The incidence of urinary lithiasis differs according to the studied area, ranging from 2.66 to 12.89 per thousand inhabitants/year [18, 19]. Studies of prevalence show a male predominance with a variable male/female ratio from 1.26–2.4:1 [18, 20]. This pathology affects younger adults more frequently than the elderly [21, 22].

There are also more differences between young and elderly patients. The clinical presentation (e.g., colicky pain in the loin, recurrent painful desire to micturate with only a small amount of urine passed each time) is not so clear in the old, and in many cases patients present with complications (e.g., infection, obstruction, hydronephrosis) or nonspecific symptoms. In geriatric clinical medicine, it is not uncommon to find large asymptomatic staghorn calculi during a routine abdominal radiological examination. In spite of this, in an AGU, renal lithiasis is usually not an important cause of admission.

The most common calculi in the elderly are the calcium oxalate and calcium phosphate stones (80%) [21], but the incidence of uric acid stones was higher in the elderly patient group [21, 22]. This consideration is important because the uric acid stones are radio-transparent, which has to be kept in mind when deciding whether to use ultrasound, endoscopy, radiology, or CT. The probability of stone recurrence was similar in the elderly and the younger patients [21, 22].

The first line of treatment is conservative management with analgesics and anti-emetics. In most cases, nonsteroidal anti-inflammatory drugs provide effective analgesia, although opiates may be required in some cases. Intravenous fluids should be given if the patient cannot tolerate foods, but there is no therapeutic benefit from a regimen of forced diuresis (increased diuresis causes a decrease in uretic peristalsis).

The second line of treatment is urological intervention, and for that reason, the patient should be referred to the urologist. The percentage of elderly patients that need this line of treatment is similar to that of young patients [22]. In order to reduce the risk of complications and recurrence, a urological opinion should be sought, not only for the acute treatment but also for some follow-ups on discharge.

Obstructive Uropathy

Urinary obstruction means the blocking of urine flow by obstacles located between the renal calyces and the urethral meatus. In geriatric clinical medicine, prostate disease is by far the main cause of low obstructive uropathy in men. Other diseases, which can often cause this condition in elderly patients, are Lithia sis, bladder tumors, neurogenic bladder, and abdominal and pelvic tumors.

When we are confronted with any type of renal failure of unexplained origin in an elderly patient, we should consider the possibility of an obstructive uropathy, implementing the most appropriate diagnostic techniques, such as the renal ultrasound scan, which occupies a prominent place due to its safety, speed, and efficiency. Obstructive uropathy is a disease that should always kept in mind in geriatric clinical medicine, as it is initially reversible but can lead to irreversible renal failure. Obviously, therapy will depend on etiology. In elderly patients, a nephostomy and/or the placement of a vesico-ureteral or suprapubic catheter constitutes an indispensable initial therapy, prior to finding a permanent solution when possible.

Benign prostatic hyperplasia is a common problem in elderly men. In our acute geriatric unit, 36% of all men admitted during 2005 (605 patients) had been diagnosed with benign prostatic hyperplasia. The symptoms attributable to this disorder (e.g., hesitancy, poor and intermittent flow, incomplete emptying, high frequency of micturition, urgency, nocturia) can diminish their quality of life and progress to complications such as acute urinary retention, obstructive uropathy, urinary tract infections, and renal failure.

Drug therapy with alpha-1-adrenergic blockers or 5 alpha-reductase inhibitors reduces the symptoms, complications, and surgery needed [23]. Although benign prostatic hyperplasia is a pathology that can be treated on an outpatient basis, its high incidence in elderly inpatients, its possible serious complications, and the occasional difficulties these patients encounter in accessing clinics make admission a good opportunity to check for and adjust the treatment for this pathology.

Renal Masses

Currently, the incidence of renal masses is increasing due to the increasing number of coincidental findings by means of new imaging methods and due to the growth of the elderly population. Renal masses require considered use of diagnostic techniques, which are mainly based on radiology. The single abdominal X-ray enables the detection of changes in renal morphology, displacement of neighboring organs, and of difficult-to-interpret calcifications. Ultrasound, computed tomography, and magnetic resonance, appropriately used, are the best techniques, not only for the diagnosis but also for differentiating between those masses that can be considered benign, those that can be followed up carefully, and those that should be removed (or ablated) because nonmalignancy cannot be established by means of imaging studies [24]. The definitive diagnosis is made by histological examination through puncture aspiration under radiographic control or surgery.

Solitary Cyst

The uncomplicated renal cyst is the most commonly encountered fluid-filled lesion of the kidney [24]. Being a radiological finding, it is usually asymptomatic. Although most cysts are nonmalignant, it is important to rule out symptoms such as hemorrhage, infection, inflammation, and ischemia. In these cases, we could be faced with other pathologies (Figure 2.6).

Renal Polycystic Disease

The autosomal dominant type of polycystic kidney disease is the third leading cause of end-stage chronic renal failure [25] and represents 10% of all causes for hemodialysis [26]. In these cases, the diagnosis was usually made during adult age, but there are mild forms of the disease without symptoms or with mild renal failure that may be diagnosed during old age. The most common associated abnormalities are hepatic cysts, cerebral aneurysms, and colonic diverticulosis [26]. There is no specific treatment for this illness, and the goal is to prevent the natural progression to chronic renal failure (for more details, see Chapter 18).

Tumors

Renal cell carcinoma and bladder and prostate cancer are associated with age, and their incidence rises in the elderly. In 2005, our study showed that 0.5% of inpatients were diagnosed with renal cell carcinoma (Figure 2.7), 1.8% with bladder carcinoma, and 7.5% of all men admitted were diagnosed with prostate cancer. These incidences are low if we compare them to other studies, but we have to consider that these pathologies are usually admitted

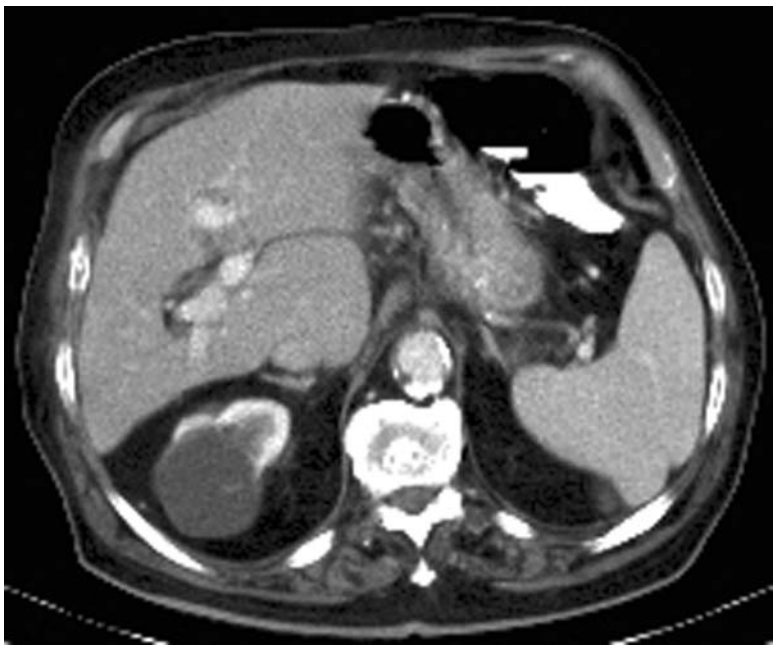

Fig. 2.6 Right renal cyst.
(*Source:* Geriatric and Radiology Departments 2005. University Hospital of Getafe.)

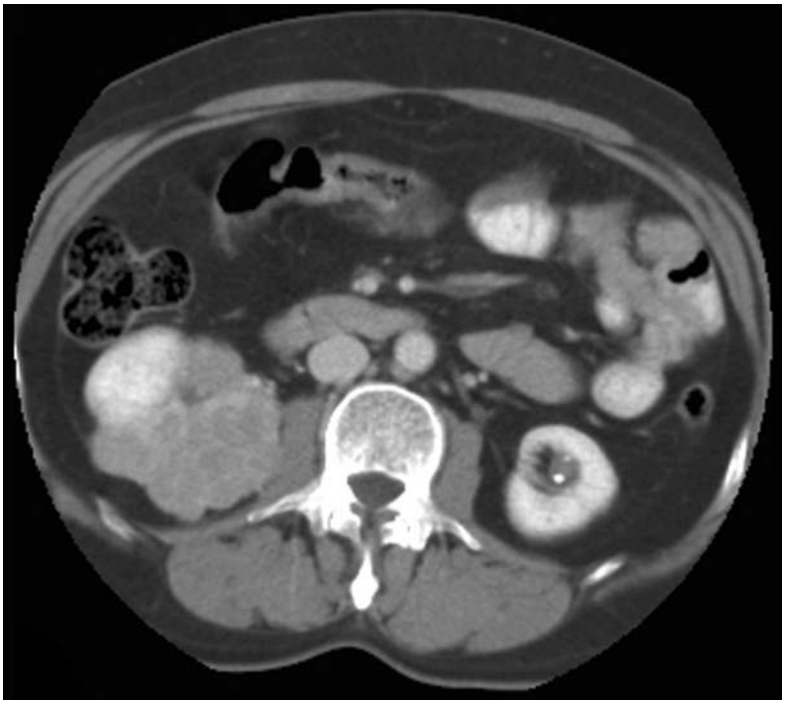

Fig. 2.7 Right kidney hypernephroma.
(*Source:* Geriatric and Radiology Departments 2005. University Hospital of Getafe.)

to other wards, mainly urology. In order to devise a good treatment plan, it is important to consider not only the tumor extension, but also the level of dependence in the activities of daily living, the co-morbidities, and the life expectancy. Therefore, cooperation between specialists is important.

Renal Tuberculosis

Although tuberculosis is a relatively uncommon disease, its incidence is rising, particularly in regions with a high prevalence of immunocompromised individuals (HIV, patients on dialysis). *M. tuberculosis* is, by far, the principal cause, but other bacilli could be involved. The most common form of extra-pulmonary tuberculosis, after lymphadenopathy, is genitourinary disease [27], which is sometimes caused by reactivation in the elderly.

Clinical diagnosis is very difficult. Many patients have the typical symptoms of urinary tract infection, occasionally with hematuria or flank pain. Suspicion should arise when the response to the antibacterial drugs is not satisfactory. In other instances, the finding is pyuria without other signs and symptoms. Other possible presentations include interstitial nephritis, glomerular disease, or progressive renal failure. In summary, the presentation of renal tuberculosis is very nonspecific [28].

There are various possible radiological changes. In the early stages of the disease, the changes are simple, such as the typical calcification on the plain film. In the advanced-disease stages, fibrotic masses with genitourinary system distortion can appear. The lesions depend not only on the state of

illness, but also on the virulence of the organism and the immune status of the patient. Intravenous urography and ultrasound are adequate in helping us reach a diagnosis.

A short course of antituberculosis drug regimens is, in fact, effective. In the case of renal failure, special considerations should be taken with ethambutol, streptomycin, and other aminoglycosides, because they are excreted by the kidney [28]. In some cases, surgical intervention may be indicated.

Geriatric Syndrome, Prevalent Illness, and Renal Disease

We have included in this section the main geriatric syndromes related to renal disease as well as the main diseases of high prevalence in the elderly impacting directly on renal function, such as diabetes and arterial hypertension. Both of these conditions are covered in detail in corresponding chapters of this book (diabetes in Chapter 17, and hypertension in Chapter 11).

Dehydration and Desalination

Dehydration is a frequent morbidity in elderly patients and by far the most common cause of changes in the fluid and electrolyte balance. Geriatric patients are increasingly being admitted to the hospital because of dehydration rather than because of their main illness.

Age-related changes make older people more vulnerable to shifts in water balance. The mechanisms involved are the reduced sensation of thirst, a percentage increase in fat, renal changes, and difficulties in accessing fluids due to a functional or cognitive impairment [29]. There are many possible contributing factors like gastrointestinal losses (e.g., vomiting, acute or chronic diarrhea, fistulas), cutaneomucosal losses (sweating during fever and intense dyspnea), and renal losses (e.g., indiscriminate use of diuretics, polyuria, and post-obstructive nephropathy). However, most often, dehydration in elderly patients is the result of a combination of several causes.

Dehydration can be a cause of multiple complications, such as acute renal impairment (the leading cause in elderly patients), with a high risk of residual renal failure. Therefore, it is important not only to quickly treat but also to employ preventive strategies in the acute geriatric units and other hospital wards to ensure an adequate liquid balance in medical scenarios such as the perioperative period, treatment with diuretics, or fever syndromes (for more details, see Chapters 8 and 10).

Arterial Hypertension

High blood pressure is a frequent phenomenon among the elderly population. Following "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure" (JNC VII) [30], where the limits for hypertension were set as 140/90, the prevalence of this pathology in our AGU in 2005 was 68.8% of admitted patients. Of these patients (n = 1190), 21% had chronic renal failure, while 76% of the patients with CRF (n = 315) had been diagnosed with hypertension. Due to its high prevalence and its clear association with cardiovascular disease

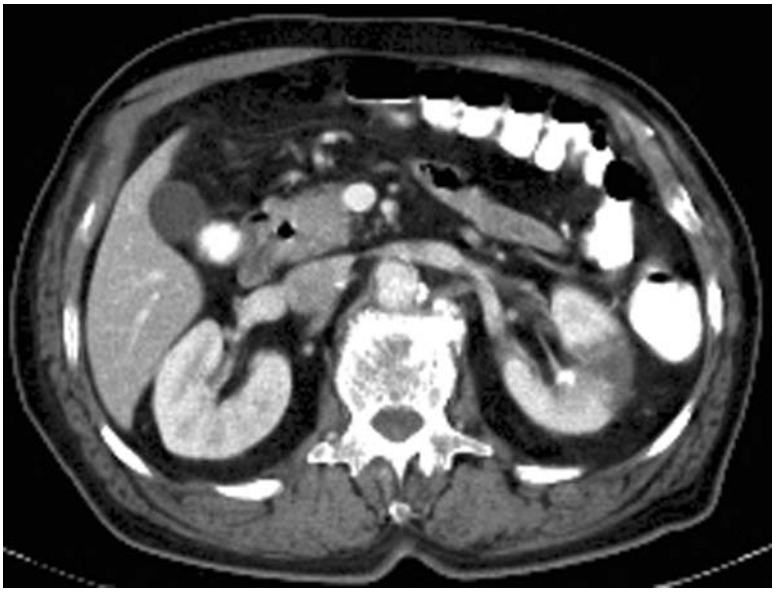

Fig. 2.8 Left kidney infarct.
(*Source:* Geriatric and Radiology Departments 2005. University Hospital of Getafe.)

and renal impairment (Figure 2.8), besides its frequent presentation with other cardiovascular risk factors, its good management is a priority.

The ultimate public health goal of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality [30]. Admissions are a good opportunity to put in order the hypertension treatment as well as prevent, diagnose, and treat the possible complications. Sometimes this is not possible due to the high demand and limited capacity in an acute geriatric unit, but at the very least, hypertensive control should be checked and specialist referral considered.

The guidelines recommend achieving a BP < 140/90, except in patients with hypertension and diabetes or renal disease, in whom the goal is to maintain a BP of less than 130/80 [30, 31].

A healthy lifestyle is an indispensable part of the treatment of these patients. It decreases BP, enhances antihypertensive drugs' efficacy, and decreases cardiovascular risk [30].The second step is pharmacological treatment. Several classes of drugs can reduce the complications of hypertension: thiazide-type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers [32, 33].

Patients with chronic kidney disease (glomerular filtration rate < 60 mL/min or albuminuria > 300mg/d) often need three or more drugs to reach the treatment goal [34]. In order to choose the most suitable antihypertensive drug, we should also consider the co-morbidities.

In the elderly, we have to keep in mind that changes in drug pharmacokinetics and pharmacodynamics due to aging and the high number of side effects force us to use lower initial drug doses. Therefore, it is often necessary to require multiple drugs in the elderly.

On other hand, the aged often reach their life expectancy with a mental or physical disability. In these cases, we should not be so strict with the goal (for more details, see Chapter 11).

Diabetes Mellitus

The prevalence of diabetes in the elderly varies between different populations and races. In 2005, 32% of all patients admitted to our acute geriatric unit were diabetics. We assume that the actual prevalence is higher, as it has been demonstrated that approximately one-third of all older diabetic people over 70 years remain undiagnosed [35].

Diabetes is associated with functional impairment and disability [36]. Only part of this relationship can be explained by the typical complications such as macro- and microvascular disease, such as diabetic nephropathy. In our study, 20% of the diabetic patients admitted ($n = 553$) had chronic renal failure; the prevalence of albuminuria and proteinuria was not known because we did not always check for them and because acute illness can cause false positives. Although microangiopathy is the main cause of renal failure in the elderly diabetic, we should not forget other causes such as co-morbidities, infections, and drugs.

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers have demonstrated a decrease in albuminuria compared to other drugs [37]. The guidelines [38] recommend that elderly diabetic patients with hypertension and albuminuria or proteinuria should be treated with ACE inhibitors or angiotensin-receptor blockers (when the ACEI are not tolerated), while in patients without diabetic nephropathy the hypertensive management will be similar to nondiabetic patients.

Heart Failure

In chronic heart failure, a reduction in the circulating volume stimulates the sympathetic and the renin-angiotensin-aldosterone system. These systems increase some hormonal concentrations like atrial and brain natriuretic peptides. Although this is a meant as a defensive mechanism, in continuously high levels it becomes a dangerous reaction that produces a reduction in renal plasma flow and glomerular filtration rate with secondary renal dysfunction [39]. Renal impairment in chronic heart failure is associated with a poor prognosis and a high mortality [3,4,10]. Due to drug side effects, it is difficult to treat both heart and renal failure.

In acute heart failure, the inappropriate use of diuretics is the most important risk factor for producing volume depletion. It is associated with a prolonged hospital stay [8]. In 2005 in our AGU, diuretic treatment was the third-largest cause of inadequate liquid balance after dehydration and gastrointestinal losses. In the elderly, the best option is to slowly and progressively create a negative fluid balance, while periodically checking renal function (for more details, see Chapter 12).

Multiple Myeloma

Multiple myeloma is a clonal B-cell disease of slowly proliferating plasma cells that are accompanied by monoclonal protein production and lytic bone

lesions. Often, there are no symptoms in the early stages of myeloma. When they are present, symptoms may be vague and similar to other conditions (e.g., pain in the lower back or ribs, loss of appetite, fatigue, muscle weakness). For this reason, patients with these nonspecific symptoms are commonly admitted to acute geriatric units for diagnostic testing. In some cases, myeloma may be discovered coincidentally during routine blood testing (e.g., hypercalcemia, anemia). Sometimes, the initial presentation is a pathological fracture; these patients are usually seen in other geriatric areas such orthogeriatric units or osteoporosis/falls clinics.

In patients with multiple myeloma, renal failure is a common complication. There are many causes of renal impairment. It is strongly associated with an excess of immunoglobulin light chains in the urine. Other possible factors include hypercalcemia, hyperviscosity, Bence Jones proteinuria, Fanconi's syndrome, hyperuricemia, amyloidosis, and glomerulosclerosis. Changes in the aging kidney and concomitants events can favor renal failure in elderly patients with myeloma. Dehydration, infections, and several drugs could be some of these concomitant factors. The majority of renal impairments should improve with simple measures such as rehydration, correction of hypercalcemia with bisphosphonates, treatment of infections, fluid rehydration, administration of glucocorticoids, and discontinuation of nephrotoxic drugs.

Iatrogenia

Iatrogenic renal disease is caused by a functional or structural impairment of the kidney due to a diagnostic or therapeutic plan. The renal changes in aging make the kidney more susceptible to nephrotoxic damage caused by drugs affecting glomerular autoregulation through microvascular mechanisms [6]. Nephrotoxic drugs can contribute to the development of acute renal failure in 66% of patients with this treatment-related pathology [7]. This damage can be caused by several types of disorders such as acute tubular necrosis, interstitial nephritis, glomerulopathies caused by immune complexes, and vasculitis. The drugs that most often cause renal damage in geriatric clinical medicine are antibiotics (e.g., penicillin, aminoglycosides, sulphonamides, polymyxin, amphotericin), analgesics (e.g., nonsteroidal anti-inflammatory, phenylbutazone, fenoprofen, indomethacin), and ACE inhibitors. Not only therapeutic measures can produce this damage, as the contrast medium can be a pathogenic factor in up to 16.9% of iatrogenic acute renal failure [7].

A good liquid balance is another measure taken to prevent the renal damage. Some frequent medical situations such as the postoperative period, heart failure, and sepsis can cause a hypoperfusion situation, the most common cause of the pre-renal type of acute renal failure in the elderly.

Greater attention to renal changes in aging and an increased dissemination of preventive measures could reduce the incidence of this serious and potentially lethal disease. In a Spanish study comparing the incidence of acute renal failure before and after the institution of prevention measures, the iatrogenic factors were reduced from 75% to 25% and the incidence of ARF was reduced from 1.6% to 0.65%, with the difference being statistically significant. It is advisable to implement these measures.

Conclusion

The incidence of renal pathology is high in patients admitted to an acute geriatric unit. Renal impairment is favored not only by the aging of the renal system but also by the great prevalence of other diseases such as diabetes mellitus, hypertension, infections, or dehydration, which contribute to renal failure. Not only early diagnosis but also preventative measures are needed in an acute geriatric unit to avoid the medical situations that favor renal impairment, its progression, and its complications. One should not forget the importance of the cardiovascular risk factors. In-patient admission of the elderly is often the only opportunity to screen for these conditions and to check their control.

The elderly patient frequently has a functional and/or cognitive impairment with a limited life expectancy. It is therefore necessary when making both diagnostic and therapeutic decisions to use the guidelines in an individualized way, after performing an integral geriatric evaluation. In terms of decision making, it is advisable that the different specialists cooperate with each other. Patients should always be admitted in wards with multidisciplinary teams trained in the care of elderly patients. This has demonstrated a decrease in the functional deterioration, institutionalization, and mortality of inpatients.

On some occasions, the clinical diagnosis is difficult in the elderly. The atypical presentation of the disease, scanty detection of the symptoms, and the presence of co-morbidity make it necessary for doctors to thoroughly look for diseases in the elderly.

The effect of muscle mass on plasma creatinine levels is diminished in the elderly. In our opinion, it is therefore necessary to use creatinine clearance as the marker of glomerular filtration rather than blood creatinine levels. With regards to the diagnostic tools, the most commonly used ones are non-invasive, with few side effects for the patients such as the abdominal X-ray, ultrasound scan, and CT scan. In fact, ultrasound is the most important imaging technique in the elderly due to its high sensitivity and low rate of side effects. Invasive techniques are not frequently used in the elderly. Nevertheless, age "per se" should not be used as the only factor in denying patients any technical diagnostic or treatment procedure such as kidney biopsy, hemodialysis, or renal transplantation.

References

1. McInnes, E.G., Levy, D.W., Chaudhuri, M.D., et al. Renal failure in the elderly. *Q. J. Med*. 1987; 64(243):583–588.
2. Pascual, J., Orofino, L., Liano, F., el al. Incidence and prognosis of acute renal failure in older patients. *J. Am. Geriatr. Soc*. 1990; 38(1):25–30.
3. Romao Jr., J.E., Haiashi, A.R., Vidonho Jr. A.F., et al. Causes and prognosis of acute renal failure in elderly patients. *Rev. Assoc. Med. Bras*. 2000; 46(3):212–217.
4. Macías-Núñez, J.F., López Novoa, J.M., Martínez Maldonado, M. Acute renal failure in the aged. *Semen. Nephrol*. 1996; 16(4):330–338.
5. Pascual, J., Liano, F. Causes and prognosis of acute renal failure in the very old. Madrid Acute Renal Failure Study Group. *J. Am. Geriatr. Soc*. 1998; 46(6): 721–725.
6. Baralde, A., Ballestri, M., Rapana, R., et al. Acute renal failure of medical type in an elderly population. *Nephrol. Dial. Transplant*. 1998; 13 Suppl 7:25–29.

7. Kohli, H.S., Bhaskaran, M.C., Muthukumar, T., et al. Treatment-related acute renal failure in the elderly: a hospital-based prospective study. *Nephrol. Dial. Transplant*. 2000; 15(2):212–217.
8. Wright, S.P., Verouhis, D., Gamble, G., et al. Factors influencing the length of hospital stay of patients with heart failure. *Eur. J. Heart Fail*. 2003; 5(2):201–209.
9. Cobat, A., Landais, P. Epidemiology of chronic renal failure in the elderly. *Rev. Prat*. 2005; 55(20):2230–2236.
10. Bommer, J. Pravalence and socioeconomic aspects of chronic kidney disease. *Nephrol. Dial. Transplant*. 2002; 17 Suppl 11:8–12.
11. Obrador, G.T., Pereira, B.J., Kausz, A.T. Chronic kidney disease in the United States: An underrecognized problem. *Semen. Nephrol*. 2002; 22(6):441–448.
12. Nicolle, L. Urinary tract infection in long-term-care facility residents. *Clin. Infect. Dis*. 2000; 31:757–761.
13. Foxman, B. Epidemiology of urinary tract infections: Incidence, morbidity and economic costs. *Am. J. Med*. 2002; 113:5S–13S.
14. Burke, J.P. Infection control: A problem for patient safety. *N. Engl. J. Med*. 2003; 348:651–656.
15. Wick, G., Jansen-Durr, P., Berger, P. et al. Diseases of aging. *Vaccine* 2000; 18:1567–1583.
16. Hermann, V., Palma, P., Geo, M.S., et al. Urinary tract infections: Pathogenesis and related conditions. *Internal Urogyn. J*. 2002; 13:210–213.
17. Bauer, R.J., Zhang, L., Foxman, B., et al. Molecular epidemiology of 3 putative virulence genes for *Escherichia coli* causing bacteremic and non bacteremic febrile urinary tract infection-usp, iha, and iron (*E. coli*). *J. Infect. Dis*. 2002; 185: 1521–1254.
18. Galvez Calderón J, Varea Herrero J, Colome Borros G. Epidemiology of urinary lithiasis. *Actas Urol. Esp*. 2001; 25(5):341–349.
19. Ripa Saldias, L., Delpon Pérez, E., Romero Fernández, F.J. Epidemiology of urinary lithiasis in La Rivera de Navarra. *Acta Urol. Esp*. 1995; 19(6):459–466.
20. Mrad, R., Ben Ammar, S., Bahlous, A., et al. Epidemiologic data in renal lithiasis in adults. *Tunis. Med*. 2001; 79 (1):15–19.
21. Usui, Y., Matsuzaki, S., Matsushita, K., et al. Urolithiasis in geriatric patients. *Tokai J. Exp. Clin. Med*. 2003; 28(2):81–87.
22. Gentle, D.L., Stoller, M.L., Bruce, J.E., et al. Geriatric urolithiasis. *J. Urol*. 1997; 158(6):2221–2224.
23. Chapple, C.R. Pharmacological therapy of benign prostatic hyperplasia/lower urinary tract symptoms: An overview for the practising clinician. *BJU Int*. 2004; 94(5):738–744.
24. Hartman, D.S., Choyke, P.L., Hartmen, M.S. From the RSNA refresher courses. A practical approach to the cystic renal mass. *Radio Graph*. 2004; 24:S101–115.
25. Bourquia, A., Ramdani, B., Jabrane, A.J., et al. Dominant renal polycystic disease. *Rev. Med. Int*. 1989; 10(4):313–318.
26. Lugagne, P.M., Benoit, G. Autosomal dominant polycystic kidney in adults. *Ann. Urol. (París)* 1990; 24(4):265–271.
27. Eastwood, J.B., Gorbishley, C.M., Grange, J.M. Tuberculosis and the kidney. *J. Am. Soc. Nephrol*. 2001; 12:1307–1314.
28. Ferry, M. Strategies for ensuring good hydration in the elderly. *Nutr. Rev*. 2005; 63(6Pt2):S22–29.
29. Chobanian, A.V., Bakris, G.L., Black, H.R., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003; 289:2560–2572.
30. American Heart Association. Treatment of hypertension in adults with diabetes. Diabetes National Kidney Foundation Gudeline. K/DOQI clinical practice guidelines for chronic kidney disease: Kidney Disease Outcome Quality Initiative. *Am. J. Kidney Dis*. 2002; 39(Suppl 2):S1–S246.

31. Ungar, A., Di Serio, C., Lambertucci, L., et al. Calcium channel blockers and nephroprotection. *Aging Clin. Exp. Res*. 2005; 17(4 Suppl):31–39.
32. Stergiou, G.S., Makris, T., Papavasiliou, M., Efstathiou, S., et al. Comparison of antihypertensive effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist and a diuretic with hypertension not controlled by angiotensin receptor blocker. *J. Hypertens*. 2005; 23(4):883–889.
33. Bakris, G.L., Williams, M., Dworkin, L., et al. for National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes. *Am. J. Kidney Dis*. 2000; 160:685–693.
34. Valderram, E., Damian, J., Ruigomez, A., et al. Chronic disease, functional status decline in community living elderly people: A systematic literature review. *Soc. Sci. Med*. 1999; 48:445–469.
35. Viberti, G., Wheeldon, N.M. MicroAlbuminuria Reduction with VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: A blood-pressure independent effect. *Circulation* 2002; 6;106(6):672–678.
36. Clinical guidelines for type 2 diabetes mellitus. European Diabetes Working Party for Older People 2004. www.eugms.org.
37. De Santo, N.G., Perna, A., Pollastro R.M., et al. The kidney in heart failure. *Semin. Nephrol*. 2005; 25(6):404–407.
38. Hillege, H.L., Girbes, A.R., de Kam, P.J., et al. Renal function, neurohormonal activation and survival in patients with chronic heart failure. *Circulation* 2000; 102(2):203–210.
39. Hillege, H., Van Gilst, W., de Zeeuw, D., et al. Renal function as a predictor of prognosis in chronic heart failure. *Heart Fail. Monit*. 2002; 2(3):78–84.

3

Anatomical Changes in the Aging Kidney

Xin J. Zhou, Zoltan G. Laszik and Fred G. Silva

Introduction

The changes to renal morphology and function in the aging human kidney have been reviewed [1–3]. However, there are many problems in the documentation of the pathological changes in the aging kidney. The confounding variables of hypertension (and ischemia), diabetes, and other co-existing renal diseases are often difficult to dissect out. The renal tissue is frequently not sampled early enough to determine if a primary renal disease is associated with the aging kidney. Most patients with "nephrosclerosis" and/or aging kidneys are not biopsied or autopsied. The nomenclature (definitions), descriptions, and documentation of the morphological changes are often imprecise and usually not quantitated. Focal lesions, especially of the vascular tree, may be missed due to inadequate sampling. There may be "nephron heterogeneity," which is difficult to quantitate/describe. The terms *nephrosclerosis*, *glomerulosclerosis*, *arterial sclerosis*, *arteriolosclerosis*, *tubular atrophy*, and perhaps even *interstitial fibrosis* are often vaguely used. And finally, there is biologic variability and various rates of structural changes in different ethnicities, countries, and even renal compartments. With these caveats in mind, this chapter tries to summarize the current knowledge of the anatomical changes in the aging human kidney, and, where appropriate, the underlying pathogenetic pathways will be briefly mentioned.

Gross Pathology

Macroscopically, aging kidneys are symmetrically contracted with a fine granular appearance of the subcapsular surface. On average, kidney weight increases from birth to about age 40–50 and then progressively declines, with the most dramatic decrease (about 20–30%) occurring in the seventh and eighth decades [1, 3, 4]. The loss of kidney mass appears to affect the renal cortex more than the medulla, with involution/thinning of the renal cortical parenchyma, which is thought to be related to vascular changes [5, 6].

Approximately one-half of all people 40 years and older have one or more acquired cysts in the kidney [7]. The cysts are generally unilocular and round

to oval, containing clear yellowish fluid. Some believe that simple cysts arise from dilated tubules or glomeruli. Others believe they arise from tubular diverticula found in increasing incidence with aging [8].

The Aging Glomerulus

Many morphological changes have been noted in the human glomerulus with aging [9–21]. These include (1) progressive decline in the number of intact or normal glomeruli, (2) increase in the number/percentage of globally sclerotic glomeruli, especially those of the outer cortical regions initially, (3) abnormal glomeruli with shunts between the afferent and efferent arterioles bypassing the glomeruli, especially the juxtamedullary ones, (4) progressive decrease, and then later increase, in the size of intact glomeruli, (5) focal or diffuse thickening of the glomerular basement membranes, and (6) increased mesangial volume and matrix (i.e., mesangial sclerosis).

The numbers of glomeruli (and hence nephrons) are extremely variable in individuals. Studies by Nyengaard and Bendtsen [15] have suggested that the mean range of the number of glomeruli per kidney is 620,000 ± 250,000, with a range of 333,000 to 1,100,000. Twenty-five percent of the population studied had fewer than 500,000 glomeruli/kidney, whereas 25% of the population had over 740,000 glomeruli/kidney. Likewise, Hughson et al. [16] showed an eightfold difference in the number of glomeruli per person (from 227,327 to 1,825,380 per kidney). On average, females have approximately 15% fewer glomeruli than males [17]. The mean glomerular number is not significantly different between Caucasians and African-Americans, but is significantly lower in Australian aborigines [14, 17]. Age is inversely proportional to the number and size of the glomeruli as well as inversely proportional to the kidney weight [14–17]. Thus, humans seem to lose glomeruli with aging.

The relationships of nephron number to birth weight, and to susceptibility to hypertension and renal diseases, have been noted [16–19]. There is a direct linear relationship between the number of glomeruli and birth weight [16]. As birth weight decreases, the number of glomeruli also decreases. In fact, regression coefficient analysis predicts a 257,426-glomeruli increase per kilogram of birth weight. There is an up to eightfold range in glomerular volume among adults, and the glomerular volume is strongly and inversely correlated with the number of glomeruli. In a study of white adults aged 35–59 who died in accidents, Keller et al. [18] have shown that patients with hypertension have approximately 50% fewer glomeruli than matched controls. This study also showed that the volume of glomeruli increases in patients with hypertension compared to matched controls, possibly a result of lower numbers of glomeruli. Based on a stereological study of autopsy kidneys from 140 adults, aged 18–65, who lived in the southeastern United States, Hughson et al. [17] found no relationships between the glomerular number, mean arterial blood pressure (MAP), and birth weights in African-Americans. In contrast, there was a strong correlation of the glomerular number with both birth weight and inversely with MAP in white adults. These data indicate that low nephron number and possibly low birth weight may play a role in the development of hypertension in whites but not in African-Americans.

Samuel et al. [19] analyzed the distributions of volumes of individual glomeruli in the superficial, middle, and juxtamedullary cortex of normal

human kidneys using unbiased, stereological techniques. They found no significant zonal differences in the young (aged 20–30) or those with body surface areas (BSA) ≤ 2.11 m^2. In contrast, superficial glomeruli in the older age group (aged 51–69), in those with BSA > 2.11 m^2, and in Caucasians were significantly larger than juxtamedullary glomeruli. African-Americans showed significantly larger glomerular volume than whites that was most marked in the juxtamedullary zone and independent of age, BSA, and glomerular number.

Numerous studies have demonstrated that the percentage of glomeruli showing global glomerulosclerosis is increased with age. Utilizing standard morphometric techniques and multiple linear regression statistics, Kasiske [10] showed a direct correlation between the number/percentage of globally sclerotic glomeruli and age (and also to intrarenal vascular disease). In fact, together age and intrarenal vascular disease, especially outer cortical vessel disease (with or without hypertension), are best directly correlated with global glomerulosclerosis. Glomerular size is best directly correlated with heart weight and coronary artery atherosclerosis rather than global glomerulosclerosis in Kasiske's studies. There is a strong inverse relationship between intrarenal arterial lumen area and global glomerulosclerosis. Relative arteriolar wall area correlates directly with age and outer cortical global glomerulosclerosis. Aortic atherosclerosis also correlates directly with global glomerulosclerosis. Kasiske indicated that it was uncertain whether the arterial luminal narrowing/vascular disease led to the global glomerulosclerosis or, alternatively, whether some other factor(s) led independently to both intrarenal vascular disease and global glomerulosclerosis [10].

There are many types of glomerulosclerosis, and the routes to glomerulosclerosis are diverse. Some of the solidified versions are ancient (very small and almost imperceptible), others larger and more recent (Figure 3.1). Some

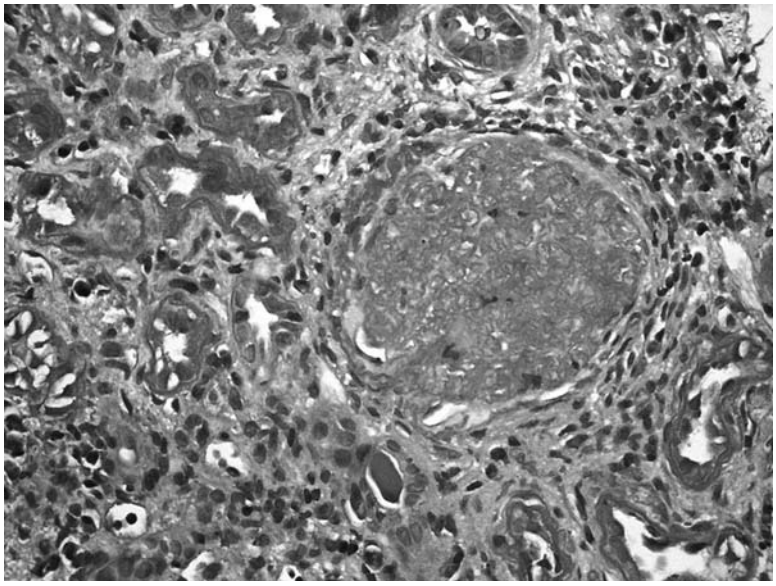

Fig. 3.1 Solidified global glomerulosclerosis. This type of global sclerosis is characterized by the solidification of the entire glomerular tuft (PAS; x 400).

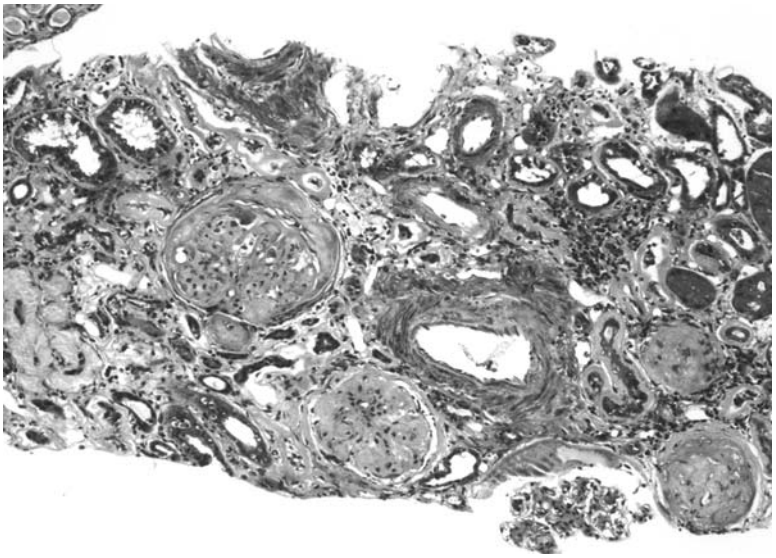

Fig. 3.2 Advanced diabetic glomerulosclerosis. Although the two glomeruli (center) reveal advanced sclerotic changes, they still retain a relatively large size. The two glomeruli at the right corner of the field are solidified and small (trichrome; x 200).

may even be enlarged if something is added to them (such as amyloid or diabetes) (Figure 3.2). The characteristic ischemic obsolescent glomerulus displays initial shrinkage of the glomerular tuft, with wrinkling and thickening of the glomerular basement membrane (GBM), and collagen deposition internal to Bowman's capsule, near the vascular hilum initially; then with progressive collagen deposition filling all of Bowman's space (Figure 3.3)

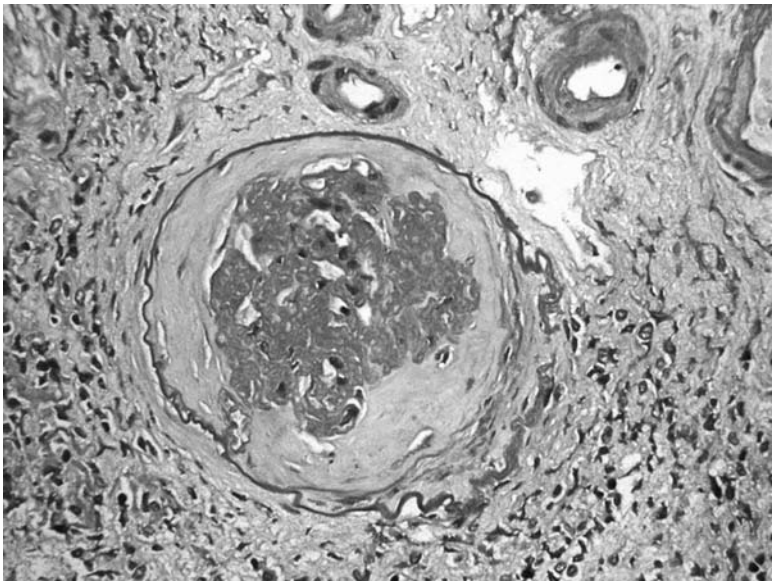

Fig. 3.3 Ischemic glomerular obsolescence. The glomerular tuft is sclerosed with collagenous material filling the Bowman's space (PAS; x 400).

[1, 3]. Glomerular inflammation, as with extensive crescent formation, can lead to glomerulosclerosis. Many have suggested this can be detected in retrospect with "gaps" or breaks in the basal lamina of Bowman's capsule (Figure 3.4) [20, 21]. As with any native renal tissue from a patient, in addition to careful study of the patient's history and laboratory findings, immunofluorescence and electron microscopy must be performed in order to exclude certain diseases (such as IgA nephropathy, ANCA-related disease, SLE, etc.).

The search for globally sclerotic glomeruli in renal tissues may be problematic. It has been shown that single-section examinations grossly underestimate global glomerulosclerosis [22]. Special light microscopic stains (such as PAS, silver methenamine, and trichrome stains) may aid in identifying small, shrunken globally sclerotic glomeruli because the globally sclerotic glomeruli may almost disappear imperceptibly in the adjacent scarred (and sometimes inflamed) interstitium in H&E-stained sections. Thus, when inspecting glomeruli with glomerulosclerosis, it is important to document the type of change (i.e., segmental vs. global; solidified vs. obsolescent), whether the altered glomeruli are high cortical or juxtamedullary, and whether special stains and multiple sections have been utilized. Other confounding or coexisting glomerular diseases need to be excluded.

The percentage of globally sclerotic glomeruli that can be considered "normal" depends on the age of the patient. The forensic study of Kaplan et al. [23] suggests that under the age of 40 years, up to 10% of the glomeruli can be globally sclerotic. As a result of normal senescence or due to specific disease itself, the percentage of globally sclerotic glomeruli that can be considered normal is difficult to establish in people after the age of 40 years. A study

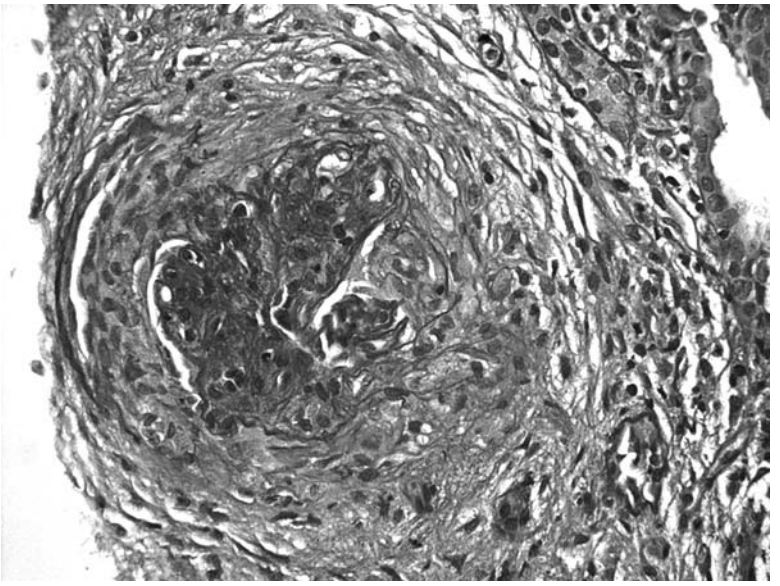

Fig. 3.4 Glomerulus with fibrous/fibrocellular crescent. Note the focal disruption of the glomerular basement membrane and the breaks in the basal lamina of Bowman's capsule (PAS; x 400).

by Smith et al. [24] suggested that the best percentage indicating disease was when the number exceeded the patient's age/divided by 2 minus 10.

The pathogenesis of global glomerulosclerosis seen in aging humans is unclear and probably multifactorial. However, the pathogenesis of focal segmental glomerulosclerosis has been fairly well studied over the past two decades and may be relevant to the glomerulosclerosis in aging kidneys. According to Brenner [25, 26], dysautoregulation of the afferent and efferent arterioles of the glomerulus may lead to increased glomerular plasma flow, increased glomerular intracapillary pressures, and subsequent glomerular injury with mesangial matrix accumulation. It is clear that vascular adaptations to structural changes (such as loss of nephrons) may help preserve the glomerular filtration rate (GFR) by producing a state of hyperperfusion and hyperfiltration in the surviving nephrons. Thus, loss or alteration of glomeruli may lead not only to systemic hypertension but also to glomerular hypertension and glomerular hypertrophy, with subsequent or consequent mesangial matrix increase (possibly secondary to transforming growth factor ß as well as increases in other molecules) and eventually focal segmental glomerulosclerosis. Several examples of "hyperperfusion" injury in human glomerular diseases have been noted, including oligomeganephronia, diabetic nephropathy, morbid obesity, and reflux nephropathy. Newbold et al. [27] have suggested that vascular/ischemic changes seen in aging kidneys first affect the cortical glomeruli, leading to global sclerosis with subsequent juxtamedullary glomerular hypertrophy, the latter leading to juxtamedullary glomerulosclerosis. As time progresses, glomeruli at all regions are involved in the disease process. In contrast, Samuel et al. [19] noted that the glomeruli in the superficial cortex were 20% larger than in the juxtamedullary zone in 12 adult males aged 51 to 69 years. They suggested that loss of glomeruli in the superficial cortex might shift perfusion to adjacent functional glomeruli within the peripheral vascular supply of the superficial cortex and promote their enlargement. It should be noted that the glomerulus has enormous capability to "correct itself" after injury. Just as Pirani and Silva [28] stated, "The glomerulus is a self-cleansing and renewable filter"; "although frequently exposed to a large variety of potentially noxious factors, the glomerulus is extremely resistant to injury."

Finally, the aging human kidney is associated with mesangial sclerosis and thickening of the GBM. However, these changes are nonspecific and may be seen with hypertension, diabetes (i.e., diffuse diabetic glomerulosclerosis), and many other renal conditions. The increase in the mesangial matrix often directly correlates with the GBM thickening, but not necessarily with proteinuria. Likewise, thickening of the GBM does not automatically coincide with proteinuria. The mechanisms leading to the GBM and mesangial alterations are unknown, but probably represent a dynamic interplay between increased synthesis of the GBM and mesangial matrix and/or decreased removal or breakdown. It should be noted that a number of investigators have not found a relationship between the relative volume of the mesangium or regular thickening of the GBM in humans with aging. For example, studies by Steffes et al. [9] found the GBM thicker in females than males with increasing width until the age of 40, then a decrease in the thickness of the GBM. A number of other glomerular changes are noted in the aged kidney, but these are also thought to be either nonspecific or related to the reason the kidney was sampled (i.e., superimposed renal disease).

The Aging Tubules and Interstitium

Because there is such an intimate relationship between renal tubules and the continuous interstitium, these two compartments will be considered together; alterations of one often lead to alteration of the other component. Several tubulointerstitial changes have been noted in the aging kidney [1, 3, 29–32]. These include (1) decreased tubular volume, length, and number, (2) increased numbers of tubular diverticula, especially of the distal convoluted tubules, (3) tubular atrophy, often with simplification of the tubular epithelium and thickening of the tubular basement membranes, and (4) increase in the interstitial volume with interstitial fibrosis, and sometimes even inflammatory cells. It is well known that renal function (e.g., serum creatinine, creatinine clearance, urine osmolality) is best correlated with changes in the tubulointerstitium rather than those in glomeruli or vessels [30, 31].

Three types of tubular atrophy have been identified, including (1) the "classic form" with wrinkling and thickening of the tubular basement membranes and simplification of the tubular epithelium (Figure 3.5), (2) the "endocrine form" (first described by Hans Seyle), which shows simplified tubular epithelium with thin basement membranes; the tubules are full of mitochondria (Figure 3.6), and (3) the "thyroidization form," which reveals somewhat uniform dilatation of tubules with regular hyaline casts (Figure 3.7) [32]. These three types can be found as a result of imperfect healing due to any type of renal injury, although the "endocrine" type is said to be most often seen with vascular ischemia, and the "thyroidization" type most often in cases of chronic pyelonephritis and other severe renal injuries. Using the microdissection technique, Baert and Steg [8] found that all kidneys of adults and elderly people have diverticula of distal tubules with increasing numbers proportional to age (Figure 3.8). They believe that diverticula in distal and collecting tubules are precursors of simple cysts seen in the aging kidney. It

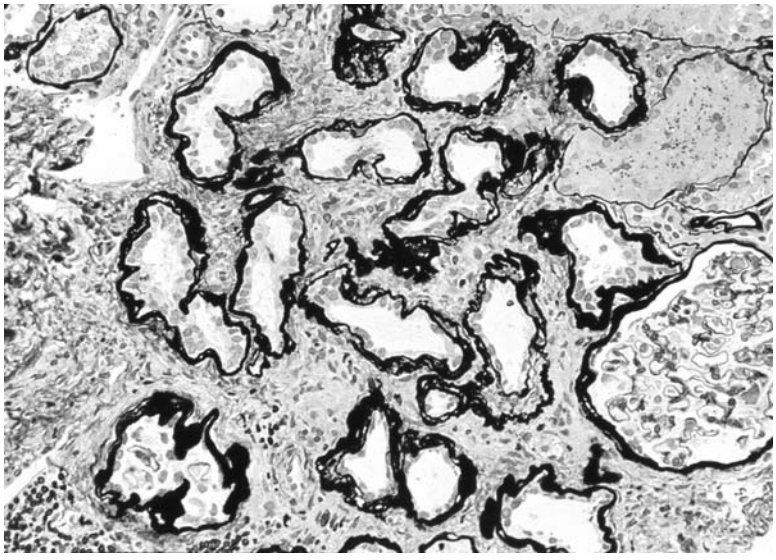

Fig. 3.5 Tubular atrophy, classic type. Note the thickening and lamellation of the tubular basement membranes (methenamine silver; x 200).

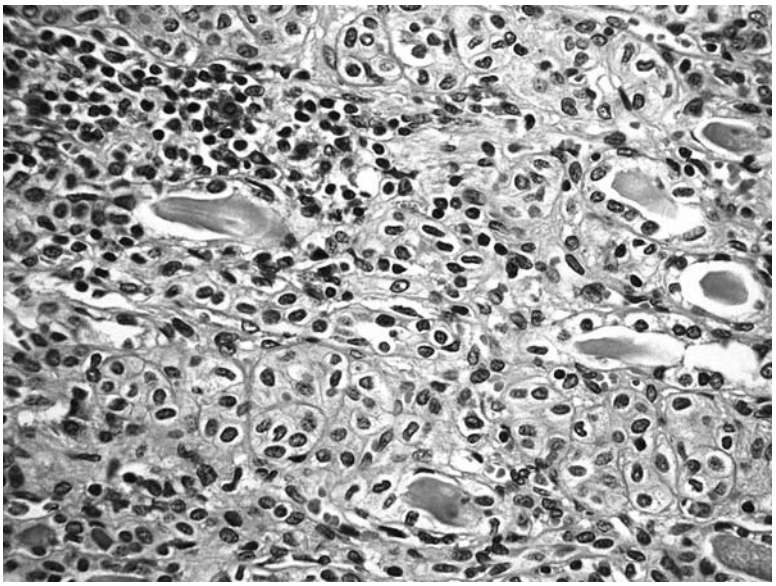

Fig. 3.6 Tubular atrophy, endocrine type. Note the small tubules with pale-staining cytoplasm resembling endocrine glands. The clear cells are full of mitochondria. This type of tubular atrophy is most often seen in vascular ischemia (H&E; x 400).

has also been suggested that by harboring organisms, these diverticula may contribute to the frequent kidney infections in elderly people.

Although the terms *tubular atrophy* and *interstitial fibrosis* may intuitively denote chronic, static, and irreversible injury and scarring, it should be noted that these regions of injury represent active disease processes. There may be

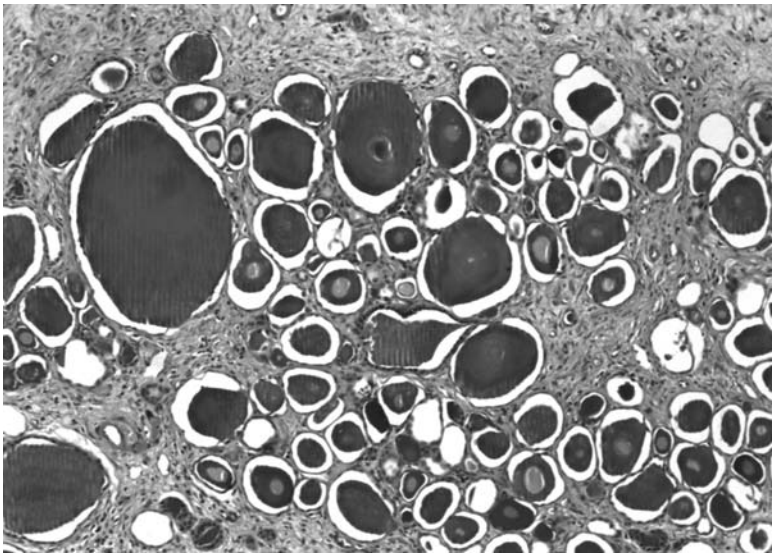

Fig. 3.7 Tubular atrophy, thyroidization. Note that the atrophic tubules are filled with homogeneous casts, resembling thyroid tissue. This change is frequently seen, although not limited to, chronic pyelonephritis (H&E; x 400).

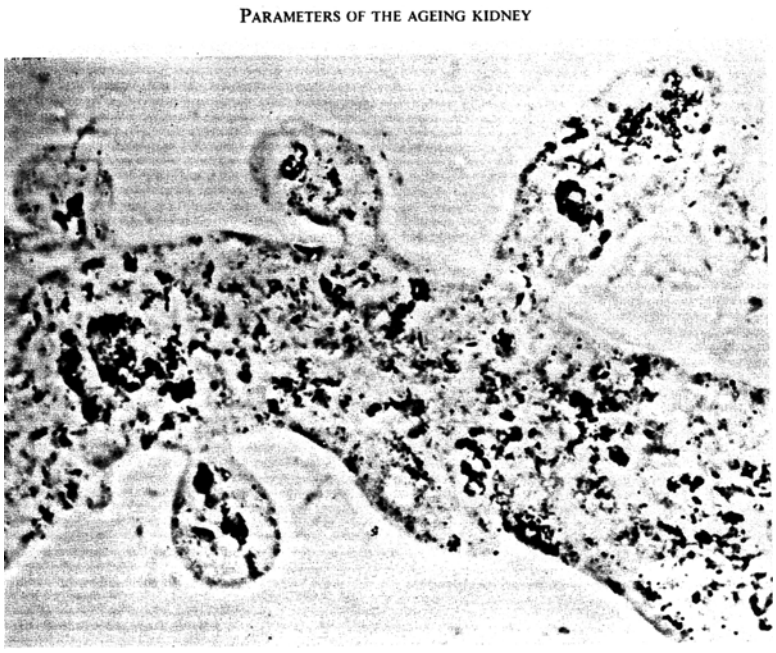

Fig. 3.8 Microdissection of distal convoluted tubules from an aging kidney. Note a few diverticula. (*Source*: McLachlan, M. Anatomic structural and vascular changes in the aging kidney. In Cameron, J.S., Macias-Núñez, J.F., eds. *Renal Function and Disease in Elderly*. New York: Butterworth-Heinemann. 1987; pp. 3–26.)

ongoing tubular injury and repair, focal tubular cell proliferation, activation of myofibroblasts from around the vascular tree, macrophage infiltration with increased production of adhesive proteins (e.g., osteopontin, adhesion molecules, collagen type IV), loss of peritubular capillary network, increased apoptosis, and altered nitric oxide expression. Thus, the tubulointerstitial regions in disease are anything but static and nondynamic [33].

The Aging Renal Vasculature

A number of changes in the renal vasculature have been documented in the aging human kidney [1, 3, 13, 34–40]. These include (1) "fibroelastic hyperplasia" of the arcuate and subarcuate arteries, (2) tortuous/spiraling interlobar arteries with thickening of the medial muscle cell basement membranes, (3) intimal fibroplasia of the interlobular arteries, (4) "hyaline" change/plasmatic insudation of the afferent arterioles, and (5) vascular "simplification" with direct channels forming between the afferent and efferent arterioles. Although none of these changes is pathognomonic or specific to aging and may be much less severe in certain aging populations, all have been found in the aged kidney.

Arterial sclerosis is noted in increasing frequency of patients aged 10–19, 20–39, 40–64, and above 65 years of age [1, 3, 13, 34]. The term *arterial sclerosis* is usually used to denote thickening of the arterial wall and narrowing of the vascular lumen (Figure 3.9), which can be caused by a variety of

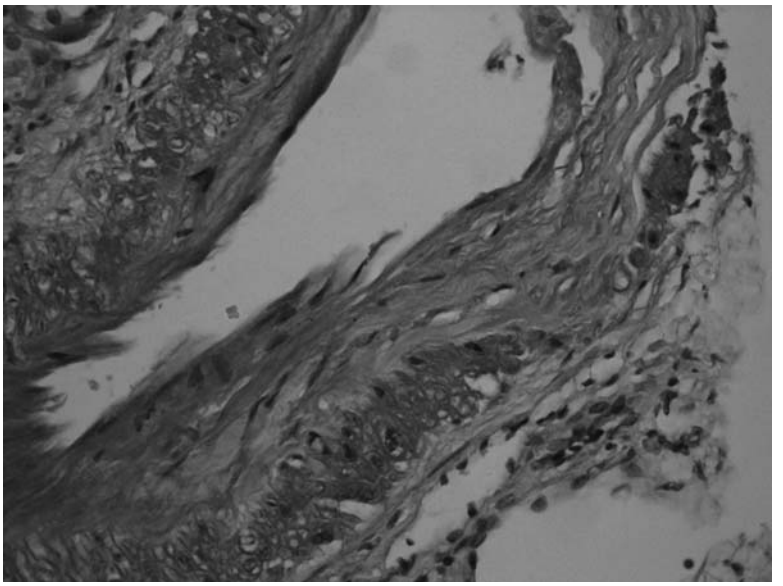

Fig. 3.9 Arteriosclerosis in a subarcuate/arcuate artery. Note the severe intimal and medial fibrosis with destruction of the medial smooth muscle cells, thickening of the medial muscle cell basement membranes, and subsequent luminal narrowing (PAS; x 400).

morphological changes such as thickening of the medial muscle cell basement membrane, fibrosis of the media, and intimal thickening [1, 3]. The term *arterial sclerosis* may be associated with a number of conditions including aging, hypertension, and diabetes.

Intimal fibroplasia refers to collagenous thickening or fibrosis of the intima of the arteries (Figure 3.10). This lesion has been found to be omnipresent in every elderly individual, even those patients who are normotensive and without cardiovascular disease. The underlying media often shrink/wither or disappear with increasing multiple layers of intimal fibroplasia. It is seen primarily in arteries of the interlobular range (80–300 μm in diameter). The *patterns* of progression are alike in all patients, but the *rates* vary from country to country and even city to city [35–40]. Intimal fibroplasia is accentuated/accelerated by hypertension and is indistinguishable from the morphological changes characteristic of hypertension. The arteries are "rigid" since they do not collapse with emersion fixation or distend with perfusion fixation. The intimal fibroplasia is heterogeneous, being focal in its distribution, possibly leading to ischemic nephron heterogeneity. The etiology of intimal fibroplasia is unclear, but it is clear that it starts fairly early in life. According to Tracy et al. [35–38], there is an irreducible minimum rate of progression possible for the human species, and no one escapes the process entirely. Tracy has suggested that the changes are found more commonly in the "conduit" vessels nearer the heart than the downstream vessels and that these "rigid" diseased conduits allow the transmission of the pulse wave abnormally into the tiny distal branches, leading to morphological changes in these distal vessels. Alternatively, intimal fibrosis may itself, later on, be accelerated by hyaline changes downstream in the afferent arterioles. Global

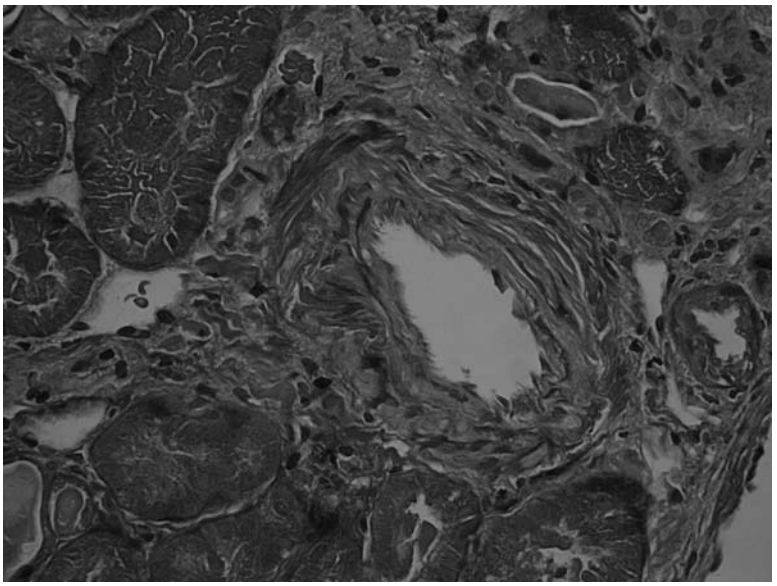

Fig. 3.10 Intimal fibroplasia of an interlobular artery. Note the fibrous thickening and migration of medial muscle cells into the media. The smooth muscle layer (media) shrinks/withers (Trichrome; x 400).

glomerulosclerosis seems to be more directly associated with intimal fibrosis than hyaline arteriolar change.

In studying the ratio of vessel wall thickness to vessel diameter, Tracy et al. [40] have suggested that for each year of aging one can add 0.15 units of intimal fibrosis of "close" arteries (i.e., arteries closer to the heart, about 300 μm in diameter) and 0.11 units of intimal fibrosis of remote or smaller arteries. For each mmHg increase in blood pressure, there are 1 year of aging in the "close" interlobular arteries and 2 years of aging in the "remote" arterial systems.

Hyaline arteriolosclerosis, referring to "plasmatic insudation" or pushing of plasma proteins into the afferent arteriolar walls (vessels 10–30 μm in diameter) due to endothelial injury and increased pressure, is another common feature of the aging kidney (Figure 3.11). These acellular "beaded" masses giving rise to the appearance of liquids encroach on the vascular lumen in immersion fixed kidneys, but interestingly flatten out into the thinned media with restoration of the lumen and decrease in tortuosity with perfusion fixation [39]. This change is less well-correlated with systemic hypertension than intimal fibrosis in most but not all studies and may be seen in patients with hypertension and/or diabetes. It is most severe and most commonly seen in patients with advancing diabetes mellitus with or without hypertension. Its etiology is unclear and can certainly be seen in patients without evidence of hypertension and in younger patients.

Aging kidney is associated with a high percentage of afferent and efferent arterioles that communicate directly with each other, particularly in the juxtamedullary zone, resulting from loss of glomerulus and shunting of blood flow from the afferent to the efferent arterioles. This appearance is also

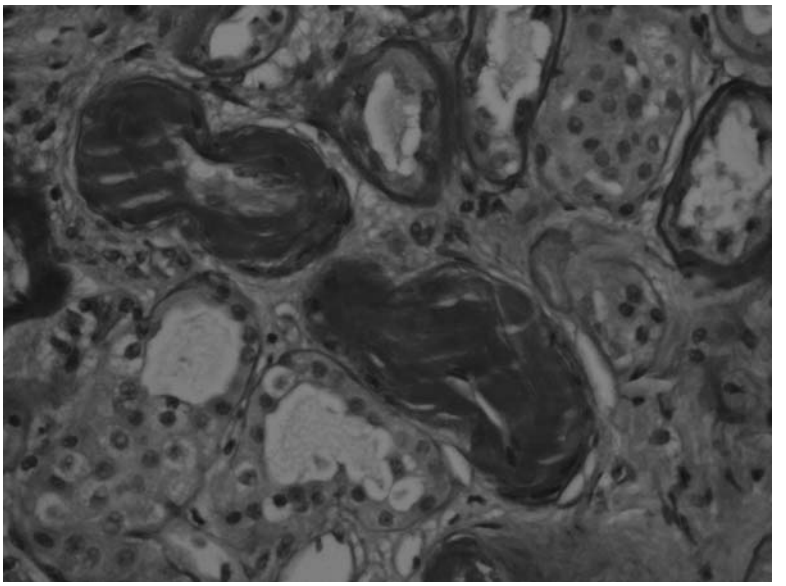

Fig. 3.11 Arteriolar hyalinization. Note the large subendothelial hyaline deposit (homogeneous material). This lesion involves plasma protein insudation and can be seen in conditions such as hypertension, diabetes, or possibly aging (PAS x 400).

referred to as "aglomerular arterioles" [13] (Figure 3.12). In a morphometric study of arterioles and glomeruli, Hill and associates [41] suggested that there is focal loss of autoregulation in the aging kidney. The dilatation of the afferent arterioles, glomerular capillary lumens (especially hilar), and enlarged glomeruli suggest a dysregulation between the afferent and efferent arterioles, somewhat reminiscent of the loss of autoregulation and vascular disease seen in experimental animals (and perhaps patients) with focal segmental glomerulosclerosis [41].

The term *nephrosclerosis,* first coined by Dr. Fahr [42], is often used to denote that the normally smooth renal cortex has been converted, through underlying vascular disease, to a lumpy-bumpy or granular surface. These macroscopic renal cortical changes are secondary to the underlying vascular disease, which leads to small regions of the outer renal cortex undergoing global glomerulosclerosis, tubular atrophy, and interstitial fibrosis, resulting in contraction and pitting of the cortical surface. Although these cortical changes can be seen with any type of chronic vascular narrowing, they are best correlated with intimal fibrosis of the interlobular arteries. The etiology of nephrosclerosis is unclear but often betrays an underlying vascular disease associated with hypertension, diabetes, or aging. Unfortunately, most patients with the diagnosis of nephrosclerosis have not had a renal biopsy, and the renovascular disease has not been evaluated. If there is a renal biopsy late in the course, it is possible to see vascular disease with other primary advanced forms of renal disease (e.g., glomerulonephritis, etc.). However, it seems that only a small fraction of the entire mildly to moderately hypertensive population is at risk for clinically significant renal disease.

Whether hypertension is the cause or effect of the morphological vascular disorder remains uncertain. Tracy et al. [35–40] suggest that interlobular

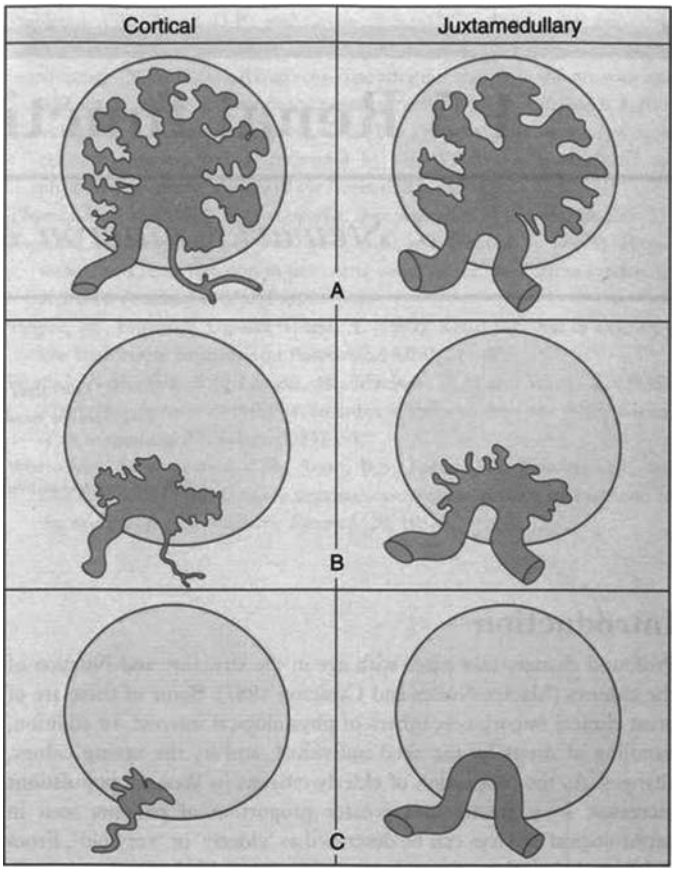

Fig. 3.12 Micro-angiography demonstrates important differences in the vascular consequences of glomerular degeneration in juxtamedullary (right) and the more peripheral nephrons (left). Changes are shown progressing from top to bottom (A-C). In healthy peripheral nephrons the afferent arteriole forms glomerular capillaries which then join to become efferent arterioles; in, juxtamedullary nephrons glomerular capillaries more closely resemble side branches of a continuous afferent-efferent arteriolar unit. When peripheral glomeruli degenerate, afferent arterioles end blindly; degeneration of juxtamedullary glomeruli results in direct communication between afferent and efferent arterioles (After Ljungqvist and Lagergren, 1962 and Takazakura *et al*., 1972)

arteries of aging kidneys develop progressive arterial sclerosis, which may precede rather than follow systemic hypertension. Mean blood pressure rises by 1.6 mmHg for each l-μm increase in intimal thickness in a 100-μm-diameter artery because of microischemia in scattered nephrons. This source of hypertension, according to Tracy, can account in full for the rise in blood pressure with age and all its variations between the populations of the world so far examined. He notes that some hypertensive patients with renal biopsy or necropsy have minimal morphological changes in their renal vessels. The rate of decrease of renal plasma flow is accelerated by hypertension. Mean arterial blood pressure is directly proportional to the rate of decline of creatinine clearance. Increase in hypertension is a strong independent risk factor in end-stage renal disease, especially in African-Americans [43]. Thus, hypertension

and morphological changes are intricately intertwined and, at this point, not easily dissectable. It certainly would appear that the vascular changes of intimal fibrosis and hyaline arteriolosclerosis seen in aging are accentuated by hypertension, and probably diabetes mellitus as well. Thus, patients with hypertension have arteries that appear older than those seen in normotensive patients.

Summary

Aging is a physiological process that causes structural and functional changes in humans. However, as Frocht and Fillit [44] have stated, "although there are physiologic and anatomic changes of the kidney that occur almost universally with aging, no specific kidney disease that is totally confined to the geriatric population has been identified." Many points should be considered in the morphological study of kidneys in the aged. The interrelationships between the four components of the kidney (i.e., glomeruli, tubules, interstitium, and vessels) are complex and dynamic. Not all "glomerulosclerosis," "tubular atrophy," "arterial sclerosis," or "nephrosclerosis" is the same. The morphological changes need to be well defined and well documented with acceptable and clear terminology. It also should be pointed out that investigations containing both excellent pathologic data and clinical information/clinical follow-up in the same study population are rare, and further studies to better combine the two are clearly needed. Despite all the difficulties and shortcomings, significant insights have been gained regarding age-related renal morphological changes. These include a decrease in the size and weight of the kidney with a greater loss of tissue in the cortex than in the medulla, decreased total glomerular number, and increased glomerular volume. The aging kidney is also associated with decreased tubular number, length, and volume as well as increased tubular diverticula. In addition, intimal fibroplasia is universally present in every elderly individual, and even in those who are normotensive and without cardiovascular disease.

Mark Twain once said, "The older we grow the greater becomes our wonder at how much ignorance one can contain without bursting one's clothes." Indeed, although much work has been done, we are still young as to our understanding of the aging kidney. Hopefully, our knowledge about the aging kidney will continue to increase with age. A greater understanding of the anatomical, physiological, and pathological changes of the aging kidney will enable us to design methods to retard or prevent the decremental changes in kidney function that can occur with aging.

References

1. Silva, F.G. The aging kidney: A review—Part I. *Int. Urol. Nephrol*. 2005; 37: 185–205.
2. Silva, F.G. The aging kidney: A review—Part II. *Int. Urol. Nephrol*. 2005; 37: 419–432.
3. McLachlan, M. Anatomic structural and vascular changes in the aging kidney. In Cameron, J.S., Macias Núñez, J.F., eds. *Renal Function and Disease in Elderly*. Butterworth-Heinemann, New York 1987; pp. 3–26.
4. Tauchi, H., Tsuboi, K., Okutomi, J. Age changes in the human kidney of different races. *Gerontologia* 1971; 17:87–97.

5. Bax, L., van der Fraaf, Y., Rabelink, A.J., Algra, A., Beutler, J.J., Mali, W.P.; SMART Study Group. Influence of atherosclerosis on age-related changes in renal size and function. *Eur. J. Clin. Invest* 2003; 22:34–40.
6. Kasiske, B.L., Umen, A.J. The influence of age, sex, race and body habits on kidney weight in humans. *Arch. Path.* 1986; 110:44–60.
7. Tada, S., Yamagishi, J., Kobayashi, H., Hata, Y., Kobari, T. The incidence of simple renal cysts by computed tomography. *Clin. Radiol.* 1983; 34:437–439.
8. Baert, L., Steg, A. Is the diverticulum of the distal and collecting tubules a preliminary stage of the simple cyst in the adult? *J. Urol.* 1977; 118:707–710.
9. Steffes, M.W., Barbosa, J., Basgen, J.M., Sutherland, D.E.R., Najarian, S.J., Mauer, S.M. Quantitative glomerular morphology of the normal human kidney. *Lab. Invest.* 1983; 49:82–86.
10. Kasiske, B.L. Relationship between vascular disease and age-associated changes in the human kidney. *Kidney Int.* 1987; 1154–1159.
11. Neugarten, J., Gallo, G., Sibiger, S., Kasiske, B. Glomerulosclerosis in aging humans is not influenced by gender. *Am. J. Kid. Dis*. 1999; 34:884–888.
12. Li, M., Nicholls, K.M., Becker, G.J. Glomerular size and global glomerulosclerosis in normal Caucasian donor kidneys: Effects of aging and gender. *J. Nephrol.* 2002; 15:614–619.
13. Takazakura, E., Sawabu, N., Handa, A., Takada, A., Shinoda, A., Takeuchi, J. Intrarenal vascular changes with age and disease. *Kidney Int*. 1972; 2:224–230.
14. Newbold, K.M., Sandison, A., Howie, A.J. Comparison of size of juxtamedullary and outer cortical glomeruli in normal adult kidney. *Virchows Arch. A Path. Anat. Histopathol.* 1992; 420:127–129.
15. Nyengaard, J.R., Bendtsen, T.F. Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat. Rec*. 1992; 232:194–201.
16. Hughson, M., Farris, A.B. III, Douglas-Denton, R., Hoy, W.E., Bertram, J.F. Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney Int.* 2003; 63:2113–2122.
17. Hughson, M.D., Douglas-Denton, R., Bertram, J.F., Hoy, W.E. Hypertension, glomerular number, and birth weigh in African Americans and Whites subjects in the Southeastern United States. *Kidney Int.* 2006; 69:671–678.
18. Keller, G., Zimmer, G., Mall, G., Ritz, E., Amann, K. Nephron number in patients with primary hypertension. *N. Engl. J. Med.* 2003; 348:101–108.
19. Samuel, T., Hoy, W.E., Douglas-Denton, R., Hughson, M.D., Bertram, J.F. Determinants of glomerular volume in different cortical zones of the human kidney. *J. Am. Soc. Nephrol.* 2005; 16:3102–3109.
20. Meadows, R. *Renal Histopathology,* 2nd ed. Oxford: Oxford University Press. 1978; Chapter 9: The Obsolescent Glomerulus and the Disappearance of Glomeruli from Kidneys, pp. 154–163.
21. Verani, R., Silva, F., Hogg, R., and the Southwest Pediatric Nephrology Study Group. A clinico-pathologic study of crescentic glomerulonephritis in 50 children. *Kidney Int.* 1985; 27:450–458.
22. Remuzzi, A., Mazerska, M., Gephardt, G.N., Novick, A.C., Brenner, B.M., Remuzzi, G. Three-dimensional analysis of glomerular morphology in patients with subtotal nephrectomy. *Kidney Int.* 1995; 48:155–162.
23. Kaplan, C., Pasternack, B., Shah, H., Gallo, G. Age-related incidence of sclerotic glomeruli in human kidneys. *Am. J. Path.* 1995; 80:227–234.
24. Smith, S.M., Hoy, W.E., Cobb, L. Low incidence of glomerulosclerosis in normal kidneys. *Arch. Path. Lab. Med.* 1989; 118:1253–1255.
25. Taal, M.W., Luycks, V.A., Brenner, B.M. Adaptation to nephron loss. In *Brenner and Rector's*, *The Kidney,* 7th ed., Brenner, B.M., ed. Philadelphia, Saunders. 2004; pp. 1955–1997.
26. Brenner, B.M. Nephrology forum: Hemodynamically mediated glomerular injury and the progressive nature of renal disease. *Kidney Int.* 1983; 23:647–655.

27. Newbold, K.M., Sandison, A., Howie, A.J. Comparison of size of juxtamedullary and outer cortical glomeruli in normal adult kidney. *Virchows Arch. A Path. Anat. Histopath.* 1992; 420:127–129.
28. Piranci, C.L., Silva, F.G. The glomerulus: Current concepts. In *Hemostasis, Prostaglandins and Renal Disease*, Remuzzi, G., Mecca, G., and de Gaetano, G., eds., New York: Raven Press. 1980; pp. 25–44.
29. Lindeman, R.D., Goldman, R. Anatomic and physiologic age changes in the kidney. *Exp. Geront.* 1986; 21:379–406.
30. Nath, K.A. Tubulointerstitial changes as a major determinant in the progression of renal damage. *Am. J. Kidney Dis.* 1992; 20:1.
31. Eknoyan, G., McDonald, M.A., Appel, D., Truong, J.D. Chronic tubulo-interstitial nephritis: Correlation between structural and functional findings. *Kidney Int.* 1990; 38:736–743.
32. Nadasdy, T., Laszik, Z., Blick, K., Johnson, D.L., Silva, F.G. Tubular atrophy in the end-stage kidney: A lectin and immunohistochemical study. *Human Path.* 1994; 25:22–28.
33. Meguid, E.L., Nahas, E. Plasticity of kidney cells: Role in kidney remodeling and scarring. *Kidney Int.* 2003; 64:1553–1563.
34. Greenfeld, Z., Baylis, C. Aging and the renal circulation. In *Advances in Organ Biology* Stamford, CT: JAI Press. 2000; 9:255–274.
35. Tracy, R.E., Malcom, G.T., Oalmann, M.C., Qureshi, U., Ishii, T., Velez-Duran, M. Renal microvascular features of hypertension in Japan, Guatemala and the Unites States. *Arch. Path. Lab. Med.* 1992; 116:50–55.
36. Tracy, R.E., Parra, D., Eisaguirre, W., Balanza, R.A.T. Influence of arteriolar hyalinization on arterial intimal fibroplasias in the renal cortex of subjects in the United States, Peru and Bolivia, applicable also to other populations. *Am. J. Hypertension* 2002; 15:1064–1073.
37. Tracy, R.E., Ishii, T. What is "nephrosclerosis?" Lessons from the US, Japan and Mexico. *Nephrol. Dial. Transplant.* 2002; 15:1337–1366.
38. Tracy, R.E., Newmann, W.P. III, Wattigney, W.A., Srinivasan, S.R., Strong, J.P., Berenson, G.S. Histologic features of atherosclerosis and hypertension from autopsies of young individuals in a defined geographic population: The Bogalusa heart study. *Atherosclerosis* 1995; 116:163–179.
39. Tracy, R.E., Overall, E.O. Arterioles of perfusion-fixed hypertensive and aged kidneys. *Arch. Path.* 1966; 82:526–534.
40. Tracy, R.E. Histologic characteristics of coronary artery in relation to the renovasculopathies of hypertension. *Ann. Diagnostic Path.* 1998; 2:159–166.
41. Hill, G.S., Hedes, D., Bariety, J. Morphometric study of arterioles and glomeruli in the aging kidney suggests focal loss of autoregulation. *Kidney Int.* 2003; 63: 1027–1036.
42. Volhard, F., Fahr, T. *Die Brightische Nierenkrankheit*. Berlin: Springer-Verlag, 1914.
43. Fogo, A., Breyer, J.A., Smith, M.C., Cleveland, W.H., Agodoa, L., Kirk, K.A., Glassock, R. Accuracy of the diagnosis of hypertensive nephrosclerosis in African Americans: A report from the African American study of Kidney Disease (AASK) Trial. AASK Pilot Study Investigators. *Kidney Int.* 1997; 51:244–252.
44. Frocht, A., Fillit, H. Renal disease in the geriatric patient. *J. Am. Geriatr. Soc.* 1984; 32:28–43.

4

Biology of the Aging Process and Its Clinical Consequences

Juan-Florencio Macías-Núñez, José-Manuel Ribera Casado, Mónica de la Fuente del Rey, Gustavo Barja Quiroga, Jesus A. F. Tresguerres, Carmen Ariznavarreta and José M. López-Novoa

Introduction

Aging is a cumulative, universal, progressive, intrinsic, and deleterious process; it can be referred to using the acronyms CUPID and/or CEPID [1]:

- Cumulative: It is a series of changes that occur throughout life.
- Universal: Nothing is exempt from the aging process.
- Progressive: The changes occur gradually over time.
- Intrinsic: It happens within the body with or without environmental influences.
- Deleterious: It leads to a decrease in functional capacity.

Aging should be differentiated from "age-associated diseases," e.g., those diseases whose prevalence increases dramatically with age. The major difference is that these diseases do not affect all the subjects without exception. For instance, increased arterial stiffness is characteristic of aging, but atherosclerosis is not. Aging is modulated by racial, hereditary, environmental, and dietary factors as well as the provision and availability of healthcare facilities. No single mechanism may explain it; it is multifactorial, multiform, and asynchronous. Therefore, it is interesting to note that not all organs age uniformly. Some functions are conserved from youth into old age, while others decline in function much sooner. The fundamental characteristic of the physiological aging process is the attenuation of functional capacity. However, the rate of functional capacity varies within individuals and with the type of function assessed.

The most characteristic sign of aging is not the decrease in body functions, but the impaired response of body functions when the individual is challenged. In other words, aging is characterized by a decreased ability to adapt physiological functions to environmental changes or challenges.

Let us illustrate this with an example: Suppose there are two well-trained athletes of 20 and 76 years of age, and we are asked to guess their chances of successfully completing a marathon. Undoubtedly, both of them will succeed because both have sufficient resources. Therefore, healthy aging is

not invariably linked to loss of capacity. However, the time each of the runners takes will differ, with the younger runner completing the race in a shorter time. This occurs because of the physiological decline in function and not due to a pathological condition. This reduced functional ability leads to older people taking longer or sometimes being unable to adapt to biological, physical, psychological, environmental, or social situations of overload or restriction.

Equally, defining aging is problematic, and each expert in the field will have his or her own version. We believe that aging is the consequence of two associated, but not identical, processes: the decline in function and the reduction in adaptive capacity.

Hypothesis for Mechanisms of Aging

Since the beginning of time, each culture has longed to discover the secret of eternal life, experimenting with exercise, diet, and religion or even seeking the mythical Philosophers´ Stone. So far, the common theme, at least from experimental models, is that a reduction in calorie intake seems to prolong life.

Three groups of theories have been proposed to explain the aging phenomenon: environmental, genetic, and mixed theory, extensively reviewed in Refs. 1–5. The first says that genes play no role in aging, aging being the result of environmental insults; the second proposes that genes are solely responsible for aging, whereas the third theory proposes that both genes and environmental damage contribute to aging. The environmental, or exogenous, theory proposes that multiple factors from the environment, diet, or derivatives of metabolism exert a series of injuries on macromolecules, cells, and tissues but do not directly affect DNA.

The genetic theory proposes that aging is due to a predetermined genotype that specifies the appearance of phenotypical changes associated with age. This theory is deterministic, which means that among the different programs (genotypes) responsible for many of our personal characteristics such as the color of our eyes or our height, we inherit genetic variations that will determine and drive the rate of aging**.** In other words, the velocity of aging is genetically preprogrammed at birth.

Some scientists agree that aging is coded within the DNA of each cell, whereas others believe that aging is encoded in genes that regulate the function of the systems that regulate and control the entire organism, i.e., the endocrine, nervous, and immune systems. However, it appears that the age-associated changes observed in the nervous and endocrine systems are more a consequence than a cause of aging, although this is still under debate for the immune system.

The genetic and environmental theories of aging are not mutually exclusive: The mixed theory suggests that repetitive, exogenous injury to DNA over time can modify the expression of genes involved in the aging process. Therefore, each organism has a certain genetic predisposition to aging, which can be modulated by the action of exogenous agents or products of its own metabolism. It is evident that genes are implicated in longevity, as human studies have shown that the lifespan of monozygotic twins is significantly more similar than that of dizygotic twins. Nevertheless, there must also be

some exogenous influence, as genetic factors only account for 25% of the variance in human life span [2]. In contrast to the deterministic, pure genetic theory, the mixed theory is stochastic, as it does not allow us to accurately predict the speed of aging, because it is influenced by many random environmental variables acting on the genetic code. This damage cannot be properly corrected by the organism's repair processes**,** leading to modifications that accompany the physiological aging process or facilitates the **instauration** of illness (the giants, i.e., incontinence, immobility, instability and falls, mental incompetence), weakness, dependence, and death (Figure 4.1).

Why, then, did genes affecting the aging process arise in the first place? What is the evolutionary basis for aging? In the wild, animals die young and the aging phenotype is rarely observed in such conditions. Therefore, it is unlikely that aging has evolved out of evolutionary necessity as a form of population control, as is often supposed. On the contrary, species are genetically programmed for reproduction, but not for indefinite survival. Kirkwood [3] explains this in his *disposable soma theory.* The durability and maintenance of the germ line, or reproductive tissue, must be sufficient to ensure its viability through several generations. In contrast, the somatic, or nonreproductive, tissues need only be maintained for the duration of the normal life expectancy in the wild, plus a degree of reserve. This allows, therefore, the

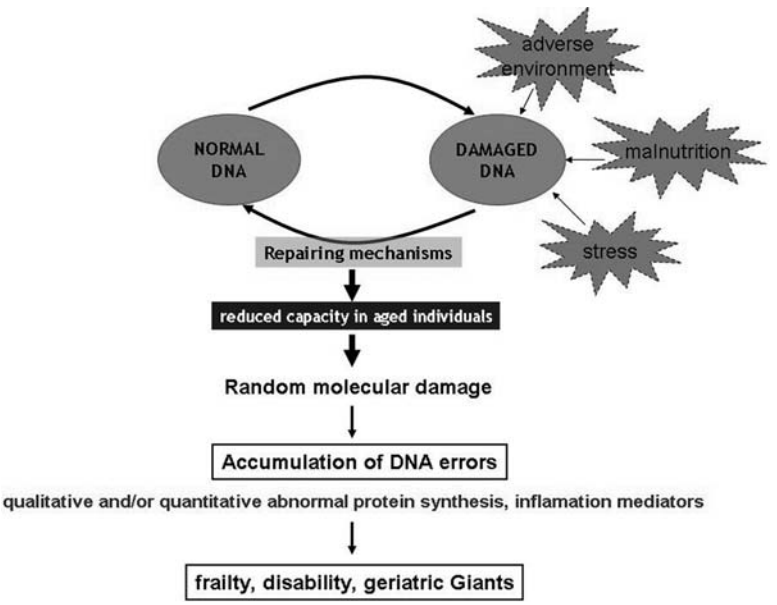

Fig. 4.1 Schematic representation of mechanisms leading to modifications accompanying the physiological aging process and instauration of illnesses. DNA is continuously damaged and repaired, and both processes are in equilibrium until adulthood. Age increases the damaging mechanisms and attenuates the repairing capacity. The relentless accumulation of cellular damage progressively interferes with functional capacity, functional reserve, and the ability do adapt to adverse circumstances as is the rule in the physiological aging process. As time passes, the accumulation of damaged DNA facilitates the instauration of illness clinically expressed as the geriatric giants (incontinence, immobility, instability, and mental incompetence) that eventually will lead to frailty, dependence, and death if they are not detected and prevented on time.

accumulation of damage or mutations over time, which begin to take effect after the expected lifetime of the organism has passed. These could include late-acting mutations [4] or pleiotropic genes (having more than one effect), which have beneficial effects earlier on and then have a deleterious effect later in life, or the *theory of antagonistic pleiotropy* [5]. In support of this theory, an aging process has been observed in the somatic cells of all species with a clearly separated distribution of somatic and germ line cells, whereas this is not true of organisms without this distinction, such as the freshwater Hydra.

Taking into account the ideas and observations above, we have a strong foundation to explain why aging occurs and how the process has evolved. Although aging is not preprogrammed by specific genes, the following genetic factors are implicated:

1. Genes involved in the repair and maintenance of somatic DNA
2. Pleiotropic genes with deleterious effects later in life
3. Mutations affecting the phenotype after reproductive age

Before we consider the details of genetic and environmental influences, the hypothesis of cellular aging and its importance in the aging process will be briefly discussed.

Cellular Aging

Hayflick and Moorhead [6] observed that normal human fibroblasts have a limited capacity for replication *in vitro*. The authors interpreted this as a cellular aging phenomenon, and this model has since become one of the most widely used in experimental gerontology. It assumes that the rate of aging of any organism can be considered as the sum of the rates of aging of its individual cells. This reductionist affirmation has some experimental support but many theoretical inconsistencies; therefore, it has received much criticism from several authors in the field.

The generalization of conclusions drawn from the study of cellular aging *in vitro* and their application to aging of the whole animal has been widely discussed and probably has many weaknesses in its theoretical basis. First, even if we accept that a cell ages in culture, it could well be that this *in vitro* observation bears no resemblance to the true process occurring *in vivo*. For example, the decreased proliferative capacity of cells *in vitro* can be regarded more as a consequence of differentiation than of the aging process. Second, little evidence exists that this fundamental phenomenon observed during *in vitro* aging actually occurs *in vivo*. Moreover, no relationship has been found between loss of proliferative capacity of different types of cells *in vivo* and the aging of the organism. Finally, higher mammals should not be thought of as a group of cells, but rather as a group of complex interactions between the different cell types that form the organs, and also as interactions between each organ. The aging processes must be viewed as an alteration between these relations more than as an intrinsic cellular phenomenon. These conclusions can be derived from studies in which cells from organs of aged animals show evident functional defects as an effect of the aging process; however, when they are cultured, their function *in vitro* is no different to that of normal, young cells. In fact, some authors believe that studies of aging *in vitro* or

cellular aging are not valid for studying the aging process. However, one exception could be the effect of age on the immune system. We should always bear in mind the possible defects in the validity of the model and exercise caution when extrapolating findings from the cellular studies *in vitro* to the whole organism.

Exogenous or Environmental Theory

Nutritional Factors

The most basic exogenous influence on living organisms is their relationship with the fundamental processes of life: obtaining nutrients and oxygen from the external environment, and performing the oxidation reactions necessary to maintain cellular function and homeostasis [1]. The most important evidence in this field is that reduction in caloric intake has the capacity to increase life expectancy and diminish the symptoms of aging, as much in the fruit fly *D. melanogaster* and in the nematode *C. elegans* as in rodents such as rats and mice, and even primates. The restriction of calories not only increases survival and maintenance of a youthful appearance, but it also helps to maintain basic aspects of structure and function. These include increased tissue sensitivity to hormones and *decrease* of collagen cross-linking. These benefits appear to be mediated by a reduced accumulation of lipids, proteins, and nucleic acids that have been damaged by oxidative stress, although their precise role in the aging process is not clear. Other evidence to support this theory is provided by the inverse relationship observed between metabolic rate and the average lifespan of diverse species of mammals. Nevertheless, to date, the exact mechanisms responsible for this observation are not known [7].

End Products of Advanced Glycosylation

The utilization of oxygen is not the only fuel-consuming process that may cause injury to macromolecules, cells, and tissues. Some fuels are also reactive molecules and can themselves produce damage; the most studied of these is glucose. Glucose, like other reduced sugars, does not need enzymatic catalysis in order to react with amino groups attached to proteins. After several successive reactions, it results in the "advanced glycosylation end products" (AGEs). The exact chemical structure of these products varies, and it is not well known. However, what is known is that by modifying the protein's chemical structure, its functional activity may also be modified, including enzymatic function, ligand binding, and membrane position, which alter mechanical properties (e.g., elasticity and torsion resistance).

It must be noted that in addition to the appearance of proteins containing AGEs, there are also mechanisms that protect against the injuries they inflict. Therefore, the accumulation of AGEs is a direct consequence of the balance between its formation and degradation. Consequently, the injuries associated with age could be due to an increase in the formation of proteins with AGEs or a decrease in their elimination rate.

In addition to their interaction with proteins, reduced sugars can also form bridges with DNA, thereby producing cross-links with proteins. Therefore, glycosylation can also be implicated in the genomic changes contributing to aging.

Accumulation of Metabolic Waste Products

It has been proposed that accumulation of damaged macromolecules produced by the chemical reactions previously discussed could be a factor contributing to cellular aging. For example, it has been observed that when several different types of cells have been cultured, lipofuscin accumulates in secondary lysosomes in proportion to the number of cell divisions. The lipofuscin is a product of non-enzymatic glycosylation of proteins and DNA. Glycoside radicals oxidize and form massive cross-links among proteins, lipids, and nucleic acids. It is essential to define whether accumulation of lipofuscin has any role in cellular aging or is simply a consequence of it, as it has been demonstrated that several lysosomic proteolysis pathways display diminished activity with age.

The degradation of proteins in different organs and cell types decreases with age. *In vitro* cells have shown that protein catabolism is slower in older human fibroblasts. This can explain certain characteristics of aging cells, such as the increasing amount of proteins and the accumulation of abnormal proteins.

Genetic Theory

Programmed Aging

The proponents of the idea that duration of life and the rate of decrease in biological activity are actively programmed in the genome base their theory on examples of aging and cellular programmed death. For example, the rapid aging and death of salmon after spawning, the fast degeneration of muscle cells during the metamorphosis of insects, and the death of specific cells during the development of nematodes are all genetically programmed phenomena. Equally, it has been observed that **introducing into** immortal cell lines the human chromosomes 1, 4, 6,7 11, 18, and X confers a finite limit to the number of possible cell divisions [8]. Nevertheless, the real importance of these phenomena in the relationship of the aging of the organism and the cellular aging, which is not as clear. For example, it has already been demonstrated that aged fibroblasts lose their capacity to divide, but remain metabolically active for months.

Regulation of the Genetic Control of Metabolism

One of the few mutations in a single gene associated with longer life in mammals is the *df* mutation [9]. Heterozygotic mice with this mutation have one serious deficiency in the development of the hypophysis that determines an almost total absence of the growth hormone prolactin and the thyroid-stimulating hormone. These deficient animals have 68% and 50% longer lives (females and males, respectively) than their siblings with the nonmutated gene. This questions the role of growth hormones and metabolism in life duration, and how their genetic regulation could be related to aging. A further example, at the cellular level, is the CLK-1 gene, which contributes to the synthesis of co-enzyme Q (ubiquinone) in the mitochondrial respiratory chain. Overexpression of CLK-1 increases the rate of oxidative phosphorylation and reduces life expectancy.

Codon Restriction

It has been proposed that a way to regulate the production of different proteins in different stages of the development is by using several codons to code for

the same amino acid in different genes. Therefore, as the number of possible base triplets is finite, their changing use with age would result in a diminished translation of certain essential genes.

Sequential Inactivation of Reiterative Genes

This theory suggests that cellular aging, or its capacity to proliferate, is due to the existence of genes with several copies in different locations on the genome. If, due to any cause, a copy of a gene is injured or selectively inactivated, other copies can be activated until the inactivation or the injury of the last copy occurs, which produces cellular aging due to the absence of an important protein. However, many important proteins are codified by a single gene without there being other copies in the genome. Therefore, generalization of this theory appears improbable.

Telomere Shortening

Telomeres are complexes of proteins and nucleic acids that are found at the end of chromosomes, protecting them against degradation and thereby allowing replication of the genome without the loss of terminal coding sequences. They are synthesized by the enzyme telomerase, which is absent in somatic tissues, and consequently the telomeres shorten by 80–300 base pairs with each cell division. Therefore, after a finite number of cell divisions, the telomeres can no longer fulfill their protective role, leading to incomplete replication of the chromosome. For this reason, telomeres have been dubbed the "biological clock" counting the number of cell divisions. It has been demonstrated that the size of telomeres in human fibroblasts *in vitro* decreases from 4 Kb to 2 Kb during aging; this reduction has also been observed in cells of patients with Progeria. These authors speculate that if one or more telomeres were completely lost, it could result in a complete blockade of cell proliferation [10]

Terminal Differentiation

This theory explains programmed cellular aging by the activation of a certain number of genes induced by successive cellular divisions. These genes could codify some proteins that inhibit the entrance to phase S of the cellular cycle. It has been observed that aged fibroblasts preferably express some proteins such as fibronectin. In fibroblasts of patients with Werner´s syndrome, it has been identified that the overexpression of certain proteins, that could be associated to proliferation, diminishes. In aged endothelial cells, it has been demonstrated that the overexpression of interleukin-1 also inhibits cellular proliferation. It has also been demonstrated that as aging progresses, there is a reduced expression of certain genes with proteins capable of stimulating cellular proliferation.

Mixed Theory

Oxidant–Antioxidant Balance

Aerobic cells constantly produce free radicals through the univalent reduction of oxygen. These "reactive oxygen species" (ROS) damage macromolecules within cells, although this damage is minimized by the action of antioxidants. However, many studies have demonstrated that antioxidants do not modify the rate of aging [11]. Therefore, what is the relationship between oxidative stress and aging? Available studies suggest two possibilities. The first is the

rate of mitochondrial ROS production. Studies to date have found that ROS production in mitochondria, isolated from postmitotic tissues, is less in species with longer life spans [11]. This is true of all long-lived, warm-blooded animals. This key observation could also explain the inverse relationship between levels of antioxidants and longevity: The animals with longest life spans have lower levels of antioxidants simply because their rate of ROS production is lower.

Furthermore, it has been found that the oxidative damage to mitochondrial DNA, measured as 8-hydroxy-2´-deoxyguanosine (8-oxodG), also correlates negatively with longevity in mammals, while this is not observed in nuclear DNA [12]. Studies conducted in cardiac and cerebral tissue, in 11 species, have also demonstrated that the levels of oxidative stress are several times greater in mitochondrial than nuclear DNA [12].

The greater production of ROS in the mitochondria of shorter-lived species could be responsible for the accelerated accumulation of somatic mutations in the mitochondrial DNA. In humans this accumulation of somatic mutations takes 70–100 years compared with only 2–3 years in mice. Given that 8-oxodG in DNA is mutagenic, the higher level of 8-oxodG in short-lived, as opposed to long-lived, animals would contribute to their higher rate of accumulation of mutations in mitochondrial DNA. The higher levels of 8-oxodG in mitochondrial DNA compared to nuclear DNA could also explain the greater intensity of somatic mutation in the former. The final result is a progressive compromise of cellular function as the individual ages.

Studies comparing the production of free radicals by mitochondria and oxidative stress to mitochondrial DNA support the theory of aging due to free radicals. However, these correlations, although supporting the predictions of the theory, do not necessarily imply the existence of a causal relationship between these parameters. For this purpose, it would be interesting to investigate whether these parameters, when modified appropriately, would be capable of altering the rate of aging. Such a task is not simple. Fortunately, there is an experimental manipulation that can increase maximum longevity by counteract the rate of aging; this is achieved by restricting the number of calories that animal ingests. This increased longevity due to restriction of calories has been demonstrated countless times [13–17] in laboratory rodents, and also in other species including nematodes, rotifers, insects, arachnids, and fish. Current studies have noted that this phenomenon also occurs in simians; therefore, it is reasonable to assume that it may be possible to extrapolate to humans.

To determine whether the effect of caloric restriction on longevity is mediated by changes in the mitochondrial production of ROS, subsequent damage to mitochondrial DNA has been addressed in experimental models of cells from young and old rats [13]. The effect of caloric restriction in short- and long-term studies of ROS production, in the cardiac tissue of young and old rats, clarifies whether such changes take place, where they occur in the respiration cycle, and what is the causal mechanism, as we will immediately discuss [13]. Short-term caloric restriction (6 weeks) did not change any of the parameters studied. However, long-term caloric restriction (1 year) in rats decreased mitochondrial ROS production by almost half and also decreased the oxidative damage to mitochondrial DNA, without affecting the oxidative damage to nuclear DNA [13]. Decreases in mitochondrial ROS production

were also observed in the liver after both short- and long-term caloric restriction, in skeletal muscle after long-term restriction, but not in the kidney after short-term restriction. Recent studies by other authors have confirmed the generalized reduction in mitochondrial ROS production following caloric restriction in other mammalian tissues [14]. On the other hand, it has been observed that restriction of protein, without intense caloric restriction, also decreases mitochondrial ROS production in the short term [15]. In contrast, caloric restriction does not consistently change the activity [16] or the genetic expression [17] of the antioxidant enzymes SOD, catalase, or glutathione peroxidase. The decrease in ROS-induced damage and 8-oxodG levels in mitochondrial DNA during caloric restriction indicates that the equilibrium of oxidative damage (attack and repair) in this DNA must be less in calorie-restricted animals compared to those fed *ad libitum*, as it is in the case of long-lived compared to short-lived animals [18]. In fact, it has been shown that caloric restriction reduces the expression of several genes coding for DNA repair mechanisms [19].

If the mitochondrial production of radicals is involved in the control of the rate of aging, it is very important to clarify the site of production within the mitochondrial respiratory chain. It is known that, in the case of mitochondria in cardiac tissue, ROS production occurs as much in complex I as in complex III. However, of these two complexes, only complex I is implicated in the reduced production of radicals that occurs during calorie restriction, since this only occurs when piruvate/malate are used as substrates, but not when the electrons are introduced into the respiratory chain using succinate in the presence of rotenone [13]. Also, another important aspect that has been explained is the mechanism of decreased radical production during calorie restriction. It is not a simple reduction in the consumption of oxygen, as this is unaltered in the mitochondria of calorie-restricted animals, but there is a decrease in the rate of production of ROS for a fixed ATP production. This is related to the degree of electronic reduction in the generator of ROS in complex I, as the difference between calorie-restricted animals and controls is only observed when the degree of reduction is partial, but not total [13]. Similar results have been found in hepatic mitochondria, with the difference that the changes are produced earlier in this organ; they are already detectable after six weeks of calorie restriction [20]. Studies in rat hearts indicate that the level of oxidative modification of mitochondrial proteins is also less in calorie-restricted animals [21]. In summary, the available information suggests that a low mitochondrial production of ROS is a key characteristic in increased longevity, so much as between different species as during calorie restriction in the same species of animal.

One of the mechanisms of injury is the use of oxygen in the energy production processes. The oxidation process may produce an oxygen derivative with great reactive capacity, the superoxide radical. A family of enzymes present in the cells, the superoxide dismutases, can eliminate this radical through their capacity to catalyze the transformation of the superoxide ion into hydrogen peroxide. Hydrogen peroxide (H_2O_2) can also be generated by other chemical reactions; it is a highly reactive metabolite and can be eliminated by reactions catalyzed by the peroxidases and catalases enzymes. Also, hydrogen peroxide and the superoxide radical can react together to produce a hydroxide radical (OH^-), which is also highly reactive. The fact

that animals are capable of living for a long time, continually producing large amounts of highly reactive substances, is due to the presence of their defense mechanisms against these lesions, including mechanisms to repair the injuries. However, a substantial body of evidence suggests that, in spite of all this, and perhaps due to occasional periods of increased production of mitochondrial free radicals, the capacity of the defense system is exceeded, producing accumulative lesions in the macromolecules (nucleic acids, proteins, lipids), leading to progressive changes in function (Figure 4.1). It is of paramount importance to understand the decline in functional capacity in healthy elderly people and the biological, physiological, clinical, and social interplay among these factors, as they are probably the major contribution of geriatrics to medical science [22].

Evidence that injuries produced by mitochondrial free radicals are related to aging is based on the following observations:

1. The accumulation of mitochondrial free radicals in organs of aging animals
2. The accumulation of macromolecules, structurally altered due to mitochondrial free radicals, such as lipid peroxidases
3. Strains of *D. melanogaster*, which contain extra copies of the enzymes superoxide dismutase and catalase gene, have a longer median life than strains without mutations, as do age-1 mutants of *C. elegans*, which also have an increased expression of the superoxide dismutase

The practical consequence from the above studies is that lowering the production more than adding external antioxidants is the best way to protect against ROS damage induced in macromolecules, cells, tissues, and organs. This contradicts the widely accepted idea that addition of external antioxidants will prolong life in humans. Consequently, many of the "anti-aging" maneuvers promoting the addition of external antioxidants should be taken with caution.

Somatic Mutations

It has been observed that chromosomal abnormalities increase in older cells. On the other hand, short-lived lines of mice accumulate chromosomal abnormalities faster than lines with longer life spans. It is not clear if this age-related increase is produced by an accumulation of occasional injuries due to external agents (radiation, etc.), endogenous agents (free radicals, glycosylation, etc.), or an age-related decrease in DNA repairing capacity**.**

p53—"The Guardian of the Genome"

p53 is a protein with a number of anticancerous functions, interrupting the cell cycle or causing cell death following damage to DNA, hypoxia, oxidative stress, excessive mitogenic stimulation, or excessive telomere shortening. p53 prevents the development of cancer, although excessive activity of p53 favors the aging process. There are multiple processes, such as failures of DNA repair, telomere shortening, and oxidative stress, that allow us to explain, at least in part, the aging process. p53 is involved in each of these three processes. Damage to DNA, produced by exposure to environmental factors or defects in the repair mechanisms, is sensed by p53. As a result, if aging is caused by such damage, the activation of p53 must play a role in the generation of cellular responses related to aging [23].

Catastrophe Theory

Thirty-five years ago, Orgel [24] proposed one of the most popular and widely accepted theories to explain cellular aging. This theory proposes that protein synthesis produces an accumulation of exponential errors leading to a *cellular catastrophe*, an inevitable consequence of two phenomena:

1. DNA and RNA information transfer does not always occur with absolute fidelity.
2. Proteins also participate in this information transfer process.

Thus, a very small proportion of altered proteins implicated in transcription or translation would induce a progressive and continued production of malfunctioning proteins. If this exceeded the cellular capacity to repair or eliminate abnormal proteins or oligonucleotides, this would lead to cellular catastrophe. This theory predicts, therefore, an abnormal protein accumulation in aged cells—which is true.

However, it has been seen that most of the alterations observed in these proteins are not due to errors in translation but to posttranslational modifications, such as non-enzymatic glycosylation, free radicals, and other causes previously mentioned. Alternatively, experimental data exist that seem to refute this theory: The fidelity of protein synthesis in aged cells is similar to that in young cells. Currently, it is believed that a constant and low error rate can be maintained indefinitely, not inevitably producing a cellular catastrophe.

In conclusion, as a result of all the above theories, we can conclude that, although not all of the approaches to studying the aging process *in vitro* may be applied to an animal as a whole, we believe that knowledge about the possible complex mechanisms allowing the individual cells to modify their function with age can help us to better understand the changes that occur in the function of the organism as a whole with age.

Aging of Organs and Body Systems

The study of the modifications that age induces in the function of the organism and its different systems has important methodological difficulties. The most important is in identifying a group of healthy, older individuals wide enough to obtain reference values for this age group. Another important methodological problem would be determining the cut-off for "old age." There has been great difficulty in reaching an agreement between gerontologists in this area, probably due to the fact that the age of 65 is more a political than a biological distinction. It originates from the time of the creation of the German Social Security System by the chancellor Otto von Bismarck, issued in three consecutive laws published in the Kaiserliche Botschaft. The first of these was passed in 1883, "Gesetz betreffend die Krankenversicherung der Arbeiter," giving workers the right to insurance against illness. The second in 1884, "Unfallversicherungsgesetz," conferred the right to insurance against accidents. The third, and possibly most important, was passed in 1889, "Gesetz betreffend der Invaliditäts-und Altersversversicherung," allowing financial support in case of incapacity and in old age, defined as the age of 65. Since then the age of retirement has been associated with biological decline, which is now accepted in many Western countries. In other parts of the world, particularly

in underdeveloped and developing countries, the age of 60 is considered the limit between adulthood and old age. As a result, it is important to consider this in the methodology of different publications.

A new age group of "very old" or "old-old" people aged 85 and over is flourishing, and doctors and other members of the healthcare community should be prepared to take care of them. Obviously, the first task is in distinguishing between physiological aging and illness. We should not accept the same limits for biological parameters used in adults, which have been very well studied and contrasted over the last 100 years. We must remember that when pediatrics started at the beginning of the last century, the first pediatricians faced the same question, which is, "Are the same ranges of biochemical values used for adults valid for children?" Furthermore, are they the same for newborns, infants, and adolescents? These questions should be answered before labeling an old person as ill, or suffering from renal or cardiac insufficiency, as opposed to a healthy older person with reduction of GFR, loss of atrial pacemaker cells, or thickening of the posterior wall of the left ventricle.

Animal experimentation contributes greatly to the examination of certain functional changes. However, the results of these studies may not always be extrapolated to humans.

We will now discuss the main changes that aging produces in the structure and function of several organs and systems.

The Immune System

Immune function is a marker of health and a predictor of longevity [25]. Furthermore, a positive relationship has been shown between maintenance of several T lymphocyte, natural killer (NK), and phagocyte cell functions and longevity [26, 27]; therefore, immune parameters can be considered appropriate biomarkers of "biological age." In fact, our group has proposed such parameters, which we have standardized at different ages in mice and humans, as useful markers of "biological age," and they have been validated using a model of premature aging in mice. These prematurely aging mice (PAM) show values characteristic of chronologically older animals for the immune parameters mentioned above. Moreover, we have observed that these PAM show a significantly decreased life span [28,29]. The changes that occur with age in the function of the immune cells are due in great proportion to the chronic oxidative stress to which they are exposed over time. In fact, recent studies by our group show that the production and release of oxidant and proinflammatory compounds such as extracellular superoxide anion, TNFα, prostaglandin E2 (PGE2), oxidized glutathione (GSSG), and the GSSG/GSH ratio (an index of oxidative state) increase with age. By contrast, the level and activity of antioxidant defenses, such as reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), decrease in peritoneal leukocytes from mice. As a consequence of this oxidative stress, an increase in biomolecular damage, such as lipid peroxidation and DNA damage, appears [30]. An important question related to the above is whether the immune system has a relevant role in the changes linked to chronic oxidative stress that take place with the passage of time. We should remember that immune cells, in order to

fulfill their defensive function, show an oxidative and inflammatory response, producing factors such as TNFα and ROS. Thus, the immune system, with the passage of time, has to face numerous foreign agents, producing more and more oxidants and inflammatory compounds with resulting chronic oxidative stress. Moreover, as a result of the oxidative injury that immune cells suffer with age, these cells may lose some of their capacity to regulate their own redox balance, which would result in a vicious circle in which factors such as the nuclear factor kappa B (NF-kB), which is involved with the expression of genes of oxidant and inflammatory compounds and that shows a great activation in situations of oxidative stress [31] as it happens in aging, could be implicated, stimulating oxidative stress even further.

In summary, some immunological responses attenuate with age, while a few of them exacerbate. Among the former are cell-mediated immunity, antibody production, function of monocytes, response to vaccines, macrophage function, delayed-type hypersensitivity, cell proliferation response to mitogens, ability of hematopoietic stem cells to replicate, IL-2 and its subsequent responsiveness, production of B cells by bone marrow, and size of the thymus and production of thymic hormones. Among the increased activities are increased levels of auto-antibodies, interleukin IL-6, and levels of memory T cells (CD-45). Natural killer cells, however, have not been shown to display altered functions associated with aging.

Immunosenescence

The functions of the immune system that impair with aging are known as immunosenecence. Presently, although there are conflicting results on this subject, it is accepted that nearly every component of the immune system undergoes striking age-associated restructuring, leading to changes that may include enhanced as well as diminished function. One of the main reasons for the existence of these conflicting results in the literature seems to be the age of the animals considered to be young or old, between which the comparisons are made. A sequential study of the changes to immune functions with age eliminates this problem. Recently, the age-related changes in several pivotal functions of three relevant immune cells, namely lymphocytes, phagocytes, and natural killer cells, in experimental animals and humans have been studied [32–34] Thus, in phagocytes, functions such as chemotaxis and phagocytosis decrease with aging. These cells act as a first line of defense, showing adherence to tissues, migration to the infectious focus or chemotaxis, ingestion of the microorganisms, and destruction of them through production of free radicals (the first of which is the superoxide anion), which, if generated in high amounts and if they leave the cells, can damage the tissues. Inflammatory cytokines such as tumor necrosis factor alpha (TNFα) are also released in the infectious process. Lymphocytes are important cells in the immune response and show adherence and migration ability that allows their arrival at the site of antigen recognition. After recognition they start a proliferative response and production of the cytokines needed to support the immune response, the first of which is interleukin-2 (IL-2). In these cells functions such as chemotaxis, proliferative response to mitogens, and IL-2 release decrease with aging. However, other functions very closely linked to oxidative stress, such as adherence of leukocytes and release of free radicals and proinflammatory cytokines (namely TNFα), increase with age. All these changes with aging are similar in leukocytes from both mice and humans. This may explain the

vulnerability and ease to **develop sepsis**, a risk factor for mortality in patients older than 65 admitted to intensive care units particularly in the presence of multiple organ dysfunction syndrome (MODS) (see Chapter 21).

Aging of the Neuroimmune Communication

The immune system has a key role in the preservation of homeostasis; for that, this system is presently considered a genuine regulatory system, comparable to the "classic" regulatory systems, namely the nervous and endocrine systems. Moreover, the immune system does not work in isolation, but it functions in close relationship with the organism's other regulatory systems, carrying out a bidirectional communication between them. It is presently accepted that the three above-mentioned regulatory systems share receptors and, therefore, any influence exerted on the immune system will have an effect on the nervous and endocrine systems, and vice versa [34, 35]. Thus, there is a "neuroendocrine-immune" system that allows the preservation of homeostasis and, therefore, of health. Moreover, the changes with aging in this communication between the immune and nervous systems have been reported as a possible cause of physiological senescence [36]. Recently, there are studies confirming this fact [34, 37] as well as the idea that the impairment of immune system with aging affects, through increasing oxidative stress, the function of the other regulatory systems [30, 38].

The Endocrine System

Growth Hormone and Aging

Growth hormone (GH) is the most abundant anterior pituitary hormone in the human adult [39]. Its main action is exerted on several organs and tissues through the stimulation of IGF-1. GH is an anabolic hormone that induces positive nitrogen and phosphorus balance and causes cells to grow and multiply. It acts by directly increasing the rate at which amino acids enter cells, resulting in an increased substrate pool for protein synthesis. GH stimulates protein anabolism, inducing an increase in the growth rate of long bones and skeletal muscles during childhood and teenage years.

GH also stimulates lipolysis, that is, the breakdown of triglycerides into fatty acids and glycerol, and promotes fat catabolism to provide substrates for glucose neosynthesis; thus, it has a sparing effect on glucose utilization [39].

GH action on carbohydrates has been described as diabetogenic. In normal subjects, GH stimulates insulin secretion, but at the same time, this hormone reduces the sensitivity of peripheral tissues, like muscle or adipose tissue, to insulin. Elevated plasma glucose levels then stimulate further insulin secretion.

GH deficiency in adults has only recently been recognized as a specific clinical syndrome, characterized by a combination of metabolic and cardiovascular features that are more evident in women than in men. The syndrome includes a high prevalence of dyslipidemia, glucose intolerance, central obesity, and hypertension. Early arteriosclerosis is found in this asymptomatic hypopituitary GH deficiency. All these factors make an important contribution to increased cardiovascular risk [40].

GH-deficient subjects exhibit endothelium-dependent alterations, which recover after substitutive GH treatment. GH also has important actions on lipid metabolism that play a role in vascular and endothelial function.

Actions of GH on the cardiovascular system include stimulation of the growth of cardiomyocytes and IGF-I-induced NO production. NO, besides other vascular effects, has an important role in vascular smooth muscle relaxation. GH has also shown to restore incipient structural alterations in the vessel wall. GH and IGF secretion decrease with age; very low levels of GH and IGF-I are found more often in elderly people compared with younger adults [41]. An increase in exercise capacity has been reported in elderly people after initiation of GH therapy [42].

Our group has described that the vasodilator response to Isoprenaline, an endothelium-dependent vasodilator, is more marked in young than in old rats. Treatment with GH increased vascular smooth muscle relaxation in older animals; therefore, GH treatment is capable of improving the vascular dysfunction associated with old age in male rats.

The central nervous system is a target for the actions of growth hormone (GH) and also for melatonin. The hippocampus, a region of the brain involved in spatial and episodic memory may contribute significantly to the age-associated decline in cognitive abilities We have estimated the rate of neurogenesis and found a dramatic reduction with age. The administration of melatonin to aged rats increased neurogenesis, and the same effect was observed following estrogen therapy in ovarierectomized female rats of advanced age.

GH exerts important effects on CNS [43] such as increasing psychological capacity in adults including memory, concentration, alertness, and capacity for work. Some neurotransmitters also change during treatment with GH.

Male Reproductive Axis

The main androgen is testosterone, which is secreted mainly by the testes. Testosterone is produced in response to trophic hormones: Hypothalamus releases GnRH, which stimulates the anterior pituitary to release LH and FSH. LH stimulates testosterone secretion and, together with FSH, promotes spermatogenesis. Testosterone plays a key role in developing and maintaining male sexual organs and promotes secondary sexual characteristics including the appearance of facial hair, sexual desire, and sexual behavior. Testosterone stimulates the metabolism, which promotes fat burning and accelerates muscle growth. In addition to sexual function, testosterone is also responsible for numerous biological processes including protein synthesis, oxygen uptake by cells, cholesterol regulation, and immune surveillance. It also affects many metabolic activities such as the production of red blood cells in the bone marrow and inhibits cells called osteoclasts that enhance bone breakdown, lipid metabolism, carbohydrate metabolism, liver function, and prostate gland growth.

The testes in men begin to function at puberty in two capacities: gamete production and hormone secretion. Testosterone secretion continues until death, but from 50 years onwards an important reduction in plasma testosterone levels has been observed [44]. There is also a reduction in sperm production, and the secretory circadian rhythm appears to be lost. As a result, gonadotropins, especially FSH, are increased gradually with aging. Age is

inversely correlated with sexual activity, and an increase in sexual dysfunction has been described with aging [45].

Female Reproductive Axis

The ovary produces hormones and gametes in special structures called follicles. The total number of follicles at puberty is approximately 400,000 and gradually declines with age until their complete disappearance at menopause. Estrogens are steroid hormones with 18 carbon atoms and with a phenolic A ring produced in the granulosa cells of the follicle and the luteinic cells of the corpus luteum. Its main actions are exerted on the female secondary sexual characteristics/organs (especially the uterus, mammary glands, and fat distribution) but have also been described as protective agents, protecting women's cardiovascular health.

Changes in the neuroendocrine system due to the loss of ovarian function have an important biological role in the control of several functions: mood regulation, memory, cognition, behavior, immune function, the locomotor system, and cardiovascular functions.

It has been observed that, while estrogens help retain a youthful synaptic phenotype by some measures, the aged synapse may differ from the young synapse in several key respects, particularly general plasticity and endocrine influences on the synapse [46].

Aging in both males and females is associated with a decline in the secretion of androgens and estrogens, and it is possible that this decline could also have implications for the aging of neurons in the brain.

Prolactin

Prolactin has an important role in the morphological and biochemical differentiation of the epithelial cells during pregnancy and regulates milk protein synthesis during lactation [47]. However, it does not have a known physiological role in men, although an effect on the libido has been described. Levels of prolactin-releasing hormone seem to be unchanged with age as well as in women who have had their ovaries removed and in postmenopausal women, or in men [48].

Melatonin

Melatonin, an indolic hormone secreted by the pineal gland, is closely related to biological rhythms. It is one of the physiological inducers of sleep, especially of slow wave sleep (SWS). In addition to its role as a hormone, melatonin is a ubiquitous direct free radical scavenger and an indirect antioxidant, exerting protective effects in several diseases and experimental models [49]. A very important reduction in melatonin secretion has been detected with aging, and this could be involved in the decline in cell and tissue performance that takes place in the elderly, as well as the declining amount and quality of sleep. Several findings also indicate that exogenous melatonin is neuroprotective, to a certain extent, in old age.

Thyroid Hormones

The two most important thyroid hormones are tetraiodothyronine (thyroxine or T_4) and triiodothyronine (T_3). These hormones are essential for life and have many effects on body metabolism, growth, and development. The thyroid gland is regulated by thyroid-stimulating hormone (TSH) from the pituitary gland, whose secretion is controlled by the thyrotrophin-releasing hormone (TRH) from the hypothalamus. The active hormone is mainly T_3, which is usually

obtained by the selective deiodination of T_4 in the tissues. In the elderly, a discrete reduction in T_3 production but not in T_4 or TSH response has been described, and increased TSH basal levels in females have also been observed Apparently, aging alters the activity of 5'-deiodinase in several tissues, with reduced T_3 and, consequently, a reduction in basal metabolic rate [50].

The response of TSH to TRH in the elderly was unchanged for some authors or decreased for others, explaining the hypothyroidism often found in aged persons. On the other hand, the rate of release of hypothalamic TRH seems to be unchanged in older females. Thyroid regulation in the elderly is a complex mechanism and probably involves more factors than have been discussed here.

Adrenal Glands

The adrenal cortex produces the steroid hormones aldosterone and cortisol. Aldosterone regulates fluid and electrolyte balance and decreases with age. Cortisol acts as the "stress response hormone." It affects the breakdown of glucose, protein, and fat and has anti-inflammatory and anti-allergy effects.

It seems that cortisol levels remain constant during aging, but the rhythm of secretion can vary. Plasma levels of ACTH are the same in the young and elderly, but the rhythmicity seems to be altered. The response to different stressors is also unchanged in older individuals, as well as the response to exogenous ACTH or GRF administration [51]. Nevertheless, other authors have found a reduced responsiveness in the adrenal axis to glucocorticoid feedback inhibition by cortisol in elderly healthy subjects, compared to young ones [52].

Pancreas

Although studies on the effects of aging on pancreatic function have had some contradictory results, it seems that the exocrine function of the pancreas is maintained normally during aging. However, we can observe some histological alterations, such as weight decrease, ductal epithelial hyperplasia, interlobular fibrosis, and acini cell degranulation. Some studies show a small decrease in the secretion of enzymes and bicarbonate in response to secretine and ceruleine in older people, but the decrease is so small that it does not have any functional importance. What does seem to be diminished is the pancreatic trophic response to hormonal stimuli as well as the capacity to respond to dietary modifications by changing the enzymatic composition of pancreatic juice, which can represent a deficit in the adaptive capacity to nutritional stimuli associated with age.

Pancreatic endocrine function is also altered with age, with a reduction of insulin synthesis, leading to considerably greater incidence of diabetes in aged people. Age-related changes interact with genetic background to explain the increased prevalence of diabetes with aging. This is due to the fact that cells become less sensitive to the effects of insulin, probably because of a loss in the number of insulin receptor sites. This affects glucose metabolism even in the absence of diabetes [53].

The Cardiocirculatory System

Morphological Changes to the Heart

Before we outline the morphological changes that occur in the heart with aging, we must emphasize that it is very difficult to separate changes due to

physiology from those due to pathology, produced by diseases or environmental factors. In the same way, it is difficult to distinguish between morphological and functional changes. We know that there is interdependence among many of these changes and that in the origin of many structural changes we can find functional alterations. In other instances, we can attribute some functional changes to structural alterations linked to the aging process.

In the description of the morphological changes, we can establish a subdivision among different structures: the mechanical component (including valves), the coronary arteries, and the conduction system.

Mechanical Components

Perhaps the main change we can find is an increase of left ventricular wall thickness, especially of the left ventricular free wall. This was well known some time ago from necropsy studies [54], and it has been confirmed more recently by echocardiography [55]. This increasing thickness is usually attributed to the increase in the systolic arterial pressure levels which occurs throughout life, with the correspondent increase in arterial stiffness and impedance. We know today that other factors are also involved in this phenomenon. Among them, an increase in the activity of the sympathetic nervous system, an age-associated tendency to insulin resistance, and genetic factors have been suggested. This thickness is more marked in subjects with heart disease. There is a good correlation between the thickness of the left ventricular wall and the increase in the isovolumetric relaxation time: the so-called prolonged isometric contraction. This hypertrophy has certain biochemical and functional similarities with what has been called the "cardiomyopathy of overload" and may contribute to the high incidence of diastolic heart failure in the elderly [56].

Myocytes also show important changes. There is a decrease in their number, explained by the loss of some cells. We also have some evidence that the reduction in the number of myocytes is attributable to apoptosis, as well as to necrosis. Cardiac myocyte apoptosis occurs after acute myocardial infarction, as well as in the hypertrophied heart and the aging heart, conditions frequently associated with the development of heart failure. Lakatta [57] has commented on changes in cardiac gene expression that are known to accompany advancing age and associated structural and functional changes that relate to these changes in gene expression.

There is a partially compensatory increase in the size of myocytes that survive. These surviving myocytes show nuclear enlargement, irregularities, replication, and probably a modified contractile behavior. Dead myocytes are replaced by functionally inert fibrous tissue. There is also a decrease in the levels of myocyte calcium ATPase, as well as in the concentration of the V-1 isoform of the myosin heavy chain that is substituted by the V-3 isoform [58].

Other well-known changes in the mechanical cardiac structure are

1. An increase in the thickness of the aortic and mitral valves, with progressive dystrophic calcification of both valves
2. Aortic valve sclerosis and degenerative calcification, which help to explain the high incidence of significant aortic stenosis in this age group and that may be the expression of the prolonged action of traditional cardiovascular risk factors such as hypertension, tobacco, alcohol, being overweight, hyperlipidemia, and glucose intolerance
3. Mitral annular calcification after the age of 70

4. Foci of fibrosis distributed diffusely in the subendocardium and myocardium, which are probably an expression of previous microinfarcts
5. Increased amount of interstitial collagen
6. Age-related accumulation of lipofuscin and an age-related accumulation of amyloid, especially over the age of 90 [59]

Cardiac chambers also change with age. There is a mild decrease in internal systolic and diastolic left ventricular dimensions [60]. The left atrium becomes enlarged as the left ventricle requires assistance in achieving adequate diastolic filling.

Conduction System

There is a substantial loss of pacemaker cells between the ages of 20 and 75 years that may reach 90% of the cells [61]. However, normal rhythm in the elderly is sinus rhythm; thus, any other rhythm has to be considered abnormal, and a search for occult disease has to be started. Atrial fibrillation can never be considered as a "normal rhythm" in an elderly person, even in centenarians. Other changes in the conduction system include fibrosis, fatty infiltration, and loss of specialized conduction tissues. These changes cause difficulties in impulse transmission that may contribute to the lengthening of the P-Q interval and the increase in the prevalence of conduction disorders observed in elderly people. Finally, and it is probably the most important change from the functional point of view, there is a loss in the number and responsiveness of beta-adrenergic receptors [62].

Coronary Arteries

Coronary arteries become tortuous and dilated, with an increase in the number and size of coronary collaterals. There is a progressive thickening of the intima due to increasing deposition of calcium, phospholipids, and cholesterol, independent of atherosclerosis [58]. The endothelial cells become heterogeneous in size, shape, and axial orientation. In the media the most important changes are fragmentation of elastin fibers and increased calcification [63]. A decrease in elastin production or repair with aging could be involved in the enhanced elastin fiber breakage with aging. Another important change in the endothelium of the artery is a decrease with age of nitric oxide production. In summary, there are an age-related increase in media thickness, collagen content, and the collagen/elastin ratio, and a decrease in elastin density and the number of smooth muscle cell nuclei.

Structural changes that occur with aging are associated with changes in both active and passive stiffness [64]. The main consequences of these coronary changes are a narrowing of the lumen with a loss of elasticity, an increase in stiffness, enhanced pulse wave velocity, and early reflected pulse waves. All these changes foster the development of atheromatous plaques.

It is important to take into account that many of these changes are similar to those that can be observed in the aorta, especially the increasing stiffness, because we know that the age-related increase in systolic blood pressure is one of the more important determinants of cardiac functional changes throughout the aging process. This point is especially relevant if we consider that about two-thirds of people over 65 years old suffer from high blood pressure.

Humoral Changes

There is a strong relationship with morphological and functional changes. The main neurohormonal changes are those related with the increase in

the activity of the sympathetic nervous system [62]. A poor cardiac beta-adrenergic response leads to an increase in the production of catecholamines and their peripheral levels. Because of this, the plasma norepinephrine rate in the healthy aged is in the higher limits of normality or slightly increased with respect to healthy young adults. A clinical consequence of this will be an impaired response of beta-adrenergic receptors to physiological (and pharmacological) stimulation and blockade [62]. At the same time, a decrease in plasma renin activity and in plasma angiotensin II and aldosterone concentrations are found, as discussed in Chapter 5.

Plasma atrial natriuretic peptide (ANP) concentrations show a trend to be increased, although end-organ responsiveness to this hormone is decreased [65].

Dependent and independent vasoconstrictive hormone levels increase with age in the resting state and in response to neurohumoral stimulation.

The key point of the humoral changes is the decrease in the cardiac beta-adrenergic responsiveness, one of the major determinants of the functional cardiac changes related to aging. Many factors can explain this phenomenon; among them receptor downregulation, decreased in agonist binding by beta-1 receptors, an uncoupling of beta-2 receptors, and an abnormal G protein-mediated signal transduction [66].

Some of these humoral parameters have been used as markers for mortality or morbidity. For example, ANP levels are an independent risk factor for mortality in frail older individuals, and the levels of ANP may indicate homeostatic failure to adapt to fluid volume changes or may even reflect the presence of subclinical heart disease [67].

Functional Changes

Functional changes are strongly related with morphological and humoral changes and cannot be considered separately. The most important change in cardiovascular function is probably a gradually prolonged contraction (systole) due to delayed relaxation. The decrease with aging in the rate at which the sarcoplasmic reticulum pumps calcium and the reduction in the activity of calcium-myosin-ATPase and mRNA play an important role in this relaxation deficiency [68].

In practice, this means that the early diastolic ventricular filling rate is markedly reduced and becomes increasingly dependent on atrial contraction to maintain a normal end-diastolic filling volume. It also implies poorer ventricular filling, especially when tachycardia or heart disease is present, and impaired coronary perfusion. We must remember that coronary perfusion takes place during diastole.

The main reason for this change is a rise in systolic blood pressure due to the reduced capacitance (increased rigidity) of the elastic arteries. The resulting increase in afterload, together with the neurohumoral changes, leads to hypertrophy, increased rigidity, and lengthening of the relaxation period of the left ventricle.

It is also important to remember that the baroreceptor-reflex function is attenuated, mediated in part by the decreased arterial distensibility. This implies less efficient adaptation to volume and postural changes and can explain the increased incidence of orthostatic hypotension, syncope, and falls in elderly people.

Most of the elderly population has important limitations to their cardiac performance during exercise. This is due in part to extracardiac factors, essentially muscular or pulmonary problems.

Cardiovascular function at rest in healthy elderly individuals is adequate to meet body needs [69]. The prolonged contractile activation and a minor heterogeneity of myocardial relaxation occurring within different regions of the left ventricle are not enough to alter this normal pattern. Cardiac output, cardiac index, ejection fraction, stroke volume, and contractility markers of overall systolic cardiac pump function remain practically unchanged. It should be emphasized that this is true for healthy elderly people; many elderly persons have several cardiac (i.e., clinical or subclinical coronary disease) or extracardiac diseases (hypertension, diabetes, renal or pulmonary failure, etc.) that compromise the normality of these markers.

A careful, precise selection of healthy subjects is necessary to understand the aging changes related to cardiovascular function with exercise. With exercise we can observe a striking decrease in the maximal heart rate response. The way to maintain normal or near-normal cardiac output during exercise in healthy elderly subjects is to increase the stroke volume and ejection fraction, based on an augmented cardiac filling (preload). Left ventricular volume at end-diastole and throughout the cardiac cycle is greater in older than in younger persons. In other words, the elderly heart uses the classical Frank–Starling mechanism to maintain a normal output during exercise, while in young individuals a higher maximal heart rate, a better inotropic response, and an afterload reduction are used to adapt well to exercise.

At rest, heart rate in the healthy aged exhibits a modest and nonsignificant reduction with respect to young individuals, although there is a moderate tendency to bradycardia, especially at night and in the upright position. There is also attenuation in heart rate respiratory changes and in those that take place spontaneously. The inability to reach high maximal heart rate, with different degrees of exercise, that takes place during the aging process is a decisive phenomenon that explains the cardiovascular functional changes with aging. The role that an impaired beta-adrenergic response plays in this limitation was confirmed pharmacologically by the observation of a defective heart rate response to an isoproterenol stimulus in senescent animals when compared with young ones.

In summary, an increased end diastolic volume (preload), an increased afterload, a decreased contractility, and limitation in achieving high maximal heart rate response are found in the elderly when compared with younger individuals.

Blood Vessels

Changes in blood vessels are similar to those occurring in coronary arteries [58, 63, 64]. One important consequence of these changes is an increase in peripheral resistance, which contributes significantly to increased blood pressure. All these changes occur both in the aorta and in the elastic arteries, resulting in an increase in vascular resistance, the major pathogenic mechanism for the development of hypertension in aged persons (see Chapter 3). The modifications the endothelium undergoes with age are discussed in Chapter 7.

Respiratory System

With regards to the external thoracic components, the chest wall becomes less efficient with age. A gross change in tissue composition is calcification of the cartilaginous joints of the spine, ribs, and sternum, as well as progressive loss of bone density (osteopenia and osteoporosis), something that is easily noticed on chest radiographs with age. As a result, the anterioposterior diameter of the chest increases, while the transverse and longitudinal dimensions decrease [70]. The above changes, together with some degree of kyfosis, may produce some degree of diaphragmatic relaxation leading to gastroesophageal regurgitation that may cause minor continuous bleeding, a not unusual etiology of anemia in otherwise healthy aged individuals. The rib cage becomes more rigid with reduced mobility, as progressive curvature limits the compliance of the chest wall. This accounts for the greater dependence on abdominal and diaphragmatic contributions to ventilation than in younger subjects.

Lung Structural Changes

The respiratory muscles tend to atrophy with age, losing mass and strength. This causes an added restriction in the respiratory movements and also contributes to the gradual decline in the efficiency of ventilation, a major determinant of lung function in the elderly. However, in the absence of malnutrition, reduction in diaphragm muscle mass with aging is negligible.

The conducting airways consist of the air passages from the mouth to the level of respiratory bronchioles. The large cartilaginous airways show a modest increase in size with age. There are similar changes in the tracheal and bronchial walls (tendency to calcification, stiffness, and an increase in lumen diameter). Beside this, at the extrapulmonary airway level, there are also a loss in the number of cilia, particularly in smokers, and hypertrophy of bronchial mucous glands.

The lungs of elderly persons dying with no history of pulmonary disease appear smaller and flabbier than those of younger persons examined at autopsy. In concordance with this, lung weight is decreased in advanced old age [71].

At the beginning of last century, the medical literature used the term “senile emphysema” to describe changes in the shape and compliance of the thorax with age consistent with airspace enlargement. This represented a common finding in elderly people, especially men, but was clearly associated with lifestyle and environmental factors and not so much to physiological aging. So this term was formally abandoned because the age-appropriate upper limit of normal for airspace diameter had not been defined. In any case, a collapse of small intra-pulmonary airways due to loss of elasticity in lung tissue takes place with age, resulting in increased resistance to air flow.

Although there is great individual variability, there are also important morphological changes in the functional lung tissue. The surface area of the terminal part of the airways, the alveoli, decreases by about 5% with each decade of life, starting in the 30s. At the same time, the alveolar wall becomes thinner and contains fewer capillaries. These changes, combined with the loss of elasticity and recoil, cause an increase in the size of the alveoli. This overall enlargement of alveolar ducts is called *ductectasia* and contributes to a decrease in the surface area of the lung. A decrease in collagen content may

contribute to increased lung compliance, reduced expiratory airway diameter, or airflow limitation.

It is the loss of recoil that creates an increased susceptibility to airway collapse, the major factor contributing to the altered distribution of air within the lungs. The loss of recoil and the loss of distal capillaries facilitate the development of emphysema in the elderly, especially when environmental or pathological factors are taken into account.

Bronchial circulation may decline with the aging process, and atherosclerotic plaques can develop. Pulmonary circulation may also decline, reducing the capacity to respond to demand when an increased supply of oxygen to the tissues is needed, i.e., during physical exercise. The pulmonary vascular response to hypoxia (hypoxic vasoconstriction) is blunted in the elderly.

Functional Changes

During the aging process, total lung capacity (TLC) is maintained without significant changes. However, the other subdivisions of lung volume are affected by age [72]. The volume of the conducting airways determines the anatomical dead space. There is a larger portion of dead air space in the respiratory tree, which increases with age. Vital capacity (VC), a useful parameter of lung function, is reduced with aging. This is primarily due to an increase in the residual volume (RV) (the amount of air remaining in the lung at the end of a forced exhalation). The main reason for this increase in RV is the aforementioned loss of chest wall compliance. Conversely, the amount of air that can be forcibly exhaled decreases. The rate of this decline is higher in men than in women.

The exchange of oxygen and carbon dioxide between alveoli and capillaries is altered during aging. This is a functional consequence of airway collapse and redistribution of blood flow. In the elderly, larger areas of the lung become perfused but not ventilated, while in young people each area of the lung where blood is available for gas exchange is ventilated, giving a perfect match between ventilation and perfusion. Therefore, in the elderly, even if the respiratory rate increases with need, the ventilation/perfusion ratio is decreased, resulting in less gas exchange. The consequence is a reduction in the amount of oxygen delivered to arterial blood, or in other words, an increase of deoxygenated blood in the general circulation and a decreased efficiency of the respiratory system, especially in any circumstance that demands greater oxygen consumption.

This poor response can be increased if, as often happens, there is impaired cardiac function. People who exercise consistently have less decrease in lung function. For most people, their reserve capacity is greater if the person has remained active throughout life.

Normal elderly subjects at rest breathe with minute ventilations identical to those of younger subjects but with smaller tidal volumes and a faster breathing rate. There is controversy about the role of central neuromuscular control mechanisms in these changes, as well about the possibility of a blunted response to hypoxia or hypercapnia in healthy elderly subjects.

Another important clinical consequence of all these changes is that the lungs become more and more susceptible to infection with age. The losses in mechanical thoracic functions increase the risk of aspiration from the upper digestive tract. With age, the coordination of swallowing may be adversely affected by strokes, seizures, muscle weakness, or other neurological disease,

resulting in inadvertent aspiration. In addition, the gag and cough reflex are diminished, causing a reduced effectiveness in the cough reflex. The decline in ciliary action, which normally moves secretions and foreign bodies up and out of the lungs, has a similar effect.

Many drugs produce a significant negative effect on respiration in the elderly, especially hypnotics, sedatives, and analgesic drugs that act on the respiratory center of the brain.

In summary, the changes to the structure and function of the respiratory system that occur between maturity and senescence in healthy individuals take place so gradually that, in the absence of acute or chronic disease, older people are capable of effortless breathing. There is no evidence that the changes in the respiratory system with aging impact the day-to-day function of older adults, but they may become evident under circumstances when physiological demand reaches the limits of supply. In this sense it is well known that the incidence of respiratory failure increases almost exponentially with age and that older patients have a longer duration of mechanical ventilation and are more likely to require reintubation in the evolution of MODS.

Kidneys

In otherwise healthy individuals, aging produces a series of anatomical and functional changes that are not observed in younger adults; these are discussed at length in Chapters 3 and 5. In summary, there is a loss of renal mass, mainly due to atrophy of the renal cortex. The reasons for these age-related changes are still uncertain. One hypothesis postulates that as the number of glomeruli decreases, those that remain are subject to an increase in capillary pressure. This high pressure produces intrarenal endothelial damage, platelet aggregation, and thrombin production, leading to release of growth factors such as fibroblast growth factor, platelet activating factor, tumor necrosis factor, and epidermal growth factor. These factors increase the production of collagen and also provoke mesangial cell sclerosis. This in turn induces an alteration of vascular hemodynamics by increasing angiotensin II secretion. Therefore, in hypertensive patients, it is important to protect the kidney against the evolution of further renal damage and renal insufficiency using agents that modulate the renin-angiotensin system. The other hypothesis proposes that an imbalance between the synthesis and degradation of matrix protein is the major cause of glomerular sclerosis. Functionally, the renal blood flow decreases by approximately 10% per decade, following its peak in early adulthood, and reaching an average 50% reduction in the elderly. Glomerular filtration rate (GFR), assessed as inulin clearance, declines with age from a mean of 122 to 65 mL/min between the ages of 30 and 90 years [73]. The lower limit of inulin clearance (mean-2SD) may be as low as only 40 mL/min/1.73 $m^2$for a population of apparently healthy normal 80-year-olds in the absence of renal insufficiency**.** It is also interesting to note that in elderly people as in prepuberal children, there is no gender difference in GFR [74]. In cross-sectional studies using creatinine clearance as an index of GFR, the decrease in GFR with age has also been observed. In the Baltimore longitudinal study where some of the subjects were followed with repeated measurements for more than 30 years, there was no uniformity in this decrease. Despite a mean calculated reduction in creatinine clearance of 0.75 mL/min/year for the whole group,

92 of the 254 individuals studied showed no reduction in creatinine clearance, and a few even increased their clearances [75]. An important practical point is that despite the usual decline in creatinine clearance in otherwise healthy individuals, in the majority of studies, there is no corresponding increase in plasma creatinine with age [76]. At this point we should remember that the decrease of GFR, assessed as creatinine clearance, with normal serum creatinine for healthy adults in absence of other signs and symptoms of chronic renal insufficiency, reflects the physiological aging of the kidney and by no means signifies chronic renal insufficiency.

Another feature of the normal aging kidney is the impaired capacity to reabsorb sodium, due to a reduction in the functional capacity of the ascending limb of the loop of Henle. This is clinically relevant, as it readily facilitates hyponatremia when salt is restricted, and even more so if we add diuretics.

All the above factors contribute to the easiness of instauration of acute renal failure in over 65 years of age (see Chapters 5 and 8).

Nervous System

There are many studies evaluating the changes in volume and weight that the brain experiences with age. Some of them, particularly the old ones, may be biased due to their methodologies, i.e., sample collection and/or measurements. Nevertheless, in the majority of studies it was found that the brain weighs 357 g at birth, increasing to a maximal size of 1300 g at the age of 20 years. This weight is maintained until the age of 65 years. From there begins a progressive loss of weight through the age of 80 with a decrease of 11% in mean weight or a 6% decrease in mean brain size in the old relative to the young adult. This decline is not related to the number of neurons in the cerebellum nor in the cerebral cortex, because using techniques of fresh brain tissue, it has been shown that there is no decrease in the mean number of neurons in the cerebral cortex between the ages of 20 and 120 in either females or males [77]. In normal aging, a decrease in the size of the nerve cell body, in synaptic density in some regions, and in glial cell numbers takes place. It may be that the loss of synaptic activity and complexity, more than the number of lost neurons, may underlie the cognitive loss as supported by the Nun Study [78], keeping with the widespread clinical observation that short-term memory abilities decrease as we grow older. The data of this study find a close inverse relationship between linguistic ability in youth and the risk of mortality in later life. A possibility may be that suboptimal neuronal development leads to a decreased synaptic complexity, manifested as a lower linguistic ability. The simpler connectivity of the neuronal network can lead to decreased buffering against neuronal insults and, as a result, a more receptive field for neurodegenerative diseases [79]. This observation suggests that our neuronal competence when we grow old may be determined by the quality of neuronal development when we are young. If this is true, it will mean that it is important for neuronal healthy development and prevention of later neuronal degenerative diseases, to provide children with an optimal diet, a challenging environment, and adequate emotional support [78, 79]. If the number of neurons does not significantly decrease with age, some neurotransmitters do, such as acetylcholine in the hippocampus, dopamine in the subtantia nigra and the striatal pathway, norepinephrine and serotonin in portions of the brain

stem, and gamma-aminobutyric acid (GABA) in the thalamus. These changes are often accompanied by a reduction in the number of receptors and their binding affinity [80]. In conclusion, normal aging does not exhibit a universal decrease in neurotransmitter activity and, at least at rest, there are only minor age-related changes in neurotransmission. However, the already-mentioned decreases and localized changes appear to play a major role in the development of behavioral age-related changes and the significantly diminished range of modulation of the nerve signal when the organism is stimulated. Many studies explore the age-related metabolic changes in the human brain. The generalized conclusion is that brain metabolism remains comparable to that of the younger healthy subjects or it decreases, but never increases. In healthy aged subjects, cerebral blood flow (CBF) does not decrease while at rest. However, mental stimulation shows some decrease in regional CBF and in regional glucose consumption. A correlation suggesting that zonal hypometabolism may be one of the causes of the age-related cognitive dysfunction observed in some individuals has been hypothesized [81].

It is well known that the autonomic nervous system (ANS) loses competence for thermoregulation (hypothermia), baroreceptor function, and rapid adaptation to postural changes (orthostatic hypotension) with age. ß-adrenergic receptors in the ANS of older people are less sensitive than in younger people, especially ß1-receptors, which are more prevalent in heart tissue than ß2-receptors. The clinical consequence is that the threshold for brain blood flow autoregulation is shifted to the right and, consequently, we should be aware of it at the time when prescribing antihypertensive drugs.

Reduction in vascular density and vascular atrophy has been demonstrated in normal aging. These would support the increase in permeability of the blood–brain barrier, explaining why the elderly are generally more susceptible to drugs that can cross this barrier.

Another finding, even in intellectually normal elderly people, is the appearance of clusters of neurofibrillary tangles at certain specific areas, i.e., the anterior temporal lobe, which, however, are very rare in other zones such as the neocortex. Persons suffering from senile dementia have a much greater number of neurofibrillary tangles in the anterior temporal lobe than normal individuals [1].

Musculoskeletal System

Muscles

There is an age-related decrease in muscle mass (sarcopenia) and power. The basal metabolic rate decreases by 4% per year after the age of 50. The basal metabolic rate and regenerative capacity of muscle also decline with advancing age. A plethora of hormonal and immunological factors influence the normal balance between muscle breakdown and synthesis [82]. Altered rates of production with advancing age therefore have a sizeable effect on muscle bulk and composition.

Testosterone and glucocorticoids exert a strong catabolic effect on muscle tissue, and reduced levels later in life parallel the reduction in muscle bulk. Cytokines, growth hormone, and Insulin-like growth factor also affect the equilibrium between muscle production and degradation [83]. Decreasing levels of thyroid hormone (T_3) in old age influence the type of muscle fibers

synthesized, favoring a shift from fast- to slow-twitch fibers [84]. Electrophysiological studies demonstrate a reduced number of motor neurons and an increase in the size of the average motor unit in the muscle tissue of older people. This reduced innervation is a key reason for decline in muscle strength, and it is interesting to note that the age-related atrophy is only observed in fast-twitch fibers [83], which generate more power than slow-twitch fibers. In a 12-year longitudinal study in healthy sedentary men, a loss of isokinetic muscle strength in the knee and elbow extensors and flexors ranging from 20–30% has been demonstrated. By means of computerized tomography, a reduction of cross-sectional area of 14.7% of all thigh muscle, 16.1% of quadriceps femoris muscle, and 14.9% of flexor muscles was proven [85]. Interestingly enough, a 10-week progressive resistance exercise training program increased muscle strength by 113 ± 8% vs. 3 ± 9% in non-exercising subjects. Gait velocity increased by 11.8 ± 3.8%, and stair power climbing improved in exercisers. Cross-sectional thigh muscle area increased by 2.7 ± 1.8% in exercisers but declined by 1.8 ± 2% in non-exercisers [86].

Skeleton

The entire skeleton is subject to dynamic bone remodeling throughout life. The balance of bone deposition and resorption depends on the relative activity of osteoblasts and osteoclasts, respectively. It is also affected by sex, the regulation of calcium metabolism, and lifestyle factors. The most significant change observed in aged bone is the loss of bone mineral content; in fact, it begins to decline in the third decade of life. With age, blood calcium is maintained more by resorption of calcium from bone than from intestinal resorption from foods.

Both sexes lose cortical and trabecular bone, although women lose a disproportionately higher mass from the cortex and undergo a period of accelerated bone loss immediately after menopause. For example, the average man with a 4000-g skeleton can expect to lose 450 g of bone mass (12%) steadily over 30 years, while a woman with a skeleton weighing 3000 g will lose about 750 g (25%) in the first few postmenopausal years [1]. This is due to the loss of the protective effect of estrogen, as estrogenic hormones reduce the stimulating effect exerted by the parathyroid hormone on osteoclasts. Estrogen also affects the rate of calcium absorption and exertion and improves the efficiency of calcium utilization within the body.

Also, with advancing age the parathyroid glands are less sensitive to calcium, the kidney is not as responsive to parathyroid hormone, and the intestine displays reduced sensitivity to vitamin D. These factors combined cause reduced availability of calcium and increased osteoclast activity, leading to a decrease in bone mass [87].

Older bones are also more brittle, as the ratio of organic to inorganic components is lower. This is clinically important as it results in a higher incidence of fractures in the elderly. This is a normal part of the aging process and should be distinguished from osteoporosis, which refers to the pathological decrease in bone mass with no change in the chemical ratio of mineral to protein matrix.

Although bone mass will inevitability decline with age, lifestyle factors can play an important role in attenuating the rate of loss. Weight-bearing activity throughout life is beneficial, as it builds bone mass in young adults and helps conserve it into middle age and beyond. Sufficient dietary calcium

intake is also important, and supplementation can be helpful in the elderly as it is a moderate physical training. It is also possible to improve bone mineral density of the femoral neck in young and older healthy men and women, with a trend to be greater in the young, with a 6-month resistance training exercise program [88]. Smoking and long-term steroid use accelerate the rate of bone loss in both sexes.

Digestive System

Mouth, Pharynx, and Esophagus

The decrease in the number of teeth has an obvious effect on the efficiency of mastication. This, along with decreased saliva secretion capacity, makes formation of a food bolus more difficult. The process of swallowing requires the very fine coordination of several skeletal muscles in the pharynx, controlled by the medullar swallowing center. A disturbance in the coordination of this process seems to be responsible for the increased rate of dysphagia and regurgitation observed in the elderly. In addition, there is usually a disturbance of esophageal motility, with decreased amplitude of the peristaltic waves, the presence of multiphase waves, relaxation of the gullet, and incomplete relaxation of cardiac sphincter. These disturbances have given rise to the term *presbi-esophagus*, but not all the authors agree on its prevalence. Atrophy of the papillae contributes to a diminution of taste sensations and loss of appetite [89].

Stomach

Although it has been frequently described, there does not seem to be any conclusive evidence showing either an increase or a decrease in hydrochloric acid or pepsin secretion associated with aging. However, there is an increased susceptibility of the gastric mucosa to injuries produced by the gastric juices, which is associated with several factors. First, there is a decrease in the amount and effectiveness of the gel layer secreted by nonparietal gastric cells. Second, the cellular synthesis of protective prostaglandins decreases. Third, there is a decrease in the repair capacity of the gastric epithelium due to a lower proliferation rate, which seems to be caused by a reduction in synthesis of local growth factors. Fourth, blood flow to the gastric mucosa is reduced, which has been shown in experimental animal studies to be a key factor in its protection, since it contributes oxygen, nutrients, and humoral growth factors and removes toxic products.

Decreased gastric secretion of intrinsic factor, necessary for vitamin B absorption in the small intestine, has also been reported. This fact does not seem to depend on age, but on the greater prevalence of atrophic gastritis [1, 89, 90].

Small Intestine

In human studies, no decrease has been found in the nutrient absorption capacity of the small intestine, probably due to the large functional reserve offered by the surface area available for absorption. However, some studies of aging in rats have demonstrated a decrease in the absorption of specific nutrients. The capacity to secrete digestive enzymes does not seem to be modified with age either, at least not sufficiently to alter digestion. A small decrease in the transit time has been reported in older males but not in females,

although the functional importance of this finding is unknown [91]. Regarding the response of the small bowel to resection, it has been proven in rats that aged small bowel mucosa exhibit a proliferative and adaptive capacity similar to that observed in young animals [92].

Large Intestine

The aging process seems to be associated with diverse changes in the function of the large intestine, including changes in mucosal cell growth and differentiation, intestinal motility, metabolism, and immunity [90]. Some studies indicate that aging alters the susceptibility of the colonic mucosa to carcinogenesis, which seems to be due to an increase in the proliferative capacity of epithelial cells in response to mutagenic agents and growth factors like the TGFα, although it could also be a consequence of an increased exposure to carcinogenic toxins due to retention of feces. Another frequently observed alteration is diverticulosis, sometimes leading to diverticulitis. These alterations are the effects of aging on the structure or neuromuscular function of the large intestine, and several pathogenic mechanisms have been indicated:

1. Decreased colonic motility with increased transit time, which seems to be due to the decreased number of neurons, synapses, and release of acetylcholine in the myoenteric plexus associated with age
2. Increased hardness of feces, secondary to decreased fiber consumption and increased water absorption due to longer transit time
3. Increased amounts of collagen in the wall of the colon, with the consequent reduction of its elasticity

All these factors, some of which have not been experimentally demonstrated, along with others that increase intra-luminal pressure, seem to predispose the aging colon to diverticular disease. Constipation, suffered by a great number of the elderly, is strongly related to all of the above factors, although some old people also have fecal incontinence, probably due to a disturbance in the neurological control mechanisms for defecation [89–91].

Liver and Bile Function

Most studies measuring classic hepatic parameters such as serum bilirubin and serum transaminases have not found significant changes in hepatic function associated with aging, although clear reductions in hepatic blood flow and bile clearance of certain substances have been observed, together with a 30% reduction in hepatic perfusion and volume. The reason for this apparent discrepancy is that hepatic function has to diminish by over 70% before clinical changes can be observed. Some studies indicate that the liver of older rats is more susceptible to toxic injury than that of younger ones. This seems to be based on a decrease in hepatic regeneration capacity caused by a decrease in cellular proliferation and a reduced response to growth factors, such as epithelial growth factor or hepatic growth factor. Older liver seems to be more vulnerable to stress due, among other factors, to an age-related reduction in mitogen-activated protein kinase activity [93].

There seems to be an increased prevalence of cholelithiasis associated with age, caused by an increased precipitation of supersaturated bile, cholesterol and calcium bilirubinate crystallization, and alterations in gallbladder function. Some animal studies have observed a decrease in the number of

cholecystokinine receptors, although blood levels of cholecystokinine after a meal tend to increase with age, compensating for the lack of receptors.

Some studies have demonstrated an increase in gallbladder volume, incomplete emptying, and reduced response to physiological stimuli, such as food, in patients over 65 years old [94].

Hematological System

The hematological system does not show any marked decline in function during aging. Anemia is not a normal finding in older persons [95]. However, a slight increase in the prevalence of anemia, particularly in those over 75, and an age-related reduction in the ability to respond to stimulation similar to that observed in the immune response are seen. This raises the important clinical question of whether aging alters the response to injected growth factors such as erythropoietin. In the absence of co-morbidity, current evidence suggests that it is unaffected [95]; however, significant abnormalities of the hematological system may result from the combined effect of co-morbid conditions and the aging process. Anemia, when present in older persons, apart from being an independent risk for mortality over 5 years, may also lead to frailty, immobility syndrome, and falls [96].

Coagulation

Platelet count does not alter with age nor do common coagulation tests such as thrombin time, prothombrin time, activated partial thromboplastin time, and fibrinogen. There is evidence from sensitive markers of coagulation activation that background turnover of the proteins involved in the hemostatic process is increased with age [97]. The circulating concentrations of various clotting factors increase with age, including factors VII and VIII. Fibrin formation is also increased and d-dimers levels are elevated in aged patients with myocardial infarction as well as in healthy older people. These factors may contribute to the hypercoagulability observed in some aged [98].

Vitamin B_{12}, Folate, and Homocysteine

Low levels of vitamin B_{12} and folate are frequently observed in older people [99], although there is not always evidence of an accompanying macrocytosis or megaloblastic anemia. Up to 10% of apparently healthy people aged 70 may have vitamin B_{12} or folate deficiency. The most common causes of low folate levels in the elderly are alcohol abuse, drugs that interfere with folate absorption, and inadequate dietary intake. The most common cause of B_{12} deficiency is atrophic gastritis.

Although there is evidence that low vitamin B_{12} levels contribute to cognitive loss and significant neurological deficits in the elderly, there is not a clear concrete link between this and dementia at the present time. Nevertheless, levels should be measured in patients with cognitive decline or those deemed to be at high risk of deficiency or coronary artery disease.

Low levels of vitamin B_{12} or folate are accompanied by increased levels of homocysteine. There may be a relationship between coronary artery disease and low vitamin B_{12} and elevated homocysteine in older people. Homocysteine levels can be reduced by folic acid supplements.

Skin

In the epidermis, atrophic changes, hyperpigmentation of the basal membrane, and a degree of hyperkeratosis take place. In the dermis, more evident in exposed areas, there are atrophy and degeneration of the collagen, producing senile elastosis, and actinic degeneration associated with vessel dilatation and vascular damage in response to insignificant trauma, resulting in senile purpura. These changes induce sagging and wrinkling of the skin. Other functions of the skin modified by age are delay in wound healing, inmunosurveillance, and regulation of body temperature [100].

Hearing

Several structural changes are observed in the auditory system with aging that can interfere with its function. These changes include thinning of the walls of the external auditory canal, drying out of cerumen, making it more likely to become impacted, and thickening of the tympanic membrane. Within the cochlea, there are neuronal loss and loss of sensory hair cells and fibrocytes in the organ of Corti, increased rigidity of the basilar membrane, and calcification of auditory structures. Finally, within the stria, vascularis capillaries become thicker, endolymph production decreases, and there is reduced Na^+,K^+ ATPase activity. Not everyone is affected to the same degree by these degenerative changes, and at present it is not possible to precisely correlate these changes with the degree of hearing loss.

Central processing of sound is also affected by aging. For example, when competing speech stimuli are simultaneously presented to both ears, it is usual for one ear to have an advantage over the other. This difference has been shown to increase with age. It has been postulated that this difference may be due to a decrease in efficiency of transfer of auditory information between the hemispheres of the brain [1, 101].

Vision

The eye is susceptible to many age-related changes and can also be affected by chronic diseases common in older people, for example, diabetes mellitus. Distinct from pathological disease changes, many physiological changes in vision occur with age. These include impaired adaptation in dark, increased short-sightedness (presbyopia), decreased contrast sensitivity, decrease in static acuity (minimal), decrease in dynamic acuity, and decreased tear production. These functional changes are due to certain structural changes, including aggregation of proteins in the lens, decrease in photoreceptor density, loss of ganglion cells and retinal pigment epithelium, thinning of the vitreous body, concentration of collagen fibers, and thinning, yellowing, and loss of elasticity of the sclera. Cataract formation also increases with age, and age-related macular degeneration is the leading nonpreventable cause of visual impairment in the West. Currently, the mechanism for this change is unknown.

Thus, visual impairment is common in the elderly. It can greatly impact their ability to perform activities of daily living and may impair cognitive function. Therefore, it has a significant effect on social independence [1, 102, 103].

Smell

The capacity to perceive odors diminishes with age. It is not clear so far if the alterations in olfactory function are an age-related phenomenon or the result of cumulative effects of external pathogens (cumulative viral attacks, exposure to air pollution, neurodegenerative diseases, or exposure to rhino-environmental lesive agents). To explore the ability to smell, the University of Pennsylvania Smell Identification Test (UPSIT) can be helpful. From studies using UPSIT, it is evident that the age-related decline in olfaction is part of the physiological aging process [104].

Taste

This sense does not seem to be affected by intrinsic age-related changes. In accordance with this is the observation that the number and distribution of taste buds and receptors do not decrease with age. Nevertheless, as persons age, the ability to discern salty, bitter, and sour tastes decreases, perhaps confounded by other factors, i.e., the use of dentures or smoking. Another possible explanation is that taste buds are innervated by different sets of CNS. These nerves are less susceptible to agents than the delicate olfactory filaments. It is of clinical relevance to remember that complaints of loss taste often reflect the loss of flavor sensation derived from retro nasal stimulation of the receptors [105].

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References

1. Arking, R. *The Biology of Aging: Observations and Principles*, 3rd ed. Oxford: Oxford University Press, 2006.
2. Cournil, A., Kirkwood, T.B.L. If you would live long, choose your parents well. *Trends Genet*. 2001; 17:233–235.
3. Kirkwood, T.B.L. The origins of human ageing. *Phil. Trans. Roy. Soc. Lond. Ser. B*, *Biol. Sci*. 1997; 352:1765–1772.
4. Medawar, P.B. *An Unsolved Problem of Biology*. London: Lewis, 1952.
5. Williams, G.C. Pleiotropy, natural selection and the evolution of senescence. *Evolution* 1957; 11:398–411.
6. Hayflick, L., Moorhead, P.S. The limited *in vitro* lifetime of human diploid cell strains. *Exp. Cell Res*. 1961; 25:585–621.
7. Peinado, M.A., del Moral, M.L., Esteban, F.J., Martínez-Lara, E., Siles, E., Jimenez, A., Hernández-Cobo, R., Blanco, S., Rodrigo, J., Pedrosa, A. Aging and neurodegeneration: Molecular and cellular bases. *Rev. Neurol*. 2000; 31: 1054–1065.
8. Campisi, D., Dimri, G., Hara, E. Control of replicative senescence. In *Handbook of the Biology of Aging,* Schneider, E.L. and Rowe, J.W. eds.. San Diego: Academic Press. 1996, pp. 121–149.
9. Flurkey, K., Papaconstantinou, J., Miller, R.A., Harrison, D.E. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proc. Natl. Acad. Sci. USA*. 2001; 98:6736–6741.
10. Harley, C.B., Futcher, A.B., Greider, C.W. Telomeres shorten during aging of human fibroblasts. *Nature* 1990; 345:458–460.

11. Barja, G. Aging in vertebrates and the effect of caloric restriction: A mitochondrial free radical production-DNA damage mechanism? *Biol. Rev*. 2004; 79: 235–251.
12. Barja, G., Herrero, A. Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals. *FASEB J*. 2000; 14:312–318.
13. Gredilla, R., Sanz, A., López-Torres, M., Barja, G. Caloric restriction decreases mitochondrial free radical generation at complex I and lowers oxidative damage to mitochondrial DNA in the rat heart. *FASEB J*. 2001; 15:1589–1591.
14. Gredilla, R., Barja, G. Caloric restriction, aging and oxidative stress. *Endocrinology* 2005; 146:3713–3717.
15. Sanz, A., Caro, P., Barja, G. Protein restriction without strong caloric restriction decreases mitochondrial oxygen radical production and oxidative DNA damage in rat liver. *J. Bioenerg. Biomembr*. 2004; 36:545–552.
16. Sohal, R.S., Ku, H.H., Agarwal, S., Forster, M.J., Lal, H Oxidative damage, mitochondrial oxidant generation and antioxidant defenses during aging and in response to food restriction. *Mech. Ageing Dev*. 1994; 74:121–133.
17. Weindruch, R., Kayo, T., Lee, C.L., Prolla, T.A. Microfile profiling of gene expression in aging and its alteration by caloric restriction in mice. *J. Nutr*. 2001; 131:918S–923S.
18. Barja, G. The flux of free radical attack through mitochondrial DNA is related to aging rate. *Aging Clin. Exper. Res*. 2000; 12:342–355.
19. Petrini, J.H. The mammalian Mre11-Rad50-nbs1 protein complex: Integration of functions in the cellular damage response. *Am. J. Hum. Genet*. 1999; 64: 1264–1269.
20. Gredilla, R., Barja, G., López-Torres, M. Effect of short-term caloric restriction on H_2O_2 production and oxidative DNA damage in rat liver mitochondria, and location of the free radical source. *J. Bioenerg. Biomembr*. 2001; 33:279–287.
21. Pamplona, R., Portero-Otín, M., Bellmunt, M.J., Gredilla, R., Barja, G. Aging increases $N^{epsilon}$-(Carboxymethyl)lysine and caloric restriction decreases $N^{epsilon}$-(Carboxyethyl)lysine and $N^{epsilon}$-(Malondialdehyde)lysine in rat heart mitochondrial proteins. *Free Rad. Res*. 2002; 36:47–54.
22. Grimley Evans, J., Bond, J. The challenges of age research. *Age and Ageing* 1997; 26–54.
23. Kirkwood, T.B. p53 and ageing: Too much as a good thing. *Bioassays* 2002; 24:577–579.
24. Orgel, L.E. The maintenance of the accuracy of protein synthesis and its relevance to aging. *Proc. Natl. Acad. Sci. USA*, 1963; 49:5117–5521.
25. Wayne, S.J., Rhyne, R.L., Garry, P.J., Goodwin, J.S. Cell-mediated immunity as a predictor of morbidity and mortality in subjects over 60. *J. Gerontol*. 1990; 45: M45–48.
26. De la Fuente, M. Effects of antioxidants on immune system ageing. *Eur. J. Clin. Nutr*. 2002; 56:51–54
27. De la Fuente, M. The immune system as a marker of health and longevity. *Antiaging Med*. 2004; 1:31–41.
28. Guayerbas, N., Catalán, M., Victor, V.M., Miquel, J., De la Fuente, M. Relation of behaviour and macrophage function to life span in a murine model of premature immunosenescence. *Brain Behav. Res*. 2002; 134:41–48.
29. Guayerbas, N., De la Fuente, M. An impairment of phagocytic function is linked to a shorter life span in two strains of prematurely-ageing mice. *Develop. Comp. Immunol*, 2003; 27:339–350.
30. De la Fuente, M., Hernanz, A., Vallejo, M.C. The immune system in the oxidation stress conditions of ageing and hypertension. Favorable effects of antioxidants and physical exercise. *Antioxid. Redox Sign*. 2005; 7:1356–1366.
31. Victor, V.M., Rocha, M., Esplugues, J.V., De la Fuente, M. Role of free radicals in sepsis: Antioxidant therapy. *Curr. Pharm. Des*. 2005; 11:3141–3158.

32. De la Fuente, M., Baeza, I., Guayerbas, N., Puerto, M., Castillo, C., Salazar, V., Ariznavarreta, C., Tresguerres, J.A.F. Changes with ageing in several leukocyte functions of male and female rats. *Biogerontology* 2004; 5:389–400.
33. De la Fuente, M., Hernanz, A., Guayerbas, N., Puerto, M., Alvarez, P., Alvarado, C. Changes with age in peritoneal macrophage functions. Implication of leukocytes in the oxidative stress of senescence. *Cell. Mol. Biol*. 2004; 50:OL683–OL690.
34. De la Fuente, M., Medina, S. NPY and phagocytic cell functions. In *The NPY Family of Peptides in Immune Disorders*, *Inflammation*, *Angiogenesis and Cancer*, Z. Zukowska and G.Z. Feuerstein, eds. Basel/Switzerland: Birkhaüser Verlag. 2005, pp. 107–122.
35. Blalock, J.E. The immune system as the sixth sense. *J. Intern. Med*. 2005; 257:126–138.
36. Fabris, N. A neuroendocrine-immune theory of ageing. *Int. J. Neurosci*. 1990; 51:373–375.
37. 'Puerto, M., Guayerbas, N., Alvarez, P., De la Fuente, M. Modulation of neuropeptide Y and norepinephrine on several leucocyte functions in adult, old and very old mice. *J. Neuroimmunol*. 2005; 165:33–40.
38. Guayerbas, N., Puerto, M., Hernanz, A., Miquel, J., De la Fuente, M. Thiolic antioxidant supplementation of the diet reverses age-related behavioral dysfunction in prematurely ageing mice. *Pharmacol. Biochem. Behav*. 2005; 80:45–51.
39. Arce, V., Devesa, J. Hormona de crecimiento. In *Tratado de Endocrinología Básica y Clínica*. J.A.F. Tresguerres, ed. Madrid: Síntesis. 2000, pp. 337–378.
40. Rosen, T., Bengtsson, B.A. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990; 336:285–288.
41. Toogood, A.A., Shalet, S.M. Ageing and growth hormone status. In *Growth Hormone in Adults. Bailliere's Clinical Endocrinology and Metabolism,* S.M. Shalet, ed. 1998; 12(2): 281–296.
42. Cuttica, C.M., Castoldi, L., Gorrini, G.P., et al. Effects of six-month administration of rhGH to healthy elderly subjects. *Ageing* 1997; 9:193–197.
43. Nyberg, F. GH in the brain: Characteristics of specific brain targets for the hormone and their functional significance. *Front. Neuroendocrinol*. 2000; 21:330–348.
44. Vermeulen, A., Deslypere, J.P., De Merleir, K. A new look to the andropause: Altered function of the gonadotrops. *J. Steroid Biochem*. 1989; 32:163–165.
45. Schiavi, R.S., Schreiner-Engel, P., Mandeli, J., et al. Healthy aging and male sexual function. *Am. J. Psychiatry* 1990; 147:766–771.
46. Adams, M.M., Morrison, J.H. Estrogen and the ageing hippocampal synapse. *Cereb Cortex.* 2003; 13:1271–1275.
47. Groner, B. Transcription factor regulation in mammary epithelial cells. *Domest. Anim. Endocrinol*. 2002; 23:25–32.
48. Blackman, M.R. Pituitary hormones and ageing. *Endocrinol*, *Metab*, *Clin*, 1987; 16:981–994.
49. Frago, L.M., Paneda, C., Dickson, S.L., et al. Growth hormone (GH) and GH-releasing peptide-6 increase brain insulin-like growth factor-I expression and activate intracellular signaling pathways involved in neuroprotection. *Endocrinology* 2002; 143:4113–4122.
50. Donda, A., Lemarchand-Beraud, T. Aging alters the activity of 5'-deiodinase in the adenohypophysis, thyroid gland, and liver of the male rat. *Endocrinology* 1989; 124(3):1305–1309.
51. Montanini, V., Simoni, M., Chiossi, G., et al. Age-related changes in plasma dehydroepiandrosterone sulphate, cortisol, testosterone and free testosterone circulant rhythms in adult men. *Horm. Res*. 1988; 29:1–6.

52. Wilkinson, C.W., Peskind, E.R., Raskind, M.A. Decreased hipothalamic-pituitary-adrenal axis sensitivity to cortisol feedback inhibition in human ageing. *Neuroendocrinology* 1997; 65:79–90.
53. Vaag, A., Henriksen, J.E., Madsbad, S., et al. Insulin secretion, insulin action and hepatic glucose production in identical twins for non-insulin-dependent diabetes mellitus. *J. Clin. Invest*. 1995; 95:690–698.
54. Smith, H.L. The relation of the weight of the heart to the weight of the body and the weight of the heart to age. *Am. Heart J*. 1928; 4:79–93.
55. Marcomichelakis, R., Withers, R., Newman, G.B., et al. Age related changes in the thickness of the interventricular septum, the posterior left ventricular wall, and their ratio. *Int. J. Cardiol*. 1983; 4:405–415.
56. Olivetti, G., Melissari, M., Capasso, J.M., Anversa, P. Cardiomyopathy of the aging human heart. Myocite loss and reactive cellular hypertrophy. *Circ. Res*. 1991; 68:1560–1568.
57. Lakatta, E.G. Cardiovascular aging research: The next horizons. *J. Am. Geriatr. Soc*. 1999; 47:613–625.
58. Wei, J.Y., Spurgeon, H.A., Lakatta, E.G. Excitation-contraction in rat myocardium: Alterations with adult aging. *Am. J. Physiol*. 1984; 246:H784.
59. Benson, M.D. Aging, amyloid and cardiomyopathy. *N. Engl. J. Med*. 1997; 336:502–504.
60. Henry, W.L., Gardin, J.M., Ware, J.H. Echocardiographic measurements in normal subjects from infancy to old age. *Circulation* 1980; 62:1054–1061.
61. Lev, M. Aging changes in the human sinoatrial node. *J. Gerontol*. 1984; 39:1–9.
62. Lakatta, E.G. Diminished beta-adrenergic modulation of cardiovascular function in advanced age. *Cardiol. Clin*. 1986; 4:185–200.
63. Kitzman, D.W., Edwards, W.D. Age-related changes in the anatomy of the normal human heart. *J. Gerontol*. 1990; 45(2) :M33–M39.
64. Gaballa, M.A., Jacob, C.T., Raya, T.E., Liu, J., Simon, B., Goldman, S. Large artery remodeling during aging: Biaxial passive and active stiffness. *Hypertension* 1998; 32:437–443.
65. Clark, B.A., Elahi, D., Shannon, R.P., Wei, J.Y., Epstein, F.H. Influence of age and dose on the end-organ responses to atrial natriuretic peptide in humans. *Am. J. Hypertens*. 1991; 4:500–507.
66. Bristow, M.R., Minobe, W., Rasmussen, R. et al. Beta-adrenergic neuroeffector abnormalities in the failing human heart are produced by local, rather than systemic mechanisms. *J. Clin. Invest*. 1992; 89:803–815.
67. Knight, E.L., Kiely, D.K., Fish, L.C., Marcantonio, E.R., Minaker, K.L. Atrial natriuretic peptide level contributes to a model of future mortality in the oldest old. *J. Am. Geriatr. Soc*. 1998; 46:453–457.
68. Kaufman, T.M., Horton, J.W., White, J., Larson, E.B., Bruce, R.A. Health benefits of exercise in an aging society. *Arch. Intern. Med*. 1987; 147:353–356.
69. Lakatta, E.G. Changes in cardiovascular function in aging. *Eur. Heart J*. 1990; 11(Suppl C):22–29.
70. Krumpe, P.E., Knudson, R.J., Parsons, G. The aging respiratory system. *Clin. Geriatr. Med*. 1986; 1:143–176.
71. Campbell, W.J. Physiologic changes in respiratory function. In *Principles and Practice of Geriatric Surgery*, R.A. Roshenthal, W.E. Zenilmen, and M.R. Katlic, eds. New York: Springer-Verlag. 2001, pp. 396–405.
72. Age associated changes in pulmonary reserve. In *Oxford Textbook of Geriatric Medicine*, 2nd ed., J. Grimley-Evans, J. Franklin Williams, B. Lynn Beattie, J.P. Michael, and G.K. Wilcock, eds. London: Oxford University Press. 2003, pp. 483–497.
73. Renal hemodynamics in physiological states. In *Physiology of the Human Kidney*, L.G. Wesson, ed. New York: Grune and Stratton. 1969, p. 96.

74. Macías-Núñez, J.F., Cameron, J.S. The ageing kidney. In *Oxford Textbook of Clinical Nephrology*, 3rd ed., A.L. Davison, J.S. Cameron, J.P. Grünfeld, et al., eds. Oxford: Oxford University Press. 2005, pp. 73–85.
75. Lindeman, R.D. Overview: Renal physiology and pathophysiology of aging. *Am. J. Kidney Dis*. 1990; 16:275–282.
76. Rowe, J., Shock, N.W., De Fronzo, R.A. The influence of age on the water deprivation in man. *Nephron* 1976; 17:270–278.
77. Haug, H., Eggers, R. Morphometry of the human cortex cerebri and corpus striatum during aging. *Neurobiol. Aging* 1991; 12:336–338.
78. Snowden, D.A. Healthy aging and dementia: Findings from the Nun Study. *Ann. Inter. Med*. 2003, 139:450–454.
79. Snowden, D.A., Dane, L., Besson, G.L., et al. Is early natural menopause a biologic marker of health and aging? *Am. J. Public Health* 1989; 79:709–714.
80. Pedigo, N.W. Jr. Neurotransmitter receptor plasticity in aging. *Life Sci*. 1994; 55:1985–1991.
81. Grady, C.L. Age-related changes in cortical blood flow activation during perception and memory. *Ann. NY Acad. Sci*. 1996; 777:14–21.
82. Cannon, J.G. Intrinsic and extrinsic factors in muscle aging. *Ann. NY Acad. Sci*. 1998; 854:72–77.
83. Welle, S. Growth hormone and insulin like growth factor I as anabolic agents. *Curr. Opin. Clin. Nutr. Metab. Care* 1998; 1:257–262.
84. Sonntag, W.E. Hormone secretion and action in aging animals. *Rev. Biol. Res. Aging* 1987; 3:299–335.
85. Frontera, W.R., Hughes, V.A., Fielding, R.A., et al. Aging of skeletal muscle: A 12-year longitudinal study. *J. Appl. Physiol*. 200; 88:1321–1326.
86. Fiatarone, M.A., O´Neill, E.F., Ryan, N.D., et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N. Engl. J. Med*. 1994; 330:1769–1775.
87. Kevorkian, R. Physiology of aging. In *Principles and Practice of Geriatric Medicine*, 4th ed., M.S.J. Pathy, A.J. Sinclair, and J.E. Morley, eds. Chichester, UK: John Wiley and Sons. 2006, pp. 37–46.
88. Ryan, A.S., Ivey, F.M., Hurlbut, D.E., et al. Regional bone mineral density after resistive training in young and older men and women. *Scand. J. Med. Sci. Sports* 2004; 14:16–23.
89. Raner, C.K., Horowitz, M. Changes in gastrointestinal motor and sensory function associated with aging. In *Principles and Practice of Geriatric Medicine*, 4th ed., M.S.J. Pathy, A.J. Sinclair, and J.E. Morley, eds. Chichester, UK: John Wiley and Sons. 2006, pp. 357–369.
90. Orr, W.C., Chen, C.L. Aging and neural control of the GI tract: IV. Clinical and physiological aspects of gastrointestinal motility and aging. *Am. J. Physiol. Gastrointest. Liver Physiol*. 2002; 283:GI226–231.
91. Madsen, J.L., Graff, J. Effects of ageing on gastrointestinal motor function. *Age and Ageing* 2004; 33:154–159.
92. Thomas, R.P., Slogoff, M., Smith, F.W., et al. Effect of aging on the adaptive and proliferative capacity of the small bowel. *J. Gastrointest. Surg*. 2003; 7:88–95.
93. Liu, Y., Guyton, K.Z., Gorospe, M., et al. Age related decline in mitogen activated protein kinase activity in epidermal growth factor stimulated rat hepatocytes. *J. Biochem*. 1996; 271:3604–3607.
94. Afronti, J. Biliary disease in the elderly patient. *Clin. Geriatr. Med*. 1999; 15: 571–579.
95. Tran, K.H., Udden, M.M., Taffer, G.E., et al. Erythropoietin regulation of hematopoiesis is preserved in healthy elderly people. *Clin. Res*. 1993; 41:116A.
96. Izaks, G.J., Westendorp, R.G.J., Knook, D.L. The definition of anemia in older persons. *JAMA* 1999; 281:1714–1717.

97. Mari, D., Manucci, P.M., Coppola, R., et al. Hypercoagulability in centenarians: The paradox of successful aging. *Blood* 1995; 85:3144.
98. Tataru, M.C., Heinrich, J., Junker, S., et al. D-dimers in relation to the severity of arteriosclerosis in patients with stable angina pectoris after myocardial infarction. *Eur. Heart J*. 1999; 20:1493–1502.
99. Clarke, R., Evans, G., Schneede, J., et al. Vitamin B12 and folate deficiency in later life. *Age and Ageing* 2004; 33:34–41.
100. Gilchrest, B.A. Skin aging and photoaging: An overview. *J. Am. Acad. Derm.* 1989; 21:610–613.
101. Davis, A.C. The prevalence of hearing impairment and reported hearing disability among adults in Great Britain. *Int. J. Epid*. 1989; 18:911–917.
102. Tumosa, N. Disorders of the eye. In *Principles and Practice of Geriatric Medicine*, 4th ed., M.S.J. Pathy, A.J. Sinclair, and J.E. Morley, eds. Chichester, UK: John Wiley and Sons. 2006, pp. 1205–1210.
103. Buch, E.R., Young, S., Contreras-Vidal, J.L. Visuomotor adaptation in normal aging. *Learning and Memory* 2003; 55–63.
104. Ship, J.A., Weiffenbach, J.M. Age, gender, medical treatment and medication effects on smell identification. *J. Gerontol*. 1993; 48:M26–M32.
105. Deems, D.A., Doty, R.L., Settle, R.G., et al. Smell and taste disorders. A study of 750 patients from the University of Pennsylvania Smell and Taste Center. *Arch. Otolaryngology-Head and Neck Surg*. 1991; 117:519–528.

5

Physiology of the Healthy Aging Kidney

Juan-Florencio Macías-Núñez and José M. López-Novoa

Introduction

It should be remembered before any consideration that physiology refers to the normal function of organs, whereas "insufficiency" or "failure" is a pathological status. We should keep in mind that renal aging is a physiological rather than a pathological process. Therefore, to speak about the aging kidney function as a "physiological renal insufficiency" is a gross conceptual error, because the aging kidney is able to maintain the extracellular volume equilibrium in conditions of health, although its resources and ability to adapt to challenges of restriction or overload are limited. Because of this, it is necessary for health professionals caring for aged patients to be able to recognize this reduced capacity and prevent the deleterious effect of any therapeutic decision at the time of planning drug administration, fluid replacement, diuretic regime, or salt and water restriction This chapter will review some fundamentals of the normal physiology necessary to understand the changes occurring with age and provide facts to distinguish between chronic renal insufficiency (CRF) and the normal renal aging evolution. The physiology of renal acidification, calcium, phosphate, magnesium, and uric acid are dealt with in Chapter 9 together with the particulars of the normal aging kidney in the handling of these elements.

Glomerular Filtration Rate

The normal human kidney receives a blood flow of about 1200 mL/min, which, assuming a haematocrit of 45%, corresponds to 660 mL/min of plasma flow. At the same time, the glomeruli form 125 mL/min of glomerular ultrafiltrate. Thus, the filtration fraction, which is defined as the ratio of the glomerular filtration rate (GFR) to renal plasma flow, is 125/660 = 0.19. This means that 19% of the plasma entering the kidney is filtered.

Two main characteristics differentiate glomerular ultrafiltration from transcapillary exchange in other organs: [1] the glomerular filter exhibits an extraordinarily high permeability to water and small solutes; and [2] the glomerular filter is almost impermeable to proteins of the size of albumin and larger.

Glomerular filtration is a process determined by three factors: [1] the properties of both the filter and the molecules to be filtered; [2] the interactions between molecules and the filter; and [3] the balance of hydrostatic, osmotic, and colloid osmotic forces across the filter, according to Starling's law.

GFR Markers

Inulin

Inulin is an oligosaccharide that possesses all conditions required to be considered the "ideal marker" of GFR.

Inulin Clearance in the Healthy Aged Inulin is filtered at the glomerulus without restriction and practically neither secreted nor reabsorbed in the tubules. Because of that, it has been considered the goal standard method to asses GFR.

In cross-sectional studies, Davies and Shock [1] showed that inulin clearance increases from approximately 20 mL/min at birth to its peak of 120 mL/min at the age of 30 years. From them begins a slow regression of inulin clearance, reaching 65 mL/min at the age of 90 years (Figure 5.1).

Creatinine

Creatinine (2-amino-1,5-dihydro-1-methyl-4H-imidazol-4-one) has a molecular weight of 113.12 Kd. It is derived from the metabolism of creatine in skeletal muscle and from dietary meat intake. Creatinine is released into the circulation at a relatively constant rate, maintaining a stable plasma concentration.

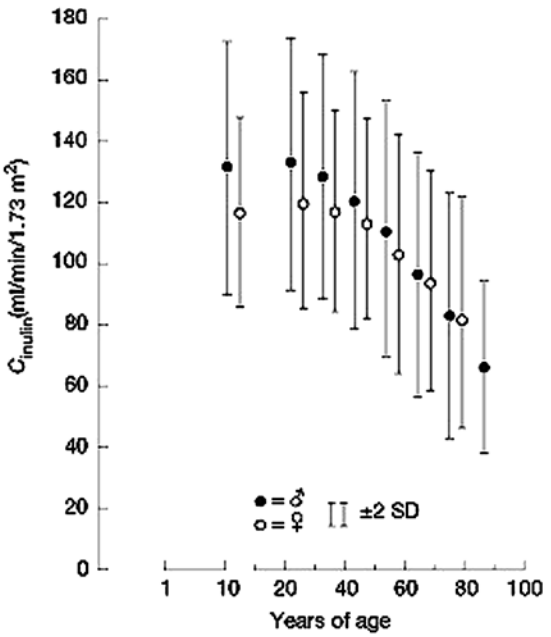

Fig. 5.1 Evolution of GFR measured as inulin clearance along with age. (*Source*: Macías-Núñez, J.F., Cameron, J.S. The ageing kidney. In *Oxford Textbook of Clinical Nephrology*, 3rd ed. A.M. Davison, J.S. Cameron, J.P. Grünfeld et al., eds. Oxford: Oxford University Press. 2005; pp. 73–85.)

Renal Handling of Creatinine Creatinine is freely filtered across the glomerulus. In many papers and books, it appears as if its tubular management and metabolism are negligible, i.e., neither reabsorbed nor secreted by the renal tubule. Nevertheless, it is known that as much as 15–30% of the creatinine present in the urine comes from tubular secretion linked to the organic cation secretory pathways in the proximal tubule [2]. Tubular reabsorption of creatinine has been shown experimentally in rats [3] and in dogs [4] at extremely low urine flow rates.

In humans, creatinine has been proven to be reabsorbed and secreted by the renal tubuli [5]. Tubular secretion of creatinine may be influenced, among other circumstances, by the status of the circulating volume. In this sense, a group of healthy subjects were submitted to severe dehydration followed by rehydration, while urine flow, inulin clearance, PAH clearance, creatinine clearance, and excretion fractions of those substances were measured. In basal conditions, creatinine clearance was 130 mL/min, decreasing to 96 mL/min during acute dehydration and increasing to 160 mL/min after rehydration. Similarly, fractional excretion of creatinine moved from 124% in basal conditions to 147% after rehydration. This is interpreted, depending on the author, as an increase in creatinine secretion, a decrease in creatinine reabsorption, or an increase in tubular secretion and a decrease in tubular reabsorption [5].

In some comparative studies of GFR using inulin and creatinine clearances, it was hypothesized that when the ratio of creatinine clearance to inulin clearance reaches 1:4, it means that about 28% of the total creatinine collected in the urine is excreted by the tubules [5]. Accordingly, these data indicate that creatinine is not a reliable marker of GFR in all possible situations.

We should remember that the healthy aged are routinely advised to reduce salt intake. That, in conjunction with the reduced renal capacity to retain sodium and the low-thirst sensation, may produce an almost "permanent" situation of low extracellular volume, borderline to dehydration/desalination (see Chapter 8). So far, research taking into account the possible effect that this common situation may play upon the tubular handling of creatinine by the renal tubule of the healthy aged and, consequently, its incidence in the calculation of GFR assessed as creatinine clearance is lacking. In this regard, we evaluate the difference in GFR among young (<65 years) and old (>65 years) healthy persons of either gender (Table 5.1). It can be seen that GFR assessed as creatinine clearance or Cr^{51}-EDTA is lower in the aged than in the young group [6]. Another observation is that the ratio of creatinine clearance to Cr^{51}-EDTA is higher than 1 in 9 out of 10 tested healthy young individuals, whereas it is 1 or lower than 1 in 5 out of 13 healthy aged individuals.

In Animal Models In rats, at low endogenous plasma levels of creatinine, the filtered creatinine is extensively reabsorbed by the renal tubule. In contrast, at elevated levels of plasma creatinine induced by exogenous infusion of creatinine, when the ratio of C_{cr} to C_{in} exceeds 1, it indicates tubular secretion [3].

Creatinine in the Newborn It has been seen that creatinine clearance in neonatal animals was lower than inulin clearance ($C_{cr}/C_{in} = 0.84$). Similarly, blood creatinine in the newborn human exceeds that seen in their mothers.

Table 5.1 GFR in Young and Old Healthy People Measured by Creatinine Clearance, Cr^{51} EDTA, and Estimated by the MDRD Formula.

YOUNG

YOUNG

Age	Sex	Blood Creatinine	Urine Creatinine	GFR CrCl	GFR Cr^{51} EDTA	Dif	RATIO	Abbreviated MDRD study equation GFR (mL/min per 1,73 m2)
14	M	0,8	70	**152,72**	**102,48**	49,52	1.49	**140,8260857**
25	M	0,9	55	**79,51**	**114,73**	-35,22	0.69	**109,2786363**
27	M	0,8	305	**102,27**	**100,34**	1,93	1.01	**123,2481063**
32	M	1	175	**125,42**	**95,3**	30,12	1.31	**92,03806905**
34	M	0,7	125	**144,69**	**108,48**	36,21	1.33	**137,208048**
38	M	0,8	45	**126,7**	**81,83**	44,87	1.54	**114,9876052**
42	F	0,7	40	**121,53**	**101,9**	19,63	1.19	**97,53356651**
46	M	0,8	138	**115,66**	**86,53**	29,13	1.33	**110,6132771**
48	M	0,8	80	**132,53**	**128,45**	4,08	1.03	**109,6617389**
52	M	0,8	185	**165,27**	**96,72**	68,55	1.70	**107,8942798**

OLD

Age	Sex	Blood Creatinine	Urine Creatinine	GFR Cr Cl	GFR Cr^{51} EDTA	Dif	RATIO	Abbreviated MDRD study equation GFR (mL/min per 1,73 m2)
68	M	0,9	118	**105,94**	**83,51**	22,43	1.26	**89,19033169**
71	F	0,8	72	**84,39**	**85,38**	-0,99	0.98	**75,15286815**
72	M	1	85	**75,14**	**89,04**	-13,9	0.84	**78,06825058**
73	F	0,7	70	**83,12**	**75,99**	7,13	1.09	**87,18046291**
73	M	0,8	120	**69,64**	**68,42**	1,22	1.01	**100,7146293**
73	F	0,9	80	**136,73**	**89,6**	47,13	1.52	**65,232865**
73	F	0,7	50	**106,48**	**107,43**	-0,95	0.99	**87,18046291**
73	F	1	70	**79,07**	**75,99**	3,08	1.04	**57,76467163**
74	M	0,9	50	**142,32**	**78,54**	63,78	1.81	**87,67243106**
78	M	1	85	**63,99**	**80,71**	-16,72	0.79	**76,80999554**
79	M	0,9	112	**89,18**	**85,61**	3,57	1.04	**86,51646951**

Notice that persons with same age, gender, and serum creatinine have different urine creatinine. However, they have the same estimated GFR estimated by MDRD formula.

According to Smith [7] and Guyton and Hall [8], there is only one physiological explanation for this finding: The tubular reabsorption that occurs in the newborn may be due to backflow of creatinine across leaky immature tubular structures.

Creatinine Clearance in the Old The normal value for the creatinine clearance oscillates between 95 ± 20 mL/min in young female and 120 ± 25 mL/min in young male healthy individuals. It is widely accepted that the GFR declines with age, regardless of the marker used to assess it. However, some studies question that the decline in GFR is either universal or inevitable. Creatinine clearance may be influenced not only by the status of the circulating volume but also by the nutritional situation. In this sense, Kimmel et al. [9] showed that elderly subjects eating more than 1 g/day of protein/kg had a creatinine clearance in the range of 90–100 mL/min/1.73m^2, while those with a lower protein intake had a lower creatinine clearance.

In the Baltimore longitudinal study, an important extended longitudinal survey in which some of the subjects were followed for more than 30 years, it was reported that in spite of a mean calculated reduction in creatinine clearance of 0.75 mL/min/year for the whole group, 92 of the 254 individuals studied showed no reduction in creatinine clearance, and a few even increased their clearance [10]. Larsson et al. [11] also found no decline in GFR in individuals between the ages of 70 and 79, although plasma creatinine increased from 91 to 96 μmol/L in women and from 100 to 107 μmol/L in men.

Using the creatinine clearance as an index of GFR, Kampmann et al. [12] and Rowe et al. [13], among others, made the same observation in cross-sectional studies: GFR declines with age. One problem at the time to interpret these studies was that they did use comparable populations. Rowe et al. [13] examined apparently healthy aged individuals in the community, while Kampmann et al. [12] studied a hospital population, excluding patients with increased plasma creatinine level, whereas Cockroft and Gault [14] used hospital patients, but this time all individuals, regardless of their renal function, were included.

An important practical point is that in spite of the observation that creatinine clearance diminishes with age, in otherwise healthy individuals there is no corresponding increase in plasma creatinine with age [13]. Thus, the normal values for plasma creatinine are substantially the same at the ages of 20 and 80 years [12, 13], indicating that the normal plasma creatinine in an aged individual often conceals a physiological reduction in GFR. This apparent paradox arises because the production of creatinine, and hence the urinary creatinine output, decreases steadily with age in relation to the decreasing muscle mass and total body weight and perhaps with the tubular management of creatinine in the healthy aged. The significance of a modestly elevated plasma creatinine in aged persons is thus even greater than in the young. As we have already commented, the possibility that a different magnitude of the tubular handling of creatinine exhibited by the healthy aged in comparison with the healthy young adult may influence the creatinine clearance in the aged has never been considered. From the above reports, it is clear that creatinine clearance is not always an accurate method to estimate GFR. Because of this, techniques other than creatinine clearance have been developed.

Formulas Used to Determine GFR

There are several formulas using plasma creatinine level together with other variables such as age, gender, body weight, and height to calculate GFR (see Table 5.2). Kampmann et al. [12], Cockroft and Gault [14], and Rowe et al. [13] have all constructed nomograms that, theoretically, allow a better estimation of GFR than plasma creatinine in clinical practice. The nomogram of Cockroft and Gault [14] is the most widely used, although it has been questioned due to the fact that it overestimates the decline in GFR, at least in persons aged over 80 years. However, Nicoll et al. [15] found a good correlation in 18 individuals aged 66–82 years between GFR calculated as the nomogram of Cockroft and Gault and the clearance of [^{99}Tc ^{m}] diethylen-etriamine penta-acetic acid (DTPA). In 1987, Keller [16] pointed out that the simplest formula to estimate the expected normal mean creatinine clearance

Table 5.2 Some Formulas to Predict GFR from Serum Creatinine.

Year	Author	Formula GGR (mL/min/1.73 m^2)
1973	Jellife	GFR = 98 - [0.8 × (age –20)/SCr × (BSA/1.73) × [0.9 if female]
1974	Kampmann	GFR = Ucre × weight × 100/Scre
1976	Rowe	GFR = 133 – 0.64 × age
1976	Cockcroft	GFR = (140 - age) × weight (× 0.85 if female)/(Scr × 72)
1987	Keller	GFR = 130 – age
1993	Walser	GFR = 7.57 × (Scre mmol/L)$^{-1}$ – 0.103 × age + 0.096 × weight$^{-6.66}$
1995	Nankivell	GFR = 6.7/Scre (mmol/L) + 0.25 × weight – 0.5 × urea - 0.01 × height^2 + 35 (25 if female)
1997	Baracskay	GFR = 1/2[100/Scre] + 88 – age
1999	MDRD	GFR = 170 × [Pcr]$^{-0.999}$ × [Age]$^{-0.175}$ × [0.762 if patient is female] × [1,180 if patient is black] × [SUN]$^{-0.170}$ × [Alb]$^{+0.318}$
2003	MDRD	GFR = 186.3 × [Scre]$^{-1.154}$ × [age]$^{-0.203}$ × [0.742 if female] × [1.142 if black]
2004	MDRD	GFR = 224 × [Scre]$^{-1.190}$ × [age]$^{-0.236}$ × 0.796 [if female] × 1.26 [in healthy]

in mL/min from 25 to 100 years of age is [130 – age (in years)]. Recently, other formulas to predict the GFR based on blood creatinine levels have been developed [17, 18] as well as several formulas developed by the Modified Diet in Renal Disease (MDRD) group [19]. It is interesting that in spite of the fact that the MDRD formula is not validated for persons aged over 70 years, patients with diabetic nephropathy, pregnant females, very ill patients, or healthy individuals, it is widely used to calculate GFR in all the above-listed circumstances. Its accuracy as a marker of chronic renal disease has recently been questioned in hypertensive patients and their siblings [20] and in healthy aged persons [21]. Although the GFR estimated with any of the formulas in Table 5.2 are indicative in general, for older persons, the individual variation obtained with any of these formulas may be considerable [22].

As Table 5.1 shows, there are differences in GFR using creatinine clearance, ^{51}Cr- EDTA clearance, and the MDRD formula. It can be seen at the bottom of the table that in two persons, both 80 years old, males, with the same blood creatinine, the GFR substantially differs depending on the used marker. Because both of them are male, with the same age and same plasma creatinine, both have the same GFR calculated with the MDRD formula (98.8 mL/min). If we use creatinine clearance instead of the MDRD formula, one of them has a GFR of 99 mL/min, whereas in the other it is only 56.3 mL/min. Interestingly enough, both have a rather comparable GFR (76 and 60) when the marker used is Cr^{51}-EDTA.

Cystatin-C

Because of the problems with changes in creatinine production and secretion, other endogenous compounds have been evaluated in an effort to provide a more accurate estimation of GFR. Perhaps the most promising is cystatin-C, a low-molecular-weight protein that is a member of the cystatin superfamily of cysteine protease inhibitors. It is mainly removed from the extracellular fluid by the kidneys, practically freely filtered in the glomeruli, and completely

absorbed and rapidly broken down by the proximal tubular cells. Cystatin-C is produced by all nucleated cells, and its rate of production is relatively constant. It is not clear whether or not it could be altered by inflammatory conditions or any other factors.

In a 2004 study, the serum level of cystatin-C in healthy individuals was measured as a normal value range of 0.7 to 1.57 and a reference interval of 1.05 ± 0.18 μg/mL (mean ± 1.96 SD); 95% confidence limits for the upper references limit were 1.4 μg/mL [23].

A recent meta-analysis concluded that serum cystatin-C level is a superior marker of renal function compared with serum creatinine level. However, some factors could affect cystatin-C serum levels, such as older age, male gender, being overweight, having greater height, currently smoking cigarettes, and higher serum C-reactive protein (CRP), all of them associated with an increase in serum cystatin-C [24].

Cystatin-C in Mild Renal Insufficiency Shemesh et al. [25] have published a well-designed study comparing the sensitivity of the serum creatinine and cystatin-C concentrations for early detection of mild renal insufficiency [25]. These authors conclude that when GFR was determined by the clearance of radioactive iothalamate, serum cystatin-C levels began to increase when the GFR was 88 mL/min/1.73 m^2, while the serum creatinine concentration increased when the GFR was only 75 mL/min/1.73 m^2.

Cystatin-C in the Old Cystatin-C is a promising alternative that might be in the works. Whether measurement of cystatin-C levels will become available clinically and, if so, improve patient care is at present unknown.

In an unpublished study (undertaken by Professor José Luis Rodicio) of 224 patients, of whom 108 were male, 116 female, and 118 over 60 years of age, the GFR was calculated in patients with a creatinine clearance higher and lower than 60 mL/min using four different methods: serum creatinine, serum cystatin-C, the MDRD, and the Cockcroft–Gault formula. The results showed that for patients who had a creatinine clearance between 60 and 90 mL/min, serum creatinine had higher specificity (0.943 vs. 0.700) than cystatin-C for ruling out renal insufficiency. However, in the group with creatinine clearance lower than 60 mL/min, the serum cystatin-C had a higher sensitivity (0.954 vs. 0.862) than the serum creatinine for detecting renal failure. Nevertheless, neither method was as accurate as the MDRD or the Cockcroft–Gault formula for detecting renal insufficency (courtesy of Dr. José Luis Rodicio, Universidad Complutense, Madrid).

Independently from its accuracy as a marker of GFR, cystatin-C has been postulated as a predictor for morbidity and mortality in the aged. One study performed in Sweden with a follow-up period of 4 years, including 792 men over the age of 77 years, has associated the increase in serum cystatin-C with a higher morbidity and mortality in the elderly population [26].

Tubular Handling of Sodium, Potassium, Chloride, Urea, and Water

Proximal Tubule

This segment is heterogeneous with respect to function and structure exhibiting some differential characteristics along its length.

Convoluted Proximal Segment

Sodium (Na^+) The majority of glucose, amino acids, small proteins, and bicarbonate and 60–80% of the filtered Na^+ and water are reabsorbed in this segment (Figure 5.2). The first movement in the transport of Na^+ from the tubular lumen (luminal or apical) to peritubular vessels is a passive movement of Na^+ from the lumen to the interior (cytosol) of the tubular cell. Once in the cell, part of it is transported to the paracellular and basal space. Because the interior of the cell is electronegative and Na^+ concentration is lower in the cytosol that outside the cell, additional force is needed to transport Na^+ from the cell to the paracellular and peritubular vessels. The energy for this transport is provided by a sodium ATP-ase-dependent pump (Na^+-K^+-ATP-ase) located in the basolateral membrane. This pump, which extrudes Na^+ from the cell, generates an electrochemical gradient that promotes the passive entry of Na^+

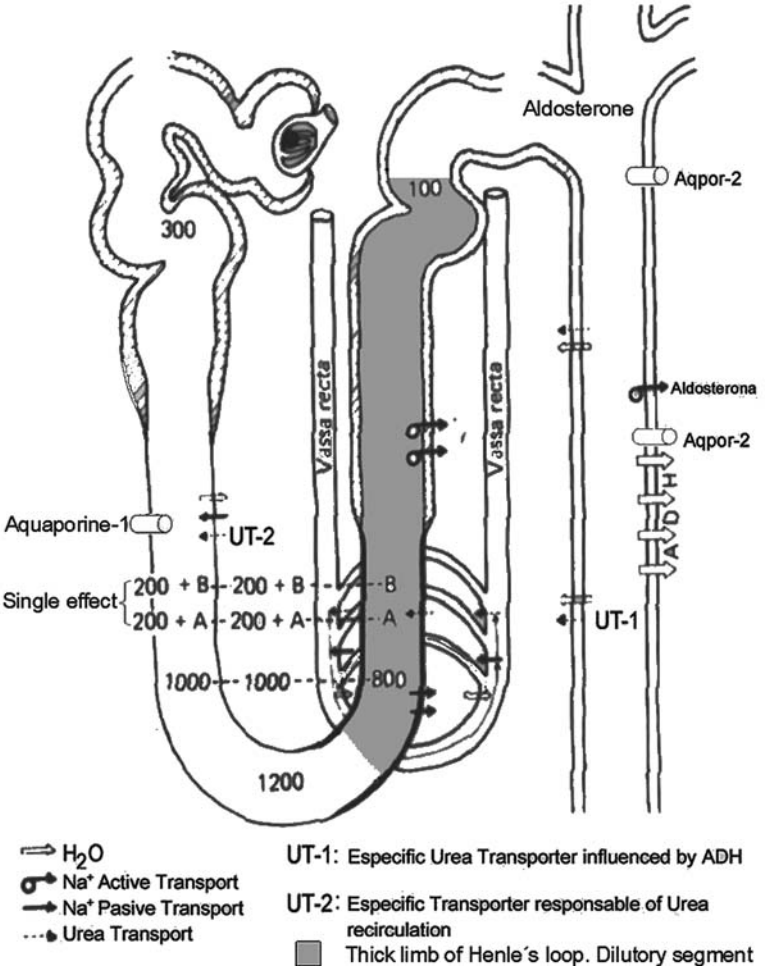

Fig. 5.2 Representation of the nephron. The shadowed area corresponds to the ascending limb of the loop of Henle, whose ability to reabsorb sodium diminishes with age.

from the tubular fluid to the interior of the cell. This movement of Na^+ shares some co-transporters that reabsorb glucose, peptides, and amino acids.

Water Approximately 60–80% of water filtered by the glomerulus is reabsorbed passively in the proximal tubule following sodium gradient; water follows sodium to the paracellular space. As water accumulates in the basolateral space, the increase of hydrostatic pressure releases water to the peritubular space. Approximately 60–80% of the water filtered by the glomerulus is reabsorbed passively in the proximal tubule following Na^+ transport. The back flow of water and Na, from the basolateral space to the tubular lumen, depends on the degree of extracellular volume expansion. Water and electrolytes enter the peritubular vessels because of the oncotic pressure of the intravascular proteins. Transport in the proximal tubule is isoosmotic, which means that there is no concentration or dilution of the tubular fluid in this segment, i.e., the tubule synchronically reabsorbs 300 mOsm of solutes and 1 L of water (Figure 5.2).

Proximal Tubular Function in the Healthy Aged

The handling of Na^+, water, and bicarbonate does not differ from the young in functional clearances studies performed in healthy aged, as there are no differences in tubular clearance of lithium (a well-known marker of proximal tubular competence) [27].

The Thin Descending Limb of the Loop of Henle

The characteristic of membrane permeability differs from the previous segments of the proximal tubule (Figure 5.2). The descending limb is highly permeable to water due to the presence of the channel water aquaporine but quite impermeable to sodium, potassium, and chloride. Although there is some passage of these electrolytes in both directions (from the lumen to the peritubular space, and vice versa), it is of limited quantitative importance. This segment is also permeable to urea (from the interstitium to the tubular lumen) by the action of the urea transporter UT2. As tubular fluid flows downward in the descending limb, the osmolarity of the fluid equilibrates with the osmolarity of the interstitium, which increases from the entrance (300 mOsm/L) to the tip of the papilla (1200 mOsm/L). Due to this movement of water across the membrane of the cells of the descending limb, the tubular fluid is becoming increasingly more concentrated, reaching 1200 mOsm/L at the tip of the descending limb, i.e., in the bend of the loop.

The Thin Ascending Limb of the Loop of Henle

The thin ascending limb is impermeable to water and highly permeable to Na^+ and urea due to the presence of UT2 channels. In the thin ascending limb, sodium moves passively from the lumen to the interstitium by means of a concentration gradient, resulting in a net Na reabsorption.

The Thick Ascending Limb of the Loop of Henles

The characteristics of permeability of the membrane of the tubular cells change again in this segment, which is impermeable to water and urea but permeable to the transport of Na^+ from the lumen to the interstitium. As a result, as fluid ascends in the thick ascending limb, electrolytes pass to the interstitium, but water remains in the lumen. In this segment, the transport of

Na^+ is carried out by the electrochemical gradient generated by the Na^+-K^+-ATP-ase pump located at the basolateral membrane of the tubular cell and the co-transporter Na^+-K^+-$2Cl^-$ (NKCC2 protein) located in the brush border of the tubular cells, codified by the SCL 12A1 gene located at 5q15-21. The activity of this co-transporter is regulated by the levels of the antidiuretic hormone (ADH). As in this nephron segment, solutes are reabsorbed without water reabsorption, in a process called "free water formation." The ascending limb and the early part of the distal convoluted tubule have been named the *diluting segment* (Figure 5.2). The osmolarity of the tubular fluid when it leaves the thick ascending limb of the loop of Henle approaches 100 mOsm. The competence of this segment can be ascertained by means of the free water clearance measurement under conditions of ADH functional blockade [28–30].

The Thick Ascending Limb of the Loop of Henle in the Healthy Aged

The capacity to reabsorb Na^+ is less effective in persons aged over 65 years than in the young in this particular segment of the nephron (Figure 5.2, shadowed area).

Distal Convoluted Tubule

The early part of the distal convoluted tubule exhibits similar properties of those of the thick ascending limb of the loop of Henle, and tubular fluid therefore continues to be diluted. The late part of the distal convoluted tubule is less permeable to Na^+. In this segment, Na^+ is actively reabsorbed against an electrochemical and concentration gradient by action of the Na^+-K^+-ATP-ase located at the basolateral membrane of the tubular cell and favored by aldosterone. In any case, the total capacity for sodium reabsorption in this segment is limited.

Collecting Duct

The amount of Na^+ reabsorbed in the collecting duct is approximately 3% of the total present in the glomerular filtrate [31]. However, this almost negligible quantity is of paramount importance in the context of body balance, as this segment adjusts the amount of Na^+ reabsorbed or excreted depending on the physiological requirements of salt or the status of the extracellular volume. The collecting duct is also responsible for the final control of the urinary Na^+ excretion. The gradient against which Na^+ is reabsorbed in this segment is very high. An active transport is therefore required, which is modulated by aldosterone. The reabsorption of Na^+ mediated by aldosterone favors the active secretion of K^+ and H^+. The movement of these three elements is coupled and modulated by the intracellular concentration of these elements. An electrogenic active reabsorption of Na^+ that generates a lumen negative electrical potential responsible for active reabsorption of Cl^-has been observed.

Aldosterone exerts its effect by combination with intracellular receptors promoting, in the nucleus, mRNA synthesis of the Na^+ pump subunits. This way is rather slow. Aldosterone may also increase Na^+ reabsorption by increasing the number of Na^+ transporters at the luminal membrane of the tubular cells. As a result, the amount of Na^+ entering the cell from the luminal

fluid greatens, increasing the intracellular concentration of Na^+ that ought to be expelled from the cell to the interstitium by means of Na^+-K^+-ATP-ase.

The synthesis of aldosterone by the adrenal cortex is controlled by angiotensin II, plasma concentration of Na^+ and K^+, and ACTH. Extracellular volume depletion—induced by negative balance of Na^+—and renal sympathetic stimulation stimulate renin secretion with the subsequent increase in angiotensin II and aldosterone synthesis. The level of plasma Na^+ has little influence on aldosterone synthesis. To the contrary, the cells secreting aldosterone in the adrenal cortex are very sensitive to the concentration of K^+ in the extracellular fluid. The increase in potassium intake increases extracellular potassium, which directly stimulates the production of aldosterone in the adrenal cortex. The increase in plasma aldosterone concentration stimulates K^+ secretion in the cortical collecting duct. This is the way to eliminate the excess of potassium and prevent hyperkalemia.

Aldosterone in the Healthy Aged

It has been proven that aged persons on an unrestricted diet for salt and water have lower levels of aldosterone plasma with a lower response to salt restriction and walking than that seen in healthy young persons [29, 32]. The most common clinical consequence is the development of hyperkalemia in aged patients treated with antialdosterone agents**.**

Water

In the final part of the distal convoluted tubule (connecting segment) and the collecting duct, the final and fine adjustment of urinary osmolarity mediated by the antidiuretic hormone (ADH) takes place. Water is passively reabsorbed under the influence of ADH and transepithelial osmotic gradient. ADH is secreted by the hypophysis in response to changes in plasma osmolarity. High plasma osmolarity strongly stimulates AHD secretion, whereas a low plasma osmolarity attenuates it. The urinary elimination of water is controlled by the circulating levels of ADH. The distal tubule is practically impermeable to water. The permeability of the collecting tubule is low in the absence of ADH and high when ADH is present. ADH turns the collecting tubule permeable to water by insertion of water-permeable channels (aquaporin 2) (Figure 5.2). The reabsorption of ClNa in the absence of ADH is responsible for a hypoosmotic tubular fluid with respect to plasma and, consequently, the elimination of a great quantity of water via urine with a urinary osmolarity lower than plasma. In the presence of ADH, this segment of the tubule turns permeable with water, allowing the passage of water from the tubular fluid to the inner medulla and renal papilla. As the osmolarity in the renal interstitium and papilla is much higher than that of the tubular fluid, a considerable amount of water passes from the tubular fluid to the interstitium. As a result, the elimination of water diminishes in the urine, but the amount of solutes in the tubular fluid remains unaltered. Consequently, the urine becomes concentrated. Thus, the osmolarity of the urine is higher than that observed in the plasma.

Urea

Urea is reabsorbed in the proximal straight and convoluted tubules before the thin descending limb of the loop of Henle. At this point, we should remember that the thick ascending limb of the loop, the distal tubule, and the cortical

segment of the collecting ducts are impermeable to urea. To the contrary, the medullar segment of the collecting duct is permeable to urea. For this reason, the intratubular concentration of urea increases along the distal tubule and the medullar collecting duct. When tubular fluid reaches the medullar segment of the collecting duct, the concentration of urea in the tubular fluid is very high. This gradient of concentration is the reason why urea passively diffuses from the tubular fluid to the medullar interstitium. This passive movement is possible by the insertion of two specifics transporters of urea (UT1 and UT2) (Figure 5.2) Both have been identified and cloned [33]. UT1, modulated by aldosterone, is responsible for urea transport in the medullar segment of the collecting tubules. The expression of ADH induces the insertion of more UT1. UT2 is not influenced by ADH, but it is responsible for urea recirculation because it regulates the entry of urea accumulated in the interstitium to the descending and ascending limbs of the loop of Henle. The high concentration of urea in the interstitium or the trapping of urea is possible due to medullar recirculation and the countercurrent exchange mechanism.

Renal Handling of Urea by the Healthy Aging Kidney

The healthy aged exhibits a higher fractional excretion of urea than the young controls (Table 5.3). The reason is not clear so far, but perhaps an alteration in urea transporter may account for this observation.

Urinary Concentration and Dilution

The same mechanisms are responsible for both the concentration and the dilution of urine: the generation and the maintenance of the hyperosmolar interstitium. It is necessary to remember that two different processes are involved. The first starts in the ascending limb of the loop of Henle. This process makes the interstitium hypertonic due to both the transport of electrolytes from the lumen to the interstitium and the water impermeability of this segment.

Two phenomena, the single effect and the countercurrent multiplier, are involved in the generation of the interstitial hyperosmolarity and the countercurrent exchanger (Figure 5.2). The second process does not participate in the generation of hyperosmolar interstitium, but it is responsible for its maintenance. In other words, it protects the interstitial medullary gradient against the dilution by the water coming from the distal tubule and collecting ducts. The special configuration of the vasa recta is able to maintain the recirculation movement and is the mechanism responsible for the hyperosmolar maintenance in the interstitium.

Table 5.3 Key Parameters of Renal Function in Healthy Adults, Old Individuals (>65 Years), and Very Old Individuals (>80 Years).

	Adult	Old	Very Old
Hb (g/L)	14.7	14.1	14.3
Epo (U/L)	14	13	17
Creatinine clearance (mL/min)	111	71	47
FENa (%)	0.5	1.3	1.4
FEU (%)	30	59	61

FENa = fractional excretion of sodium.
FEU = fractional excretion of urea.

The permeability of the collecting duct controlled by ADH must also be considered when taking the final urinary concentration into account. As we have seen, in the ascending limb of the loop, Na^+ and Cl^- are transported from the lumen to the interstitium, while water remains in the interior of the tubular lumen. Therefore, the fluid that moves upwards in the ascending limb gradually becomes more and more diluted. The interstitium remains hypertonic due to the processes already mentioned. The concentration gradient that can be achieved at any point along the ascending limb of Henle´s loop is 200 mOsm/L lower than its horizontal level of the interstitium and the descending limb of the loop. This is known as the "single effect" (Figure 5.2). This means that, regardless, the osmolarity of the tubular fluid at any point of the ascending limb must be 200 mOsm lower than the osmolarity existing at the same horizontal level of the interstitium and the descending limb of Henle's loop. As we have commented, the osmolarity at the bend of Henle's loop is 1200. Thus, if we consider that intratubular osmolarity at another point beyond the bend is 800, its corresponding horizontal level in the interstitium and descending limb is 1000. In successive steps, the intratubular content is diluted. All in all, although the gradient that can be achieved at any point is 200, the osmolarity is considerably higher at the end of the descending limb, 1200 mOsm/L, than when fluid enters it, 300 mOsm/L. The 200 mOsm/L-gradient results are multiplied due to the countercurrent flow. This system is known as a *countercurrent multiplier*. It is obvious that solutes cannot indefinitely accumulate in the medullary interstitium and must be adequately removed and replaced in order to preserve the interstitial hyperosmolarity.

The removal of solutes and water is accomplished via the special structural arrangement of the hairpin of Henle's loop and of the medullary vessels (vasa recta) (Figure 5.2). This particular anatomical arrangement is able to maintain urea, electrolytes, and water moving in a circular fashion "as if they were in a circular movement" from the ascending part of the vasa recta to its descending limb. In this way, a small amount of urea leaves the recirculation movement "circle" only to be immediately restored by passage of urea from the tubular fluid of the collecting ducts to the interstitium via UT2. Blood enters the capillary loop with an osmolarity of 300 mOsm/L. Water passively diffuses from the vessels to the hypertonic interstitium, and solutes move from the interstitium to the vascular lumen. As blood moves deeper into the medulla, its osmolarity gradually increases. In the ascending limb of the vasa recta, the overall movement of water and solutes changes. Solutes diffuse into the medullary interstitium and water flows into the vessels, diluting the intravascular content. When blood leaves the descending limb, its osmolarity is about 325 mOsm/L. The vasae rectae do not only interchange with interstitial tissue, but the descending and the ascending vasae rectae interchange with each other as well. In this manner, a diffusion gradient is established and the ascending vasa recta gives up solutes to the descending limb. The movement of both water and solutes across the vasae rectae is passive in nature. These vessels do not generate the hyperosmolar medullary gradient: Their action is limited to preserve the medullary interstitial gradient. The mechanisms just mentioned are known as a countercurrent exchanger.

By means of these coordinated events, the vasae rectae prevent the organism from unnecessary spillage of water and electrolytes. These vessels combine to provide adequate conditions to incorporate and remove the excessive

interstitial amount of solutes and water that could interfere with the steady-state interstitial gradient. Any alteration in the renal blood flow to the medullae, either excessive or defective impairment of a functional of the loop of Henle, interstitial fibrosis, or the presence of any factor interfering with the normal steady-state gradient will substantially alter the urinary concentration or dilution, or both functions.

Concentration and Dilution by the Healthy Aging Kidney

It is a universal observation that the kidney of normal aged persons has a reduced capacity to maximally concentrate the urine [34] by 5% with every 10 years of age [35], from a maximum urinary specific gravity of 1030 at 40 years of age to 1023 at 89 years of age. Rowe et al. [13] found a mean maximum osmolality of 1109 mOsm/kg in individuals aged 20–39 years, with a minimum urine flow rate of 0.49 ± 0.03 mL/min, 1051 mOsm/kg in 40–59-year-olds, and only 882 mOsm/kg in those aged 60–79 years, in whom the minimum urinary flow rate was more than double that of the young, at 1.03 mL/min. The data of Lindeman [10] are similar to those of Kirkland et al. [36], which noted that even healthy individuals aged 60–80 years showed a greater excretion of water, sodium, and potassium during the night than younger controls, with a high prevalence of complaints of nocturia. This alteration in circadian rhythm does not depend upon the inability to concentrate the urine alone, but upon the defects in sodium handling and aldosterone secretion and sensitivity already mentioned.

The origin of the decreased concentration ability is also complex; the small differences between the amount of liquid consumed by young and elderly individuals cannot completely explain the differences in solutes and urinary elimination observed during water deprivation. The diminution of the concentrating ability has been related to the decrement in GFR that occurs with age, with induction of an osmotic diuresis in the remaining nephrons [37]. Despite this, some data do not reveal a close relationship between the reduction in the GFR and the capacity to concentrate urine in elderly persons [13]. The relative increase in medullary blood flow noted above could contribute to the impairment of renal concentration capacity [38, 39].

Nevertheless, data supporting this suggestion are not available. Inappropriately low ADH does not seem to be a factor in the genesis of the defect, as already discussed. The defect in NaCl reabsorption in the ascending limb of Henle's loop, which is the basic mechanism for the operation of the countercurrent concentration mechanism, may be an important factor for the decrease in the capacity to concentrate urine seen in aged individuals; this is also discussed above.

Urine Dilution Ability in the Aged

Only a few reports deal with the capacity of the aging kidney to dilute urine, but generally it has been found to be decreased [40]. Lindeman [10] and Dontas et al. [34] found a minimum urine concentration of 92 mOsm/kg in elderly individuals, compared with 52 mOsm/kg in the young. Maximum free water clearance (C H_2O) was also reduced in elderly individuals, from 16.2 to 5.9 mL/min. This is probably mainly dependent upon the reduced GFR, but the C H_2O/GFR was also somewhat reduced in the older participants (9.1 vs. 10.2%). Again, the functional impairment of the diluting segment of the

thick ascending limb described above seems to account for the remainder of the diminution in the capacity to dilute urine observed in aged persons [28].

Potassium

Measurements of total exchangeable body potassium by various isotopic dilution methods agree that total body potassium is 15% lower in elderly than in young people [41,42], but administration of extra potassium does not raise the body potassium [43]. The reasons for these differences are not altogether clear: Muscle mass is a major site for potassium storage, and it is diminished in the aged. Studies of red cell potassium exchange as a surrogate for muscle cell membrane activity have given conflicting results and may not be relevant to muscle.

Although small amounts of K^+ are lost each day in stool (5 to 10 mmol) and sweat (0 to 10 mmol), the kidney plays the major role in the maintenance of K^+ balance, appropriately varying K^+ secretion with changes in dietary intake (the normal range is 40 to 120 meq/day). The primary event in urinary K^+ excretion is the secretion of K^+ from the tubular cell into the lumen in the distal nephron, particularly in the principal cells in the cortical collecting tubule and in the cells in the adjacent connecting segment and outer medullary collecting tubule.

If the clearance of K^+ is compared to that of inulin, it may help us understand the tubular handling of K^+. For instance, a fall in the CK^+/C_{in} ratio indicates that K^+ has been removed from the tubular fluid (or reabsorbed), and an elevation in the ratio indicates that K^+ has been secreted to the tubular fluid. Almost all of the filtered K^+ is reabsorbed in the proximal tubule and loop of Henle, so that less than 10% of the filtered load is delivered to the early distal tubule ($CK^+/C_{in} < 0.1$). Proximal K^+ transport appears to passively follow that of Na^+ and water, whereas reabsorption in the thick ascending limb of the loop of Henle is mediated by the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane.

In comparison to these reabsorptive processes, K^+ is secreted by the connecting segment, the principal cells in the cortical and outer medullary collecting, and the papillary (or inner medullary) collecting duct. Secretion in these segments can be modified according to physiological needs and is generally responsible for most of the urinary K^+ excretion. Distal K^+ secretion is regulated by aldosterone, which in turn is regulated by extracellular volume through angiotensin II levels and by plasma K^+ concentration.

Distal secretion can be partially counteracted by K^+ reabsorption by the intercalated cells in the cortical and outer medullary collecting tubules. This process may be mediated by an active H^+-K^+-ATPase pump in the luminal membrane, which results in both H^+ secretion and K^+ reabsorption. The activity of this pump is increased with K^+ depletion and is reduced with K^+ loading. The former adaptation is probably responsible for the observation that net K^+ reabsorption, not secretion, appropriately occurs in the distal nephron with K^+ depletion. Selective inhibition of the H^+-K^+-ATPase pump in the setting of K^+ depletion abolishes distal K^+ reabsorption.

The K^+ reabsorbed in the thick ascending limb initially enters the medullary interstitium. Some of this K^+ is then secreted into either the S3 segment of the late proximal tubule or the thin descending limb of the loop of Henle; this extra

K^+ can be reabsorbed when it enters the outer medulla. Thus, K^+ is recycled within the medulla, resulting in the attainment of a relatively high concentration in the interstitium. The physiological function of this phenomenon is uncertain. It is possible, for example, that K^+ accumulation in the interstitium promotes K^+ excretion by minimizing the degree of passive back leak out of the collecting tubular lumen (where the highest urine K^+ concentrations are attained). The high interstitial K^+ concentration also may contribute to K^+ excretion by a second mechanism, by diminishing the gradient for passive K^+ reabsorption via the Na^+-K^+-$2Cl^-$ carrier in the loop of Henle. This process is similar to NH_4^+ recycling between the loop of Henle and the medullary collecting tubule that promotes net NH_4^+ excretion.

Potassium Handling by the Healthy Aged Kidney

Despite the spontaneous ingestion of lower amounts of potassium by the elderly (<60 mmol/24 h) because of a diet low in meat, fruit, and vegetables, plasma potassium concentrations in aged persons do not differ from those of the younger population [44]. However, when diuretics are taken, the elderly develop hypokalemia much more rapidly and frequently than do the young. As might be expected from intake, the basal urinary excretion of potassium is also lower than in the young, although the FE K is actually increased as a result of diminished GFR [45]. Biswas and Mulkerrin [46] obtained similar results and postulated that physiological changes such as low aldosterone and the tendency to retain K associated with age would tend to predispose the elderly to hyperkalemia, especially if angiotensin-converting enzyme inhibitors are used [47].

Chloride

Chloride is reabsorbed with sodium throughout the nephron. As a result, the rate of excretion of these ions is usually similar, and measurement of the urine Cl^- excretion generally adds little to the information obtained from the more routinely measured urine Na^+ excretion.

However, as many as 30% of hypovolemic patients have more than a 15-mEq/L difference between the urine Na^+ and Cl^- concentrations. This is due to the excretion of Na^+ with another anion (such as HCO_3^- or carbenicillin) or to the excretion of Cl^- with another cation (such as NH_4^+ in metabolic acidosis). Thus, it may be helpful to measure the urine Cl^- concentration in a patient who seems to be volume-depleted, although Cl^- urinary output is lower than that of Na^+.

Renal apical chloride-base exchangers are essential to electrolyte and acid-base homeostasis. Different functional isoforms of apical anion exchangers have been identified in the kidney proximal tubule and cortical collecting duct. Included among these are the following: chloride-formate, chloride-oxalate, and chloride-hydroxyl exchangers in the proximal tubule; and chloride-bicarbonate exchanger in the cortical collecting duct. Chloride-formate exchange, which was first identified in the kidney proximal tubule, works in parallel with the apical sodium-hydrogen exchanger and is thought to reabsorb the bulk of luminal chloride. Despite numerous studies, the molecular identities of apical chloride-base exchangers have remained unknown.

Table 5.4 Demographic and Renal Function Parameters in Old Healthy Patients and in Patients with Chronic Renal Failure.

		Mean (± SD)	P
Nap (mmol/L)	0	143 ± 2	0.001
	1	137 ± 5	
Kp (mmol/L)	0	4.4 ± 0.4	N/S
	1	4.2 ± 0.5	
Gp (mg/dL)	0	90 ± 10	N/S
	1	86 ± 10	
Up (mg/dL)	0	32 ± 6	<0.001
	1	75 ± 34	
Cp (mg/dL)	0	0.9 ± 0.1	0.007
	1	2.3 ± 1.6	
Nau (mmol/L)	0	120 ± 47	<0.001
	1	57 ± 27	
Ku (mmol/L)	0	32 ± 18	N/S
	1	31 ± 14	
Uu (mg/dL)	0	1298 ± 618	N/S
	1	1215 ± 531	
Cu (mg/dL)	0	66 ± 39	0.01
	1	57 ± 26	
OP (mOsm/L)	0	295 ± 52	N/S
	1	92 ± 8	
OU (mOsm/L)	0	514 ± 180	0.01
	1	382 ± 141	
Vu (mL/day)	0	1520 ± 789	N/S
	1	1858 ± 822	
TTKG	0	4 ± 2	0.004
	1	6 ± 2	
CrCl (mL/min)	0	62 ± 23	0.003
	1	39 ± 22	
Age (years)	0	76 ± 9	0.04
	1	66 ± 16	
Height (m)	0	1.57 ± 0.0	0.001
	1	81.66 ± 0.08	
Weight (kg)	0	67.7 ± 16	N/S
	1	69.5 ± 12	

Old group: 0
Chronic Renal Failure: 1
Nap = plasma sodium.
Kp = plasma potassium.
Gp =plasma glucose.
Up = plasma urea.
Cp = plasma creatinine.
Nau = urine sodium.
Ku = urine potassium.
Uu = urine urea.
Cu = urine creatinine.
Vu = urine volume.
CrCl = creatinine clearance.
TTKG = transtubular potassium concentration gradient.
Adapted from Musso, C., Liakopoulos, V., De Miguel, R., et al. *Int. Urol. Nephrol.* 2006; 38:387–390.

Chloride Handling by the Healthy Aged Kidney

Studies specifically addressing the segmental tubular handling of Cl^- in healthy aged persons are lacking. We have found that Cl^-, in basal conditions and after volume expansion, parallels Na^+, as described earlier in this chapter [29].

In conclusion, in this chapter we have seen that the healthy aging kidney has some functions comparable to that in the healthy young individual. Proximal functions do not differ, in the absence of restriction or overload, from those of the adult. Some others such as creatinine clearance is lower in the healthy aged than in the young (Table 5.3), although it does not mean that aged persons with a GFR lower than 60 mL/min, calculated as creatinine clearance, have chronic renal failure, as can be seen in Table 5.3, in which erythropoietin levels do not differ among the young, old, and very old in spite of statistically lower GFR among groups of young, old, and very old healthy individuals [48]. Other functions such as the renal management of urea or the handling of Na by the thick ascending limb of the loop of Henle and the segments where aldosterone works are less efficient in the aged than in the young. Finally, we can see the differences between some daily biochemical parameters in healthy aged people and in patients with renal failure (Table 5.4) [49].

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References

1. Davies, D.F., Shock, N.W. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J. Clin. Invest*. 1950; 29:490–507.
2. Berglund, F. Urinary excretion patterns for substances with simultaneous secretion and reabsorption by active transport. *Acta Physiol. Scand*. 1961; 52:276–290.
3. Namnun, P., Insogna, K., Baggish, D., Hayslett, J.P. Evidence for bidirectional net movement of creatinine in the rat kidney. *Am. J. Physiol*. 1983; 224:F719–F723.
4. Lee, K.E., Behrendt, G., Kaczmarczyk, G., Mohnhaupt, R., Reindhart, H.W. Estimation of glomerular filtration rate in conscious dogs following a bolus of creatinine. *Pflügers Arch*. 1983; 396:176–178.
5. Sjostrom, P.A., Odlind, B.G., Wolgast, M. Extensive tubular secretion and reabsorption of creatinine in humans. *Scand. J. Urol. Nephrol*. 1988; 22(2): 129–131.
6. Macías-Núñez, J.F., Garcia Iglesias, C., Tabernero Romo, J., Bondia, A., Rodriguez Commes, J.L., Corbacho, L., Martin, M., De Pablo, F., De Castro, S. Estudio del filtrado glomerular en viejos sanos. *Rev. Esp. Geriatr. Gerontol*. 1981; 16(2):113–124.
7. Smith, H.W. *The Kidney*, *Structure and Function in Health and Disease*. New York: Oxford University Press. 1957; pp. 39–63, 182–194.
8. Guyton, A.G., Hall, J.E. *Textbook of Medical Physiology*. Philadelphia: WB Saunders. 1996; p. 348.
9. Kimmel, P.L., Lew, S.Q., Bosch, J.P. Nutrition, ageing and GFR: Is age-associated decline inevitable? *Nephrol.*, *Dial.*, *Transplant*. 1996; 11:85–87.
10. Lindeman, R.D. Overview: Renal physiology and pathophysiology of aging. *Am. J. Kidney Dis*. 1990; 16:275–282.

11. Larsson, M., Jagenburg, R., Landahl, S. Renal function in an elderly population. *Scand. J. Clin. Lab. Invest*. 1986; 46:593–598.
12. Kampmann, J., Siersbaek-Nielsen, K., Kristensen, K., Molholm-Hansen, J. Rapid evaluation of creatinine clearance. *Acta Med. Scand*. 1974; 196:517–520.
13. Rowe, J.W., Shock, N., De Fronzo, R.A. The influence of age on the renal response to water deprivation in man. *Nephron* 1976; 17:270–278.
14. Cockroft, D.W., Gault, M.N. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31–41.
15. Nicholl, S.R., et al. Assessment of creatinine clearance in healthy subjects over 65 years of age. *Nephron* 1991; 59:621–625.
16. Keller, F. Kidney function and age (letter). *Nephrol.*, *Dial.*, *Transplant*. 1087; 2:382.
17. Nankivell, B.J., Gruenwald, S.M., Allen, R.D., Chapman, J.R. Predicting glomerular filtration rate after kidney transplantation. *Transplant*. 1995; 59: 1683–1689.
18. Baracskay, K., Jarjoura, D., Cugino, A., et al. Geriatric renal function: Estimating glomerular filtration in an ambulatory elderly population. *Clin. Nephrol*. 1997; 47:222–228.
19. Levey, A.S., Bosch, J.P., Lewis, J.B., Greene, T., Rogers, N., Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann. Intern. Med*. 1999; 130:461–470.
20. Rule, A.D., Jacobsen, S.J., Schwartz, G.L., Mosley, T.H., Scott, C.G., Kardia, S.L., Boerwinkle, E., Turner, S.T. A comparison of serum creatinine-based methods for identifying chronic kidney diseases in hypertensive individuals and their siblings. *A.J.H*. 2006; 19:608–661.
21. Musso, C., Macías-Núñez, J.F., Oreopoulos, D.G. The aged kidney and the chronically aged one. *Ann. Intern. Med*. Oct. 4, 2006 (letter, in press).
22. Durakovic, Z. Creatinine clearance in the elderly: A comparison of direct measurement and calculation from serum creatinine. *Nephron* 1986; 44:66–69.
23. Xu, X., Zou, J., Ding, X., Xin, D., Ren, Y. Clinical value of serum cystatin-C by Elisa for estimation of glomerular filtration rate. *J. Clin. Lab. Anal*. 2004; 18(2):61–64.
24. Knigt, E.L., Verhave, J.C., Spiegelman, D., Hillege, H., De Zeeuw, D., Curham, G.C., De Jong, P.E. Factors influencing serum cystatin-C levels other than renal function and the impact on renal function measurement. *Kidney Int*. 2004; 65:1416–1421.
25. Shemesh, O., Golbetz, H., Kriss, J.P., Myers, B.D. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int*. 1985; 28(5):830–838.
26. Larsson, A., Helmersson, J., Hansson, L.O., Basu, S. Increased serum cystatin-C is associated with increased mortality in elderly men. *Scand. J. Clin. Invest*. 2005; 65(4):301–305.
27. De Santo, N., Anastasio, P., Coppola, S., Barba, G., Jadanza, A., Capasso, G. Age-related changes in renal reserve and renal tubular function in healthy humans. *Child Nephrol. Urol*. 1991; 11:33–40.
28. Macías-Núñez, J.F., et al. Renal handling of sodium in old people: A functional study. *Age and Ageing* 1978; 7:178–181.
29. Macías-Núñez, J.F., Cameron, J.S. The ageing kidney. In *Oxford Textbook of Clinical Nephrology*, 3rd ed. A.M. Davison, J.S. Cameron, J.P. Grünfeld et al., eds. Oxford: Oxford University Press. 2005; pp. 73–85.
30. Musso, C., López-Novoa, J.M., Macías-Núñez, J.F. Handling of water and sodium by the senescent kidney. Interpretation of a clearance technique for functional study. *Rev. Esp. Ger*. 2005; 40(2):114–119.
31. Burg, M.B. The renal handling of sodium chloride. In *The Kidney*, B.M. Brenner and F.C. Rector, eds. Oxford: Saunders. 1976; pp. 272–298.

32. Refoyo, A., Macías-Núñez, J.F. The maintenance of sodium in healthy aged. *Geriatr. Nephrol. Urol*. 1991; 1:65–68.
33. You, G., Smith, C.P., Kanay, Y., et al. Cloning and expression of the vasopressin-regulated urea transporter. *Nature* 1993; 365–844.
34. Dontas, A.S., Marketos, S., Papanayioutou, P. Mechanisms of renal tubular defects in old age. *Postgraduate Med. J*. 1972; 48:295–303.
35. Lewis, W.H., Alving, A.S. Changes with age in the renal function of adult men. Clearance of urea, amount of urea nitrogen in the blood, concentrating ability of kidneys. *Am. J. Physiol*. 1938; 123:505–515.
36. Kirkland, J.L., Lye, M., Levy, D.W., Banerjee, A.K. Patterns of urine flow and electrolyte secretion in healthy elderly people. *Br. Med. J*. 1985; 285:1665–1667.
37. Kleeman, C.R. Water metabolism. In *Clinical Disorders of Fluid and Electrolyte Balance*, M.H. Maxwell and C.R. Kleeman, eds. New York: McGraw-Hill. 1972; p. 697.
38. Takazakura, E., Sawabu, N., Handa, A., Takada, A., Shinada, A., Takeuchi, J. Intrarenal vascular change with age and disease. *Kidney Int*. 1972; 2:224–230.
39. Hollenberg, N.K., Adams, D.F., Solomon, H.S., Rashid, A., Abrams, H.L., Merrill, J.P. Senescence and the renal vasculature in normal man. *Circ. Res*. 1974; 34:309–316.
40. Crowe, M.J., Forsling, M.L., Philips, P.A., Ledinghan, J.G., Smith, R.F. Altered water excretion in healthy elderly men. *Age and Ageing* 1987; 16:285–293.
41. Hiraide, K. Alterations in electrolytes with aging. *Nihon Univ. J. Med*. 1981; 23:21–31.
42. Lye, M. Distribution of body potassium in healthy elderly subjects. *Gerontology* 1981; 27:286.
43. Kromhout, D., Broberg, U., Carlmark, B., Karlsson, S., Nissel, O., Reizenstein, P. Potassium depletion and ageing. *Comprehensive Therapeutics* 1977; 3:32–37.
44. Burini, R., Da Silva, C.A., Ribeiro, M.A.C., Campana, A.D. Concentraçao de sodio e de potassio no soro e plasma de individuos normais. Influencia da idade, do sexo e do sistema de colheita do sangue sobre os resultados. *Revista de Hospitale Clinico da Facultad do Medicina de Saõ Paulo* 1973; 28:9–14.
45. Macías-Núñez, J.F., García-Iglesias, C., Tabernero-Romo, J.M., Rodríguez-Commes, J.L., Corbacho-Becerra, L., Sanchez-Tomero, J.A. Renal management of sodium under indomethacin and aldosterone in the elderly. *Age and Ageing* 1980; 9:165–172.
46. Biswas, K., Mulkerrin, E.C. Potassium homoeostasis in the elderly. *Quar. J. Med*. 1997; 90:487–492.
47. Rodriguez-Puyol, D. The aging kidney. *Kidney Int*. 1998; 54:2247–2265.
48. Musso, C.G., Musso, C.A., Joseph, H., De Miguel, R., Rendo, P., Gonzalez, E., Algranati, L., dos Ramos Farias, E. Plasma erythropoietin levels in the oldest old. *Int. Urol. Nephrol*. 2004; 36(2):259–262.
49. Musso, C., Liakopoulos, V., De Miguel, R., Imperiali, N., Algranati, L. Transtubular potassium concentration gradient: Comparison between healthy old people and chronic renal failure patients. *Int. Urol. Nephrol*. 2006; 38:387–390.

6

The Mechanisms of Age-Associated Glomerular Sclerosis

José M. López-Novoa

Introduction

From middle age onward, GFR declines in most individuals as a consequence of alterations in various parts of the kidney. Usually, the age-dependent reduction in GFR progresses slowly, and function remains sufficient enough to maintain hydro-electrolyte homeostasis. However, if other diseases such as hypertension or diabetes are present, the aging kidney becomes more vulnerable to failure than the kidney in young individuals. In addition, the aging kidney is more susceptible to drug toxicity than that in young people due to alterations in renal handling of drugs and their metabolites and in the balance between vasoconstrictor and vasodilator influences [1]. However, the results of the Baltimore Longitudinal Study have demonstrated that the age-dependent fall in GFR is not inevitable [2]. Thus, age-related changes in renal function have to be separated into normal aging, on the one hand, and an increased incidence of specific renal diseases, on the other hand. In any case, the frequency of chronic kidney disease is increased in the otherwise healthy, aging population, and glomerulosclerosis is one major cause of age-associated renal dysfunction [3]. Thus, the main purpose of this chapter is to study the characteristics of glomerular sclerosis in the aging kidney as well as to define the possible mechanisms that lead to this rather specific renal injury.

Age-Dependent Glomerular Injury

Age-related glomerular lesions have been described as chronic nephritis, glomerulonephrosis, and most often as chronic progressive nephrosis, the term proposed by Gray [4]. Today, the most accepted term is age-associated glomerulosclerosis, as it is very similar to glomerular sclerosis induced by other pathological processes. Briefly summarized, age-related glomerular sclerosis is characterized by the following alterations: The glomerular basement membrane undergoes progressive folding and then thickening. Eventually, the folded and thickened glomerular basement membrane condenses into hyaline material with collapse of the glomerular tuft. Glomerular capillary tuft is simplified with the formation of free anastomoses between a reduced number of capillary loops. Dilatation of the afferent

arteriole near the hilum is frequently observed at this stage. Degeneration of cortical glomeruli results in atrophy of the afferent and efferent arterioles, with eventual global sclerosis. A different pattern of change predominates in the juxtamedullary area. In these units, sclerosis of the glomerular tuft is accompanied by the formation of a direct channel between the afferent and efferent arterioles, resulting in the *arteriolae rectae verae*, or aglomerular arterioles [5] (see Chapter 3). These aglomerular arterioles are rarely found in kidneys from healthy young persons; their frequency increases both in aging kidneys and in kidneys of patients with intrinsic renal disease [5].

Other alterations frequently observed in the glomeruli include enlargement of the whole glomerulus, expansion of the mesangial domain, accumulation of extracellular matrix, fusion of the capillary tuft with Bowman's capsule, occlusion of glomerular capillaries, and, ultimately, destruction of the whole glomerulus. Glomerular sclerosis appears in the kidney in a focal and segmental way [6].

The incidence of sclerotic glomeruli increases with advancing age. Before the age of 40, sclerotic glomeruli constitute fewer than 5% of the total number of glomeruli. With increasing age, the incidence of glomerular sclerosis increases to nearly 40% of the total glomerular population by the eighth decade [7]. Accordingly, diminished glomerular lobulation and glomerular loss contribute to a reduction of the surface area available for filtration and thus to the observed age-related decline in glomerular filtration rate [8].

Mechanisms of the Age-Dependent Glomerular Sclerosis

Many factors have been involved in the pathogenesis of age-dependent glomerulosclerosis glomerulopathy. We will study some of them independently, but most probably, age-dependent gomerulosclerosis results from the confluence of several of these factors, some of which are strongly related.

Decreased Nephron Number

There is general agreement that the number of nephrons decreases with age, whereas the size of the remaining glomeruli increases as a consequence of glomerular hypertrophy [8, 9]. However, at least in rats, the impact of aging on nephron number differs according to strains. In Sprague–Dawley rats, the number of functional glomeruli falls significantly with aging, accompanied by the appearance of glomerulosclerosis [10]. In contrast, female Fischer 344 rats and female and male WAGIRij rats, which are free of age-dependent renal injury, exhibit a constant number of glomeruli up to 30 months of age [11]. Furthermore, glomerular number is unchanged in ddY/SLC female mice between 30 and 90 weeks, which corresponds to the mean survival of the colony [12]. Thus, it seems likely that the number of nephrons does not inevitably decrease with age in rodents but is related to degenerative nephropathy.

The decrease in the number of functioning nephrons leads to compensatory mechanisms in the remaining nephrons (glomerular hypertension, hyperfiltration, hypertrophy), which increase their vulnerability to any further challenge; and a proteinuric glomerular disease leads, by one way or another,

to tubulointerstitial inflammation and fibrosis, accounting for the further deterioration of renal function.

Glomerular Capillary Hypertension

Glomerular hypertension derives from pre-glomerular vasodilatation, which allows delivery of a greater fraction of the renal perfusion pressure to the glomerular capillaries, and it has been implicated in age-dependent glomerular damage [13]. Elevation in glomerular pressure has been closely associated with the development of glomerular sclerosis in several experimental models of hypertension. Anderson et al. [14] reported that intraglomerular pressure was increased in normotensive Munich–Wistar rats at 2 years of age, primarily as a result of a decline in arteriolar resistance. Similarly, Zhang and co-workers [15] and Fujihara et al. [16] observed an increase in intraglomerular pressure of 6–7 mmHg in old compared with young-adult normotensive Sprague–Dawley rats. In both of these studies, morphological examination revealed significant glomerular injury in the kidneys of older rats at the time of micropuncture study. Glomerular hypertension precedes glomerular sclerosis in the spontaneously hypertensive rat [17]. The mechanisms by which glomerular capillary hypertension induces glomerular damage are complex, but at least two different mechanisms have been well studied, and they seem to play a major role in glomerular sclerosis: increased glomerular cell stretch and increased transcapillary filtration (hyperfiltration), both of which are deeply related. Both mechanisms will be analyzed later.

However, glomerular capillary hypertension cannot be the only mechanism involved in age-dependent glomerular sclerosis, as glomerular blood pressure does not invariably increase in aging and, at least in some cases, structural damage precedes the increase in intraglomerular blood pressure, as demonstrated in male Munich–Wistar rats [18], in male MWF/ZTM rats, a rat strain that exhibits accelerated kidney disease in the absence of increased intraglomerular blood pressure [19], and in spontaneously hypertensive rats [20]. Furthermore, Reckelhoff et al. [10] reported that intraglomerular pressure was not increased in 20- to 22-month-old Sprague–Dawley rats, despite the presence of glomerular sclerosis. These authors concluded that glomerular hypertension alone did not account for age-associated glomerular injury. Komatsu et al. [21] assessed glomerular hemodynamics in 73-week-old SHR, a time when significant glomerular injury was already present. They observed an average increase in glomerular pressure of only 4 mmHg compared with similarly aged WKY rats. From the above described data, we cannot determine whether glomerular hypertension was the cause or a consequence of glomerulosclerosis.

Glomerular Cell Stretch

Increased glomerular capillary pressure or an increased change in intraglomerular pressure in each cardiac cycle induces an increased physical deformation of the glomerular cells (mechanical stretch). Endothelial cells exposed to physical stretch *in vitro* may augment their production of prostacyclin, which either directly or by stimulation of other hormones or autacoids may potentiate renal damage [22]. Tension or stress could also directly damage endothelial cells, resulting in platelet activation, a process that has

a pathogenic role in the glomerular damage of renal ablation. In addition, increased tension could conceivably alter the interaction of endothelial or epithelial cells with the basement membrane. Damage to the capillary wall and its increased permeability to protein could result in mesangial accumulation of protein and ultimately in glomerular sclerosis.

Located in the center of the glomerular lobule, mesangial cells extend cytoplasmic projections that attach to the peripheral basement membrane at the points where it deflects from its pericapillary course and at pericapillary areas. In the presence of capillary hypertension, pressure-induced glomerular expansion causes an outward displacement of these anchoring points caused by distending capillaries and mesangium, resulting in intense mesangial cell stretch. Mesangial cell stretch leads to a profound change in synthesis and catabolism of extracellular matrix components by the mesangial cells, resulting in its accumulation in the mesangial area, which is a characteristic of mesangial sclerosis [23]. Cyclic stretch of mesangial cells induces the overexpression of the cytokine-transforming growth factor-β1 (TGF-β1) and the upregulation of its specific receptors in these cells [24]. TGF-β1 plays a major role in increasing the synthesis and reducing the degradation of collagen, fibronectin, and other components of the extracellular matrix. TGF-β1 has been found to be overexpressed in the glomeruli of aging rats [25].

Hyperfiltration and Protein Overload

Hyperfiltration and the strongly related phenomenon of increased protein filtration through the glomerular basal membrane and the consequent tubular protein overload have been extensively studied as a cause of glomerular and tubule-interstitial damage as a consequence of diabetes, hypertension, or reduced nephron number [13, 20, 26, 27].

Systemic Hypertension

There is almost a general agreement that systemic hypertension worsens glomerular injury [13, 26], and it is likely that this is based on the subsequent increase in glomerular blood pressure, which, in turn, will exacerbate the underlying development of age-dependent glomerular damage [27]. As reported in Chapter 11, arterial blood pressure is generally increased in the aged, and it has been demonstrated that hypertension accelerates renal dysfunction in aging people [28]. In addition, control of blood pressure in aging people leads to a significant decrease in glomerular damage. Thus, increased arterial blood pressure can play a major role in the genesis of age-related glomerular sclerosis.

Glomerular Hypertrophy

Glomerular tuft hypertrophy is another risk factor for development of glomerular injury, via increased intramural tension leading to physical disruption of glomerular integrity [22]. The mechanism by which increased glomerular volume causes glomerular damage is through an increase in tension within the glomerulus as predicted by the Laplace relationship, whereby tension equals $\Delta p \cdots r$, where Δp is the pressure across the wall of a sphere and r is its radius. Thus, increases in the size of a glomerulus, even at constant

transmural pressure, would result in an increase in tension. Glomerular volume does increase with aging, and there is multiple evidence that this glomerular hypertrophy is related to age-dependent glomerular sclerosis [29]. Furthermore, maneuvers such as castration that inhibit glomerular hypertrophy in male Wistar rats also inhibit glomerular injury and subsequent proteinuria [30]. However, glomerular injury and glomerular hypertrophy can be dissociated in some cases. Thus, whereas both glomerular hypertension and glomerular hypertrophy will cause glomerular injury, age-dependent glomerulopathy can develop in the absence of these hemodynamic risk factors, as occurs with the glomerular damage observed in the Munich–Wistar rat [18].

The mechanisms of glomerular hypertrophy in aging are not completely understood. However, because the total number of glomerular cells was not increased and there was no obvious mesangial matrix expansion in early postmenopausal mice, an increase in the size of individual glomerular cells may be a main contributor [31]. An aging phenotype has also been found in the mesangial cells of Fischer 344 rats that is related with an increased oxidative stress [32]. This mechanism will be discussed later in this chapter.

Mesangial Matrix Expansion

Mesangial cell expansion and extracellular matrix accumulation play a primary pathogenic role in some forms of glomerular injury, and increased matrix accumulation is seen in most aging rats and precedes the appearance of focal sclerosis [33]. In the Wistar rat, mesangial cell expansion and extracellular matrix accumulation, which seem to play a primary pathogenic role in some forms of glomerular injury, have been observed in aging males but not in females and correlate with the degree of glomerular injury [34]. To the contrary, age-related mesangial matrix expansion is greater in female than in male WAGIRij rats and is not associated with any glomeruloselerosis [35]. In the Wistar–Lou strain, mesangial matrix and mesangial cellularity are barely modified with age, and no glomerular injury develops in very old rats of either gender [36]. From these studies, it appears that mesangial expansion is not necessarily associated with glomerulosclerosis but the development of glomerulosclerosis is usually preceded by mesangial expansion, especially in males.

Sex Hormones

Gender is an important determinant of the rate at which chronic progressive nephrosis appears. In many strains of rats and in humans, renal disease occurs earlier in life and to a more severe extent in males than in females [37]. In the Wistar rat, mesangial cell expansion and extracellular matrix accumulation, which seem to play a primary pathogenic role in some forms of glomerular injury, have been observed in aging males but not in females and correlate with the degree of glomerular injury [34]. The greater susceptibility of the old male of most strains to develop glomerular sclerosis may be related to androgens, which can increase the synthesis of extracellular matrix material [38]. In addition, after gonadal ablation, administration of testosterone amplifies compensatory glomerular growth in uninephrectomized male and female rats [39]. The greater susceptibility of old males to glomerular sclerosis can also be due to the absence of estrogens. A major role for

estrogens in protecting the kidney from damage derives from the studies of Maric et al. [39] reporting in female Dahl salt-sensitive rats maintained on a low-salt diet that the severity of glomerulosclerosis and cortical tubulointerstitial fibrosis in aging animals was augmented with ovariectomy and attenuated with estradiol. In the old animals, ovariectomy was also associated with increased deposition and expression of laminin and increased expression of TGF-beta. Estradiol replacement opposed these effects [39]. Thus, it can be concluded that estradiol is renoprotective in the aging Dahl salt-sensitive rat by attenuating extracellular matrix deposition. Furthermore, estrogens also inhibit extracellular matrix synthesis by mesangial cells [40]. In addition to increased synthesis, reduced rates of degradation will also cause accumulation of mesangial matrix products. For instance, the activity of a glomerular metalloprotease responsible for degradation of mesangial matrix products is low in intact old male Munich–Wistar rats that exhibit glomerular injury, but elevated in females and castrated rats of both sexes, which are protected from damage [41]. Ovariectomy in Dahl salt-sensitive rats, with increased renal damage, also decreased the activity of cortical metalloprotease-9 [39].

In view of these findings, and because castration of the male is protective, it seems that the presence of the androgens, or the absence of ovarian hormones, promotes age-dependent glomerular damage.

Accumulation of Advanced Glycation End Products

The accumulation of advanced glycation end products (AGE) within the glomeruli has also been proposed as a major cause of renal lesions in aging rats. AGE accumulate in the kidney of senescent rats, increase the synthesis of extracellular matrix, and expand the glomerular mesangium [42]. Chronic administration of the AGE inhibitor aminoguanidine to female Sprague–Dawley rats from 6 to 24 months of age reduces the accumulation of AGE in the kidney and the incidence of glomerulosclerosis and nephron loss [43]. Similarly, administration of aminoguanidine in male WAGIRij rats from 24 to 30 months reduces mesangial expansion without causing a change in the age-related renal hypertrophy. Because aminoguanidine has a number of other actions, however, including preferential inhibition of the inducible nitric oxide synthase, the mechanism by which aminoguanidine protects the aging kidney from injury is still unclear.

Food Intake and the Environment

Some strains of rats in which body weight continues to increase after young adulthood, such as Sprague–Dawley and Fisher 344 rats, develop glomerular sclerosis early in life, and by 24 months of age exhibit severe renal disease. However, rat strains that remain small even when fed *ad libitum,* such as the Wistar, Long–Evans, and Brown–Norway strains, are less susceptible to glomerular sclerosis [44]. These observations led to the hypothesis that age-related renal lesions could be linked to overfeeding and that control of nutrition might protect the senescent kidney from disease. It has been reported that a low-protein diet was protective and that restriction of food was the most effective method of preventing glomerular sclerosis [45]. The striking effect of food restriction on the prevention of renal disease in aging rats

prompted investigators to test whether this was due to restriction of one element of the diet or to calorie restriction per se. Restriction of dietary salt has little effect on the progression of glomerular sclerosis. Restriction of dietary fat and dietary substitution of polyunsaturated fatty acids are protective in various models of underlying renal disease, and a deranged plasma lipid profile may contribute to age-dependent glomerulosclerosis in the female analbuminemic rat [46]. However, there is little direct evidence that lipid restriction protects against kidney aging. In contrast, reducing the animal protein content of the diet delays the appearance of renal lesions. Restriction of calories, however, is more powerful than any other dietary manipulation in preserving renal structure in senescent rodents. Not only does this retard the onset of chronic progressive nephrosis, but it completely prevents the development of renal failure in the oldest animals [47]. The conclusion we can obtain today is that the total amount of food ingested by the animal during its life is a determinant of the extent of renal damage. The mechanism of the beneficial effect of food restriction is not certain, although reduced generation of free radicals and protein glycation could be involved. As we explain later, increased oxidants and formation of AGE, both of which accumulate in aging, have been implicated in glomerular injury by enhancing extracellular matrix expression.

The environment may also play a role in the development of chronic progressive nephrosis. Maintenance of animals in a pathogen-free environment throughout their lives lowers the incidence of renal disease in *ad libitum-fed* animals, although this is not as efficient as food restriction [48]. Overall, these experiments indicate that the severe chronic progressive nephrosis described in old rats is related more to disease than to true aging processes. It is clear that renal disease in aging rodents is not an obligatory event. This analysis prompted investigators to combine conditions known to minimize renal failure in their development of experimental models of kidney aging free of renal disease. Strains of rats were selected that remained lean even when fed *ad libitum* and that were resistant to chronic progressive nephrosis. The rats were maintained under pathogen-free conditions and fed a diet in which animal proteins were substituted with vegetable and fish proteins and that contained a moderate amount of calories. By combining these optimal conditions, it has been possible to produce extremely old rats that are free of chronic progressive nephrosis [49].

Increased Oxidative Stress

There is a general agreement that increased oxidative stress plays a major role in tissue aging (see Chapter 4). Supporting this hypothesis, the glomerular synthesis of oxygen peroxide and superoxide anion is higher in 18-month-old rats than in 3-month-old young-adult animals [50]. However, the antioxidant capacity also increases with age, perhaps as a compensatory mechanism. Nevertheless, the final balance is an increase in oxidative stress, as reflected by an increase in lipid peroxidation. In addition, increased oxidative stress seems also to be involved in the TGF-β1 overexpression and the subsequent increase in extracellular matrix protein synthesis. Thus, hydrogen peroxide is able to stimulate the synthesis of TGF-β1 and collagen in cultured mesangial cells [51]. In addition, chronic antioxidant administration in aging rats prevented

the overexpression of TGF-β1 and collagen in these animals [52]. Thus, it is possible to suggest that the increased oxidative stress in the aging kidney plays a major role in the TGF-β1 overexpression observed in glomeruli from aging animals and in the subsequent increase in extracellular matrix component synthesis and deposition.

However, the reason for increased oxidative stress in the aging glomeruli remains unresolved. It is possible now to suggest that telomere shortening could play a role in this misbalance between oxidative stress and antioxidant enzymes. Telomere shortening has been reported in the aging kidney [53]. Telomere shortening above a critical length could result in increased oxidative stress and, in turn, oxidative stress can accelerate telomere shortening [54] (see Chapter 7).

Renin-Angiotensin System

Substantial reductions in plasma renin activity (PRA) have been reported in a number of species including humans, and possible clinical consequences of this reduction in the elderly have been recently reviewed [55]. In the rat, a decline in PRA occurs in both sexes in association with a fall in renal renin content and a reduction in renin synthesis in individual juxtaglomerular apparatuses [56]. A fall in PRA precedes glomerulosclerosis in susceptible animals and also occurs in rat strains protected from chronic progressive nephrosis, although severe glomerular pathology is associated with the lowest values of PRA [57]. This unusual association of reduced PRA with increasing kidney damage may reflect loss of individual juxtaglomerular apparatuses secondary to loss of nephrons during injury. In aging spontaneously hypertensive rats, reduced renal activity of the renin-angiotensin system leads to arteriolar vasodilatation and glomerular hypertension that may contribute to the subsequent appearance of glomerular sclerosis and progressive renal failure in these rats [17].

The role of the renin-angiotensin system in the development of age-dependent kidney damage has also been assessed by studying the effect of chronic ACEI on aging processes (see Chapter 12). Treatment of normotensive mice from birth to 24 months results in increased survival and a decrease in the incidence of glomerulosclerosis [58]. Chronic ACEI protects against glomerulosclerosis and reduced proteinuria and lowers blood pressure in aging male Munich–Wistar rats treated from 3 to 30 months of age [14]. Administration of ACEI from birth in the male WAGIRij rat also lowers blood pressure, renal vascular resistance, proteinuria, and expansion of the mesangial matrix, without influencing glomerular volume, renal blood flow, or GFR [59]. In any case, chronic ACEI administration does not prevent the age-associated glomerulosclerosis, but delays its appearance.

Endothelial Factors

Endothelin

Endothelial factors are reviewed in Chapter 7. In regard to glomerulus, endothelin (ET) is an extremely potent vasoconstrictor synthesized by vascular endothelial cells that is normally present in extremely low concentrations in the plasma. In terms of the aging kidney, there is little information about the activity of endothelin in the aging kidney, although infusion of ET produces

an exaggerated fall in renal plasma flow in late middle-aged Sprague–Dawley rats [60]. Inhibition of endogenous ET with the mixed receptor antagonist Bosentan has no renal hemodynamic effect in young or old conscious male Sprague–Dawley rats [61]. A line of transgenic mice overexpressing the ET-1 gene under the direction of its own promoter exhibited two- to fourfold increases in the ET-1 levels measured in the plasma, heart, kidney, and aorta. There were no apparent histological abnormalities in the visceral organs of young transgenic mice, nor was their blood pressure elevated. However, aged transgenic mice showed renal damage characterized by interstitial fibrosis, renal cysts, glomerulosclerosis, and narrowing of arterioles. These pathological changes were accompanied by decreased creatinine clearance, elevated urinary protein excretion, and salt-dependent hypertension. It thus appears that mild, chronic overproduction of ET-1 triggers damaging changes in the kidney [62]. Recently it has been described that in senescent animals, renal medullary ET-3 content increased 3.4-fold compared with adults, whereas aging did not affect ET-3 levels in the cortex. Local NO bioavailability, determined by NO metabolite tissue measurements, decreased in the cortex only. ET receptor binding capacity—predominantly due to ETB receptor binding—was lower in the medulla than in the cortex. Aging had no effect on ET-1 binding capacity or ET receptor distribution, whereas with advanced age gene expression of both receptors decreased. In conclusion, aging causes distinctive expressional changes of the renal endothelin system in otherwise healthy rats. The pronounced increase of endothelin-3 in the renal medulla is associated with preservation of local NO metabolite levels, whereas these changes were not observed in the cortex [63].

Eicosanoids

It is well established that in aging there is a widespread reduction in prostacyclin (PGI2) synthesis throughout the vascular endothelium, including the kidney of the old rat as reflected by an elevation of the ratio of thromboxane to prostacyclin in the urine, glomeruli, and inner and outer medulla [64]. This shift away from production of the vasodilatory prostaglandins puts the older kidney at risk in any vasoconstricted state and may be responsible, in part, for the sensitivity of the kidney of the old rat to ischemic and toxic insults [1]. In addition, the aging kidney reacts to adrenergic stimulation with a more pronounced and prolonged vasoconstriction than the young kidney, which is probably caused by a defect in prostaglandin modulation of endothelin activity. Autoregulation of GFR is maintained at the expense of increased intraglomerular pressure, and this could cause glomerular sclerosis, as described earlier.

Nitric Oxide

Nitric oxide (NO) plays a major physiological role in the maintenance of peripheral and renal vascular tone. With aging, the peripheral vasculature has a diminished ability to produce NO and may also exhibit an impaired vascular response to administered nitrodilators [65]. Data supporting the notion that total NO production falls with age could reflect a fall in NO synthesis in the vasculature, perhaps due to reduced NO synthase (NOS), reduced substrate (L-arginine) availability, increased breakdown of NO by oxidants, or the presence of circulating inhibitors of NO synthesis such as asymmetric dimethylarginine. This compound is cleared by the kidney,

resulting in increased levels in renal impairment, at levels of renal dysfunction that are common in aging patients [66]. Generalized NO deficiency may also contribute to age-dependent kidney damage.

Taken together, it is likely that age-dependent declines in NO generation contribute to age-dependent kidney damage [67].

Conclusion

Glomerular sclerosis in the aging kidney is a complex and multifactorial process in which many different factors are involved. Figure 6.1 displays an inclusive and personal scheme that tries to include as many of the factors as possible that have been involved to date in renal aging. There is no doubt that in each case an individual factor or group of factors can have more weight than others. Another major concern of this scheme is that most of the factors

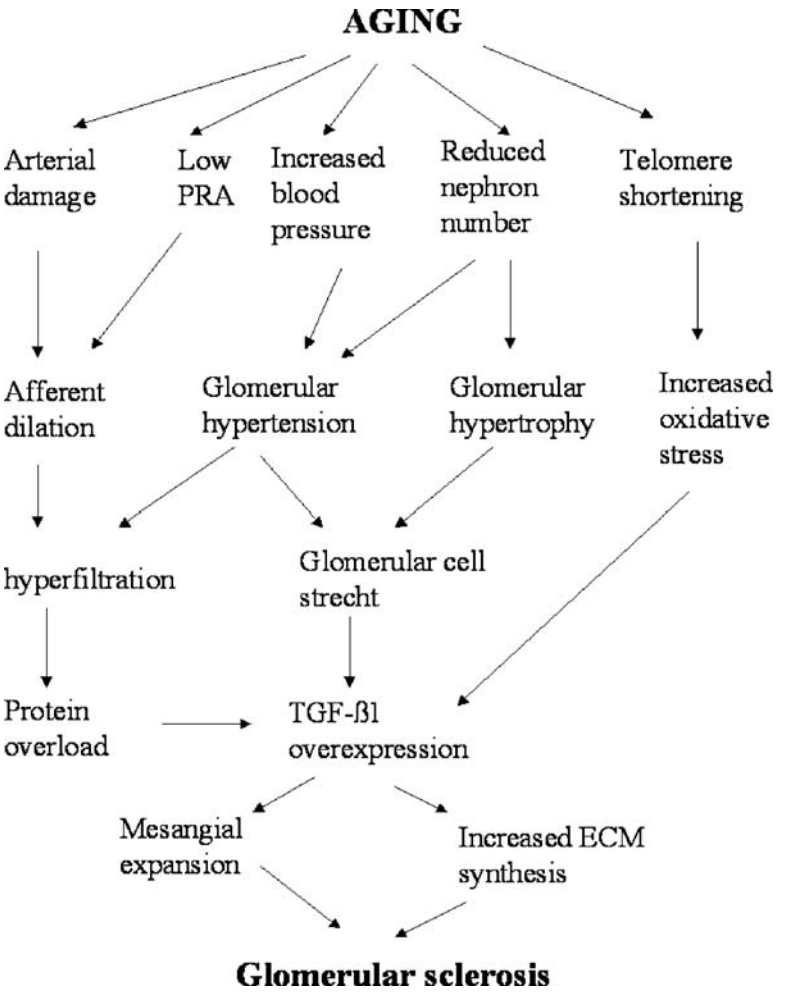

Fig. 6.1 Possible mechanisms and relationship between factors involved in the aged-related glomerulosclerosis.

described above and reflected in it have been almost exclusively analyzed in rodents; thus, it is possible that its actual importance in glomerular sclerosis in the human kidney has been over- or understated.

References

1. Jerkic, M., Vojvodic, S., López-Novoa, J.M. The mechanism of increased renal susceptibility to toxic substances in the elderly. Part I. The role of increased vasoconstriction. *Int. Urol. Nephrol*. 2001; 32:539–547.
2. Rowe, J.W., Andres, R., Tobin, J.D., Norris, A.H., Shock, N.W. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J. Gerontol*. 1976; 1:155–163.
3. Coresh, J., Astor, B.C., Greene, T., Eknoyan, G., Levey, A.S. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis*. 2003, 41:1–12; U.S. Renal Data System: USRDS 1999 Annual Report. 1999 The National Institutes of Health, NIDDK, Washington, DC.
4. Gray, I. Chronic progressive nephrosis in the albino rats. *CRC Crit. Rev. Toxicol.* 1977; 5:115–143.
5. Takazakura, E., Sawabu, N., Handa, A., Takada, A., Shinoda, A., Takeuchi, J. lntrarenal vascular changes with age and disease. *Kidney Int.* 1972; 2:224–230.
6. López-Novoa, J.M., Montañés, I. Changes in renal function and morphology in aging laboratory animals. In *Renal Function and Disease in the Elderly*, J.F. Macías-Núñez and J. Stewart Cameron, eds. London: Butterworth & Co. Ltd. 1987; pp. 162–183.
7. Kappel, B., Olsen, S. Cortical interstitial tissue and sclerosed glomeruli in the normal human kidney, related to age and sex. A quantitative study. *Virchows Arch*. 1980; 387:271–277.
8. McLachlan, M.S.F. The ageing kidney. *Lancet* 1978; II:143–146.
9. Goyal, V.K. Changes with age in the human kidney. *Exp. Gerontol*. 1982; 17: 321–331.
10. Reekelhoff, I.F., Samsell, L., Racusen, L., Dey, R., Baylis, C. The effect of aging on glomerular hemodynamics in the Sprague–Dawley rat. *Am. J. Kidney Dis*. 1992; 20:70–75.
11. Corman, B., Pratz, L., Poujeol, P. Changes in anatomy, glomerular filtration, and solute excretion in aging rat kidney. *Am. J. Physiol.* 1985; 248:R282–287.
12. Sato, F., Tsuchihashi, T., Kawashima, N. Age changes in number and size of the murine renal glomeruli. *Exp. Gerontol*. 1975; 10:325–331.
13. Anderson, S., Brenner, B.M. Effects of aging on the renal glomerulus. *Am. J. Med*. 1986; 80:435–442.
14. Anderson, S., Rennke, H.G., Zatz, R. Glomerular adaptations with normal aging and with long-term converting enzyme inhibition in rats. *Am. J. Physiol. Renal Fluid Electrolyte Physiol*. 1994; 267:F35–43.
15. Zhang, X.-Z., Qiu, C., Baylis, C. Sensitivity of the segmental renal arterioles to angiotensin II in the aging rat. *Mech. Ageing Dev*. 1997; 97:183–192.
16. Fujihara, C.K., Limongi, D.M.Z.P., De Oliveira, H.C.F., Zatz, R. Absence of focal glomerulosclerosis in aging analbuminemic rats. *Am. J. Physiol. Regulatory Integrative Comp. Physiol*. 1992; 262:R947–954.
17. Tolbert, E.M., Weisstuch, J., Feiner, H.D., Dworkin, L.D. Onset of glomerular hypertension with aging precedes injury in the spontaneously hypertensive rat. *Am. J. Physiol. Renal Physiol*. 2000; 278:F839–846.
18. Baylis, C. Age-dependent glomerular damage in the rat: Dissociation between glomerular injury and both glomerular hypertension and hypertrophy. Male gender as a primary risk factor. *J. Clin. Invest*. 1994; 94:1823–1829.

19. Remuzzi, A., Puntorieri, S., Mazzoleni, A. Sex related differences in glomerular ultrafiltration and proteinuria in Munich–Wistar rats. *Kidney Int.* 1988; 34: 481–486.
20. Arendshorst, W.J., Beierwaltes, W.H. Renal and nephron hemodynamics in spontaneously hypertensive rats. *Am. J. Physiol. Renal Fluid Electrolyte Physiol*. 1979; 236:F246–251.
21. Komatsu, K., Frohlich, E.D., Ono, H., Ono, Y., Numabe, A., Willis, G.W. Glomerular dynamics and morphology of aged spontaneously hypertensive rats: Effects of angiotensin-converting enzyme inhibition. *Hypertension* 1995; 25: 207–213.
22. Daniels, B.S., Hostetter, T.H. Adverse effects of growth in the glomerular microcirculation. *Am. J. Physiol. Renal Fluid Electrolyte Physiol*. 1990; 258:F1409–1416.
23. Krepinsky, J.C., Li, Y., Chang, Y., Liu, L., Peng, F., Wu, D., Tang, D., Scholey, J., Ingram, A.J. Akt mediates mechanical strain-induced collagen production by mesangial cells. *J. Am. Soc. Nephrol*. 2005; 16:1661–1672.
24. Cortes, P., Riser, B.L., Yee, J., Narins, R.G. Mechanical strain of glomerular mesangial cells in the pathogenesis of glomerulosclerosis: Clinical implications. *Nephrol. Dial. Transplant* 1999; 14:1351–1354.
25. Ruiz-Torres, M.P., Bosch, R.J., O'Valle, F., Del Moral, R.G., Ramirez, C., Masseroli, M., Perez-Caballero, C., Iglesias, M.C., Rodriguez-Puyol, M., Rodriguez-Puyol, D. Age-related increase in expression of TGF-beta1 in the rat kidney: Relationship to morphologic changes. *J. Am. Soc. Nephrol*. 1998; 9: 782–791.
26. Goldstein, R.S., Tarloff, J.B., Hook, J.B. Age-related nephropathy in laboratory rats. *FASEB J.* 1988; 2:2241–2251.
27. Brenner, B.M. Nephron adaptation to renal injury on ablation. *Am. J. Physiol*. 1985; 249:F324–328.
28. Lindeman, R.D., Tobin, J.D., Shock, N.W. Association between blood pressure and the rate of decline in renal function with age. *Kidney Int*. 1984; 26:861–868.
29. Zatz, R., Fujihara, C.K. Glomerular hypertrophy and progressive glomerulopathy: Is there a definite pathogenetic correlation? *Kidney Int. Suppl.* 1994; 45:S27–29.
30. Gafter, U., Ben-Bassat, M., Levi, I. Castration inhibits glomerular hypertrophy and proteinuria in uninephrectomized male rats. *Eur. J. Clin. Invest*. 1990; 20: 360–365.
31. Zheng, F., Plati, A.R., Potier, M., Schulman, Y., Berho, M., Banerjee, A., Leclercq, B., Zisman, A., Striker, L.J., Striker, G.E. Resistance to glomerulosclerosis in B6 mice disappears after menopause. *Am. J. Pathol*. 2003; 162:1339–1348.
32. Ruiz-Torres, P., Lucio, J., Gonzalez-Rubio, M., Rodriguez-Puyol, M., Rodriguez-Puyol, D. Oxidant/antioxidant balance in isolated glomeruli and cultured mesangial cells. *Free Rad. Biol. Med*. 1997; 22:49–56.
33. Floege, I., Johnson, R.I., Couser, W.G. Mesangial cells in the pathogenesis of progressive glomerular disease in animal models. *J. Clin. Invest.* 1992; 70: 857–864.
34. Elema, I.D., Arends, A. Focal and segmental glomerular hyalinosis and sclerosis in the rat. *Lab. Invest.* 1975; 33:554–561.
35. Francois, V., Heudes, D., Baniety, J., Bruneval, P., Corman, B. Glomerular capillary network of cortical nephron is reduced in male but not in female aging rats. *Mech. Ageing Dev.* 1996; 91:11–22.
36. Corman, B., Roinel, N. Single nephron filtration rate and proximal reabsorption in aging rats. *Am. J. Physiol*. 1990; 266:F75–80.
37. Silbiger, S.R., Neugarten, I. The impact of gender on the progression of chronic renal disease. *Am. J. Kidney Dis*. 1995; 25:515–533.
38. Zeier, M., Schonherr, R., Amann, K., Ritz, E. Effects of testosterone on glomerular growth after uninephrectomy. *Nephrol. Dial. Transplant* 1998;13:2234–2240.

39. Maric, C., Sandberg, K., Hinojosa-Laborde, C. Glomerulosclerosis and tubulointerstitial fibrosis are attenuated with 17beta-estradiol in the aging Dahl salt-sensitive rat. *J. Am. Soc. Nephrol*. 2004; 15:1546–1556.
40. Kwan, G., Neugarten, J., Sherman, M., Ding, Q., Fotadar, U., Lei, J., Silbiger, S. Effects of sex hormones on mesangial cell proliferation and collagen synthesis. *Kidney Int*. 1996; 50:1173–1179.
41. Reckelhoff, I.F., Baylis, C. Glomerular metalloprotease activity is suppressed by androgens in the aging kidney. *J. Am. Soc. Nephrol*. 1993; 3:1835–1838.
42. Venbeke, P., Periehon, M., Bonot-Laloi, C., Shaeverbeke, J., Bakala, H. Accumulation of advanced glycation end products in the rat nephron: Link with circulating AGEs during aging. *J. Histochem. Cytochem*. 1997; 45:1059–1068.
43. Li, Y., Steffes, M., Donelly, T., Liu, C., Fuh, H., Basgen, L., Bucala, R., Vlassara, H. Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine. *Proc. Natl. Acad. Sci. USA* 1996; 93: 3902–3907.
44. Baylis, C., Corman, B. The aging kidney: Insights from experimental studies. *J. Am. Soc. Nephrol*. 1998; 9:699–709.
45. Zawada, E.T., Alavi, F.K., Santella, R.N., Maddox, D.A. Influence of dietary macronutrients on glomerular senescence. *Curr. Nephrol*. 1997; 20:1–47.
46. Joles, J.A., Goon, H., Van Den Honst, L.C., Van Tol, A., Elema, I.D., Koomans, H.A. High lipid levels in very low density lipoprotein and intermediate density lipoprotein may cause proteinuria and glomerulosclerosis in aging female analbuminemic rats. *Lab. Invest.* 1995; 6:912–921.
47. Wyndham, J.R., Everitt, A.V., Everitt, S. Effect of isolation and food restriction begun at 50 days on the development of age-associated renal disease in the male Wistar rat. *Arch. Gerontol. Geriatr*. 1983; 2:317–332.
48. Pollard, M., Kajima, M. Lesions in aged, germ-free Wistar rats. *Am. J. Pathol*. 1970; 61:25–36.
49. Dodane, V., Chevalier, I., Baniety, I., Pnatz, I., Corman, B. Longitudinal study of solute excretion and glomerular ultrastructure in an experimental model of aging rats free of kidney disease. *Lab. Invest.* 1991; 64:377–391.
50. Ruiz-Torres, P., Lucio, J., González-Rubio, M., Rodríguez-Puyol, M., Rodríguez-Puyol, D. Oxidant/antioxidant balance in isolated glomeruli and cultured mesangial cells. *Free Rad. Biol. Med*. 1997; 22:49–56.
51. Iglesias-De La Cruz, M.C., Ruiz-Torres, P., Alcami, J., Díez-Marques, L., Ortega-Velázquez, R., Chen, S., Rodríguez-Puyol, M., Ziyadeh, F.N., Rodríguez-Puyol, D. Hydrogen peroxide increases extracellular matrix mRNA through TGF-beta in human mesangial cells. *Kidney Int.* 2001; 59:87–95.
52. Cruz, C.I., Ruiz-Torres, P., Del Moral, R.G., Rodríguez-Puyol, M., Rodríguez-Puyol, D. Age-related progressive renal fibrosis in rats and its prevention with ACE inhibitors and taurine. *Am. J. Physiol. Renal Physiol.* 2000; 278:F122–129.
53. Melk, A., Ramassar, V., Helms, L.M., Moore, R., Rayner, D., Solez, K., Halloran, P.F. Telomere shortening in kidneys with age. *J. Am. Soc. Nephrol*. 2000; 11: 444–453.
54. Saretzki, G., Von Zglinicki, T. Replicative aging, telomeres, and oxidative stress. *Ann. NY Acad. Sci*. 2002; 959:24–29.
55. Belmin, J., Levy, B.I., Michel, I.B. Changes in the renin-angiotensin-aldosterona axis in the later life. *Drugs Aging* 1994; 5:391–400.
56. Corman, B., Michel, I.B. Renin-angiotensin system, converting enzyme inhibition, and kidney function in aging female rats. *Am. J. Phvsiol.* 1986; 251:R450–455.
57. Magro, A.M., Rudofsky, U.H. Plasma renin activity decrease precedes spontaneous focal glomerular sclerosis in aging rats. *Nephron* 1982; 31:245–253.
58. Fender, L., Insenra, F., Romano, L., Ercole, L., Pszenny, V. Decrease of glomerulosclerosis in aging by angiotensin-converting-enzyme inhibitions. *J. Am. Soc. Nephrol*. 1994; 5:1147–1152.

59. Heudes, D., Michel, O., Chevalier, I., Scalbert, J., Ezan, E., Bariety, I., Zimmerman, A., Corman, B. Effect of chronic ANG I converting enzyme inhibition on aging processes. I. Kidney structure and function. *Am. J. Physiol.* 1994; 266:Rl038–105l.
60. Tank, J.E., Vora, J.P., Houghton, D.C., Anderson, S. Altered renal vascular responses in the aging rat kidney. *Am. J. Physiol*. 1994; 266:F942–948.
61. Greenfeld, Z., Engels, K., Samsell, L., Baylis, C. The role of endothelin in the age-dependent increase in renal vascular resistance in the rat kidney. *Mech. Ageing Dev*. 1998; 10:145–152.
62. Shindo, T., Kurihara, H., Maemura, K., Kurihara, Y., Ueda, O., Suzuki, H., Kuwaki, T., Ju, K.H., Wang, Y., Ebihara, A., Nishimatsu, H., Moriyama, N., Fukuda, M., Akimoto, Y., Hirano, H., Morita, H., Kumada, M., Yazaki, Y., Nagai, R., Kimura, K. Renal damage and salt-dependent hypertension in aged transgenic mice overexpressing endothelin-1. *J. Mol. Med*. 2002; 80:105–116.
63. Lattmann, T., Shaw, S., Munter, K., Vetter, W., Barton, M. Anatomically distinct activation of endothelin-3 and the L-arginine/nitric oxide pathway in the kidney with advanced aging. *Biochem. Biophys. Res. Commun*. 2005; 327:234–241.
64. Rathaus, M., Greenfeld, Z., Podjamy, E., Brezis, M., Bennheim, J. Sodium loading and renal prostaglandins in old rats. *Prostaglandins Leukotrienes Essential Fatty Acids* 1993; 49:815–819.
65. Tominaga, M., Fujii, K., Abe, I., Takata, Y., Kobayashi, K., Fujishima, M. Hypertension and aging impair acetyleholine-induced vasodilation in rats. *J. Hvpertens.* 1994; 12:259–268.
66. Fleck, C., Janz, A., Schweitzer, F., Karge, E., Schwertfeger, M., Stein, G. Serum concentrations of asymmetric (ADMA) and symmetric (SDMA) dimethylarginine in renal failure patients. *Kidney Int*. 2001; 78:S14–18.
67. Baylis, C. Changes in renal hemodynamics and structure in the aging kidney; sexual dimorphism and the nitric oxide system. *Exp. Gerontol*. 2005; 40:271–278.

7

Endothelial Function in the Healthy Aged

Leocadio Rodríguez-Mañas, Mariam El Assar De La Fuente and Marta Castro Rodríguez

Introduction

Over the last two decades it has become evident that the endothelium is not a mere monolayer of cells covering the internal surface of blood vessels. In fact, it plays a key role in regulating vascular tone and structure, since it possesses anticoagulatory, antiadhesive, and antiprolifertaive properties and generates a number of vasoactive substances. Therefore, the functional integrity of the endothelium is essential for preventing vascular leakage and the formation of atherosclerotic lesions [1]. We will focus on the functional properties of the endothelium and its changes during aging. First, though, we will make a general and brief review of the endothelial physiology and of the different mechanisms that may induce endothelial dysfunction and its consequences.

Under physiological conditions, the activation of endothelial cells by physical or chemical stimuli can lead to the production and release of relaxing and contracting factors toward the adjacent smooth muscle cells (SMC).

Main Relaxing Factors Produced by Endothelial Cells

Nitric Oxide

Nitric Oxide (NO) is formed from the metabolism of L-arginine by three isoforms of nitric oxide synthase (NOS) in response to several stimuli [2], including increment of shear stress during increased blood flow or muscarinic receptor stimulation. NOS is a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxygenase that requires tetrahydrobiopterin (BH4), flavine adenine dinucleotide (FAD), and flavine adenine mononucleotide (FMN) as cofactors [3].

In the endothelium, the most relevant isoform is the endothelial nitric oxide synthase (eNOS), which produces NO at moderate rates. Another important isoform is the inducible nitric oxide synthase (iNOS), which is stimulated by the action of cytokines and bacterial endotoxins. iNOS is responsible for producing elevated levels of NO, mainly located in smooth muscle cells.

Prostacyclin

Prostacyclin (PGI) is produced from arachidonic acid by a series of enzymes including cyclo-oxygenase (COX) and prostaglandin polymerase. COX exists in two isoforms: COX-1, which is a constitutively expressed isoform, and COX-2, which is the inducible isoform [4].

Endothelium-Derived Hyperpolarizing Factor

This factor, abbreviated as EDHF, can induce relaxation by hyperpolarizing vascular SMC, but its identity is still controversial. It seems that the importance of EDHF in endothelium-dependent vasodilatation increases in small vessels [5].

Major Contracting Factors Released by the Endothelium

Prostaglandins

PGH2, or one of its metabolites, thromboxane A2 (TXA2), induces vasoconstriction by binding to their receptors in vascular SMC [6].

Reactive Oxygen Species

Both endothelial cells and SMC can release oxygen-derived free radicals when stimulated. The main reactive oxygen species (ROS) involved in producing endothelial dysfunction is the superoxide anion. Superoxide anions are produced by several enzymes such as NADPH/NADH oxidase, NOS, xanthine oxidase, COX, and angiotensin.

Endothelin-1

Endothelial cells express endothelin-converting enzymes, which, in turn, will generate endothelin (ET-1), known to be a very potent vasoconstrictor [8].

Angiotensin II

Endothelial cells also have an angiotensin-converting enzyme (ACE) that converts the circulating angiotensin I into the potent vasoconstrictor angiotensin II [9].

Endothelial Dysfunction

The balance between vasodilator/vasoconstrictor substances is very important, not only for vascular tone control, but also for vascular wall physiology. Under physiological conditions, the balance is shifted toward vasodilatation, antiaggregation/antiadhesion, and antiproliferative pattern. When this situation is disrupted, endothelial dysfunction (ED) shows up.

Among the tissues that are more vulnerable to stress, the endothelium cells can be listed at the top simply because their location exposes them to incessant external stresses. It has been reported that endothelial function can be altered under certain conditions or in the presence of cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking, and aging)

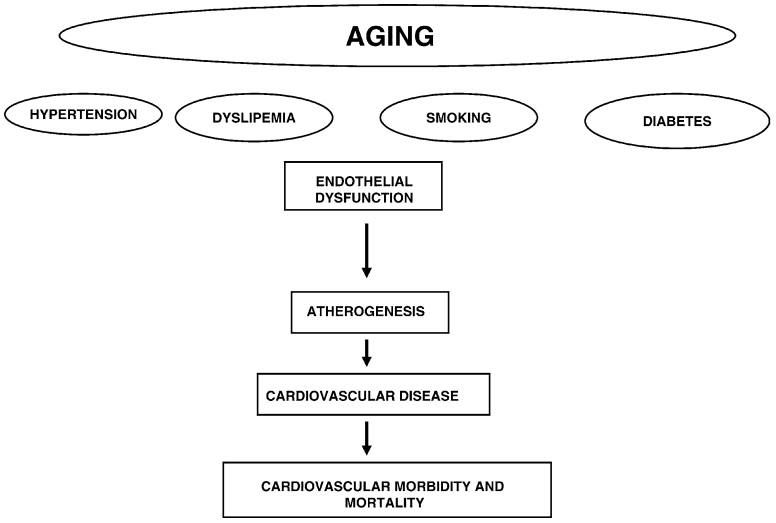

Fig. 7.1 Modifications induced by cardiovascular risk factors in endothelial function.

(see Figure 7.1). A widely popular definition of endothelial dysfunction entails an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) endothelial cells or between antithrombotic and antiadhesive properties, or a disturbance of the regulation of vascular permeability. However, the major focus of both experimental and clinical studies concerning ED has been the reduced endothelium-dependent vasodilatation.

Hypotheses to Explain the Endothelial Dysfunction as Cardiovascular Risk Factor

Oxidative Stress

Reactive oxygen species and especially O_2^- are important modulators of NO activity under various pathological conditions [10] and are thought to be involved in the aging process (see Chapter 4). The ROS superoxide anion and NO react to form the powerful oxidant peroxynitrite, which can easily penetrate cells and initiate oxidative modifications of proteins, thereby rendering inactive certain functionally important regulatory proteins, like receptors or enzymes. ROS also reduce NO synthase activity and increase NO breakdown and thereby reduce the bioactivity of NO. In addition, ROS lower the availability of tetrahydropiopterin, causing a deficiency of this cofactor. As a consequence of the pathogenic uncoupling of NOS—if it occurs—more ROS are produced instead of NO [11]. Oxidative stress can activate redx-sensitive transcription factors, like nuclear factor-KB (NF-KB). The latter may play a key role in regulating the activation of various inflammatory genes. NF-KB is known to regulate the transcription of pro-inflammatory cytokines like tumor necrosis factor α (TNF-α), adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), and inflammatory enzymes such as iNOS and COX-2, thus contributing to endothelial injury [12].

Sources of Oxidative Stress

Recent evidence indicates that one of the major sources of oxidative stress generation is membrane-bound NAD(P)H oxidase [13]. As mentioned, this element is an important enzyme for NOS function and production of NO, so if its function is altered, it will produce ROS and contribute to NOS uncoupling. In addition, NOS uncoupling is another important source of ROS production in the vascular wall under certain pathophysiological conditions. The latter could happen if the availability of its substrate (L-arginine) or its cofactor (BH4) decreases. Any of this two possibilities will facilitate an increase in superoxide production due to the fact that NOS will switch from a coupled state to an uncoupled state, leading to vascular damage [14].

Xanthine oxidoreductase is also considered to be another important enzyme able to produce superoxide anion under pathological conditions. This enzyme has been linked to different vascular diseases characterized by both functional alterations and remodeling [15]. Furthermore, the mitochondria were proposed to be another source of oxidative stress. It has been found that the mitochondria may become uncoupled under pathophysiological conditions, leading to increased superoxide production [16].

Other factors that could promote oxidative stress are inflammation, endothelin, and angiotensin (see below), raising the framework for the collaboration and potentiation of the mechanisms involved in the endothelial dysfunction.

Inflammation Injury to the endothelial monolayer results in inflammatory remodeling of the vessel wall. This process will play a key role in the pathogenesis of vascular disease, leading to the development of atherosclerotic lesions. It has been demonstrated that a pro-inflammatory pattern is common to various diseases [17] and that there is a clear relationship among endothelium injury, inflammation, and tissue and organ dysfunction. In fact, during the inflammatory reaction, the endothelium is exposed to various ROS and inflammatory mediators, resulting in alterations of cellular redox levels, causing both phenotypic and functional changes in endothelial cells as a result of modifications in nuclear transcription factors' activation [18]. Inflammation also decreases the activity of natural anticoagulant mechanisms, inducing impairment in the fibrinolytic system, which in turn may increase the loss of endothelial barrier function [19]. Recent studies suggest that C-reactive protein (CRP), besides being a marker of inflammation, may also directly contribute to endothelial dysfunction [20].

Endothelin Several lines of evidence suggest a role of the potent vasoconstrictor and pro-inflammatory peptide ET-1 in the pathophysiology of vascular dysfunction and cardiovascular diseases [21]. A close interaction between NO and ET-1 in the vascular wall has been identified. The existence of this interaction may participate in the pathogenesis of endothelial dysfunction. In healthy arteries, the ET_B receptor located on the endothelium signals the release of NO and modulates the vasoconstrictor effects of ET bound to smooth muscle ET_A and ET_B receptors.

Although inconclusive evidence exists about increased plasma levels of ET-1 in certain diseases, the vasoconstrictor activity of this peptide is increased along with diminished availability of NO. Under these circumstances, the inhibitory effect of NO on ET-1 production may be impaired [22],

causing an imbalance between the two systems and the consecutive enhancement in the vasoconstrictor and proliferogenic activity of ET-1 [23].

It has been recently found in both *in vitro* and *in vivo* studies that ET-1 contributes to endothelial dysfunction via the stimulation of reactive oxygen species formation [24]. Another possible mechanism behind the effect of ET-1 on endothelium-dependent vasodilatation includes the stimulation of vascular wall inflammation through the stimulation of several pro-inflammatory cytokines such as IL-6 and NF-KB and accumulation of leukocytes [25].

ECA-Angiotensin It has been well established by experimental and clinical data that the activation of the renin-angiotensin system is involved in the onset and progression of some diseases and that its main effector, angiotensin II (Ang II), induces vascular damage due to its pro-inflammatory activity, which, in turn, induces the expression of cytokines, chemokines, adhesion molecules, growth factors, and reactive oxygen species [26]. Several lines of evidence also indicate that Ang II promotes NAD(P)H oxidase activity and enhances the migration of VSMCs [27].

It is very important to point out that the above-mentioned mechanisms that are implicated in the genesis of endothelial dysfunction do not act separately in different pathways but are closely related to each other and possibly modulate one another in many ways. For instance, Kim et al. have recently reported that iNOS specifically binds to COX-2 and S-nitrosylates, enhancing its catalytic activity [28]. These two inducible isoforms are increased under pathophysiological conditions associated with endothelial dysfunction. iNOS induction within the vascular wall would be expected to further promote oxidative stress via two mechanisms: First, it will become a peroxynitrite generator formed from the reaction of iNOS-derived NO, leading to a dramatic increase in ROS production. Second, iNOS would also be a source of oxidative stress by generating O_2^- following uncoupling or the depletion of L-arginine and subsequent transfer of electrons to O_2. Moreover, the inflammatory system is closely linked to the NO system at different levels, since NO stimulates the production of prostaglandins *in vivo* in macrophages, and COX-2 activation induces oxidative stress. These inducible isoforms are in turn determined, at least in part, by pro-inflammatory cytokines. Therefore, oxidative stress and inflammation can positively modulate one another, acting as a mutual amplifying mechanism.

After reviewing previous data, it is necessary to underscore that a difference may exist between the mechanisms responsible for triggering endothelial injury. Under several diseases and conditions inducing endothelial dysfunction, especially in its initial stages, whatever was the initial cause that may have set off the development of endothelial injury, the final steps of the endothelial response to these aggressions involve a common pathway. When the nonreturn point leading to endothelial dysfunction is reached, oxidative stress and inflammation are present and will contribute to the amplification of endothelial dysfunction and to vascular damage.

Endothelium and Aging

General Considerations

Physiological aging is associated with several changes and modifications in different human structures and systems (see Chapter 4). The arterial wall in

general and the endothelium, in particular, are not exceptions to this general principle. These important modifications associated with senescence affect the structure and function of the endothelial cells, but are not due to diseases. Their intensity and rate of development are variable among different individuals and vascular beds, although as we have just commented, they are present in different degrees in the physiological aging of vascular beds.

Among the most common structural changes of the aged endothelium are a higher number of cells with polyploid nuclei, increased endothelial permeability, alterations in the cytoskeleton integrity, and the appearance of senescence-associated β-galactosidase staining [27].

As already mentioned, the functional characteristics of the endothelium in the young modify as we grow older. Many of the substances released by the endothelium change with advancing age. These changes may quantitatively or qualitatively modify the relationship between mechanisms or may affect the final/effector mechanisms. For example, endothelial cells from aged arteries secrete more plasminogen activator inhibitor-1, but simultaneously, there is reduced NO bioavailability [29]. The result of the simultaneous action of these two mechanisms is a trend toward thrombosis.

What are the main changes associated with aging in the endothelial function, their intermediate mechanisms, and their origins? In a very brief and simplistic way, changes in endothelial function associated with aging could be summarized as a reduction in vasodilator and an increase in the contractile factors.

Furthermore, inflammatory process and increased oxidative stress are also present in the arterial wall of the healthy aged, creating a metabolically and enzymatically active milieu, very prone to facilitate the initiation and/or progression of vascular diseases.

All these changes are summarized in Table 7.1.

Table 7.1 Age-Related Changes in Arterial Structure, Function, and Composition.

Age related changes in arterial structure, function, and composition				
Arterial parameter	**Humans >65 years**	**Monkeys 15–20 years**	**Rats 24–30 months**	**Rabbits 3–6 years**
Lumenal dilation	+	+	+	+
Increased stiffness	+	+	+	+
Endothelial dysfunction	+	+	+	+
Diffuse intimal thickening	+	+	+	+
Increased Local Ang II-ACE	+	+	+	+
Increased NADPH oxidase	?	?	+	?
Decreased VEGF	+	?	?	+
Decreased NO bioavailability	?	?	+	+
Decreased telomere length	+	+	+	?

?Unknown

Modified from Najjar et al (Reference 27)

Endothelial Modifications That Accompany the Normal Aging Process

The principal mechanisms for endothelial repair in the aged are telomerase and endothelial progenitor cells (EPC).

Endothelial dysfunction is the result of the balance between damage and repair. The main endothelial elements implicated with vascular damage are nitric oxide (NO) pathway, ciclo-oxygenase (COX) pathway, endothelin, angiotensin II- and endothelial-derived hyperpolarizing factor (EDHF).

The Nitric Oxide Pathway

NO availability results from a dynamic equilibrium between its production and inactivation. Five aspects are implicated in this pathway: [1] the substrate, [2] eNOS endogenous inhibitor, [3] eNOS cofactors, [4] eNOS expression, and [5] NO bioavailability.

The substrate for eNOS is arginine. Experimental data [30] show an improvement in the endothelial responses when L-arginine is co-infused with muscarinic agonist in old persons, suggesting a potential role for the substrate of NOS in determining endothelial dysfunction in the aged.

e-NOS Endogenous Inhibitor

As there is no difference between the circulating levels of arginine between adult and aged rats, a possible explanation for the blunted response to NO with aging may be an impaired intracellular availability and/or mobilization of arginine. Among the possible candidates blamed for this decreased availability of L-arginine is the asymmetrical dimethylarginine (ADMA), an endogenously formed compound that inhibits NOS activity by displacing L-arginine from the substrate binding site [31]. Infusion of ADMA impairs endothelium-mediated vasodilatation. Elevated ADMA plasma levels are associated not only with endothelial dysfunction but also with increased oxidative stress, thereby linking endothelial dysfunction and redox mechanisms in vascular disease. High plasma ADMA concentrations are found in the healthy aged and in diabetic patients. Functional impairment or decreased expression of the ADMA-degrading enzyme could be one of the possible mechanisms responsible for the elevated ADMA concentrations observed in diabetes. This may be due, at least in part, to a dysregulation of the redox-mediated DDAH activity and could also explain the high concentration of ADMA observed in the healthy aged.

e-NOS Cofactor

Tetrahydrobiopterin is the main eNOS cofactor and, consequently, its deficiency induces a decrease in the activity of the enzyme associated with reduced NO production and increased oxygen free radical formation (uncoupling). This uncoupling mechanism may be present in physiological aging. In this regard, recent reports have proven that infusion of BH4 improves vasodilatation in the human forearm [32]. Because of the above findings, the possibility has been raised that the improvement exerted by the infusion of L-arginine in the defective endothelium-mediated responses in old people could also be mediated by a reversion of NOS uncoupling by L-arginine.

e-NOS Expression

In an attempt to find the possible mechanism responsible for the low vascular concentration of NO observed in the aged endothelium, the levels of NOS mRNA, protein expression, and activity have been determined in experimental animal models. The rationale for this search is the possibility that a reduced production of NO by NOS may be one of the causes that could explain the lower production of NO in the vascular bed, although, at present, human data are lacking. Changes in mRNA expression and NOS activity in mesothelial human cells, ontologically very close to endothelial cell, have been observed recently. In these cells, there are no changes in eNOS mRNA expression, whereas an increased expression of iNOS mRNA, total NOS activity, and NOx (nitrite plus nitrate) production [33] was found. Preliminary data from our group in human microvessels seem to confirm these data (unpublished results). To the contrary, in the aorta and small mesenteric arteries from aged rats, there is an increased, instead of a decreased, expression of eNOS. Because of the already-mentioned discrepancies, more studies in humans are needed. Furthermore, one should be very careful at this time to extrapolate data from aged animals to aged humans.

NO Bioavailability

In order to regulate the redox steady state of endothelial cells, equilibrium between the production of NO and O_2^- issnecessary. Under physiological conditions, this equilibrium is achieved by the action of endogenous antioxidant defense mechanisms such as superoxide dismutase. However, the balance between pro- and antioxidant equilibrium may be altered, especially during the aging process. This imbalance may lead either to the generation of an excess of oxygen-derived free radicals or to a decrease in biologically active NO, leading to impaired endothelial vasodilatation. Indeed, many studies have pointed out that oxidative damage increases with age (see Chapter 4). As NO inactivates O_2^-, it is possible that reduced NO production may trigger oxidative stress. Under certain conditions, the interaction between NO and O_2^- leads to the production of biologically active compounds such as peroxynitrites and hidroxyl radicals. Enhanced O_2^- production by the endothelium has been reported in the aorta of aged rats. Data from studies using vitamin C as an ROS scavenger have shown that sedentary old people have a patent oxidative stress that impairs the endothelium-dependent responses *in vivo* [34]**.** Although there are no convincing data about the nature of the ROS involved in these phenomena, the main candidate for this role is the superoxide anion, as previously commented. Added to trapping NO, oxidative stress due to superoxide anions, when combined with NO, may induce the production of increased amounts of peroxynitrite, a very reactive and dangerous substance that induces deleterious changes at cellular and subcellular components. The main sources of O_2^- are NOS itself (uncoupling), xanthine oxidase, and NADPH oxidase [35]. Hamilton et al. [36] have shown that O_2^- generation increased with age in the aorta and the carotid arteries of the rat and could contribute to age-related decreased vasodilatation. There are no data in humans to propose or discard definitively any of the potential sources of the oxidative stress during human endothelial aging. To the contrary, some data suggest that the source for the increased amount of NO could be iNOS, but not eNOS. This will support the hypothesis that decreased NO bioavailability is one of

the main mechanisms involved in the endothelial dysfunction associated with aging.

The Cyclo-Oxygenase Pathway

In the microvessels of healthy humans aged 18 to 93 years old using myographic techniques (Mulvany), we have evaluated the role of cyclo-oxygenase (COX) in the endothelial dysfunction associated with aging. From our results, COX seems to participate in two major ways: One way is by attenuating the endothelium-dependent vasodilatation mediated by the loss of a COX-derivate that induces vasodilatation (probably prostacyclin). The second is by increasing the release of a vasoconstrictor metabolite derived from COX (probably thromboxane). In this regard, indomethacin improves endothelium-dependent responses in the forearm of old people [30]. Some of these results confirm data obtained in animals, where the use of an antagonist of the TXA2/endoperoxide receptor improves acetylcholine-induced relaxation in the aorta and in the small mesenteric arteries from aged rats.

The Endothelin Pathway

Although the role of ET in aged-associated endothelial dysfunction is strongly supported in animal studies, the scattered data available in healthy persons prevent us from reaching definitive conclusions concerning the role of ET in human aging.

It has been shown in healthy rodents that aging is associated with a marked upregulation of the renal ET-1 protein content and a decrease in tissue nitrite/nitrate levels in the kidney. Furthermore, in the intact aorta of aged rats, mRNA expression of preproendothelin-1 (the precursor of ET-1) and ET-1 protein was increased.

In addition, an alteration of the equilibrium between the ET-1 and NO pathways seems to be an attractive explanation for the reduced endothelium-dependent vasodilatation observed in the course of aging, although not all investigators endorse this hypothesis [37].

The Angiotensin II Pathway

Increased production of angiotensin II may be another attractive hypothesis to explain the age-related decrease in endothelial relaxation. Angiotensin II causes impairment of the EPC proliferative activity in humans through two mechanisms. The first takes place by the induction of gp91phox expression at the AT1 level, which produces an increase in peroxynitrite and a decrease in telomerase activity, leading to EPC senescence. The second is the role developed by angiotensin and angiotensin-converting enzyme. In animals, there is strong evidence of the important role played by angiotensin II and angiotensin-converting enzyme in endothelial aging [26]. Nevertheless, data to support this mechanism in human are not so evident.

Endothelium Derived Hyperpolarizing Factor

Nearly 10 years ago a seminal report by Urakami-Harasawa et al. [38] showed a decrease in the responses mediated by EDHF with advancing

age. Again, although data from animal studies point to the importance of this mechanism, studies in humans are lacking. These mechanisms do not work in an isolated manner; they work together by provoking aged-related endothelial dysfunction. As an example, it is known that iNOS increases COX-2 activity, while, at the same time, peroxynitrite could act on COX and COX metabolite(s) receptors; also, angiotensin II induces oxidative stress, which, in turn, promotes uncoupling of NOS, etc. Another possibility is that ED is mediated by regulation of vascular genes: Oxidative stress is accompanied by an increased formation of hydrogen peroxide, superoxide anions, and peroxynitrites, which, in turn, are endogenous inducers of DNA breakage [4]. Furthermore, the same compound may exert its actions at different levels, ranging from modulating gene expression and activity to generating the final endothelial injuring agent, peroxynitrite. All these possibilities form a great and complex picture that we are just beginning to uncover.

Repair Mechanisms

The other arm of the balance finally determining the development of endothelial dysfunction is composed of the mechanisms that repair endothelial damage and their functionality. We will focus on telomere-telomerase and endothelial progenitor cells (EPC).

Telomere-Telomerase and Endothelial Progenitor Cells

As discussed in Chapter 4, the length of telomere more than the chronological age may modulate the aging of tissues. Briefly, telomeres are specialized structures located at the end of chromosomes, which shorten in each replication unless they are rescued by the enzyme telomerase reverse transcriptase. When the telomere length reaches a critical size, reflecting numerous cycles of attrition, no further replication is possible and the cell becomes senescent. Telomere length has been shown to be inversely associated with chronological age in endothelial cells from the human abdominal aorta, iliac arteries, and iliac veins. Interestingly enough, nitric oxide seems to play some regulatory role in the telomerase activity at least in cultured aged endothelium *in vitro* [39]. The impact of telomere-induced vascular senescence may be accentuated in older individuals, in whom recent studies indicate that the number and activity of endothelial progenitor cells are reduced, suggesting an age-associated diminution in regenerative capacity, which may contribute to the age-associated impairment in angiogenesis [40].

Potential Consequences

It is well known that the incidence and prevalence of cerebral and cardiovascular disease are much higher in aged persons than in the young, with similar classical risk factors for heart and brain damage (see Chapter 11). This may be due to the role the vascular aging process plays as an additional risk factor for the appearance of cerebral and cardiovascular adverse events. The limited knowledge and little attention paid until now to the mechanisms involved in the modifications that accompany the physiological aging process may explain why many doctors think that aging is an irreversible, nonmodifiable process and consequently ineligible for prevention. But, as we are gaining

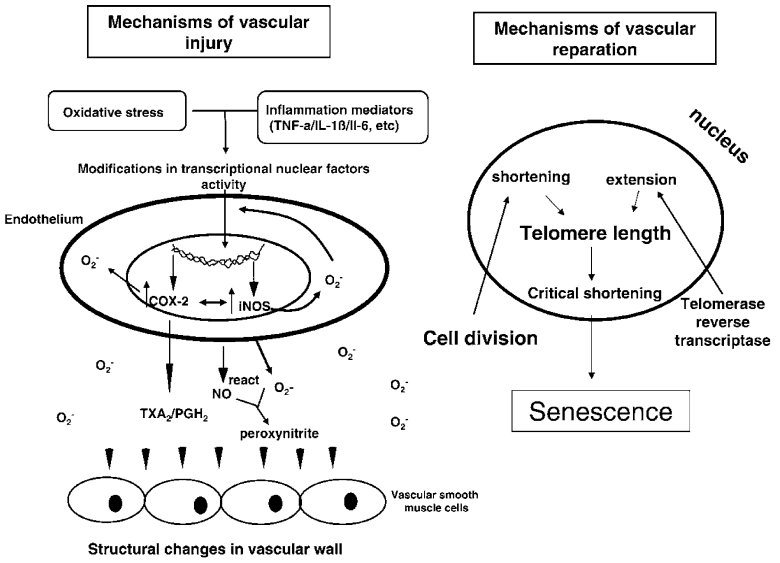

Fig. 7.2 Effect of cellular senescence on the mechanisms of vascular injury and repairing.

insight into the mechanisms involved in the vascular aging process, we are learning that the presentation of these events may be delayed, if not reversed, or are at least susceptible to prevention. For instance, in many studies the possibility has been raised that very well-controlled programs of physical activity may be able to slow down or even reverse age-related endothelial dysfunction.

It is worth bearing in mind that as traditional risk factors such as diabetes, arterial hypertension, and hypercholesterolemia share some common mechanisms with the aging process, their presence may add additional risk to normal aging. Conversely, minute additional insult provoked by traditional risk factors to an aged organism in which the mechanism of defense has been overcome may induce considerable, and sometimes irreversible, damage. This damage may be prevented if persons caring for the aged are familiar with the characteristics of the endothelial aging process.

Acknowledgments

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References

1. Taddei, S., Virdis, A., Ghiadoni, L., et al. Endothelium, aging, and hypertension. *Curr. Hypertens. Rep*. 2006; 8(1):84–89.
2. Nathan, C., Xie, Q.W. Regulation of biosynthesis of nitric oxide. *J. Biol. Chem.* 1994; 269:13725–13728.
3. Moncada, S., Palmer, R.M., Higgs, E.A. Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacol. Rev*. 1991; 43(2):109–142.
4. Matz, R.L., Andriantsitohaina, R. Age-related endothelial dysfunction potential implications for pharmacotherapy. *Drugs Aging* 2003; 20(7):527–550.

5. Shi, Y., Ku, D.D., Man, R.Y., et al. Augmented EDHF-mediated relaxations attenuate endothelial dysfunction in femoral and mesenteric, but not in carotid arteries from type I diabetic rats. *J. Pharmacol. Exp. Ther.* 2006; 318(1):276–281.
6. Onguru, O., Casey, M.B., Kajita, S., et al. Cyclooxigenase-2 and thromboxane synthase in non-endocrine and endocrine tumors: A review. *Endocr. Pathol*. 2005; 16(4):253–278.
7. Madamanchi, N.R., Vendrov, A., Runge, M.S. Oxidative stress and vascular disease. *Arterioscler. Thromb. Vasc. Biol*. 2005; 25:29–38.
8. Langleben, D., Dupuis, J., Langleben, I., et al. Etiology-specific endothelin-1 clearance in human precapillary pulmonary hypertension. *Chest* 2006; 129(3):689–695.
9. Baudin, B. New aspects on angiotensin-converting enzyme: From gene to disease. *Clin. Chem. Lab. Med*. 2002; 40(3):256–265.
10. Forstermann, U., Munzel, T. Endothelial nitric oxide synthase in vascular disease: From marvel to menace. *Circulation* 2006; 113(13):1708–1714.
11. Deanfield, J., Donald, A., Ferri, C., et al. Part I: Methodological issues for assessment in the different vascular beds: A statement by the Working Group on endothelin and endothelial factors of the European Society of Hypertension. *J. Hypertens*. 2005; 23:7–17.
12. Chung, H.Y., Kim, H.J., Kim, K.W., et al. Molecular inflammation hypothesis of aging based on the anti-aging mechanism of calorie restriction. *Microsc. Res. Tech*. 2002; 59:264–272.
13. Harrison, D., Griendling, K.K., Landmesser, U., et al. Role of oxidative stress in atherosclerosis. *Am. J. Cardiol*. 2003; 91:7A–11A.
14. Ferroni, P., Basili, S., Paoletti, V., et al. Endothelial dysfunction and oxidative stress in arterial hypertension. *Nutr. Metab. Cardiovasc. Dis.* 2006; 16(3):222–233.
15. Berry, C.E., Hare, J.M. Xanthine oxidoreductase and cardiovascular disease: Molecular mechanisms and pathophysiological implications. *J. Physiol*. 2004; 555(Pt 3):589–606.
16. Douette, P., Sluse, F.E. Mitochondrial uncoupling proteins: New insights from functional and proteomic studies. *Free Rad. Biol. Med*. 2006; 40(7):1097–1107.
17. Esch, T., Stefano, G. Proinflammation: A common denominator or initiator of different pathophysiological disease processes. *Med. Sci. Monit*. 2002; 8:HY1–HY9.
18. Alessio, P. Aging and the endothelium. *Exp. Gerontol*. 2004; 39:165–171.
19. Esmon, C.T. The interactions between inflammation and coaguation. *Br. J. Haematol*. 2005; 131(4):417–430.
20. Pasceri, V., Willerson, J.T., Yeh, E.T.H. Direct proinflammatory effect of C-reactive protein in human endothelial cells. *Circulation* 2000; 102:2165–2168.
21. Schiffrin, E.L. Role of endothelin-1 in hypertension and vascular disease. *Am. J. Hypertens*. 2001; 14:S83–S89.
22. Taddei, S., Virdis, A., Ghiadoni, L., et al. Vasoconstriction to endogenous endothelin-1 is increased in the peripheral circulation of patients with essential hypertension. *Circulation* 1999; 100:1680–1683.
23. Haynes, W.G., Webb, D.J. Endothelin as a regulator of cardiovascular function in health and disease. *J. Hypertens.* 1998; 16:1081–1098.
24. Bohm, F., Settergren, M., Pernow, J. Vitamin C blocks vascular dysfunction and release of interleukin-6 induced by endothelin-1 in humans *in vivo*. *Atherosclerosis* 2006 Mar 7; [Epub ahead of print].
25. Cheng, Z.J., Vapaatalo, H., Mervaala, E. Angiotensin II and vascular inflammation. *Med. Sci. Monit*. 2005; 1186:RA194–205.
26. Imanishi, T., Hano, T., Nishio, I. Angiotensin II accelerates endothelial progenitor cell senescence through induction of oxidative stress. *J. Hypertens*. 2005; 23:97–104.

27. Najjar, S.S., Scureti, A., Lakatta, E.G. Arterial aging, is it an immutable cardiovascular risk factor? *Hypertension* 2005; 46:454–462.
28. Kim, S.F., Huri, D.A., Snyder, S.H. Inducible nitric oxide synthase binds S-nitrosylates, and activates cyclooxygenase-2. *Science* 2005; 310(5756):1966–1970.
29. Van der Loo, B., Labugger, R., Skepper, J., et al. Enhanced peroxynitrite formation is associated with vascular aging. *J. Exp. Med*. 2000; 192(12):1731–1743.
30. Taddei, S., Virdis, A., Ghiadoni, L. Cyclooxygenase inhibition restores nitric oxide activity in essential hypertension. *Hypertension* 1997; 29(2):274–279.
31. Boger, R., Schwedhelm, E., Maas, R., et al. ADMA and oxidative stress may relate to the progression of renal disease: Rationale design of the VIVALDI study. *Vasc. Med*. 2005; 10:S97–102.
32. Singh, N., Prasad, S., Singer, D., MacAllister, R. Ageing is associated with impairment of nitric oxide and prostanoid dilator pathways in the human forearm. *Clin. Sci*. 2002; 102:595–600.
33. Massimo, C., Scarpelli, P., Di Lorenzo, N., et al. Impaired plasma nitric oxide availability and extracellular superoxide dismutase activity in healthy humans with advancing age. *Life Sci*. 2006; 78:1163–1167.
34. Eskurza, I., Myerburgh, L.A., Kahn, Z.D. Tetrahydrobiopterin augments endothelium-dependent dilatation in sedentary but not in habitually exercising older adults. *J. Physiol*. 2005; 568(3):1057–1065.
35. Bachschmid, M., Van der Loo, B., Schüler, K., et al. Oxidative stress-associated vascular aging is independent of the protein kinase C/NAD(P)H oxidase pathway. *Arch. Gerontol. Geriatr*. 2004; 38:181–190.
36. Hamilton, C.A., Brosnan, M.L., Mclntyre, M., Graham, D., Dominiczak, A.F. Superoxide excess in hypertension and aging: a common cause of endothelial dysfunction. *Hypertension*. 2001 Feb; 37:529–34.
37. Gössl, M., Lerman, A. Endothelin: Beyond a vasoconstrictor. *Circulation* 2006; 113:1156–1158.
38. Urakami-Harasawa, L., Shimokawa, H., Nakashima, M., et al. Importance of endothelium-derived hyperpolarizing factor in human arteries. *J. Clin. Invest*. 2006; 100(11):2793–2799.
39. Vasa, M., Breitschopf, Z.A.. Nitric oxide activates telomerase and delays endothelial cell senescence. *Circ. Res*. 2000; 87(7):540–542.
40. Brandes, R., Fleming, I., Busse, R. Endothelial aging. *Cardiovas. Res*. 2005; 66:286–294; *J. Physiol*. 2005; 568(3):1057–1065.

8

Renal Handling of Water and Electrolytes in the Old and Old-Old Healthy Aged

Carlos G. Musso and Juan-Florencio Macías-Núñez

Introduction

The main principles that explain the particular aspects of the water and electrolytes balance in the elderly are their *frail homeostasis* and the *physiological nephrogeriatric giants*.

Frailty of the Senile Homeostasis

This concept fits in very well with the progressive loss-of-complexity characteristic of the aging process (see Chapter 4). Biological systems work due to coordination among their multiple constitutive systems or microsystems. This coordination of systems or *complexity* makes the organism flexible and adaptable to environmental changes. The senescence process weakens these microsystems and their intercoordination, resulting in a frail organism. Therefore, even though healthy elderly people can handle their water and electrolytes balance under basal conditions, they easily lose the ability to adapt to challenging situations such as hot weather or sepsis. This senile homeostasis frailty also explains why the elderly are equally exposed to opposite electrolytic disorders, such as hyponatremia or hypernatremia, depending on the clinical circumstances [1].

Nephrogeriatric Giants

As has been discussed in Chapter 1, Bernard Isaacs coined the term "clinical geriatric giants": incontinence, immobility, instability, and intellectual impairment, because these "giants" are the most common presenting symptoms of illnesses in elderly patients.

In renal physiology, other very common findings are present in the great majority of healthy aged individuals: *the* "physiological nephrogeriatric giants."

This is a concept forged by geriatric nephrology, which summarizes the structural and physiological changes that accompany the normal renal aging process. We should always keep them in mind, as they play an important role

in the development of the diseases and treatments in this age segment of the life cycle.

The physiological nephrogeriatric giants are [2]

1. Renal vascular dysautonomy: This term refers to a reduction of the autonomic renal vascular reflex that protects the kidney from hypotensive and hypertensive states.
2. Senile hypofiltration: The progressive reduction in glomerular filtration due to the senescence process. This reduction starts around the age of 30 and continues to decline at a rate of approximately 1 mL per year.
3. Tubular dysfunction: The reduction of the tubular maximal capacity to reabsorb or excrete some substances such as glucose or phosphate (see Chapter 5) or the tendency to reduce both secretion of K^+ and reabsorption of Na^+.
4. Tubular frailty: In the elderly, renal tubular cells are more vulnerable to hypoxic or nephrotoxic injury and take longer to recover from acute tubular necrosis.
5. Medullary hypotonicity: In older people, the renal medulla has a lower tonicity compared to younger healthy individuals. This phenomenon produces a reduction in the effect of antidiuretic hormone and, as a consequence, a reduction in water reabsorption. The above, combined with a decreased sensation of thirst, may lead to severe dehydration.

Three of these *giants* (senile hypofiltration, tubular dysfunction, and medullary hypotonicity) modulate the characteristics of water and electrolytes balance maintenance in the healthy aged.

As a rule, under normal circumstances the aged kidney is able to maintain plasma electrolyte concentrations [3], but, as with other organs, the functional characteristic of the aged kidney is a slow response or sometimes a complete inability to adapt to situations of overload or restriction.

Renal Sodium Handling in the Elderly

In the elderly, the renal response to sodium loading and especially sodium depletion is blunted. There are minor discrepancies regarding the ability of the aging kidney to excrete an extra sodium load, but most researchers suggest that this capacity diminishes with age [4–8]. As a result, if we were to give a salt load to an aged individual, it would take him longer to eliminate it, due to the reduction in the glomerular filtration rate (GFR) [9]. On the other hand, if an elderly person follows a sodium-restricted diet, a sodium balance would eventually be achieved, but the required period would be substantially longer, with significantly greater urinary sodium losses than in younger individuals before the new state of equilibrium would be attained [9]. The capacity of the aging kidney to adapt to a chronic moderately low salt intake (50 mmol/24 h) is also reduced [10, 11].

In the latter study, young people reached sodium equilibrium in 5 days, whereas the elderly participants were unable to reach a sodium balance, in spite of a mean loss of 1.3 kg of body weight during the 9 days of 50 mmol/24 hr sodium intake [12, 13] (Figure 8.1).

As a result of these slow adaptations, both intravascular volume expansion and contraction are frequent findings in patients on geriatric wards [14–16].

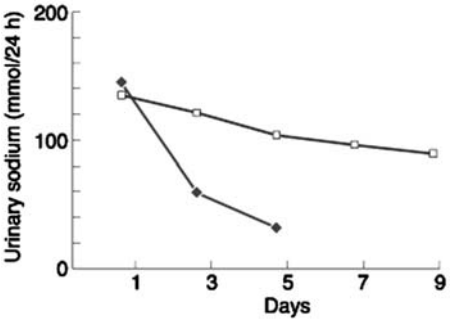

Fig. 8.1 The kidney's ability in healthy young individuals (closed diamonds) and the elderly (open diamonds) to adapt to a 50-mmol Na^+ restriction. The younger individuals reached sodium balance within 5 days; the elderly ones failed to reach balance within 9 days and continued to excrete more than double of the administered sodium per 24 hours. (*Source*: Macías-Núñez, J.F., Cameron S. The ageing kidney. In *Oxford Textbook of Clinical Nephrology*, J.S. Cameron, ed. Oxford: Oxford University Press. 2005.)

Furthermore, a clinical picture of hyponatremia secondary to chronic sodium urinary loss—"senile sodium leakage hyponatremia"—has been described in the elderly [17]. It is more frequent in situations of salt restriction and diuretics. We have seen this hyponatremia in healthy people on a normal diet without diuretics but complaining of a remarkable loss of appetite for weeks. It is easily understandable that if the aged do not eat foods, their salt and fluid intake is almost negligible. The above, in combination with an inefficient capability of the kidney to reabsorb Na^+, leads to hyponatremia due to renal Na^+ spilling. The senile sodium leakage hyponatremia of either etiology is rather common in geriatrics, internal medicine, or surgical wards. In general, there are no distinctive clinical manifestations different than those seen in other hyponatremias (see Chapter 10) except that it is not unusual for it to present as instability, falls, or acute mental impairment syndrome, which resolve naturally after Na^+ replacement [17]. However, one study did not show any differences in the renal handling of sodium in the elderly compared to younger people [18].

Kirkland et al. [19] found a greater urinary elimination of water and electrolytes during the night in the elderly, and Musso [20] saw a higher urea output in the 24-hour urine of the healthy aged compared to the young. Both of these studies may contribute to finding an explanation for the nocturia observed in 70% of elderly men and women.

Urinary Sodium Output in the Elderly

There is no universal and "normal" urinary Na^+ output value for a healthy aged person on a normal, unrestricted salt diet. It is known that in the area of the University of Iwate in Japan, the mean urinary Na^+ output (MuNaOp) is 236 ± 22 mmol/L/24 hr [21]. In a collaborative study between the Universities of Catanzaro (Italy) and Oslo (Norway) [22], the MuNaOp was 115 ± 5.3. In the area of Buenos Aires under the care of the Hospital Italiano, the mean urinary sodium output was 110 ± 35 mmol/L [23], and in the area served by the

University Hospital in Salamanca in Spain, the MuNaOp was 165 ± 97 [24]. All observers agree that there is a diminished capacity to conserve sodium with increasing age, which again is consistent with clinical observations that large sodium excretion rates and sodium depletion are frequently found in patients on geriatric wards [24–26].

Sites of Sodium Loss Within the Nephron

Proximal Tubule

From studies on the clearance of lithium, which is mainly reabsorbed in the proximal tubule to an extent comparable with the reabsorption of sodium and water, it can be concluded that fractional reabsorption of sodium from the proximal tubule does not change significantly with age [27] (Figure 8.2). The above findings are in concordance with our previous results, which revealed that the reabsorption capacity of the proximal tubule is not impaired in the aged [26].

Loop of Henle

A clearance study employing the hyposaline overload test, which is believed to be able to discriminate the functional capacity of the "proximal nephron" [the segment running between the beginning of the proximal convoluted tubule to the bend of the thin descending limb of the loop of Henle (see Chapter 5)] from that of the "distal nephron" [thick ascending limb of the loop of Henle (Figure 8.3)] showed that that the "proximal nephron" behaves similarly in the young and in the elderly. Schou et al. [27] have supported this finding. However, in the "distal nephron." a clear difference in the handling of sodium was found in 85% of the tested aged subjects. These results have recently confirmed by Abreu et al. [28] and Fliser et al. [29].

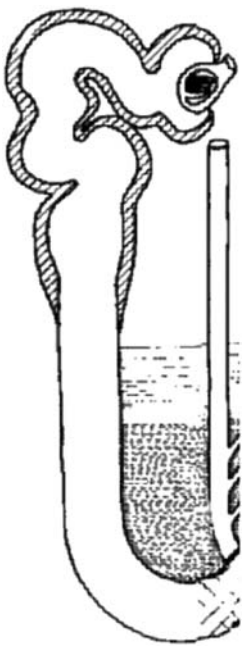

Fig. 8.2 "Proximal segment": In this segment there is no difference in the tubular handling of sodium among young, old, and old-old healthy people.

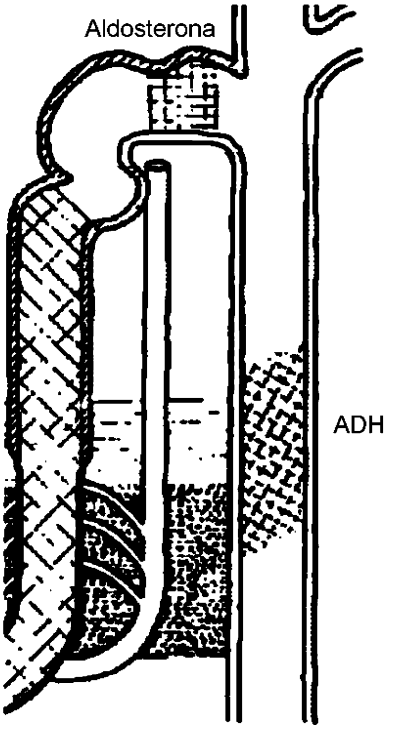

Fig. 8.3 "Distal segment": Ascending limb of the loop of Henle. The ability of this segment to reabsorb Na is statistically lower in the old and old-old compared to young healthy individuals.

Distal Tubule

Apart from the "intrinsic" reduction in the functional capacity of the ascending limb of the loop of Henle, other factors such as lower aldosterone concentrations in plasma and urine [30] and the blunted response of the renin-aldosterone system to stimulation such as standing up, walking, and salt restriction also contribute to the attenuated capacity of the normal aging kidney to retain salt [10, 13, 24, 30].

In summary, the ascending limb of the loop of Henle and other tubular segments where aldosterone exerts its effect are primarily responsible for the aging kidney's impairment in tubular sodium handling. The diminished capacity of healthy aged kidneys to reabsorb sodium by the ascending limb of the loop of Henle has two important direct consequences: First, the amount of sodium arriving at more distal segments of the nephron (distal convoluted and collecting tubules) increases, and second, the medullary interstitium´s capacity to concentrate is diminished. As a consequence, elderly individuals exhibit both an increased sodium excretion and the inability to maximally concentrate the urine.

Potassium Handling in Aged Individuals

Even though the ingestion of potassium by the elderly is low, as their diet has a low content of meat, fruit, and vegetables, plasma potassium concentrations in the aged do not differ from those observed in younger populations [31–33].

Despite plasma potassium being normal in healthy elderly individuals, the elderly can develop hypokalemia more rapidly than the young when they

are on diuretic treatment [34, 35]. Measurements of total exchangeable body potassium by various isotopic dilution methods all show that total body potassium is 15% lower in the aged compared to young people (2500 mmol vs. 3000 mmol) [6, 36]. However, the administration of extra potassium does not raise the body potassium in the elderly [37]. This phenomenon could be the consequence of the reduced muscle mass in the elderly, as this tissue represents the major site for potassium storage.

As one of us has shown [10], the urinary potassium output is significantly lowered in the aged compared with the young, in concordance with the findings communicated by Biswas et al. [38], who postulated that physiological changes associated with age would predispose the elderly to hyperkalemia. This is particularly the case when they are treated with anti-aldosterone agents, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers [39].

When the values of two potassium excretion markers—the fractional excretion of potassium (FEK) and the transtubular potassium concentration gradient (TTKG)—observed in healthy elderly patients are compared to other situations causing an altered GFR, i.e., in patients with chronic renal disease, the aged show lower values [40, 41] (Figure 8.4).

Water Metabolism in the Elderly

Total body water slightly diminishes with age, so that it comprises only 54% of total body weight [42]. This could be explained by the fact that elderly people have a greater proportion of fat in their body weight than the young [42, 43]. The diminution seems to be predominantly intracellular. Cross-sectional and longitudinal studies have demonstrated that plasma and blood volume do not change as a result of age alone in healthy adults [44,45], although elderly women had a significantly greater plasma volume than young women [46]. We have found that plasma and blood volume measurements using radiolabeled albumin do not differ between young and healthy elderly

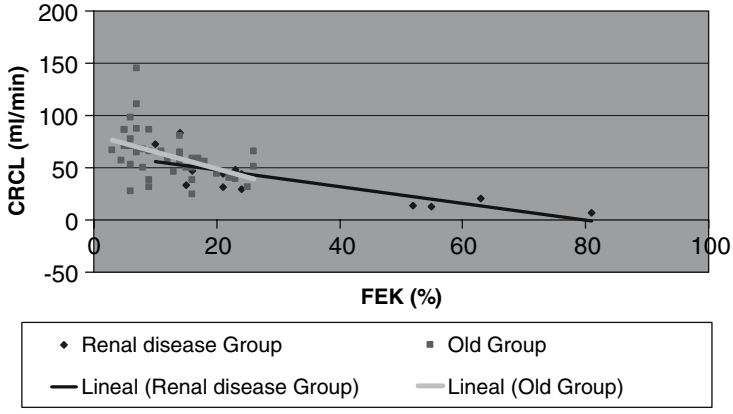

Fig. 8.4 Relationship between creatinine clearance and FEK (fractional excretion of k) in healthy elderly and patients with low GFR due to chronic renal insufficiency Musso CG, De Miguel R, Algranati L, et al. Renal potassium excretion: comparison between chronic disease patients and old people.
Source : Musso et al. Reference 40.

volunteers. Males have a greater volume than females, regardless of age [13]. Thus, a diminished plasma volume in an elderly individual is almost always the result of disease.

Water Balance and the Renal Handling of Water

Water equilibrium is achieved through a balance between water intake and water disposal. This balance is controlled by the regulation of thirst, the neurohypophyseal function, and the renal capacity for water management [47]. Thirst and the intake of liquids diminish with age. When healthy active elderly volunteers were water-restricted for 24 hours, the threshold for thirst was increased and water intake reduced in comparison to a control group of younger individuals. Despite the reduction in water intake and thirst, a considerable increase in blood osmolality, plasma sodium concentration, and circulating vasopressin occurred during water deprivation [13]. Osmotic release of Arginine vasopressin (AVP) in response to intravenous hypertonic saline in elderly people is greater than in the young. However, the AVP response to volume depletion is blunted [48], as in the aged rat [49], in which insensitivity of the cortical collecting duct to AVP with a reduced generation of cAMP rather than a reduced medullary hyperosmolality appeared to be responsible.

This lack of thirst sensation in elderly people, despite an increase in plasma tonicity, remains unexplained. Dryness of the mouth and a decrease of taste with age may contribute to the diminution of the sensation of thirst [50]. Another possible mechanism might be an alteration in mental capacity [51] or cortical cerebral dysfunction [52]. It has also been suggested that a reduction in the sensitivity of the osmoreceptors responsible for thirst regulation may play a part in water-handling alterations in elderly persons. A contrary view has arisen from the study of Helderman et al. [53], in which an increase in the sensitivity of the osmoreceptors that regulate the release of vasopressin was observed.

Reduced thirst may also result from an inappropriate response to hypovolemia. Age diminishes the sensitivity of the baroreceptors and the release of vasopressin mediated by them [48]. Finally, angiotensin concentrations, a powerful generator of thirst, are diminished in elderly people. Therefore, stimulation of thirst requires severe hypovolemia and/or hypotension [54]. There is, as noted above, no difference in the plasma concentration of vasopressin between young and elderly persons before or after water deprivation [47].

Urinary Concentration and Dilution

Urine Concentration

Aging reduces the capacity of the kidney to concentrate urine [55, 56]. The maximal capacity to concentrate urine gradually decreases by 5% per decade of age [57], ranging from a maximum urinary specific gravity of 1030 at 40 years of age to 1023 at 89 years of age. Rowe et al. [56] found a mean maximal urinary osmolality of 1109 mOsm/kg in individuals aged 20 to 39 years, with a minimum urine flow rate of 0.49 ± 0.03 mL/min. In the aged, maximal urinary osmolarity reached 1051 mOsm/kg in 40- to 59-year-olds, and 882 mOsm/kg in those aged 60 to 79 years, in whom the minimal urinary

flow rate (1.03 mL/min) was more than double that of the young. The study of Lindeman et al. [58] showed similar results. Kirkland et al. [59] noted that a high percentage of healthy individuals aged 60 to 80 years have a higher excretion of water, sodium, and potassium during the night than younger controls as well as complaints of nocturia. This alteration in circadian rhythm does not only depend on the inability to concentrate the urine, but also upon the defects in sodium handling and aldosterone secretion, together with the increased urinary urea excretion already mentioned [20, 59].

The origin of the reduction in concentration is also complex. The small differences in the amount of fluid intake between young and elderly individuals cannot completely explain the differences in solutes and urinary elimination observed during water deprivation [56]. The diminution of the concentrating ability has been related to the decrease in glomerular filtration rate that occurs with age. It is assumed that as the number of functioning nephrons decreases with age, the remainder are subjected to osmotic diuresis, which impairs the ability to concentrate urine [58, 60]. Despite this, some data do not show a close relationship between the reduction of the glomerular filtration rate and the capacity to concentrate urine in the elderly [56]. The relative increase in medullary blood flow noted above could contribute to the impairment of renal concentration capacity by means of medullary "wash out" [61, 62].

Nevertheless, data to support this suggestion are not available. As already discussed, inappropriately low ADH levels are not a factor in the genesis of the defect. The defect in sodium chloride reabsorption in the ascending limb of the loop of Henle, which is the basic underlying principle for the operation of the countercurrent concentration mechanism, may be an important factor for the decrease in the capacity to concentrate urine seen in aged individuals.

Urine Dilution

Only a few reports deal with the capacity of the aging kidney to dilute urine, but it has been found to be decreased [13, 55, 58]. Dontas et al. [55] found a minimum urine concentration of 92 mOsm/kg in elderly individuals compared with 52 mOsm/kg in the young. Maximum free water clearance (C_{H2O}) was also reduced in elderly individuals from 16.2 to 5.9 mL/min. Some authors speculate that the reduced glomerular filtration rate is responsible for these reductions, but the C_{H2O} GFR was somewhat reduced in the elderly (9.1 vs. 10.2%). The functional impairment of the diluting segment of the thick ascending limb of the loop of Henle described above seems to account for the remainder of the declined capacity to dilute urine observed in the aged [25].

Water and Electrolytes Handling in Special Groups

Old-Old People

As we have previously discussed, a few clearance studies test the tubular segmental competence of the nephron in the old (65–79 years), but none deals with the healthy old-old population (80 years and over). We compared, by means of clearance studies, the response to a hyposaline overload of five healthy volunteers aged 80–87 years on their normal diet with that of five healthy young volunteers, who were also on their normal diet (without salt restriction), following our laboratory's standard procedure [10, 24]. Following a complete geriatric evaluation (see Chapter 1) including clinical examination,

Table 8.1 Results of the response to a saline overload in healthy old-old and young volunteers. Observe that the percentage of Na^+ reabsorption in the loop of Henle (distal nephron) is significantly lower in healthy old-old than in young subjects.

	Na Clearance	Free water Cl	"Proximal"	"Distal"
Young (n=5)	2.6 ± 1.14	15.32 ± 2.63	17.93 ± 3.11	85.72 ± 4.51
Old-old (n=5)	1.64 ± 0.31	5.92 ± 0.71∗	7.82 ± 0.81∗	75.64 ± 4.47∗

geriatric scales, blood biochemistry, and renal and cardiac ultrasonography, detectable pathology was ruled out. As shown in Table 8.1, under basal conditions the mean urinary Na^+ output (Na^+ clearance) was diminished in the old-old compared to young controls. In the alimentary questionnaire, we found that all of the old-old were on a low-salt diet. Because of this, we interpreted the low urinary Na^+ output in basal conditions (before the hyposaline overload test was given) as the normal renal response to prolonged salt restriction. The reason for their low-salt intake is most probably the usual worldwide recommendation to reduce salt intake. Consequently, the tubule's "proximal nephron" [from the very beginning of the proximal convoluted tubule to the bend of the loop of Henle (see Chapter 5)] was able to reabsorb almost all filtered sodium, as expected in a healthy kidney. As a result of the above, the distal delivery of Na^+, i.e., the remaining percentage of the filtered sodium, which does not undergo tubular reabsorption in this segment and reaches the bend of the loop of Henle, is significantly lower than that observed in healthy younger patients (Table 8.1).

In spite of the above, the "distal nephron" (ascending limb of the loop of Henle) was capable of reabsorbing 75%, while the healthy young were able to reabsorb 85.7%. These results are comparable to those observed in healthy elderly volunteers [62, 63] (Table 8.1).

Intellectual Impairment Syndrome

In untreated elderly patients with mental disorders, an alteration in intracellular, extracellular, and total body water has been found [63]. Deterioration of verbal learning is associated with an increase in body water, intracellular and extracellular fluid, and exchangeable sodium and potassium in relation to dry body weight. The decline in verbal ability was associated with a shift of water from the extracellular to the intracellular compartments and a reduction in the amount of interchangeable sodium in relation to lean body weight. In addition to this, lithium or other drugs may affect water and electrolyte handling. Regarding water metabolism, we have not been able to show differences in plasma ADH levels between elderly people with and without dementia, although a tendency toward higher amounts of body water was demonstrated in the group with dementia [64] (Table 8.2). Independent of the above, the importance of checking plasma electrolytes and urea in confused elderly individuals hardly needs mentioning because many of the acute or chronic electrolyte imbalances may present as an acute confusional syndrome.

Immobility Syndrome

The immobility syndrome (IS) consists of a reduction in the capability to perform daily activities due to a deterioration in motor function that leads to

Table 8.2 Water metabolism in elderly patients with dementia CrCl: creatinine clearance, PNa: plasma sodium, PK: plasma potassium, PO: plasma osmolality, lean body mass (LBM), antidiuretic hormone (ADH), real body water (BW), real body water / theoretical body water (BWR),

	Healthy Patients		Patients with Dementia		
	$\overline{X}$	SD	$\overline{X}$	SD	p
Weight (kg)	61, 8	15, 5	49, 6	11, 4	0, 007
Height (m)	1, 5	0, 1	1, 5	0, 1	n/s
CrCl (ml/min)	59, 6	17, 3	48, 8	12, 4	0, 03
PNa (mEq/l)	141	5	141	4	n/s
PK (mEq/l)	4, 1	0, 4	3, 8	0, 5	n/s
PO (mOs/l)	292	12	293	9	n/s
LBM (kg)	46	9	41	9	n/s
ADH (pg/ml)	3, 1	2, 9	4, 2	2, 9	n/s
BW (%)	55	9	59	10	n/s
BWR	1, 14	0, 2	1, 22	0, 2	n/s

characteristic changes in body structure and physiology (see Chapter 1). The prevalence of this syndrome is linked to the patient's age and environment. In noninstitutionalized people older than 64 years of age, the prevalence of immobility is around 12%, while in those older than 79 years it is about 27%. Moreover, in the institutionalized old, the IS reaches a prevalence of 30% [67].

The body alterations in people suffering from IS included reduced muscle mass and strength, joint contractures, reduced lung tidal volumes and maximal breathing capacity, diminished cardiac output, orthostatism, capillary leakage, increased daily nitrogen loss, hypercalciuria, reduced bowel peristalsis, and decreased intellectual capacity [67, 68].

As we have mentioned, a reduced GFR is demonstrated by the lower creatinine clearance in the IS group [69]. The conjunction of the reduced GFR together with a low fractional excretion of sodium usually points toward a pre-renal hypoperfusion situation's being the cause. These situations often occur due to reduced cardiac output and capillary leakage, which are usually present in immobile patients.

As shown in Table 8.3, patients with IS have a tendency to retain free water, as shown by the increased body water content, lower plasma sodium, and lower osmolality found in patients with IS compared to the healthy aged population. Even though plasma ADH was not significantly different in these

Table 8.3 Water metabolism in elderly patients with immobility syndrome Plasma Na (PNa), plasma osmolality (PO), antidiuretic hormone (ADH), lean mass (LM), Real body water (BW), real body water / theoretical body water (BWR).

	PNa (mEq/l)	PO (mOs/l)	ADH (pg/dl)	BW (%)	BWR
(M) X, SD	143 +/– 1,28	281 +/– 5,22	4,2 +/– 3,56	50 +/– 9,8	0,99 +/– 1,3
(IS) X, SD	140 +/– 5,16	270 +/– 10	3,4 +/– 2,6	61 +/– 7,7	1,3 +/– 0,16
P	0,014	0,025	N/S	0,0003	0,0001

two groups, a possible explanation to conciliate the relatively higher ADH plasma concentration with its serum osmolality level may be water retention, as the immobility syndrome group had significantly higher body water (BW). It could be hypothesized that pre-renal hypoperfusion could induce the well-known relative ADH excess found in patients with IS [69].

References

1. Musso, C.G. Clinical catastrophic events in geriatrics: Its physiopathological bases. *Int. Urol.Nephrol*. (in press).
2. Musso, C.G. Geriatric nephrology and the "nephrogeriatric giants." *Int. Urol. Nephrol*. 2002; 34(2):255–256.
3. Refoyo, A., Macías-Núñez, J.F. The maintenance of plasma sodium in the healthy aged. *Geriatr. Nephrol. Urol.* 1991; 1:65–68.
4. Yamada, T., Endo, T., Ito, K., Nagata, H., Izumiyama, T. Age-related changes in endocrine and renal function in patients with essential hypertension. *J. Am. Geriatr. Soc*. 1979; 27:280–292.
5. Bengelé, H.N., Mathias, R.S., Alexander, E.A. Impaired natriuresis after volume expansion in the aged rat. *Ren. Physiol.* 1981; 4:22–29.
6. Hiraide, K. Alterations in electrolytes with aging. *Nihon Univ. J. Med.*1981; 23: 21–31.
7. Hackbarth, H., Harrison, D.E. Changes with age in renal function and morphology in C57BL/6, CBA/HT6, and B6CBAFI mice. *J. Gerontol*. 1982; 37: 540–547.
8. Myers, J., Morgan, T., Waga, S., Manley, K. The effect of sodium intake on blood pressure related to the age of the patients. *Clin. Exp. Pharmacol. Physiol*. 1982; 9:287–289.
9. Meyer, B.R. Renal function in aging. *J. Am. Geriatr. Soc*. 1989; 37:791–800.
10. Macías-Núñez, J.F., García-Iglesias, C., Tabernero-Romo, J.M., Rodríguez-Commes, J.L., Corbacho-Becerra, L., Sanchez-Tomero, J.A. Renal management of sodium under indomethacin and aldosterone in the elderly. *Age and Ageing* 1980; 9:165–172.
11. Epstein, M., Hollenberg, N.H. Age as a determinant of renal sodium conservation in normal man. *J. Lab. Clin. Med.* 1976; 87:411–417.
12. Musso, C., López-Novoa, J.M., Macías-Núñez, J.F. Renal tubular function in the old old. *Rev. Esp. Geriatr. Gerontol*. 2004; 39(5):314–319.
13. Macías-Núñez, J.F., Bondía Román, A., Rodriguez-Commes, J.L. Physiology and disorders of water balance and electrolytes in the elderly. In *Renal Function and Disease in the Elderly,* J.F. Macías-Núñez and J.S. Cameron, eds. London: Butterworths. 1987; pp. 67–93.
14. Solomon, L.R., Lye, M. Hypernatraemia in the elderly patient. *Gerontology* 1990; 36:171–179.
15. Solomon, L.R., Sangster, G., Lye, M. Hyponatremia in the elderly patient. *Geriatr. Nephrol. Urol*. 1992; 2:63–74.
16. Roberts, M.M., Robinson, A.G. Hyponatremia in the elderly: Diagnosis and management. *Geriatr. Nephrol. Urol*. 1993; 3:43–50.
17. Macías-Núñez, J.F., Musso, C.G., Rivera, H., Imperiali, N., Algranati, L. Sodium loss induced hyponatremia in the elderly on a low sodium diet. Biomed.uninet.edu. May–August 2006.
18. Karlberg, B.E., Tolagen, K. Relationships between blood pressure, age, plasma renin activity and electrolyte excretion in normotensive subjects. *Scand. J. Clin. Lab. Invest*. 1977; 37:521–528.
19. Kirkland, J.L., Lye, M., Levy, D.W., Banerjee, A.K. Patterns of urine flow and electrolyte secretion in healthy elderly people. *Br. Med. J*. 1983; 285:1665–1667.

20. Musso, C.G., López Novoa, J., Macías–Núñez, J.F. Handling of water and sodium by the senescent kidney. Interpretation of a clearance technique for functional study. *Rev. Esp. Geriatr. Gerontol*. 2005; 40(2):114–119.
21. Adachi, T., Kawamura, M., Owada, M., Hiramori, K. Effect of age on renal functional and orthostatic vascular response in healthy men. *Clin. Exp. Pharmacol. Physiol*. 2001; 28:877–880.
22. Fuiano, G., Sund, S., Mazza, G., Rosa, M., Caglioti, A., Gallo, G., Natale, G., Andreucci, M., Memoli, B., De Nicola, L., Conte, G. Renal hemodynamic response to maximal vasodilating stimulus in healthy older subjects. *Kidney Int*. 2001; 59:1052–1058.
23. Musso, C.G., Macías–Núñez, J.F., Musso, C.A.F., Algranati, S., dos Ramos Farias, E. Fractional excretion of sodium in old people on low sodium diet. *FASEB J*. 2000; 14:A659.
24. Macías-Núñez, J.F., García-Iglesias, C., Tabernero-Romo, J.M., Rodríguez-Commes, J.L., Corbacho-Becerra, L., Sanchez-Tomero, J.A. Renal management of sodium under indomethacin and aldosterone in the elderly. *Age and Ageing* 1980; 9:165–172.
25. Epstein, M., Hollenberg, N.H. Age as a determinant of renal sodium conservation in normal man. *J. Lab. Clin. Med*. 1976; 87:411–417.
26. Macías-Núñez, J.F., et al. Renal handling of sodium in old people: A functional study. *Age and Ageing* 1978; 7:178–181.
27. Schou, M., Thomson, K., Vestergaard, P. The renal lithium clearance and its correlation with other biological variables: Observation in a large group of physically healthy persons. *Clin. Nephrol.* 1986; 25:207–211.
28. Abreu, P.F., Ramos, L.R., Sesso, R. Abnormalities of renal function in the elderly. *Geriatr*, *Nephrol*, *Urol*. 1999; 9:141–145.
29. Fliser, D., Franek, E., Joest, M., Block, S., Mutschler, E., Ritz, E. Renal function in the elderly: Impact of hypertension and cardiac function. *Kidney Int.* 1997; 51:1196–1204.
30. Ceruso, D., Squadrito, G., Quartarone, M., Parisi, M. Comportamento della funzionalita renale e degli elettroliti ematici ed urinari dopo aldosterone in soggetti anziani. *Giornale di Gerontol.* 1970; 18:1–6.
31. Videbaek, A., Ackermann, P.G. The potassium content of plasma red cells in various age groups. *J. Gerontol.* 1953; 8:63–64.
32. Dall, J.L.C., Paulose, S., Fergusson, J.A. Potassium intake of elderly patients in hospital. *Gerontol. Clin*. 1971; 13:114–118.
33. Burini, R., Da Silva, C.A., Ribeiro, M.A.C., Campana, A.D. Concentracão de sodio e de potassio no soro e plasma de individuos normais. Influencia da idade, do sexo e do sistema de colheita do sangue sobre os resultados. *Revista de Hospitale Clinico da Facultad do Medicina de São Paulo* 1973; 28:9–14.
34. Dall, J.L.C., Gardiner, N.S. Dietary intake of potassium by geriatric patients. *Gerontol. Clin*. 1971; 13:119–124.
35. Sunderam, S.G., Mankikar, G.D. Hyponatremia in the elderly. *Age and Ageing* 1983; 12:77–80.
36. Lye, M. Distribution of body potassium in healthy elderly subjects. *Gerontology* 1981; 27:286.
37. Kromhout, D., Broberg, U., Carlmark, B., Karlsson, S., Nisell, O., Reizenstein, P. Potassium depletion and ageing. *Comp. Ther*. 1977; 3:32–37.
38. Biswas, K., Mulkerrin, E.C. Potassium homoeostasis in the elderly. *Quar. J. Med*. 1997; 90:487–492.
39. Rodriguez-Puyol, D. The aging kidney. *Kidney Int*. 1998; 54:2247–2265.
40. Musso, C.G., De Miguel, R., Algranati, L., Dos Ramos Farias, E. Renal potassium excretion: Comparison between chronic disease patients and old people. *Int. Urol. Nephrol*. 2005; 37:167–170.

41. Musso, C., Liakopoulos, V., De Miguel, R., Imperiali, N., Algranati, L. *Int. Urol. Nephrol.* 2006; 38:387–390.
42. Edelman, I.S., Leibman, J. Anatomy of body water and electrolytes. *Am. J. Med.* 1959; 27:256–260.
43. Edmonds, C.J., Jasani, B.M., Smith, T. Total body potassium and body fat estimation in relationship to height, sex, age, malnutrition and obesity. *Clin. Sci. Molec. Med.* 1975; 48:431–440.
44. Cohn, J.E., Shock, N.W. Blood volume studies in middle aged and elderly males. *Am, J, Med, Sci.* 1949; 217:388–391.
45. Chien, S., Usami, S., Simmons, R.L. Blood volume and age: Repeated measurements on normal men. *J. Appl. Physiol.* 1966; 21:583–588.
46. Wörum, I., Fulöp, T., Csongör, J., Foris, G., Leóvey, A. Interrelation between body composition and endocrine system in healthy elderly people. *Mech. Ageing Develop.*1984; 28:315–324.
47. Shannon, R.P., Minaker, K.L., Rowe, J.W. Aging and water balance in humans. *Sem. Nephrol.* 1984; 4:346–353.
48. Rowe, J.W., Minaker, K.L., Sparrow, D., Robertson, G.L. Age-related failure of volume-pressure-mediated vasopressin release. *J. Clin. Endocrinol. Metab.* 1982; 54:661–664.
49. Bengelé, H.N., Mathias, R., Perkins, J.N., McNamara, E.R., Alexander, E.A. Impaired renal and extrarenal adaption in old rats. *Kidney Int.* 1983; 23:684–690.
50. Hugonot, R., Dubos, G., Mathes, G. Étude expérimentale des troubles de la soif du vieillard. *La Rev. Gériatrie* 1978; 4:179–191.
51. Seymour, D.G., Henschke, P.J., Cape, R.D.T., Campbell, A.J. Acute confusional states and dementia in the elderly: The role of dehydration/volume depletion, physical illness and age. *Age and Ageing* 1980; 9:137–406.
52. Miller, P.D., Krebs, R.A., Neal, B.J., McIntyre, D.O. Hypodypsia in geriatric patients. *Am. J. Med.* 1982; 73:354–356.
53. Helderman, J.H., Vestal, R.E., Rowe, J.W., Tobin, J.D., Andres, R., Robertson, G.L. The response of arginine vasopressin to intravenous ethanol and hypertonic saline in man: The impact of aging. *J. Gerontol.* 1978; 33:39–47.
54. Robertson, G.L. Abnormalities of thirst regulation. *Kidney Int.* 1984; 25:460–469.
55. Dontas, A.S., Marketos, S., Papanayioutou, P. Mechanisms of renal tubular defects in old age. *Postgraduate Med. J.* 1972; 48:295–303.
56. Rowe, J.W., Shock, N.W., De Fronzo, R.A. The influence of age on the renal response to water deprivation in man. *Nephron* 1976; 17:270–278.
57. Lewis, W.H., Alving, A.S. Changes with age in the renal function of adult men. Clearance of urea, amount of urea nitrogen in the blood, concentrating ability of kidneys. *Am. J. Physiol.* 1938; 123:505–515.
58. Lindeman, R.D., Van Buren, H.C., Raisz, L.G. Osmolar renal concentrating ability in healthy young men and hospitalized patients without renal disease. *N. Engl. J. Med.* 1960; 262:1396–1409.
59. Kirkland, J.L., Lye, D.W., Banerjee, A.K. Patterns of urine flow and electrolyte secretion in healthy elderly people. *Br. Med. J.* 1983; 285:1665–1667.
60. Kleeman, C.R. Water metabolism. In *Clinical Disorders of Fluid and Electrolyte Balance,* M.H. Maxwell and C.R. Kleeman, eds. New York: McGraw-Hill. 1972; p. 697.
61. Takazakura, E., Sawabu, N., Handa, A., Takada, A., Shinada, A., Takeuchi, J. Intrarenal vascular change with age and disease. *Kidney Int.* 1972; 2:224–230.
62. Hollenberg, N.K., Adams, D.F., Solomon, H.S., Rashid, A., Abrams, H.L., Merrill, J.P. Senescence and the renal vasculature in normal man. *Circ. Res.* 1974; 34:309–316.
63. Macías-Núñez, J.F., Cameron S. The ageing kidney. In *Oxford Textbook of Clinical Nephrology*, J.S. Cameron, ed. Oxford: Oxford University Press. 2005.

64. Musso, C.G., Macías-Núñez, J.F. Renal physiology in the oldest old: The Sphinx remakes her question. *Int. Urol.Nephrol*. 2005; 37:653–654.
65. Cox, J.R., Orme, J.E. Body water, electrolytes and psychological test performance in elderly patients. *Gerontol. Clin*. 1973; 15:203–208.
66. Musso, C.G., Macías-Núñez, J.F., Algranati, S., dos Ramos Farias, E. Water metabolism in demented elderly. *FASEB J*. 2000; 14:A659.
67. Vazquez Pedrazuela, C., Lazaro del Nogal, M., Verdejo Bravo, C., Royuela Arte, T., Torrijos Torrijos, M., Ribera Casado, J.M. Immobility syndrome in patients being care for in a home care unit. *Ann. Intern. Med.* 1995; 12(10):489–491.
68. Perez Almeida, E., Blanco Pascual, E. El paciente con sindrome de inmovilidad. En *Geriatría desde el Principio*, J.F. Macías-Núñez, F. Guillén Llera, and J.M. Ribera Casado, eds. Barcelona: Glosa. 2000; pp. 135–152.
69. Musso, C.G., De Miguel, R., Imperiali, N., Algranati, L. Water metabolism in the elderly with immobility syndrome. *Proc. 8th Int. Conf. Geriatr. Nephrol. Urol*., Thessaloniki, Greece: Syllabus. 2005; p. 285.

9

Renal Handling of Uric Acid, Magnesium,Phosphorus, Calcium, and Acid Base in the Elderly

Carlos G. Musso, Joaquin Antonio Alvarez Gregori, and Juan-Florencio Macías-Núñez

Introduction

Few studies deal with the competence of the aging kidney to handle uric acid, magnesium, phosphate, calcium, and acidification. The majority of these studies were carried out on ill patients admitted to medical wards, attending outpatient follow-ups, or institutionalized in home care for the elderly. The above-named capacities have not been explored in the old-old. We discuss the ability of the aging kidney to handle the above-mentioned elements in groups of old and old-old healthy persons after ruling out detectable pathologies by means of a holistic geriatric evaluation (see Chapter 1).

Uric Acid

Uric acid is the end product of the purine metabolism in humans and is synthesized from the xanthine and hypoxanthine bases by the action of the xanthine oxidase enzyme. Since the pK of uric acid is 5.4, in solutions most of it (99%) is in the form of urate. In urine, where the pH oscilates between 4.7 and 8.0, the ratio of uric acid to urate varies with pH, being entirely uric acid at a urinary pH of 5.0 or less [1, 2].

The normal plasma uric acid level is 2.2–7.5 mg/dL in adult males and is slightly lower (2.1–6.6 mg/dL) in premenopausal females [3]. Normally, two-thirds of uric acid is eliminated by the kidney and one-third by the gut [4]. Only 4% of this substance is bound to plasma proteins; thus, most of it is freely filterable [5]. Around 10% of the filtrated urate is finally excreted in the urine. This process is usually greater in males than females: Fractional excretion of uric acid (FEUAc) is around 12% and 8%, respectively [2].

Renal Handling

In the kidney, uric acid is mainly handled in the proximal tubule, where it undergoes two main processes: reabsorption and secretion. Reabsorption takes

place more specifically in the S_1 segment, where uric acid is transported across the brush border through indirect coupling to a sodium transporter. On the other hand, uric acid tubular secretion, which takes place in the S_2 segment, appears to be mediated principally by a voltage-sensitive transporter [6, 7].

Many substances can influence the renal handling of uric acid. Some of them reduce its renal excretion, such as low doses of cyclo-oxygenase inhibitors, diuretics, pyrazinamide, ethambutol, and ethanol and lead intoxication. Conversely, high doses of cyclo-oxygenase inhibitors increase uric acid excretion [2, 8].

Uric Acid in the Aged

In healthy old people, serum uric acid levels and FEUAc do not differ from those of a healthy young population. Even more, when healthy old people undergo volume expansion, they show no significant difference in their renal uric excretion before and after the procedure (see Table 9.1).

Hypouricemia in the elderly is observed in the many different settings. These include the administration of uricosuric agents (benzbromarone), acquired proximal tubular defects, syndrome of inappropriate antidiuretic hormone secretion, hematological malignant disorders, and as a consequence of the use of corticosteroids, losartan, and nonsteroidal anti- inflammatory drugs [2, 9–11].

Hyperuricemia in the elderly is observed in gouty inflammatory arthritis, uric acid urolithiasis, chronic renal disease, acute hyperuricemic nephropathy (tumoral lysis), rhabdomyolysis (crush injuries), and prolonged immobilization [12–14].

In the majority of patients with gout, hyperuricemia results from a polygenically inherited tendency to have a reduced fractional excretion of uric acid, and this is almost always coupled with a large intake of dietary purine. In this context, there is an increased tubular reabsorption of uric acid, since FEUAc is around 5% [12].

Even though in the first stages of chronic renal failure (CRF) serum urate increases at the same rate as creatinine, as the creatininemia increases further, the uricemia does not due to the increase in uric acid excretion, which can reach 85% or more, in advanced renal failure. Furthermore, there is an increased gut secretion of uric acid in CRF [13].

Table 9.1 Fractional Excretion of Calcium, Phosphorus, Magnesium, and Uric Acid, in Basal Conditions and After Hyposaline Volume Overload in Healthy Young and Old-Old Volunteers.

	Young (Basal)	Old-Old (Basal)	*p*	Young (Expansion)	Old-Old (Expansion)	*p*
FECa (%)	0.8 (0.1–1.3)	0.8 (0.2–1.4)	NS	1.6 (1.3–2.3)	2.3 (1.7–4.1)	0.013
FEP (%)	7.5 (1–10.5)	9.5 (0.3–19)	NS	9.6 (2.3–35)	9.8 (2.4–100)	NS
FEMg (%)	4.1 (2.6–5)	2.8 (2–4.6)	NS	3.2 (2.5–6.2)	5.1 (2.2–15)	0.02
FEAU (%)	7 (3.5–10.4)	6.2 (3.9–22)	NS	12 (9–14)	10 (1.9–31)	NS

FECa = fractional excretion of calcium.
FEP = fractional excretion of phosphorus.
FEMg = fractional excretion of magnesium.
FEAU = fractional excretion of uric acid.

Magnesium

Magnesium (Mg) is the main intracellular divalent cation, as 99% of it is located in the intracellular space [15]. Under basal conditions, the small intestine absorbs 30–50% of the dietary Mg, a number that can reach 80% in Mg-deficient states [16]. This intestinal absorption process is controlled in part by the action of 1,25-dihydroxyvitamin D.

Since the vitamin D level may be reduced in the elderly due to poor sun exposure or malnourishment, it could contribute to the low Mg intestinal absorption capability documented in the aged [17].

The normal range of serum Mg is 1.7–2.3 mg/dL, with no difference between the healthy young and the elderly.

Renal Handling

Approximately 20% of serum Mg is bound to albumin, and in spite of the fact that 80% of this cation is filtered at the glomerulus, only 3% of it is finally excreted in the urine [17]. Renal excretion is determined largely by the rate of filtration and the rate of tubular reabsorption. Tubular Mg secretion does not appear to play a significant role in its balance [18].

The Proximal Tubule

Between 10–15% of the filtered Mg is reabsorbed in the proximal convoluted tubules [19].

The Loop of Henle

In the thick ascending limb of the loop of Henle, 60–70% of Mg is passively reabsorbed via paracellular channels due to a lumen-positive transepithelial gradient generated by the luminal $Na^+K^+2Cl^-$ cotransporter and potassium recycling into the lumen [20–22]. In addition, this nephronal segment has a calcium-sensitive receptor on the basolateral pole that is sensitive to increased plasma calcium or magnesium concentration. This receptor activates the arachidonic acid cascade to inhibit the luminal $Na^+K^+2Cl^-$ cotransporter and the apical potassium channel, reducing the transepithelial positive potential, leading to hypercalciuria and hypermagnesuria. Hypocalcemia and hypomagnesaemia have the opposite effect on this calcium sensor [22, 23].

The Distal Tubule

In the distal convoluted tubules, Mg is still significantly reabsorbed. This mechanism is responsible for the fine control of its excretion [21].

Urinary Mg excretion is increased by high natriuresis, osmotic load, and metabolic acidosis, while it is reduced by the parathyroid hormone, metabolic alkalosis, and perhaps calcitonin action. Vitamin D seems to have no influence on its renal handling [19].

Magnesium in the Aged Population

In healthy old people, the fractional excretion of magnesium (FEMg) does not differ from that in a healthy young population. However, in the setting of volume expansion, old people are prone to developing a significant increase in their FEMg, leading to a reduction in their serum Mg level: basal magnesemia of 2.1 mg/dL (1.9–2.3) and post-volume expansion of 1.8 mg/dL (1.7–2.0) (p: 0.004) (see Table 9.1).

Since most of the filtered Mg is normally reabsorbed in the thick ascending limb of the loop of Henle, and this segment shows some degree of incompetence for the reabsorbtion of Na^+ (see Chapters 5 and 8), the handling of Mg in the elderly may be less effective than in the young.

Serum Mg concentrations have been found to correlate poorly with the Mg body status; in patients with body Mg deficiency, the level of serum Mg may be normal [17]. The Mgtolerance test is the best technique for evaluating the body Mgcontent. This opinion is based on the observation that Mg-deficient patients retain a greater proportion of an exogenous load of Mg^{2+} and excrete less in the urine than normal individuals. As the infused Mg is immediately incorporated into the intracellular compartment, a small amount of it remains in plasma, where it is available to be filtered by the glomerulus. This test is invalid in situations of impaired renal function or renal Mg-wasting states [22].

In the healthy old population, a reduced capacity of the bowel and the kidney to reabsorb Mg has been described. This may be one of the causes responsible for the state of hypomagnesemia observed in otherwise healthy aged persons. The main mechanisms that may cause magnesium deficiency in the elderly are malnutrition, gastrointestinal tract loss (e.g., malabsorption), urinary loss (e.g., diuretics), and intracellular shift (e.g., hungry bone syndrome) [12, 15].

Magnesium deficiency of nutritional origin can be observed in alcoholism, not infrequently seen in the aged, and refeeding syndrome [15, 24]. Renal Mg^{2+} wasting occurs with osmotic diuresis (e.g., glusosuria, polyuric phase of recovery from acute renal failure, postobstructive diuresis), loop diuretics, nephrotoxins (cisplatin, amphotericine, aminoglycosides), tubulointerstitial nephropathies, and Fanconi syndrome [15, 25]. High serum ionized calcium levels directly induce renal Mg wasting due to stimulation of the calcium sensor in the loop of Henle [26].

Hypomagnesemia may cause tachyarrhythmias, which may be resistant to standard therapy responding to Mg repletion only. In addition, hypomagnesemia facilitates the development of digoxin cardiotoxicity as well as symptoms and signs of neuromuscular irritability, i.e., Trousseau and Chvostek signs, tetany, and seizures. Furthermore, many of the cardiac and neurological manifestations attributed to Mgdeficiency may also be explained by the coexistence of hypokalemia or hypocalcemia. However, hypomagnesemia by itself can induce hypokalemia. This hypokalemia may be corrected by Mg replenishment [15, 27–29]. In addition, intravenous administration of large amounts of $MgSO_4$ may acutely induce a hypocalcemia, which is worsened by an additional increase in urinary calcium excretion and the formation of calcium sulfate complexes [30–33].

Hypermagnesemia

The kidney has a very large capacity to excrete Mg because, when the renal threshold is exceeded, most of the excess filtered Mg is excreted into the final urine. Thus, hypermagnesemia generally occurs in two clinical situations: compromised renal function and excessive Mg intake. In chronic renal failure, the remaining nephrons adapt to the decreased filtered load of Mg by increasing its fractional excretion.Then, serum Mg levels are usually well maintained until the creatinine clearance falls below 20 mL/min.However, in advanced renal insufficiency, significant hypermagnesemia is rare unless the patient receives exogenous Mg in the form of antacids or cathartics[3].

Other causes of hypermagnesemia are lithium use,hypothyroidism, and Addison's disease [22, 34]. Magnesium toxicity is a serious condition, with its symptoms usually beginning after the magnesium serum concentration exceeds 4–6 mg/dL. The symptoms are hypotension, nausea, vomiting, facial flushing, urinary retention, ileus, depression, and lethargy. If untreated, it may progress to flaccid skeletal muscular paralysis, hyporeflexia, bradyarrhythmias, respiratory depression, and cardiac arrest [35].

Phosphorus

The normal serum concentration for phosphorus ranges between 2.5 and 5.0 mg/dL. Approximately 1% of total body phosphorus is in the extracellular space. Homeostasis of phosphorus is maintained by the transport of phosphate (Pi) across renal and intestinal epithelia. This is mediated at least in part by means of the LC34 gene family of solute carriers, which encode three Na-dependent Pi cotransporters [36]. The majority of body phosphorus comes from the digestive tract, where it is absorbed in the small intestine, more specifically in the duodenum and jejunum. This absorption is mediated in part by the solute carrier transporter NaPi-IIb (CLS34A2), which is very abundant in the brush-border membrane of the intestine. Normally, the amount of phosphate in the diet exceeds 1000 mg/day, and its net absorption is more than 60% of the intake. This process can be enhanced by vitamin D [19].

Renal Handling

The Proximal Tubule

Approximately 80% of renal phosphate reabsorption takes place in the proximal tubuleby means of a sodium-dependent phosphate transporter [36]. Transport of Pi across the apical membrane is mediated by SLC34 of solute carriers, NaPi-IIa (SLC34A1) and PI-IIc (SCL34A3). Both are specifically expressed in the brush-border membrane of the proximal tubular cells. This mechanism is stimulated by serum phosphate depletion. Severe phosphate depletion can reduce the electrolyte reabsorption capability of the proximal and distal tubules [36, 37].

The Distal Tubule

About 5–10% of filtrated phosphorus is reabsorbed by the distal tubules. Phosphorus excretion is stimulated by high natriuresis, metabolic acidosis, and parathyroid hormone [4]. Moreover, there are factors that can stimulate phosphorus movement toward the intracellular compartment such as glucose infusion, insulin, and hyperventilation [19].

Phosphorus in the Aged

There is no significant difference in either the serum phosphorus level or its fractional excretion between the young and the healthy aged. Even more, when healthy old people undergo volume expansion, they do not show a significant increase in their fractional excretion of phosphorus compared to their basal level (see Table 9.1).

Hyperphosphatemia

Hyperphosphatemia is defined as a serum phosphate level above 5.0 mg/dL in adults [36]. We should be aware that spurious hyperphosphatemia may be present in cases of paraproteinemia (e.g., multiple myeloma, etc.), hyperlipidemia. or hyperbilirubinemia [38–40]. Exogenous intake of phosphorus can only lead to hyperphosphatemia in the presence of marked renal insufficiency [36]. A reduction in the glomerular filtration rate below 25 mL/min is the most common cause of hyperphosphatemia. Above this level of GFR, renal patients are able to maintain a normal phosphate serum level due to a progressive increase in their fractional excretion of phosphate [41]. Other causes of hyperphosphatemia secondary to a reduced phosphorus renal excretion capability are hypoparathyroidism and pseudohypoparathyroidism [22].

Efflux of phosphate from the intracellular to extracellular space is responsible for hyperphosphatemia in acute respiratory acidosis and massive cytolysis [36, 42, 43].

Most of the major clinical manifestations of hyperphosphatemia are derived from hypocalcemia, which frequently accompanies it. Hyperphosphatemia can lead to secondary hypocalcemia by causing calcium precipitation, decreasing the production of 1,25 vitamin D, and decreasing intestinal calcium absorption [22]. When the product of serum calcium and serum phosphorus exceeds 70, the risk for ectopic calcium precipitation is significant. The skin, vessels, cornea, and joints are often affected in this setting. Additionally, hyperphosphatemia can also lead to hypocalcemia by inducing secondary hyperparathyroidism.

Hypophosphatemia

Hypophosphatemia is defined as a serum phosphate level below 2.5 mg/dL in adults. However, symptoms of hypophosphatemia usually appear when the serum phosphate level is below 1 mg/dL [36, 44]. Malnutrition is one of the main causes of hypophosphatemia in the elderly.

Increased renal excretion is generally the result of an excessive PTH level. Both primary and secondary hyperparathyroidism may lead to hyperphosphaturia and consequently to hypophosphatemia. An excess of parathyroid hormone directly decreases the renal phosphate reabsorption, inducing an increased renal phosphate excretion. The secondary hyperparathyroidism observed in CRF is typically associated with hyperphosphatemia [41, 45].

Other causes of urinary phosphate wasting are polyuric acute renal failure, postobstructive polyuria, proximal diuretics, corticosteroids, and proximal tubule dysfunction due to inherited disorders, antineoplasic agents, etc. [46].

Decreased intestinal absorption can be observed in small intestine disorders, vitamin D deficiency, and treatment based on corticosteroids or high doses of phosphate-binding antacids [36, 46, 47].

In chronically malnourished individuals, rapid refeeding can result in significant hypophosphatemia. The mechanism for this phenomenon is related to increased cellular phosphate uptake and utilization. Thus, malnourished patients receiving hyperalimentation should have adequate phosphorus supplementation to avoid this complication [48].

Hypophosphatemia is a common problem in alcoholic patients and in those suffering from diabetes mellitus due to their poor phosphorus intake, vitamin D deficiency, and heavy use of phosphate-binding antacids. Alcohol-induced proximal tubule dysfunction also contributes to phosphate depletion

[46,47,49]. Administration of intravenous glucose in alcoholic patients stimulates the shift of phosphorus into cells, provoking severe hypophosphatemia. In diabetic patients, the administration of insulin stimulates the cellular uptake of phosphorus, and thus the serum phosphate level can fall dramatically with treatment [50]. Hypophosphatemia may be observed in acute leukemia and in the leukemic phases of the lymphomas.It is thought that rapid cell growth with consequent phosphorus utilization is responsible for this complication. Hypophosphatemia is also observed in sepsis, hepatic disease, and heat stroke [22, 46]. The clinical manifestations of hypophosphatemia generally result from a decrease in intracellular ATP levels. Additionally, erythrocytes experience a decrease in 2,3-diphosphoglycerate levels, which increases hemoglobin-oxygen affinity and alters oxygen transport efficiency. Hemolysis results from increased red cell rigidity.

Severe hypophosphatemia can also induce a dysfunction in the white cell phagocytosis, rhabdomyolysis, and a disturbance in the renal tubular, heart, and respiratory function. Prolonged phosphate depletion can lead to osteomalacia [46].

Calcium

Calcium is critical for many metabolic functions. While 99% of body calcium is found as part of the structure of bone and teeth, the remaining 1% found in plasma and body cells is crucial for many functions such as blood clotting, nerve impulse conduction, and muscle contraction. The homeostasis of calcium is complex because the gastrointestinal tract, the bones, and the kidneys all affect calcium balance. The normal total serum calcium concentration oscillates between 9 and 10.5 mg/dL, and approximately 50% of serum calcium is bound to albumin. A small amount of it is complexed to anions, while the remainder is in the form of free ionized calcium.

Renal Handling of Calcium

The kidney is critically important for the maintenance of overall Ca^{2+} homeostasis in mammals by determining the excretion of Ca^{2+} from the body and by conversion of vitamin D to its active metabolite, 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$] [47]. To maintain a net Ca^{2+} balance, 98% of the Ca^{2+} filtered at the glomerulus must be reabsorbed along the nephrons [48,49].

The Proximal Tubule and the Loop of Henle

The main percentage of Ca^{2+} reabsorption takes place along the proximal tubule and the thick ascending limb of the loop of Henle through paracellular pathways.

Distal and Collecting Tubules

The remaining 15% of Ca^{2+} reabsorption occurs in the distal convoluted tubules (DCT), the connecting tubules (CNT), and the initial portion of the cortical collecting duct (CCD). The relative contribution of these individual segments to active Ca^{2+} reabsorption appears to differ among species [50]. In these nephronal segments, Ca^{2+} reabsorption occurs against the existing electrochemical gradient. Together with the fact that the tight junctions are relatively impermeable for Ca^{2+} ions, this substantiates that Ca^{2+} is reabsorbed

in these segments through an active transcellular pathway [48]. Transcellular Ca^{2+} transport is generally envisaged as a three-step process consisting of passive entry of Ca^{2+} across the apical membrane, cytosolic diffusion of Ca^{2+} bound to vitamin D_3-sensitive calcium-binding proteins (calbindin-D28K), and active extrusion of Ca^{2+} across the opposite basolateral membrane [50]. From an energetic perspective, it is attractive to consider the apical influx of Ca^{2+}as the rate-limiting step in this process and, therefore, presumably the final regulatory target for stimulatory and inhibitory hormones [48, 51, 52]. The molecular nature of this apical influx mechanism has remained obscure so far, but the recently cloned epithelial Ca^{2+} channel (ECaC) exhibits the defining characteristics of transepithelial Ca^{2+} transport [53]. The rate of active Ca^{2+} transport is tightly controlled by the calciotropic hormones, and classical representatives of this group are $1,25(OH)_2D_3$, parathyroid hormone (PTH), and calcitonin. $1,25(OH)_2D_3$ stimulates Ca^{2+} reabsorption in a genomic fashion analogous to classic steroid hormones, whereas PTH and calcitonin have been postulated to act in a cAMP-dependent manner [54, 55]. Recent studies have implicated other hormones as potential regulators of active Ca^{2+} reabsorption in renal tubular cells [56–59]. These studies also provided evidence for new signaling pathways that are independent of cAMP.

Since the ionized form is the physiologically relevant one, in situations of hypoalbuminemia in order to correct the serum calcium level to that of the albuminemia, 0.8 mg/dL of calcium should be added for every 1-mg reduction in serum albumin below 4 mg/dL. The serum ionized calcium level increases in acidosis since in this context there is a reduction in the calcium bound to plasma albumin, while the ionized calcium decreases in metabolic alkalosis due to the opposite mechanism [47].

Vitamin D_3

Dietary vitamin D_3 is activated by ultraviolet light exposure in the skin and subsequently undergoes 25-hydroxylation in the liver, followed by a further 1-hydroxylation in the kidney. The active form of vitamin D stimulates the intestinal absorption of calcium, while the activation of this vitamin is induced by the action of the parathyroid hormone. In addition, serum calcium levels regulate parathyroid hormone release, with hypocalcemia being a stimulus for an increase in parathyroid hormone secretion. The actions of vitamin D and the parathyroid hormone action increase serum calcium levels since the former induces intestinal calcium absorption, the latter increases its renal reabsorption, while both stimulate bone turnover.

Calcitonin counterbalances the actions of parathyroid hormone, since it has the milder and opposite bone and renal actions and is secreted in the setting of hypercalcemia [18].

Calcium in the Aged

In healthy old people, calcemia and fractional excretion of calcium (FECa) do not differ from those in a healthy young population. However, when healthy old people undergo volume expansion, they develop a significant increase in their FECa compared to basal conditions (previous to the test) (Table 9.1). This increased FECa provokes a significant reduction in their calcemia: basal value, 8.75 mg/dL [8–10]; volume expansion, 8.2 mg/dL (7.5–8.6), *p*: 0.005 (see Table 9.1).

Healthy elderly people under the conditions of an adequate diet and sun exposure, have normal levels of blood calcium, blood phosphate, vitamin D, PTH and urinary calcium, and phosphate output. However, since this population frequently has a dietary content of low vitamin D, reduced sunlight exposure, and low serum levels of sexual hormones, they have a tendency to develop hypercalciuria. The latter phenomenon, together with poor calcium intestinal absorption, may account for the senile secondary hyperparathyroidism reported by some authors [60–62].

Hypercalcemia

Hypercalcemia is most commonly seen in cases of increased osteoclastic bone resorption states such as hyperparathyroidism or excessive production of parathyroid hormone-related protein. These clinical situations represent approximately 90% of the cases of hypercalcemia. Another cause of hypercalcemia is an excess of circulating 1,25-dihydroxyvitamin D, which induces an excessive bone resorption and intestinal calcium absorption. Normally, the kidney plays a protective role against the development of hypercalcemia since extracellular calcium itself appears to have a calciuric effect on the renal tubule by its direct action on the calcium-sensing receptor of the thick ascending limb of the loop of Henle. However, the kidney sometimes contributes to the development of hypercalcemia, as is the case in thiazide treatment or familial hypocalciuric hypercalcemia. Hypercalcemia may provoke neuromuscular derangements, altered mental status (depression), fatigue, muscle weakness, cardiologic alterations (shortened QT interval and heart block), digestive disorders (constipation, nausea, peptic ulcer, pancreatitis), and renal diseases such as nephrogenic diabetes insipidus, nephrolithiasis, and nephrocalcinosis [60]. The entities that can induce hypercalcemia in the elderly are primary hyperparathyroidism [61–64], nonparathyroid endocrinopathies such as adrenal insufficiency [60], malignancy-associated hypercalcemia, i.e., parathyroid hormone-related protein, bone metastasis, multiple myeloma [60, 65, 66], medication such as lithium, vitamin A, estrogens, antiestrogens, and thiazides [67,68], immobility syndrome [68–70], granulomatous diseases, i.e., sarcoidosis, among others [71–73].

Hypocalcemia

Symptoms of chronic hypocalcemia are predominantly neuromuscular. The most common clinical manifestations are muscle cramps and numbness in the fingers. Severe hypocalcemia can cause laryngeal and carpopedal spasm, bronchospasm, seizures, depression, and decreased cognitive capacity. An electrocardiogram may show shortening of the QT interval and arrhythmias. Bedside signs of hypocalcemia are the Chvostek and Trousseau signs. Even though both signs are characteristic of hypocalcemia, they are often negative in hypocalcemic patients.

Causes of hypocalcemia are hypoparathyroidism, phenytoin, bisphosphonates, calcitonin [62], chronic hypomagnesemia, acute hypermagnesemia [15, 60, 74], vitamin D deficiency in cases of low exposure to sunlight, malabsorption [73, 75], pancreatitis [76], chronic renal disease [77], massive cellular lysis, i.e., rapidly growing hematological malignancies, and rhabdomyolysis [14].

Renal Acidification (Renal Control of pH)

The kidney is a key organ for the maintenance of acid-base equilibrium by means of the renal acid-base homeostasis. This is roughly achieved by two processes: reabsorption of filtered bicarbonate (HCO_3^-) and excretion of fixed acids mediated by the same basic process: renal H^+ secretion [78].

The Proximal Tubule

The reabsorption of HCO_3^- is mainly accomplished in the proximal tubule, where 70–90% of the filtered HCO_3^- is reabsorbed, whereas excretion of fixed acid, achieved through the acidification of urinary buffers and the excretion of ammonium ion, mainly occurs in the distal tubule.

Net HCO_3^- reabsorption is higher in the first segment of the proximal tubule (S1) than in the middle (S2) and terminal ones (S3). As HCO_3^- is freely filtered across the glomeruli, the concentration in S1 is equal to that of the plasma, i.e., 25 mmol/L, decreasing to 5–10 mmol/L at the end of S3. The more important processes in these segments are H^+ secretion at the luminal (apical) membrane via a specific Na^+-H^+ exchanger (NHE-3) and HCO_3^- transport across the basolateral membrane via the Na^+-HCO_3^-cotransporter (NBC-1). The secreted H^+ reacts in the tubular lumen with filtered HCO_3^- generating CO_2 and H_2O, a reaction catalyzed by luminal type IV carbonic anhydrase. CO_2 diffuses across the luminal membrane into the cytosol of the proximal tubular cell reacting with H_2O in the presence of type II carbonic anhydrase [79]. In each cycle, NBC-1 passively extrudes from the cell three molecules of $HCO_3^-$and one molecule of Na^+. Additional Na^+ is actively transported out of the cell via the basolateral membrane by the action of Na-K-ATP-ase. The result of these Na^+ transport mechanisms is that the intracellular Na^+ concentration remains low. This low intracellular Na^+ concentration provides the force necessary to extrude $H^+$from the cell into the lumen by action of NHE-3 transporter. The decrease in the concentration of bicarbonate in the luminal fluid facilitates the diffusion of bicarbonate from the peritubular capillaries into the lumen via paracellular pathways. The factors influencing renal proximal tubular reabsorption are luminal HCO_3^- concentration, peritubular HCO_3^- concentration, tubular flow rate, extracellular volume, $P_{CO2,}$ Cl^-, K^+, glucocorticoids, Ca^{2+}, phosphate, PTH, angiotensin II, and α-adrenergic tone [80].

Renal ammonia (NH_3) is mainly synthesized in the S1 and S2 segments of the proximal tubule by the metabolism of glutamine. Almost all the ammonium eliminated in the urine is produced in these two segments. NH_3 diffuses to late segments of the nephron, where it reacts with H^+, giving ammonium ions (NH_4^+), which are excreted in the urine. Excreted NH_4^+ returns an equal amount of bicarbonate to the blood.

The Loop of Henle

The thick ascending limb of the loop of Henle reabsorbs about 15% of the filtered HCO_3^- by a mechanism equal to that present in the proximal tubular cells, i.e., an Na^+-H^+ apical exchanger and a basolateral Na^+-HCO_3^- cotransporter.

Between 50-80% of the NH_3/NH_4 secreted by the proximal tubule and delivered to the loop of Henle is reabsorbed in the thick ascending limb of the loop by ionic transport. Due to the fact that the apical membrane is not

permeable to NH_3/NH_4, the reabsorption (transport) of NH_3/NH_4^+into the thick ascending limb of the loop of Henleis carried out by means of three mechanisms: [1] substitution of K^+ for NH_4^+ in the $Na^+K^+2Cl^-$ cotransport; [2] substitution of K^+ for NH_4^+ in the K^+H^-antiporter; [3] paracellular transport across the tight junctions driven by the positive lumen voltage. The countercurrent multiplication mechanism generates a medullary concentration gradient through secretion of NH_4^+ into the proximal tubule and possibly into the descending limb of the loop. As the medullary thick ascending limb of the loop of Henle possesses a low permeability to NH_3, limiting its back diffusion, the accumulation of NH_3 in the medullary interstitium facilitates the diffusion of NH_3 into the collecting tubule. This process is facilitated by the high acidity of the tubular fluid at this level [81].

The Distal Tubule

The acidification of the urine is accomplished in the distal nephron (mainly cortical and medullary collecting ducts) by three related processes:

1. Reabsorption of the small amount of bicarbonate that escapes proximal reabsorption (5–20%).
2. Conversion (titration) of the divalent basic phosphate $HPO_4^=$ to the monovalent acid form HPO_4^-(titratable acid).
3. Accumulation of ammonia (NH_3) intraluminally, which reacts with H^+ to form the nondiffusible ammonium ion (NH_4^+). All these processes are based in the active secretion of H^+ ions by an active transport, the H^+-ATPase present in the brush borders of some distal cells (intercalated type A cells).

The collecting tubule has the capability to generate and maintain a high urinary acidity due to the relative impermeability of its luminal membrane to back diffusion of carbonic acid and H^+ ions. This confers the possibility of achieving a urinary pH as low as 4.4, generating a 1000-fold transtubular gradient of H^+, which secures the trapping of NH_4^+ and the maximal titration of urinary buffers.

The regulation of tubular pH takes place in intercalated type A (α-cells) and intercalated type B (β-cells), which are functionally and structurally different. The α-cells are responsible for H^+ secretion into the luminal fluid of the distal tubules, whereas the β-cells, present only in the cortical segment of the collecting tubules, are responsible for HCO_3^-secretion. The remaining cells, approximately two-thirds of the cells in the collecting duct, commonly known as principal cells, are responsible for reabsorption of Na^+ and the secretion of K^+ [78]. Factors influencing the acidification in the distal nephron include aldosterone, potassium stores, sodium intake, extracellular fluid volume, and acid-based status [79].

Acidification in Normal Aging

So far only five studies have evaluated the response of the normal aging kidney to a challenge with acid overload [82–86].

Urinary pH

The kidney of healthy aged persons is able to lower the urinary pH in response to acid overload to a value similar to that reached by healthy young-adult

subjects in response to the same stimulus [85,86]. Even more, one study [83] reported that the fall in urinary pH was more intense in the aged, i.e., 4.85 ± 0.23 vs. 4.96 ± 0.52 in the young subjects. In a different study, the urinary pH reached in response to acid overload varies from 4.5 ± 0.1 in the young to 4.93 ± 0.07 in the aged [84].

Titratable acid elimination behaves similarly in the young and in the aged [83–85], but in one study it was reported that it is higher in subjects above 60 years compared to the young [86].

Ammonia

There is almost a general consensus that NH_4^+ elimination is lower in the aged than in young subjects, except in one study [85] in which differences between young and aged persons were not found. In this latter study, it was proven that the aged need more time to reach peak acid excretion (between 6–8 hours) and that the same dose of ammonium chloride induces a greater decline in blood bicarbonate in the aged than in young individuals (Table 9.2). Several factors can influence NH_4^+ metabolism, such as blood electrolytes status prior to the acid challenge, nutrition, subject position (recumbent, sitting, standing, or walking), urine collection time, degree of blood acidification following acute acid overload, and health assessment. Some of these factors have not been evaluated, and some factors are not equal in all the studies; because of this, the results from the different studies are difficult to compare. In an attempt to find an explanation for the discrepancy regarding the dysfunction in NH_4^+ excretion in aged people found in the above-mentioned studies, a few possible mechanisms have been postulated: First, absorption of NH_4^+ in the thick ascending limb of the loop of Henle takes place by the substitution of K^+ for NH_4^+in the cotransporter $Na^+K^+2Cl^-$. As we have analyzed in Chapters 4 and 8, there is a certain degree of incompetence in the thick ascending limb of the loop of Henle to retain Na^+. It is known that the cotransporter $Na^+K^+2Cl^-$ plays a first-order role in the absorption of Na in this segment. So one possibility is that the $Na^+K^+2Cl^-$ cotransporter is less efficient in the aged than in the young in reabsorbing both Na^+ and NH_4^+. Although the clinical significance of the altered acidification in the loop of Henle is poorly understood, in some patients renal tubular acidosis may originate, at least in part, from an abnormal function of the loop of Henle [79]. Another possible explanation is that standing from a supine position is associated with a significant decrease in creatinine clearance [87]. As all data are corrected for GFR, it may introduce some error in the final calculation. An important difference among the studies is the observation period between acid administration and collection time. As can be seen in Table 9.2, in some studies the time varied from subject to subject in the same study [83,84]. In others these data are not given [82]. In one study the collection period was 5 hours [86], and in our study the collection time was extended to 8 hours [85]. Another finding is that the healthy aged person has a lower plasma concentration rate of aldosterone [88], which influences urinary acidification, as we have already mentioned.

Bicarbonate Threshold

In the only study that has specifically examined the renal tubular handling of bicarbonate following an acute acid overload, it was found that age does not affect bicarbonate threshold [86].

Table 9.2 Aging and Renal Tubular Acidification—Comparison of the Response to an Acid Overload in the Four Studies Available Until Now. Basal Condition, Intensity of Acidification, and Collecting Period Differ Among Them.

		Methodology of Published Studies					
Authors	**Gender**	**Nutritional Status (albumin g/L)**	**Health Assessment**	**Urine Collection Time**	**Subject Position**	**Plasma Electrolytes**	**Blood CO_3HNa**
Schock and Yiengst (1949)	M	Not given	Not given	Not given	Not given	Not given	Not given
Alder et al. (1968)	M/F	Not given	Bladder catheter	Variable	Not given	Not given	4.6
Agarbal and Cabebe (1980)	M/F	Not given	Not given	Variable	Not given	NS	2.5
Macías-Núñez et al. (1983)	M/F	E. 42.6 ± 0.7 Y. 42.6 ± 0.8	Healthy	8 hr	Recumbent	NS	5.9
Schück and Nádvomilkova (1987)	M/F	Not given	Not given	5 hr	Sitting, standing or walking	Not given	Not given

	Results of Published Studies		
Authors	**Urinary pH**	**NH_4^+ Elimination**	**Titratable**	**CO_3HNa Threshold**
Alder et al. (1968)	NS	Diminished	NS	Not given
Agarbal and Cabebe (1980)	NS	Diminished	NS	Not given
Macías-Núñez el al. (1983)	NS	NS	NS	NS
Schück and Nádvomilkova (1987)	NS	Impaired above 50	Increased impaired above 60	Not given

(*Source:* Macías-Núñez, J.F., Cameron, J.S. The ageing kidney. In *Oxford Textbook of Clinical Nephrology*, 3rd ed., A.M. Davison, J.S. Cameron, J.P. Grünfeld, et al., eds. Oxford: Oxford University Press. 2005; pp. 73–85.)

In summary, from the few comprehensive studies available so far, it can be concluded that

1. The basal conditions and techniques used differ from study to study, resulting in consequent difficulties in comparing results.
2. Urinary pH and titratable acid behave similarly in the aged and in the young.
3. The renal threshold for bicarbonate is comparable in the aged and in the young [85].
4. Plasma pH and P_{CO2} take longer to be restored after an acid load in the aged compared to the young [82].
5. Ammonium ion excretion is less efficient or, at least, takes longer to reach its peak in response to an acute acid overload in the aged than in the young, but there is no absolute deficit in the function.

References

1. Stone, T.W., Simmonds, H.A. *Purines: Basic and Clinical Aspects*. London: Kluwer. 1991.
2. Beck, L. Transtornos clinicos del metabolismo del ácido úrico. In *Clinicas Medicas de Norteamérica*, L. Beck, ed. Mexico City: Iteramericana. 1981; pp. 397–408.

3. Hershfield, M. Gout and uric acid metabolism. In *Cecil Textbook of Medicine*, J.C. Bennett and F. Plum, eds. Philadelphia: WB Saunders Company. 1996; pp. 1508–1515.
4. Sorensen, L.B. Gout secondary to chronic renal disease: Studies on urate metabolism. *Ann. Rheum. Dis*.1980; 39:424–430.
5. Kovarsky, J., Holmes, E., Kelley, W.N. Absence of significant urate binding to plasma proteins. *J. Lab. Clin. Med*. 1979; 93:85–91.
6. Maesaka, J.K., Fishbane, S. Regulation of renal urate excretion: A critical review. *Am. J. Kidney Dis*. 1998; 32:917–933.
7. Grassl, S.M. Facilitated diffusion of urate in avian brush border membrane vesicles. *Am. J. Physiol. Cell Physiol*. 2002; 283:c1155–c1162.
8. Cameron, S., Simmonds, A. Uric acid. In *Oxford Textbook of Nephrology*, S. Cameron, ed. Oxford: Oxford University Press. 2006.
9. Keidar, S., Kohan, R., Levy, J., Grenadier, E., Palant, A., Ben-Ari, J. Non-oliguric acute renal failure alters treatment with sulfinpyrazone. *Clin,. Nephrol*. 1982; 17:266–267.
10. Sommers, D.K., Shoenman, H.S. Drug interactions with urate excretion in man. *Eur. J. Pharmacol*. 1987; 32:499–502.
11. Bunier, M., Roch-Ramel, F., Brunner, H.R. Renal effects of angiotensin II receptor blockade in normotensive subjects. *Kidney Int*. 1996; 49:1787–1790.
12. Rodríguez Mañas, L., Solís Jiménez, J. Patología reumatológica en geriatría. In *Manual de Geriatria* A. Salgado, F. Guillén, and I. Ruipérez, eds. Barcelona: Masson. 2002; pp. 477–492.
13. Danovitch, G.M., Weinberger, J., Berlyne, G.M. Uric acid in advanced renal failure. *Clin. Sci*. 1972; 43:331–341.
14. Jones, D.P., Mahmoud, H., Chesney, R.W. Tumor lysis syndrome: Pathogenesis and management. *Pediatr. Nephrol*. 1995; 9:206–212.
15. Kelepouris, E., Agus, Z. Hypomagnesemia: Renal magnesium handling. *Sem. Nephrol*. 1998; 18:58–73.
16. Graham, L.A., Caesar, J.J., Burgen, A.S.V. Gastrointestinal absorption and excretion of magnesium in man. *Metabolism* 1960; 9:646–659.
17. Rude, R. Magnesium disorders. In *Fluids and Electrolytes,* J. Kokko and R. Tannen, eds. Philadelphia: W.B. Saunders. 1996; pp. 421–445.
18. Guyton, A., Hall, J. *Manual de Fisiología Médica*. Madrid: McGraw-Hill, Interamericana. 2002.
19. Wen, S.F., Evanson, R.L., Dirks, J.H. Micropuncture study of renal magnesium transport in proximal and distal tubule of dog. *Am. J. Physiol*. 1970; 219:570–576.
20. Brunette, M.G., Vigneault, N., Carriere, S. Micropuncture study of magnesium transport along the nephron in the young rat. *Am. J. Physiol*. 1974; 227:891–896.
21. Shareghi, G.R., Agus, Z.S. Magnesium transport in the cortical thick ascending limb of Henle's loop of the rabbit. *J. Clin. Invest*. 1982; 69:759–769.
22. Yu, A. Renal transport of calcium, magnesium and phosphate. In *Brenner & Rector's The Kidney*, B. Brenner, ed. Philadelphia: Saunders. 2004; pp. 535–571.
23. Riccardi, D., Hall, A.E., Chattopadhyay, N., et al. Localization of the extracellular calcium sensing protein in the rat kidney. *Am. J. Physiol*. 1998; 274:F611–F622.
24. Bowling, T.E., Silk, D.B. Refeeding remembered. *Nutrition* 1995; 11:32–34.
25. Braden, G.L., Germain, M.J., Fitzgibbons, J.P. Impaired potassium and magnesium homeostasis in acute tubulo-interstitial nephritis. *Nephron* 1985; 41:273–278.
26. Quamme, G.A. Effect of hypercalcemia on renal tubular handling of calcium and magnesium. *Can. J. Physiol. Parmacol*. 1982 ; 60:1275–1280.
27. Millane, T.A., Ward, D.E., Camm, A.J. Electrophysiology, pacing and arrhythmia. *Clin. Cardiol.* 1992; 15:103.
28. Oster, J.R., Epstein, M. Management of magnesium depletion. *Am. J. Nephrol.* 1988; 8:349–354.

29. Rude, R.K. Magnesium metabolism and deficiency. *Endocrinol. Metab. Clin. North Am*. 1993; 22:377.
30. Eisenbud, E., LoBue, C.C. Hypocalcemia after therapeutic use of magnesium sulphate. *Arch. Intern. Med*. 1976; 136:688–691.
31. Navarro, J., Oster, J.R., Gknosos, P.J., et al. Tetany induced on separate occasions by administration of potassium and magnesium in a patient with hungry-bone syndrome. *Miner Electrolyte Metab*. 1991; 17:340–344.
32. Bundy, J.T., Connito, D., Mahoney, M.D., et al. Treatment of idiopathic renal magnesium wasting with amiloride. *Am. J. Nephrol.* 1995; 15:75–77.
33. Devane, J., Ryan, M.P. The effects of amiloride and triamterene on urinary magnesium excretion in conscious saline-loaded rats. *Br. J. Pharmacol*. 1981; 72:285–289.
34. Christiansen, C., Baastrup, P.C., Transbol, L. Lithium, hypercalcemia, hypermagnesemia, and hyperparathyroidism (letter). *Lancet* 1976; 2:969.
35. Alfrey, A. Disorders of magnesium metabolism. In *Cecil Textbook of Medicine,* J.C. Bennett and F. Plum, eds. Philadelphia: W.B. Saunders. 1996; pp. 1137–1138.
36. Forster, I.C., Hernando, N., Biber, J., Murer, H. Proximal tubular handling of phosphate: A molecular perspective. *Kidney Int*. 2006; 70:1548–1559.
37. Goldfarb, S., Westby, G.R., Goldberg, M., et al. Renal tubular effects of chronic phosphate depletion. *J. Clin. Invest*. 1977; 59:770–779.
38. Larner, A.J. Pseudohyperphosphatemia. *Clin. Biochem.* 1995; 28: 391–393.
39. Leehey, D.J., Daugirdas, J.T., Ing, T.S., et al. Spurious hyperphosphatemia due to hyperlipidemia. *Arch. Intern. Med.* 1985; 145:743–744.
40. Adler, S.G., Laidlaw, S.A., Lubran, M.M., Kopple, J.D. Hyperglobulinemia may spuriously elevate measured serum inorganic phosphate levels. *Am. J. Kidney Dis*. 1988; 11:260–263.
41. Swartz, R. Fluid, electrolyte, and acid-base changes during renal failure. In *Fluids and Electrolytes,* J. Kokko and R. Tannen, eds. Philadelphia: W.B. Saunders. 1996; pp. 359–390.
42. Zusman, J., Brown, D.M., Nesbit, M.E. Hyperphosphatemia, hyperphosphaturia and hypocalcemia in acute lymphoblastic leukemia. *N. Engl. J. Med*. 1973; 289:1335–1340.
43. Schelling, J.R., Ghandour, F.Z., Stickland, T.J. et al. Management of tumor lysis syndrome with standard continuous arteriovenous hemodialysis: Case report and review of the literature. *Ren. Fail*. 1998; 20:635–644.
44. Knochel, J.P. The pathophysiology and clinical characteristics of severe hypophosphatemia. *Arch. Intern. Med.* 1977; 137:203–220.
45. Biber, J., Hernando, N., Traebert, M., et al. Parathyroid hormone-mediated regulation of renal phosphate reabsorption. *Nephrol. Dial. Transplant* 2000; 15(Suppl 6):29–30.
46. Nachman, B., Kleeman, C. Hipofosfatemia e hiperfosfatemia: Aspectos clínicos y fisiopatológicos. In *Transtornos Clínicos Hedroelectrolíticos*, M.H. Maxwell, C.R. Kleeman, and R.G. Narins, eds. Buenos Aires: Panamericana. 1991; pp. 688–723.
47. Shields, H.M. Rapid fall of serum phosphorus secondary to antacid therapy. *Gastroenterology* 1978; 75:1137–1141.
48. Friedman, P.A., Gesek, F.A. Cellular calcium transport in renal epithelia: Measurements, mechanism and regulation. *Physiol. Rev*. 1995; 75:429–471.
49. Suki, W.N., Rose, D. Renal transport of calcium, magnesium and phosphate. In *The Kidney*, B.M. Brenner, ed. Philadelphia: Saunders. 1996; Vol. I, pp. 472–515.
50. Bindels, R.J.M. Calcium handling by the mammalian kidney. *J. Exp. Biol*. 1993; 184:89–104.
51. Raber, G., Willems, M., Lang, F., Nitschke, C.H., Bindels, R.J.M. Coordinated control of apical calcium influx and basolateral calcium efflux in rabbit cortical collecting system. *Cell. Calcium* 1997; 22:157–166.
52. Yu, A.S. Calcium channels. *Curr. Opin. Nephrol. Hypertens*. 1994; 3:497–503.

53. Hoenderop, J.G.J., Van der Kemp, A.W.C.M., Hartog, A., Van de Graaf, S.F.J., Van Os, C.H., Willems, P.H.G.M., Bindels, R.J.M. Molecular identification of the apical Ca^{2+} channel in 1,25-dihydroxyvitamin D_3-responsive epithelia. *J. Biol. Chem.* 1999; 274:8375–8378.
54. Van Baal, J., De Jong, M.D., Zijlstra, F.J., Willems, P.H.G.M., Bindels, R.J.M. Endogenously produced prostanoids stimulate calcium reabsorption in the rabbit cortical collecting system. *J. Physiol*. 1996; 497:229–239.
55. Van Baal, J., Yu, A., Hartog, A., Willems, P.H.G.M., Lytton, J., Bindels, R.J.M. Localization and regulation by vitamin D of calcium transport proteins in rabbit cortical collecting system. *Am. J. Physiol*. 1996; 271:f985–f993.
56. Hoenderop, J.G., Hartog, A., Willems, P.H.G.M., Bindels, R.J.M. Adenosine-stimulated Ca^{2+} reabsorption is mediated by apical A1 receptors in rabbit cortical collecting system. *Am. J. Physiol. Renal Physiol*. 1998; 274:f736–f743.
57. Hoenderop, J.G.J., Vaandrager, A.B., Dijkink, L., Smolenski, A., Gambaryan, S., Lohmann, S.M., De Jonge, H.R., Willems, P.H.G.M., Bindels, R.J.M. ANP-stimulated Ca^{2+} reabsorption in rabbit kidney requires membrane-targeted cAMP-dependent protein kinase type. *Proc. Natl. Acad. Sci. USA* 1999; 96:6048–6089.
58. Koster, H.P.G., Hartog, A., Van Os, C.H., Bindels, R.J.M. Inhibition on $Na^{+}$and Ca^{2+} reabsorption by P2upurinoceptors requires protein kinase C but not Ca^{2+} signaling. *Am. J. Physiol. Renal Fluid Electrolyte Physiol.* 1996; 270:f53–f60.
59. Van Baal, J.G., Raber, G., De Sletge, J., Pieters, R., Bindels, R.J.M., Willems, P.H.G.M. Vasopressin-stimulated Ca^{2+} reabsorption in rabbit cortical collecting system: Effects on cAMP and cytosolic Ca^{2+}. *Pflugers Arch*. 1996; 433:109–115.
60. Plantalech, L. Hiperparatiroidismo en ancianos. In *Paratiroides,* A. Sanchez and J.L. Novelli, eds. Rosario, Argentina: Universidad de Rosario. 2000.
61. Farsi, J., Russo Picasso, M.F., Furci, A., Sorroche, P., Jáuregui, R., Plantalech, L. Variaciones estacionales de 25-hidroxivitamina D en jóvenes y ancianos de la ciudad de Buenos Aires. *Medicina* 2003; 63:215–220.
62. Plantalech, L., Knoblovits, P., Cambiazzo, E., Balzaretti, M., Oyamburu, J., Bonetto, A., Signorelli, C., Faistein, I., Gutman, R.. Hipovitaminosis D en ancianos institucionalizados de Buenos Aires. *Medicina* 1997; 57:29–35.
63. Pollak, M.R., Yu, A.S. Clinical disturbances of calcium, magnesium, and phosphate metabolism. In *Brenner & Rector's The Kidney*, B. Brenner, ed. Philadelphia: Saunders. 2006; pp. 1041–1076.
64. Silverberg, S.J., Bone, H.G., Marriot, T.B., et al. Short-term inhibition of parathyroid hormone secretion by a calcium-receptor agonist in patients with primary hyperparathyroidism. *N. Engl. J. Med*. 1997; 337:1506–1510.
65. Heath, H. Primary hyperparathyroidism: Recent advances in pathogenesis, diagnosis, and management. *Adv. Intern. Med*. 1991; 37:275.
66. Cosman, F., Shen, V., Xie, F., et al. Estrogen protection against bone resorbing effects of parathyroid hormone infusion. Assessment by use of biochemical markers. *Ann. Intern. Med*. 1993; 118:337–343.
67. Broadus, A.E., Mangin, M., Ikeda, K., et al. Humoral hypercalcemia of cancer. *N. Engl. J. Med*. 1988; 319:556.
68. Kremer, R., Shustic, C., Tabak, T., et al. Parathyroid hormone related peptide in hematologic malignancies. *Am. J. Med*. 1996; 100:406–411.
69. Breslau, N.A., McGuire, J.L., Zerwekh, J.E., et al. Hypercalcemia associated with increased serum calcitriol levels in three patients with lynphoma. *Ann. Intern. Med.* 1984; 100:1–6.
70. Bennett, W.N., Burdmann, E.A., Andoh, T.F., et al. Nephrotoxicity of immuno-suppressive drugs. *Nephrol. Dial. Transplant* 1994; 9(Suppl 4):141–145.
71. Lacy, C., Armstrong, L., Goldman, M. *Drug Information Handbook International*. Hudson, NY: Lexi-Comp. 2004.
72. Stewart, A.F., Adler, M., Byers, C.M., et al. Calcium homeostasis in immobilization: An example of resorptive hypercalciuria. *N. Engl. J. Med*. 1982; 306:1136–1140.

73. López Guzman, J.A., D'Hyver de las Deses, C. Síndrome de inmovilidad. In *Geriatría,* C. D'Hyver de las Deses and L.M. Gutiérrez Robledo, eds. Mexico City: Manual Moderno. 2006; pp. 519–525.
74. Barbour, G.L., Coburn, J.W., Slatopolsky, E., et al. Hypercalcemia in an anephric patient with sarcoidosis: Evidence for extrarenal generation of 1.25-dihydroxyvitamin D. *N. Engl. J. Med*. 1981; 305:440–443.
75. Spiegel, A. The parathyroid glands, hypercalcemia, and hypocalcemia. In *Cecil Textbook of Medicine*, J.C. Bennett and F. Plum, eds. Philadelphia: W.B. Saunders. 1996; pp. 1365–1371.
76. Pérez del Molino Martín, J., Álvarez Álvarez, L. Enfermedades metabólicas óseas en el anciano. In *Manual de Geriatría*, A. Salgado, F. Guillén, and I. Ruipérez, eds. Barcelona: Masson. 2002; pp. 447–476.
77. See, A.C., Soo, K.C. Hypocalcemia following thyroidectomy for thyrotoxicosis. *Br. J. Surg*. 1997; 84:95–97.
78. Rodriguez Soriano, J. Renal tubular acidosis: The clinical entity. *J. Am. Soc. Nephrol*. 2002; 13:2160–2217.
79. Adrogué, H.J., Madias, N.E. Renal tubular acidosis. In *Oxford Textbook of Clinical Nephrology*, 3rd ed., A.M. Davison, J.S. Cameron, J.P. Grünfeld, et al., eds. Oxford: Oxford University Press. 2005; pp. 975–994.
80. Maddox, D.A., Deen, W.M., Gennari, F.J. Control of bicarbonate reabsorption in the proximal convoluted tubule. *Semin. Nephrol.* 1987; 7:72–81.
81. DuBose, T.D., Good, D.W., Hamm, L.L., Wall, S.M. Ammonium transport in the kidney. New physiological concepts and their clinical implications. *J. Am. Soc. Nephrol*. 1991; 1:1193–1120.
82. Shock, N.W., Yiengst, M.J. Experimental displacement of the acid-base equilibrium of the blood in aged males. *Federation Proc*. 1948; 7:114–119.
83. Adler, S., Lindeman, R., Yiengst, M.J., et al. Effect of acute acid loading on urinary acid excretion by the aging human kidney. *J. Lab. Clin. Med*. 1968; 72:278–289.
84. Agarwal, R., Cabebe, F.G. Renal acidification in elderly subjects. *Nephron* 1980; 26:291–295.
85. Macías-Núñez, J.F., García Iglesias, C., Tabernero, J.M., et al. Comportamiento del riñón del viejo en la sobrecarga de ácidos. *Nefrología* 1983; pp. 11–16.
86. Schück, O., Nádvornikova, H. Short acidification test and its interpretation with respect to age. *Nephron* 1987; 46:215–216.
87. Adachi, T., Kawamura, M., Owada, M., et al. Effect of age on renal functional and orthostatic vascular response in healthy men. *Clin. Exp. Pharmacol. Physiol*. 2001; 28:877–880.
88. Macías-Núñez, J.F., Cameron, J.S. The ageing kidney. *Oxford Textbook of Clinical Nephrology*, 3rd ed., A.M. Davison, J.S. Cameron, J.P. Grünfeld, et al., eds. Oxford: Oxford University Press. 2005; pp. 73–85.

10

Dysnatremias: Diagnosis and Treatment

Steven Achinger and Juan Carlos Ayus

Introduction

Disorders of water metabolism are a very common problem encountered in the elderly population and are seen in both inpatient and outpatient settings. Diseases of water balance (hyponatremia and hypernatremia) occur when the normal homeostatic mechanisms that keep water intake and excretion precisely balanced are impaired. Although this is true for young adults, this does not always apply to the elderly, as their renal physiology differs from that of the young. Hyponatremia in the elderly is sometimes caused by renal sodium spillage rather than water retention (dilutional hyponatremia). The characteristics of the renal physiology in the aged as well as their handling of water and sodium are extensively discussed in Chapters 5 and 8. The causes of impairments in these homeostatic functions are numerous, such as renal failure, use of diuretics, and non-osmotic release of antidiuretic hormone (ADH) due to nausea, pain, or other stimuli. Poor outcomes still commonly occur among elderly patients with hyponatremia and hypernatremia despite what is currently known about these diseases. One of the main factors in this persisting problem is the failure to promptly recognize a life-threatening condition and initiate appropriate treatment. This chapter will focus on the pathophysiology of sodium disturbances with an emphasis on the common clinical presentations of these diseases in the elderly.

Regulation of Water Balance

Disturbances in the serum sodium are generally a reflection of problems in water balance and occur when water intake and water excretion are not balanced. The extracellular fluid (ECF) tonicity is usually proportional to the concentration of the serum sodium. As most cell membranes are permeable to water, the total body water will equilibrate between the extracellular fluid and intracellular fluid such that the osmolality will be the same in both compartments. Therefore, the serum sodium is proportional to the total body exchangeable sodium plus the total body exchangeable potassium (exchangeable sodium and potassium are in soluble form, e.g., not in the bone) [Eq. (1)]. As water intake and excretion are tightly regulated processes such

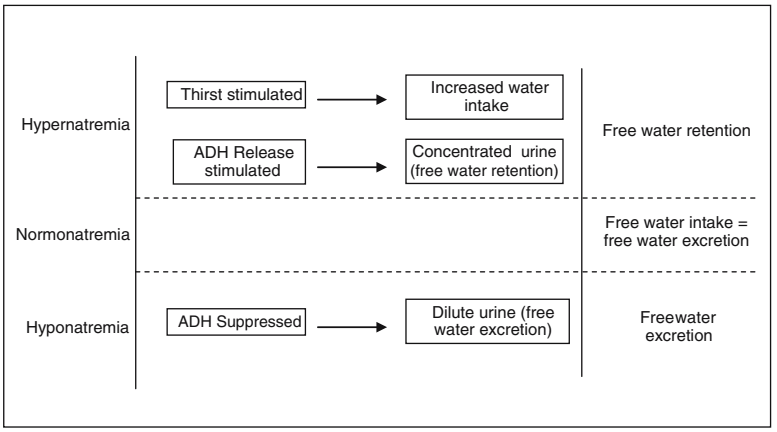

Fig. 10.1 Physiologic responses to disturbances in serum sodium. In hypernatremia, anti-aquaretic responses coupled with increased thirst lead to net water gain. On the other hand, hyponatremia leads to an aquaretic response and free water loss. (Used with permission from Achinger, S.G., Ayus J.C. Fluid and Electrolytes. In *Critical Care,* 4th ed., Civetta, Taylor, Kirby, eds.)

that intake and excretion are matched, a near-constant plasma osmolality is maintained (Figure 10.1). The body handles solute balance through difference mechanisms; therefore, disorders of the serum sodium are almost always caused by disturbances in water balance.

$$\frac{[Na^+]_e + [K^+]_e}{TBW} \propto [Na^+]_{pl} \qquad (1)$$

TBW is Total body water, where Na_e = total body exchangeable sodium, K_e = total body exchangeable potassium, and $[Na]_{pl}$ = plasma sodium concentration.

Renal Water Handling

Antidiuretic hormone (ADH), a.k.a. arginine vasopressin (AVP) [1], is the principal hormone that regulates kidney water excretion. This hormone is secreted from the pituitary gland in response to input from brain osmoreceptors when serum osmolality is elevated. ADH acts at the level of the collecting duct and leads to water reabsorption from the urine and excretion of concentrated urine. The kidney can excrete urine with a wide range of concentrations (from as low as 50 mOsm/kg when ADH activity is absent to as high as 1200 mOsm/kg when ADH activity is maximal). Therefore, when necessary, the kidney can either excrete a large water load in very dilute urine or conserve water significantly. These ranges apply to patients with normal kidney function. In renal failure or certain renal diseases (especially tubulointerstitial disease), the possible range of urine osmolality is much narrower, centered around isotonicity. In the elderly, tubulointerstitial renal disease is relatively common, and the range of urinary concentration can be more restricted. With a reduced range of urinary concentrations available, the patient is more susceptible to developing a disturbance in the serum sodium. In summary, when kidney function is not impaired, the body can achieve

water balance across a very wide range of water intake. Disruption in the processes that maintain water balance can lead to either hypernatremia or hyponatremia.

Electrolyte Free Water

An understanding of water losses and water gain from the body is imperative to understanding the approach to the patient with a disturbance in the serum sodium. The electrolyte free water is a conceptual volume of a body fluid that represents the volume of that fluid required to dilute the electrolytes contained within that fluid to the same tonicity as plasma electrolytes (Figure 10.2). The key to understand is that it is not simply water losses that are important (any amount of urine contains water), it is the loss of water *relative* to the loss of electrolyte that is important. If the urine contains the same concentration of sodium and potassium as the plasma, there is no net excretion of water. If the number of electrolytes in the urine is less than that in the serum, there is net excretion of water. Electrolyte free water is the quantity of water lost out of proportion with the loss of electrolytes; therefore, if this volume of water is not replaced, this will increase the serum sodium. A few points must be understood about electrolyte free water. First, this is truly a conceptual volume. As can be seen from Eq. (2), the electrolyte free water clearance can take on a negative value. This is the situation when the electrolyte concentration in the urine is greater than that in the plasma. When this occurs, there is net retention of electrolyte free water. Furthermore, electrolyte free water clearance emphasizes that the concentration of electrolytes in the urine, not the urine osmolality, determines net water excretion. The urine osmolality may be high; however, if the urine contains mainly urea and very few electrolytes relative to the serum, there will be a net loss of water. This concept is illustrated in detail in case #5 below. Electrolyte free water clearance, which can also be thought of as the ongoing electrolyte free water losses, is calculated by using the following formula:

$$\left(1 - \frac{[Na^+]_u + [K^+]_u}{[Na^+]_{pl} + [K^+]_{pl}}\right) \times \text{urine output rate} = \text{rate of urinary water losses} \quad (2)$$

Clinical Utility of Electrolyte Free Water Clearance

As stated above, the *urine electrolytes* and not the *urine osmolality* determine the amount of free water excreted in the urine. It is not always necessary to

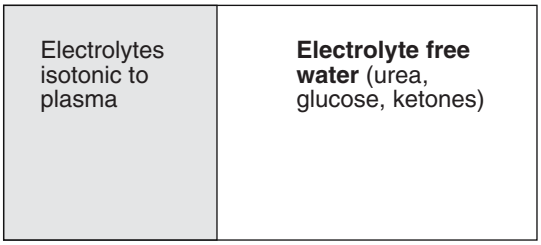

Fig. 10.2 (Used with permission from Achinger, S.G., Ayus J.C. Fluid and Electrolytes. In Civetta, Taylor, Kirby – Critical Care, 4th edition.)

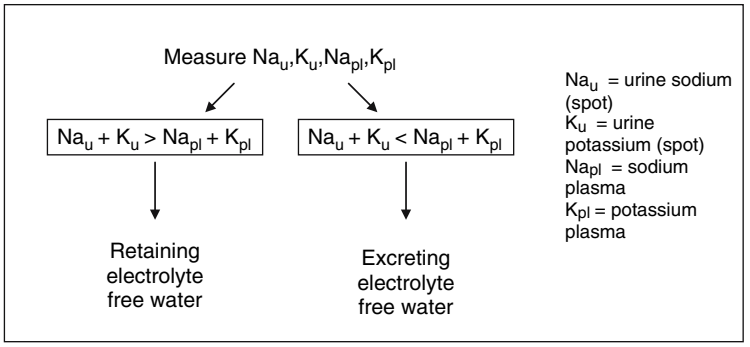

Fig. 10.3 (Used with permission from Achinger, S.G., Ayus J.C. Fluid and Electrolytes. In Civetta, Taylor, Kirby – Critical Care, 4^{th} edition.)

calculate a value for the electrolyte free water clearance if the relationship between the plasma electrolytes and the urine electrolytes is understood. This important relationship is illustrated in (Figure 10.3). When the concentration of electrolytes in the urine exceeds the concentration of electrolytes in the plasma, then free water is not being excreted in the urine. On the other hand, when the concentration of electrolytes in the urine is less than that in the plasma, then free water is being excreted in the urine.

Hypernatremia

Introduction

Hypernatremia (serum sodium of greater than 145 mEq/L) is a commonly encountered clinical problem in the elderly. Due to its pathogenesis, hypernatremia also has a predilection to affect children and hospitalized patients. As we will discuss, hypernatremia results when water losses exceed water intake. Restricted access to water is nearly always necessary for this to occur since the thirst mechanism is such a powerful stimulus. In the elderly, restricted access to water commonly occurs in a nursing home setting in patients with dementia or on tube feedings. Other clinical factors that can contribute to hypernatremia by augmenting water losses are the use of loop diuretics and gastrointestinal fluid losses. Most cases of hypernatremia in the elderly have some combination of factors that lead to impaired access to water, often worsened by ongoing electrolyte free water losses.

The Pathogenesis of Hypernatremia

When water intake fails to replace ongoing water losses, the proportion of exchangeable electrolytes relative to total body water increases, leading to an increase in the serum sodium [Eq. (1)]. When access to water is unlimited, developing hypernatremia is rare, regardless of the degree of ongoing water losses, because the thirst mechanism will lead to increased water intake to exactly match the ongoing losses and maintain a constant plasma osmolality. A list of the common etiologies of hypernatremia in the elderly is presented in Table 10.1.

Table 10.1 Common Causes of Hypernatremia in the Elderly.

Lack of water intake
Decreased thirst (dementia, neurological impairment)
Tube feedings
Bowel rest/nasogastric suction
Increased water losses
Loop diuretics
Solute diuresis (high urea load from high-protein feedings, hypercatabolic state such as sepsis; or hyperglycemia)
Gastrointestinal losses (especially osmotic cathartics)
Diabetes insipidus

Hypernatremia subjects the body's cells to osmolar stress, which leads to movement of water out of the cells. The main target organ is the brain; hypernatremia can lead to severe central nervous system dysfunction and permanent brain damage. During hypernatremic states, the brain counteracts the osmolar stress through a series of adaptations. Principal among these mechanisms are accumulation of osmotically active ions and *de novo* generation of osmotically active idiogenic osmoles. Sodium and potassium are the cations that the brain accumulates during the early response to hypernatremia. Idiogenic osmoles are a group of substances that the cell generates that remain intracellular in order to exert an osmotic effect to counteract the osmotic forces favoring water removal from the cells. These are mainly glycerophosphocholine, choline, myoinositol, and sorbitol [2, 3]. These responses occur relatively quickly; following one week of hypernatremia, no further changes in brain osmolality are observed in animal models [4]. These defense mechanisms are aimed at maintaining the brain volume during hypernatremic states to prevent significant decrease in brain size due to osmotic water losses in the brain. When correcting chronic hypernatremia, it must be kept in mind that idiogenic osmoles are not rapidly dissipated; therefore, quickly lowering the serum osmolality can induce cerebral edema due to the increased intracellular osmolality.

Clinical Manifestations of Hypernatremia

Since the brain is the most important end-organ target in hypernatremia, symptoms related to central nervous system dysfunction induced by cerebral dehydration and cell shrinkage are the most important clinical manifestations. Typically, hypernatremia will present in the elderly with fairly nonspecific symptoms such as lethargy and decreased level of consciousness. As this disease most commonly occurs in elderly patients who may already have cognitive dysfunction or who may otherwise be unable to voice complaints, a high degree of suspicion is necessary. Perhaps due to the underlying conditions that lead to its development, hypernatremia is associated with an overall mortality rate between 40 and 70% [5]. The elderly and patients with liver disease are two groups at elevated risk for complications and poor outcomes from hypernatremia. The use of lactulose as an osmotic cathartic or in the treatment of hepatic encephalopathy can result in significant water losses in the stool due to osmotic diarrhea. If the potential for these water losses is not appreciated and free water is not administered, hypernatremia can quickly develop and lead to severe morbidity.

The Approach to the Hypernatremic Patient

Key in the evaluation of hypernatremia is to determine the sources of water intake and the sources and extent of water losses. Because of the frequency of cognitive impairment and dependence on tube feedings, elderly patients are at risk for having inadequate water intake. The risk for hypernatremia is even worse when there are increased ongoing water losses. In the outpatient setting, water losses are mainly in the urine or possibly in the GI tract. Among hospitalized patients, there are several potential sources of water loss that should be addressed**:** (1) the urine, (2) the GI tract (diarrhea and nasogastric suction), and (3) insensible losses (fever, sepsis, massive diaphoresis, burns). Usually, exact amounts of gastrointestinal (except nasogastric suction) or insensible water losses cannot be determined. Urinary water losses; however, can be calculated if urine output measurements are accurate. Both the urine cationic electrolytes (sodium and potassium) and the urine osmolality should be measured. Errors can frequently be made in the interpretation of the urine osmolality, because the urine osmolality alone cannot be used to determine the presence or absence of urinary water losses.

The urine contains both electrolyte (e.g., sodium and potassium) and non-electrolyte osmoles (e.g., urea) that are excreted along with the water in the urine. Recall that it is the relative amounts of total body electrolytes and total body water that are reflected by the serum sodium [Eq. (1)]. Therefore, water that is excreted in proportion to the amount of electrolytes excreted will not have an effect on serum sodium. The urine osmolality can be very high; however, when the urine electrolytes are relatively low, this means that the water that is being excreted is mostly electrolyte free water, which will tend to increase the serum sodium. In this setting, the urine electrolyte concentration will be low and the urine osmolality high. This means that the kidney is attempting to conserve water, but there are water losses that are being obligated in order to excrete a non-electrolyte solute. This is what occurs during solute diuresis. Such a patient is typically polyuric, and the amount of water lost in the urine can be tremendous despite intact urinary concentrating mechanisms. An example of this seemingly paradoxical situation is demonstrated in case #5. Therefore, when water is excreted with very few electrolytes, the loss of water is in excess of the loss of electrolytes: Hypernatremia can develop if this water is not adequately replaced.

If the urine is not concentrated in the face of hypernatremia, a urinary concentrating defect should be suspected. The most common causes of a urinary concentrating defect are renal failure, tubulointerstitial renal disease, loop diuretics, and diabetes insipidus. In summary, all sources of water intake and water loss should be considered in assessing the hypernatremic patient with significant urinary water losses, and an imbalance favoring water loss over water intake will lead to hypernatremia.

Evaluation of the Polyuric Patient

Hypernatremia often, but not invariably, develops in patients with polyuria. The assessment of polyuria in the elderly patient often involves a narrow range of conditions. However, determining the etiology of the polyuric patient through differentiation of solute diuresis, primary polydipsia, central

diabetes insipidus, and nephrogenic diabetes insipidus is at times confusing and complex. This section will discuss these causes of polyuria in a case-based format focusing on the differences in disease pathophysiology.

Case #1: Primary Polydipsia

A 63-year-old male schizophrenic patient has routine laboratory work done prior to admission to a psychiatric hospital. His physical examination is normal. The patient's family members state that he urinates frequently and that he is always thirsty, sometimes drinking large volumes of water at a time. There is no history of seizures, and he has a normal level of consciousness.

Serum	
Sodium (mEq/L)	132
Potassium (mEq/L)	3.6
Chloride (mEq/L)	97
Bicarbonate (mEq/L)	23
BUN (mg/dL)	11
Creatinine (mg/dL)	1.2
Glucose (mg/dL)	78

Urine	
Sodium (mEq/L)	12
Potassium (mEq/L)	5
Osmolality (mOsm/kg)	70

Discussion By history, this patient appears to have polyuria. The serum electrolytes show that he is mildly hyponatremic with intact renal function. The low urine osmolality demonstrates that is a water diuresis and that the patient is appropriately excreting dilute urine as a normal response to the systemic hypoosmolality. By calculating the electrolyte free water clearance, we can quantify the amount of water losses in the urine. We do not know the exact urine output, so actual water losses cannot be ascertained; however, we can calculate the percentage of the urine that is electrolyte free water. From Eq. (2) we get $[1 - (Na_u^+ + K_u^+)/(Na_{pl}^+ + K_{pl}^+)] = [1 - (12+5)/(132+3.6)] = 0.88$. Therefore, 88% of the patient's urine output is electrolyte free water. In the absence of any electrolyte intake, this percentage of his urine output must be given in order to maintain the same plasma tonicity. It is not clear whether the water diuresis is an appropriate response to excessive water intake or if the water intake is pathological, leading to appropriate water excretion in the urine. Here, the answer is most likely primary polydipsia. If a urine concentrating defect were the primary cause of the polyuria, then the patient should not be hyponatremic, unless the patient had *both* a urinary concentrating defect *and* excessive water intake, which is not likely.

Case #2: Primary Polydipsia Versus Diabetes Insipidus

A 69-year-old female presents with frequent urination and polydipsia. The patient has no other complaints, and her medical history is significant only for a 10-year-history of hypertension. Physical examination is normal. The serum electrolytes and results of a 24-hour urine collection are given below:

Serum	
Sodium (mEq/L)	140
Potassium (mEq/L)	4.0
Chloride (mEq/L)	104
Bicarbonate (mEq/L)	24
BUN (mg/dL)	12
Creatinine (mg/dL)	0.8
Glucose (mg/dL)	80

Urine (24-hour)	
Total volume (L)	9.5
Sodium (mEq/L)	13
Potassium (mEq/L)	7
Osmolality (mOsm/kg)	70

Discussion Based on the 24-hour urine collection, we see that the patient is polyuric. The urine electrolytes and osmolality are very similar to case #1 and the presentation is that of water diuresis. The serum sodium is normal, which is not helpful in discerning the difference between primary polydipsia and diabetes insipidus. Based upon the information that is currently given, it is not known if the polyuria is an appropriate response to excessive water intake or if the primary problem is a defect in urinary concentrating ability. To distinguish between these two, a water deprivation test is necessary. This should be done in a hospitalized setting since patients with diabetes insipidus can rapidly develop hypernatremia if water intake is restricted. The basic principal of a water deprivation test is that if a patient with primary polydipsia is deprived of water and allowed to become mildly hypernatremic, then the urine will become concentrated, whereas the urine will remain dilute, despite hypernatremia, in a patient with diabetes insipidus. This type of specialized testing should be conducted in a specialized setting in consultation with a specialist.

Case #3: Nephrogenic Diabetes Insipidus

A 66-year-old female presents for a routine physical examination. The past medical history is significant only for bipolar disorder, and the patient has been treated with lithium carbonate for the last 10 years. Physical examination is normal. She complains on further questioning of frequent urination and excessive thirst. She denies any dysuria. Her chemistry profile and urine electrolytes are given below:

Serum	
Sodium (mEq/L)	148
Potassium (mEq/L)	4.1
Chloride (mEq/L)	108
Bicarbonate (mEq/L)	27
BUN (mg/dL)	17
Creatinine (mg/dL)	1.0
Glucose (mg/dL)	96

Urine	
Sodium (mEq/L)	28
Potassium (mEq/L)	20
Osmolality (mOsm/kg)	150

Discussion This patient's presentation and laboratory studies are most consistent with diabetes insipidus because of the elevated serum sodium and failure to appropriately concentrate the urine. The fact that we have confirmed a low urine osmolality during a time of hypernatremia lets us immediately make the distinction between diabetes insipidus and primary polydipsia. Therefore, the diagnosis of diabetes insipidus is confirmed, and the addition of a water deprivation test would not add to what we already know. Based solely on the information above, it is still not known whether the patient has central or nephrogenic diabetes insipidus. Nephrogenic diabetes insipidus is a complication of lithium therapy. A rational next step in the evaluation would be to stop the lithium, if possible, and reevaluate the patient.

Case #4: Central Diabetes Insipidus

A 77-year-old male arrives in the emergency room after sustaining severe head trauma. The patient has a past medical history significant for elevated cholesterol, hypertension, and coronary artery disease. He undergoes emergency surgery for an acute epidural hematoma. During the course of the procedure, his hourly urine output increases from 35 cc per hour initially to over 350 cc per hour at the end of the surgery. The initial serum sodium is 139 mEq/L, taken upon arrival at the hospital. Serum chemistry profile and urine studies drawn upon arrival into the intensive care unit are given below:

Serum	
Sodium (mEq/L)	149
Potassium (mEq/L)	3.9
Chloride (mEq/L)	111
Bicarbonate (mEq/L)	27
BUN (mg/dL)	16
Creatinine (mg/dL)	1.1
Glucose (mg/dL)	124

Urine	
Sodium (mEq/L)	21
Potassium (mEq/L)	12
Osmolality (mOsm/ kg)	115

Discussion The urine electrolytes show the polyuria to be due to water diuresis. As in case #3, there is a diagnosis of diabetes insipidus because we have simultaneous measurements showing hypernatremia and dilute urine. This information, however, does not allow us to discern whether the patient has central or nephrogenic diabetes insipidus. In the setting of such a

suggestive history of central diabetes insipidus, it is prudent to administer DDAVP®, a vasopressin analog, and assess the clinical response. If the patient fails to concentrate the urine following administration of DDAVP®, then he has nephrogenic diabetes insipidus, whereas if the urine becomes concentrated, then the diagnosis is central diabetes insipidus. A water deprivation test is not necessary because in a sense, by allowing the patient to become hypernatremic, we have already performed a water deprivation test. When DDAVP® is administered, water intake needs to be adjusted appropriately to avoid precipitation of significant hyponatremia, and serial serum electrolytes should be monitored during dose titration [6]. With an established diagnosis of central diabetes insipidus, DDAVP® can be given either subcutaneously or intranasally. As specific therapy is indicated in the setting of central diabetes insipidus and since hypernatremia can develop rapidly in a fluid-restricted patient, it is important to recognize the condition early, before significant hypernatremia develops.

Case #5: Solute Diuresis from Excess Urea Load

A 74-year-old male presents with abdominal pain, fever, and nausea for 3 days. He is noted to have diverticulitis and undergoes an emergency laparotomy. A sigmoid colectomy is performed, and the patient currently has a colostomy. He has a history of alcohol abuse without evidence of chronic liver disease. He weighs 72 kg. Admission labs are listed below The patient has been kept without enteral intake and is maintained on 5% dextrose in normal saline at 75 cc per hour. Twenty-four hours after the surgery, he is started on total parenteral nutrition with a total volume of 1.5 L, 120 mEq of sodium, and high amino acid content overnight, and the IV fluids are switched to normal saline at 50 cc per hour. Serum sodium is 146. During the next 24 hours, urine output increases. The chemistries and urine studies are listed below:

	Admission	48 Hours After Admission
Sodium (mEq/L)	137	154
Potassium (mEq/L)	4.0	3.1
Chloride (mEq/L)	101	119
Bicarbonate (mmol/L)	24	26
Urea nitrogen (mg/dL)	28	58
Creatinine (mg/dL)	1.4	0.9
Urine sodium (mEq/L)	–	60
Urine potassium (mEq/L)	–	10
Urine osmolality (mOsm/kg)	–	510
Urine output (mL/hr)	25	175

Discussion This patient, like several of the previous cases, has developed polyuria and hypernatremia. This presentation is seen frequently in hospitalized patients, and this case is very typical of solute diuresis leading to hypernatremia. It is important to note that the urine osmolality is high, and therefore ADH activity is present. This will at times confuse clinicians who interpret the elevated urine osmolality as evidence that there are no urinary water losses. To demonstrate urinary water losses, it is necessary to consider

the electrolyte free water clearance. The ratio of the sodium + potassium in the urine to the sodium + potassium in the serum is 70/157 = 0.44. At the current rate of urine output, the patient is losing (100 – 0.44) × 175 cc/hr = 98 cc of electrolyte free water per hour in the urine.

Loss of free water occurring with an increased urinary concentration may appear somewhat paradoxical, but it is the presence of the non-electrolyte osmole in the urine that is "obligating" water loss. This is shown by the presence of a low urine sodium and potassium at a time when the urine osmolality is relatively high. Therefore, the etiology of the water losses is an osmotic diuresis secondary to a high urea load and the necessity to excrete large amounts of urea. Patients with renal insufficiency, as is common in the elderly, are at higher risk for this complication, as urinary concentrating ability is typically impaired, worsening the water losses from a solute diuresis. The high urea load in this case is probably multifactorial, being secondary to the hypercatabolic state secondary to critical illness/stress (in critical illness, protein breakdown is increased, leading to significant urea generation), and also the high protein in the total parenteral nutrition is exacerbating the urea load. This problem is easily preventable by appreciating the degrees of water loss in polyuric patients and providing appropriate amounts of replacement free water and reducing protein intake if appropriate.

Treatment of Hypernatremia

In the treatment of hypernatremia, the first step is the restoration of normal circulatory blood volume in patients with volume depletion using either normal saline or colloid solutions. The next step would then be to correct the serum sodium appropriately with free water replacement (Table 10.2). Another important consideration is to know the ongoing water losses so that the appropriate amount of replacement water can be given. The equation 2 gives the rate of urinary water losses (which is the same as electrolyte free water clearance):

If there are extra-renal fluid losses, these fluid losses will need to be estimated as accurate counts are typically not available. Insulin resistance has been observed (7) to develop in hypernatremic patients. In this circumstance, hyperglycemia can result when dextrose-containing solutions are used. For

Table 10.2 Treatment of Hypernatremia.

1. Replete intravascular volume with colloid solution, isotonic saline, or plasma.
2. Estimate water deficit. Deficit should be replaced over 48–72 hours, aiming for a correction of 1 mOsm/L per hour. In severe hypernatremia (>170 mEq/L), serum sodium should not be corrected to below 150 mEq/L in the first 48–72 hours. Replacement of ongoing water losses are given in addition to the deficit.
3. Hypotonic fluid should be used. Usual replacement fluid is 77 mEq/L (0.45 N saline); a lower sodium concentration may be needed if there is a renal concentrating defect or sodium overload. Glucose-containing solutions should be avoided and an oral route of administration should be used.
4. Monitor plasma electrolytes should be monitored every 2 hours until patient is neurologically stable.

Source: Used with permission of MKSAP, 2006.

this reason, glucose-containing solutions should be avoided if possible. When intravenous glucose solutions are used (for example, 5% dextrose in water), the plasma glucose should be closely monitored. Measurement of serum electrolytes every 2 hours is necessary in a severely hypernatremic patient until the patient is neurologically stable. In patients without central nervous system symptoms, the serum sodium should not be corrected more quickly than 1 mEq/hr or 15 mEq/24 hr. In severe cases (>170 mEq/L), sodium should not be corrected to below 150 mEq/L in the first 48 to 72 hours.

The Prevention and Management of Hypernatremia

Patients at high risk for the development of hypernatremia are those with impaired access to water (for example, infants and the elderly and hospitalized patients). In the evaluation of the polyuric patient, urine electrolytes and urine osmolality should be measured, keeping in mind that the amount of electrolytes in the urine is a better reflection of water losses. Volume expansion with normal saline or colloid should precede the correction of hypernatremia in volume-depleted patients, and the correction should not be too rapid (in order to avoid cerebral edema).

Hyponatremia

Epidemiology

Hyponatremia is a common condition in hospital settings and is increasingly recognized in outpatients. The condition frequently affects the elderly, as comorbid conditions such as congestive heart failure, cancer, and pulmonary disease are more common in this group. Additionally, use of medications is an important risk factor for hyponatremia, and the elderly again tend to use more medicines than other populations. The definition of hyponatremia is a serum sodium less than 135 mEq/L, which is relatively common among hospitalized patients. As we will discuss later in this chapter, age and gender are very important risk factors for the development of hyponatremic encephalopathy, and these two factors impact how the hyponatremic patient should be managed.

Clinical Manifestations

Often times hyponatremia is asymptomatic and tolerated well chronically. However, it is increasingly recognized that chronic hyponatremia can lead to subtle neurological findings, and this can translate into poor outcomes (especially in the elderly, who may be less tolerant of subtle ataxia and prone to suffering falls) [8, 9]. However, hyponatremic encephalopathy (central nervous system symptoms secondary to cerebral edema) can be a presenting sign of hyponatremia [10–12], and this situation is a medical emergency that must be diagnosed promptly and treated quickly to prevent death or devastating neurological complications [13,14]. It is important to differentiate between these two opposite ends of the spectrum since the management is much different depending upon the degree of symptoms. In the elderly, this can be difficult since the presentation of hyponatremic encephalopathy can be atypical, such as a fall and subsequent orthopedic trauma.

Diagnostic Approach to the Hyponatremic Patient

Patients develop hyponatremia when water intake exceeds water excretion because of an impairment or inhibition of the normal homeostatic mechanisms that act to balance water intake and excretion. This occurs in a variety of settings, which are important to recognize. As noted earlier in Eq. (1), the serum sodium is a reflection of total body exchangeable electrolytes relative to total body water. This is true under normal conditions; however, when a substance is relatively confined to the extracellular space, osmotic movement of water from the intracellular space into the extracellular space in order to equalize the concentration in both compartments leads to a decrease in the serum sodium concentration despite a net increase in serum osmolality. It is important, when possible, to measure the serum osmolality before instituting therapy with hypertonic solutions to be sure that a true hypoosmolar state exists and the sodium values are not spurious. However, when faced with a hyponatremic patient and a normal glucose level with clear signs of hyponatremic encephalopathy, therapy can be initiated if serum osmolality cannot be obtained quickly. When the glucose is elevated, the serum sodium must be "corrected" by adding 1.6 mEq/L for every 100-mg/dL increase of the serum glucose above 100 mg/dL. Pseudohyponatremia should also be kept in mind. With the use of potentiometric methodologies, pseudohyponatremia due to hyperproteinemia and hyperlipidemia alone is not a problem. However, if *samples are diluted* prior to measurement of the serum sodium, hyperproteinemia and hyperlipidemia can alter serum sodium measurements. When pseudohyponatremia is present, the measured serum osmolality is normal. The diagnostic approach is further based on the history, urinary electrolytes, and assessment of the patient's extracellular volume status (Figure 10.4). In the following sections, we present several cases that demonstrate the evaluation of the hyponatremic patient in a case-based format, with an emphasis on common presentations of the disease in the elderly.

Pathogenesis of Hyponatremia

Hyponatremia develops when the water intake exceeds the excretion of water. The excretory capacity of the typical adult (assuming normal renal function) is tremendous: Approximately 15 L of free water per day in the urine can be excreted in the urine. Excess ingestion of water as the sole cause of hyponatremia is therefore rare except in the case of mental illness and primary polydipsia. There are many conditions that impair free water excretion (Table 10.3).In these settings, hyponatremia can easily develop. There are states of impaired water excretion in which ADH release is a response to a physiological stimulus such as pain, nausea, volume depletion, post-operative state, or congestive heart failure. Additionally, ADH release can also be pathophysiological, for example, in the setting of SIADH, with thiazide diuretics, or with other types of medications such as antiepileptic drugs. The use of thiazide diuretics is common in the elderly and is a frequent cause of hyponatremia in this population.

Brain Defenses Against Cerebral Edema

Hyponatremia results in an osmotic gradient favoring water movement from the extracellular compartment into the intracellular compartment. The movement of water results in brain swelling that leads to neurological manifestations. The brain is enclosed within a specialized compartment and is

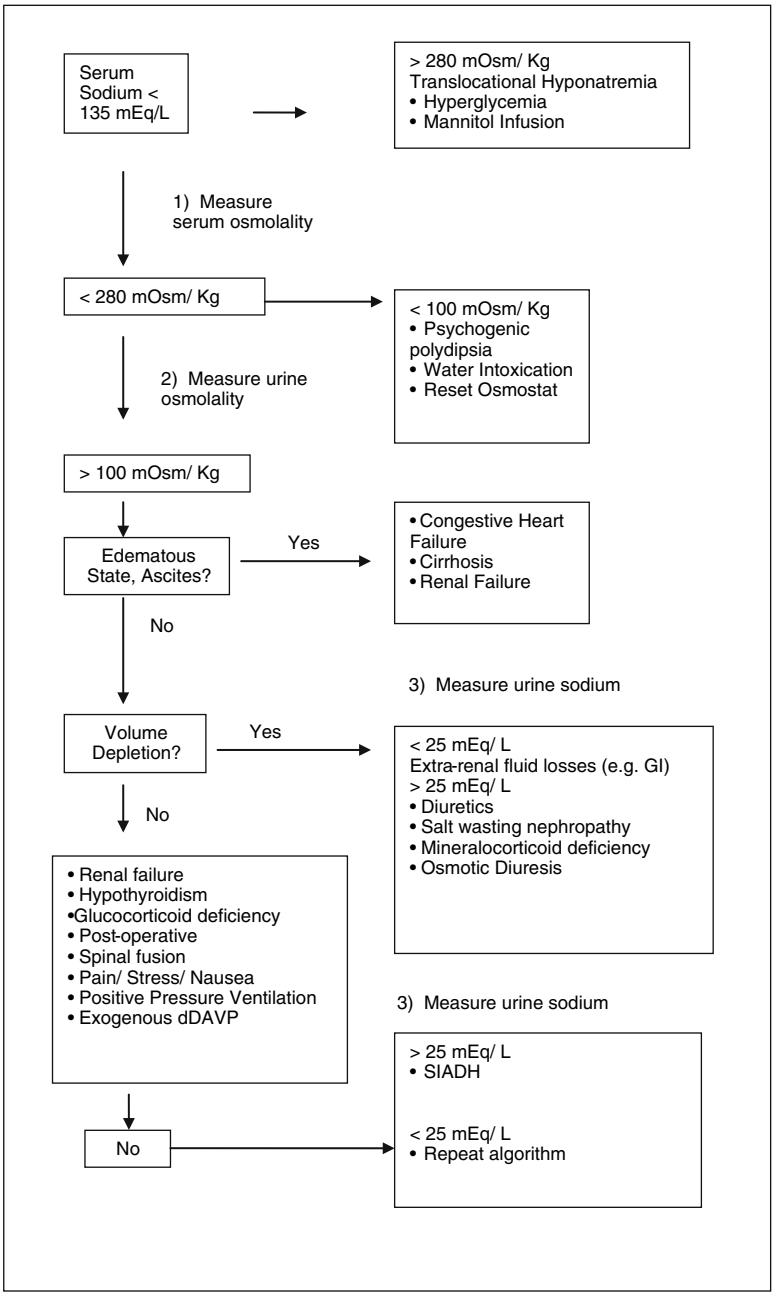

Fig. 10.4 Diagnostic Approach to Hyponatremia ***(Adapted from MKSAP 2006.)***

therefore sequestered from the systemic circulation by the blood-brain barrier. The blood-brain barrier impedes the entry of water and other substances into the brain and has special sites for handling water fluxes [15–17]. The first line in the blood-brain barrier is the tight junctions between vascular endothelial cells [18–20] in the brain capillaries. These endothelial cells of the blood-brain barrier form an interface with the end-foot processes of astrocytes; together,

Table 10.3 States of Impaired Water Excretion.

Volume-Depleted States
Volume depletion
Diuretics
Normal Volume States
SIADH
Pain
Post-operative state
Nausea
Hypothyroidism
Volume-Expanded States
Congestive heart failure
Renal failure
Cirrhosis

Source: Used with permission from Achinger, S.G., Ayus J.C. Fluid and electrolytes. In *Critical Care*, 4th ed., Civetta, Taylor, Kirby, eds.

these form a very specialized structure [21]**.** Astrocytes are highly specialized cells that are responsible for many supporting functions involved with fluid and electrolyte balance in the microenvironment of the brain's extracellular fluid [22,23]. These cells express a concentration of aquaporin 4 (AQ4) water channels and Kir4.1 potassium channel on their foot processes that surround the perivascular space of the brain capillaries [15]. One of the functions of the astrocytes is to take up potassium from the brain microenvironment near the neurons and release it with accompanying water, into the perivascular space, away from neuron cell bodies. It is known that astrocytes selectively swell in response to hypotonicity, whereas neurons do not. The mechanism for this is the presence of AQ4 on the astrocytes and not neuronal cells. Interestingly, mice with targeted deletion of AQ4 do not develop cerebral edema in the face of hyponatremia, suggesting that AQ4 plays an important role in hyponatremia-induced cerebral edema [24]. The astocyte, therefore, is the main regulator of brain water content and, during hypotonicity, appears to be a main portal of water entry into the brain. The response of the astrocyte is an important determinant of the brain's response to hyponatremia-induced cerebral edema.

Several mechanisms protect the brain from hyponatremia-induced cerebral edema. An immediate response is the shunting of cerebrospinal fluid from within the brain. This is a quick response with only a limited capacity to buffer significant volume changes [25]. To decrease the brain size following hyponatremia-induced cerebral edema, cell volume regulatory mechanisms in astrocytes must be active. This is accomplished through reduction in cellular osmolyte content. The astrocyte utilizes an ATP-dependent mechanism [26] that requires Na^+/K^+ ATPase during which ions are extruded from the glial cell. By reducing brain electrolyte content, water obligatorily follows the extruded ions, thereby decreasing brain volume. Following induction of acute hyponatremia in animal models, brain water content is near the baseline value after 6 hours [27].

Clinical Manifestations

The clinical manifestations of hyponatremia are caused by osmotic swelling of the brain, which places pressure on the brain parenchyma as the brain pushes upon the rigid structures encasing the central nervous system. The severity of symptoms is variable and is not always correlated with the level of the serum sodium. Life-threatening hyponatremic encephalopathy with seizures and respiratory arrest can present in patients with a serum sodium as high as 128 mEq/L [28]. However, a serum sodium of 120 mEq/L or lower is not unusual in cirrhosis or severe congestive heart failure without symptoms of cerebral edema. In the typical progression of manifestations of hyponatremic encephalopathy, there are early signs of nausea, vomiting, and headaches [29], which are usually nonspecific and can go unrecognized. If the condition is not recognized and is left without treatment, brainstem herniation with subsequent respiratory arrest and death or severe neurological morbidity can occur [6].

Risk Factors for Hyponatremic Encephalopathy

Age and Gender in Hyponatremic Encephalopathy It is now appreciated that there are patient-specific risk factors for poor outcomes following the development of hyponatremic encephalopathy. Children are at elevated risk for poor outcomes due to the high ratio of brain size to skull size in this group [29]. The skull reaches full size approximately at age 16, whereas the brain reaches its adult size at approximately age 6 [30, 31]. Because of this anatomical difference, children are more susceptible to the detrimental effects of cerebral edema since the brain is not allowed as much room to expand as it is in adults.

Being a woman of premenopausal age is another risk factor in terms of neurological outcomes following hyponatremia. Premenopausal females are at 25 times increased risk of death following hyponatremic encephalopathy over control patients [28]. The greater predisposition to death among females due to hyponatremia is on account of differences in adaptive responses in brain cell volume regulation during hyponatremic stress. It is known that ATP-dependent mechanisms are important in the adaptive responses to cerebral edema. Estrogens, by having a similar steroidal structure to ouabain and other cardiac glycosides (such as digoxin), have inhibitory activity against the sodium potassium ATPase [32]. Female sex hormones have been shown to inhibit the Na^+/K^+ ATPase pump in diverse tissues such as heart, muscle, liver, and red blood cells [33]. These observations apply to animal models of brain adaptation in the setting of hyponatremia, where female rats suffer increased morbidity from hyponatremia [34, 35]. Furthermore, synaptosomes isolated from female hyponatremic rats have increased uptake of sodium compared with male synaptosomes isolated from male hyponatremic rats, suggesting an impairment in sodium extrusion [34, 36]. Also, the regulatory volume decrease that serves to decrease cell volume following hypotonic stress is inhibited by the presence of estrogen/progesterone in rat astrocytes treated *in vitro* [37]. Finally, female rats undergo increased vasoconstriction in response to vasopressin compared with male rats [35]. Vasoconstriction can lead to brain hypoxia and, as will be discussed in the following section, hypoxia is another factor that can worsen brain adaptation. These studies support a mechanism involving the effect of estrogens on brain cell adaptation

for the clinical observation that premenopausal females suffer worse outcomes following hyponatremia.

Hypoxia and the Development of Hyponatremic Encephalopathy Hypoxia at presentation, even after adjustment for co-morbid conditions, is a strong risk factor for poor outcomes in patients with hyponatremic encephalopathy, as previous epidemiologic studies have shown [28, 38]. The mechanism for this association has recently been studied in animal models. As astrocyte cell volume regulatory responses have been shown to be important in explaining the poor outcomes seen in premenopausal females, the response of these cells to hypoxic stress has been proposed also to affect these processes. It is known that brain ischemia alone can lead to cerebral edema; the most dramatic example of this is diffuse edema following asphyxiation or cardiac arrest. This is termed *cytotoxic edema* and is thought to be due to impairment of cell volume regulatory mechanisms. In the setting of hyponatremia, which induces cerebral edema, if there is further impairment of volume regulatory mechanisms, it is likely that there will be more severe cerebral edema than if hypoxia were absent. This occurs because of an insufficient regulatory volume decrease in the brain when hypoxia is present [39]. In the setting of hypoxia, the cell responds by trying to maintain the levels of ATP [40]. Pathways that increase ATP such as glycolysis are upregulated, and pathways that consume ATP are downregulated. Na^+/K^+ ATPase activity is a large consumer of ATP; therefore, this is one of the processes that are downregulated during hypoxia, which is mediated through increased targeting for endocytosis. Animal studies have demonstrated that survival is significantly decreased and that brain adaptation is significantly impaired in the setting of brain hypoxia [39, 41]. Therefore, hypoxic conditions can impair the brain's ability to decrease astrocyte cell volume in response to a hyponatremic stress, which leads to worsened survival among hyponatremic rodents. These animal studies suggest a cellular mechanism for impaired brain adaptation and the increased risk of death when hypoxia occurs simultaneously with hyponatremia.

Two mechanisms are responsible for the development of hypoxia in patients with hyponatremic encephalopathy. These are hypercapneic respiratory failure and neurogenic pulmonary edema [42, 43]. Hypercapneic respiratory failure is a sign of impending brainstem herniation, can develop in untreated hyponatremic encephalopathy, and leads to hypoxia through decreased respiratory drive. Neurogenic pulmonary edema, which develops in the setting of cerebral edema, has been reported to occur with hyponatremic encephalopathy [42,43]. Neurogenic pulmonary edema is believed to be secondary to increased vascular permeability and increased catecholamine release due to increased intracranial pressure [44]. The hypoxemia that develops due to these conditions can then further worsen astrocyte cell volume regulatory mechanisms, which can cause further worsening of the cerebral edema. This can initiate a cascade effect that, unless broken, results in worsening of the underlying cerebral edema and poor patient outcomes (Figure 10.5). Hypoxemia is therefore both a risk factor and a pathogenetic mechanism in the development of severe cerebral edema due to hyponatremia.

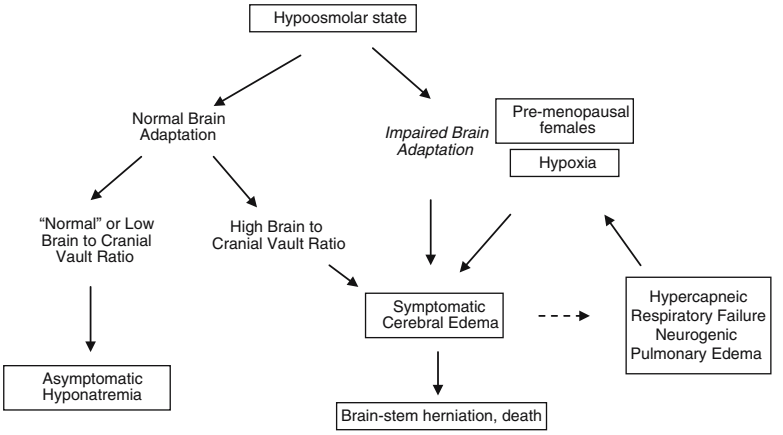

Fig. 10.5 (Used with permission from Achinger, S.G., Ayus J.C. Fluid and Electrolytes. In Civetta, Taylor, Kirby – Critical Care, 4^{th} edition.)

Principles of Treatment of Hyponatremic Encephalopathy

Hyponatremic encephalopathy is a life-threatening medical emergency and should be treated promptly and appropriately. Several critical issues must be understood in the treatment of hyponatremic encephalopathy: (1) Patients who do not have central nervous system symptoms do not require treatment with hypertonic saline; (20) patients with hyponatremic encephalopathy (central nervous system symptoms secondary to cerebral edema) should be treated promptly with hypertonic saline; (3) patients at risk for a poor outcome need to be identified and hypoxia, if present, must be corrected; (4) the absolute change in serum sodium should not exceed 15–20 mEq/L over 48 hours; and (5) the patient should not be corrected to normonatremic levels or hypernatremic levels. The use of hypertonic saline is the best treatment for hypernatremic encephalopathy; following these guidelines will reduce the likelihood of therapy-induced brain injury.

When treating a patient with hyponatremic encephalopathy with hypertonic saline, three goals should be kept in mind: (1) Quickly reduce edema in patients with severe manifestations (respiratory arrest or continuous seizures); (2) correct serum sodium to a safe, mildly hyponatremic level (not to normonatremic or hypernatremic levels); and (3) maintain this level of serum sodium [6] (Figure 10.6). In patients with severe manifestations (active seizures or respiratory failure), a bolus of 100 cc of 3% saline (given over 10 minutes) can be given to quickly increase the serum sodium. The goal of the bolus is to increase the serum sodium by approximately 2–4 mEq/L. A bolus may be repeated if necessary to get the desired effect. Following the bolus of hypertonic saline, an infusion of hypertonic saline should be started with the intention to raise the serum sodium to mildly hyponatremic levels. In order to prevent therapy-induced cerebral injury, it is important that the total change in serum sodium should not exceed 15–20 mEq/L over 48 hours [14]. To treat patients with hyponatremic encephalopathy who do not exhibit ongoing seizures or respiratory arrest, an infusion of 3% saline without a bolus is appropriate initial management. In patients with congestive heart failure, pulmonary edema may develop with the use of hypertonic saline.

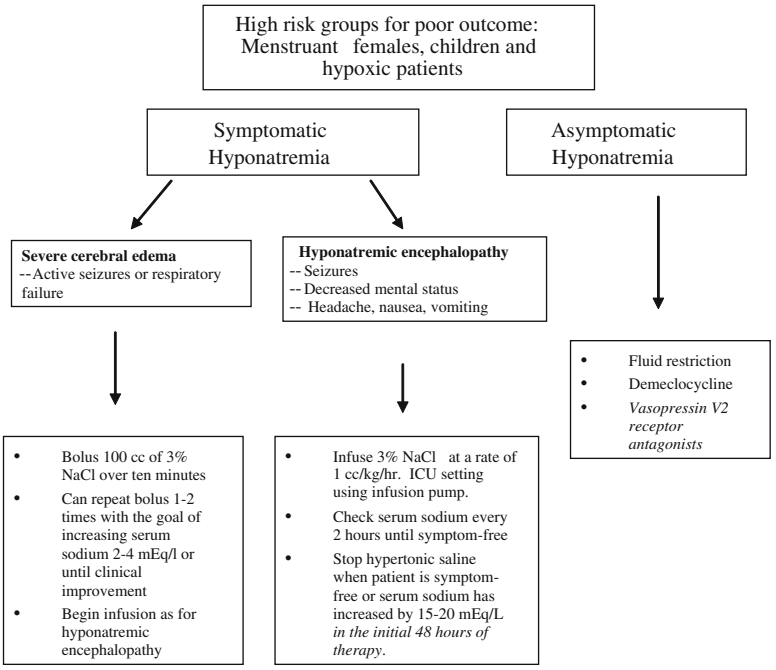

Fig. 10.6 Treatment of hyponatremia. (Adapted with permission with permission from Achinger, S.G., Moritz, M.L., Ayus J.C. Dysnatremias: Why are patients still dying? South Medical J 2006; 99(4): 353-362.)

Furosemide should be given to these patients in addition to hypertonic saline. Such patients require close monitoring.

In our own practice, we do not use formulas to determine the amount of hypertonic saline to give, and we do not recommend such a practice. The danger of using formulas is that if they are employed as a substitute for close patient monitoring, overcorrection of the serum sodium can easily occur. The main reason that this can occur is that formulas are based on a closed-system assumption, where ongoing water losses are not accounted for. If a patient undergoes spontaneous water diuresis, the serum sodium will continue to increase as the patient "autocorrects." This most commonly occurs when the stimulus for water retention is removed and the body begins to respond appropriately to hypotonicity by suppressing ADH release and excreting dilute urine.

A precipitous increase in urine output is the first sign that this is occurring. For this reason, hourly urine output should be followed closely in all patients being treated for hyponatremic encephalopathy. Additionally, all patients receiving an infusion of 3% saline for hyponatremic encephalopathy should have frequent monitoring of the serum sodium (at least every 2 hours) until they are clinically stable and the serum sodium values are stable. Any patient with manifestations of hyponatremic encephalopathy should be treated in an intensive care unit setting until the patient is clinically stable. In lieu of a calculated infusion rate, an assumption that can be used is that an infusion of 1 mL/kg of 3% NaCl will raise the serum sodium by approximately 1 mEq/L. After the initial infusion rate is chosen, the rate of infusion should be

titrated based upon measured serum sodium values and the clinical status of the patient. Finally, when possible, prior to starting treatment with hypertonic saline, the serum osmolality should be measured to verify that a hypotonic state exists [29].

Risk Factors for Cerebral Demyelination During Correction of Hyponatremia

Cerebral demyelination has been associated with the correction of hyponatremia, and risk factors for this complication should be understood so that it can be avoided. The symptoms of cerebral demyelination usually become apparent days to weeks following correction of hyponatremia. The range of manifestations is broad, as the symptoms can be minimal to none or as severe as a pseudocoma with a "locked-in stare." A key point is that the absolute change in serum sodium over 48 hours is most predictive of the development of cerebral demyelination, whereas the hourly rate of correction of serum sodium by itself is not [14]. This is a key point because it is not appropriate to treat a patient with respiratory arrest due to hyponatremic encephalopathy with a "slow" infusion of hypertonic saline to increase the serum sodium by 0.5 to 1 mEq/hr. We believe that this type of patient, with impending brainstem herniation, should be treated with a bolus of hypertonic saline to quickly reduce brain volume. When such a patient is out of immediate danger, then the hourly rate of correction should be more modest, the total change in serum sodium should not exceed 15–20 mEq/L over 48 hours, and the patient should not be corrected to normonatremic levels. Additionally, other clinical factors not related to degree of correction such as liver disease and hypoxia increase the risk of cerebral demyelination, and care must be exercised in treating these patients [14]. Remember that p*atients with liver disease are very susceptible to cerebral demyelination, and a great degree of caution should be exercised in this group. The safe degree of correction over 48 hours in this group is not known and might be less than 15–20 mEq/L over 48 hours* [14].

Treatment of Asymptomatic Hyponatremia

In treating asymptomatic hyponatremia, the underlying cause should be addressed and corrected when possible. Precipitating medications should be stopped when possible. Irrespective of the serum sodium level, asymptomatic hyponatremia does not require prompt treatment with hypertonic saline. Fluid restriction can be helpful in selected cases; however, in cases where electrolyte free water excretion is minimal or negative, this is often not enough. When chronic hyponatremia is refractory to fluid restriction, demeclocycline can be used. This agent has been used traditionally to lower urine osmolality and increase free water excretion. Selective vasopressin receptor (V2) blockers are newly available agents, show promise for the treatment of chronic hyponatremia [45], and may become the mainstay of therapy in the future.

The Prevention and Management of Hyponatremia

Hospitalized patients should be considered at risk for the development of hyponatremia, and hypotonic fluids should not be administered unless there is a free water deficit. Normal saline (0.9% NaCl) is the most appropriate fluid to use in the post-operative setting, and hypotonic fluids should not be administered following surgery unless there is a free water deficit. Patients

taking thiazide diuretics, especially the elderly, should be weighed before and after starting therapy to screen for water retention, and serum electrolytes must be monitored as hyponatremia can develop. Hyponatremic encephalopathy should be promptly recognized and treated with 3% hypertonic saline. Risk factors for poor outcomes with hyponatremic encephalopathy are menstruating females, hypoxic patients, and children. Hypoxia should be corrected during treatment of hyponatremic encephalopathy.

Case #6: Hyponatremia Associated with Colonoscopy

A 71-year-old female with a past medical history significant only for hypertension is scheduled to undergo an elective colonoscopy. She is prescribed a polyethylene glycol bowel preparation. While taking this, she becomes nauseated and vomits several times throughout the day. She develops diarrhea, and her fluid intake increases during this time. Overnight she continues to be nauseated and develops a headache. In the morning, just prior to the procedure, her husband finds the patient unconscious and difficult to arouse. En route to the hospital, she has a generalized seizure. On arrival at the hospital, her serum sodium is 112 mEq/L.

Discussion Preparation for colonoscopy has been shown to be associated with hyponatremic encephalopathy. The reduction in plasma volume associated with the significant diarrhea that can develop from a bowel preparation is thought to lead to increased thirst [12]. By replacing these fluid losses with hypotonic fluids, she is at risk of development of hyponatremia. Concomitantly, the patient can develop impaired free water excretion due to elevated ADH levels due to nausea and volume depletion. This potential complication can be avoided if a patient is instructed about the danger of taking in significant amounts of fluid during the preparation for a colonoscopy.

Case #7: DDAVP Withdrawal

A 66-year-old female has a history of central diabetes insipidus that developed after the resection of a pituitary tumor 7 years ago. She is evaluated in an emergency room after she had a generalized seizure at home. She had been taking DDAVP® 10 mcg intranasally twice a day for this condition. The patient is found to be lethargic and unresponsive, without current seizure activity. The serum sodium is 117 mEq/L, and the serum potassium is 4.2 mEq/L. Her urine sodium is 100 mEq/L, and the urine potassium is 35 mEq/L with a urine osmolality of 640 mOsm/kg. The patient is given 2 L of 0.9% saline in the emergency room. Serum sodium is found to be 126 mEq/L after presentation following this treatment. She is admitted for management of hyponatremia. The admitting physician decides to hold the DDAVP®; the patient's urine output increases significantly overnight. In the morning following admission, the serum sodium is 153 mEq/L, urine sodium is 16 mEq/L, urine potassium is less than 10 mEq/L, and urine osmolality is 70 mOsm/kg.

Discussion DDAVP® by itself does not lead directly to hyponatremia. DDAVP® leads to retention of free water; therefore, the dose of the medication must be titrated with consideration of the patient's fluid intake. The patient must be closely monitored and the serum electrolytes carefully followed. Patients will at times increase fluid intake, and water intoxication can result, as happened in this case. When this happens, if DDAVP® is

withheld, free water diuresis will ensue. This "autocorrection" of the serum sodium can occur quite rapidly, and dangerous overcorrection of the serum sodium may result. This concern is greatest in patients with diabetes insipidus, who will continue to rapidly excrete large volumes of dilute urine, even after the serum sodium has exceeded 140 mEq/L. A better approach that we advocate in a patient with hyponatremic encephalopathy due to DDAVP®-associated hyponatremia is to continue DDAVP® and restrict all enteral fluid intake. Then 3% NaCl can be given to correct the serum sodium to the preferred degree and ultimately stopped. The DDAVP should be continued throughout this time. Absolutely no hypotonic fluids should be administered, and the patient must be closely monitored to restrict all fluid intake. If a patient is allowed fluid intake while DDAVP is given, hyponatremia can rapidly develop. If necessary, a slow infusion of 0.9% saline can be given, which will support the patient's volume status. This approach can prevent the type of overcorrection of the serum sodium that can occur when a patient is allowed to "autocorrect" with an uncontrolled water diuresis. Consultation with a specialist is mandatory in a complex case such as this. The hourly urine output should be followed closely in all patients being treated for hyponatremic encephalopathy, as a significant increase in urine output will be the first clinical sign that a water diuresis is occurring.

Case #8: Hyponatremia Due to SIADH

A 78-year-old male patient with small cell lung cancer who had been treated with chemotherapy and achieved a remission last year has recently come to the hospital and been diagnosed with recurrent disease. He is seen in follow-up after being discharged from the hospital, where he was found to have pneumonia and bilateral pleural effusions secondary to metastatic disease. His serum sodium was decreased throughout the hospitalization, which was managed with fluid restriction. His other medical problems include hypertension. Current medications include oral levofloxacin and atenolol. Currently, he is significantly improved since hospital discharge 3 days ago. Physical exam reveals BP 110/50, P 65, and T 98.8. The remainder of the physical exam is significant for a very thin male who is in no acute distress. Lungs are found to have decreased breath sound in both bases, and the cardiac exam is normal. There is no peripheral edema. Laboratory values drawn in the clinic are given below:

Serum	
aSodium (mEq/L)	110
Potassium (mEq/L)	4.0
Chloride (mEq/L)	80
Bicarbonate (mEq/L)	19
BUN (mg/dL)	6
Creatinine (mg/dL)	0.7
Glucose (mg/dL)	87
Phosphorus (mg/dL)	3.0
Albumin (g/dL)	3.4
Osmolality (mOsm/kg)	234

Urine	
Sodium (mEq/L)	110
Potassium (mEq/L)	30
Osmolality (mOsm/kg)	625

Discussion SIADH is a syndrome of hypotonic hyponatremia, with a urine osmolality > 100 mOsm/kg in the absence of causes of physiological ADH release or other conditions associated with hyponatremia such as volume depletion, adrenal insufficiency, congestive heart failure, hypothyroidism, cirrhosis, and/or renal impairment. In the case presented above, the laboratory values support SIADH given the decreased serum osmolality and the high urine osmolality.

The normal response to hypotonicity would be to excrete dilute urine, which is not occurring in this case; in fact, the urine is very concentrated. Before SIADH is diagnosed, it is important be sure that the patient does not have another cause of a water-retentive state that is a physiological response: These conditions are most commonly congestive heart failure, cirrhosis, and volume depletion. The urine electrolytes can be a helpful adjunct in making this discrimination. A state of low effective circulating blood volume such as occurs with these conditions leads to activation of both sodium- and water-retentive mechanisms. An elevated urine osmolality can be expected; however, the urine sodium should not be elevated (> than 40 mEq/L) in these conditions. During states of antinatriuresis, the urine sodium is typically less than 20 mEq/L. However, it must be kept in mind that many patients with cirrhosis and congestive heart failure receive diuretics; therefore, the serum sodium must be interpreted cautiously in this setting. Other conditions that can lead to ADH release should also be considered and ruled out before SIADH is diagnosed. These include post-operative stress, medications, trauma, pain, and nausea.

Case #9: Hyponatremic Encephalopathy Presenting with a Fall

A 74-year-old female patient presents to the emergency room after having fallen in her home. According to the patient's family, she has been slightly confused over the past three days. Past medical history is significant only for osteoporosis and hypertension. The patient's daughter recalls that one week ago, her mother's primary care physician started her on hydrochlorothiazide. Physical exam revealed BP 108/55; P 90; T 96.9. She is confused and not responding to questioning appropriately. Lungs are clear, and cardiac exam is normal. She has no pedal edema.

Serum	
Sodium (mEq/L)	108
Potassium (mEq/L)	2.6
Chloride (mEq/L)	74
Bicarbonate (mEq/L)	21
BUN (mg/dL)	16
Creatinine (mg/dL)	1.4
Glucose (mg/dL)	86

Discussion Hydrochlorothiazide is a fairly common cause of hyponatremia in the outpatient setting. By acting at the level of the cortical collecting duct, thiazide diuretics can impair urinary diluting capacity but do not affect the capacity to concentrate the urine. This is in contrast to loop diuretics, which can impair both diluting and concentrating capacity. Thiazide diuretics induce a state of effective circulating volume depletion that can stimulate ADH secretion. This leads to increased urinary concentration and water retention. Chronic hyponatremia is a cause of more subtle neurological impairment that in the elderly can present with a fall [9]. Recent data show that with sophisticated testing, neurological impairment may occur even at a serum sodium as high as 132 mEq/L [8]. When using thiazide diuretics, the clinician must be vigilant for the potential complication of hyponatremia, especially in the elderly. A proposed measure to detect water retention is to have patients weigh themselves before and 48 hours after starting the medication. If patients fail to lose weight or gain weight during this time, then the medication should be stopped and serum electrolytes checked. Additionally, all patients on thiazide diuretics should have the electrolytes measured especially after the onset of therapy or dose adjustments.

References

1. Dunn, F.L., Brennan, T.J., Nelson, A.E., Robertson, G.L. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. *J. Clin. Invest.* 1973; 52(12):3212–3219.
2. Heilig, C.W., Stromski, M.E., Blumenfeld, J.D., Lee, J.P., Gullans, S.R. Characterization of the major brain osmolytes that accumulate in salt-loaded rats. *Am. J. Physiol*. 1989; 257(6 Pt 2):F1108–1116.
3. Lien, Y.H., Shapiro, J.I., Chan, L. Effects of hypernatremia on organic brain osmoles. *J. Clin. Invest.* 1990; 85(5):1427–1435.
4. Ayus, J.C., Armstrong, D.L., Arieff, A.I. Effects of hypernatraemia in the central nervous system and its therapy in rats and rabbits. *J. Physiol*. 1996; 492 (Pt 1):243–255.
5. Moritz, M.L., Ayus, J.C. The changing pattern of hypernatremia in hospitalized children. *Pediatrics* 1999; 104(3 Pt 1):435–439.
6. Achinger, S.G., Moritz, M.L., Ayus, J.C. Dysnatremias: Why are patients still dying? *South Med. J.* 2006; 99(4):1–12.
7. Ayus, J.C., Krothapalli, R.K. Hyperglycemia (HG) associated with non-diabetic hypernatremia (NDH) patients. *J. Am. Soc. Nephrol.* 1990; 1:317A.
8. Renneboog, B., Sattar, L., Decaux, G. Determination of thresholds for the attention and gait deficits encountered in chronic hyponatremia. *J. Am. Soc. Nephrol*. 2006; 17:37A (Abstract).
9. Ayus, J.C., Arieff, A.I. Chronic hyponatremic encephalopathy in postmenopausal women: Association of therapies with morbidity and mortality. *JAMA* 1999; 281(24):2299–2304.
10. Arieff, A.I., Ayus, J.C. Endometrial ablation complicated by fatal hyponatremic encephalopathy. *JAMA* 1993; 270(10):1230–1232.
11. Arieff, A.I., Ayus, J.C. Pathogenesis of hyponatremic encephalopathy. Current concepts. *Chest* 1993; 103(2):607–610.
12. Ayus, J.C., Levine, R., Arieff, A.I. Fatal dysnatraemia caused by elective colonoscopy. *BMJ* 2003; 326(7385):382–384.
13. Arieff, A.I., Ayus, J.C., Fraser, C.L. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ* 1992; 304(6836):1218–1222.

14. Ayus, J.C., Krothapalli, R.K., Arieff, A.I. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. *N. Engl. J. Med.* 1987; 317(19):1190–1195.
15. Nielsen, S., Nagelhus, E.A., Amiry-Moghaddam, M., Bourque, C., Agre, P., Ottersen, O.P. Specialized membrane domains for water transport in glial cells: High-resolution immunogold cytochemistry of aquaporin-4 in rat brain. *J. Neurosci.* 1997; 17(1):171–180.
16. Agre, P., Preston, G.M., Smith, B.L., et al. Aquaporin CHIP: The archetypal molecular water channel. *Am. J. Physiol.* 1993; 265(4 Pt 2):F463–476.
17. Nielsen, S., Smith, B.L., Christensen, E.I., Agre, P. Distribution of the aquaporin CHIP in secretory and resorptive epithelia and capillary endothelia. *Proc. Natl. Acad. Sci. USA* 1993; 90(15):7275–7279.
18. Simard, M., Arcuino, G., Takano, T., Liu, Q.S., Nedergaard, M. Signaling at the gliovascular interface. *J. Neurosci*. 2003; 23(27):9254–9262.
19. Amiry-Moghaddam, M., Ottersen, O.P. The molecular basis of water transport in the brain. *Nat. Rev. Neurosci*. 2003; 4(12):991–1001.
20. Dolman, D., Drndarski, S., Abbott, N.J., Rattray, M. Induction of aquaporin 1 but not aquaporin 4 messenger RNA in rat primary brain microvessel endothelial cells in culture. *J. Neurochem*. 2005; 93(4):825–833.
21. Abbott, N.J., Ronnback, L., Hansson, E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat. Rev. Neurosci*. 2006; 7(1):41–53.
22. Simard, M., Nedergaard, M. The neurobiology of glia in the context of water and ion homeostasis. *Neuroscience* 2004; 129(4):877–896.
23. Paulson, O.B., Newman, E.A. Does the release of potassium from astrocyte endfeet regulate cerebral blood flow? *Science* 1987; 237(4817):896–868.
24. Manley, G.T., Fujimura, M., Ma, T., et al. Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. *Nat. Med.* 2000; 6(2):159–163.
25. Reulen, H.J., Tsuyumu, M., Tack, A., Fenske, A.R., Prioleau, G.R. Clearance of edema fluid into cerebrospinal fluid. A mechanism for resolution of vasogenic brain edema. *J. Neurosurg.* 1978; 48(5):754–764.
26. Olson, J.E., Sankar, R., Holtzman, D., James, A., Fleischhacker, D. Energy-dependent volume regulation in primary cultured cerebral astrocytes. *J. Cell Physiol*. 1986; 128(2):209–215.
27. Melton, J.E., Patlak, C.S., Pettigrew, K.D., Cserr, H.F. Volume regulatory loss of Na, Cl, and K from rat brain during acute hyponatremia. *Am. J. Physiol.* 1987; 252(4 Pt 2):F661–669.
28. Ayus, J.C., Wheeler, J.M., Arieff, A.I. Postoperative hyponatremic encephalopathy in menstruant women. *Ann. Intern. Med.* 1992; 117(11):891–897.
29. Moritz, M.L., Ayus, J.C. The pathophysiology and treatment of hyponatraemic encephalopathy: An update. *Nephrol. Dial. Transplant* 2003; 18(12):2486–2491.
30. Xenos, C., Sgouros, S., Natarajan, K. Ventricular volume change in childhood. *J. Neurosurg*. 2002; 97(3):584–590.
31. Sgouros, S., Goldin, J.H., Hockley, A.D., Wake, M.J., Natarajan, K. Intracranial volume change in childhood. *J. Neurosurg*. 1999; 91(4):610–616.
32. Chen, J.Q., Contreras, R.G., Wang, R., et al. Sodium/potasium ATPase (Na(+), K (+)-ATPase) and ouabain/related cardiac glycosides: A new paradigm for development of anti-breast cancer drugs? *Breast Can. Res. Treat*. 2006; 96(1):1–15.
33. Davis, R.A., Kern, F., Jr., Showalter, R., Sutherland, E., Sinensky, M., Simon, F.R. Alterations of hepatic Na+,K+-atpase and bile flow by estrogen: Effects on liver surface membrane lipid structure and function. *Proc. Natl. Acad. Sci. USA* 1978; 75(9):4130–4134.
34. Fraser, C.L., Kucharczyk, J., Arieff, A.I., Rollin, C., Sarnacki, P., Norman, D. Sex differences result in increased morbidity from hyponatremia in female rats. *Am. J. Physiol*. 1989; 256(4 Pt 2):R880–885.

35. Arieff, A.I., Kozniewska, E., Roberts, T.P., Vexler, Z.S., Ayus, J.C., Kucharczyk, J. Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. *Am. J. Physiol.* 1995; 268(5 Pt 2):R1143–1152.
36. Fraser, C.L., Sarnacki, P. Na+-K+-ATPase pump function in rat brain synaptosomes is different in males and females. *Am. J. Physiol*. 1989; 257(2 Pt 1): E284–289.
37. Fraser, C.L., Swanson, R.A. Female sex hormones inhibit volume regulation in rat brain astrocyte culture. *Am. J. Physiol*. 1994; 267(4 Pt 1):C909–914.
38. Nzerue, C.M., Baffoe-Bonnie, H., You, W., Falana, B., Dai, S. Predictors of outcome in hospitalized patients with severe hyponatremia. *J. Natl. Med. Assoc.* 2003; 95(5):335–343.
39. Vexler, Z.S., Ayus, J.C., Roberts, T.P., Fraser, C.L., Kucharczyk, J., Arieff, A.I. Hypoxic and ischemic hypoxia exacerbate brain injury associated with metabolic encephalopathy in laboratory animals. *J. Clin. Invest*. 1994; 93(1):256–264.
40. Hochachka, P.W., Buck, L.T., Doll, C.J., Land, S.C. Unifying theory of hypoxia tolerance: Molecular/metabolic defense and rescue mechanisms for surviving oxygen lack. *Proc. Natl. Acad. Sci. USA* 1996; 93(18):9493–9498.
41. Ayus, J.C., Armstrong, D., Arieff, A.I. Hyponatremia with hypoxia: Effects on brain adaptation, perfusion, and histology in rodents. *Kidney Int.* 2006; 69(8):1319–1325.
42. Ayus, J.C., Arieff, A.I. Pulmonary complications of hyponatremic encephalopathy. Noncardiogenic pulmonary edema and hypercapnic respiratory failure. *Chest* 1995; 107(2):517–521.
43. Ayus, J.C., Varon, J., Arieff, A.I. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Ann. Intern. Med.* 2000; 132(9): 711–714.
44. McClellan, M.D., Dauber, I.M., Weil, J.V. Elevated intracranial pressure increases pulmonary vascular permeability to protein. *J. Appl. Physiol.* 1989; 67(3): 1185–1191.
45. Schrier, R.W., Gross, P., Gheorghiade, M., et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N. Engl. J. Med.* 2006; 355(20):2099–2112.

11

Hypertension in the Elderly

José A. Garcia-Donaire, José Luís Rodicio Díaz,
and Prof. Luis M. Ruilope

Introduction

Hypertension is considered the most frequent chronic condition for which people see a healthcare provider [1] and the most common attributable cause of preventable death in developed nations, with an increasing importance in developed countries [2].

In the last decades of the 20th century, a demographic expansion was observed, basically dependent on the abrupt fall in birth rate, health and scientific advances, an improved management of the different pathologies and their consequences, and, finally, a marked social development that accounts for a better quality of life for the general population. As a result of all these factors, the proportion of elderly people has grown continuously. In this population, hypertension represents the most powerful risk factor for cardiovascular death [3].

Although blood pressure (BP) rises normally with age, it is not a physiological phenomenon and hypertension is not less harmful for elderly than for young people. The combination of aging and the accompanying rise in BP has contributed to multiply the prevalence of elevated blood pressure among elderly people, and absolute rates of 70% are expected in the coming years for this specific population.

Multiple studies have demonstrated that elevated systolic blood pressure (SBP) is more prevalent in older people [4]. Current international guidelines for the classification of arterial hypertension, identical for adults and the elderly without antihypertensive treatment, set the threshold to consider a patient as hypertensive at an SBP of 140 mmHg or higher and at a diastolic blood pressure (DBP) of 90 mmHg or higher; isolated systolic hypertension is defined as persistent SBP equal to or higher than 140 mmHg, with DBP lower than 90 mmHg (Table 11.1). The European Society of Hypertension and European Society of Cardiology Hypertension (ESH/ESC) Guidelines [5] were published in 2003 and classify hypertension in order to stratify total cardiovascular risk to patients (Table 11.2).

Table 11.1 Definitions and Classification of Blood Pressure Levels

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Pre-hypertension	120–139	80–89
Stage 1 hypertension	140–159	90–99
Stage 2 hypertension	>160	>100

Source: National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Hypertension 2003; 42:1206–1252.

Pathophysiological Characteristics of Hypertension in the Elderly

Numerous studies have demonstrated that aging is accompanied by the development of modifications in cardiovascular and renal systems. These alterations are particularly prevalent when hypertension is present [6,7]. The heart suffers diverse changes, both in the mechanical component (hypertrophy of the left ventricle's posterior wall) and in the electrical system (see Chapter 4). Therefore, cardiac output can be decreased in the elderly because of minor myocardial contractility, and the heart rate is not modified due to the reduced activity of the adrenergic receptors [8].

The effects on the renal system are related to vasoconstriction and afferent arterial progressive occlusion, leading to glomeruli loss and mechanical dilatation of the nonaffected nephrons caused by flow redistribution, which may produce glomerular injury and progressive renal damage. The decrease in the glomerular filtration rate (GFR) in the elderly as a result of glomerular sclerosis may affect 40% of glomeruli by the eighth decade. These variations are accompanied by a decreased capability in sodium handling, probably as a consequence of a nephron's dilutor segment defect. Changes in the properties of the cardiovascular system may alter the hemodynamic characteristics of the arteries and accelerate the atherosclerosis process. Hypertension can produce arterial stiffness by functional and structural mechanisms, amplified by aging, as a result of increased intramural pressure, the load-bearing elastic lamellae stretch, and vasoconstriction.

Table 11.2 Definitions and Classification of Blood Pressure Levels

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	<120	<80
Normal	120–129	80–84
High normal	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥180	≥110
Isolated systolic hypertension	≥140	<90

Source: ESH/ESC Hypertension Guidelines Committee. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J. Hypertens*. 2003; 21:1779–1786.

The renin-aldosterone-angiotensin system (RAAS) becomes less effective, leading to diminished angiotensin II formation and aldosterone secretion. Although plasma norepinephrine levels are enhanced with aging, attenuation in α- and β-receptors' sensitivity has been demonstrated. Sensitivity to salt is also present in some of the elderly hypertensive and contributes to the development of rise in BP. At this point, it is necessary to distinguish between salt sensitivity and the increased time taken by the healthy aged to excrete a given amount of salt. As a result of the physiological decrease in the GFR (see Chapter 5), if we were to provide an equal amount of salt to an aged person and a young adult, the aged person would take more time to excrete the given amount of salt than the young person. However, this does not mean that the elderly are salt-resistant.

In elderly people with hypertension, a minor production of natriuretic substances as prostaglandin E2 or dopamine could contribute to the development of salt sensitivity [9].

Subsequently, pathophysiological features of hypertension in the elderly are rather different than in younger adults; cardiac output, heart frequency, ejection volume, intravascular volume, renal flow, and renin activity are decreased in the elderly.

Clinical Characteristics of Hypertension in the Elderly

The specific pathophysiological conditions of hypertension in the elderly confer singularity to this population in order to achieve the optimal management, and clinical features may also be different from adult essential hypertensive patients. The specific hemodynamic features of the cardiovascular and renal system cause more increased peripheral and renal resistances.

Aging modifications create a propitious situation to develop hypertension through a drop in cardiac output drop, an increase of peripheral resistances, a progressive occlusion of renal resistance arteries leading to a disproportionate reduction of renal plasma flow, and also by a defective response of baroreceptors to the increment in BP.

On the other hand, the higher stiffness of big arteries justifies a higher SBP. In fact, the findings of altered pulse pressure (PP) can be considered as target organ damage (TOD). Subsequently, systolic pressure is higher with stiffer vascular walls. As elasticity decreases, pressure wave velocity (PWV) rises, facilitating the conjunction of both waves (incident and reflexed), reaching the sum in the systolic peak and leading to the presence of isolated systolic hypertension (ISH).

In this situation, hemodynamic studies have shown that cardiac output is not increased, but peripheral resistances are increased. When ISH is present, due to compliance reduction, even a diastolic pressure of 85 mmHg may reflect an increase in peripheral resistances. Thus, the main determinant for the elevation of the systolic blood pressure is the loss of the elastic characteristics of large arteries [10].

The degree of wave reflection and the pulse wave morphology are directly dependent on aging and arterial stiffness. The development of increasing arterial stiffness and increasing wave reflection with aging and hypertension completely abolishes the central and peripheral pulse pressure by age 50 to 60 years.

The left ventricle is impacted by arterial stiffness by generating a higher early systolic pressure from the ejection of the stroke into a stiff aorta and by creating an increase of central systolic pressure and ventricular overload caused by the return to the aortic root of the reflected pulse waves.

In elderly patients with isolated systolic hypertension, aortic systolic pressure can be increased by as much as 30 to 40 mmHg as a result of the early return of wave reflection. Left ventricular workload is thus ultimately dependent on systemic vascular resistance; early systolic impedance increases to the forward-traveling wave caused by proximal aortic stiffening and late systolic impedance increases caused by early return of the reflected pressure wave [11].

Hence, cardiovascular risk is more closely related to peak systolic blood pressure in the central ascending aorta, which is the principal determinant of left ventricular cardiac output, than to simultaneously recorded systolic blood pressure readings in peripheral arteries.

Therapeutical Options

Evidence about the benefits of antihypertensive treatment in the elderly is unanimously agreed upon, achieving the reduction of cardiovascular morbidity and mortality in cases of both systo-diastolic hypertension and isolated systolic hypertension.

A meta-analysis conducted by Staessen et al. [12] demonstrates significant reductions in stroke incidence, coronary heart disease, cardiovascular mortality, and global mortality in patients receiving medical treatment compared to a placebo. These benefits are present beyond 80 years of age [13], showing that treatment prevents stroke in 34%, heart failure in 39%, and 2% in all cardiovascular events but not global mortality.

Global cardiovascular risk determination is the optimal approach in order to decide who may benefit from a pharmacological intervention to reduce blood pressure level. The ESH/ESC guidelines suggest a classification of global cardiovascular risk based on the blood pressure categories, including normal and high-normal BP. The terms "low-moderate-high-very high added risk" indicate an absolute 10-year risk of cardiovascular disease of <15%, 15–20%, 20–30%, and >30%, respectively (Framingham criteria), or a 10-year risk of fatal cardiovascular disease of <4%, 4–5%, 5–8%, and >8% (SCORE criteria) (Table 11.3).

The most frequent cardiovascular risk factors, criteria to consider target organ damage, and proper qualifying of diabetes and associated clinical conditions are expressed in Table 11.4.

In any case, intensity of the assessment to be completed in elderly patients, as in younger adults, must be just necessary to meet enough elements for defining cardiovascular risk and choosing the most appropriate therapeutical decision. The establishment of hypertensive therapy must follow the same therapeutic recommendations as in younger adults or in general hypertensive patients. Many patients also have other risk factors, target organ damage, and associated clinical conditions. Thus, stratification of risk to quantify prognosis and election of the first antihypertensive drug has to fit with these conditions. In addition, many elderly people will need two or more drugs to control blood pressure due to their difficulty to decrease SBP below 140 mmHg.

Table 11.3 Stratification of Risk to Quantify Prognosis

Other Risk Factors and Disease History	Normal SBP 120–129 or DBP 80–84	High Normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Associated clinical conditions	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

TOD = target organ damage.
SBP = systolic blood pressure.
DBP = diastolic blood pressure.
Source: ESH/ESC Hypertension Guidelines Committee. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J. Hypertens.* 2003; 21:1779–1786.

On the other hand, other factors are able to make problems for treatment and must be taken into account. These are related to physiological changes associated with aging or other frequent situations in the elderly (Table 11.5).

The capability of lifestyle modifications to reduce blood pressure levels in the elderly has been demonstrated [14]. As an example, the Trial of Nonpharmacologic Interventions in the Elderly (TONE) analyzed 975 patients aged 60–80 with BP levels controlled in monotherapy [15]. Patients were randomly distributed into four groups and received different nonpharmacological therapy: lower-sodium diet, weight loss program, combination of both, or usual medical care. After 3 months, antihypertensive treatment was suspended. During the next 30 months, the percentage of patients remaining normotensive without drug therapy was 43.6% in the diet and weight loss combination group, 35% in those assigned to just one intervention, and 16% in those receiving usual care. These effects were achieved with very slight modifications in the sodium quantity of the diet (mean 40 mmol/day) or weight reduction (mean 4.7 kg).

In most cases, a moderate limitation of sodium intake to 100–120 mmol/day is recommended, and its antihypertensive importance increases progressively with age. Nevertheless, the elderly have two obstacles to overcome in order to obtain that reduction: a minor gustative sensitivity, usually accompanied by elevated salt intake; and a higher dependence on precooked food, which is usually rich in sodium. On the other hand, a structured hypocaloric diet together with physical activity is suggested in overweight or obese patients. In order to prevent an increase in body weight, moderate physical activity

Table 11.4 Considering Factors to Stratify Cardiovascular Risk

Risk Factors for Cardiovascular DiseaseUsed for Stratification	Target Organ Damage (TOD)	Diabetes Mellitus	Associated Clinical Conditions
Levels of systolic and diastolic BP • Men > 55 years • Women > 65 years • Smoking • Dyslipidemia(total cholesterol > 6.5 mmol/L, > 250 mg/dL_or LDL cholesterol > 4.0 mmol/L, > 155 mg/dL,or HDL cholesterol M > 1.0,W > 1.2 mmol/L,M > 40, W > 48 mg/dL) • Family history of premature cardiovascular disease(at age < 55 years M, < 65 years W) • Abdominal obesity(abdominal circumference M > 102 cm, W > 88 cm) • C-reactive protein > 1 mg/dL	• Left ventricular hypertrophy (electrocardiogram: Sokolow–Lyons > 38 mm; Cornell > 2440 mm/msec; echocardiogram: LVMI M > 125, W > 110 g/m^2) • Ultrasound evidence of arterial wall thickening(carotid IMT > 0.9 mm) or atherosclerotic plaque • Slight increase in serum creatinine (M 115–133, W 107–124 μmol/L;M 1.3–1.5, W 1.2–1.4 mg/dL) • Microalbuminuria (30–300 mg/24 hr; albumin-creatinine ratio M > 22, W > 31 mg/g; M > 2.5,W > 3.5 mg/mmol)	• Fasting plasma glucose> 7.0 mmol/L (> 126 mg/dL) • Postprandial plasma glucose > 11.0 mmol/L (> 198 mg/dL)	• Cerebrovascular disease: ischemic stroke; cerebral hemorrhage; transient ischemic attack • Heart disease: myocardial infarction; angina; coronary revascularization; congestive heart failure • Renal disease: diabetic nephropathy; renal impairment (serum creatinine M > 133, W > 124 μmol/L; M > 1.5, W > 1.4 mg/dL) proteinuria (> 300 mg/24 hr) • Peripheral vascular disease • Advanced retinopathy: hemorrhages or exudates, papilloedema

M = men.
W = women.
LDL = low-density lipoprotein.
HDL = high-density lipoprotein.
LVMI = left ventricular mass index.
IMT = intima–media thickness.
Source: ESH/ESC Hypertension Guidelines Committee. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J. Hypertens*. 2003; 21:1779–1786.

for 60–80 min or 35 min of stronger activity at least 3 to 4 times weekly is adequate.

At this time, a large therapeutic arsenal is available for the pharmacological treatment of hypertension.

Some considerations, based on current evidence must be highlighted: ISH must be a priority target to pursue on diagnosis and treatment in elderly

Table 11.5 Factors Related to Antihypertensive Treatment in the Elderly

Factors	Complications
Decreased activity baroreceptors	Orthostatic hypotension
Cerebral self-regulation alteration	Cerebral ischemia under modest systemic BP decrease
Minor intravascular volume	Orthostatic hypotension Hypovolemia Hyponatremia
Sensivity to hypokalemia	Arrhythmia Muscular weakness
Minor renal and hepatic function	Drug accumulation
Polypharmacy	Drug interactions
Central nervous system alteration	Depression Confusion

people. The recommended target to achieve is a BP level lower than 140/90 mmHg. In patients with diabetes and/or chronic kidney disease, the BP goal must be lower than 130/80. There is no upper age limit to stop hypertension treatment, albeit data in people above 80 years are scarce [13]; the HYVET study will clarify this issue [16].

The pharmacological approach is not different in elderly as compared to younger adults, but it is necessary to notice possible adverse events secondary to gathering of several risk factors, co-morbidities, polypharmacy, and target organ damage [1,5]. In every case and in elderly hypertensives, in particular, caution with initial doses, slow uptitration, and close examination of tolerability and side effects must guide the therapeutical attitude.

Monotherapy Versus Drug Combination

Specific therapeutical options are related to clinical complexity due to morbidity and physical disability, common occurrences in these patients. Several factors contribute to make the election of the optimal pharmacological treatment in the elderly difficult. First, few studies including patients older then 80 years old are published due to the existence of chronic pathologies, ethical use of placebo, poor therapeutic accomplishment, and co-morbidity. Another trouble is created by the need to add supplementary morbidity and mortality parameters such as disability, quality of life, or cognitive status to the traditional ones used in the pharmacological studies. Although controlled study results suggest that medical treatment may reduce ISH-related morbidity and mortality in the elderly, most of the studies did not include patients who were older than 80 years or institutionalized.

The only study including hypertensive patients older than 80 years is HYVET [16], with about 2100 elderly randomly assigned to indapamide +/– perindopril or placebo +/- placebo in order to evaluate the benefits of treating hypertension in this group and the viability of developing these studies among aged persons.

The current tendency in pharmacological management of elderly hypertensives consists of avoiding sudden changes in BP because of associated clinical conditions that could interfere with tolerability such as renal insufficiency, chronic obstructive lung disease, reduction of baroreceptors activity and intravascular volume, orthostatic hypotension, urinary incontinence, cognitive impairment, or depression. All these causes represent the origin for the drug

combination therapy with lower doses as first-line therapy in elderly hypertensive patients.

This strategy may generate an increase in the drug response rate with lesser adverse effects and reduce the necessary time to achieve the target BP levels. In addition, advantages of this perspective might be a decrease in the number of healthcare provider visits and better therapeutic accomplishment, which are essential conditions in efficacy of and adherence to treatment in the elderly.

The combination of a diuretic and an ACE-i/AIIRB seems to be especially attractive since the compensatory activation of the renin-angiotensin system in response to the diuretic augmentation could be inhibited by the ACE-i/AIIRB, counteracting negative consequences of an increase in the renin. In addition, potassium retention caused by ACE-i/AIIRB can limit the diuretic-induced potassium leak. The same benefits could be obtained with a calcium channel blocker (CCB) and an ACE-i/ARB combo [17].

Long-term results of the perindopril-indapamide combination have been analyzed by Chalmers et al. [18], including patients aged 65–85. After 4 weeks, 67% had normalized BP under combination therapy. Ninety-five percent of treated patients achieved normal BP in one or more visits, and 79% did by the one-year follow-up.

Several studies, such as SHEP [19] or SYST-EUR [20], have shown that ISH reduction in the elderly reduces cardiovascular events. At the same time, data from those studies highlight the failure of monotherapy in controlling ISH. In fact, just 30% achieved normalization with monotherapy, whereas 80% of those on combination therapy did. The frequency of adverse events with combination therapy was comparable with a placebo and the same as each drug on monotherapy.

Another study compared this combination with 50 mg of atenolol. Data indicate that in patients older than 65, combination therapy induces a significantly greater BP reduction in a 12-month period if compared to atenolol, and patients tolerated this dose of atenolol well.

Low doses of bisoprolol, 6.25 mg, and hydrochlorothyazide, 6.25 mg, have been designated as an adequate combination to treat this population. It demonstrated a comparable efficacy and tolerability with 5 mg of amlodipine, with fewer dose-dependent secondary effects.

In summary, because of the intrinsic complexity in the elderly population, every antihypertensive approach must consider the sum of conditioning factors to preserve treatment efficiency and security. Results of controlled studies based on low- and very low-dose drug combination therapies have demonstrated the efficacy of this strategy, and it can be concluded that this is a valid first-line therapy in the treatment of the elderly hypertensive.

References

1. National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206–1252.
2. Ezzati, M., Lopez, A.D., Rogers, A., van der Hoorn, S., Murray, C.J. Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet* 2003; 360:1347–1360.

3. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Prospect. Studies Collabor. Lancet* 2002; 360:1903–1913.
4. Banegas, J.R., Segura, J., Ruilope, L.M., Luque, M., García-Robles, R., et al. Blood pressure control and physician management of hypertension in hospital hypertension units in Spain. *Hypertension* 2004; 43:1338–1344.
5. ESH/ESC Hypertension Guidelines Committee. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J. Hypertens*. 2003; 21:1779–1786.
6. Plante, G.E. Impact of aging on the body's vascular system. *Metabolism* 2003; 52:31–35.
7. Messerly, F.H., Ventura, H.O., Glade, L.B., Sundgaard, K., Dunn, F.G., Frohlich, E.D. Essential hypertension in the elderly: Hemodynamics, intravascular volume, plasma renin activity and circulating catecholamine levels. *Lancet* 1983; 2: 983–986.
8. Amery, A., Wasir, H., Bulpitt, C. et al. Aging and the cardiovascular system. *Acta Cardiol*. 1978; 33:443–448.
9. Macías-Núñez, J.F., Garcia Iglesias, C., Baudia, A., Rodriguez Gomes, J.L., Corbacho, J.L., Tabernero, J.M., De Castro, S. Renal handling of sodium in old people. *Age and Ageing* 1978; 7:178–189.
10. Nichols, W.W., O'Rourke, M.F. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Principles,* 3rd ed. London: Edward Arnold. 1990.
11. Nichols, W.W., Edwards, D.G. Arterial elastance and wave reflection augmentation of systolic blood pressure: Deleterious effects and implications for therapy. *J. Cardiovasc. Pharmacol. Ther*. 2001; 6:5–21.
12. Staessen, J., Gasowsky, J., Wang Ji, G., Thijs, L., Den Hond, E., Boissel, J.P., et al. Risks of untreated and treated isolated systolic hypertension in the elderly: Meta-analysis of outcome trials. *Lancet* 2000; 355:865–872.
13. Gueyffer, F., Bulpitt, C., Boissel, J.P., Schron, E., Ekbom, T., Fagard, R., et al. Antyhypertensive drugs in very old people: A subgroup meta-analysis of randomised controlled trials. *Lancet* 1999; 353:793–796.
14. Kaplan, N. *Clinical Hypertension*, 8th ed. Philadelphia: Williams and Wilkins Lippincott. 2002.
15. Whelton, P.K., Appel, L.J., Espeland, M.A., et al. Sodium reduction and weight loss in the treatment of hypertension in older persons. *JAMA* 1998; 279:839–846.
16. Elliot, W.J. Management of hypertension in the very elderly patient. *Hypertension* 2004; 44:800–804.
17. Dahlof, B., Sever, P.S., Poulter, N.R., et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 2005; 366:895–906.
18. Chalmers, J., Castaigne, A., Morgan, T., Chastang, C. Long-term efficacy of a new, fixed, very-low-dose angiotensin-converting enzyme-inhibitor/diuretic combination as first-line therapy in elderly hypertensive patients. *J. Hypertens*. 2000; 18:327–337.
19. SHEP Co-operative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results on the systolic hypertension in the elderly program (SHEP). *JAMA* 1991; 265: 3255–3264.
20. Staessen, J., Fagrad, R., Thijs, L., et al. Morbidity and mortality in the placebo controlled European Trial on Isolated Systolic Hypertension in the Elderly (SYST-EUR). *Lancet* 1997; 360:757–764.

12

The Renin-Angiotensin System and the Aging Process

Léon Ferder and Manuel Martinez-Maldonado

Introduction

The natural process of aging is associated with changes common to all species, which signify a progressive modification and, ultimately, a decreased functional capacity of organ function with respect to young adults. In general, a correlation exists between the structural and functional alterations associated with aging. In mammals, degenerative processes such as arteriosclerosis, the development of senile plaques in the brain, and the replacement of functional parenchyma by fibroconnective tissue in a variety of organs are seen more frequently in aged individuals [1, 2] (see Chapters 4 and 6).

The renin-angiotensin system (RAS) through the effect of angiotensin II (AngII) on its specific receptors exerts a wide variety of physiological actions, including arterial blood pressure regulation, sodium and water homeostasis, stimulation of other endocrine systems, and sympathetic activity modulation. Many of these actions are endocrine effects modulated by AngII. Nevertheless, this peptide is known to act as a paracrine, autocrine, and intracrine factor, whose mechanisms of action range from influences on cell growth, alterations of intracellular signaling pathways, apoptosis, extracellular matrix deposition regulation, and excitation or depression of organs. We present evidence in this chapter that the RAS plays a major role in the process of aging in rodents and speculate about its potential role in human aging.

Mitochondria and Aging

Deposition of lipofuscine pigment and a reduction in the number of cellular organelles, such as mitochondria, are common in the aging process [3, 4]. Mitochondria are energy-producing organelles that also conduct other key cellular tasks. They are involved in the regulation of tissue oxygen gradients [5], the modulation of apoptosis [6], and nitric oxide signaling [7]. Nitric oxide signaling is diverse and involves its reaction with free radicals, metalloproteins, and specific protein amino acid residues. A well-characterized site of nitric oxide binding is the terminal complex of the mitochondrial respiratory chain, cytochrome *c* oxidase; however, the downstream signaling

effects of this interaction remain unclear. It has also been recognized that the intracellular formation of hydrogen peroxide by controlled mechanisms contributes to the so-called redox tone and regulates the activity and activation thresholds of redox-sensitive signaling pathways [7] (see Chapters 4 and 7). Hence, mitochondrial damage such as that seen in aging may be the cause rather than the result of tissue dysfunction as organisms grow older. For example, lifelong free radical production could play a role in reducing the number of mitochondria and altering their structure and function [8, 9].

Reactive oxygen species (ROS) produced by the action of AngII may be causally involved in the aging process [1, 8]. Mice chronically treated with enalapril, a non-sulfhydryl-containing angiotensin II-converting enzyme inhibitor (ACEi), exhibited reduced age-associated cardiovascular and renal damage in association with an increase in the number of mitochondria in myocardiocytes and hepatocytes and an increase in survival of treated mice [10]. It was also observed that both enalapril and captopril can tip the oxidant/antioxidant balance toward the latter and protect cells from oxidative damage [11, 12]. Likewise, in a model of aged mice, the effects of enalapril suggested the existence of a relationship among the improvement of antioxidant enzyme activity, increased mitochondrial number and myocardiocyte replicative capacity, reduced apoptosis, and improved myocardial fibrosis [13].

Aging and Blood Pressure

The cardiovascular changes observed during aging are similar to those resulting from high blood pressure (BP) with respect to biochemical, mechanical, and electrophysiological properties of the cardiovascular system [14, 15]. Increased BP is usually observed in aged humans and rats (see Chapter 11). In this sense, some reports have indicated that hypotensive agents like ACEi and angiotensin II receptor blockers (ATrB) can lower BP in *normotensive*, normoreninemic animals [16–18]. ACEi may be more effective than ATrB if the favorable effects on cardiovascular fibrosis detected in experimental studies [19] also occur in humans. The pharmacological actions of ACEi include blockade of bradykinin metabolism in addition to reduced AngII formation, but both medication classes are able to revert part of the aging process in rodents, suggesting that bradykinin is not a fundamental mediator of the effect.

Cognitive Behavior and Aging

Changes in cognitive behavior due to advanced age have also been studied in the rat, with older animals showing a decreased performance in memory acquisition and retention tests and a significantly lower level of locomotion activity. In general, both cognitive performance and noncognitive behavior are altered in senescent rats.

The presence of a separate RAS in the mammalian brain has been reported [20]. Binding sites for AngII have been identified in various brain regions including the cortex, hippocampus, and midbrain [21]. The function of AngII in the central nervous system is synaptic and involves the interaction of

the polypeptide with neurotransmitters such as acetylcholine, catecholamine, serotonin, and other peptides [22, 23]. Therefore, it is conceivable that the RAS may be involved in altered cognitive states of aging. In fact, the use of either an angiotensin-converting enzyme inhibitor (cilazapril) or an angiotensin II type 1 receptor antagonist (E4177) has shown that long-term inhibition of the renin-angiotensin system in aged normotensive Dahl rats [24] improves cognitive function, indicating that the functional alteration is not blood pressure-dependent. Memory function was tested with a passive avoidance task, and the improvement observed was associated with significant preservation of neuronal cells and capillary densities in the hippocampus, indicating that AngII inhibition maintains cognitive function in the aged rat through protection of vascular vessels and neuronal cells responsible for memory function and that the effect is most likely mediated through AT1 receptors.

Effects of Aging on Behavioral Function

Age-related changes in behavior have been studied in the rat. Older animals have decreased performance in memory acquisition and memory retention tests compared with younger rats. Locomotor activity is also significantly lower in aged animals and, as mentioned above, cognitive performance and noncognitive behavior are altered in senescent rats.

Age-related spatial memory deficits are correlated with degeneration of the septohippocampal cholinergic system [25–27]. Yamada et al. [28, 29] have examined whether changes in NO production in the brain may be involved in aging-associated brain dysfunction. The performance of aged rats (30 months old) in a radial-arm maze task was significantly impaired compared to that of adult rats (3 months old). The number of neurons containing NADPH-diaphorase (NADPH-d) reactivity in the cerebral cortex and striatum of aged rats was significantly less than that in the adult rats. The daily administration of NG-nitro-L-arginine methyl ester (L-NAME; 10-60 mg/kg, i.p.) to inhibit NO production resulted in a dose-dependent impairment of acquisition in the radial-arm maze task, while it failed to affect previously acquired performance, i.e., retention, in the adult rats. These findings demonstrate that reduced NO production in the brain in aged rats could be responsible for impaired memory processes, especially in the acquisition, but not in the retention, of spatial learning [28, 29].

We found that chronic RAS inhibition in Wistar rats from weaning until 10 months old with either enalapril or losartan improved behavioral parameters. Testing was performed in an eight-arm maze made of crystal clear acrylic. The acquisition of spatial working memory was attained in a significantly shorter period in treated than in untreated control animals. In addition, more treated animals than controls reached the established criterion for spatial working memory acquisition. During the 40-day analysis period, the mean number of errors and emotionality (measured by the number of defecation pellets; fewer pellets, fewer errors) were lower in both treated groups. Motor performance (measured by locomotion speed) was also improved by both treatments. These data suggest that emotionality, learning, memory, and motor performance in the adult rat are, at least partly, controlled by AngII [30]. Moreover, chronic enalapril (10 mg/kg/day) or losartan (30 mg/kg/day) treatment had important

effects on spatial working memory, locomotor activity, and emotionality in the senile rat when treatment was begun at 12 months of age. At 18 months of age, spatial working memory acquisition was reached by all the treated animals in a shorter period and the mean number of errors in 40 days was reduced. The number of animals that reached the established criterion for spatial working memory acquisition was larger in the treated groups. Emotionality was diminished by both treatments, while motor performance was increased by both treatments [31]. These data suggest that reduction in AngII formation by ACEi and blockade of AngII actions by ATrB reduce emotionality and improve learning, memory, and motor performance in the aged rat.

It would be appropriate to examine if, in elder patients receiving either drug, these functions are improved as compared to other antihypertensive drugs (such as calcium channel blockers) or whether changes in these functions existing before commencing therapy improve afterwards.

Effects of RAS on Aging of the Heart

The anatomical, physiological, and functional characteristics of the aging heart and vessels have been extensively discussed in Chapter 4. In short, aged rats exhibit an increase in left ventricular weight and myocardial fibrosis [32]. The abnormal structure and function of the aged arterial wall consist mainly of enhanced stiffness [33] related to smooth muscle cell hypertrophy and collagen accumulation [16]. Endothelial and smooth muscle dysfunction with aging have been described in conduit vessels such as the rat aorta [34] (see Chapter 7).

AngII leads to structural changes in the cardiovascular system, particularly the vasculature, mostly through hemodynamic effects, but also through its cell growth-promoting properties [35]. Both ACEi and ATrB can prevent vascular hypertrophy in a variety of experimental models [36] and protect against the structural changes in the vasculature. These protective actions seem to be independent of arterial pressure since they are exerted to a similar extent in normotensive and hypertensive animals, and structural protection correlates poorly if at all with blood pressure control.

Blockade of the RAS can prevent left ventricular hypertrophy (LVH) and myocardiosclerosis in animals as well as in humans [18, 32]. Experiments in Wistar rats indicate that chronic treatment (6 or 18 months) with the ACEi (enalapril) or the ATrB (losartan) can lead to reduction in heart weight and reversal of myocardiosclerosis [37, 38].

Moreover, 6 months of treatment with either enalapril or losartan prevented the BP increase observed in normal rats as they go from infancy to early adulthood, indicating the participation of the RAS in the regulation of BP in normal early aging conditions. The hypertension of aging is frequently attributed to the stiffening of blood vessels (diminished vascular compliance), but it seems conceivable that the evolution of blood pressure levels from low to higher values, including hypertension, is under the control of the RAS and that its role in this context may be greater than previously appreciated.

Both ACEi and ATrB induced reductions in cardiac DNA and collagen concentration as well as in the percentage of tissue fibrosis. These effects could be related to a protective action of these pharmacological agents on the myocardium by preventing or diminishing cell hypertrophy and collagen

accumulation, which are the main alterations seen in the aging heart [39]. A striking finding in these studies was that nitric oxide synthase (NOS) activity rose dramatically in the aorta with the chronic administration of both compounds. Moreover, urinary excretion of nitrate + nitrite, a marker of systemic NO production, was significantly higher in treated than in control rats. Since NO counteracts many of the effects of AngII on smooth muscle and endothelial cells, these results point to a protective cardiovascular effect of RAS blockade, not only due to AngII inhibition, but also due to enhanced NO production in the young adult normal rat [37].

Further experiments in 18-month-old (aged) normal rats revealed that both ACEi and ATrB treatment also abolished the increment in BP observed in untreated animals that had attained a similar age and delayed cardiac and left ventricular hypertrophy/hyperplasia and aortic growth.

Aging leads to decreased aortic compliance, which promotes left ventricular hypertrophy. Decreased aortic compliance in older control animals is suggested by their higher aortic mass and increased vessel wall width. AngII is a major promoter of myocyte hypertrophy and matrix deposition beyond its hypertensive effect; therefore, inhibition of the RAS may prevent left ventricular hypertrophy by preventing increased aortic stiffness. Moreover, NOS activity in the aortic endothelium diminishes with age, as previously reported in WKY rats [40], and endothelium-dependent relaxation of the rat aorta in response to acetylcholine is decreased by aging and/or hypertension as a result of impaired formation of NO [34]. In aged animals, both ACEi and ATrB preserved NOS activity in endothelial cells of elastic arteries, and both drugs increased aortic endothelium NOS activity in 6-month-old (normal young adult) treated animals [38].

To further analyze the protective cardiovascular effect of RAS inhibition, we have treated 12-month-old rats for 6 months with either enalapril or losartan. Results have demonstrated that both drugs reduced heart and aorta hypertrophy/hyperplasia, cardiac fibrosis, and α-smooth muscle actin and collagen III deposition. In general, long-term blockade of AngII seems to delay the development of age-related changes in the cardiovascular system in experimental studies in rodents [41]. This therapy may be beneficial by preventing AngII effects through oxidative stress, a mechanism proposed by others as a pathogenic mechanism in kidney diseases [42].

Effects of RAS on the Aging of the Kidney

The characteristics of the aging kidney have been discussed in Chapters 3 through 7. In short, the progressive development of glomerulosclerosis is widely known to occur in the aging kidney in both humans and rats and is considered a biological characteristic of aging. The number of functional glomeruli declines roughly proportionally to renal weight decrease. We have found that only 25% of glomeruli remained in the renal cortex of aged mice compared to young mice [43]. In humans, the number of sclerotic glomeruli rises with advancing age from less than 5% at the age of 40 to represent 10–30% of the total glomerular population by the eighth decade [44].

Enalapril, administered to mice in their drinking water for 24 months, significantly decreases both mesangial expansion and glomerulosclerosis and attenuates the loss of glomeruli normally associated with aging [43].

Furthermore, chronic ACEi treatment during the whole life span of the rat reduces proteinuria and albumin accumulation in podocytes, delays the progression of glomerulosclerosis, and prevents the accelerated hypertrophy of the glomerular mesangial domain [45].

Glomerulosclerosis also occurs in a variety of experimental models of renal injury. In the remnant kidney model, Hostetter et al. [46] have demonstrated that ACEi and ATrB can attenuate glomerulosclerosis and lower intraglomerular pressure by altering the resistance of the efferent arteriole. These investigators have proposed that glomerular hyperfiltration is an underlying factor in glomerulosclerosis development. In other models, reduction of intraglomerular pressure by ACEi seems to accounts for the attenuation of glomerular injury [47].

In addition to its protective actions on glomerular structure, chronic enalapril administration decreases both peritubular and medullar interstitial sclerosis in aging mice [48], a finding that may account for improved overall renal function resulting from ACEi and ATrB treatment in experimental animals.

As already mentioned, ACEi are also able to prevent renal damage in normotensive experimental models, indicating that their beneficial effects on aging are independent of their antihypertensive action. Furthermore, using doses that do not modify the systemic arterial pressure in experimental hypertensive animals with subtotal nephrectomy also retards the appearance of glomerulosclerosis [49].

AngII is a growth factor [50] and activates a number of intracellular signaling pathways associated with cell growth [51]; it also induces the proliferation of a variety of cells.

In mesangial cells, AngII induces proliferation, activation of DNA synthesis, and the expression of early growth-related genes [52] (see Chapter 6). Renal tubular cells have been shown to express the genes of several cytokines, chemokines, and other mediators of the inflammatory response, including the production of AngII from proteins synthesized from genes encoding the components of the RAS [53]. Locally produced AngII could participate in renal tissue damage by inducing or amplifying the inflammatory response in all glomerular diseases, but also in tubulointerstitial diseases, independently of their initiating etiology. Moreover, AngII stimulates production of monocyte chemoattractant protein-1 (MCP-1), which is involved importantly in the inflammatory process [54]. Data obtained in various studies support the idea that the RAS plays an important role in the development of tubulointerstitial fibrosis in various experimental models including ureteral obstruction [55–58], systemic or intrarenal AngII infusion, and SHR rats. In all these models, treatment with ACEi or with ATrB prevents the deposition of matrix, collagen, and the fibrogenic TGF-β1 [59, 60]. Moreover, blockade of the RAS in aged animals reduces urinary albumin excretion [61]; thus, therapy may exert its protective effect by interference with cytokine stimulation induced by proteinuria, as demonstrated in various other models [62, 63]. TGF-β1could also be involved in the pathogenesis of tissue lesions due to aging since enalapril and losartan reduce TGF-β1 immunostaining in treated as compared to untreated control rats [64].

Interstitial extracellular matrix accumulation and damage may contribute to reactive oxygen species (ROS) overproduction and vice versa, and the

inflammatory cell infiltrates present in this environment could be an additional source of ROS. Mitochondrial count reduction and age-related oxidation mechanisms in old animals are attenuated in the kidneys of enalapril- or losartan-treated old rats, indicating increased antioxidant defenses secondary to inhibition of the RAS and, in view of the effects of specific ATrB, mainly mediated through AT1 receptors [65].

A role of the RAS in producing both peritubular and medullary interstitial sclerosis in aging mice [48] can be inferred because Wistar rats treated since weaning with either enalapril (10 mg/kg/day) or losartan (30 mg/kg/day) for 18 months exhibit significant decreases in tubular atrophy and glomerular and interstitial fibrosis [41]. Even when treatment with either ACEi or ATrB was started later in life (from 12 to 18 months of age), Wistar rats exhibited improvements in the structure and function of the kidney. Figure 12.2 shows the results of the histological structural evaluation of periglomerular fibrosis, mesangial matrix, focal sclerosis, tubular dilatation, interstitial cortical fibrosis, interstitial medullar fibrosis, and α-smooth muscle-actin deposition. Both enalapril and losartan had beneficial effects; the former proved to be more effective than losartan in the preservation of renal structure, when compared to the control group [64]. Electron microscopy also revealed a significantly higher number and ultrastructural conservation of mitochondria; a better-preserved structure of proximal tubule microvilli was also observed in treated animals.

Spermatogenesis, Penile Tissue, Reproduction, and Angiotensin II

It is clear that the RAS is important for sexual function, spermatogenesis, and fertility. For example, angiotensin I-converting enzyme (ACE; CD143, kininase II, EC 3.4.15.1) is known to be crucial for male fertility in animal models. The expression of tubular (t) ACEmRNA varies with the type of cell and the site within the seminiferous tubules of adult men and increases markedly during cell differentiation. The enzyme seems to be strictly confined to the adluminal membrane site of elongating spermatids and localized at the neck and midpiece region of released and ejaculated spermatozoa. On the other hand, somatic (s) ACEmRNA is expressed heterogeneously in Leydig cells and endothelial cells of the testicular interstitium, and homogeneously along the luminal surface of epithelial cells lining the ductuli efferents, the corpus and cauda of the epididymis, and the vas deferens [66].

It remains to be seen whether aging affects distribution and expression of somatic and tubular ACEmRNA and what its consequences are. Moreover, it is not known whether changes in sperm structure, motility, and function occurring with age can be modified by manipulation of the activity of the RAS. A possible role of the RAS is suggested by experiments showing that AngII stimulates capacitating and fertilizing ability in mammalian spermatozoa when binding of AngII to its receptors results in stimulation of cAMP production in both uncapacitated and capacitated cells [66]. This study investigated possible mechanisms whereby AngII affects cAMP availability. Extracellular Ca^{2+} is required for responses to AngII by mouse spermatozoa, a response blocked by the pertussis toxin, suggesting the involvement of an

inhibitory G alpha subunit; dideoxyadenosine, a specific membrane-associated adenylyl cyclase (mAC) P-site inhibitor, also blocked responses, suggesting involvement of an mAC. Both reagents also abolished AngII stimulation of cAMP. In contrast, nifedipine, a Ca^{2+} channel blocker, did not inhibit AngII effects on spermatozoa. Finally, in capacitated suspensions, both pertussis toxin and dideoxyadenosine were again shown to block AngII stimulation of cAMP. These results suggest that spermatozoa responses to AngII involve an inhibitory G protein and an mAC, but it is likely that AII-receptor coupling does not stimulate directly mAC, but rather does so in an indirect manner, perhaps by altering the intracellular Ca^{2+} concentration [67].

Capacitation *in vitro* in mammalian spermatozoa can be regulated by a number of first messengers, including fertilization, promoting peptide, adenosine, calcitonin, and AngII, all of which are found in seminal plasma. The responses appear to involve several separate signal transduction pathways that have a common end point. These seminal plasma-derived first messengers can bind to specific receptors and directly or indirectly modulate the activity of membrane-associated adenylyl cyclase isoforms and production of the second messenger cAMP. Responses to all of these except AngII involve initial acceleration of cAMP production and capacitation followed by inhibition of both cAMP production and spontaneous acrosome loss, resulting in maintenance of fertilizing potential. Appropriate G proteins and various phosphodiesterase isoforms also appear to be involved. The transition from stimulatory to inhibitory responses involves loss of decapacitation factors (DF) from receptors (DF-R) on the external surface; a DF-R present on both mouse and human spermatozoa has recently been identified as phosphatidylethanolamine-binding protein 1. The presence or absence of DF appears to cause changes in the plasma membrane that then alter the functionality of various membrane-associated proteins, including receptors. Since spermatozoa contact these first messengers at ejaculation, it is plausible that their actions observed *in vitro* also occur *in vivo*, allowing these molecules to play a pivotal role in enhancing the chances of successful fertilization [68], mechanisms that may be lost with aging. In addition, the response to AngII and other messengers by these cells may be exaggerated in aging, therefore leading to loss of spermatogenesis and function of spermatozoa.

Of interest is the fact that AngII values in paired blood plasma and seminal plasma from infertile men with azoospermia, with asthenozoopermia, or with normal semen parameters revealed that the mean concentration of seminal plasma AngII was four times as high as that of blood plasma. Seminal plasma AngII of azoospermic patients was higher than that of other infertile men and controls, but no correlation existed between seminal plasma AngII values and other traditional parameters of sperm. This indicates that seminal plasma AngII may be secreted locally in the male reproductive tract. In addition to the testis and epididymis, the prostate and/or seminal vesicle may also be a source of AngII. The reason why the seminal plasma AngII of azoospermic patients is higher than that of others remains unknown. Further study is required to clarify the exact role of seminal plasma AngII in the mechanisms of male fertility regulation [69], but as suggested above, it may play a role in the loss of fertility in aging and brings up the possibility that ACEi or ATrB may have beneficial effects in sustaining fertility in the elderly.

Normal aging also produces erectile dysfunction; therefore, we have evaluated in adult rats the effect of chronic blockade of AngII on the structure of the corpus cavernosum. In 7-month-old animals, the degree of corpus cavernosum fibrosis was less in rats treated with enalapril than in controls (Inserra et al., presented at the VIth Brazilian Congress on Sexual Impotence, Rio de Janeiro, June 2001). Similar protection of the cavernous tissue, unrelated to blood pressure control, was seen using the ATrB candesartan in an SHR model [70].

Mechanisms by Which ACE Inhibitors and Angiotensin II Antagonists May Alter the Aging Process

Under physiological conditions, mitochondrial respiration is considered the most important source of ROS, which can oxidize mitochondrial DNA, proteins, and lipids [71]. The possibility that alterations in the mitochondrial genome are decisive in the aging process is supported by studies demonstrating that mitochondrial DNA is more prone to mutation than nuclear DNA [72]. That other mitochondrial changes are important in aging is also supported by the following experimental observations: [1] Aging is accompanied by a decrease in the number of tissue mitochondria [73]; [2] aging is associated with a decrease in mitochondrial DNA but not in total DNA [74]; [3] mitochondrial DNA isolated from the heart and brain shows an increase in the number of catenated dimers, probably due to errors in the replication of the mitochondrial genome, as a consequence of which mitochondria lose their replicative ability, causing the total number of mitochondria to decrease. The number and functionality of mitochondria may play a key role in cellular aging. Poor function and oxidative damage to mitochondria could account for some of the age-related changes in mitochondrial function.

In addition to their hemodynamic effects, ACEi may function as free radical scavengers. Captopril and other ACEi containing a sulfhydryl group have a nonspecific antioxidant action [75]. In *in vitro* experiments, we found that therapeutic doses of captopril have antioxidant properties. Although most studies have been unable to demonstrate a free radical scavenger action of enalapril, the beneficial effects it exerts on the heart of mice may be related to other antioxidant properties of this compound [11,13]. Conceivably, enalapril may stimulate mechanisms that offset the action of free radicals, such as the activity of superoxide dismutase. In support of this hypothesis, we found an increase of cytosolic and mitochondrial superoxide dismutase activities in the liver of mice treated with enalapril or captopril for 3 months [76].

We have also shown that 7 months of losartan treatment can increase superoxide dismutase activity and total glutathione content, which would also counteract the effect of free radicals in several rat tissues, including the kidneys. This enhancement of antioxidant defenses is associated with a decrease in lipid oxidation compared to untreated controls [12].

A protective role of enhanced antioxidant defenses has been reported under experimental conditions. Exogenously administered superoxide dismutase and catalase reduce the cellular lesions caused by myocardial ischemia reperfusion in dogs [77]. Moreover, the simultaneous overexpression of superoxide dismutase and catalase diminished oxidative stress and increased maximum

life span in *Drosophila melanogaster* [78, 79]. We would anticipate similar effects on oxidative stress and life span for the ACEi and ATrB if they increased the activity of antioxidant enzymes.

Chronic enalapril or losartan administration can prevent age-associated changes in the kidney that may be related to mitochondrial function. Kidney mitochondria of enalapril- or losartan-treated animals showed a decrease in superoxide generation and improved production of energy [65]. To further clarify the possible mechanisms involved in this response, we have analyzed the function of kidney mitochondria in control animals and those treated with enalapril or losartan. We studied whether chronic enalapril or losartan treatment could prevent the decline of the respiratory control ratio and/or the increase of hydrogen peroxide production that occurs in mitochondria upon aging. Male Wistar rats (14 months old) were divided into three groups that received enalapril, losartan, or water for 8 months. Mitochondrial O_2 consumption, H_2O_2 production, antioxidant enzymes activities, and GSH were determined. After 8 months on the respective treatment, body and kidney weights were similar among the groups. The mitochondrial respiratory control ratio (state3:state4) was higher on either ACEi or ATrB than in controls. H_2O_2 production (nmol/min/mg protein) was lower in both treated groups than in controls. On the other hand, kidney total glutathione content (nmol GSH equiv/g wet tissue) was higher in ATrB than in controls, but kidney GSH/GSSG was higher in both treated groups. These results indicate that inhibition of the RAS can lead to regulation of kidney mitochondrial respiration and amelioration of certain functional changes that occur with age [65].

Angiotensin II can induce oxidant stress by stimulating the generation of both NO [80] and NAD(P)H oxidase-derived superoxide [81], thereby enhancing peroxynitrite formation, an oxidant known to inactivate Mn-SOD [82]. We have assessed the impact of hypertension on kidney mitochondrial function and the effects of angiotensin II receptor blockade on potential mitochondrial changes in the spontaneously hypertensive rat (SHR) [83]. Control animals were treated with a calcium channel blocker, an antihypertensive agent with a mechanism of action distinct from ATrB. It became clear that in SHR hypertension occurs concurrently with a decline of kidney mitochondrial function. ATrB and calcium channel blocker treatments were equally effective in reducing blood pressure, but only losartan prevented mitochondrial dysfunction and attenuated structural and functional changes in the kidney. Clearly, at least part of the mitochondrial protection afforded by losartan was unrelated to blood pressure, which was not responsible for the adverse tissue or organelle effects. In agreement with these results, previous studies from our laboratory showed that in normotensive aging mice, inhibition of the RAS protects cardiac and hepatic mitochondria in the absence of blood pressure changes. Moreover, the number of mitochondria in myocardiocytes was higher in the treated groups compared to control animals, and morphometric studies showed lower myocardial sclerosis in animals receiving ACEi; the number of mitochondria per myocardiocyte or hepatocyte was higher in the groups receiving enalapril as compared to aged controls [10, 18]. It is of interest in this context that in rats with experimental diabetes, AngII receptor blockade prevents mitochondrial decay without significant reduction of blood pressure (unpublished data).

Markers of oxidant stress in the kidney are increased in SHR, as indicated by a higher oxidation of the glutathione pool, when compared to WKY [84]. Losartan, but not the calcium channel blocker amlodipine, reduced oxidant stress, as revealed by [1] the maintenance of the glutathione pool in a relatively more reduced state, [2] the preservation of Mn-SOD activity, and [3] the attenuation of uncoupling protein-2 (UCP-2) content reduction in losartan-treated SHR, relative to untreated SHR.

We evaluated mitochondrial function by using a nonclassical group of indicators, such as UCP-2 content, Mn-SOD, NOS mitochondrial activities, and (membrane potential. The concentration of UCP-2 may play a role in the attenuation of excessive mitochondrial superoxide production (and therefore in protection against disease and oxidative damage at the expense of a small loss of energy) and in the modulation of cellular signaling (perhaps as part of a signaling pathway to regulate insulin secretion in pancreatic β cells, for example) [85]. Mn-SOD converts mitochondrial superoxide into hydrogen peroxide (a proposed mitochondrial-derived cellular messenger), thus diverting superoxide from reacting with NO and inhibiting the formation of mitochondrial peroxinitrite, thus inactivation of Mn-SOD [82]. To function as an intracellular signaling molecule, H_2O_2 must be imported into the cytosol. Cytosolic H_2O_2 enhances protein tyrosine phosphorylation by inactivating protein tyrosine phosphatases while activating protein tyrosine kinases. Transient protection of the H_2O_2 signal from abundant cytosolic peroxiredoxin appears to result from the reversible inactivation of these enzymes through either hyperoxidation or phosphorylation [86]. Interference with the protection afforded by hyperoxidation or phosphorylation will enhance the noxious effects of peroxide. Mitochondrial NOS activity is also important because NO is a physiological regulator that acts directly on the mitochondrial respiratory chain and modulates mitochondrial redox signaling [87].

UCP-2 is purported to act as an oxidant stress-compensating mechanism, and a protective role for this protein in cellular pathophysiological processes that involve ROS has been suggested [88]. An altered expression of UCP-2 may be related to the pathophysiology of hypertension in stroke-prone SHR (SHR-SP) [89]. In addition**,** several agents that upregulate NOS also increase UCP-2 expression, possibly to prevent excessive $O_2^{\cdot}$ production [7]. Consequently, the observed modulation of NOS activity and UCP-2 protein level in mitochondria as a result of the ATrB losartan suggests that the blocker's protective action may rely on a mechanism that involves both NO and UCP-2.

Treatment with losartan, but not with the antihypertensive calcium channel blocker amlodipine, prevented the decrease in NOS activity observed in mitochondria obtained from SHR rats. Whenever mitochondrial derangement prompts electron transport inhibition, electrons are forwarded into an increased generation of ROS [90]. This is in agreement with the observed increase of H_2O_2 production in mitochondria from SHR. Increased mitochondrial ROS generation was suggested to underlie tissue injury associated with hyperglycemia [91]; clearly, it may also participate in the deterioration of kidney structure and function in SHR [85]. It has also been suggested that increased ROS content may adversely impact mitochondrial membrane fluidity and composition, which may in turn affect the capacity of the mitochondria to generate sufficient membrane potential to adequately

respond to cell energy demands and impair mitochondria-derived redox signaling, potentially modifying cellular regulatory pathways [92]. In losartan-treated animals, excessive mitochondrial hydrogen peroxide production was abolished or curtailed, an effect that may have contributed to the maintenance of mitochondrial membrane potential within the values displayed by nonhypertensive rats.

In addition to enhancing ROS production and reducing the mitochondrial membrane potential, AngII enhances superoxide production through the activation of NAD(P)H oxidase [93] and by eNOS uncoupling [94]. These effects were reversed by ATrB but not by non-RAS interfering agents, such as calcium channel blockers. It is significant that AngII is associated with downregulation of PPAR-alpha [95], a transcription factor that stimulates the expression of nuclear genes involved in mitochondrial fatty acid oxidation. It also modulates the UCP-2 [96] and Mn-SOD [97] gene expression. Consequently, by upregulating PPAR-alpha, losartan, but not amlodipine, may have enhanced not only UCP-2 and Mn-SOD contents, but also the generation of electron donors for the respiratory chain and ATP production.

Finally, lesion scores in the renal tubulointerstitium are inversely related to Mn-SOD activity and UCP-2 content, suggesting that in addition to cytoplasmic oxidant stress resulting from membrane-bound oxidase activation, the mitochondrial dysfunction that accompanies hypertension may mediate renal architectural damage. Consequently, the renal-protective effects of ATrB in essential hypertension may be related to the improvement of mitochondrial function, and this may be an additional or alternative way to explain some of the beneficial effects on organ structures of this type of drug reported in clinical studies.

More specific approaches are needed to address if mitochondrial dysfunction is the individual result of high AngII or hypertension, and if it is a major cause of renal damage. A causal relationship has found between a mitochondrial mutation and hypertension, suggesting that mitochondrial dysfunction can precede the emergence of hypertension [98].

Angiotensin II, Diabetes, and Aging Processes

The kidneys are main targets of mitochondrial impairment at the onset of and throughout streptozotocin (STZ)-induced diabetes mellitus. Insulin treatment is unable to restore normal organelle function, suggesting that early diabetic damage results from factors other than the state of hyperglycemia [99]. A marked increase in mitochondrial oxidative stress, indicated by an elevation in oxygen species production, is accompanied by changes in mitochondrial lipid oxidation and reduction in antioxidant defense levels in the pancreas, kidney, brain, and liver from rats rendered diabetic by STZ injection. As mentioned, AngII receptor blockade prevents mitochondrial decay without significant reduction of blood pressure in rats with experimental diabetes [100].

A possible link between these experimental findings and human diabetes mellitus is the fact that, in the latter, chronic inhibition of the renin-angiotensin system (RAS) can delay the onset and progression of diabetic nephropathy by reducing blood pressure and by other mechanisms that could include improvement in the mitochondrial changes mentioned above [101–104]. RAS inhibition can also prevent the development of type II diabetes. In view of

the effect of AngII on mitochondrial function and the formation of oxygen radicals and peroxinitrite, these effects may participate in the development and maintenance of diabetes mellitus [105–107].

We have shown in rodents that inhibition of the RAS attenuates both the diabetes-associated modification of oxidant damage indicators and structural changes, including mitochondria, in the kidney of rats with streptozotocin-induced diabetes mellitus [65,108]. Moreover, the expression of genes related to fatty acid beta-oxidation, mitochondrial proton-electron coupling, and oxidative phosphorylation was upregulated in myocardiocytes of captopril-treated diabetic animals, suggesting that RAS inhibition with ACEi may also protect the myocardium by enhancing energy supply [109–111].

Pharmacological interruption of the renin-angiotensin system by ACEi or ATrB is increasingly being advocated as a standard therapeutic intervention for patients with chronic nephropathies, regardless of whether systemic hypertension is an associated feature [112]. Prospective, randomized, placebo-controlled trials found that, at comparable BP control, ACEi are more effective than non-ACEi therapy in limiting progression to ESRD in patients with type 1 diabetic nephropathy [102] or with nondiabetic, proteinuric chronic nephropathies [113–115] . Two recent trials found that the ATrBs losartan [104] and irbesartan [103] led to an improvement in renal outcomes in patients with type 2 diabetes and overt nephropathy, unrelated to blood pressure control. Similar data were found in the Losartan Intervention For Endpoint reduction (LIFE) study, which had 9193 hypertensive patients with left ventricular hypertrophy (LVH), including 1195 diabetics. The mean age of patients was 67 years [106].

We examined whether chronic AT1 receptor blockade could protect kidney mitochondrial function from the effects of diabetes, in the streptozotocin model of type I diabetes (unpublished data). We found that the kidneys of hyperglycemic STZ-diabetic rats improved with losartan, but not amlodipine (a calcium channel blocker) without effect on AngII receptors. ATrB [1] prevented structural and functional organ decay, [2] prevented increased mitochondrial oxidant generation, [3] improved mitochondrial function, and [4] attenuated oxidant stress. Although Ca^{2+} channel blocker therapy reduced blood pressure to the same extent as ATrB, only the latter prevented mitochondrial function impairment and blunted structural and functional kidney changes in diabetic rats, suggesting that, as in humans, the renal and mitochondrial protective action displayed by losartan treatment occurred independently of blood pressure changes.

Aging Response to AII Blockade

It has long been recognized that plasma renin and aldosterone levels fall with advancing age. Studies in both aging animals and humans indicate that both renal renin formation and release are reduced and contribute to the fall in plasma renin concentration. Curiously, increasing age is associated with the development of hypertension, which in turn could be a factor in the reduced activity of the RAS. Surprisingly, elderly patients respond with a fall in blood pressure to the administration of both ATrB and ACE, suggesting that despite reductions in the circulating levels of renin and angiotensin, the RAS system

may be a participant in the mechanism that increases and sustains blood pressure in aging subjects.

We have described [10] that CF1 mice treated with the angiotensin I-converting enzyme inhibitor enalapril and Wistar rats treated with an ATrB exhibited a reduction of pathological age-associated cardiovascular and renal changes as well as an increase in the mitochondrial number within cells, associated with an increase in the survival and life span of the animals. The beneficial effect of RAS blockade occurs despite the fact that plasma renin concentration and intrarenal renin mRNA are reduced in older animals [43]. Nevertheless, the results are consistent with the finding that an increase in angiotensin II formation or action within the kidney exists in these animals [43] and supports the concepts that the intrarenal RAS contributes to hypertension and renal damage in aging subjects and that it is regulated independently of the circulating system in this group as well as in other subjects.

Moreover, plasma levels of AngI and AngII were low in control (untreated) aged animals, but, as expected in non-aged normal animals, aged rats receiving ATrB exhibited elevated levels of plasma renin, AngI, and AngII, an indication that the angiotensin-renin feedback mechanism is intact in aged rats. Aging was accompanied by high glomerular angiotensin II receptor density, as demonstrated by autoradiography [116].

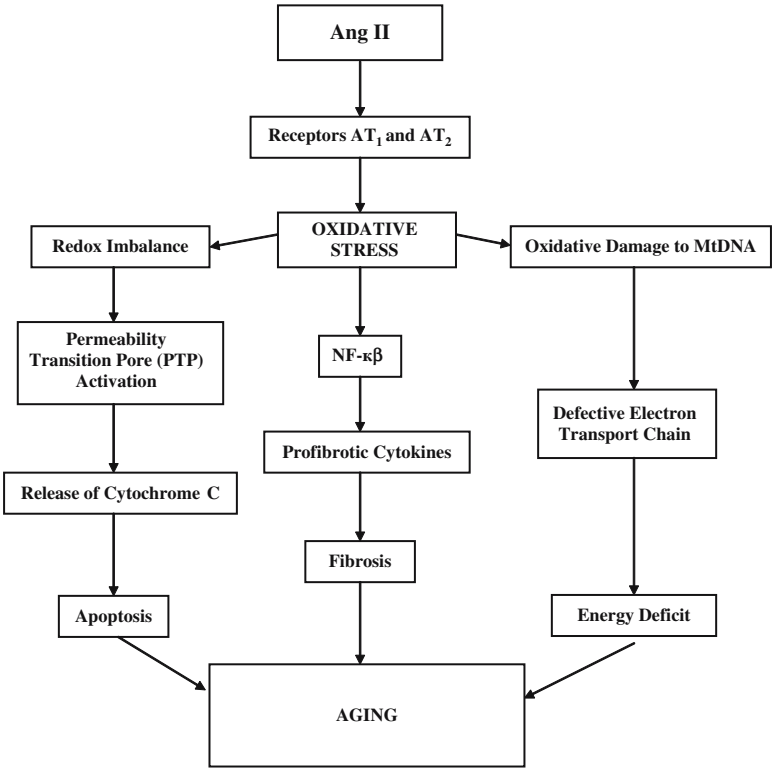

Fig. 12.1 Ang II increases oxidative stress. Oxidative stress [1] produces induction of genes related with cytokines and growth factors, inflammatory process, and fibrosis, [2] changes the permeability of the mitochondria and cytochrome C stimulating apoptosis, [3] produces oxidative stress damage mtDNA and produce energy deficit.

These results strongly suggest that the RAS plays an important role in the mechanisms by which aging affects renal function and that abnormal regulation of AngII receptors may be responsible for functional alterations in the kidney. Moreover, AngII-induced increases in the production of reactive oxygen species and damage of mitochondria and their function can be responsible for these alterations. This hypothesis is supported by the findings that ACEi and ATrB decrease tissue oxidative state and improve mitochondrial number and function, leading to higher animal survival and prolonged life span (see Figure 12.1).

Conclusions

Chronic long-term inhibition of the RAS induces a significant protective effect on the changes accompanying the physiological aging process, hypertension, and diabetes mellitus, and on the cardiovascular system, the kidney, and the brain. Increased activity of NOS in the aortic endothelium and in cardiac and kidney mitochondria and preliminary results in the brain suggest that blocking the formation or actions of AngII reduces oxidative stress in mitochondria and thus protects the integrity of tissues and organ function. AngII induces excessive release of vascular superoxide radicals generated by stimulation of NADH/NADPH oxidase that inactivates NO and forms peroxinitrite. The sustained decreased oxidative burden may account for the protective effect of agents such as ATrB and ACEi. Inhibition of AngII formation would attenuate oxidative stress and improve vasodilatation by permitting unhindered production of NO. The lower rate of oxidative stress also reduces the inflammatory processes and cytokine and growth factor production. Blockade of this pathway will diminish fibrosis and preserve function and structure in target organs, such as the corpus cavernosum (see Figure 12.2). AngII blockade also leads to protection of mitochondrial DNA

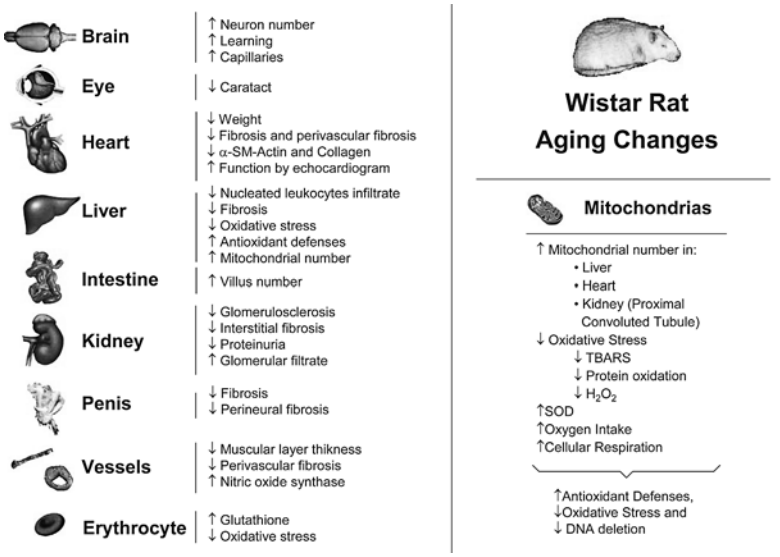

Fig. 12.2 Effects of renin-angiotensin system blockade in different organs and tissues

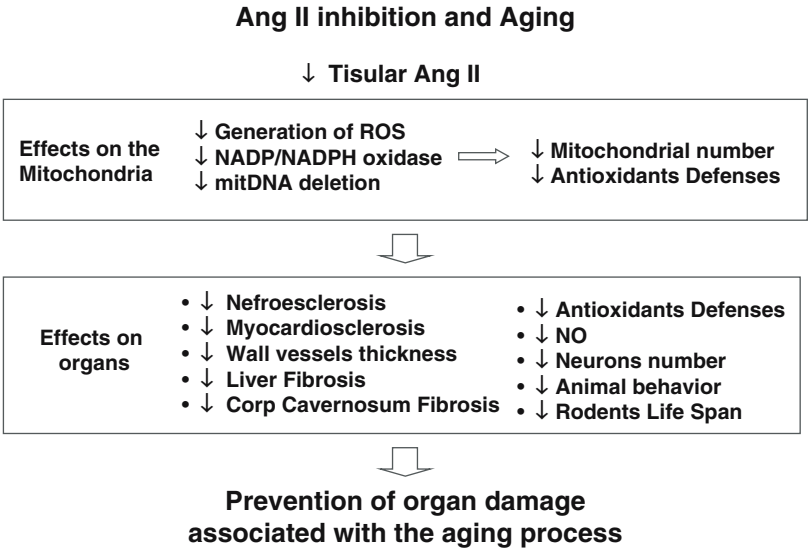

Fig. 12.3 Effects of Ang II inhibition on aging. Reducing levels of Ang II (ACE inhibitors) or blocking the effects of Ang II (angiotensin-receptor antagonists) leads to effects on mitochondria and organs that could explain the apparent activity of these classes of drugs to retard the aging process in rodents*(ROS = reactive oxygen species)*.

from deletion and mitochondrial membrane damage, thus preventing decreases in mitochondrial numbers, and might be a useful tool to delay the normal aging processes (see Figure 12.3). Although extrapolation of experimental results to the clinical setting may be fraught with pitfalls, a variety of data support that ATrB and ACE inhibitors exert beneficial effects in hypertension and diabetes in humans. Presently, no data exist to suggest that ACE inhibitors or angiotensin-receptor antagonists can retard the aging process in humans, whether healthy or not. A clear-cut effect on some of the processes of human aging awaits a properly designed study.

References

1. Harman, D. The aging process. *Proc. Natl. Acad. Sci. USA* 1981; 78(11): 7124–7128.
2. Shock, N.W. Physiologic aspects of aging. *J. Am. Diet. Assoc.* 1970; 56(6): 491–496.
3. Hayflick, L. Recent advances in the cell biology of aging. Mech, Ageing *Dev*. 1980; 14(1–2):59–79.
4. Miquel, J., Economos, A.C., Fleming, J., Johnson, J.E., Jr. Mitochondrial role in cell aging. *Exp. Gerontol*. 1980; 15(6):575–591.
5. Thomas, D.D., Liu, X., Kantrow, SP., Lancaster, J.R., Jr. The biological lifetime of nitric oxide: Implications for the perivascular dynamics of NO and O_2. *Proc. Natl. Acad. Sci. USA* 2001; 98(1):355–360.
6. Brookes, P.S., Salinas, E.P., Darley-Usmar, K., et al. Concentration-dependent effects of nitric oxide on mitochondrial permeability transition and cytochrome C release. *J. Biol. Chem.* 2000; 275(27):20474–20479.

7. Brookes, P., Darley-Usmar, V.M. Hypothesis: The mitochondrial NO(*) signaling pathway, and the transduction of nitrosative to oxidative cell signals: An alternative function for cytochrome C oxidase. *Free Radic. Biol. Med.* 2002; 32(4):370–374.
8. Harman, D. Free radical theory of aging: Consequence of mitochondrial aging. *Age* 1983; 6:86–94.
9. Pollack, M., Leeuwenburgh, C. Apoptosis and aging: Role of the mitochondria. *J. Gerontol. A Biol. Sci. Med. Sci.* 2001; 56(11):B475–482.
10. Ferder, L., Inserra, F., Romano, L., Ercole, L., Pszenny, V. Effects of angiotensin-converting enzyme inhibition on mitochondrial number in the aging mouse. *Am. J. Physiol*. 1993; 265(1 Pt 1):C15–18.
11. de Cavanagh, E.M., Fraga, C.G., Ferder, L., Inserra, F. Enalapril and captopril enhance antioxidant defenses in mouse tissues. *Am. J. Physiol.* 1997; 272(2 Pt 2):R514–518.
12. de Cavanagh, E.M., Inserra, F., Ferder, L., Fraga, C.G. Enalapril and captopril enhance glutathione-dependent antioxidant defenses in mouse tissues. *Am. J. Physiol. Regul. Integr. Comp. Physiol*. 2000; 278(3):R572–577.
13. Ferder, L., Romano, L.A., Ercole, L.B., Stella, I., Inserra, F. Biomolecular changes in the aging myocardium: The effect of enalapril. *Am. J. Hypertens.* 1998; 11(11 Pt 1):1297–1304.
14. Assayag, P., Charlemagne, D., de Leiris, J., et al. Senescent heart compared with pressure overload-induced hypertrophy. *Hypertension* 1997; 29(1 Pt 1):15–21.
15. Benetos, A., Laurent, S., Hoeks, A.P., Boutouyrie, P.H., Safar, M.E. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. *Arterioscler. Thromb*. 1993; 13(1):90–97.
16. Michel, J.B., Azizi, M., Salzmann, J.L., Levy, B., Menard, J. Effect of vasodilatators on the structure of the aorta in normotensive ageing rats. *J. Hypertens. Suppl.* 1987; 5(5):S165–168.
17. Collister, J.P., Hornfeldt, B.J., Osborn, J.W. Hypotensive response to losartan in normal rats. Role of Ang II and the area postrema. *Hypertension* 1996; 27(3 Pt 2):598–606.
18. Inserra, F., Romano, L., Ercole, L., de Cavanagh, E.M., Ferder, L. Cardiovascular changes by long-term inhibition of the renin-angiotensin system in aging. *Hypertension* 1995; 25(3):437–442.
19. Keeley, F.W., Elmoselhi, A., Leenen, F.H. Enalapril suppresses normal accumulation of elastin and collagen in cardiovascular tissues of growing rats. *Am. J. Physiol.* 1992; 262(4 Pt 2):H1013–1021.
20. Bunnemann, B., Fuxe, K., Ganten, D. The renin-angiotensin system in the brain: An update. *Regul. Pept*. 1993; 46(3):487–509.
21. Wright, J.W., Harding, J.W. Brain angiotensin receptor subtypes in the control of physiological and behavioral responses. *Neurosci. Biobehav. Rev*. 1994; 18(1):21–53.
22. Phillips, M.I. Functions of angiotensin in the central nervous system. *Ann. Rev. Physiol*. 1987; 49:413–435.
23. Unger, T., Chung, O., Csikos, T., et al. Angiotensin receptors. *J. Hypertens. Suppl.* 1996; 14(5):S95–103.
24. Hirawa, N., Uehara, Y., Kawabata, Y., et al. Long-term inhibition of renin-angiotensin system sustains memory function in aged Dahl rats. *Hypertension* 1999; 34(3):496–502.
25. Stemmelin, J., Cassel, J.C., Will, B., Kelche, C. Sensitivity to cholinergic drug treatments of aged rats with variable degrees of spatial memory impairment. *Behav. Brain Res*. 1999; 98(1):53–66.
26. Colombo, P.J., Gallagher, M. Individual differences in spatial memory and striatal ChAT activity among young and aged rats. *Neurobiol. Learn. Mem.* 1998; 70(3):314–327.

27. Sugaya, K., Greene, R., Personett, D., et al. Septo-hippocampal cholinergic and neurotrophin markers in age-induced cognitive decline. *Neurobiol. Aging* 1998; 19(4):351–361.
28. Yamada, K., Noda, Y., Komori, Y., Sugihara, H., Hasegawa, T., Nabeshima, T. Reduction in the number of NADPH-diaphorase-positive cells in the cerebral cortex and striatum in aged rats. *Neurosci. Res.* 1996; 24(4):393–402.
29. Noda, Y., Yamada, K., Nabeshima, T. Role of nitric oxide in the effect of aging on spatial memory in rats. *Behav. Brain Res.* 1997; 83(1–2):153–158.
30. Basso, N., Altamirano, S., Paglia, N., Ferder, L., Inserra, F., Lores Arnaiz, M. Long-term inhibition of the RAS improves spatial working memory in the rat. *J. Hypertens*. 2000; 18(Suppl 4):S77.
31. Basso, N., Altamirano, S., Terragno, N., Ferder, L., Inserra, F., Lores Arnaiz, M. Inhibition of the renin-angiotensin system improves spatial working memory in the senile normal rat. *J. Hypertens*. 2002; 20(Suppl 4):S134.
32. Michel, J.B., Salzmann, J.L., Cerol, M.L., et al. Myocardial effect of converting enzyme inhibition in hypertensive and normotensive rats. *Am. J. Med.* 1988; 84(3A):12–21.
33. Gaballa, M.A., Jacob, C.T., Raya, T.E., Liu, J., Simon, B., Goldman, S. Large artery remodeling during aging: Biaxial passive and active stiffness. *Hypertension* 1998; 32(3):437–443.
34. Kung, C.F., Luscher, T.F. Different mechanisms of endothelial dysfunction with aging and hypertension in rat aorta. *Hypertension* 1995; 25(2):194–200.
35. Heagerty, A.M. Functional and structural effects of ACE inhibitors on the cardiovascular system. *Cardiology* 1991; 79(Suppl 1):3–9.
36. Park, J.B., Intengan, H.D., Schiffrin, E.L. Reduction of resistance artery stiffness by treatment with the AT(1)-receptor antagonist losartan in essential hypertension. *J. Renin Angiotensin Aldosterone Syst*. 2000; 1(1):40–45.
37. Gonzalez Bosc, L., Kurnjek, M.L., Muller, A., Basso, N. Effect of chronic angiotensin II inhibition on the cardiovascular system of the normal rat. *Am. J. Hypertens*. 2000; 13(12):1301–1307.
38. Gonzalez Bosc, L.V., Kurnjek, M.L., Muller, A., Terragno, N.A., Basso, N. Effect of chronic angiotensin II inhibition on the nitric oxide synthase in the normal rat during aging. *J. Hypertens.* 2001; 19(8):1403–1409.
39. Anversa, P., Palackal, T., Sonnenblick, E.H., Olivetti, G., Meggs, L.G., Capasso, J.M. Myocyte cell loss and myocyte cellular hyperplasia in the hypertrophied aging rat heart. *Circ. Res.* 1990; 67(4):871–885.
40. Chou, T.C., Yen, M.H., Li, C.Y., Ding, Y.A. Alterations of nitric oxide synthase expression with aging and hypertension in rats. *Hypertension* 1998; 31(2): 643–648.
41. Ferder, L.F., Inserra, F., Basso, N. Advances in our understanding of aging: Role of the renin-angiotensin system. *Curr. Opin. Pharmacol.* 2002; 2(2): 189–194.
42. Binder, C.J., Weiher, H., Exner, M., Kerjaschki, D. Glomerular overproduction of oxygen radicals in Mpv17 gene-inactivated mice causes podocyte foot process flattening and proteinuria: A model of steroid-resistant nephrosis sensitive to radical scavenger therapy. *Am. J. Pathol.* 1999; 154(4):1067–1075.
43. Ferder, L., Inserra, F., Romano, L., Ercole, L., Pszenny, V. Decreased glomerulosclerosis in aging by angiotensin-converting enzyme inhibitors. *J. Am. Soc. Nephrol.* 1994; 5(4):1147–1152.
44. Kaplan, C., Pasternack, B., Shah, H., Gallo, G. Age-related incidence of sclerotic glomeruli in human kidneys. *Am. J. Pathol*. 1975; 80(2):227–234.
45. Heudes, D., Michel, O., Chevalier, J., et al. Effect of chronic ANG I-converting enzyme inhibition on aging processes. I. Kidney structure and function. *Am. J. Physiol.* 1994; 266(3 Pt 2):R1038–1051.

46. Hostetter, T.H., Olson, J.L., Rennke, H.G., Venkatachalam, M.A., Brenner, B.M. Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *Am. J. Physiol*. 1981; 241(1):F85–93.
47. Anderson, S., Meyer, T.W., Rennke, H.G., Brenner, B.M. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J. Clin. Invest*. 1985; 76(2):612–619.
48. Inserra, F., Romano, L.A., de Cavanagh, E.M., Ercole, L., Ferder, L.F., Gomez, R.A. Renal interstitial sclerosis in aging: Effects of enalapril and nifedipine. *J. Am. Soc. Nephrol*. 1996; 7(5):676–680.
49. Kakinuma, Y., Kawamura, T., Bills, T., Yoshioka, T., Ichikawa, I., Fogo, A. Blood pressure-independent effect of angiotensin inhibition on vascular lesions of chronic renal failure. *Kidney Int*. 1992; 42(1):46–55.
50. Norman, J.T. The role of angiotensin II in renal growth. *Ren. Physiol. Biochem.* 1991; 14(4–5):175–185.
51. Fine, L. The biology of renal hypertrophy. *Kidney Int,* 1986; 29(3):619–634.
52. Abboud, H.E. Resident glomerular cells in glomerular injury: Mesangial cells. *Semin. Nephrol*. 1991; 11(3):304–311.
53. Rovin, B.H., Phan, L.T. Chemotactic factors and renal inflammation. *Am. J. Kidney Dis*. 1998; 31(6):1065–1084.
54. Kato, S., Luyckx, V.A., Ots, M., et al. Renin-angiotensin blockade lowers MCP-1 expression in diabetic rats. *Kidney Int*. 1999; 56(3):1037–1048.
55. Pimentel, J.L., Jr., Montero, A., Wang, S., Yosipiv, I., el-Dahr, S., Martinez-Maldonado, M. Sequential changes in renal expression of renin-angiotensin system genes in acute unilateral ureteral obstruction. *Kidney Int.* 1995; 48(4):1247–1253.
56. Pimentel, J.L., Jr., Sundell, C.L., Wang, S., Kopp, J.B., Montero, A., Martinez-Maldonado, M. Role of angiotensin II in the expression and regulation of transforming growth factor-beta in obstructive nephropathy. *Kidney Int*. 1995; 48(4):1233–1246.
57. Pimentel, J.L., Jr., Wang, S., Martinez-Maldonado, M. Regulation of the renal angiotensin II receptor gene in acute unilateral ureteral obstruction. *Kidney Int*. 1994; 45(6):1614–1621.
58. Pimentel, J.L., Jr., Martinez-Maldonado, M., Wilcox, J.N., Wang, S., Luo, C. Regulation of renin-angiotensin system in unilateral ureteral obstruction. *Kidney Int*. 1993; 44(2):390–400.
59. Manucha, W., Carrizo, L., Ruete, C., Molina, H., Valles, P. Angiotensin II type I antagonist on oxidative stress and heat shock protein 70 (HSP 70) expression in obstructive nephropathy. *Cell Mol. Biol.* (Noisy-le-grand) 2005; 51(6): 547–555.
60. Klahr, S., Morrissey, J.J. The role of growth factors, cytokines, and vasoactive compounds in obstructive nephropathy. *Semin. Nephrol.* 1998; 18(6):622–632.
61. Thompson, M.M., Oyama, T.T., Kelly, F.J., Kennefick, T.M., Anderson, S. Activity and responsiveness of the renin-angiotensin system in the aging rat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2000; 279(5):R1787–1794.
62. Shagdarsuren, E., Wellner, M., Braesen, J.H., et al. Complement activation in angiotensin II-induced organ damage. *Circ. Res.* 2005; 97(7):716–724.
63. Cha, D.R., Kang, Y.S., Han, S.Y., et al. Role of aldosterone in diabetic nephropathy. *Nephrology* (Carlton) 2005; 10 (Suppl):S37–39.
64. Inserra, F., Stella, I., Kurnjek, M., et al. Losartan and enalapril protect against age related kidney lesions in normal rats treated from 12 to 18 months of age. *J. Am. Soc. Nephrol*. 2001; 12:679A.
65. de Cavanagh, E.M., Piotrkowski, B., Basso, N., et al. Enalapril and losartan attenuate mitochondrial dysfunction in aged rats. *FASEB J.* 2003; 17(9): 1096–1098.

66. Pauls, K., Metzger, R., Steger, K., Klonisch, T., Danilov, S., Franke, F.E. Isoforms of angiotensin I-converting enzyme in the development and differentiation of human testis and epididymis. *Andrologia* 2003; 35(1):32–43.
67. Mededovic, S., Fraser, L.R. Mechanisms of action of angiotensin II on mammalian sperm function. *Reproduction* 2005; 129(2):211–218.
68. Fraser, L.R., Adeoya-Osiguwa, S.A., Baxendale, R.W., Gibbons, R. Regulation of mammalian sperm capacitation by endogenous molecules. *Front. Biosci*. 2006; 11:1636–1645.
69. Zheng, S., Li, Z., Wang, Y.X., Xiang, Z.Q. [Seminal plasma angiotensin II detection and its clinical implication.] [in Chinese] *Zhonghua Nan Ke Xue* 2003; 9(9):669–672.
70. Toblli, J., Stella, I., Nestor Mazza, O., Ferder, L., Inserra, F. Protection of cavernous tissue in male spontaneously hypertensive rats. Beyond blood pressure control. *Am. J. Hypertens*. 2004; 17(6):516–522.
71. Cadenas, E., Davies, K.J. Mitochondrial free radical generation, oxidative stress, and aging. *Free Radic. Biol. Med*. 2000; 29(3–4):222–230.
72. Hart, R., Turturro, A. Theories of aging. *Rev. Biol. Res. Aging* 1983; 1:5–17.
73. Murfitt, R.R., Rao Sanadi, D. Evidence for increased degeneration of mitochondria in old rats. A brief note. *Mech. Ageing Dev.* 1978; 8(3):197–201.
74. Polson, C., Webster, J. Loss of mitochondrial DNA in mouse tissues with age. *Age* 1982; 5:5–133.
75. Kukreja, R.C., Kontos, H.A., Hess, M.L. Captopril and enalapril do not scavenge the superoxide anion. *Am. J. Cardiol*. 1990; 65(19):24I–27I.
76. de Cavanagh, E.M., Inserra, F., Ferder, L., Romano, L., Ercole, L., Fraga, C.G. Superoxide dismutase and glutathione peroxidase activities are increased by enalapril and captopril in mouse liver. *FEBS Lett*. 1995; 361(1):22–24.
77. Jolly, S.R., Kane, W.J., Bailie, M.B., Abrams, G.D., Lucchesi, B.R. Canine myocardial reperfusion injury. Its reduction by the combined administration of superoxide dismutase and catalase. *Circ. Res.* 1984; 54(3):277–285.
78. Orr, W.C., Sohal, R.S. Extension of life-span by overexpression of superoxide dismutase and catalase in *Drosophila melanogaster*. *Science* 1994; 263(5150):1128–1130.
79. Das, N., Levine, R.L., Orr, W.C., Sohal, R.S. Selectivity of protein oxidative damage during aging in *Drosophila melanogaster*. *Biochem. J.* 2001; 360(Pt 1):209–216.
80. Pueyo, M.E., Arnal, J.F., Rami, J., Michel, J.B. Angiotensin II stimulates the production of NO and peroxynitrite in endothelial cells. *Am. J. Physiol*. 1998; 274(1 Pt 1):C214–220.
81. Rueckschloss, U., Quinn, M.T., Holtz, J., Morawietz, H. Dose-dependent regulation of NAD(P)H oxidase expression by angiotensin II in human endothelial cells: Protective effect of angiotensin II type 1 receptor blockade in patients with coronary artery disease. *Arterioscler. Thromb. Vasc. Biol.* 2002; 22(11):1845–1851.
82. Radi, R., Cassina, A., Hodara, R., Quijano, C., Castro, L. Peroxynitrite reactions and formation in mitochondria. *Free Radic. Biol. Med.* 2002; 33(11):1451–1464.
83. de Cavanagh, E.M., Toblli, J.E., Ferder, L., Piotrkowski, B., Stella, I., Inserra, F. Renal mitochondrial dysfunction in spontaneously hypertensive rats is attenuated by losartan but not by amlodipine. *Am. J. Physiol. Regul. Integr. Comp. Physiol*. 2006; 290(6):R1616–1625.
84. Newaz, M.A., Nawal, N.N. Effect of gamma-tocotrienol on blood pressure, lipid peroxidation and total antioxidant status in spontaneously hypertensive rats (SHR). *Clin. Exp. Hypertens*. 1999; 21(8):1297–1313.
85. Brand, M.D., Affourtit, C., Esteves, T.C., et al. Mitochondrial superoxide: Production, biological effects, and activation of uncoupling proteins. *Free Radic. Biol. Med*. 2004; 37(6):755–767.

86. Rhee, S.G. Cell signaling. H_2O_2, a necessary evil for cell signaling. *Science* 2006; 312(5782):1882–1883.
87. Cadenas, E., Poderoso, J.J., Antunes, F., Boveris, A. Analysis of the pathways of nitric oxide utilization in mitochondria. *Free Radic. Res.* 2000; 33(6):747–756.
88. Negre-Salvayre, A., Hirtz, C., Carrera, G., et al. A role for uncoupling protein-2 as a regulator of mitochondrial hydrogen peroxide generation. *FASEB J.* 1997; 11(10):809–815.
89. Fukunaga, Y., Itoh, H., Hosoda, K., et al. Altered gene expression of uncoupling protein-2 and -3 in stroke-prone spontaneously hypertensive rats. *J. Hypertens.* 2000; 18(9):1233–1238.
90. Wallace, D.C. A mitochondrial paradigm for degenerative diseases and aging. *Novartis Found. Symp*. 2001; 235:247–263; discussion 63–66.
91. Nishikawa, T., Edelstein, D., Du, X.L., et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000; 404(6779):787–790.
92. Hagen, T.M., Yowe, D.L., Bartholomew, J.C., et al. Mitochondrial decay in hepatocytes from old rats: Membrane potential declines, heterogeneity and oxidants increase. *Proc. Natl. Acad. Sci. USA* 1997; 94(7):3064–3069.
93. Kimura, S., Zhang, G.X., Nishiyama, A., et al. Mitochondria-derived reactive oxygen species and vascular MAP kinases: Comparison of angiotensin II and diazoxide. *Hypertension* 2005; 45(3):438–444.
94. Laursen, J.B., Rajagopalan, S., Galis, Z., Tarpey, M., Freeman, B.A., Harrison, D.G. Role of superoxide in angiotensin II-induced but not catecholamine-induced hypertension. *Circulation* 1997; 95(3):588–593.
95. Tham, D.M., Martin-McNulty, B., Wang, Y.X., et al. Angiotensin II is associated with activation of NF-kappaB-mediated genes and downregulation of PPARs. *Physiol. Genomics* 2002; 11(1):21–30.
96. Nakatani, T., Tsuboyama-Kasaoka, N., Takahashi, M., Miura, S., Ezaki, O. Mechanism for peroxisome proliferator-activated receptor-alpha activator-induced up-regulation of UCP2 mRNA in rodent hepatocytes. *J. Biol. Chem.* 2002; 277(11):9562–9569.
97. Takahashi, M., Tsuboyama-Kasaoka, N., Nakatani, T., et al. Fish oil feeding alters liver gene expressions to defend against PPARalpha activation and ROS production. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2002; 282(2):G338–348.
98. Wilson, F.H., Hariri, A., Farhi, A., et al. A cluster of metabolic defects caused by mutation in a mitochondrial tRNA. *Science* 2004; 306(5699):1190–1194.
99. Katyare, S.S., Satav, J.G. Effect of streptozotocin-induced diabetes on oxidative energy metabolism in rat kidney mitochondria. A comparative study of early and late effects. *Diabetes Obes. Metab.* 2005; 7(5):555–562.
100. Raza, H., Prabu, S.K., Robin, M.A., Avadhani, N.G. Elevated mitochondrial cytochrome P450 2E1 and glutathione S-transferase A4–4 in streptozotocin-induced diabetic rats: Tissue-specific variations and roles in oxidative stress. *Diabetes* 2004; 53(1):185–194.
101. Remuzzi, G., Schieppati, A., Ruggenenti, P. Clinical practice. Nephropathy in patients with type 2 diabetes. *N. Engl. J. Med*. 2002; 346(15):1145–1151.
102. Lewis, E.J., Hunsicker, L.G., Bain, R.P., Rohde, R.D. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N. Engl. J. Med*. 1993; 329(20):1456–1462.
103. Lewis, E.J., Hunsicker, L.G., Clarke, W.R., et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N. Engl. J. Med.* 2001; 345(12):851–860.
104. Brenner, B.M., Cooper, M.E., de Zeeuw, D., et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N. Engl. J. Med*. 2001; 345(12):861–869.

105. Hansson, L., Lindholm, L.H., Niskanen, L., et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; 353(9153):611–616.
106. Lindholm, L.H., Ibsen, H., Dahlof, B., et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 2002; 359(9311):1004–1010.
107. Julius, S., Kjeldsen, S.E., Brunner, H., et al. VALUE trial: Long-term blood pressure trends in 13,449 patients with hypertension and high cardiovascular risk. *Am. J. Hypertens.* 2003; 16(7):544–548.
108. de Cavanagh, E.M., Inserra, F., Toblli, J., Stella, I., Fraga, C.G., Ferder, L. Enalapril attenuates oxidative stress in diabetic rats. *Hypertension* 2001; 38(5):1130–1136.
109. Chen, G., Lin, L.X., Zhuang, W.T., et al. [Effects of captopril on myocardial tissue energy metabolism and inflammation in rats with diabetic cardiomyopathy.] [in Chinese] *Di Yi Jun Yi Da Xue Xue Bao* 2004; 24(7):827–828, 831.
110. Inserra, F., Daccordi, H., Ippolito, J.L., Romano, L., Zelechower, H., Ferder, L. Decrease of exercise-induced microalbuminuria in patients with type I diabetes by means of an angiotensin-converting enzyme inhibitor. *Am. J. Kidney Dis.* 1996; 27(1):26–33.
111. Ferder, L., Daccordi, H., Martello, M., Panzalis, M., Inserra, F. Angiotensin converting enzyme inhibitors versus calcium antagonists in the treatment of diabetic hypertensive patients. *Hypertension* 1992; 19(2 Suppl):II237–242.
112. Remuzzi, G., Bertani, T. Pathophysiology of progressive nephropathies. *N. Engl. J. Med*. 1998; 339(20):1448–1456.
113. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997; 349(9069):1857–1863.
114. Ruggenenti, P., Perna, A., Gherardi, G., et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; 354(9176):359–364.
115. Wright, J.T., Jr., Bakris, G., Greene, T., et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 2002; 288(19):2421–2431.
116. Kasper, S.O., Basso, N., Kurnjek, M.L., et al. Divergent regulation of circulating and intrarenal renin-angiotensin systems in response to long-term blockade. *Am. J. Nephrol*. 2005; 25(4):335–341.

13

Prevention of Chronic Renal Diseases in the Elderly

Sanjib Kumar Sharma, Norberto Perico, Piero Ruggenenti, and Giuseppe Remuzzi

Introduction

Chronic kidney disease is a major public health problem worldwide, as Chapter 23 discusses further. In the United States, the number of persons treated with end-stage renal disease (ESRD) has increased substantially over the past 20 years [1]. This growth has occurred primarily in individuals older than 65 years of age [1] (see Chapter 23).

The incidence of renal replacement therapy (RRT) for ESRD continues to increase also in other geographical areas of the world, but at rates that vary considerably among countries. Over the last decade, RRT registries have reported average annual increases of 11% in Japan [2], 9% in Australia and 6.5% in New Zealand [3], and 6.1% in Canada [4]. In the same period, data from national and regional registries and from repeated cross-sectional surveys in Western Europe have shown increases in rates ranging from 2 to 4.3% per year in Germany [5], Spain [6], the UK [7], and France [8]. A more recent analysis from nine countries participating in the new European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) registry [9] reported that the adjusted (for age and gender) incidence rate of RRT increased from 79.4 per million population (pmp) in 1990–1991 to 117.1 pmp in 1998–1999, i.e., a 4.8% increase each year. This increase did not flatten out at the end of decade except in the Netherlands and was greater in men than women, 5.2 versus 4.0% per year. In most countries, the incidence rate remained stable for those younger than 45 years; it rose by 2.2% per year on average in those between 45 and 64 years old and by 7.0% among those aged 65–74 years; it tripled over the decade in those 75 years or older, and by 1998–1999, it ranged from 140.9 to 540.4 pmp, depending on the country. In the same countries, the incidence of ESRD due to diabetes, hypertension, and renal vascular disease nearly doubled over 10 years; in 1998–1999, it varied among countries from 10.2 to 39.3 pmp for diabetes, from 5.8 to 21.0 for hypertension, and from 1.0 to 15.5 for renal vascular disease [9]. Thus, RRT incidence continues to rise at various rates throughout the world, with the gap between countries resulting from enlarging differences in incidence

in the elderly and to some extent due to diabetes, hypertension, and renal vascular disease, which may reflect ethnic differences [10].

ESRD requiring replacement therapy, however, represents only a small proportion of the kidney disease: For every person with ESRD, 29 people have an elevated serum creatinine [11]. Kidney dysfunction is especially common among older persons, affecting 10 to 15% of persons older than 70 years of age [12]. Even though debate continues as to the significance of this observation—is it a physiological consequence of aging, or does it represent the consequence of disease(s) (see Chapter 5)?—the loss of renal reserve is present nevertheless. In 2002, approximately 1 million Americans over the age of 65 years self-reported "weak or failing kidneys." Data from National Health and Nutrition Examination Surveys (NHANES) III, a study of community-dwelling adults, estimated that 25% of all Americans 70 years of age and older had moderate or severe decreased kidney function compared with similar young adults. Studies in Europe have also shown the near-exponential rise in chronic kidney disease (CKD) in the elderly [13, 14]. An age-stratified analysis in a French urban area was performed, revealing a striking increase in the annual incidence of CKD as age increased, with incidence rates in patients aged >75 years being almost 7 times higher than those of patients aged 20 to 39 years (619 pmp versus 92 pmp) and more than twice those of patients aged 40 to 59 years (619 pmp versus 264 pmp) [15]. In a predominantly Caucasian UK population who were unknown to renal services, the prevalence of CKD (defined by serum creatinine cut-off values of $\geq$2.03 mg/dL in men and $\geq$1.53 mg/dL in women) was 5554 pmp: The median patient age was 83 years [16]. In a Spanish general population study, it was found that the prevalence of stages 2 and 3 CKD increased with age (especially >65) and did more so in women than in men [17].

Besides renal dysfunction indicated by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 of body surface area, the presence of chronic kidney damage is defined also most commonly by the finding of albuminuria present for three or more consecutive months [18]. Of note, urinary albumin excretion increases with age [12, 19]; for instance, among persons 60 to 69 years of age, approximately 18% have albuminuria [19]. For example, in England the incidence of advanced chronic kidney disease was 282, 503, and 588 per million population in the age group of 60–69, 70–79, and >80 years, respectively [20]. Finally evidence continues to accumulate that strongly suggests that CKD is an independent risk factor for cardiovascular disease, even at a low level of albuminuria (30–300 mg of albumin per day, the equivalent of microalbuminuria) or at only a moderate reduction in the estimated GFR (30–59 mL/min/1.73 m^2, the equivalent of stage 3 disease) [21].

The implications of these cardiovascular complications associated with CKD are particularly profound in the older adult population, which carries independent risk factors for these co-morbidities [22]. Old age itself is a risk factor for malnutrition, another complication of CKD. Protein-energy malnutrition and inflammation are commonly seen in individuals with ESRD. Malnutrition and inflammation are possibly a consequence of poor nutrient intake, hypercatabolic state, or decreased clearance of cytokines such as IL-6 and TNF-α [23, 24] and carry special concern for older subjects, who are already at risk for protein malnutrition because of their aging physiology as well as economic constraints. Further increasing the risk of the frail older adult for osteoporosis is renal osteodystrophy secondary to CKD [25]. These

multiple morbidities, associated with CKD, particularly the life-threatening cardiovascular disease, point out the need to concentrate our efforts on the prevention of renal diseases and their progression to ESRD.

Etiologies and Risk Factors for Chronic Kidney Disease in the Elderly

Effort to reduce the burden of CKD requires the understanding of their causes and risk factors.

Glomerulonephritis

Among the idiopathic glomerulonephritides, membranous glomerulonephritis and antiglomerular basement membrane antibody disease are diagnosed more often in the elderly than in younger subjects. The association of membranous glomerulonephritis with solid tumors is important to identify, as both occur more commonly in the elderly and successful treatment of the underlying malignancy may cure the glomerulonephritis [26]. Other secondary glomerular diseases are also present with increased frequency in the older population [11, 27–29]. In several kidney biopsy reports in elderly patients (age $\geq$ 60 years), vasculitis (pauci-immune segmental necrosis with or without crescents), amyloidosis, and paraprotein-mediated kidney disease all occurred with increased incidence compared with the younger adult [27–29].

Interstitial Nephropathies

However, the most common single "cause" of chronic renal failure in elderly patients is a state often characterized by the finding of rather or definitively small kidneys of no obvious etiology. This finding is commonly associated with hypertension and vascular sclerosis, but not invariably. In line with this finding, tubulointerstitial patterns of renal injury are reported with increased frequency on histological study in the elderly population as well [30]. Chronic tubulointerstitial nephritis is classically seen with nonsteroidal anti-inflammatory drugs, which give a more indolent course without associated symptoms. Tubulointerstitial nephritis is also associated with other potentially toxic exposures, such as viral infections, heavy metals, individual herbs, metabolic disorders, or radiation. The elderly population has an increased incidence of this disease state; biopsies series report interstitial nephritis in up to 18% of cases [27,28,30]. This percentage is potentially an underestimation of the true incidence, because far from all of these patients with this clinical presentation are biopsied (see Chapter 17). The elderly population's exposure to polypharmacy is one probable explanation for this increased incidence [30].

Hereditary Kidney Diseases

Kidney diseases are in part genetically determined; therefore, individuals with a familial history of renal failure have a three- to ninefold greater risk of ESRD. The rate of progression of renal disease in hereditary kidney diseases such as autosomal-dominant polycystic kidney disease is highly variable, due to genetic heterogeneity [31] (see Chapter 19). Individuals with mutations in

polycystic kidney disease 1 (PKD1) experience a more severe disease course, ultimately progressing to ESRD by the average age of 54, while individuals with mutations in *PKD2* experience loss of renal function approximately 20 years later [32]. When renal function falls below 75% of normal, the decline is rapid, requiring renal replacement therapy in a matter of 5 to 10 years [33].

Hypertension

One of the leading causes of CKD in the elderly population is hypertension. Elevated blood pressure (BP) is a strong independent risk factor for developing ESRD [34, 35]. A growing body of work suggests that, among older persons, systolic BP and possibly pulse pressure are more strongly correlated with coronary heart disease, congestive heart failure, and mortality than diastolic BP or mean arterial pressure [19, 36–43]. The relative association of each BP component with kidney dysfunction in the elderly is as yet ill-defined. Among 2181 men and women enrolled in the placebo arm of the Systolic Hypertension in the Elderly Program (SHEP), systolic BP was found to be a strong independent risk factor for a decline in kidney function among older persons with isolated systolic hypertension [44]. This is especially important given that most cases of uncontrolled hypertension are due to systolic hypertension among older adults [45]. Therefore, prevention and treatment of systolic hypertension could help stem the growing epidemic of kidney dysfunction among older persons. Moreover, uncontrolled hypertension contributes to accelerated renal dysfunction in other kidney diseases. Hypertensive atherosclerosis is also a disease of aging and is increasingly recognized as a cause of CKD progression to ESRD in the elderly [27]. By contributing to hypertension, hemodynamically significant atherosclerosis renovascular disease may increase the risk of coronary heart disease and stroke in the elderly [46].

Diabetes Mellitus

Diabetes is, however, the most prevalent single cause of CKD in the elderly population. Indeed, the majority of people with diabetes in developed countries are over 64 years of age [47]. In contrast, in developing countries, most people with diabetes are in the 45- to 64-year age range [47]. Moreover, by 2030, it is estimated that the number of people over 64 with diabetes will exceed 48 million in developed countries and 82 million in developing countries [47]. Diabetic nephropathy develops in about one-third of patients with diabetes after a decade or more, and its incidence is sharply increasing worldwide. Diabetic nephropathy is most prevalent in African Americans, Asians, and Native Americans than Caucasians [48]. In the United States, the prevalence of diabetes in older adults reaches approximately 25% in certain ethnic minorities [23] and continues to increase [49]. Between 1988 and 1994, the prevalence of diabetes in all adults aged 60 to 74 years was 13%, but was as high as 21% in non-Hispanic blacks and 24% in Mexican Americans [23]. Diabetes is the one of the most frequent causes of CKD and the single largest cause for initiation of renal replacement therapy. As recently as 1980, diabetes was the cause of ESRD in just under 13% of new patients in the United States. Twenty years later, however, it was the primary renal diagnosis in 55–64% of Hispanic and 43% of non-Hispanic ESRD patients [48]. In

parallel with this, most ESRD patients in the United States are now older than 64.5 years at initiation of renal replacement therapy. By 2030, almost 60% of the projected 2.24 million prevalent ESRD patients are expected to have diabetes, and more than half of those will be at least 65 years [48].

According to a survey published in 2003 [50], diabetic nephropathy was the most common cause of end-stage renal disease in 9 of 10 Asian countries, with an incidence that had increased from 1.2% of the overall population with ESRD in 1998 to 14.1% in 2000. In China, the proportion of cases of ESRD that were caused by diabetic nephropathy increased from 17% in the 1990s to 30% in 2000. In India, diabetic nephropathy is expected to develop in 6.6 million of the 30 million patients with diabetes. Although figures of diabetic nephropathy by age in these Asia-Pacific regions are scanty, the disease is expected to be more common in the elderly than in younger individuals.

Also, data from 10 registries in Europe (1991–2000) have documented an increase in patients with diabetic nephropathy entering RRT (+11.9% annually), but large differences in RRT incidence in this disease continue to exist among countries [51]. The mean age of those with type 2 diabetic nephropathy starting RRT varied from 65 years in Norway to 68 years in the Spanish region of Catalonia. Overall, the mean age of these patients in the 10 european registries increased from 64 years in 1991 to 67 years in 2000. Thus, despite ethnic differences, the renal consequences of diabetes constitute a substantial problem in both clinical and economic terms, especially for the elderly.

Mechanisms of Renal Disease Progression

During the last 20 years, research in animals and people has helped our understanding of the mechanism by which chronic kidney diseases progress. A large numbers of studies established that progressive deterioration of renal function is the result of compensatory glomerular hemodynamic changes in response to nephron loss. In a widely used experimental model of renal mass reduction, the remaining nephrons undergo hypertrophy, reduced arteriolar resistance, and increased glomerular blood flow [52]. *In vivo*, angiotensin II enhances the vascular tone of both afferent and efferent glomerular arterioles and modulates intraglomerular capillary pressure and glomerular filtration rate (GFR) [53]. Aside from these glomerular hemodynamic effects of angiotensin II, other studies have revealed several nonhemodynamic effects of angiotensin II that may also be important. These findings have suggested that angiotensin II may alter permselective properties of the glomerular capillary barrier by mediating contraction of foot processes, ultimately changing the slit-diaphragm architecture and allowing proteins to escape more easily into the urinary space [54]. Abnormal protein trafficking through the glomerular capillary wall might contribute to the progression of renal disease. Indeed, recent data support the possibility that the excessive protein load on the podocyte can be a factor underlying progressive injury to these glomerular cells and through their release of transforming growth factor ß1, ultimately allowing myofibroblast differentiation of mesangial cells [55]. Moreover, excessive protein reabsorption by proximal tubuli provided further intrinsic toxicity to this nephron segment. Thus, both *in vitro* and *in vivo*, protein overload causes increased production of vasoactive and inflammatory mediators such as endothelin-1, monocyte chemoattractant

protein-1, RANTES (regulated upon activation, normal T cells expressed and secreted)—a chemotactic cytokine for monocyte and memory T cells—and osteopontin [56]. The activation of a variety of molecules such as cytokines, growth factors, and vasoactive substances may result in abnormal accumulation of extracellular matrix collagen, fibronectin, and other components that are responsible for interstitial fibrosis. Proinflammatory mediators promote local recruitment of macrophages and lymphocytes [57], which, in turn, can stimulate the transformation of interstitial cells into myofibroblasts. Proximal tubular epithelial cells can interact with interstitial fibroblasts to promote fibrogenesis via release of profibrogenic molecules [57]. In summary, there is robust experimental evidence that proteinuria is responsible for interstitial inflammation and subsequent fibrosis, thereby contributing to progressive renal function loss.

There are, however, nonproteinuric chronic nephropathies that still progressively evolve to ESRD, which are also relevant to aging. This applies to atherosclerotic renovascular disease, mostly related to sustained dyslipidemia and high blood pressure [46]. The principal mechanism underlying these pathophysiological changes has been shown to involve (among many other factors) the local renal endothelial system [58]. Animal models have been instrumental in demonstrating the natural progression of nephrosclerosis to ESRD, through increased arterial pressure, enhanced afferent and efferent glomerular arteriolar resistances, and reduced total renal blood flow [59]. These result in segmental or global glomerular and arteriolar sclerosis associated with inflammatory cell infiltration, interstitial fibrosis, and tubular atrophy, so that renal disease progression is inevitable. These studies strongly indicate that the severity of renal damage is dependent upon the intensity and duration of hypertension [60]. High blood pressure also contributes to the rate of progression of renal disease in hereditary kidney diseases such as ADPKD, in which significant proteinuria rarely occurs. The most significant defect in ADPKD is the progressive development and growth of thousands of cysts in both kidneys (see Chapter 19). This results in replacement of the normal renal tissue and significant overall growth of the organ. To this genetic mechanistic background, elevated blood pressure, frequently observed in this condition, adds further renal damage, and eventually the majority of (but not all) patients experience renal failure [61]. Insight into these pathophysiological mechanisms of renal disease progression has helped to indicate possible preventive methods that in general could be extended to older individuals, with some specific recommendations. While these renoprotective interventions may postpone ESRD in a younger person, in the elderly it may obviate the need for dialysis altogether, death eventually occurring from other causes.

Renoprotection in Nondiabetic Proteinuric Nephropathies

Experimental evidence in nondiabetic proteinuric nephropathy suggests that chronic renal disease progresses by way of common mechanisms, so that therapeutic interventions targeting this pathway may be successful in slowing the rate of progression to ESRD, regardless of the initiating cause. To this, blockade of angiotensin II with ACE inhibitors and/or ARBs slowed the progressive loss of renal function in different animal models of CKD mainly by normalizing blood pressure and limiting or preventing abnormal protein

traffic through the glomerular capillary barrier. Along this line, clinical evidence indicates that whenever proteinuria is decreased, progression to ESRD is reduced [62–65]. Results of the Modification of Diet in Renal Disease (MDRD) study [62] established that a reduction of proteinuria was associated with a decrease in the rate of decline in GFR and that the protection of renal function achieved by lowering blood pressure was dependent on the extent of initial proteinuria.

The role of proteinuria as a promoter of progression and its impact on renal outcome were also explored by the Ramipril Efficacy in Nephropathy (REIN) study [65]. This study was designed to assess the hypothesis that ACE inhibition could be superior to other antihypertensive drugs in reducing proteinuria, limiting the decline in GFR, and preventing end-stage renal disease in patients with chronic nephropathies. In this study, patients were randomly assigned to receive ramipril or conventional antihypertensive therapy to maintain diastolic blood pressure at 90 mm Hg or less. A prestratification strategy recognized two levels of proteinuria (stratum 1: >1 and <3 g/24 hr; stratum 2: $\geq$3 g/24 hr). The study showed that, while blood pressure control was similar in the two treatment groups, ACE inhibitor therapy decreased the progression to end-stage renal disease by 50% [65,66]. Patients in the study, who had more proteinuria to start with, benefited more from blood pressure-lowering treatment than those who had less proteinuria.

A meta-analysis [67] in 1860 patients with chronic nephropathies also recorded that the benefit of ACE inhibition was greatest in patients with high urine protein excretion at baseline. This drug class seems to have a greater antiproteinuric effect than other antihypertensive drugs despite equal effects on blood pressure. The investigators concluded that proteinuria is the most important modifiable risk factor to slow progression and that reduction of urine protein excretion is the main goal for treatment. The REIN study was continued for 2 years (the REIN follow-up study), during which time all patients previously on placebo were switched to an ACE inhibitor [67]. In patients continuing to receive ramipril, GFR further decreased to approximately 1 mL/min/year during follow-up, a figure similar to that associated with normal aging. Patients who switched from conventional therapy to ramipril also benefited from treatment. One of the most impressive findings of this prolonged follow-up was that after about 36 months of treatment with ramipril, no additional patients progressed to the point of requiring dialysis, whereas patients switched from conventional therapy to ramipril continued to develop ESRD. To further investigate the nature of the time-dependent improvement in GFR change, researchers looked for a breakpoint in the individual GFR slopes of patients receiving continued ramipril therapy. It could be predicted that after the breakpoint, 10 patients receiving continued ramipril therapy would never progress to ESRD and that 10 had such improved GFR slopes that progression to end-stage renal disease would be delayed by about 5 years. The analysis provides evidence that the tendency of GFR to decline with time can be halted and remission is achievable in some patients with chronic renal disease.

Although specific clinical trials on renoprotection in the elderly are lacking, the potential benefit of renin-angiotensin system (RAS) inhibition should not prevent its use in old patients with proteinuric CKD. Of note, post hoc analyses of many ACEi-based clinical trials demonstrate the greatest slowing of renal

disease progression in patients with the greatest degree of renal insufficiency at study initiation [68, 69]. Nevertheless, despite the fact that many studies have documented the usefulness of ACE inhibitors and ARBs in delaying the decline in renal function and reducing protenuria, many physicians fail to use these drug classes in patients with renal insufficiency, particularly in the elderly population, for fear that either serum creatinine or potassium level will increase. However, data from clinical trials with ACE inhibitors in chronic proteinuric renal disease demonstrate that if an elevation in serum creatinine occurs, it stabilizes quickly and does not progressively worsen [68]. Thus, no patient should be denied a long-term trial of an ACEi because of a preexisting elevation in serum creatinine level, or one that increases up to 30% above baseline and stabilize within 2 to 3 weeks. If chronic increases in serum creatinine level of more than 30% following 4 or more weeks of ACEi therapy occur, the patient should be evaluated for drug withdrawal.

Anecdotal reports, however, do suggest that in the elderly with chronic renal disease, ACE inhibition may be more dangerous with regard to a decline in renal function [70], but large bodies of data to support this view are lacking. Actually, in the Evaluation of Losartan in the Elderly (ELITE) study, which included heart failure patients with left ventricular systolic dysfunction, aged 65 and older with serum creatinine up to 3.5 mg/dL, for patients receiving captopril or losartan, the incidence of persistent renal dysfunction was observed in about 10%, but only 2% had to discontinue the use of the drugs [71]. Regarding serum potassium concentration, in a pooled analysis of six published trials including 1514 diabetic and nondiabetic patients with proteinuric chronic nephropathies [12, 24, 64, 72, 73], we have found that the incidence of dropouts because of uncontrolled hyperkalemia was similar and was less than 2% in both ACEi and conventional treatment groups. Interestingly, the REIN study [65] found that differences in serum potassium levels between ramipril-treated patients and controls never exceeded 0.3 mEq/L throughout the whole follow-up period. Similar data can be derived (although the numbers are small) from the analyses of studies on ARBs alone or in combination with ACEi. The risk of hyperkalemia was minimized by excluding patients with renovascular disease. Moreover, serum potassium was closely monitored, hyperglycemia and metabolic acidosis were carefully treated, and thiazide or loop diuretics were frequently used in combination with ACEi. Adherence to these simple guidelines is therefore recommended in the management of patients with drugs that inhibit the RAS, particularly in the elderly. This is in line with National Kidney Foundation (NKF) guidelines, which recommend blood pressure, GFR, and serum potassium measurements in all patients with CKD at the initiation of either ACE inhibitor or ARB therapy, and also with each increase in dose of either agent [74].

Renoprotection in Diabetic Nephropathy

The decade of large clinical trials in proteinuric chronic nephropathy was closed when the results of three important studies were published in the *New England Journal of Medicine* [64, 75, 76]. All three studies examined the role of ARBs in type 2 diabetic nephropathy. One study evaluated the renoprotective effect of the ARB irbesartan in hypertensive patients with incipient nephropathy (urinary albumin excretion $\geq$20–200 μg/min) [76]. The endpoint

of the study was the time of onset of overt albuminuria (≥200 μg/min). In a 2-year follow-up, only 5.2% of patients receiving 300 mg of irbesartan reached the endpoint, as compared with 14.9% of patients on placebo. The groups had similar blood pressure control, a finding that suggests that ARBs are renoprotective independently of their antihypertensive effect.

The role of ARB in overt diabetic nephropathy was explored in two other trials published in 2001 [64, 75]. In both studies, treatment with ARB resulted in a significant reduction of proteinuria, the incidence of doubling serum creatinine, and the risk of ESRD. In particular, the Irbesartan Diabetic Nephropathy Trial (IDNT) compared the effect of the ARB irbesartan to that of the dihydropyridine calcium channel blocker amlodipine or standard antihypertensive therapy in 1715 hypertensive type 2 diabetic patients with overt nephropathy [64]. The percent of patients who reached the primary composite endpoint of doubling serum creatinine level, ESRD, or death was lower (32.6%) in the irbesartan-treated than amlodipine-treated (41.1%) group or placebo (39%). The beneficial effect remained even after correction for the difference in the blood pressure between treatment group and placebo and was mainly attributed to higher reduction of proteinuria with irbesartan (33%) than with amlodipine (6%) or placebo (10%).

Similar results have been reported by the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, which evaluated the renoprotection afforded by the ARB losartan as compared to placebo (on top of conventional antihypertensive therapy) on 1513 patients with overt type 2 diabetic nephropathy [75]. Losartan reduced the incidence of doubling serum creatinine by 25% and the risk of ESRD by 28% as compared to placebo, at comparable blood pressure control. Again, the renoprotection was related to the antiproteinuric effect of losartan. Post hoc analysis of the RENAAL study also documented that RAS blockade is an appropriate therapy for these patients regardless of the baseline level of renal function [77]. Of note, treatment was also more renoprotective and cost-effective for levels of renal function between 10 and 30 mL/min. Thus, RAS inhibition/blockade should be considered even when the GFR approximates a level approaching renal replacement therapy. This is important given that it is estimated that only 50% of patients in need are currently offered the renoprotective treatment [64, 75], a figure that decreases to 11–12% when GFR is severely impaired [78].

The RENAAL trial also provides the best evidence to date supporting the use of drugs that block RAS in the elderly with diabetic nephropathy (Figure 13.1). Using original data from this study, the investigators found no indication that the effectiveness of losartan treatment differed by age [79]. Furthermore, in adjusted analysis restricted to the 421 patients over 65 years of age, losartan significantly reduced the event rate of ESRD by 50% compared with placebo. Similarly, the rate of doubling serum creatinine in the elderly patients was reduced by 38% with losartan treatment. Analysis of adverse event rates revealed no evidence that age increased the risk of important side effects from losartan therapy. The only adverse effect that was more frequent in patients with losartan was hyperkalemia, but this increased risk was present in all ages. This provides evidence that RAS blockade is equally efficacious and carries no greater risk than in younger patients with type 2 diabetes and overt nephropathy. The evidence from this study is potentially

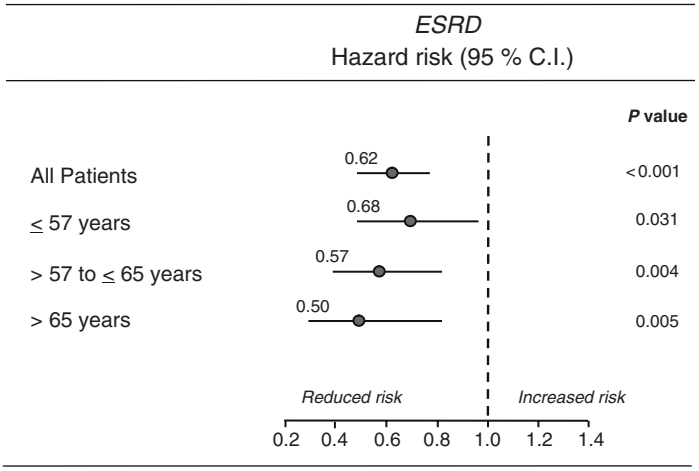

Fig. 13.1 In type 2 diabetes with overt nephropathy, elderly patients had the same level of benefits (lowering risk of ESRD) as younger patients from treatment with the ARB losartan. Post hoc analysis of the RENAAL Trial in 505 patients aged ≤57 years, 587 aged between 57 and 65 years, and 421 aged >65 years (modified from W.C. Winkelmayer et al. [79]). Multivariate Cox model with treatment group (losartan or placebo) as covariates adjusted for baseline proteinuria, serum albumin, serum creatinine and hemoglobin.

important in light of the underuse of therapeutic RAS blockade, especially in elderly patients with diabetes. A recent study in Medicare beneficiaries in two eastern states of the United States found that, as recently as in 2003, only half of therapy-dependent diabetic subjects with hypertension and/or proteinuria received ACE inhibitor or ARB treatment [80]. In that study, age was a powerful and independent predictor of lower use of these medications. In comparison with patients aged between 65 and 74 years, patients aged 75 to 84 years were 8% less likely to receive ACE inhibitor or ARB therapy, and patients over 85 years of age were 30% less likely [80]. Among relatively younger patients enrolled in a large western U.S. evaluation, 54% of patients with albuminuria, 64% of patients with hypertension, and 74% of patients with both albuminuria and hypertension received ACEi or ARB therapy in 2000. Thus, the underuse of these medications may be partly responsible for the high rates of renal replacement therapy in the elderly, incurring substantial opportunity lost for society overall. In a recent economic evaluation, it has been documented that providing free ACEi therapy to all elderly Medicare beneficiaries with diabetes in the United States would be a highly cost-effective strategy because it would extend life and actually result in substantial societal cost savings [81].

Several factors may be responsible for the underuse of RAS blockade in elderly patients with diabetes. Healthcare providers may be hesitant to prescribe ACE inhibitors or ARB to these patients for several reasons. One might be the perception that the risk-benefit ratio of such therapies is unfavorable in the elderly because they are at greater risk of adverse events from these treatments, as discussed above. Whether this is actually the case is unclear for diabetics. Age was not a predictor of hyperkalemia in 119 patients (67% with a history of diabetes and 85% with chronic renal

failure) using RAS inhibitors [82]. Another cause of underprescribing may be some physicians' perception that the reduced life expectation of elderly patients with diabetes and the time delay until the benefits from such therapies become apparent warrant prioritization of other treatment strategies with more immediate benefits. Data from the RENAAL trial clearly demonstrate that this perception is wrong and that even elderly diabetic patients benefit greatly from RAS blockade treatment. However, it is uncertain whether both effectiveness and risks associated with ARB as observed in the elderly participants in the RENAAL study can be generalized to older patients in a more typical care setting. The tight monitoring schedule of a clinical trial may not reflect the surveillance environment present in a typical practice setting, but it can provide important informations about adverse events. Hence, the results from the analyses of adverse event rates provide particularly important information for medical decision making regarding RAS blockade in elderly diabetic patients. Thus, renoprotection via RAS blockade should be a mandatory component of comprehensive diabetes care in elderly patients with nephropathy, under appropriate monitoring.

More Renoprotection with a Multidrug Approach

A significant number of patients treated with ACEi/ARB showed only a partial antiproteinuric response, and this heralded a progressive loss of renal function in most cases [64, 65, 69, 75, 76]. Thus, a multidrug approach may likely be the next improvement. We recently formalized a multifactorial approach to chronic proteinuric nephropathies in an interventional protocol (named remission clinic) as the ultimate treatment for progressive renal disease [83]. Patients with chronic kidney disease and proteinuria greater than 1 g/24 hr are initially treated with a low starting dose of an ACE-I, which is then increased to the maximum dose. Then, if the goals of blood pressure <120/80 mmHg and proteinuria <0.3 g/24 hr are not achieved, an ARB is added at half-maximum dose. Again, the dose is increased stepwise. Throughout this uptitration of ACE-I or ARB, the addition of diuretics is usually needed for optimal blood pressure control or prevention of hyperkalemia. If, after this step**,** target blood pressure and proteinuria are still not achieved, the next antiproteinuric drug to be added is usually a nondihydropiridinic calcium channel blocker. In those with low-density lipoprotein (LDL) cholesterol >100 mg/dL, a statin is added, and in those with diabetes glycemic control is reinforced to achieve hemoglobin A_{1c} (HbA_{1c}) <7.0%. Both interventions (lipid reduction and tight glycemic control) are supposed to contribute to renoprotection [84, 85]. Regarding older patients more closely in this study, subgroup analysis of clinical trial data of statin therapies support lipid control in elderly individuals at high risk for cardiovascular disease [86, 87], but there are limited data specifically for elderly patients with diabetes. Current diabetes treatment guidelines recommend aggressive lipid control in all patients with diabetes but do not make specific recommendations for elderly individuals. Higher glycemic goals may also be appropriate for individuals with severe or frequent hypoglycemia, a common problem for elderly individuals. Citing the lack of clinical trial data in elderly patients, the American Diabetes Association recommends that "less stringent treatment goals" may be appropriate in elderly patients. The *Merck Manual of Geriatrics* [88] recommends a glycemic

goal of HbA_{1c} <7% for all elderly patients but states that "most elderly patients can be treated as aggressively as younger patients, but some require modifications based on their life expectancy, functional status, cognitive abilities, and preferences."

The multidrug approach has been tested in more than 40 patients in our unit, and we showed that is both feasible and apparently effective. However, it is difficult to test in a controlled study, since any further addition of a new or old drug to ACE-I or ARBs in a multiple intervention trial would require a very large number of subjects and would be too costly for any company to support [89]. We probably should make better use of a small but well-designed and rigorously conducted study with a carefully selected marker of renal disease progression.

The multidrug approach, however, requires safety considerations when elderly persons with CKD are the target. Indeed, there has been concern about the potential risk of aggressive blood pressure lowering, particularly in elderly diabetic patients, as may result from uptitration of ACE inhibitors or dual blockade of RAS [92]. Thus, it is generally thought that blood pressure always should be lowered gradually, to avoid complications in elderly hypertensive patients with diabetes. Nevertheless, there is no convincing evidence that reducing diastolic blood pressure below 85 mmHg may actually increase cardiovascular risk [93, 94]. Carotid artery occlusion, however, needs to be considered as a potential contraindication to lower blood pressure in the elderly. Thus, ideally every elderly patient with chronic nephropathy should have a carotid artery ultrasound before being considered suitable for antihypertensive and renoprotective treatment. In patients with carotid occlusion, however, treatment of hypertension should not be too aggressive, because in some of them a relatively slight decrease in blood pressure can induce cerebral ischemia [95]. However, the blood pressure level one should aim for in these elderly patients has never been systematically studied and should be considered as a pointer for future work. Yet the incontrovertible fact remains that—as shown in the PROGRESS trial, a randomized study of a perindopril-based blood pressure-lowering regimen among 6105 individuals (mean age: 64 years) with previous stroke or transient ischemic attack—specifically for patients with blood pressure below 160/90 mmHg, the combined antihypertensive treatment reduced the absolute rate of major vascular events from 4.4 to 3.5% per annum [96]. In other words, one major vascular event can be prevented by treating 22 near-normotensive patients for 5 years with the combination of perindopril and indapamide, or with any other drug or combination of drugs that lowers blood pressure by 12/5 mmHg—regardless of existing antihypertensive treatment [96]. In addition, in elderly patients with CKD, titration of ACE inhibition or combination with ARB may cause hyperkalemia and/or worsening of anemia or orthostatic hypotension with its attendant risk of falls and fracture, which also need close monitoring [97–100].

Lifestyle Changes

In looking for more effective treatments, the role of lifestyle changes should not be overlooked. Of note, smoking cessation per se may reduce disease progression by 30%, which qualifies as the single most important renoprotective measure [90]. The efficacy of multifactorial intervention is supported

by a target-driven, long-term (mean follow-up: 7.8 years), intensified intervention aimed at multiple risk factors in 80 patients with type 2 diabetes and microalbuminuria, which reduced the risk of nephropathy and cardiovascular and microvascular events by about 50% [91].

Renoprotection in Nonproteinuric CKD in the Elderly

Isolated systolic hypertension (ISH) is associated with a greater risk of development of CKD, compared with elevated diastolic blood pressure, and should not be viewed as a normal result of aging. Patients with ISH should be brought to the same target blood goals as are recommended for all adults: <140/90 mmHg for those with uncomplicated hypertension or <130/80 mmHg for those with CKD [101]. The optimal treatment for preserving kidney function in patients with ISH remains uncertain. In SHEP—a trial conducted in individuals aged at least 65 years with ISH—diuretic-based treatment, compared with placebo, prevented the development of CVD events and did not affect the risk of creatinine levels' becoming elevated during follow-up [102]. However, hypokalemia occurred frequently among diuretic-treated participants. In the Systolic Hypertension in Europe (Syst-Eur) study in 4695 patients over the age of 60 years with ISN, treatment with the dihydropyridine calcium channel blocker nitrendipine reduced all fatal and nonfatal cardiac endpoints by 26%. The incidence of mild renal dysfunction decreased by 64% [103]. Nevertheless, to lower blood pressure sufficiently and in a timely manner, combination antihypertensive therapy is recommended as the initial therapy in patients with systolic blood pressure >20 mmHg above their pressure goal. However, caution is advised in initiating therapy with multiple agents in patients who may be at risk for orthostatic hypotension, such as older patients, particularly diabetics with autonomic dysfunction [104].

As with the elderly with proteinuric renal disease, stopping cigarette smoking, reducing excess weight, and incorporating exercise in an overall program of life style modification could be a reasonable complement to drugs for renoprotection but is difficult to substantiate. Smoking cessation, weight reduction, and incorporation of foods viewed as "healthy" are objectives more extolled than attained. Other than limited reports of low-level reductions in smoking or sustained weight loss at 1 year, the advice, though well motivated, is largely hopeful rather than predictive of change.

Nephrosclerosis, benign nephrosclerosis, hypertensive kidney disease, and nephroangiosclerosis are terms that clinicians use to identify renal damage associated with essential hypertension. Nephrosclerosis has actually been seen as a form of intrarenal renovascular disease [105]. There are few studies dealing with treatment for nephrosclerosis. The African American Study of Kidney Disease and Hypertension [106] recruited 1094 African Americans with hypertensive renal disease who were randomly assigned to one of the two mean blood pressure goals (102 and 100mmHg) and to treatment based on a beta-blocker, an ACE inhibitor, or a calcium channel blocker. The outcome was comparable in the two blood pressure groups. Patients receiving the ACE inhibitor-based therapy showed a 22% reduction in risk of the composite endpoint, which included unfavorable renal outcomes and death. A retrospective analysis of 295 Spanish patients (mean age: 58.9 $\pm$ 11.6 years) with nephrosclerosis, moderate renal insufficiency, and no proteinuria at baseline represents an example of the efficacy

of ACE inhibitors to slow the progression of hypertensive renal disease even in the elderly [107]. During a 7-year follow-up, blood pressure values remained significantly more elevated in the ACEi group than in the non-ACEi group, even though patients were taking more drugs. In the ACEi group, 23% of patients were on monotherapy; a calcium channel blocker was added in 46%; a diuretic, in 41% patients; and a β-blocker in 9%. In the non-ACEi group, a calcium channel blocker was administered to 67% of patients, 33% received a β-blocker, and 31% were given a diuretic. Despite less blood pressure control, treatment with an ACEi alone or in combination significantly reduced the incidence of renal events (such as 50% reduction in creatinine clearance or entry in a dialysis program). With the limit of the retrospective character of the study, these findings point clearly in the direction of ACEi for the therapy in patients with hypertensive nephrosclerosis.

Prevention of Diabetic Nephropathy Itself

The first clinical sign of renal dysfunction in patients with diabetes is generally microalbuminuria (a sign of endothelial dysfunction not necessarily confined to the kidney) [108], which develops in 2 to 5% of patients every year [109, 110]. In type 2 diabetes, unlike type 1 diabetes [111], microalbuminuria is seldom reversible [76], but instead progresses to overt

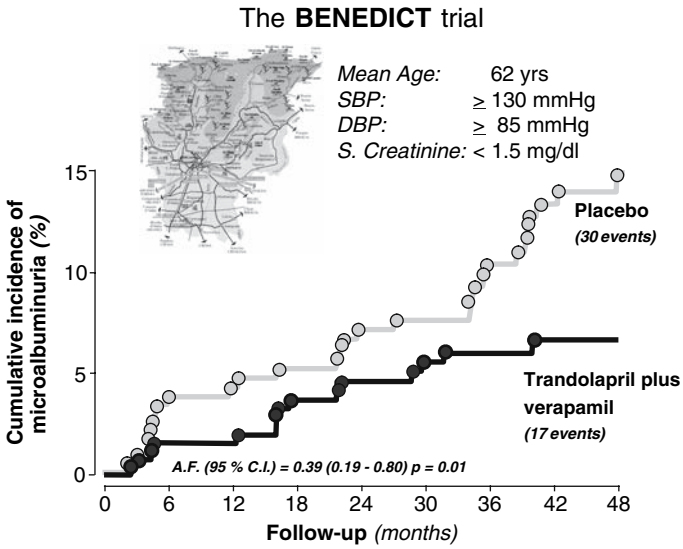

Fig. 13.2 The BErgamo NEphrologic DIabetes Complications Trial (BENEDICT) is a multicenter, double-blind, randomized study designed to assess whether the ACE inhibitor trandolapril and the non-dihydropyridine calcium channel blocker verapamil, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion. The mean age of patients at baseline was 62 years. Here are the Kaplan–Meier curves for the percentages of subjects with microalbuminuria during treatment with trandolapril plus verapamil or placebo. The difference between the two groups adjusted for prespecified baseline covariates was significant ($P = 0.01$) according to the accelerated failure-time model [118].

proteinuria in 20 to 40% of patients [112, 113]. Forty to 50% of patients with type 2 diabetes who have microalbuminuria eventually die of cardiovascular disease [114, 115]. This is three times as high a rate of death from cardiac causes as among patients who have diabetes but have no evidence of renal disease. Thus, preventing or delaying development of microalbuminuria (incipient nephropathy) would be more relevant than retarding progression of incipient/overt nephropathy in diabetic patients. Treatment with the ACE inhibitor enalapril over a period of six years decreased the incidence of microalbuminuria in patients with type 2 diabetes who were normotensive and not obese [116]. Until recently, however, it was unclear whether these medications could prevent microalbuminuria when given to patients with hypertension, type 2 diabetes, and normal urinary albumin excretion. The BErgamo NEphrologic DIabetes Complication Trial (BENEDICT) [117], a multicenter, double-blinded, placebo-controlled randomized study in 1204 subjects, approached this issue by examining the effect of the ACE inhibitor trandolapril alone or in combination with the nondihydropyridine calcium channel blocker verapamil, verapamil alone, and placebo on microalbuminuria [118] (see Figure 13.2). Of note, the mean age of the enrolled diabetic patients was 62 years, which makes it notable to consider these patients as an

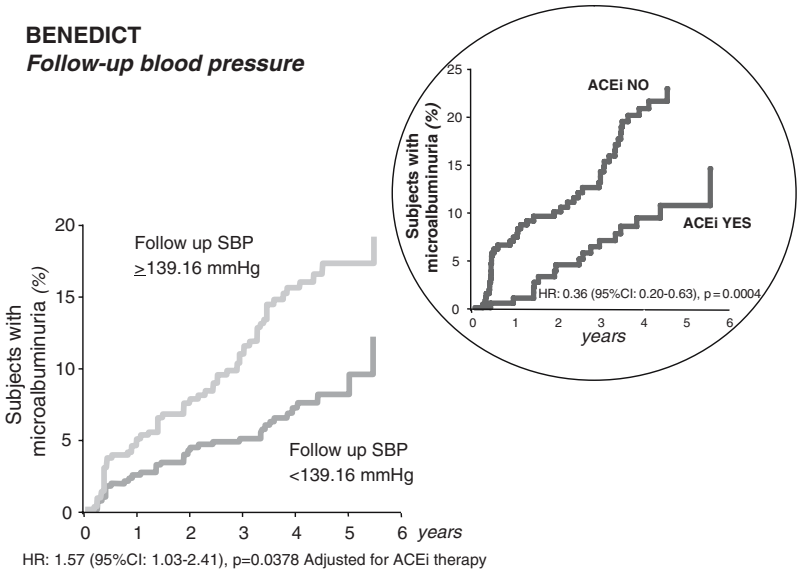

Fig. 13.3 Patients who developed microalbuminuria throughout the study period of the BENEDICT trial according to follow-up systolic blood pressure (SBP). These are patients with type 2 diabetes, arterial hypertension, and normoalbuminuria at baseline, with an average age of 62 years. Effective systolic blood pressure reduction below the median (<139.16 mmHg) has specific and independent protective effects against the development of microalbuminuria. The risk reduction for microalbuminuria that was achieved by ACEi therapy in patients with follow-up SBP above the median (≥139.16 mmHg) was highly significant even after adjustment for baseline covariates and concomitant treatment with non-dihydropyridine calcium channel blockers. Thus, ACE inhibitor therapy had a further protective effect, in particular when SBP was less effectively controlled (inset).

elderly population. The BENEDICT study found that over 4 years of follow-up trandolapril alone or of trandolapril plus verapamil delayed the onset of microalbuminuria in more than 40% of patients as compared to placebo. The effect of verapamil alone was similar to that of placebo. This indicates that the apparent advantage of ACE inhibitors over other antihypertensive agents also includes a protective effect on the kidney against the development of microalbuminuria, at least in type 2 diabetic patients.

Moreover, finding that this effect was significant even after adjustment for baseline and follow-up systolic and diastolic blood pressure provided the endeavor of a specific renoprotective effect of ACE inhibition therapy against the development of microalbuminuria that was independent of the level of blood pressure control achieved. In a post hoc analysis of the BENEDICT trial [119], it was also shown that in patients with type 2 diabetes and arterial hypertension, effective blood pressure reduction has a specific and independent protective effect against the development of microalbuminuria. Nevertheless, ACE inhibition therapy has a further protective effect, in particular when blood pressure is poorly controlled, whereas the nondihydropyridine calcium channel blocker therapy is ineffective at any level of achieved blood pressure (Figure 13.3). The finding that the risk for development of microalbuminuria was not associated with baseline blood pressure provided consistent evidence that the lower incidence of microalbuminuria observed with more effective blood pressure reduction reflected a benefit of treatment and not simply less severe hypertension at study entry (Figure 13.4). Therefore, these results extend, to the very early stages of diabetic renal disease, the previous evidence

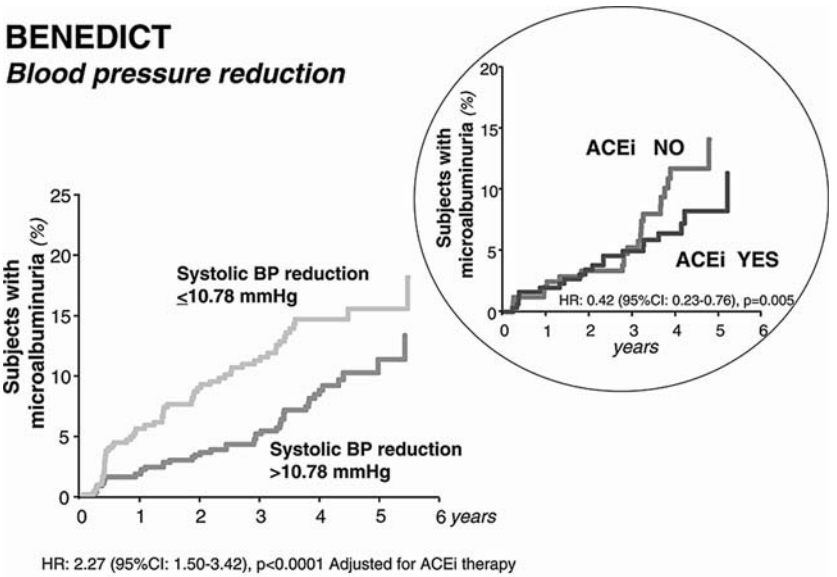

Fig. 13.4 In the BENEDICT study, the extent of SBP reduction had a specific and independent effect against the development of microalbuminuria. ACE inhibitor therapy had a further protective effect, in particular when the SBP was less effectively controlled (inset).

of a renoprotective effect of blood pressure control in people with diabetes and established nephropathy [120–124].

The specific benefit of the ACEi therapy is confirmed by the data from a meta-analysis of 16 trials that included 7603 patients with type 2 diabetes, hypertension, and normoalbuminuria, which showed a 42% reduction in the risk for development of microalbuminuria with ACE inhibitors, whereas the effect of other antihypertensive medications did not differ from those of the placebo [125]. Given a 10% incidence of microalbuminuria in patients with diabetes and hypertension over 2 to 3 years, approximately 25 people would need to be treated to prevent one more case of microalbuminuria [126]. Because microalbuminuria is a strong predictor of kidney failure and cardiovascular morbidity/mortality, the specific protective effect of ACE inhibition therapy against the development of microalbuminuria should be taken into consideration in the treatment guidelines for the practicing physician [127]. Thus, ACE inhibitors should be considered the treatment of choice in hypertensive patients with diabetes.

Conclusion

A relatively large number of the newly diagnosed CKD patients every year are elderly. The increased incidence of CKD among the elderly translates into a similarly increased prevalence. The leading causes of these expanding CKD populations is type 2 diabetes, which represents one of the most current challenges for healthcare providers. There is, however, evidence that preventing nephropathy is more important than retarding progression, and this should be the main goal for nephrologists and diabetologists. Nevertheless, treatment of renal patients so far has been aimed to limit or prevent progression to ESRD.

While we are trying to reduce the number of patients who reach ESRD, the real problem is patients who actually die before even reaching end-stage renal failure. Indeed, in more than 400,000 Medicare patients with diabetes and chronic kidney disease, over a 2-year follow-up, the risk of death (29%) far exceeded that of developing ESRD (6%) [128]. This observation is confirmed by the analysis of the United Kingdom Prospective Diabetes Study (UKPDS 64) showing that among 5,000 type 2 diabetics followed for up to 8 years, death due to cardiovascular disease is far more common than development of ESRD [110]. Thus, for the future, the goal will be not only to concentrate on reducing the number of patients who reach end-stage renal failure, but also to prevent mostly vascular morbidity and mortality in those who are at risk of dying of myocardial infarction or other cardiovascular diseases before they reach end-stage renal failure. Thus, our efforts should now be to find these patients and treat them before they develop cardiac or brain events.

Eventually, the final step will be to prevent diabetes. Recent trials have shown that this is possible in a significant proportion of people by lifestyle changes, or even medication including ACE inhibitors [129, 130]. These data provide hope to the younger members of the million families worldwide in which one elderly member is already affected by type 2 diabetes with renal and cardiovascular disease complications.

References

1. Incidence and prevalence of ESRD. USRDS. United States Renal Data System. *Am. J. Kidney Dis*. 1997; 30:S40–53.
2. Usami, T., Koyama, K., Takeuchi, O., Morozumi, K., Kimura, G. Regional variations in the incidence of end-stage renal failure in Japan. *JAMA* 2000; 284:2622–2624.
3. Disney, A.P. Some trends in chronic renal replacement therapy in Australia and New Zealand. *Nephrol. Dial. Transplant*. 1998; 13:854–859.
4. Report. *Dialysis and Renal Transplantation*, *Canadian Organ Replacement Register*. Ottawa, Ontario: Canadian Institute for Health Information. 2001.
5. Frei, U., Schober-Halstenberg, H.J. Annual Report of the German Renal Registry 1998. QuaSi-Niere Task Group for Quality Assurance in Renal Replacement Therapy. *Nephrol. Dial. Transplant* 1999; 14:1085–1090.
6. Garcia Lopez, F.J., Robles, R., Gentil, M.A. En presentacion del Grupo de Registros de Enfermos Renales de Espana. Comparacion de la incidencia, prevalencia, modalidades de tratamiento y mortalidad en pacientes con tratamiento renal sustitutivo en cinco communidades autonomas espagnolas en el periodo 1991–1996. *Nefrologia* 1999; 19:443–459.
7. U.R.R.R. 2000. *UK Renal Registry*. Bristol, UK.
8. Jungers, P., Choukroun, G., Robino, C., Massy, Z.A., Taupin, P., Labrunie, M., Man, N.K., Landais, P. Epidemiology of end-stage renal disease in the Ile-de-France area: A prospective study in 1998. *Nephrol. Dial. Transplant* 2000; 15:2000–2006.
9. Stengel, B., Billon, S., Van Dijk, P.C., Jager, K.J., Dekker, F.W., Simpson, K., Briggs, J.D. Trends in the incidence of renal replacement therapy for end-stage renal disease in Europe, 1990–1999. *Nephrol. Dial. Transplant* 2003; 18: 1824–1833.
10. McCredie, M. Geographic, ethnic, age-related and temporal variation in the incidence of end-stage renal disease in Europe, Canada and the Asia-Pacific region, 1998–2002. *Nephrol. Dial. Transplant* 2006; 21:2178–2183.
11. Coresh, J., Astor, B.C., Greene, T., Eknoyan, G., Levey, A.S. Prevalence of chronic kidney disease and decreased kidney function in the adult U.S. population: Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis*. 2003; 41:1–12.
12. Hannedouche, T., Landais, P., Goldfarb, B., el Esper, N., Fournier, A., Godin, M., Durand, D., Chanard, J., Mignon, F., Suo, J.M., et al. Randomised controlled trial of enalapril and beta blockers in non-diabetic chronic renal failure. *BMJ* 1994; 309:833–837.
13. Bigazzi, R., Bianchi, S., Baldari, D., Campese, V.M. Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J. Hypertens*. 1998; 16:1325–1333.
14. Magnason, R.L., Indridason, O.S., Sigvaldason, H., Sigfusson, N., Palsson, R. Prevalence and progression of CRF in Iceland: a population-based study. *Am. J. Kidney Dis*. 2002; 40:955–963.
15. Jungers, P., Chauveau, P., Descamps-Latscha, B., Labrunie, M., Giraud, E., Man, N.K., Grunfeld, J.P., Jacobs, C. Age- and gender-related incidence of chronic renal failure in a French urban area: a prospective epidemiologic study. *Nephrol. Dial. Transplant* 1996; 11:1542–1546.
16. John, R., Webb, M., Young, A., Stevens, P.E. Unreferred chronic kidney disease: A longitudinal study. *Am. J. Kidney Dis*. 2004; 43:825–835.
17. Simal, F., Martin Escudero, J.C., Bellido, J., Arzua, D., Mena, F.J., Gonzalez Melgosa, I., Alvarez Hurtado, A.A., Tabuyo, M.B., Molina, A. [Prevalence of mild to moderate chronic kidney disease in the general population of Spain. Hortega study.] [in Spanish] *Nefrologia* 2004; 24:329–332, 334, 336–327.

18. National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am. J. Kidney Dis*. 2002; 39(Suppl 1):S1–S266.
19. Glynn, R.J., Chae, C.U., Guralnik, J.M., Taylor, J.O., Hennekens, C.H. Pulse pressure and mortality in older people. *Arch. Intern. Med*. 2000; 160:2765–2772.
20. Caskey, F.J., Schober-Halstenberg, H.J., Roderick, P.J., Edenharter, G., Ansell, D., Frei, U., Feest, T.G. Exploring the differences in epidemiology of treated ESRD between Germany and England and Wales. *Am. J. Kidney Dis*. 2006; 47:445–454.
21. Sarnak, M.J., Levey, A.S., Schoolwerth, A.C., Coresh, J., Culleton, B., Hamm, L.L., McCullough, P.A., Kasiske, B.L., Kelepouris, E., Klag, M.J., et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; 108:2154–2169.
22. Hansberry, M.R., Whittier, W.L., Krause, M.W. The elderly patient with chronic kidney disease. *Adv. Chronic Kidney Dis*. 2005; 12:71–77.
23. Harris, M.I., Flegal, K.M., Cowie, C.C., Eberhardt, M.S., Goldstein, D.E., Little, R.R., Wiedmeyer, H.M., Byrd-Holt, D.D. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 1998; 21:518–524.
24. Kamper, A.L., Strandgaard, S., Leyssac, P.P. Late outcome of a controlled trial of enalapril treatment in progressive chronic renal failure. Hard end-points and influence of proteinuria. *Nephrol. Dial. Transplant* 1995; 10:1182–1188.
25. Buemi, M., Nostro, L., Aloisi, C., Cosentini, V., Criseo, M., Frisina, N. Kidney aging: From phenotype to genetics. *Rejuvenation Res*. 2005; 8:101–109.
26. Burstein, D.M., Korbet, S.M., Schwartz, M.M. Membranous glomerulonephritis and malignancy. *Am. J. Kidney Dis*. 1993; 22:5–10.
27. Haas, M., Spargo, B.H., Wit, E.J., Meehan, S.M. Etiologies and outcome of acute renal insufficiency in older adults: A renal biopsy study of 259 cases. *Am. J. Kidney Dis*. 2000; 35:433–447.
28. Modesto-Segonds, A., Ah-Soune, M.F., Durand, D., Suc, J.M. Renal biopsy in the elderly. *Am. J. Nephrol*. 1993; 13:27–34.
29. Preston, R.A., Stemmer, C.L., Materson, B.J., Perez-Stable, E., Pardo, V. Renal biopsy in patients 65 years of age or older. An analysis of the results of 334 biopsies. *J. Am. Geriatr. Soc*. 1990; 38:669–674.
30. Davison, A.M. Renal disease in the elderly. *Nephron* 1998; 80:6–16.
31. Ruggenenti, P., Remuzzi, A., Ondei, P., Fasolini, G., Antiga, L., Ene-Iordache, B., Remuzzi, G., Epstein, F.H. Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int*. 2005; 68:206–216.
32. Johnson, A.M., Gabow, P.A. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. *J. Am. Soc. Nephrol*. 1997; 8:1560–1567.
33. King, B.F., Reed, J.E., Bergstralh, E.J., Sheedy, P.F., II, Torres, V.E. Quantification and longitudinal trends of kidney, renal cyst, and renal parenchyma volumes in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol*. 2000; 11:1505–1511.
34. Klag, M.J., Whelton, P.K., Randall, B.L., Neaton, J.D., Brancati, F.L., Ford, C.E., Shulman, N.B., Stamler, J. Blood pressure and end-stage renal disease in men. *N. Engl. J. Med*. 1996; 334:13–18.
35. Perneger, T.V., Whelton, P.K., Klag, M.J. History of hypertension in patients treated for end-stage renal disease. *J. Hypertens*. 1997; 15:451–456.

36. Psaty, B.M., Furberg, C.D., Kuller, L.H., Cushman, M., Savage, P.J., Levine, D., O'Leary, D.H., Bryan, R.N., Anderson, M., Lumley, T. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: The cardiovascular health study. *Arch. Intern. Med*. 2001; 161: 1183–1192.
37. Benetos, A., Safar, M., Rudnichi, A., Smulyan, H., Richard, J.L., Ducimetieere, P., Guize, L. Pulse pressure: A predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 1997; 30:1410–1415.
38. Franklin, S.S., Khan, S.A., Wong, N.D., Larson, M.G., Levy, D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. *Circulation* 1999; 100:354–360.
39. Chae, C.U., Pfeffer, M.A., Glynn, R.J., Mitchell, G.F., Taylor, J.O., Hennekens, C.H. Increased pulse pressure and risk of heart failure in the elderly. *JAMA* 1999; 281:634–639.
40. Sesso, H.D., Stampfer, M.J., Rosner, B., Hennekens, C.H., Gaziano, J.M., Manson, J.E., Glynn, R.J. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure as predictors of cardiovascular disease risk in men. *Hypertension* 2000; 36:801–807.
41. Blacher, J., Staessen, J.A., Girerd, X., Gasowski, J., Thijs, L., Liu, L., Wang, J.G., Fagard, R.H., Safar, M.E. Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch. Intern. Med*. 2000; 160: 1085–1089.
42. Vaccarino, V., Holford, T.R., Krumholz, H.M. Pulse pressure and risk for myocardial infarction and heart failure in the elderly. *J. Am. Coll. Cardiol*. 2000; 36:130–138.
43. Rosen, A.B., Karter, A.J., Liu, J.Y., Selby, J.V., Schneider, E.C. Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in high-risk clinical and ethnic groups with diabetes. *J. Gen. Intern. Med*. 2004; 19:669–675.
44. Young, J.H., Klag, M.J., Muntner, P., Whyte, J.L., Pahor, M., Coresh, J. Blood pressure and decline in kidney function: Findings from the Systolic Hypertension in the Elderly Program (SHEP). *J. Am. Soc. Nephrol*. 2002; 13:2776–2782.
45. Hyman, D.J., Pavlik, V.N. Characteristics of patients with uncontrolled hypertension in the United States. *N. Engl. J. Med*. 2001; 345:479–486.
46. Hansen, K.J., Edwards, M.S., Craven, T.E., Cherr, G.S., Jackson, S.A., Appel, R.G., Burke, G.L., Dean, R.H. Prevalence of renovascular disease in the elderly: A population-based study. *J. Vasc. Surg*. 2002; 36:443–451.
47. Wild, S., Roglic, G., Green, A., Sicree, R., King, H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27:1047–1053.
48. U.S.R.D. System *USRDS 2003 Annual Data Report: Atlas of End Stage Renal Disease in the United States*. Bethesda, MD: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2003.
49. Mokdad, A.H., Ford, E.S., Bowman, B.A., Nelson, D.E., Engelgau, M.M., Vinicor, F., Marks, J.S. Diabetes trends in the U.S.: 1990–1998. *Diabetes Care* 2000; 23:1278–1283.
50. Lee, G. End-stage renal disease in the Asian-Pacific region. *Semin. Nephrol*. 2003; 23:107–114.
51. Van Dijk, P.C., Jager, K.J., Stengel, B., Gronhagen-Riska, C., Feest, T.G., Briggs, J.D. Renal replacement therapy for diabetic end-stage renal disease: Data from 10 registries in Europe (1991–2000). *Kidney Int*. 2005; 67:1489–1499.
52. Anderson, S., Rennke, H.G., Brenner, B.M. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J. Clin. Invest*. 1986; 77:1993–2000.

53. Aros, C., Remuzzi, G. The renin-angiotensin system in progression, remission and regression of chronic nephropathies. *J. Hypertens. Suppl*. 2002; 20:S45–53.
54. Shake, J.G., Brandt, R.C., Daniels, B.S. Angiotensin II induces actine in the polymerization within the glomerular filtration barrier: Possible role in the local regulation of ultrafiltration. *J. Am. Soc. Nephrol*. 1992; 3:568A.
55. Wolf, G., Kalluri, R., Ziyadeh, F.N., Neilson, E.G., Stahl, R.A. Angiotensin II induces alpha3(IV) collagen expression in cultured murine proximal tubular cells. *Proc. Assoc. Am. Physicians* 1999; 111:357–364.
56. Zoja, C., Benigni, A., Remuzzi, G. Cellular responses to protein overload: Key event in renal disease progression. *Curr. Opin. Nephrol. Hypertens*. 2004; 13: 31–37.
57. Eddy, A. Role of cellular infiltrates in response to proteinuria. *Am. J. Kidney Dis*. 2001; 37:S25–29.
58. Agapitov, A.V., Haynes, W.G. Role of endothelin in cardiovascular disease. *J. Renin Angiotensin Aldosterone Syst*. 2002; 3:1–15.
59. Komatsu, K., Frohlich, E.D., Ono, H., Ono, Y., Numabe, A., Willis, G.W. Glomerular dynamics and morphology of aged spontaneously hypertensive rats. Effects of angiotensin-converting enzyme inhibition. *Hypertension* 2005; 25: 207–213.
60. Frohlich, E.D. Arthus C. Corcoran Memorial Lecture. Influence of nitric oxide and angiotensin II on renal involvement in hypertension. *Hypertension* 1997; 29:188–193.
61. Harris, P.C., Torres, V.E. Understanding pathogenic mechanisms in polycystic kidney disease provides clues for therapy. *Curr. Opin. Nephrol. Hypertens*. 2006; 15:456–463.
62. Peterson, J.C., Adler, S., Burkart, J.M., Greene, T., Hebert, L.A., Hunsicker, L.G., King, A.J., Klahr, S., Massry, S.G., Seifter, J.L. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann. Intern. Med*. 1995; 123:754–762.
63. Wapstra, F.H., Navis, G., de Jong, P.E., de Zeeuw, D. Prognostic value of the short-term antiproteinuric response to ACE inhibition for prediction of GFR decline in patients with nondiabetic renal disease. *Exp. Nephrol*. 1996; 4 (Suppl 1):47–52.
64. Lewis, E.J., Hunsicker, L.G., Clarke, W.R., Berl, T., Pohl, M.A., Lewis, J.B., Ritz, E., Atkins, R.C., Rohde, R., Raz, I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N. Engl. J. Med*. 2001; 345:851–860.
65. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997; 349:1857–1863.
66. Ruggenenti, P., Perna, A., Mosconi, L., Pisoni, R., Remuzzi, G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). *Kidney Int*. 1998; 53:1209–1216.
67. Jafar, T.H., Schmidt, C.H., Stark, P.C., Landa, M., Maschio, G., Marcantoni, C., De Jong, P.E., De Zeeuw, D., Shahinfar, S., Levey, A.S. The influence of urine protein excretion on benefit of angiotensin-converting enzyme inhibitors in patients with non-diabetic renal disease. *J. Am. Soc. Nephrol*. 2000; 11:63A.
68. Bakris, G.L., Weir, M.R. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? *Arch. Intern. Med*. 2000; 160:685–693.
69. Ruggenenti, P., Perna, A., Remuzzi, G. ACE inhibitors to prevent end-stage renal disease: When to start and why possibly never to stop: A post hoc analysis of

the REIN trial results. Ramipril Efficacy in Nephropathy. *J. Am. Soc. Nephrol*. 2001; 12:2832–2837.
70. Acone, D., Cante, D., Cillo, F., Giordano, G., Giordano, C. Blood pressure and progression of renal failure in the elderly. *Kidney Int. Suppl*. 1996; 55:S75–77.
71. Pitt, B., Segal, R., Martinez, F.A., Meurers, G., Cowley, A.J., Thomas, I., Deedwania, P.C., Ney, D.E., Snavely, D.B., Chang, P.I. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; 349:747–752.
72. Ruggenenti, P., Perna, A., Gherardi, G., Gaspari, F., Benini, R., Remuzzi, G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. *Lancet* 1998; 352:1252–1256.
73. Maschio, G., Alberti, D., Janin, G., Locatelli, F., Mann, J.F., Motolese, M., Ponticelli, C., Ritz, E., Zucchelli, P. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N. Engl. J. Med*. 1996; 334:939–945.
74. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am. J. Kidney Dis*. 2004; 43:S1–290.
75. Brenner, B.M., Cooper, M.E., de Zeeuw, D., Keane, W.F., Mitch, W.E., Parving, H.H., Remuzzi, G., Snapinn, S.M., Zhang, Z., Shahinfar, S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N. Engl. J. Med*. 2001; 345:861–869.
76. Parving, H.H., Lehnert, H., Brochner-Mortensen, J., Gomis, R., Andersen, S., Arner, P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N. Engl. J. Med*. 2001; 345:870–878.
77. Remuzzi, G., Ruggenenti, P., Perna, A., Dimitrov, B.D., de Zeeuw, D., Hille, D.A., Shahinfar, S., Carides, G.W., Brenner, B.M. Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: A post hoc analysis of the RENAAL trial results. *J. Am. Soc. Nephrol*. 2004; 15:3117–3125.
78. Brenner, B.M., Cooper, M.E., de Zeeuw, D., Grunfeld, J.P., Keane, W.F., Kurokawa, K., McGill, J.B., Mitch, W.E., Parving, H.H., Remuzzi, G., et al. The losartan renal protection study—rationale, study design and baseline characteristics of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan). *J. Renin Angiotensin Aldosterone Syst*. 2000; 1:328–335.
79. Winkelmayer, W.C., Zhang, Z., Shahinfar, S., Cooper, M.E., Avorn, J., Brenner, B.M. Efficacy and safety of angiotensin II receptor blockade in elderly patients with diabetes. *Diabetes Care* 2006; 29:2210–2217.
80. Winkelmayer, W.C., Fischer, M.A., Schneeweiss, S., Wang, P.S., Levin, R., Avorn, J. Underuse of ACE inhibitors and angiotensin II receptor blockers in elderly patients with diabetes. *Am. J. Kidney Dis*. 2005; 46:1080–1087.
81. Rosen, A.B., Hamel, M.B., Weinstein, M.C., Cutler, D.M., Fendrick, A.M., Vijan, S. Cost-effectiveness of full Medicare coverage of angiotensin-converting enzyme inhibitors for beneficiaries with diabetes. *Ann. Intern. Med*. 2005; 143:89–99.
82. Ahuja, T.S., Freeman, D., Jr., Mahnken, J.D., Agraharkar, M., Siddiqui, M., Memon, A. Predictors of the development of hyperkalemia in patients using angiotensin-converting enzyme inhibitors. *Am. J. Nephrol*. 2000; 20:268–272.
83. Ruggenenti, P., Schieppati, A., Remuzzi, G. Progression, remission, regression of chronic renal diseases. *Lancet* 2001; 357:1601–1608.
84. Parving, H.H. Diabetic nephropathy: Prevention and treatment. *Kidney Int*. 2001; 60:2041–2055.
85. Fried, L.F., Orchard, T.J., Kasiske, B.L. Effect of lipid reduction on the progression of renal disease: A meta-analysis. *Kidney Int*. 2001; 59:260–269.

86. Lewis, S.J., Moye, L.A., Sacks, F.M., Johnstone, D.E., Timmis, G., Mitchell, J., Limacher, M., Kell, S., Glasser, S.P., Grant, J., et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann. Intern. Med*. 1998; 129:681–689.
87. Sacks, F.M., Tonkin, A.M., Shepherd, J., Braunwald, E., Cobbe, S., Hawkins, C.M., Keech, A., Packard, C., Simes, J., Byington, R., et al. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: The Prospective Pravastatin Pooling Project. *Circulation* 2000; 102:1893–1900.
88. www.merck.com/mrkshared/mmg/home.jsp. *The Merck Manual of Geriatrics*. New York, Wiley: Beer MH. 2006.
89. Hostetter, T.H. The next treatments of chronic kidney disease: If we find them, can we test them? *J. Am. Soc. Nephrol*. 2002; 13:3024–3026.
90. Orth, S.R., Stockmann, A., Conradt, C., Ritz, E., Ferro, M., Kreusser, W., Piccoli, G., Rambausek, M., Roccatello, D., Schafer, K., et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney Int*. 1998; 54:926–931.
91. Gaede, P., Vedel, P., Larsen, N., Jensen, G.V., Parving, H.H., Pedersen, O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N. Engl. J. Med*. 2003; 348:383–393.
92. Wolf, G., Ziyadeh, F.N. Renal tubular hypertrophy induced by angiotensin II. *Semin. Nephrol*. 1997; 17:448–454.
93. Ritz, E., Orth, S.R. Nephropathy in patients with type 2 diabetes mellitus. *N. Engl. J. Med*. 1999; 341:1127–1133.
94. Hansson, L., Zanchetti, A., Carruthers, S.G., Dahlof, B., Elmfeldt, D., Julius, S., Menard, J., Rahn, K.H., Wedel, H., Westerling, S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; 351:1755–1762.
95. Klijn, C.J., Kappelle, L.J., Tulleken, C.A., van Gijn, J. Symptomatic carotid artery occlusion. A reappraisal of hemodynamic factors. *Stroke* 1997; 28:2084–2093.
96. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358:1033–1041.
97. Matsumura, M., Nomura, H., Koni, I., Mabuchi, H. Angiotensin-converting enzyme inhibitors are associated with the need for increased recombinant human erythropoietin maintenance doses in hemodialysis patients. Risks of Cardiac Disease in Dialysis Patients Study Group. *Nephron* 1997; 77:164–168.
98. Schmidt, A., Gruber, U., Bohmig, G., Koller, E., Mayer, G. The effect of ACE inhibitor and angiotensin II receptor antagonist therapy on serum uric acid levels and potassium homeostasis in hypertensive renal transplant recipients treated with CsA. *Nephrol. Dial. Transplant* 2001; 16:1034–1037.
99. Ruilope, L.M., Aldigier, J.C., Ponticelli, C., Oddou-Stock, P., Botteri, F., Mann, J.F. Safety of the combination of valsartan and benazepril in patients with chronic renal disease. European Group for the Investigation of Valsartan in Chronic Renal Disease. *J. Hypertens*. 2000; 18:89–95.
100. Nakao, N., Yoshimura, A., Morita, H., Takada, M., Kayano, T., Ideura, T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): A randomised controlled trial. *Lancet* 2003; 361:117–124.
101. Jamerson, K.A. Preventing chronic kidney disease in special populations. *Am. J. Hypertens*. 2005; 18:106S–111S.
102. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the

Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991; 265:3255–3264.
103. Staessen, J.A., Fagard, R., Thijs, L., Celis, H., Arabidze, G.G., Birkenhager, W.H., Bulpitt, C.J., de Leeuw, P.W., Dollery, C.T., Fletcher, A.E., et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; 350:757–764.
104. Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jr., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003; 289:2560–2572.
105. Marin, R., Gorostidi, M., Fernandez-Vega, F., Alvarez-Navascues, R. Systemic and glomerular hypertension and progression of chronic renal disease: The dilemma of nephrosclerosis. *Kidney Int Suppl.* 2005; pp. S52–56.
106. Wright, J.T., Jr., Bakris, G., Greene, T., Agodoa, L.Y., Appel, L.J., Charleston, J., Cheek, D., Douglas-Baltimore, J.G., Gassman, J., Glassock, R., et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 2002; 288: 2421–2431.
107. Segura, J., Campo, C., Rodicio, J.L., Ruilope, L.M. ACE inhibitors and appearance of renal events in hypertensive nephrosclerosis. *Hypertension* 2001; 38:645–649.
108. Ritz, E. Albuminuria and vascular damage—The vicious twins. *N. Engl. J. Med*. 2001; 348:2349–2352.
109. Gall, M.A., Hougaard, P., Borch-Johnsen, K., Parving, H.H. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: Prospective, observational study. *BMJ* 1997; 314:783–788.
110. Adler, A.I., Stevens, R.J., Manley, S.E., Bilous, R.W., Cull, C.A., Holman, R.R. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003; 63: 225–232.
111. Perkins, B.A., Ficociello, L.H., Silva, K.H., Finkelstein, D.M., Warram, J.H., Krolewski, A.S. Regression of microalbuminuria in type 1 diabetes. *N. Engl. J. Med*. 2003; 348:2285–2293.
112. Mogensen, C.E. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N. Engl. J. Med*. 1984; 310:356–360.
113. Nelson, R.G., Knowler, W.C., Pettitt, D.J., Saad, M.F., Charles, M.A., Bennett, P.H. Assessment of risk of overt nephropathy in diabetic patients from albumin excretion in untimed urine specimens. *Arch. Intern. Med*. 1991; 151:1761–1765.
114. Eurich, D.T., Majumdar, S.R., Tsuyuki, R.T., Johnson, J.A. Reduced mortality associated with the use of ACE inhibitors in patients with type 2 diabetes. *Diabetes Care* 2004; 27:1330–1334.
115. Parving, H.H., Mauer, M., Ritz, E. *Diabetic Nephropaty*. Philadelphia: Saunders. 2004; pp. 1777–1818.
116. Ravid, M., Brosh, D., Levi, Z., Bar-Dayan, Y., Ravid, D., Rachmani, R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann. Intern. Med*. 1998; 128:982–988.
117. The BErgamo NEphrologic DIabetes Complications Trial (BENEDICT): Design and baseline characteristics. *Cont. Clin. Trials* 2003; 24:442–461.

118. Ruggenenti, P., Fassi, A., Ilieva, A.P., Bruno, S., Iliev, I.P., Brusegan, V., Rubis, N., Gherardi, G., Arnoldi, F., Ganeva, M., et al. Preventing microalbuminuria in type 2 diabetes. *N. Engl. J. Med*. 2004; 351:1941–1951.
119. Ruggenenti, P., Perna, A., Ganeva, M., Ene-Iordache, B., Remuzzi, G. Impact of blood pressure control and angiotensin-converting enzyme inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: A post hoc analysis of the BENEDICT trial. *J. Am. Soc. Nephrol*. 2006; 17:3472–3481.
120. Bakris, G.L., Weir, M.R., Shanifar, S., Zhang, Z., Douglas, J., van Dijk, D.J., Brenner, B.M. Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAAL study. *Arch. Intern. Med*. 2003; 163:1555–1565.
121. Pohl, M.A., Blumenthal, S., Cordonnier, D.J., De Alvaro, F., Deferrari, G., Eisner, G., Esmatjes, E., Gilbert, R.E., Hunsicker, L.G., de Faria, J.B., et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: Clinical implications and limitations. *J. Am. Soc. Nephrol*. 2005; 16:3027–3037.
122. Remuzzi, G., Macia, M., Ruggenenti, P. Prevention and treatment of diabetic renal disease in type 2 diabetes: The BENEDICT study. *J. Am. Soc. Nephrol*. 2006; 17:S90–97.
123. Mogensen, C.E. Progression of nephropathy in long-term diabetics with proteinuria and effect of initial anti-hypertensive treatment. *Scand. J. Clin. Lab. Invest*. 1976; 36:383–388.
124. Dillon, J.J. The quantitative relationship between treated blood pressure and progression of diabetic renal disease. *Am. J. Kidney Dis*. 1993; 22:798–802.
125. Strippoli, G.F., Craig, M., Schena, F.P., Craig, J.C. Antihypertensive agents for primary prevention of diabetic nephropathy. *J. Am. Soc. Nephrol*. 2005; 16: 3081–3091.
126. Arauz-Pacheco, C., Parrott, M.A., Raskin, P. Hypertension management in adults with diabetes. *Diabetes Care* 2005; 27 (Suppl 1):S65–67.
127. Ruggenenti, P., Remuzzi, G. Time to abandon microalbuminuria? *Kidney Int*. 2006; 70:1214–1222.
128. Collins, A.J. The hemoglobin link to adverse outcomes. *Adv. Stud. Med*. 2003; 3:S14–S17.
129. Knowler, W.C., Barrett-Connor, E., Fowler, S.E., Hamman, R.F., Lachin, J.M., Walker, E.A., Nathan, D.M. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med*. 2002; 346:393–403.
130. Tuomilehto, J., Lindstrom, J., Eriksson, J.G., Valle, T.T., Hamalainen, H., Ilanne-Parikka, P., Keinanen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med*. 2001; 344:1343–1350.

14

Obstructive Uropathy and Benign Prostatic Hyperplasia

Gerasimos Alivizatos and Andreas Skolarikos

Introduction

Benign prostatic hyperplasia (BPH) remains a common cause for which men visit their family doctor. It is associated with bothersome lower urinary tract symptoms that affect quality of life by interfering with normal daily activities and sleep patterns. These symptoms require careful evaluation to determine their cause. The use of medical treatment allows many men to be treated conservatively within their community. Persistent symptoms or the development of complications such as retention or infection requires referral to an Urologist. Before invasive treatment is contemplated, these men need careful assessment so that they can be properly counseled about the likely benefit and risks of surgery. In this chapter, we review the epidemiology, etiology, pathophysiology, and natural history of BPH. We also present updated data about the diagnosis and treatment of this common condition.

Obstruction of the lower urinary tract capable of causing lower urinary tract symptoms (LUTS) in the elderly may be secondary to processes of various origins. Prostate cancer, neurological diseases, prior interventions in the lower tract or history of pelvic surgery, trauma, sexually transmitted diseases, and the use of drugs that have the potential to affect the bladder or the bladder outlet function are all potential causes of LUTS in the elderly. However, benign prostatic hyperplasia is one of the most common diseases of the aging male, affecting more than 50% of men over 60 years old. It is associated with bothersome lower urinary tract symptoms that affect quality of life by interfering with normal daily activities and sleep patterns. BPH is a frequent cause of surgical treatment in men, which is usually carried out for intractable symptoms or serious complications.

The Epidemiology of LUTS and BPH

LUTS are not a disease, but a symptom-complex characterized by bothersome voiding, which may be caused by BPH. Other important causes include idiopathic detrusor overactivity, age-related smooth muscle dysfunction, and

neurological disorders such as stroke, Parkinson's disease, dementia, and diabetes [1]. LUTS are categorized into voiding and storage symptoms (Table 14.1) [2–4].

LUTS do not usually occur in men under 50 years old [5]. The prevalence increases from 3.5% for men aged 45–49 years to 30% for men aged 85 years [6]. Among men aged over 50 years, one-third will develop LUTS and one-fourth will require surgical intervention [7]. Prostatic enlargement and BPH also become more common with increasing age. By the third decade, the prostate weighs 20 g (±6), and remains so unless BPH develops [8].By 40 years, BPH is present in 8% of men; this figure increases to 60% in men in their 60s and to 90% in men aged over 80 years [8].

About 25% of men in the community have moderate to severe LUTS, which significantly impact the quality of life of the individual [9] and his partner [10], although the precise figure depends on the criteria used [11]. Some LUTS, such as urinary incontinence, may have a much more significant impact on quality of life than others. Furthermore, the amount of irritation may differ greatly among individuals with the same degree of symptom frequency and severity due to individual and cultural variation in the degree to which symptoms are tolerated [12]. A high proportion of elderly people simply accept symptoms [13]. Erectile dysfunction [14] and painful ejaculation [15] are highly prevalent in LUTS patients, further affecting their quality of life.

Table 14.1 Lower Urinary Tract Symptoms.

Voiding Symptoms
Hesitancy: sensation of delay in onset of micturition, high reflects the time required by the detrusor muscle to overcome outlet resistance. This symptom can also be produced by weak detrusor contraction. Symptoms of **poor urinary flow** and **straining** to void develop insidiously, so that the patient may not notice the decreasing flow. A flow rate <10 mL/sec is suggestive of outflow obstruction, but can also be caused by a weak detrusor. The sensation of **incomplete bladder emptying** is a reflection that the bladder is unable to empty itself completely, causing residual urine to develop. The symptoms of terminal or post-micturition **dribbling** are associated with age-related weakness in the bulbospongiosus muscle, which aids urethral emptying. A **prolonged voiding time** is found in outlet obstruction because the reduced flow rate results in *an* increase time taken to void.
Storage Symptoms
Normal daytime frequency is *<7* per day depending on intake; **urinary frequency** is defined as a "perception of voiding too frequently during the day." It may be caused by a large residual volume (and the resultant decreased functional bladder capacity), or a small-capacity irritable bladder, which may be associated with outlet obstruction or idiopathic detrusor overactivity. **Nocturia** is defined having to wake at night to void and can significantly impair the quality of life of the patient and his partner. Nocturia is caused by nocturnal polyuria rather than low bladder volumes in approximately half of BPH patients. **Urgency** is a sudden compelling desire to void, which is difficult to defer. It tends to be found in men who also have frequency and nocturia and can be caused by BPH or by idiopathic detrusor overactivity. **Urge incontinence** is defined as involuntary leakage of urine accompanied by urgency. This is caused by detrusor overactivity, which may be associated with outlet obstruction or be "idiopathic."

Etiology and Pathophysiology of BPH

BPH has a multifactor etiology involving hormones, growth factors, and stromal epithelial interactions. Aging and testicular androgens are absolute requirements. Disruption of the normal balances between androgenic and growth factor signaling is a critical factor to development of BPH [5, 16]. Central to this is an apparent balance between factors such as TGF β1 that induce extracellular matrix production and suppress collagen breakdown and cell proliferation and factors such as FGF2 and IGF I/II that are mitogenic in the stromal compartment [17, 18]. Genomics and proteomics studies will enlighten changes in gene and protein expression in benign compared with malignant glands, which, in the long term, will provide an explanation of and novel treatment approaches to this common disease [19].

Functional studies are also providing new insights into the causes of bladder dysfunction. By signaling to smooth muscle cells in response to stretch of the urothelium through small molecules such as ATP and nitric oxide, one can exert marked effects on smooth muscle contractility. Chronic stretch of smooth muscle caused by prolonged impaired bladder emptying can result in apoptosis and fibrosis within the smooth muscle compartment, leading to weak detrusor contraction. Despite this weak contractile ability, such local changes may cause the smooth muscle to become abnormally sensitive, leading to detrusor overactivity [20].

The Natural History of BPH and LUTS

Several community and clinical studies have demonstrated the progressive nature of BPH [21]. Different surrogate endpoints of BPH progression such as symptom score, peak urinary flow rate, prostate volume, and the occurrence of acute urinary retention (AUR) have been described [12, 21]. The Olmsted county study [12] has demonstrated that men with moderate to severe LUTS, impaired flow rates, or an enlarged prostate are more likely to eventually require prostatectomy (a fourfold increase) and develop urinary retention than men of a similar age without these features [22]. Higher baseline prostate volumes and serum prostate-specific antigen (PSA) are the two most common predictors of clinical progression and are helpful to the clinician for identifying high-risk patients [12, 21, 22].

Further data are available from pharmacological studies. In short, these have shown that compared with placebo, α-adrenergic and 5-α reductase inhibitors improve symptoms and flow rates. Also compared with placebo, 5-α reductase inhibitors reduce the rate of retention and surgical intervention, and long-term alpha-adrenergic blockers may also decrease surgical intervention rates [23,24].Other studies have shown that α-blockers have a favorable effect on AUR, both in preventing it [24, 25] and also in increasing the success rates of trial without catheter and successful voiding in men presenting with AUR [25].

However, the difficulty with advocating widespread use of these agents is the poor cost-effectiveness, the number of side effects, and the fact that the actual number of events prevented is rather small [26].

Apart from the implications to the lower urinary tract, BPH is related to deterioration of the upper urinary tract function [27]. Of men presenting to

a urologist for BPH treatment, an average of 13.6% (range: 0.3% to 30%) have renal failure, implicating that renal failure in patients with advanced BPH does not simply reflect older age [28]. The role of symptoms, prostatic enlargement, and bladder outlet obstruction as risk factors for chronic renal failure in patients with BPH is still controversial. Most of the studies indicate no correlation between these parameters and the deterioration of the renal function [27]. Chronic urinary retention is the dominant mechanism by which BPH can cause chronic renal failure [27]. Progressive upper tract dilatation and a decrease in glomerular filtration rate occur in patients with high-pressure chronic retention if obstruction is not treated [27, 29–31]. Low bladder compliance, detrusor instability, and anatomical ureterovesicular junction obstruction or vesicoureteral reflux due to smooth muscle hypertrophy and connective tissue infiltration are the causal mechanisms of renal failure in men with chronic urinary retention [32–35]. Other less commonly proposed etiologies for chronic renal failure due to BPH include acute urinary retention, urinary tract infections, renal calculi, secondary hypertension from chronic urinary retention, nondilated obstructive nephropathy, and nephrogenic diabetes insipidus [27, 36–38].

Making the Diagnosis and Quantifying LUTS and BPH

The diagnosis of LUTS and benign prostatic enlargement is based on history, digital rectal and neurological examination, symptom scoring, measurement of serum PSA, and frequency volume chart recording [39]. Optional tests include uroflowmetry, postvoid residual urine, pressure-flow studies, transrectal ultrasonography, imaging of the upper urinary tract, and lower urinary tract endoscopy [39]. Simple investigations to exclude urinary tract infection and renal damage may also be helpful [3, 9].

History, Symptom Scoring, and Physical Examination

Objective evaluation of symptoms is essential in randomized controlled trials and in assessing surgical or medical outcomes [39]. Most symptom questionnaires can be self-completed and have been extensively tested for validity and reliability [2]. The international prostate symptom score (IPSS) has been adopted by the World Health Organization [40]. The instrument has excellent test-retest reliability and is internally consistent. Studies using these tools have shown a strong relationship between high preoperative symptom scores and good post-operative outcomes, although only a weak correlation is found among symptom scores and prostatic volume, peak flow rates, postvoid residual urine volumes, and age [41]. The obstructive scoring element of the IPSS may be useful in predicting disease progression [42]. Some symptoms such as frequency, urgency, and urge incontinence are associated with detrusor overactivity and a poor outcome after prostatectomy.

Several quality-of-life measures have been used. These include the Nottingham Health Profile (NHP), the EuroQol, the short form 36 (SF36), and the BPH impact index [43]. The current trend in the field is to develop more complex instruments, including various domains that may be of importance in patients with voiding dysfunction such as LUTS, incontinence, sexual dysfunction, and quality-of-life concerns [10, 43, 44].

Digital rectal examination (DRE) can exclude locally advanced prostate cancer, but not early prostate cancer. The size of the gland is important when counseling the patient on the type of surgery that may be offered.

Prostate-Specific Antigen in the Investigation of LUTS

The exclusion of prostate cancer in patients presenting with LUTS is of paramount significance. Digital rectal examination, measurement of PSA, measurement of human kallikrein 2, transrectal ultrasound, and prostatic biopsies, when indicated, are all recommended to differentiate between BPH and prostate cancer [45].

PSA has revolutionized the diagnosis of prostate cancer. It provides earlier detection of prostate cancer than digital rectal examination and allows us to identify men whose cancer is not palpable. However, PSA is not a perfect tumor marker. It lacks both sensitivity and more importantly specificity. In an effort to enhance the specificity, investigators have utilized a variety of PSA derivatives including age-specific PSA cut-offs, various PSA forms, PSA velocity, and PSA density. Unfortunately, none of these has demonstrated a major benefit in general clinical practice [45].

An evaluation of serum PSA in the adult male population is no longer limited to the diagnosis of prostate cancer, but has also found a role in the management of patients with BPH. Serum PSA increases with prostate size and age (by 3.2% per year) [46]. High PSA levels in patients with LUTS are significantly associated with bladder outflow obstruction [47, 48]. The Longitudinal Baltimore Study of Aging [49]showed a clear increase in the risk of prostate enlargement in each age cohort (from 40 to 69.9 years) for higher values of serum PSA levels. The results of the study were also of interest in light of the known relationship between prostate volume and healthcare-seeking behavior, futures episodes of AUR, and the need for prostate surgery among men with LUTS. It is proposed that men with higher PSA levels could be enrolled in a different observation scheme and that serum PSA levels could provide a method of risk stratification to be used for selecting candidates for future descriptive study treatment trials for the prevention of BPH progression [49]. PSA testing may be appropriate in men with a clinically benign gland and LUTS [48] so long as the guidelines in Table 14.2 are followed, i.e., that the patient is fully counseled as to the implications and subsequent actions that may be required following such a test. Men need to be aware that a negative PSA test is no guarantee that prostate cancer is absent. However, it seems likely that men in this age range with very low PSA levels (<1 ng/mL) have low risks of developing clinically significant prostate cancer.

Flow Rates and Pressure-Flow Studies

Flow rates are useful to monitor changes over time in watchful waiting and in the follow-up of both medical and surgical therapy [50]. In addition, low flow rates (<10 mL/s) and outlet obstruction are associated with a better surgical outcome [39]. Before advising men to undergo surgery, it is essential to counsel them about the likely success rate—even in those with "straightforward" symptoms. It is probably a counsel of perfection to advocate pressure-flow studies in all men, but a low measured flow rate (<10 mL/s) will predict outlet obstruction with good accuracy and should be carried out. Flow

Table 14.2 Counseling Guidelines.

PSA Testing
– Is not recommended for routine clinical use
– Is not recommended in men with less than 10-year life expectancy
– Should only be offered following full counseling of men about the implications
Implications of PSA Testing That Should Be Explained Prior to Testing
– The test may detect early prostate cancer in 2–3% of men aged 50 to 65 years.
– The test will fail to detect some early tumors.
– PSA testing and subsequent treatment of early prostate cancer
– May incur risk and may not improve life expectancy.
– A transrectal ultrasound scan and biopsy may be needed, which carry some morbidity.
– The test may diagnose a tumor that we are uncertain how best to treat.

rates are therefore strongly recommended in the assessment of men before treatment. On the majority of units, most men will undergo urodynamics before surgically invasive treatments and particularly if there is any suggestion that the symptoms may be related to underlying detrusor overactivity or causes other than BPH [50]. The reason is that men with proven outflow obstruction have better results following surgery and can therefore be better counseled about the likely outcome; conversely, men with no obstruction and detrusor overactivity do very poorly following surgery [50].

Treatment of LUTS

Nonoperative Treatment

This includes watchful waiting and pharmacotherapy.

Watchful Waiting

Some men wish to avoid both medical and surgical therapy. Conservative management ("watchful waiting") is a safe and acceptable alternative [51,52]. Patients under watchful waiting show no difference in the risk of prostatic surgery compared to patients undergoing medical treatment [53]. However, men managed by watchful waiting who later undergo transurethral resection of the prostate (TURP) have less improvement than men randomized to TURP initially [51]. Detrusor overactivity, a highly prevalent condition among patients with bladder outflow obstruction, persists for long periods or appears *de novo* when obstruction is left untreated [54]. The AUA guidelines recommended that patients with mild symptoms of BPH (AUA symptom score <7) and patients with moderate or severe symptoms (AUA symptom score >8) who are not bothered by their symptoms should be managed using a strategy of watchful waiting [52].

Pharmacotherapy

Over the last decade there has been a significant shift in practice [42], with a 33% increase in the numbers of men treated medically. This trend has been encouraged by increased awareness by doctors and patients of the availability of drug treatment and awareness of the potential morbidity of surgical therapy, such as loss of sexual function and urinary incontinence [52,55].

Phytotherapy. Various plant extracts have been used in treating LUTS and BPH [56]. A few short-term randomized trials and some meta-analyses show clinical efficacy without major side effects for compounds such as Pygeum africanum, Serenoa repens, and saw palmetto berry [56, 57]. In some studies, the efficacy of these compounds was found to be equivalent to finasteride and a-blockers [56–58], while in others they did not improve symptoms or objective measures of BPH [59].

Although there is some evidence showing the ability of these plant extracts to influence prostatic hyperplasia via effects on androgen metabolism [60] or on growth factor signaling pathway [47], the durability remains unproven, and their efficacy and exact molecular mechanism of action remain unclear [58, 60, 61].

α-*Adrenergic Blockade.* A-adrenoreceptor blockade has become one of the mainstays of treatment for symptomatic benign prostatic obstruction. A-blocker therapy is based on the hypothesis that clinical BPH is partly caused by α-adrenergic-mediated contraction of the smooth muscle, resulting in bladder outlet obstruction [62]. Some of the a-blockers may also cause apoptosis of the prostatic epithelium [63]. The α1-adrenoreceptor subtypes in the prostate have been extensively investigated; the most important is the α1α subtype [64]. Up to 15% of patients receiving α-blockers experience mild side effects, which include headache, dizziness, drowsiness, postural hypotension, and rarely syncope (<1%). All α1-selective blockers in current use have a rapid onset (within weeks) and a similar efficacy, producing a 40% increase in maximal flow rate with significant symptom improvement [65], producing on average a 4- to 6-point improvement in the AUA symptom index [66]. In general, patients will perceive this level of symptom improvement as a meaningful change [66]. A recent development is slow-release, once-daily preparations, which provide sustained plasma concentrations and reduce side effects [67].

5-α Reductase Inhibitors. 5-α reductase enzyme is responsible for the conversion of testosterone to dihydrotestosterone (DHT). There are two isoenzymes, I and II, with type II being found in high concentrations within the prostate [68]. Finasteride, a type II 5-α reductase inhibitor, and dutasteride, which suppresses both isoenzymes, are currently available for the treatment of BPH. It is known that finasteride suppresses DHT by about 70% in the serum and by 90% in the prostate. Serum DHT decreases by about 90% when dutasteride is used [69].

Both drugs cause atrophy of the prostatic glandular epithelial cells, which results in a 20–30% reduction in volume. Both compounds seem to work best in men with significantly enlarged prostates. Randomized controlled trials have shown that 5-α reductase inhibitors improve quality of life, decrease prostatic volume, and decrease the risk of progressing to urinary retention or prostatic surgery [70, 71]. Finasteride shows a slower onset (3–6 months) but similarly durable action compared to dutasteride [72].

When dutasteride was compared with finasteride for 1 year, the drug-related adverse events were similar for both compounds. Finasteride results in ejaculatory dysfunction (2–8%), loss of libido (1–10%), and impotence (3.4–l6%) [73]. However, compared with placebo, men treated with finasteride experienced new drug-related sexual adverse experiences with an increased incidence only during the first year of therapy [73].

Combined Treatment with α-Blockers and 5-α Reductase Inhibitors Recently, the results of a multicenter, randomized, placebo-controlled double-blinded trial (MTOPS) have shown that the combination of finasteride to doxasosin was beneficial [23]. The combination therapy was superior to either drug alone in reducing AUA symptom scores, in increasing median maximal flow rates, and in reducing the likelihood of AUR and surgery. The follow-up period of the MTOPS trial was 4.5 years, and another conclusion drawn from this study was that finasteride needs time to reveal its beneficial therapeutic capacity. Patients most likely to benefit from combination therapy are those in whom baseline risk of progression is significantly higher, generally patients with larger glands and higher prostate-specific antigen values [74].

In another study examining combination therapy, it was shown that patients with LUTS and moderately enlarged prostates initially receiving combination therapy were likely to experience no significant symptom deterioration after discontinuing the α-blocker following 9 to 12 months of combination therapy [75].

Anticholinergic Medication A substantial proportion of men with LUTS have a combination of storage and voiding symptoms, suggesting possible coexisting bladder outlet obstruction and bladder overactivity. The latter is traditionally treated with anticholinergic drugs. Efficacy and safety studies of anticholinergic medication in men with LUTS/BPH are scarce and of limited power. Preliminary data suggest that they are not associated with a substantial risk of urinary retention or with a substantial increase in residual urine volume [62].

Surgical Treatment

Surgical intervention is recommended for complications of LUTS such as AUR, gross hematuria secondary to BPH, renal failure or bladder calculi secondary to obstruction, and for severe symptoms (Table 14.3) [38].

Open Prostatectomy

Transvesical prostatectomy was popularized by Freyer in 1900 [77]. This operation is occasionally performed today if access to the bladder is required. Surgical mortality is less than 1% and usually secondary to rnyocardial infarction, pneumonia, or pulmonary embolus. Retropubic prostatectomy is

Table 14.3 American Urological Association Guidelines for TURP.

A patient has a reasonable surgical risk with one or more of the following:
1. Urinary retention tine to prostatic obstruction
2. Intractable: symptoms owing to prostatic obstruction
3. Recurrent or persistent urinary tract infection related to prostatic obstruction
A patient who is a reasonable surgical risk with two or more of the following:
1. Documented post-voiding residual urine
2. Pathophysiological changes of kidneys, ureters, or bladder caused by prostatic obstruction
3. Abnormally low urinary flow rate or a normal flow rate, but with an abnormally high voiding pressure secondary to outlet obstruction

credited to Terence Millin [78] and was popularized in the late 1940s. It has better exposure, allowing bleeding points to be visualized [78,79], and allows more accurate division of the urethra, leading to a decreased incidence of stress urinary incontinence. The mortality rate is less than 1%, but morbidity includes hemorrhage, myocardial infarction, pulmonary embolism, and cardiovascular accidents. Bladder neck contracture occurs in less than 2%, retrograde ejaculation in the majority, and impotence in 15–20% of cases [79]. The post-operative hospital stay is 5 to 7 days. Open prostatectomy is performed in fewer than 1% of patients (usually in glands over 100 g).

TURP

TURP was pioneered in 1909 [80] and, following the development of the resectoscope in the 1940s in the United States, increased in popularity. It is the hallmark of the urologist, who can perform more than 98% of all prostatectomies transurethrally. It takes 20–30 minutes to resect an average 30-g gland [80]. TURP has a mortality rate of around 0.2% to 0.4% for elective operations [3]. Patients require a catheter for 48 hours, and the total inpatient stay is 5 days [4]. There are few contraindications, the only clear ones being severe mental disturbance and limited life expectancy [81]. Relative contraindications include renal failure, extreme age, diabetes, cardiovascular and cerebrovascular disease, respiratory failure, and detrusor underactivity [80, 82]. Early post-operative problems include blood transfusion (2.4%), return to surgery for bleeding (2.0%), sepsis (8.0%),and the TUR syndrome (absorption of glycine solution with hyponatremia; <1%) [44]. Long-term complications include urethral stricture (1–29%), bladder neck contracture, impotence (5–10%), retrograde ejaculation (50%), and urinary incontinence [83]. A recent randomized controlled trial has, however, shown that TURP significantly relieves ejaculatory discomfort and pain, as compared to either watchful waiting or laser prostatectomy, and also improves erectile function [84]. Short-term results on bipolar transurethral resection, an innovation of the standard resection technique using bipolar current and normal saline as the irrigant fluid, show excellent functional outcome and reduced morbidity [85].

At present, TURP is in decline mostly due to the effectiveness of medical treatment [86]. Urinary retention is the most common indication [86]. The population at present is older, but this does not carry additional co-morbidity [86] unless men are admitted as an emergency or present with prostate cancer [3].

Acute urinary retention, acute on chronic urinary retention, and chronic urinary retention all secondary to BPH are common in elderly men. These conditions may be related to temporary or permanent renal impairment [31, 36]. Compared with those patients who undergo elective prostatectomy for symptoms alone, men presenting with acute or chronic retention have an excessive risk of death and an increased risk of perioperative complications [87, 88].

Prompt relief of urinary retention by continuous bladder catheterization or clean intermittent self-catheterizations before TURP may be valuable both in patients presenting with acute retention and in those with chronic retention, especially those with low voiding pressure [87, 88].

There are no randomized trials comparing TURP with open prostatectomy. One large U.S. study appeared to find elevated long-term, age-specific mortality rates associated with TURP [83]. This led to the establishment of

several large prospective audits to investigate outcomes [3, 89]. It appeared that the apparent increased mortality for TURP was because men were only selected for open prostatectomy if they were very fit. The American Urological Association's indications for TURP are shown in Table 14.3. To date, TURP remains the urological gold standard by which all new technology for the treatment of benign prostatic obstruction needs to be assessed.

Laser Prostatectomy

In general, laser energy can be used to produce coagulation necrosis, vaporization, or resection of tissue, procedures performed on the prostate commonly referred to as transurethral laser coagulation, transurethral vaporization, and transurethral resection/enucleation.

Early lasers included the side-firing neodymium:yttrium aluminum garnet (Nd YAG) type (coagulation laser prostatectomy) and were fraught with complications and lack of superiority against TURP [90, 91]. More recently, there has been a renewed interest in Holmium laser prostatectomy. The holmium aluminum garnet laser (Ho YAG) has characteristics making it suitable for endourological surgery [90]. Its wavelength (2140 nm) allows rapid absorption by water, which permits rapid vaporization of tissue to 0.4 mm and, at high energy, coagulation to a depth of 3–4 mm [90]. It may be used as a tissue-removing modality in 3 forms: The first, holmium laser ablation of the prostate, involves vaporization of prostate tissue using a side-firing fiber. The second, holmium laser resection of the prostate (HoLRP), combines laser resection of the prostate with division of the lobes into fragments small enough to irrigate from the bladder. The third is holmium laser enucleation of the prostate (HoLEP). In this technique, the laser acts as the finger would in an open prostatectomy and endoscopically enucleates the prostatic lobes in their entirety from the prostatic capsule. Then the enucleated lobes float freely within the bladder, from which they are morcellated and extracted [91]. A new addition to the laser field is the high-powered potassium-titanyl-phosphate (KTP) laser. It uses a side-firing technique with a high level of energy to cause large volumes of prostatic vaporization [92].

Good medium-term data [93]regarding laser prostatectomy show it to be safe and effective with outcomes equivalent to TURP. It is associated with decreased blood loss, catheter times, hospital stays, and complications [93]. It requires more time to perform than TURP, but more prostate tissue is removed, resulting in a similar efficiency in tissue retrieval, lower urinary tract symptom relief, and peak urinary flow-rate improvement [93]. The disadvantages are high start-up costs, longer procedure times, a steep learning curve [94], a higher re-treatment rate compared to TURP [93], and the lack of long-term results of randomized prospective studies [91, 93].

Other Minimally Invasive Procedures

Recent publications have described some interesting new therapies and provided data concerning long-term follow-up and cost-effectiveness that have been lacking until now [49]. These therapies include high-energy transurethral microwave thermotherapy (HE-TUMT), which applies temperatures as high as 46–60 °C and causes thermal ablation of the prostate; transurethral ethanol injection therapy, which causes chemical destruction of the prostate; transurethral needle ablation (TUNA), which uses low-level

radiofrequency energy to ablate the gland; Vaportrode loop, which by a vaporizing action using radiofrequency through a standard resectoscope vaporizes tissue; and high-intensity focused ultrasound (HIFU), which causes coagulative necrosis by delivering temperatures up to 80–100 °C [95].

Currently, among these techniques HE-TUMT seems to offer the soundest basis for management of BPH, providing the longest follow-up and the largest numbers of studies completed to date [95]. Several studies have shown that it can be given as outpatient treatment. When compared to SHAM treatment, there are subjective (mean 60% symptom score improvement) and objective (mean 50% maximum flow-rate improvement) improvements, which are maintained for 1 year [96]. When compared to TURP, the latter provides greater symptom score and urinary flow improvements and fewer subsequent BPH treatments than TUMT [97].

Conclusions

Lower urinary tract symptoms remain a common cause for men to see their family doctor. These symptoms require careful evaluation to determine the cause of such symptoms. The use of medical treatment allows many men to be treated in the community. Persistent symptoms or the development of complications such as retention or infection requires referral. Before invasive treatment is contemplated, these men need careful assessment, at least with flow rates, and in some instances with urodynamic pressure-flow studies, so that they can be properly counseled about the likely benefit and risks of surgery. The "gold standard" for surgical treatment requires removal of the obstructing tissue to achieve durable results. This may be achieved by transurethral prostatectomy or laser resection. Other modalities can sometimes be used in an outpatient setting and can alleviate symptoms, but they are less durable and less cost-effective.

References

1. Gades, N.M., Jacobson, D.J., Girman, C.J., et al. Prevalence of conditions potentially associated with lower urinary tract symptoms in men. *BJU Int.* 2005; 95(4):549–553.
2. Skolarikos, A., Thorpe, A.C., Neal, D.E. Lower urinary tract and benign prostatic hyperplasia. *Minerva Urol. Nefrol*. 2004; 56:109–122.
3. Thorpe, A.C., Cleary, R., Coles, J., et al. Deaths and complications following prostatectomy in 1400 men in the northern region of England. *Br. J. Urol*. 1994; 74:559–765.
4. Matthiesen, T., Ritting, S., Norgaard, J.P., et al. Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. *J. Urol*. 1996; 156:1292–1299.
5. Byrne, R.L., Leung, H., Neal, D.E. Peptide growth factors in the prostate as mediators of stromal epithelial interaction. *Br. J. Urol.* 1996; 77:627–633.
6. Logie, J., Clifford, G.M., Farmer, R.D. Incidence, prevalence and management of lower urinary tract symptoms in men in the UK. *BJU Int*. 2005; 95(4):557–562.
7. De la Rosette, J.J. What we do and don't know about benign prostatic hyperplasia. *Curr. Opin. Urol*. 2000; 10:1–2.
8. Barry, M.J. Epidemiology and natural history of benign prostatic hyperplasia. *Urol. Clin. North Am*. 1990; 17:495–507.

9. Roberts, R.O., Jacobsen, S.J., Rhodes, T., et al. Natural history of prostatism: Impaired health states in men with lower urinary tract symptoms. *J. Urol*. 1997; 157:1711–1717.
10. Boyle, P., Robertson, C., Mazzetta, C., et al. The relationship between lower urinary tract symptoms and health status: The UREPIK study. *BJU Int.* 2003; 92:575–580.
11. Garraway, W.M., Collins, G.N., Lee, R.J. High prevalence of benign prostatic hypertrophy in the community. *Lancet* 1991; 338:469–471.
12. Sarma, A.V., Wei, J.T., Jacobson, D.J., et al. Comparison of lower urinary tract symptom severity and associated bother between community-dwelling black and white men: The Olmsted County Study of Urinary Symptoms and Health Status and the Flint Men's Health study. *Urology* 2003; 6l:108–191.
13. Steyn, M. Just old age? A study of prostatism in general practice. *Fam. Pract*. 1988; 5:193–195.
14. Hoesl, C.E., Woll, E.M., Burkart, M., et al. Erectile dysfunction (ED) is prevalent, bothersome and underdiagnosed in patients consulting urologists for benign prostatic syndrome (BPS). *Eur. Urol*. 2005; 47(4):511–517.
15. Nickel, J.C., Elhilali, M., Vallancien, G., ALF-ONE Study Group. Benign prostatic hyperplasia (BPH) and prostatitis: Prevalence of painful ejaculation in men with clinical BPH. *BJU Int*. 2005; 95(4):571–574.
16. Roberts, R.O., Bergstralh, E.J., Cunningham, J.M., et al. Androgen receptor gene polymorphisms and increased risk of urologic measures of benign prostatic hyperplasia. *Am. J. Epidemiol*. 2004 (Feb 1); 159(3):269–276.
17. Li, Z., Habuchi, T., Tsuchiya, N., et al. Increased risk of prostate cancer and benign prostatic hyperplasia associated with transforming growth factor-beta 1 gene polymorphism at codon10. *Carcinogenesis* 2004; 25(2):237–240.
18. Berger, A.P., Kofler, K., Bektic, J., et al. Increased growth factor production in a human prostatic stromal cell culture model caused by hypoxia. *Prostate* 2003; 57:57–65.
19. Cazares, L.H., Adam, B.L., Ward, M.D., et al. Normal, benign, preneoplastic, and malignant prostate cells have distinct protein expression profiles resolved by surface enhanced laser desorption/ionization mass spectrometry. *Clin. Can. Res*. 2002; 8:254l–2552.
20. DiSanto, M.E., Stein, R., Chang, S., et al. Alteration in expression of myosin isoforms in detrusor smooth muscle following bladder outlet obstruction. *Am. J. Physiol. Cell Physiol*. 2003; 285:C1397–1410.
21. Fong, Y.K., Milani, S., Djavan, B. Natural history and clinical predictors of clinical progression in benign prostatic hyperplasia. *Curr. Opin. Urol.* 2005; 15(1):35–38.
22. Rhodes, T., Blue Bell, P.A., Jacobson, D., et al. Longitudinal prostate volume in a community-based sample: Long-term follow-up in the Olmsted County study of urinary symptoms and health status among men. *J. Urol*. 2002; l67:269.
23. McConnell, D. The long-term effects of medical therapy on the progression of BPH: Results from the MTOPS trial. *J. Urol*. 2002; l67:264.
24. Speakman, M. Tamsulosin reduces the risk of acute urinary retention. *J*, *Urol*, 2002; l67:375.
25. Lucas, M.G., Stephenson, T.P., Nargund, V. Tamsulosin in the management of patients in acute urinary retention from benign prostatic hyperplasia. *BJU Int*. 2005; 95(3):354–357.
26. Neal, D.E. Watchful waiting or drug therapy for benign prostatic hyperplasia? *Lancet* 1997; 350:305–306.
27. Rule, A.D., Lieber, M.M., Jacobsen, S.J. Is benign prostatic hyperplasia a risk factor for chronic renal failure? *J. Urol*. 2006; 173: 691–696.
28. McConnell, J.D., Barry, M.J., Bruskewitz, R.C., Bueschen, A.J., Denton, S.E., Holtgrewe, N.L., et al. Benign prostatic hyperplasia: Diagnosis and treatment. Clinical Practice Guideline, Number 8. Agency for Health Care Policy and

Research. Publication No. 04–0583, Rockville, MD: Public Health Service, U.S. Department of Health and Human Services, February 1994.
29. O'Reilly, P.H., Brooman, P.J., Farah, N.B., Mason, G.C. High pressure chronic retention. Incidence, aetiology and sinister implications. *Br. J. Urol*. 1986; 58:644.
30. George, N.G., O'Reilly, P.H., Barnard, R.G., Blacklock, N.J. High pressure chronic retention. *BMJ* 1983; 286:1780.
31. George, N.G., Feneley, R.C., Roberts, J.B. Identification of the poor risk patient with "prostatism" and detrusor failure. *Br. J. Urol*. 1986; 58:290.
32. Comiter, C.V., Sullivan, M.P., Schacterle, R.S., Cohen, L.H., Valla, S.V. Urodynamic risk factors for renal dysfunction in men with obstructive and nonobstructive voiding dysfunction. *J. Urol*. 1997; 158:181.
33. Styles, R.A., Neal, D.E., Griffiths, C.J., Ramsden, P.D. Long-term monitoring of bladder pressure in chronic retention of urine: The relationship between detrusor activity and upper tract dilatation. *J. Urol*. 1988; 140:330.
34. Jones, D.A., Giplin, S.A., Holden, D., Dixon, J.S., O'Reilly, P.H., George, N.J. Relationship between bladder morphology and long-term outcome of treatment in patients with high pressure chronic retention of urine. *Br. J. Urol.* 1991; 67:280.
35. Sutaria, P.M., Staskin, D.R. Hydronephrosis and renal deterioration in the elderly due to abnormalities of the lower urinary tract and ureterovesical junction. *Int. Urol. Nephrol*. 2000; 32:119.
36. Prakash, J., Saxena, R.K., Sharma, O.P., Usha, Spectrum of renal diseases in the elderly: Single center experience from a developing country. *Int. Urol. Nephrol*. 201; 133:227.
37. Olbrich, O., Woodford-Williams, E., Irvine, R.E., Webster, D. Renal function in prostatism. *Lancet* 1957; 1:1322.
38. Ogbonna, B.C., Madziga, A.G., AnteyIi, E.A. The impact of renal impairment on the management of patients with lower urinary tract obstruction. *Trop. Doct*. 1997; 27:75.
39. Bhargava, S., Canda, A.E., Chapple, C.R. A rational approach to benign prostatic hyperplasia evaluation: Recent advances. *Curr. Opin. Urol*. 2004; 14(1):1–6.
40. Mebust, W., Roizo, R., Schroeder, F., et al. Correlations between pathology clinical symptoms and the course of the disease. In *Proceedings of the International Consultation on Benign Protastic Hyperplasia*, A.T.K. Cockett, Y. Aso, C. Chatelain, L. Denis, K. Griffiths, S. Khoury, et al., eds. Geneva: WHO. 1991; pp. 51–62.
41. Bosch, J.L., Hop, W.C., Kirkels, W.J., et al. The international prostate symptom score in a community sample of men between 55 and 74 years of age: Prevalence and correlation of symptoms with age. Prostate volume, flow rate and residual urine volume. *Br. J. Urol*. 1995; 75:622–630.
42. Djavan, B., Wammack, R., Dobrovits, M., et al. Predictors of progression in men with mild symptoms of bladder outlet obstruction. *J. Urol*. 2002; 167:268.
43. Tubaro, A., Trucchi, A., Miano, L. Investigation of benign prostatic hyperplasia. *Curr. Opin. Urol*. 2003; 13:17–22.
44. Braun, M.H., Sommer, F., Haupt, G., et al. Lower urinary tract symptoms and erectile dysfunction: Co-morbidity or typical "Aging Male"' symptoms? Results of the "Cologne Male Survey." *Eur. Urol*. 2003; 44:588–594.
45. Chatelain, C., Denis, L., Foo, K.T., Khoury, S., Connell, J.M.C. Benign Prostatic Hyperplasia. 5th International Consultation on Benign Prostatic Hyperplasia (BPH), June 25–28, 2000, Paris. Plymouth, UK: Health Publication Ltd. 2001.
46. Di Silverio, F., Sciarra, A., D'Eramo, G., et al. Relationship among age, prostate specific antigen and prostate volume in men with lower urinary tract symptoms and in different age groups of men with and without benign and malignant prostatic diseases. *Prostate* 1998; 36:l–7.

47. Roehrborn, C.G. The potential of serum prostate-specific antigen as a predictor of clinical response in patients with lower urinary tract symptoms and benign prostatic hyperplasia. *BJU Int*. 2004; 93(Suppl 1):21–26.
48. Laniado, M.E., Ockrim, J.L., Marronaro, A., et al. Serum prostate-specific antigen to predict the presence of bladder outlet obstruction in men with urinary symptoms. *BJU Int*. 2004; 94(9):1283–1286.
49. Wright, E.J., Fang, J., Metter, E.J., et al. Prostate specific antigen predicts the long-term risk of prostate enlargement: Results from the Baltimore Longitudinal Study of Aging. *J. Urol*. 2002; 167:2484–2488.
50. Chatelain, C.H., Denis, L., Foo, K.T., et al. Evaluation and treatment of lower urinary tract symptoms in older men. Recommendations of the 5th International Consultation on Benign Prostatic Hyperplasia. June 25–28, 2000. Paris, Plymouth, UK: Health Publication Ltd. 2001; pp. 519–533.
51. Flanigan, R.C., Reda, D.J., Wasson, J.H., et al. 5-year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia. A Department of Veterans Affairs cooperative study. *J. Urol*. 1998; l60:12–16.
52. AUA Practice Guidelines Committee. AUA guideline of management of benign prostatic hyperplasia. Chapter 1: Diagnosis and treatment recommendations. *J. Urol*. 2003; 170:530–547.
53. Souverein, P.C., van Reimsdijk, M.M., de la Rosette, J.J., et al. Treatment of benign prostatic hyperplasia and occurrence of prostatic surgery and acute urinary retention: A population-based cohort study in the Netherlands. *Eur. Urol*. 2005; 47(4):505–510.
54. de Nunzio, C., Franko, G., Rocchegiani, A., et al. The evolution of detrusor overactivity after watchful waiting, medical therapy and surgery in patients with bladder outlet obstruction. *J. Urol.* 2003; 169(2):535–539.
55. Borth, C.S., Beiko, D.T., Nickel, J.C. Impact of medical therapy on transurethral resection of the prostate: A decade of change. *Urology* 2001; 57:1082–1085.
56. Fong, Y.K., Milani, S., Djavan, B. Role of phytotherapy in men with lower urinary tract symptoms. *Curr. Opin. Urol*. 2005; 15(1):45–48.
57. Lowe, F.C., Fagelman, E. Phytotherapy in the treatment of benign prostatic hyperplasia. *Curr. Opin. Urol*. 2002; 12:15–18.
58. Debruyne, F., Koch, G., Boyle, P., et al. Comparison of a phytotherapeutic agent (permixon) with an a-blocker (tamsulosin) in the treatment of benign prostatic hyperplasia: A 1-year randomized international study. *Eur. Urol*. 2002; 4l: 497–506, discussion 506–507.
59. Bent, S., Kane, C., Shinohara, K., Neuhaus, J., Hudes, E.S., Goldberg, H., Avins, A.L. Saw palmetto for benign prostatic hyperplasia. *N. Engl. J. Med*. 2006; 354(6):557–566.
60. Talpur, N., Echard, B., Bagchi, D., et al. Comparison of saw palmetto (extract and whole berry) and Cemitin on prostate growth in rats. *Mol. Cell Biochem*. 2003; 250:21–26.
61. Wadsworth, T.L., Carroll, J.M., Mallinson, R.A., et al. Saw palmetto extract suppresses insulin-like growth factor-I signaling and induces stress-activated protein kinase/c-Jun N-terminal kinase phosphorylation in human prostate epithelial cells. *Endocrinology* 2004; 145(7):3205–3214.
62. Lepor, H. The pathophysiology of lower urinary tract symptoms in the ageing male population. *Br. J. Urol*. 1998; 81:29–33.
63. Kyprianou, N. Doxazosin and terazosin suppress prostate growth by inducing apoptosis: Clinical significance. *J. Urol*. 2003; 169:1520–1525.
64. Forray, C., Bard, J.A., Wetzel, J.M., et al. The α1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned alphaC subtype. *Mol. Pharmacol*. 1994; 45:703–708.
65. Chapple, C.R. α-adrenoceptor antagonists in the year 2000: Is there anything new? *Curr. Opin. Urol*. 2001; 11:9–16.

66. Narayan, P., Evans, C.P., Moon, T. Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. *J. Urol*. 2003; 170(2 Pt 1):498–502.
67. Nordling, J. Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia. *BJU Int.* 2005; 95(7):1006–1012.
68. Bartsch, G., Rittmaster, R.S., Klocker, H. Dihydrotestosterone and the concept of 5-α reductase inhibition in human benign prostatic hyperplasia. *Eur. Urol*. 2000; 37:367–380.
69. Clark, R., Hermann, D., Gabriel, H., et al. Effective suppression of dihydrotestosterone (DHT) by GI198745, a novel, dual 5-α reductase inhibitor. *J. Urol*. 1999; 161:1037.
70. Roehrborn, C.G., Bruskewitz, R., Nickel, G.C., et al. Urinary retention in patients with BPH treated with finasteride or placebo over 4 years. Characterization of patients and ultimate outcomes. The PLESS study group. *Eur. Urol*. 2000; 37: 528–536.
71. Andriole, G.L., Kirby, R. Safety and tolerability of the dual 5α-reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. *Eur. Urol*. 2003; 44:82–88.
72. Lam, J.S., Romas, N.A., Lowe, F.C. Long-term treatment with finasteride in men with symptomatic benign prostatic hyperplasia: 10-year follow-up. *Urology* 2003; 61:354–358.
73. Wesselis, H., Roy, J., Bannow, J., et al. PLESS Study Group. Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. *Urology* 2003; 61:579–584.
74. Desgrandchamps, F. Who will benefit from combination therapy? The role of 5 alpha reductase inhibitors and alpha blockade: A reflection from MTOPS. *Curr. Opin. Urol*. 2004; 14(1):17–20.
75. Baldwin, K.G., Ginsberg, P.C., Roehrborn, C.G., et al. Discontinuation of α-blockade after initial treatment with finasteride and doxazosin in men with lower urinary tract symptoms and clinical evidence of benign prostatic hyperplasia. *Urology* 2001; 58:203–209.
76. Reynard, J.M. Does anticholinergic medication have a role for men with lower urinary tract symptoms/benign prostatic hyperplasia either alone or in combination with other agents? *Curr. Opin. Urol*. 2004; 14(1):13–16.
77. Freyer, P. One thousand cases of total enucleation of the prostate for radical cure of enlargement of that organ. *BMJ* 1912; 2:868.
78. Millin, T. *Retropubic Urinary Surgery*. London: Livingstone. 1947.
79. Walsh, T.N., Kelly, D.G. Historical review of prostatectomy. In *The Prostate,* J.M. Fitzpatrick and R.J. Krane, eds. London: Churchill Livingstone. 1989; pp. l43–147.
80. Blandy, J.P. Transurethral prostatectomy. In *The Prostate*, J.R. Blandy and B. Lytton, eds. London: Butterworth. 1986; pp. 51–61.
81. Walsh, A. Indications for prostatic surgery and selection of operation. In *The Prostate*, J.M. Fitzpatrick and R.J. Krane, eds. London: Churchill Livingstone. 1989; pp. l37–142.
82. Thomas, A.W., Cannon, A., Bartlett, E., et al. The natural history of lower urinary tract dysfunction in men: The influence of detrusor under-activity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *BJU Int*. 2004; 93(6):745–750.
83. Roos, N.P., Wennberg, J.E., Malenka, D.J., et al. Mortality and re-operation after open and transurethral resection of the prostate. *N. Engl. J. Med*. 1989; 320: 1120–1124.
84. Brookes, S.T., Donovan, J.L., Peters, T.J., et al. Sexual dysfunction in men after treatment for lower urinary tract symptoms: Evidence from randomized controlled trial. *BMJ* 2002; 324:1059–1061.

85. Smith, D., Khoubehi, B., Patel, A. Bipolar electrosurgery for benign prostatic hyperplasia: Transurethral electrovaporization and resection of the prostate. *Curr. Opin. Urol.* 2005; 15(2):95–100.
86. Wilson, J.R., Urwin, G.H., Stower, M.J. The changing practice of transurethral prostatectomy: A comparison of cases performed in 1990 and 2000. *Ann. Roy. Coll. Surg. Engl*. 2004; 86(6):428–431.
87. Pickard, R., Emberton, M., Neal, D.E. The management of men with acute urinary retention. National Prostatectomy Audit Steering Group. *Br. J. Urol*. 1998; 81(5):712–720.
88. Ghalayini, I.F., Al-Ghazo, M.A., Pickard, R.S. A prospective randomized trial comparing transurethral prostatic resection and clean intermittent self-catheterization in men with chronic urinary retention. *BJU Int*. 2005; 96(1):93–97.
89. Emberton, M., Neal, D.E., Black, N., et al. Effect of prostatectomy on symptom scoring and quality of life. *Br. J. Urol.* 1996; 77:233–247.
90. Kabelin, J.R., Gillings, P.J., Praundorfer, M.R. Hoimiumyttrium-aluminium-garnet laser prostatectomy. *Mayo Clinic Proc*. 1998; 73:792–797.
91. Tan, A.H., Gilling, P.J. Lasers in the treatment of benign prostatic hyperplasia: An update. *Curr. Opin. Urol*. 2005; 15(1):55–58.
92. Barber, N.J., Muir, G.H. High-power KTP laser prostatectomy: The new challenge to transurethral resection of the prostate. *Curr. Opin. Urol*. 2004; 14(1):21–25.
93. Hoffman, R.M., MacDonald, R., Wilt, T.J. Laser prostatectomy for benign prostatic obstruction. *Cochrane Database Syst. Rev*. 2004; (1):CD001987.
94. Seki, N., Mochida, O., Kinukawa, N., et al. Holmium laser enucleation for prostatic adenoma: Analysis of learning curve over the course of 70 consecutive cases. *J. Urol*. 2003; 170:1847–1850.
95. Naspro, R., Salonia, A., Colombo, R., et al. Update of the minimally invasive therapies for benign prostatic hyperplasia. *Curr. Opin. Urol.* 2005; 15(1):49–53.
96. Denovec, M., Houdelette, P. Columbeau, P., et al. A multicenter study of SHAM versus thermotherapy in benign prostatic hypertrophy. *J. Urol*. 1994; 151:415.
97. Hoffman, R.M., MacDonald, R., Monga, M., et al. Transurethral microwave thermotherapy vs. transurethral resection for treating benign prostatic hyperplasia: A systematic review. *BJU Int*. 2004; 94(7):1031–1036.

15

Urinary Tract Infection

Lindsay E. Nicolle

Introduction

Urinary infection is the most frequent bacterial infection in elderly populations. Symptomatic infection is common and is associated with morbidity and, rarely, mortality. Most infections are, however, asymptomatic. The heterogeneity of elderly populations means approaches to management may differ for different groups. For instance, the management of urinary infection may differ for women and men, and for the institutionalized and non-institutionalized elderly. There are also unique considerations for institutionalized elderly subjects with chronic indwelling catheters [1]. This discussion is relevant to individuals without long-term indwelling catheters, unless stated otherwise.

Asymptomatic bacteriuria is defined as isolation of organisms from a urine specimen meeting a quantitative count of $\geq 10^5$ CFU/mL and no symptoms or signs attributable to infection [2]. The term "bacteriuria" is used interchangeably with "asymptomatic urinary tract infection" in this chapter. Recurrent urinary infection may be either reinfection or relapse. Reinfection is recurrent urinary infection following antimicrobial therapy with an organism isolated that is distinct from the pre-therapy isolate. Relapse is recurrent urinary infection with similar organisms isolated pre- and post-therapy. When relapse occurs, the organism has usually remained sequestered within the urinary tract and was not eradicated with antimicrobial therapy.

Epidemiology

Asymptomatic Bacteriuria

The prevalence of asymptomatic bacteriuria increases markedly with age for both men and women, reaching about 10% for women in the community over 65 years, and 5% for men over 70 years [3]. The incidence of asymptomatic urinary infection in elderly ambulatory populations is not well studied. In one report, 10% of 209 initially nonbacteriuric ambulatory male outpatients of a veteran's hospital had at least one episode of bacteriuria during a mean of 2.8 years' follow-up [4]. Three-quarters of these episodes resolved spontaneously.

There is a remarkable prevalence of bacteriuria in institutionalized elderly populations, at 25–50% for women and 15–40% for men [3]. The incidence

of bacteriuria is also high, with 87 infections per 100 patient years reported in a group of previously bacteriuric women [5]. For men resident in a veteran's hospital, the incidence was 45/100 patient years when urine cultures were obtained every 2 weeks, and 10% of previously nonbacteriuric residents become bacteriuric every 3 months [6]. Bacteriuria in residents of long-term care facilities is dynamic. Nonbacteriuric subjects continually acquire bacteriuria, and previously bacteriuric subjects become culture-negative [7–9]. Repeated prevalence surveys in the same institution have reported acquisition of bacteriuria at one month in 11% of initially nonbacteriuric men, and 12% of women [8]. In another study, 8% of nonbacteriuric women acquired bacteriuria by 6 months, and 23% by 1 year [7]. Reversion to negative urine cultures was observed in 22% of initially bacteriuric men by 1 year [8]. For women, 12% lost bacteriuria by one month, 31% at 6 months, and 27% at 1 year [8].

Symptomatic Urinary Infection

Symptoms consistent with urinary infection in a U.S. study of community residents over 65 years occurred at a rate of 10.9/100 years in men and 14/100 years in women [10]. The rate was 15/100 years in subjects aged 65–74 years, but 12/100 years in those over 75 years. In a prospective study, symptomatic urinary infection, usually microbiologically confirmed, was 7/100 years for postmenopausal women aged 55 to 75 years [11]. The rate was 6.2/100 years in a cohort of 29 ambulatory elderly male veterans with bacteriuria [4] and was 32.3/100 years in women residents of a geriatric apartment with prior asymptomatic bacteriuria [12].

The incidence of symptomatic urinary infection in long-term-care facilities has been reported to vary from 0.1 to 2.4/1000 resident-days [13]. The wide variation reflects differences in patient populations and different surveillance definitions for symptomatic infection. With restrictive definitions requiring localizing genitourinary symptoms and a positive urine culture, the incidence is as low as 0.1 to 0.15 per bacteriuric year for men or women [5,6]. Episodes of fever attributed to urinary infection in noncatheterized nursing home residents occur at a frequency of 0.5 to 1/1000 resident-days using restrictive diagnostic criteria [14], but 6/1000 patient-days when less restrictive criteria are used [15]. From 8–30% of transfers from long-term care to an acute care facility are precipitated by urinary infection [13]. In addition, urinary infection is the most frequent reason for prescribing antimicrobial therapy in long-term-care facilities [16].

Morbidity and Mortality

Morbidity of symptomatic infection occurs along a continuum of relatively mild voiding discomfort to more severe symptoms, with a spectrum from disruption in daily activities to hospitalization. Specific measurement of the impact with urinary infection is not, however, well documented. Hospitalization for acute pyelonephritis in a Canadian province was 10–15/10,000 population for subjects over 70 years, and 1.3 times more frequent in women than men [17]. For the institutionalized population, deterioration in functional status is another measure of morbidity [18], but symptomatic infection is rarely identified as a direct cause of mortality.

No long-term adverse outcomes such as renal failure or hypertension have been attributed to asymptomatic bacteriuria [3]. In addition, while chronic genitourinary symptoms are frequent in bacteriuric institutionalized subjects, these are not attributable to urinary infection [19, 20]. Despite a high prevalence of infection with urease-producing organisms such as *Proteus mirabilis*, complications of urolithiasis have not been reported to be a common problem in institutionalized populations. Early reports from Greece and Finland, in the 1970s, found an association of asymptomatic bacteriuria and decreased survival for elderly men and women. Subsequent studies in both community and institutionalized elderly populations in Finland, the United States, and Canada have not confirmed this observation. Thus, asymptomatic bacteriuria is not currently considered to be associated with decreased survival [3].

Pathogenesis

Route and Site of Infection

The reservoir for infecting organisms is usually the normal gastrointestinal flora. Organisms colonize the periurethral area and ascend the urethra into the bladder, leading to infection. These organisms also may ascend to the kidney and, in men, to the prostate. In the normal genitourinary tract, intermittent, complete voiding is the preeminent host defense to limit urinary infection. Any structural or functional abnormality of the genitourinary tract that impairs voiding increases the risk of urinary infection [21]. Many abnormalities, including urethral or ureteric strictures, bladder diverticuli, and cystoceles, are more common in older populations. About one-half of bacteriuric elderly women have infection localized to the upper tract (kidney), with renal localization more frequent with increasing age and in residents of nursing homes [3]. The proportion of men with a prostatic site of infection is not known, but is likely substantial. Rarely, urinary infection occurs by hematogenous spread, following bacteremia from a non-urinary source.

Host Factors

Community Elderly Populations

The host factors promoting recurrent urinary tract infection in postmenopausal women living in the community include genetic associations similar to younger populations with acute uncomplicated urinary infection, as well as abnormalities of the genitourinary system associated with complicated urinary tract infection (Table 15.1) [22,23]. For postmenopausal women, the strongest predictor of urinary tract infection is any history of prior urinary infection [22, 23]. This is consistent with a life-long genetic predisposition for some women, part of which is attributable to nonsecretor status [22]. Sexual activity is not associated with recurrent infection for postmenopausal women [23]. Prior genitourinary surgery, incontinence, cystoceles, and diabetes have been reported to be associated with infection in some studies [22, 23]. All of these variables are consistent with voiding abnormalities and complicated urinary tract infection.

Prostatic hypertrophy is the most important host factor contributing to urinary infection for elderly men in the community. Prostatic hypertrophy

causes urethral obstruction and turbulent urine flow, facilitating ascension of organisms into the bladder and prostate [24]. Once bacteria are established in the prostate, they are difficult to eradicate because of restricted diffusion of antimicrobials into the prostate and the development of prostate stones with aging. These stones provide a nidus where bacteria survive within a relatively protected environment. Relapse of urinary infection with bacteria re-emerging from a prostatic focus is common, although months or even years may intervene between episodes [6].

Long-Term-Care Residents

The major predictor of bacteriuria in the institutionalized elderly man or woman is functional impairment, including incontinence of bladder and bowel, immobility, and dementia (Table 15.1) [3, 7, 25]. Impaired bladder emptying is a common accompaniment of chronic neurological diseases that often precipitate the need for institutional care. These include Alzheimer's disease, Parkinson's disease, and cerebrovascular disease. Other chronic diseases including diabetes, as well as specific medication use, have not been associated with bacteriuria in the institutionalized population. Men who have incontinence managed with external condom-collecting devices have an increased prevalence of bacteriuria [26]. In these residents, bacteria colonizing the periurethral area may ascend into the bladder, particularly if there is kinking or obstruction of the drainage tube.

Immune and Inflammatory Response

There is a local and systemic host response to symptomatic urinary infection in the elderly [3]. Inflammation in the urinary tract is evidenced by pyuria, elevated urinary cytokine levels, and an immune response by local production of urine antibody to the infecting organism. Urinary infection with systemic manifestations, such as fever, is associated with elevated C-reactive protein and serum cytokine levels including il6, and a systemic antibody response to

Table 15.1 Host Variables Associated with Urinary ract Infection in an Elderly Population.

Community	
Women	Past history urinary infection Secretor status Diabetes on treatment Incontinence Cystoceles
Men	Prostatic hypertrophy
Institutionalized men or women	Age Functional status ↓ Mental status Immobility ↑ Co-morbidi ↑ Medications Incontinence urine Incontinence bowel Condom catheter

the infecting organism develops. These inflammatory markers normalize as systemic symptoms resolve with effective antimicrobial treatment.

Elderly subjects with asymptomatic bacteriuria also usually have evidence for a local inflammatory and immune response. Over 90% of institutionalized men or women with asymptomatic bacteriuria have pyuria [3, 27, 28]. Pyuria has not been shown to have any prognostic significance in the bacteriuric elderly [29]. Pyuria is also present in as many as 30% of institutionalized subjects without bacteriuria, presumably secondary to other inflammatory processes of the genitourinary tract [27]. Urinary antibody and cytokines such as IL1 α, IL6, or IL8 are also elevated in a high proportion of subjects [3]. About one-third of those with asymptomatic bacteriuria also have elevated serum antibody levels to their infecting uropathogens. All of these findings persist while bacteriuria persists.

Microbiology

Escherichia coli is the most frequent organism isolated from urinary infection in ambulatory elderly women [3] (Table 15.2). Symptomatic renal infection (pyelonephritis) is highly associated with virulence characteristics of the infecting organism. Gram-negative organisms other than *E. coli*, and Gram-positive organisms such as *Staphylococcus epidermidis*, are isolated more frequently in men. *E. coli* remains the most frequent infecting organism in institutionalized women, although proportionally less common than in noninstitutionalized women. *P. mirabilis* is usually the most frequent organism isolated from institutionalized men. Other Gram-negative organisms are common in institutionalized populations, including Enterobacteriaceae such as *Klebsiella pneumoniae*, *Serratia spp.*, *Citrobacter spp.*, *Enterobacter spp.*, and *Morganella morganii*. *Providencia stuartii* is an organism isolated virtually only from institutionalized subjects. *Pseudomonas aeruginosa* is common,

Table 15.2 Distribution of Infecting Bacteria Isolated from Elderly Populations with Asymptomatic Urinary Infection.

	Population (% of Isolates)						
	Asymptomatic				Symptomatic		
	Community		Institutionalized		Community	Institutionalized	
Organism	**Women**	**Men**[4]	**Women**[5]	**Men**[6]	**Female**[30]	**Female***[31]	**Male**[32]
E. coli	68%	19%	47%	11%	71%	39%	11%
P. mirabilis	0.8%	4.7%	27%	30%	—	26%	17%
Klebsiella pneumoniae	10%	4.7%	6.8%	5.9%	16%	9.0%	
Citrobacter spp.	—	—	2.6%	2.5%	—	1.7%	8.6%
Enterobacter spp.	—	1.7%	0.9%	1.7%	—	2.1%	—
Providencia spp.	—	—	6.8%	16%	—	4.8%	2.9%
Morganella morganii	—	—	1.7%	2.5%	—		
Pseudomonas aeruginosa	—	4.7%	5.1%	19%	—	5.5%	23%
Group B streptococci	10%	—	—	1.7%	—	2.4%	2.9%
Enterococcus spp.	4.8%	25%	6.0%	5%	—	5.5%	8.6%
Coagulase negative staphylococci	5.6%	39%	0.9%	1.7%	—	2.1%	5.7%
Staphylococcus aureus	—	—	—	2.5%	—	2.1%	2.9%

* Includes 19 men.

as are some Gram-positive organisms including *Enterococcus spp*. Group B streptococcus may be more frequent in diabetic subjects. Polymicrobial bacteriuria occurs in 10–25% of bacteriuric institutionalized elderly subjects.

Bacterial isolates from urinary infection in institutionalized populations are generally more resistant to antimicrobials than those isolated from elderly subjects in the community [13, 33]. This is attributed to intense exposure to antimicrobials for both urinary and other infections in the institutional population, together with opportunities for transmission of organisms given the close proximity of patients and shared caregivers [34].

Clinical Presentation

Symptomatic Urinary Infection

The clinical presentation of symptomatic infection for well elderly subjects living in the community is similar to younger populations (Table 15.3). Acute cystitis presents with lower tract irritative symptoms including dysuria, frequency, urgency, and suprapubic discomfort. New or increased incontinence is a common presenting symptom for the elderly. Acute pyelonephritis presents with costovertebral angle pain and tenderness, often with fever and associated lower tract symptoms. Men with prostatic infection may present with recurrent episodes of infection, both symptomatic and asymptomatic, following relapse from a prostatic source.

The clinical diagnosis of symptomatic urinary infection in the highly functionally impaired institutionalized elderly may be problematic [16, 35]. Communication is limited because of hearing loss, dysarthria, or mental impairment, and chronic symptoms associated with co-morbid illnesses complicate clinical assessment. Many residents with chronic genitourinary symptoms have a positive urine culture given the high prevalence of bacteriuria in institutionalized residents. However, chronic genitourinary symptoms persist when bacteriuria resolves and should not be attributed to

Table 15.3 Clinical Presentations of Symptomatic Urinary ract Infection in Elderly Populations.

Probable urinary infection:
- acute lower tract irritative symptoms (frequency, dysuria, urgency, increased incontinence)
- acute pyelonephritis (fever, flank pain, and tenderness)
- fever with localizing genitourinary signs or symptoms, including
  - urinary retention or obstruction of the urinary tract
  - chronic indwelling urethral catheter
  - hematuria

Unlikely urinary infection:
- fever without localizing genitourinary signs or symptoms, noncatheterized patient
- gross hematuria without fever
- clinical deterioration without localizing genitourinary signs or symptoms

Nonsymptomatic urinary infection:
- chronic incontinence
- other chronic genitourinary symptoms
- foul-smelling urine
- cloudy urine

urinary infection [19]. New acute symptoms, or acute deterioration in chronic symptoms such as incontinence, may be attributable to urinary infection.

About 75% of institutionalized subjects with an episode of gross hematuria are bacteriuric [36]. Hematuria is invariably explained by urolithiasis, tumors, or trauma from an indwelling catheter. Bacterial hemorrhagic cystitis is an uncommon cause of gross hematuria: it was measured at only 6.3/100,000 resident-days in one study. However, secondary systemic infection may occur when hematuria from any cause develops in bacteriuric subjects. As many as 30% of institutionalized subjects presenting with gross hematuria will subsequently become febrile.

Clinical Deterioration Without Localizing Symptoms

A diagnosis of "urinary infection" is frequently made for any bacteriuric long-term-care facility resident with "nonspecific" decline in clinical status but no localizing signs or symptoms [16, 37]. With the high prevalence of bacteriuria in this population, a positive urine culture is not sufficient for a diagnosis of symptomatic urinary infection in the absence of localizing genitourinary signs or symptoms. Fever without a clinically apparent source is also a problematic clinical presentation in bacteriuric residents. As the usual prevalence of positive urine cultures is as high as 50%, attributing fever to urinary infection on the basis of a positive urine culture, without concomitant localizing clinical findings, is usually an incorrect diagnosis. Only about 10% of episodes of fever in noncatheterized residents without localizing genitourinary findings are from a urinary source [14]. Thus, a diagnosis of urinary infection with this clinical presentation will be incorrect for as many as 90% of such episodes. Clinical features to discriminate between a urinary and non-urinary source have not been identified, beyond the presence of an indwelling catheter. Thus, the diagnosis of urinary infection in the febrile institutionalized resident without localizing findings is a diagnosis of exclusion [35, 38].

An unpleasant urinary odor and cloudy urine are sometimes interpreted as symptomatic infection, and antibiotics initiated. Odor may be a concomitant of urinary infection, likely due to polyamine production by infecting organisms in the urine. However, not all malodorous urine is attributable to bacterial infection, and infected urine is not universally malodorous [35]. Addressing unpleasant urinary odor is a problem of continence management, rather than infection. Cloudy urine may be due to pyuria or crystals and is also not an indication of symptomatic infection.

Laboratory Evaluation

Microbiological Diagnosis

A urine specimen for culture obtained prior to initiation of antimicrobial therapy is necessary to confirm a diagnosis of urinary infection. The urine culture also facilitates appropriate antimicrobial selection through organism identification and susceptibility testing. A positive urine culture cannot differentiate symptomatic from asymptomatic infection, but a negative urine culture obtained prior to initiating antimicrobial therapy effectively excludes

a diagnosis of urinary infection [38]. Urine culture should be obtained for all elderly men with a clinical diagnosis of urinary infection, and all elderly women who are institutionalized or with a clinical presentation consistent with pyelonephritis or complicated urinary infection [38]. Pre-therapy culture may not be consistently required for well ambulant women presenting with characteristic symptoms of cystitis and who have not recently received antimicrobial therapy. Such women should also, however, have a pre-therapy culture obtained if the diagnosis is uncertain, or if failure of therapy or early symptomatic recurrence following therapy occurs.

An accurate microbiologic diagnosis of urinary infection requires an optimally collected and transported urine specimen from which a uropathogen is isolated in appropriate quantitative counts. Two consecutive specimens with the same organism(s) isolated at $\geq 10^5$ CFU/mL are the criteria for diagnosis of asymptomatic bacteriuria in women. For symptomatic infection, a single specimen with $\geq 10^5$ CFU/mL is consistent with infection [39]. Lower quantitative counts of $\geq 10^4$ CFU/mL of a single organism are generally considered sufficient for microbiological diagnosis for patients with a clinical presentation of acute pyelonephritis or for men with symptomatic infection. Lower quantitative counts may also be consistent with infection in selected clinical settings including renal failure, diuretic therapy, or with some uncommon infecting organisms (e.g., *Candida albicans*). The urine culture may, rarely, be negative in patients infected with unusual pathogens (such as *Hemophilus influenzae* or *Ureaplasma urealyticum*) or when infection is proximal to a site of complete obstruction. The most common reason for a negative urine culture in an infected patient, however, is specimen collection after antimicrobial therapy has been initiated.

When functional limitations interfere with optimal voided specimen collection from elderly subjects, a collection method that limits contamination from colonizing genital organisms must be used. Clean-catch voided urine specimens can usually be obtained from men. Where external urine-collecting devices are used for continence management, urine specimens can be collected from a clean condom and drainage bag applied after appropriate cleaning of the glans [40, 41]. A quantitative count of $\geq 10^5$ CFU/mL is required to diagnose infection for specimens collected using external devices; lower quantitative counts should be interpreted as contamination. If voided urine specimens cannot be collected from women, in and out catheterization should be used when a specimen is necessary for clinical management [38]. A quantitative count of $\geq 10^3$ CFU/mL of organisms is sufficient for microbiologic diagnosis for a specimen obtained by catheterization. Collection methods using "pedi bags" or bedpans are subject to contamination and cannot be recommended for specimen collection for urine culture.

Other Diagnostic Tests

Urinalysis for pus cells or leukocyte esterase dipsticks identify pyuria, rather than bacteriuria. Nitrate dipstick tests also identify bacteriuria for common infecting organisms. These tests may have low sensitivity for bacteriuria and, if positive, do not differentiate symptomatic from asymptomatic infection [42]. A negative test for pyuria does, however, have high specificity and is useful in excluding urinary infection [38]. Blood cultures to document bacteremia

and confirm the infecting organism should be obtained from patients with severe clinical presentations such as high fever, hemodynamic instability, and acute confusional states.

Antimicrobial Management

Asymptomatic Infection

While studies directly evaluating antimicrobial therapy for asymptomatic infection in elderly individuals in the community are limited, available studies consistently report no benefits with antimicrobial therapy. Several prospective cohort studies and one randomized placebo-controlled study have enrolled both pre- and postmenopausal women, with no benefit with antimicrobial treatment identified and no reported differences in outcome with age [2]. A randomized trial of antimicrobial therapy in female residents of a geriatric apartment reported that treatment of asymptomatic bacteriuria decreased the prevalence of bacteriuria at 6 months' follow-up, but did not decrease the frequency of symptomatic episodes [12].

For the institutionalized elderly, prospective, randomized trials of antimicrobial therapy or no treatment for asymptomatic bacteriuria have consistently reported no benefits with therapy. There is no decrease in subsequent symptomatic episodes, no improvement in survival, and no improvement in chronic symptoms such as incontinence [2, 5, 6, 20, 43]. At least 50% of treated subjects will be bacteriuric again by 4 to 6 weeks following antimicrobial therapy. Treatment is associated with negative outcomes, including increased frequency of adverse drug effects, emergence of infection with more resistant organisms, and increased cost. Thus, asymptomatic bacteriuria in the institutionalized elderly should not be treated. As treatment is not indicated, screening for asymptomatic bacteriuria or pyuria is also not indicated [2].

Screening for and treatment of asymptomatic bacteriuria for all elderly subjects is recommended prior to an invasive genitourinary procedure with a high risk of mucosal trauma and bleeding [2]. Prophylactic antimicrobial therapy initiated prior to the procedure will prevent postprocedure bacteremia and sepsis [44].

Symptomatic Urinary Infection

Antimicrobial Use

Ideally, results of the urine culture and susceptibility testing will be available when antimicrobial therapy is initiated for symptomatic infection. This allows selection of a specific antimicrobial agent. However, this goal is usually realistic only for subjects with relatively mild symptoms. For elderly patients presenting with moderate or severe urinary symptoms, empirical therapy will usually be initiated pending results of urine culture. Parenteral antimicrobial therapy is required for more severe clinical presentations including hemodynamic instability, severe nausea and vomiting, or uncertain gastrointestinal absorption. The majority of symptomatic episodes, however, are adequately managed with oral therapy.

Given the difficulty in definitively diagnosing symptomatic infection in the functionally impaired long-term-care facility resident, consensus guidelines suggesting when antimicrobial therapy should be initiated have been

developed [45]. These suggest, for the noncatheterized patient, that antimicrobial therapy should be initiated for presumed urinary infection only if there is either acute dysuria or fever (>39.9 °C) accompanied by at least one localizing genitourinary symptom such as new or worsening urgency, frequency, suprapubic pain, gross hematuria, costovertebral angle tenderness, or urinary incontinence.

Once urine culture results of the specimen collected prior to initiation of empirical therapy become available, usually 48–72 hours after collection, antimicrobial therapy should be reassessed. Where appropriate, therapy should be altered to complete the course of treatment based on the results. Patients in whom parenteral therapy was initiated should also be reassessed at this time, and changed to oral therapy to complete the therapeutic course if the clinical response is satisfactory and oral therapy can be tolerated.

Antimicrobial Selection

Considerations relevant to selection of a specific antimicrobial for treatment of urinary infection are similar for elderly and younger populations [46]. Consistent alterations in antimicrobial pharmacokinetics occur with aging, including increased volume of distribution and decreased renal clearance. These are not of sufficient consistency or magnitude, however, to require antimicrobial selection or dose to be altered on the basis of age alone. Antimicrobial choice is determined by appropriateness of the agent for treatment of urinary infection, known or presumed susceptibilities of the infecting organism, whether oral or parenteral therapy is indicated, patient tolerance, and renal and hepatic function. Antimicrobial cost is also often a consideration. The history of any recent prior antimicrobial therapy should also be considered, as there is an increased likelihood of reinfection with an organism resistant to recent antimicrobial therapy.

When initial treatment with parenteral therapy is indicated, aminoglycosides such as gentamicin or tobramycin remain the antibiotics of choice [47]. Ampicillin or vancomycin may be added if enterococcal infection is a concern. After assessment of the initial response to therapy, and when the pretherapy urine culture and susceptibility results are known, a decision to continue aminoglycoside therapy, change to alternate parenteral therapy, or complete the therapeutic course with oral therapy is made. Ototoxicity and nephrotoxicity with aminoglycoside therapy are unlikely when therapy is limited to 48–72 hours' duration. Many other parenteral antimicrobials are also effective, including fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin) and extended-spectrum beta lactam antimicrobials (cefotaxime, ceftazidime, piperacillin) (Table 15.4). These may be selected depending on a patient's characteristics such as renal function, or local antimicrobial susceptibilities.

The preferred oral therapy (Table 15.5) for urinary infection with susceptible Gram-negative organisms remains trimethoprim/sulfamethoxazole (TMP/SMX), as this is a relatively inexpensive agent and there is extensive clinical experience with its use [47]. Some countries, including Sweden and the UK, have restricted use of trimethoprim/sulfamethoxazole because of concerns about sulfa allergy. Where sulfa allergy precludes use of the combination, trimethoprim alone may be used. There is, however, an increasing prevalence of trimethoprim and TMP/SMX resistance globally, and local or institutional organism susceptibilities should always be considered in selection

Table 15.4 Parenteral Antimicrobial Regimens for the reatment of Urinary ract Infection.

Agent	Dose*
Preferred:	
Gentamicin	1–1.5 mg/kg q8hr or 4–5 mg/kg q24hr
Tobramycin	1–1.5 mg/kg q8hr or 4–9 mg/kg q24hr
Ampicillin**	1g q4–6hr
Cefazolin	1–2 g q8hr
Other:	
Trimethoprim-sulfamethoxazole	160/800 mg bid
Piperacillin	3g q4hr
Piperacillin/tazobactam	4g/500 mg q8hr
Cefotaxime	1–2 g q8hr
Ceftriaxone	1–2 g q24hr
Cefepime	2g q12hr
Ceftazidime	0.5–2g q8hr
Aztreonam	1–2 g q6hr
Meropenem	500 mg q6hr
Ertapenem	1 g q24hr
Amikacin	5mg/kg q8hr or 15mg/kg q24hr
Vancomycin**	500 mg q6hr or 1g q12hr
Ciprofloxacin	400 mg q12hr
Levofloxacin	500 mg q24hr
Gatifloxacin	400 mg q24hr

* Doses for normal renal function.
** For Gram-positive organisms.

Table 15.5 Oral Antimicrobial Regimens for reatment of Acute Urinary ract Infection.

Agent	Dose*
First line	
Trimethoprim/sulfamethoxazole	160/800 mg bid
Trimethoprim	100 mg bid
Nitrofurantoin	50–100 mg qid or 100 mg bid
Amoxicillin**	500 mg tid
Other	
Amoxicillin/clavulanic acid	500 mg tid
Cephalexin	500 mg qid
Cefaclor	500 mg qid
Cefadroxil	1 g od or bid
Cefixime	400 mg od
Cefuroxime axetil	250 mg bid
Cefpodoxime proxetil	100–400 mg bid
Norfloxacin	400 mg bid
Ciprofloxacin	250–500 mg bid
Ofloxacin	200–400 mg bid
Levofloxacin	250–500 mg od
Gatifloxacin	400 mg od

* Doses for normal renal function.
** For susceptible Gram-positive organisms.

of empirical therapy. Nitrofurantoin remains an appropriate antimicrobial for treatment of selected episodes of lower tract infection. This agent should not be used for patients with renal infection or renal failure and is not effective for infection with *Klebsiella pneumoniae*, *P. mirabilis*, or *P. aeruginosa*. Nitrofurantoin is, however, usually effective for infection with *Enterococcus spp*., including vancomycin-resistant enterococci. Amoxicillin is indicated for the treatment of infections with susceptible Gram-positive organisms, such as group B streptococci or enterococci. There is a high prevalence of resistance of Gram-negative organisms to amoxicillin, so this agent is not appropriate for empirical therapy. Many cephalosporins are also effective, but are not generally recommended as first-line agents because of their relatively broad spectrum of activity and, often, increased cost. In addition, about 30% of *E. coli* bacteria in the community are resistant to cephalexin. Other effective agents with a wider bacterial spectrum include amoxicillin/clavulanic acid, oral extended-spectrum cephalosporins, and fluoroquinolones. In long-term-care facilities, the prevalence of fluoroquinolone resistance in Gram-negative organisms is increasing [34]. The strongest association of isolation of a fluoroquinolone-resistant enterobacteriaceae or *P. aeruginosa* in these settings is prior therapy with a fluoroquinolone antibiotic.

Duration of Therapy

Treatment of symptomatic bladder infection in elderly women may be less effective than younger women. This observation is consistent for any duration of therapy, but shorter courses of therapy, such as a single dose or 3 days, may be proportionately less effective than 7-day courses for older women [48]. A recent study, however, reported that 3 and 7 days of ciprofloxacin gave similar cure rates for selected ambulatory elderly women presenting with symptoms of acute cystitis and without underlying complicating factors [30]. Thus, 3 days' therapy is recommended for women meeting these characteristics. Presumably, women with a complicated infection should receive 7 days of therapy, but studies defining the optimal duration of therapy have not been reported. Women with renal infection and men with acute urinary infection should receive 10–14 days of therapy. More prolonged antimicrobial therapy may be considered, rarely, for selected patients. For men with early recurrent infection from a prostatic source, re-treatment with therapy of 6 or 12 weeks will achieve higher cure rates, and these longer courses are recommended [49, 50].

Suppressive antimicrobial therapy is given to prevent recurrent symptomatic episodes or progressive renal damage in subjects in whom infection cannot be eradicated. Clinical scenarios may include recurrent invasive infection in the presence of an underlying genitourinary abnormality that cannot be corrected, persistent infection stones where stone removal is incomplete, or frequent symptomatic recurrences from a prostatic source. This approach is appropriate only for carefully selected patients. Antimicrobial selection in these cases is based on susceptibilities of the known infecting organism. Continuing antimicrobial therapy should be reevaluated intermittently to ensure it remains appropriate and effective. For a small number of patients, therapy may need to be continued indefinitely.

Outcome Following Therapy

The usual microbiological cure rate at 4–6 weeks' post-therapy for ambulatory elderly women with a normal genitourinary tract is 70–80%. For ambulatory men with prostate infection, cure is only 40–50% at 4–6 weeks, even with more prolonged therapy [49, 50]. Prostatic infection may also be associated with very late relapses, occurring a year or more after therapy. Outcomes following treatment of institutionalized men or women are similar to other populations with complicated urinary infection. Recurrent infection, either relapse or reinfection, occurs by 4–6 weeks in about 50% of therapeutic courses. Thus, high post-therapy failure rates are the norm.

Post-therapy recurrence may be symptomatic or asymptomatic. The goal of treatment of urinary infection for any elderly population is to ameliorate symptoms, not to sterilize the urine. Thus, post-therapy urine cultures are not indicated unless urinary symptoms have persisted or recurred.

Prevention

Asymptomatic Infection

The high prevalence of bacteriuria in elderly populations is attributable to genetic variables, aging changes, and associated co-morbidities. Most of these variables are not modifiable, so prevention of asymptomatic infection is likely not feasible for most individuals [16]. General measures such as optimizing management of co-morbid illnesses and nutritional status are clearly desirable in elderly populations, but there is no evidence that these interventions limit bacteriuria.

Ingesting large quantities of cranberry juice is a proposed strategy to decrease bacteriuria in institutionalized women. A suppressive effect of cranberry juice could be mediated through an antiseptic effect of hippuric acid or interference with bacterial adherence. In a study of female residents in a long-term-care facility, daily cranberry juice intake was reported to decrease the prevalence of bacteriuria with pyuria compared with placebo [51]. However, neither bacteriuria itself nor symptomatic episodes were decreased, and the initial randomization was unbalanced, with individuals in the placebo group having a higher prior frequency of infection. Thus, a benefit of cranberry juice or other cranberry products remains unproven for elderly populations.

Devices used for incontinence management contribute to the acquisition of bacteriuria. These include condom catheter drainage, intermittent catheterization, and indwelling urethral catheters. Avoidance or limitation of use of these devices should be effective in decreasing the frequency of bacteriuria. For the individual elderly subject, however, this may not be achievable, as continence management requires consideration of goals other than bacteriuria, and use of these devices may not be avoidable.

Symptomatic Infection

Some elderly ambulatory women experience frequent recurrent episodes of acute cystitis. Where such episodes are of sufficient frequency to be distressing to the patient or interfere with daily activities, long-term low-dose prophylactic antimicrobial therapy may be effective to prevent recurrence [52]. Prophylactic therapy is usually taken at bedtime, and initially continued for 6

months or 1 year. This approach is appropriate only for women without underlying genitourinary abnormalities. It is not recommended for institutionalized women, as virtually all of these will have complicating factors.

The postmenopausal period is associated with estrogen decline and alterations in the genital mucosa and vaginal microflora. The lactobacilli that predominate in premenopausal vaginal flora and maintain the acidic pH are replaced by potential uropathogens such as *E. coli* as the pH increases [53]. These changes may contribute to an increased risk for urinary infection. Estrogen replacement therapy returns the flora to lactobacillus predominance and, theoretically, decreases the frequency of infection. The clinical evidence to support the use of estrogen replacement to prevent infection is, however, conflicting. Two prospective randomized trials of topical vaginal estrogen, one with estriol and one with estradiol, have reported a benefit in decreasing symptomatic episodes in women with frequent recurrent infection [54,55]. A third prospective randomized trial using a vaginal pessary with estriol reported no benefit [56], and a prospective observational study reported an increased frequency of urinary infection with the use of topical estrogen [11]. Studies evaluating systemic estrogen, including randomized clinical trials [57, 59], prospective observational studies [8], and case control studies [60], have consistently reported no reduced frequency of urinary infection in women receiving estrogen. In fact, some studies report an increased frequency of infection, potentially attributable to increased frequency of sexual intercourse, for women on estrogen replacement [8]. Thus, the role of estrogen therapy in managing recurrent urinary infection in postmenopausal women remains controversial. Any benefit is restricted to topical preparations, and the optimal agent, dose, and population that will benefit require further investigation.

There is an increased risk for invasive urinary infection with obstructing lesions such as prostatic hypertrophy, ureteric strictures, or urolithiasis. Prompt evaluation and early intervention to ensure adequate drainage should be effective in decreasing invasive infection. Antimicrobial therapy prior to an invasive procedure prevents postprocedure bacteremia and sepsis in bacteriuric subjects with a high likelihood of mucosal bleeding [44]. Antimicrobial therapy is initiated immediately prior to the invasive procedure, preferably within one hour, and not continued after the procedure. Such procedures include cystoscopy and transurethral resection of the prostate in men, and stent or nephrostomy tube insertion or mucosal biopsies in men and women. Replacement of a long-term indwelling urethral catheter is not an indication for antimicrobial therapy [61,62].

When intermittent catheterization is used for bladder emptying, the frequency of bacteriuria and antimicrobial treatment for symptomatic urinary infection is similar in subjects whether a sterile or clean technique is used for catheterization [63]. Thus, in the long-term-care setting, a clean technique is appropriate and less costly.

Long-Term Indwelling Catheters

Epidemiology

From 5 to 10% of elderly residents of institutions have voiding managed with long-term indwelling catheters [1,64]. The usual indications for chronic

catheterization are urinary retention and continence management. A higher proportion of women have chronic catheters, as external collecting devices for continence control are not an option. A resident with a long-term indwelling catheter is always bacteriuric, usually with two to five organisms [65]. Morbidity from urinary infection is increased in these individuals. Febrile urinary infection, often without other localizing findings, is the most common clinical presentation of symptomatic infection [15]. Other complications include urolithiasis, particularly bladder stones, and local complications such as urethral abscesses. Renal inflammation consistent with acute pyelonephritis is present at autopsy more frequently in elderly subjects with a chronic indwelling catheter compared to bacteriuric individuals without catheters [66]. Because of the increased risk of complications, chronic indwelling catheters should only be used when there are compelling clinical indications, and the need for continued use in a given patient should be repeatedly reassessed. Residents with an indwelling urinary catheter also have increased mortality compared to noncatheterized residents, but this difference is likely attributable to greater co-morbidities and impaired functional status of catheterized residents, rather than being directly attributable to catheterization.

Microbiology

The indwelling catheter becomes coated with a bacterial biofilm consisting of microorganisms, extracellular polysaccharide, and urine components including metal ions and Tamm-Horsfall protein [67]. Organisms in the biofilm environment are relatively protected from both antimicrobials and the host immune response. Urine specimens obtained for culture through the catheter reflect the bacteriology of the catheter biofilm, rather than bladder urine [68, 69]. The indwelling catheter should be changed, and a urine specimen obtained through the newly inserted catheter, prior to initiating antimicrobial treatment. This ensures that bladder urine rather than biofilm is sampled for culture. Biofilm is also the cause of encrustation and catheter blocking, which is a problem for some patients [70]. Obstruction is usually caused by concretions formed by urease-producing organisms including *P. mirabilis* or *P. stuartii*. The biofilm also provides an environment within which organisms may persist during antimicrobial therapy, serving as a reservoir for organisms causing relapse following therapy.

Clinical Presentation

Symptomatic urinary infection in subjects with an indwelling urethral catheter is most frequently manifested by fever [15]. There may be localizing signs such as obstruction or catheter bypassing, or evidence of trauma to the mucosa, such as hematuria. In the absence of localizing findings, the diagnosis of urinary infection is presumptive. Fever without localizing signs or symptoms is more likely of urinary origin in patients with chronic indwelling catheters than bacteriuric subjects without catheters [14]. However, the urinary tract is still the source of fever in a minority of catheterized individuals, about 30–40% of such episodes. The consensus guideline suggests antimicrobial therapy should be initiated for presumed urinary infection in patients with a chronic indwelling catheter if one or more of temperature >39.9 °C, new costovertebral angle tenderness, rigors, or new delirium are present [43].

Treatment

Subjects with a chronic indwelling catheter have a high likelihood of emergence of resistance in infecting urinary organisms when antimicrobial therapy is given for any indication. Antimicrobial treatment of asymptomatic bacteriuria in a catheterized patient results in a significant increase in reinfection with more resistant organisms compared to no treatment, but no decrease in episodes of symptomatic urinary infection [71]. Thus, asymptomatic subjects should not be treated. Pyuria is universal in subjects with a chronic indwelling catheter and is not an indication for antimicrobial therapy.

The selection of antimicrobial therapy for symptomatic infection in elderly catheterized subjects is similar to other elderly populations with urinary infection. Where possible, antimicrobial therapy should be withheld pending urine culture results. If empirical therapy is initiated prior to culture results' becoming available, the antimicrobial choice should be reassessed once the infecting organism and susceptibilities are known. The catheter should be changed immediately prior to institution of antibiotics to facilitate urine specimen collection and improve therapeutic outcomes [72]. Catheter replacement immediately prior to therapy results in more rapid resolution of fever and a lower frequency of symptomatic relapse. The duration of therapy should be as short as possible, to limit emergence of resistant organisms; usually 7 days if a prompt clinical response occurs. There are no clinical studies, however, that define the optimal length of therapy.

Prevention

Currently, specific interventions to decrease the frequency of bacteriuria or complications of urinary infection in elderly subjects with chronic long-term indwelling catheters have not been defined. Catheter care to avoid obstruction and mucosal trauma will prevent symptomatic episodes. Maintenance of a closed drainage system delays onset of bacteriuria in subjects with short-term indwelling catheters, but benefits for a long-term indwelling catheter have not been studied. Routine catheter change, periurethral catheter care [73], or catheter irrigation [74] do not decrease the frequency of symptomatic infection or complications and are not recommended. Mucosal trauma may occur with catheter change, leading to fever. However, this is uncommon, and antibiotics are not recommended prior to catheter change. The most effective way to prevent catheter-associated urinary infection is to restrict use of the chronic indwelling catheter as much as possible.

Xanthogranulamatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a rare presentation of chronic pyelonephritis. It is characterized by infiltration and destruction of the kidney, often with extension of the process into adjacent tissues [75–78]. Usually only one kidney is affected, although there are reports of bilateral involvement. The characteristic finding on histopathology is lipid-laden macrophages, called *foam cells* [75]. The etiology of this unique process is not known. However, infection is consistently present, and urolithiasis, obstruction, and a nonfunctioning kidney are characteristic urological findings.

Xanthogranulomatous pyelonephritis may occur at any age, but is more common in middle-aged and older individuals, and is two to three times more common in women than men. Patients present with subacute or chronic

symptoms. Over two-thirds of patients have a fever, usually with flank pain. A flank mass is sometimes present [75]. Local extension to involve perinephric tissues and sinus formation may occur. *E. coli* or *P. mirabilis* are isolated from over 90% of cases [77, 78]. The diagnosis can usually be made by computed tomography [76, 77]. Characteristic findings include an enlarged kidney, calculi in the renal pelvis, and a poorly enhancing mass. The "bear paw" sign—multiple, rounded low-density areas with enhancing rings in a hydronephrotic area—is characteristic [75].

Patients with xanthogranulomatous pyelonephritis cannot be cured by antimicrobial therapy alone and require surgical removal of the affected kidney or areas of the kidney. Nephrectomy is usually necessary. Cases with localized involvement may be cured with segmental resection together with antibiotic therapy. Antimicrobial therapy is given based on the organisms isolated from culture. Postsurgical recurrence does not occur.

References

1. Warren, J.W. Catheter-associated urinary tract infections. *Infect. Dis. Clinics North Am*. 1997; 11:609–622.
2. Nicolle, L.E., Bradley, S., Colgan, R. et al. IDSA guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin. Infect. Dis*. 2005; 40: 653–654.
3. Nicolle, L.E. Asymptomatic bacteriuria in the elderly. *Infect. Dis. Clinics North Am*. 1997; 11:647–662.
4. Mims, A.D., Norman, D.C., Yamamina, R.H., et al. Clinically inapparent (asymptomatic) bacteriuria in ambulatory elderly men: Epidemiological, clinical and microbiological findings. *J. Am. Geriatr. Soc*. 1990; 38:1209–1214.
5. Nicolle, L.E., Mayhew, W.J., Bryan, L. Prospective randomized comparison of therapy and no therapy for asymptomatic bacteriuria in institutionalized elderly women. *Am. J. Med*. 1987; 83:27–33.
6. Nicolle, L.E., Bjornson, H.J., Harding, G.K.M., et al. Bacteriuria in elderly institutionalized men. *N. Engl. J. Med*. 1983; 309:1420–1426.
7. Abrutyn, E., Mossey, J., Levison, M., et al. Epidemiology of asymptomatic bacteriuria in elderly women. *J. Am. Geriatr. Soc*. 1991; 39:388–393.
8. Kasviki-Charvati, P., Drolette-Kefakis, B., Papanayiotou, P.C., et al. Turnover of bacteriuria in old age. *Age and Ageing* 1982; 11:169–174.
9. Monane, M., Gurwitz, J.H., Lipsitz, L.A., et al. Epidemiology and diagnostic aspects of bacteriuria. A longitudinal study in older women. *J. Am. Geriatr. Soc*. 1995; 43:618–622.
10. Ruben, F.L., Dearwater, S.R., Norden, C.W., et al. Clinical infections in the noninstitutionalized geriatric age group. Methods utilized and incidence of infections. *Am. J. Epidemiol*. 1995; 141:145–157.
11. Jackson, S.L., Boyko, E.J., Scholes, D., et al. Predictors of urinary tract infection after menopause: A prospective study. *Am. J. Med*. 2004; 117:903–911.
12. Boscia, J.A., Kobasa, W.D., Knight, R.A., et al. Therapy vs. no therapy for bacteriuria in elderly ambulatory non-hospitalized women. *JAMA* 1987; 257:1067–1071.
13. Nicolle, L.E., Strausbaugh, L.J., Garibaldi, R.A. Infections and antibiotic resistance in nursing homes. *Clin. Micro Rev*. 1996; 9:1–17.
14. Orr, P., Nicolle, L.E., Duckworth, H., et al. Febrile urinary infection in the institutionalized elderly. *Am. J. Med*. 1996; 100:71–77.
15. Warren, J.W., Damron, D., Tenney, J.H., et al. Fever, bacteremia, and death as complications of bacteriuria in women with long-term urethral catheters. *J. Infect. Dis*. 1987; 155:1151–1158.

16. Nicolle, L.E., SHEA Long-Term Care Committee. Urinary tract infections in long-term care facilities. *Infect. Cont. Hosp. Epidemiol*. 2001; 22:167–175.
17. Nicolle, L.E., Friesen, D., Harding, G.K.M., et al. Hospitalization for acute pyelonephritis in Manitoba, Canada, during the period from 1989 to 1992. Impact of diabetes, pregnancy and aboriginal origin. *Clin. Infect. Dis*. 1996; 22: 1051–1056.
18. High, K., Bradley, S., Loeb, M., et al. A new paradigm for clinical investigation of infectious syndromes in older adults: Assessing functional status as a risk factor and outcome measure. *J. Am. Geriatr. Soc*. 2005; 53:528–535.
19. Boscia, J.A., Kobasa, W.D., Abrutyn, E., et al. Lack of association between bacteriuria and symptoms in the elderly. *Am. J. Med*. 1986; 81:979–982.
20. Ouslander, J.G., Schapira, M., Schnelle, J.F., et al. Does eradicating bacteriuria affect the severity of chronic urinary incontinence in nursing home residents? *Ann. Intern. Med*. 1995; 12:749–754.
21. Nicolle, L.E. A practical approach to the management of complicated urinary tract infection. *Drugs and Aging* 2001; 18:243–254.
22. Raz, R., Gennesin, Y., Wasser, J., et al. Recurrent urinary tract infection in post-menopausal women. *Clin. Infect. Dis*. 2000; 30:152–156.
23. Hu, K.K., Boyko, E.J., Scholes, D., et al. Risk factors for urinary tract infections in postmenopausal women. *Arch. Intern. Med*. 2004; 164:
24. Nickel, J.C. Prostatitis: Evolving management strategies. *Urol. Clinics North Am*. 1999; 4:737–751.
25. Nicolle, L.E., Henderson, E., Bjornson, J., et al. The association of bacteriuria with resident characteristics and survival in elderly institutionalized males. *Ann. Intern. Med*. 1987; 106:682–686.
26. Ouslander, J.G., Grangold, B., Chen, S. External catheter use and urinary tract infections among incontinent male nursing home patients. *J. Am. Geriatr. Soc*. 1987; 35:1063–1067.
27. Boscia, A.J., Abrutyn, E., Levison, M.E., et al. Pyuria and asymptomatic bacteriuria in elderly ambulatory women. *Ann. Intern. Med.* 1989; 110:404–405.
28. Rodgers, K., Nicolle, L.E., McIntyre, M., et al. Pyuria in institutionalized elderly subjects. *Can. J. Infect. Dis*. 1991; 2:142–146.
29. Nicolle, L.E., Brunka, J., McIntyre, M., et al. Asymptomatic bacteriuria, urine antibody, and survival in the institutionalized elderly. *J. Am. Geriatr. Soc*. 1992; 40:607–613.
30. Vogel, T., Verreault, R., Gourdeau, M., et al. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: A double-blind randomized controlled trial. *Can. Med. Assoc. J*. 2004; 170:469–473.
31. Smith, M.A., Duke, W.M. A retrospective review of nosocomial infections in an acute rehabilitative and chronic population at a large skilled nursing facility. *J. Am. Geriatr. Soc*. 1994; 42:45–49.
32. Jacobson, C., Strausbaugh, L.J. Incidence and impact of infection in a nursing home care unit. *Am. J. Infect. Cont*. 1990; 18:151–159.
33. Wiener, J., Quinn, J.P., Bradford, P.A., et al. Multiple antibiotic-resistant Klebsiella and *Escherichia coli* in nursing homes. *JAMA* 1999; 281:517–522.
34. Muder, R.R., Brennen, C., Goetz, M., et al. Association with prior flouroquinolone therapy of widespread ciprofloxacin resistance among Gram-negative isolates in a Veteran's Affairs Medical Center. *Antimicrob. Agents Chemother*. 1991; 35: 256–258.
35. Nicolle, L.E. Urinary tract infections in the elderly: Symptomatic or asymptomatic? *Int. J. Antimicrob. Agents* 1999; 11:265–268.
36. Nicolle, L.E., Orr, P., Duckworth, H., et al. Gross hematuria in residents of long term care facilities. *Am. J. Med*. 1993; 94:611–618.
37. Berman, P., Hogan, B., Fox, R.A. The atypical presentation of infection in old age. *Age and Ageing* 1987; 16:201–207.

38. Bentley, D.W., Bradley, S., High, K., et al. Practice guideline for evaluation of fever and infection in long-term care facilities. *Clin. Infect. Dis*. 2000; 31:640–653.
39. Rubin, R.H., Shapiro, E.D., Andriole, V.T., et al. Evaluation of new anti-infective drugs for the treatment of urinary tract infection. *Clin. Infect. Dis*. 1992; 15(Suppl 1): S216–S227.
40. Nicolle, L.E., Harding, G.K.M., Kennedy, J., et al. Urine specimen collection and external devices for diagnosis of bacteriuria in elderly incontinent men. *J. Clin. Microbiol*. 1988; 26:1115–1119.
41. Ouslander, J.G., Greengold, B.A., Silverblatt, T.J., et al. An accurate method to obtain urine for culture in men with external catheters. *Arch. Intern. Med*. 1987; 147:286–288.
42. Ouslander, J.G., Schapira, M., Finegold, S., et al. Accuracy of rapid urine screening tests among incontinent nursing home residents with asymptomatic bacteriuria. *J. Am. Geriatr. Soc*. 1995; 43:772–775.
43. Abrutyn, E., Mossey, J., Berlin, J.A., et al. Does asymptomatic bacteriuria predict mortality and does antimicrobial treatment reduce mortality in elderly ambulatory women? *Ann. Intern. Med*. 1994; 120:827–833.
44. Cafferkey, M.T., Falkiner, F.R., Gillespie, W.A., et al. Antibiotics for the prevention of septicemia in urology. *J. Antimicrob. Chemother*. 1982; 9:471–477.
45. Loeb, M., Bentley, D.W., Bradley, S., et al. Development of minimum criteria for the initiation of antibiotics in residents of long term care facilities: Results of a consensus conference. *Infect. Cont. Hosp. Epidemiol*. 2001; 22:120–124.
46. Stalam, M., Kaye, D. Antibiotic agents in the elderly. *Infect. Dis. Clinics North Am*. 2004; 18:533–549.
47. Nicolle, L.E., Bentley, D., Garibaldi, R., et al. Antimicrobial use in long-term care facilities. *Infect. Cont. Hosp. Epidemiol*. 2000; 21:537–545.
48. Saginur, R., Nicolle, L.E. Canadian Infectious Diseases Society Clinical Trials Study Group. Single dose compared with three days norfloxacin for treatment of uncomplicated urinary infection in women. *Arch. Intern. Med*. 1992; 152: 1233–1232.
49. Gleckman, R., Crowley, M., Natsios, G.A. Therapy of recurrent invasive urinary tract infections of men. *N. Engl. J. Med*. 1979; 301:878–880.
50. Smith, J.W., Jones, S.R., Reed, W.P., et al. Recurrent urinary tract infections in men. *Am. Intern. Med*. 1979; 544–548.
51. Avorn, J., Monane, M., Gurwitz, J.H., et al. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994; 271:751–754.
52. Stapleton, A., Stamm, W.E. Prevention of urinary tract infection. *Infect. Dis. Clinics North Am*. 1997; 11:719–734.
53. Pabich, W.L., Fihn, S.D., Stamm, W.E., et al. Prevalence and determinants of vaginal flora alterations in postmenopausal women. *J. Infect. Dis*. 2003; 188: 1054–1058.
54. Raz, R., Stamm, W. A controlled trial of intravaginal estriol in post-menopausal women with recurrent urinary tract infections. *N. Engl. J. Med*. 1993; 329: 753–758.
55. Erikson, B.C. A randomized, open, parallel group study on the preventive effect of an estradiol-releasing vaginal ring on recurrent urinary tract infections in postmenopausal women. *Am. J. Obstet. Gyn*. 1999; 180:1072–1079.
56. Raz, R., Colodner, R., Rohana, Y., et al. Effectiveness of estriol containing vaginal pessaries and nitrofurantoin macrocrystal therapy in the prevention of recurrent urinary tract infection in post-menopausal women. *Clin. Infect. Dis*. 2003; 36:1362–1368.
57. Brown, J.W., Vittinghoff, E., Kanaga, A.M., et al. Urinary tract infections in postmenopausal women: Effect of hormone therapy and risk factors. *Obstet. Gyn*. 2001; 98:1045–1052.

58. Ouslander, J.G., Greendale, G.A., Uman, G., et al. Effects of oral estrogen and progestin on the lower urinary tract among female urinary home residents. *J. Am. Geriatr. Soc*. 2001; 49:803–807.
59. Cordozo, L., Bennes, C., Abbott, D. Low dose oestrogen prophylaxis for recurrent urinary tract infections in elderly women. *Br. J. Obstet Gyn*. 1998; 105:403–407.
60. Orlander, J.D., Jick, S.S., Dean, A.P., et al. Urinary tract infections and estrogen use in older women. *J. Am. Geriatr. Soc*. 1992; 40:817–820.
61. Jewes, L.A., Gillespie, W.A., Leadbetter, A., et al. Bacteriuria and bacteremia in patients with long-term indwelling catheters—A domiciliary study. *J. Med. Microbiol*. 1988; 26:61–65.
62. Bregenzer, T., Frei, R., Widmer, A.F., et al. Low risk of bacteremia during catheter replacement in patients with long term urinary catheters. *Arch. Intern. Med*. 1997; 157:521–525.
63. Duffy, L.M., Cleary, J., Ahern, S., et al. Clean, intermittent catheterization: Safe, cost-effective bladder management for male residents of VA nursing homes. *J. Am. Geriatr. Soc*. 1995, 43:865–870.
64. Nicolle, L.E. The chronic indwelling catheter and urinary infection in long term care facility residents. *Infect. Cont. Hosp. Epidemiol*. 2001; 22:316–321.
65. Warren, J.W., Tenney, J.H., Hoopes, J.M., et al. A prospective microbiologic study of bacteriuria in patients with chronic indwelling urethral catheters. *J. Infect. Dis*. 1982; 146:719–723.
66. Warren, J.W., Muncie, H.L., Jr., Hall-Graggs, M. Acute pyelonephritis associated with bacteriuria during long-term catheterization. A prospective clinicopathological study. *J. Infect. Dis*. 1988; 158:1341–1346.
67. Donlan, R.M. Biofilm formation: A clinically relevant microbiological process. *Clin. Infect. Dis*. 2001; 33:1387–1392.
68. Grahn, D., Norman, D.C., White, M.L., et al. Validity of urine catheter specimens for diagnosis of urinary tract infection in the elderly. *Arch. Intern. Med*. 1985; 145:1858–1860.
69. Tenney, J.H., Warren, J.W. Bacteriuria in women with long term catheters. Paired comparison of indwelling and replacement catheters. *J. Infect. Dis*. 1988; 157: 199–202.
70. Kunin, C.M. Blockage of urinary catheters: Role of microorganisms and constituents of the urine on formation of encrustations. *J. Clin. Epidemiol*. 1989; 42:835–842.
71. Warren, J.W., Anthony, W.C., Hoopes, J.M., et al. Cephalexin for susceptible bacteriuria in afebrile long-term catheterized patients. *JAMA* 1982; 248:454–458.
72. Raz, R., Schiller, D., Nicolle, L.E. Chronic indwelling catheter replacement prior to antimicrobial therapy for symptomatic urinary infection. *J. Urol*. 2000; 164: 1254–1258.
73. Burke, J.P., Garibaldi, R.A., Britt, M.R., et al. Prevention of catheter-associated urinary tract infections. Efficacy of daily meatal care regimens. *Am. J. Med.* 1981; 70:655–658.
74. Muncie, H.L., Hoopes, J.M., Damron, D.J., et al. Once daily irrigation of long term urethral catheters with normal saline. *Arch. Intern. Med*. 1989; 149:441–443.
75. Kudalkan, D., Remi, P., Canha, B.A. Xanthogranulomatous pyelonephritis complicated by psoas abscess. *Heart & Lung* 2004; 33:339–342.
76. Zorzos, I., Moutzouris, V., Korakianitis, G., Katsou, G. Analysis of 39 cases of xanthogranulomatous pyelonephritis with emphasis on CT findings. *Scand. J. Urol. Nephrol*. 2003; 37:342–347.
77. Eastham, J., Ahlering, T., Skinner, E. Xanthogranulomatous pyelonephritis: Clinical findings and surgical considerations. *Urology* 1994; 43:295–299.
78. Chuang, C.-K., Lai, M.-K., Chang, P.-L., Huang, M.-H., Chu, S.-H., Wu, C.-J., Wu, H.-R. Xanthogranulomatous pyelonephritis: Experience in 36 cases. *J. Urol.* 1992; 147:333–336.

16

Incontinence in the Elderly

Michael Ingber, Pradeep Nagaraju and Ananias Diokno

Introduction

Urinary incontinence is a highly prevalent condition worldwide, affecting men and women of all cultures and worsening with increased age [1]. Those over the age of 60 have incontinence rates ranging from 10 to 35%. These rates increase to nearly 50% in homebound or institutionalized elderly patients [2]. Despite the high prevalence of incontinence in the elderly, less than half seek treatment. The barriers to seeking treatment include embarrassment, ignorance of available treatment, and the sense that this is a normal process of aging [3].

There are significant medical, social, psychological, and economic implications of incontinence in the geriatric population, all of which may negatively impact their quality of life. Chronic urinary incontinence can lead to persistent perineal dermatitis and exacerbation of decubitus ulcers in those with restricted mobility. Recurrent urinary tract infections and sepsis can be associated with long-term urinary incontinence. Additionally, falls and fractures occur in the elderly hastening to void due to incontinence.

Chronic urinary incontinence can result in loss of self-esteem, depression, social isolation, and dependence on caregivers. There exists an independent link between urge incontinence and the decision to institutionalize an elderly individual. Providers need to be aware of effective treatment available for incontinence to reduce the medical and psychosocial complications related to it. Early treatment may help reduce the burgeoning direct medical costs of incontinence, which was estimated at $16.3 billion in the United States 1995 [4].

Age and Incontinence

Urinary continence is established by a complex series of events that involve the nervous system, bladder, and urinary sphincter (Figure 16.1). Medical events and normal aging processes can affect any one of these systems and lead to urinary incontinence. The normal bladder is compliant and allows urine to accumulate without a large increase in intravesical pressure. The urinary sphincter mechanism maintains continence by keeping the bladder neck closed during filling. Voluntary and involuntary neurological pathways assist in maintaining continence as well as in voiding.

Continence is established by bladder muscle relaxation and closure of the bladder neck and urethra. This is mediated by sympathetic nerves and beta-2

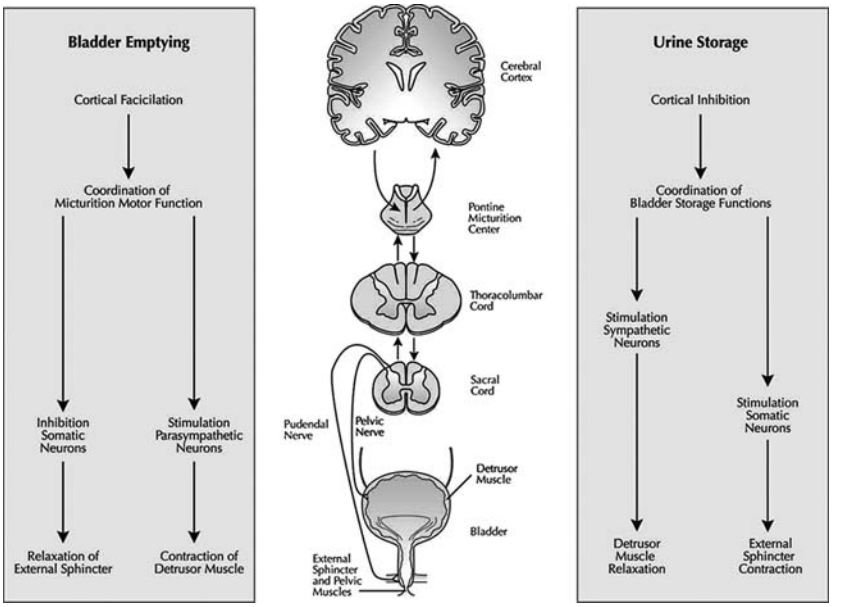

Fig. 16.1 The cerebrospinal axis and micturition pathway. Bladder storage is facilitated by continuous inhibition of the PMC. Voluntary relaxation of the external Urethral sphincter precedes bladder emptying and the micturition reflex.

receptors in the bladder and alpha-1 receptors in the bladder neck and urethra. Additionally, somatic innervation of the pelvic floor via the pudendal nerves allows for voluntary contraction of the external urinary sphincter. Voiding occurs through bladder contraction and bladder neck and urethral relaxation. Bladder contraction is mediated by parasympathetic nerves and muscarinic receptors in the bladder. Additionally, voluntary relaxation of the external sphincter is necessary.

During bladder filling, continence is dependent on central nervous inhibition of parasympathetic innervation to the bladder. Simultaneously, there is stimulation of sympathetic innervation to the bladder and bladder neck from the sacral reflex arc. This leads to a relaxed detrusor muscle and a closed bladder neck. Voluntary contraction of the external urinary sphincter further enhances continence at large urinary volumes.

Voluntary voiding is initiated by the frontal lobe. The pontine micturition center (PMC), located in the dorsolateral pons, is responsible for coordinated voiding, or detrusor-sphincter synergy [5]. This synergy involves contraction of the detrusor muscle (via parasympathetics) with simultaneous relaxation of the bladder neck and sphincter. In the resting state, there is constant inhibitory influence on the PMC from the frontal lobe, thereby preventing the reflex bladder contraction and bladder neck/sphincter relaxation. When the decision to void arises, inhibitory influence of the frontal lobe is removed. The external urinary sphincter is voluntarily relaxed and the voiding reflex, coordinated by the PMC, is initiated.

Disruption in any portion of this complex neural pathway can lead to dysfunctional voiding, and possibly urinary incontinence. A lesion above the PMC would leave coordinated voiding intact; however, inhibitory influence of the frontal lobe may become disrupted. This could lead to a lower threshold for

involuntary detrusor contractions from bladder distension or bladder irritation. This type of incontinence is noted by symptoms of urgency incontinence and may be seen after cerebrovascular accidents, Parkinson's disease, or Alzheimer disease [5].

Disruption of signaling from the PMC can be seen with injury to the spinal cord below the brainstem. Back surgery for prolapsed discs, multiple sclerosis, and traumatic spinal cord injuries are examples frequently seen. In addition to urge incontinence, these patients may also experience overflow incontinence due to elevated postvoid residual volumes from the closed bladder neck and sphincter during bladder contraction. Long-term sequelae may include chronic urinary tract infections and renal deterioration.

Injury to lower motor neurons, specifically those that innervate the bladder and pelvic floor (pelvic and pudendal nerves), results in either inability of the bladder to contract or inability to sense bladder fullness. This is seen after pelvic surgery or diabetic neuropathy of pelvic nerves. These patients may present with infrequent voiding, infection, urinary retention, and overflow incontinence.

Anatomy plays a vital role in continence mechanisms. In both genders, there exists an external urethral sphincter comprised of striated muscle under voluntary control. Traditionally, the smooth muscle components of the bladder neck are thought of as the internal urethral sphincter. In men, the bladder neck, prostatic urethra, and the membranous urethra are considered to function as such. Women have abundant smooth muscle fibers, predominantly in the bladder neck and proximal urethra. In addition, the muscles and fascial layers of the pelvic floor provide urethral support and aid in continence. Injury to or loss of function of this anatomical complex often leads to stress urinary incontinence.

The role of aging in the development of urinary incontinence is perhaps more evident in women. Postmenopausal women lose the beneficial effects of estrogen on the urethral and vaginal mucosa. This leads to thinning and atrophy of the urethral epithelium, and subsequently may lead to lower urinary tract symptoms including urgency, dysuria, and nocturia [6]. Atrophy of the urogenital tract may prevent normal coaptation of the urethra and thereby exacerbate stress urinary incontinence [7]. Older women, especially those with multiparity, may lose the normal anatomical support of the pelvic floor, leading to urethral and bladder neck hypermobility. Increases in intraabdominal pressures such as coughing or sneezing lead to stress urinary incontinence. There may also be a progressive loss of striated muscle cells in the rhabdosphincter with age [8]. Pfisterer et al. [9] studied voiding diaries and urodynamic tests on 85 women and noticed declining maximum urethral closing pressure, detrusor contraction strength, and bladder sensation with age.

Elderly men develop similar lower urinary symptoms with age. Incontinence rates, however, are less than those for elderly females. Prostatic enlargement or benign prostatic hyperplasia (BPH) is a predominant factor and is discussed later in this chapter.

In conclusion, the physiological aging process makes aged persons more vulnerable to urological pathologies such as incontinence, urinary tract infections, and prolapse. However, factors more often related to incontinence are co-morbidity, polypharmacy, and geriatric functional deterioration (see Chapter 1).

Evaluation of the Incontinent Patient

Perhaps the most important aspect in the evaluation of geriatric incontinence is the history of the incontinence. Often times, the history will establish a most likely diagnosis. In the office, caregivers should be present to assist with details of incontinence symptoms. The events preceding incontinence are important to ascertain. Urgency to void leading to incontinence is termed *urge incontinence*. Coughing, sneezing, laughing leading to incontinence is termed *stress incontinence*. *Mixed incontinence* is a combination of urgency symptoms and stress activities leading to incontinence. Patients who have continual leakage, have leakage with positional changes, or are unaware of precipitating causes may have mixed incontinence or even have urinary fistula. Validated questionnaires are often helpful to categorize incontinence, to evaluate the impact upon quality of life, and to assess response to therapies.

Fluid intake should be noted, with attention to frequency and timing of beverages, as well as intake of caffeine. One should inquire about toileting habits, including daytime and nighttime voiding frequency, and whether or not voiding is prompted by severe urgency. An assessment of bowel function must be made. Constipation in the elderly plays an important role in voiding dysfunction. Most elderly with incontinence will wear some type of absorbent diaper or pad if incontinence is bothersome. The number of these used per day should be quantified. Women should be asked about parity, menopausal status, and use of any hormones.

The evaluator should inquire about past medical history, including any major disease that may affect urological function. In addition, any history of trauma, congenital anomalies, or prior urological disease should be noted. A detailed surgical history should be obtained, specifically neurosurgical procedures and abdominal or pelvic surgeries. Medication history is important, as certain pharmaceutical agents may contribute to incontinence.

All patients presenting with urinary incontinence require a physical examination, with particular attention to neurological, pelvic, and rectal examination. Cognitive assessment should be made to assess for dementia. Neurological examination should test for gait, gross motor, and gross sensory deficits. Focal neurological testing should assess for perineal sensation, anal sphincter tone, and bulbocavernosus reflex. In the male, digital rectal exam should be performed to evaluate for prostate size and tenderness. In both genders, rectal exam is performed to evaluate for fecal impaction, rectal tone, and any masses.

Routine abdominal examination should be performed. Abdominal distention or palpable masses should be noted. In this case, consider constipation, ascites, or intraperitoneal tumors giving rise to voiding symptoms. Suprapubic fullness or tenderness may be suggestive of urinary retention.

Pelvic examination in the female should assess for evidence of pelvic organ prolapse and urogenital atrophy. A provocative stress test can be performed in patients with a full bladder by asking the patient to cough while in the lithotomy position. A bimanual exam should be performed to evaluate for any pelvic masses [5]. Examination for prolapse and incontinence should be repeated in the upright squatting position in patients who complain of symptoms that are not easily recognizable while in the lithotomy position.

Finally, the measurement of the postmicturation residual urine volume may be of value to define the pathogenesis of incontinence. For example, a high residual volume is common in overflow incontinence, detrusor hyperactivity with impaired contractility, and bladder outlet obstruction.

Laboratory evaluation in the incontinent elderly patient should begin with dipstick analysis of the urine. Urinalysis results can dictate further lab studies as necessary. For example, hematuria may require microanalysis and urine cytology to screen for urothelial cancer. Proteinuria may require further urine studies to evaluate glomerular function. Urine cultures should be ordered in the elderly patient with new-onset incontinence and signs of infection. The need for radiological testing is often based on suspicion for urinary malignancies or upper urinary tract disease (stones, hydronephrosis, etc.).

Often, incontinence in the elderly is multifactorial with recumbancy, bowel dysfunction, existing medical conditions, and medications further impacting an altered continence mechanism. In these cases, the exact nature of the incontinence may be difficult to ascertain. When a patient has failed conservative measures of treatment, urological referral is often helpful. Additionally, any history of radiation, prior pelvic surgeries, spinal injury, or neurological disease should prompt further evaluation by a urologist. Urological office testing may include bladder ultrasound, cystoscopy, and urodynamic testing.

Types of Incontinence

Incontinence in the elderly can be categorized as transient or chronic. Transient incontinence in the aged person can be due to reversible causes. Traditionally, the mnemonic "DIAPERS" has been used to identify the reversible causes of incontinence in the geriatric population (Table 16.1: Delirium, Infection, Atrophic vaginitis, Pharmaceuticals, Excess urine output, Restricted mobility, Stool impaction). Incontinence in the setting of acute delirium is usually reversible. Once the cause of the mental status change is corrected and the delirium has resolved, continence is typically regained. Urinary tract infection leads to urinary incontinence when urgency is the main symptom. Infection is relatively common in the elderly, with a prevalence of over 50% in institutionalized patients [10]. Incontinence may be the sole symptom in the elderly patient presenting with a urinary tract infection. In these cases, treating the infection may resolve the incontinence.

Incontinence can be exacerbated by urogenital atrophy in postmenopausal females. Up to 40% of postmenopausal women may have signs and symptoms

Table 16.1 The Diapers acronym.

D	Delirium, *Dementia*
I	Infection
A	Atrophic vaginitis
P	Pharmaceuticals *agents*, *Psychological causes*
E	Excess urine output, *Endocrine conditions*
R	Restricted mobility
S	Stool impaction

Adapted from Resnick, N.M. Urinary incontinence in the elderly. *Med. Grand Rounds* 1984; 3:281–290.

of urogenital atrophy [6]. Women often complain of frequency, urgency, nocturia, dysuria, and urge incontinence. A prolonged lack of stimulation of estrogen receptors in the vagina and urethra leads to dryness and atrophy of the vaginal and urethral mucosa [11]. This can lead to poor urethral coaptation and subsequent urinary incontinence. Low-dose estrogen given intravaginally has been shown to improve symptoms and clinical signs of urogenital atrophy and improve urinary incontinence [6]. Patients can easily be taught how to perform this by gently applying approximately 1 g of 0.01% estradiol cream onto the external vaginal mucosa and urethral meatus. For postmenopausal women, application of estrogen cream should be done two to three times weekly.

Pharmaceuticals can often worsen or be the cause of urinary incontinence in the elderly. Diuretics, specifically, may worsen urinary leakage by frequent filling of the bladder and stressing the continence mechanism. Patients often describe this as incontinence upon rising from a supine to prone position at night. ACE inhibitors may exacerbate stress incontinence if cough is present as a side effect of the medication. Pharmaceutical agents with alpha-agonist action can increase bladder neck resistance, leading to urine retention and overflow incontinence in men with preexisting BPH. This can be seen, for example, after taking decongestants that contain pseudoephedrine.

Anticholinergic properties of antipsychotics, antidepressants, anti-Parkinson drugs, and medications given for detrusor overactivity inhibit detrusor contractions and may lead to urinary retention and subsequent overflow incontinence [12]. Narcotics, sedatives, and calcium channel blockers can similarly contribute to retention in the elderly.

Restriction of mobility is common in the elderly and leads to urinary incontinence often from urinary urgency and a difficulty in reaching a bathroom facility. In these patients, a timed voiding schedule may be beneficial. A bedside commode or urinal container can resolve the difficulty in access to toilet facilities. Fractures from falls en route to the commode to relieve urgency have been noted in this frail elderly population.

Finally, fecal impaction is a potential reversible cause of urinary incontinence in the elderly. The rectum sits posterior to the bladder, and a distended rectum due to fecal impaction may cause worsening urgency symptoms. Additionally, constipation can lead to urinary retention and overflow incontinence due to inhibitory reflex on the bladder from stimulation of the pelvic nerves from rectal distension [13].

When none of the above reversible causes of incontinence is found in the elderly patient, further investigation is necessary. Detrusor overactivity, detrusor underactivity, bladder outlet obstruction, and stress incontinence are causes of chronic incontinence in both men and women. These topics are covered in further detail.

Detrusor Overactivity

Overactive Bladder

Detrusor overactivity (DO) presents in the elderly as frequency, urgency, nocturia, and urge incontinence. It is the most common cause of geriatric incontinence, accounting for almost 20% of incontinent women over the age

of 65 [14]. The underlying cause of DO is hyperstimulation of the cholinergic receptors in the bladder, leading to hypercontractility of the smooth muscle. Often, the cause is idiopathic with no identifiable precipitating causes. Cortical disease can cause detrusor hyperactivity by impairing the inhibitory mechanism of upper motor neurons on the voiding reflex [5]. Though the majority of elderly patients will have idiopathic detrusor overactivity, other causes of DO must be ruled out.

Bladder Outlet Obstruction

Chronic stimulation of stretch receptors of the detrusor smooth muscle is felt to be a common source for detrusor overactivity and incontinence. In men, this is precipitated by bladder outlet obstruction from benign prostatic hyperplasia (BPH). Benign prostatic hyperplasia is a common cause of lower urinary tract symptoms in men. Several epidemiologic studies have shown that the incidence of BPH in elderly men increases significantly with age, with the majority of elderly men showing symptoms of prostatic obstruction [15]. In the elderly male, urinary retention secondary to BPH is a frequent cause of recurrent cystitis and is often associated with DO. Chronic retention in men can eventually lead to bladder calculus formation, which further precipitates bladder irritation and urge incontinence.

Medical or surgical correction of the bladder outlet obstruction will frequently improve lower urinary tract symptoms and lead to dryness. Medical therapy in men includes the use of selective alpha-blockers to relax smooth muscle in the bladder neck and prostate capsule. 5-α reductase inhibitors can reduce prostate size, lowering the incidence of acute urinary retention secondary to BPH. Combining alpha-blockers with a 5-α reductase inhibitor may be more effective in relieving and preventing the progression of symptoms than either of the two drugs alone [16]. Surgical therapy includes transurethral resection of the prostate or minimally invasive procedures to reduce the prostate size (e.g., radiofrequency ablation or microwave therapy).

In women, vaginal prolapse or hypersuspension from previous stress incontinence procedures can lead to bladder outlet obstruction. Medical therapy in the form of alpha-blockers is usually reserved for women with absent relaxation of the bladder neck upon voluntary voiding and is rarely used. Surgical treatment may include correction of cystocele, transection of previous placed suburethral sling, or urethrolysis.

Detrusor Hyperactivity with Impaired Contractility

Detrusor hyperactivity with impaired contractility (DHIC) is a paradoxical syndrome that is the second leading cause of urge incontinence in the elderly [17,18]. The bladder is overactive, but its poor contractility leaves the patient with high urinary residual volumes. This leads to symptoms of frequency, urgency, and urge incontinence, in the context of an already overdistended bladder

Treatment with anticholinergics has variable success and can lead to acute urinary retention. Intermittent catheterization is necessary in some patients when residual volume is over half of their functional volume.

Atrophic Vaginitis

In elderly females, the low levels of systemic estrogen can lead to atrophy of the squamous and columnar epithelial lining of the vagina, urethra, and trigone. This atrophied lining in the distal urinary tract leaves the underlying smooth muscle penetrable to urinary irritants, leading to DO [6]. The treatment in the female is systemic or local estrogen replacement. One gram of 0.01% estradiol can be administered by patients intravaginally two to three times weekly and significantly improves the health of the vaginal and urethral mucosa.

Infectious Etiologies

Recurrent cystitis can lead to DO by its inflammatory changes to the urothelial lining. Precipitating causes of recurrent cystitis in females include atrophic vaginitis, poor perineal hygiene, and urinary retention. Treatment of these infections and underlying etiologies is the first step in treatment of incontinence. In some patients, infections persist despite treatment of the underlying anatomic pathology. These patients may benefit from long-term (3- to 6-month) suppressive antibiotic therapy with medications such as nitrofurantoin or sulfamethaxazole [19].

Pharmacological Treatment of Detrusor Overactivity

Treatment in any patient with detrusor overactivity begins with behavioral modification such as timed voiding, fluid restriction, and avoidance of urinary irritants in the diet. Avoidance of caffeinated beverages and alcohol are especially important. Some studies suggest that even chocolate, soft drinks, and spicy or acidic foods should be avoided [20].

Bladder retraining helps a patient resist urges to void by contracting his or her pelvic floor muscles (Kegel exercises) when the urge to void ensues. Patients are also taught to change their position, concentrate on a subject other than the sensation to void, or count backwards from 10. The urgency to void may then subside. Once the patient is comfortable and in control, a normal void can occur. However, only a few studies show a significant benefit to bladder retraining [20].

The gold standard in the patient with detrusor overactivity is anticholinergic therapy. Oxybutynin is the earliest of this group to have been studied and approved for use in overactive bladder. Theoretically, these drugs are tertiary amines and can cross the blood-brain barrier. The Overactive Bladder Performance of Extended Release Agents (OPERA) trial was one of the first studies to compare oxybutynin and tolterodine. Rates of somnolence, dizziness, and insomnia were similar in the two drugs.

Other anticholinergics are now available. Trospium chloride is a quaternary amine and theoretically does not cross the blood-brain barrier. Solifenacin is an anti-muscarinic that is selective for the urinary bladder. Finally, darifenacin is an M3 receptor antagonist and has a higher affinity for the bladder than the salivary glands. Drugs that have anticholinergic properties as part of their pharmacological profile, for example, tricyclic amine antidepressants, can also be used to treat urge incontinence in the elderly patient. However, these are considered second-line agents and should only be used after the other anticholinergics have been tried and failed.

Detrusor Underactivity

Detrusor underactivity is a less common cause of urinary incontinence, affecting fewer than 10% of incontinent patients [21]. A defunctionalized detrusor muscle leads to elevated residual bladder volume and can give rise to symptoms similar to detrusor overactivity: frequency, urgency, urge incontinence. This condition may give rise to urine overflow, termed *overflow incontinence*, and result in severe urine leakage; especially with rises in intraabdominal pressure, such as with changing position or coughing.

Impairment of nerves innervating the detrusor muscle is a cause of detrusor inactivity. This can occur as a result of spinal cord injury, multiple sclerosis, or pelvic surgery. Diabetes can impair detrusor function by ischemic damage to pelvic nerves. Additionally, diabetes can impair afferent stimuli from the bladder, abating the sensation of bladder fullness and leading to chronic overdistention of the detrusor muscle. Other causes of nerve impairment include alcoholism, pernicious anemia, and Parkinson's disease [5].

In men with chronic outlet obstruction from BPH, the detrusor muscle can become replaced by fibrosis, leading to a defunctionalized bladder muscle. Even after treatment of the obstruction, detrusor underactivity remains due to the change in structural anatomy [22]. Women presenting with urine retention often have no underlying etiology.

Undiagnosed detrusor underactivity and retention can lead to hydronephrosis and renal damage. To this degree, it is important to assess the upper urinary tract with radiological imaging such as ultrasound. Additionally, renal function should be evaluated with BUN and creatinine. Urosepsis can occur as a result of retained urine. Treatment must be directed to exclude these more morbid conditions as well as to reduce symptoms of incontinence, frequency, and urgency.

Treatment for incontinence related to detrusor underactivity is usually intermittent catheterization or indwelling catheterization. For patients with mild detrusor underactivity and modest residual volumes, timed voiding can be employed. Voiding at smaller bladder volumes allows for more complete bladder emptying in these patients. Medical treatment with cholinergic agonists such as bethanachol, sometimes in combination with prostaglandin E2, has been successful in only a minority of patients [23]. Lastly, neuromodulation of the sacral nerve with pacemaker technology has recently been used in some patients with nonobstructive urine retention (Interstim, Medtronic, Inc., Minneapolis, MN). Success rates, however, have been disappointingly low.

Stress Incontinence

Patients who complain of the involuntary loss of urine during coughing, sneezing, or physical activity have stress urinary incontinence. In these patients, the increase in intraabdominal pressure from the precipitating event overcomes the bladder neck and urethral resistance pressure, and leakage ensues.

Two etiologies for stress incontinence in women have been well described in the urology literature. The first is a lack of urethral and bladder neck

support. This normal musculofascial support of the female pelvic floor is thought to deteriorate with age and may be more prevalent in women who have had an increased number of vaginal deliveries [24]. Such patients have hypermobility of the bladder neck and urethra. The examiner may visualize this hypermobility on vaginal speculum examination as the bladder neck descends with cough or strain. Incontinence may be observed if the bladder is partly full.

The second etiology of stress urinary incontinence in the elderly female patient relates to the urethra itself. Intrinsic sphincter deficiency (ISD) refers to the inability of the urethra to maintain closure due to sphincteric dysfunction. The most common method of evaluating the urethral sphincter itself is during urodynamic testing. A valsalva leak point pressure less than 60 cm H_2O during urodynamic testing has traditionally been diagnostic of ISD. Some investigators believe that urethral hypermobility and ISD coexist [25].

Stress incontinence in the male patient is most often due to sphincter injury after radical prostatectomy, or transurethral resection of the prostate. Post-prostatectomy incontinence is a documented occurrence in 4–40% of patients undergoing radical prostatectomy for prostate cancer [26]. Most men recover continence by 6 months postoperatively. Over 90% of men in a recent study achieved continence by 1 year postoperatively [27]. Bladder outlet obstruction and subsequent urine retention is another cause of stress incontinence in the male patient.

Treatment of stress incontinence in the elderly begins with conservative measures. Timed voiding and Kegel exercises have shown success in 25% of patients with mild stress urinary incontinence. Kegel exercises are often performed incorrectly and may require repeated instruction. Physical therapists in continence centers can instruct proper contraction of levator muscles by using biofeedback. With proper training, women can learn to strengthen the muscles supporting the urethra and bladder [28]. Timed voiding is performed by encouraging the patient to void on schedule every two to three hours. Access to a commode must be made easy. Finally, anticholinergics can be added to those patients whose stress urinary incontinence is associated with urgency and urge incontinence.

Surgical treatment of stress incontinence continues to have long-term success rates of over of 80%. Treating the patient with urethral hypermobility involves reinforcement of the urethra or bladder neck to prevent the loss of urine. Historically, this has been in the form of open surgical procedures, namely Burch bladder neck suspensions or Marshall–Marchetti–Krantz procedures [29]. More recently, ambulatory vaginal sling procedures have evolved and are just as effective—with minimal morbidity and high success rates [30]. Ulmsten introduced the first such therapy in the form of tension-free vaginal tape (TVT) [31]. In the past several years, the transobturator approach has been developed as an alternative to TVT. Rather than passing trochars through the retropubic space, they are passed through the obturator canal. This reduces the risk of vascular or bowel injury. Transobturator slings are performed in the outpatient setting. The recovery period is usually less than one week.

Treatment of women with low leak-point pressures or intrinsic sphincter deficiency (ISD) is more difficult. These patients often have complicating factors such as previous incontinence surgeries, history of radiation, or history of pelvic trauma. Surgical treatment with retropubic slings has been the

mainstay of therapy. Periurethral injections of bulking agents have been used in those patients that have failed sling therapy or in those patients who are not surgical candidates because of various medical co-morbidities. This procedure can be done with local anesthesia in the office setting. Several different types of injectable agents exist, the most popular being bovine collagen. The durability of bulking procedures to prevent incontinence is unfortunately short-term—in the range of three months to one year. Often, multiple injections are required to achieve or maintain continence. In the most severe cases, an artificial urinary sphincter can be offered to the female who has lost all normal architecture to the urinary sphincter mechanism and has failed traditional sling and periurethral bulking therapy.

Conclusions

With the baby boomer population now approaching old age, treatment of urinary incontinence in the geriatric population will be one of the most important aspects of medical care in the years to come. Healthcare practitioners need to be educated on performing a thorough history and physical examination and identifying potential reversible causes of incontinence in the elderly patient. Behavioral therapies can always be used as treatment. However, when these fail, medical or surgical intervention is usually required. Referral to a urologist almost always provides additional support and treatment when such conservative measures are not effective. Incontinence in the elderly patient has far-reaching effects on a patient's quality of life; if managed appropriately, the effect of becoming continent can significantly improve a patient's well-being.

References

1. Minassian, V.A., Drutz, H.P., Al-Badr, A. Urinary incontinence as a worldwide problem. *Int. J. Gyn. Obstet*. 2003; 82(3):327–338.
2. Weiss, B.D. Diagnostic evaluation of urinary incontinence in geriatric patients. *Am. Fam. Phys*. 1998; 57(11):2675–2684.
3. Abrams, P., Kelleher, C., Kerr, L.A., et al. Overactive bladder significantly affects quality of life. *Am. J. Man. Care* 2000; 6(11 Suppl):S580–590.
4. Wilson, L., Brown, J., Shin, G., et al. Annual direct cost of urinary incontinence. *Obstet. Gyn*. 2001; 98(3):398–406.
5. Yuhico, M., Diokno, A.C., Amendola, M.A. Neurogenic bladder and radiology. In *Lower Genitourinary Radiology: Imaging and Intervention*, S.Z.H Jafri, A.C. Diokno, and M.A. Amendola, eds. New York: Springer. 1998.
6. Dessole, S., Rubattu, G., Ambrosini, G., et al. Efficacy of low-dose intravaginal estriol on urogenital aging in postmenopausal women. *Menopause* 2004; 11(1): 49–56.
7. Jarmy-Di Bella, Z.I., Girao, M.J., Sartori, M.F., Baracat, E.C., Lima, G.R. Power Doppler of the urethra in continent or incontinent, pre- and postmenopausal women. *Int. Urogyn. J*. 2000; 11(3):148–155.
8. Strasser, H., Tiefenthaler, M., Steinlechner, M., et al. Urinary incontinence in the elderly and age-dependent apoptosis of rhabdosphincter cells. *Lancet* 1999; 354(9182):918–919.
9. Pfisterer, M., Griffiths, D., Rosenberg, L., et al. The impact of detrusor overactivity on bladder function in younger and older women. *J. Urol*. 2006; 175(5): 1777–1783.

10. Nicolle, L.E. Urinary tract infection in the elderly. How to treat and when? *Infection* 1992; 20(Suppl 4):S261–265.
11. Cervigni, M. Hormonal influences in the lower urinary tract. In *Female Urology*, 2nd ed., S. Raz, ed. Philadelphia: W.B. Saunders.1996; pp. 539–559.
12. Resnick, N.M. Geriatric medicine. In *Harrison's Principles of Internal Medicine,* K.J. Isselbacher, E. Braunwald, J.D. Wilson, et al., eds. New York: McGraw-Hill. 1994; p. 34.
13. Hellstrom, P.M., Sjoqvist, A. Involvement of opioid and nicotinic receptors in rectal and anal reflex inhibition of urinary bladder motility in cats. *Acta Physiol. Scand.* 1988; 133:559–562.
14. Stewart, W.F., Van Rooyen, J.B., Cundiff, G.W., et al. Prevalence and burden of overactive bladder in the United States. *World J. Urol*. 2003; 20:327–336.
15. Walsh, P., Retik, A., Vaughan, E.D., et al. *Campbell's Urology*, 8th ed. Philadelphia: Saunders. 2002.
16. Bautista, O.M., Kusek, J.W., Nyberg, L. M., et al. Study design of the Medical Therapy of Prostatic Symptoms (MTOPS) trial. *Controlled Clin. Trials* 2003; 24(2): 224–243.
17. DuBeau, C.E., Resnick, N.M. Evaluation of the causes and severity of geriatric incontinence. A critical appraisal. *Urol. Clinics North Am*. 1991; 18(2): 243–256.
18. Resnick, N.M., Yalla, S.V. Detrusor hyperactivity with impaired contractile function. An unrecognized but common cause of incontinence in elderly patients. *JAMA* 1987; 257:3076.
19. Albert, X., Huertas, I., Pereiro, I., et al. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. *Cochrane Database System. Rev*. 2004; (3):CD001209.
20. Thompson, D.L., Smith, D.A. Continence nursing: A whole person approach. *Holistic Nursing Practice* 2002; 16(2):14–31.
21. Elbadawi, A., Diokno, A.C., Millard, R.J. The aging bladder: Morphology and urodynamics. *World J. Urol*. 1998; 16(Suppl 1):S10–34.
22. Thomas, A.W., Cannon, A., Bartlett, E., et al. The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *BJU Int*. 2004; 93(6):745–750.
23. Hindley, R.G., Brierly, R.D., Thomas, P.J. Prostaglandin E2 and bethanechol in combination for treating detrusor underactivity. *BJU Int*. 2004; 93(1):89–92.
24. Persson, J., Wolner-Hanssen, P., Rydhstroem, H. Obstetric risk factors for stress urinary incontinence: A population-based study. *Obstet. Gyn*. 2000; 96(3): 440–445.
25. Schick, E., Dupont, C., Bertrand, P.E., et al. Predictive value of maximum urethral closure pressure, urethral hypermobility and urethral incompetence in the diagnosis of clinically significant female genuine stress incontinence. *J. Urol*. 2004; 171(5):1871–1875.
26. Stanford, J.L., Feng, Z., Hamilton, A.S., et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: The Prostate Cancer Outcomes Study. *JAMA* 2000; 283(3):354–360.
27. Filocamo, M.T., Li Marzi, V., Del Popolo, G., et al. Effectiveness of early pelvic floor rehabilitation treatment for post-prostatectomy incontinence. *Eur. Urol*. 2005; 48(5):734–738.
28. Burns, P.A., Pranikoff, K., Nochajski, T.H., et al. A comparison of effectiveness of biofeedback and pelvic muscle exercise treatment of stress incontinence in older community-dwelling women. *J. Gerontol*. 1993; 48(4):M167–174.
29. Atanasov, A., Atanasova, Z. The treatment of stress incontinence by Burch's colposuspension. *Akusherstvo i Ginekologiia* 1993; 32(3):1–3.

30. Leach, G.E., Dmochowski, R.R., Appell, R.A., et al. Female Stress Urinary Incontinence Clinical Guidelines Panel summary report on surgical management of female stress urinary incontinence. The American Urological Association. *J. Urol*. 1997; 158:875–880.
31. Ulmsten, U., Henriksson, L., Johnson, P., et al. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. *Int. Urogyn. J.* 1996; 7:81–86.

17

The Diagnosis of Renal Diseases in Elderly Patients. What Role Is There for Biopsy?

Franco Vendemia

Introduction

Why Should We Investigate the Elderly with Renal Diseases and How Should We Do It?

During the past 10 years, the analysis of some epidemiological data has brought to light a closer than expected relationship between the aging process and the progressive decline in renal function.

The first data came from the Registries of Dialysis and Transplantation of developed countries: These records showed a relentless increase in the number of delivered renal replacement treatments and indicated that this increase largely depended upon aged patients [1]. Further information came from the third National Health and Nutrition Examination Survey. According to this report, elderly subjects with renal insufficiency are so numerous in the United States that they could induce a further major increase in the number of the patients receiving dialysis [2]. More recent information came from both public [3] and private [4] healthcare providers in the United States. These sources indicated that however many elderly people with renal insufficiency may be diagnosed today, they only are the tip of a larger iceberg; the submerged part (which usually escapes notice in ordinary surveys) includes all those renal patients dying of cardiovascular disease well before they are in need of dialysis treatment. All these data seem to give a pessimistic view of the current epidemiological picture, and even by themselves could justify all possible efforts to be undertaken to diagnose renal diseases in the elderly in a timely fashion and to highlight their unfavorable outcomes.

Besides these data, other information offers further reasons to investigate the types of lesions damaging elderly peoples´ kidney. Previous observations had depicted an epidemiological scenario quite different from that evident today: In the 1980s, the Baltimore Longitudinal Study on Aging suggested that, apart from some rare exceptions, most elderly people have only a modest decline of renal function, which is neither rapid nor severe [5]. Such a slight change might simply be due to the involutional phenomena affecting

all functions in people as they grow older. Consequently, the decline in renal function occurring in the elderly has usually been considered as a sign of the so-called aging kidney. The fairly reassuring observations of the Baltimore Study remained an isolated example for many years, but recently the substantial validity of these observations has been confirmed by two other studies carried out in the United States [6] and in Canada [7]. These new results stand in contrast with those emphasizing the "epidemic" of progressive renal disease in the elderly population.

Nevertheless, the very difference between the two sets of data concerns the percentage of subjects in whom progressive nephropathy is superimposed on the not-so-progressively aging kidney. It is likely that the actual percentage reported has been higher or lower than expected depending on the research methods used and on the population samples that have been selected. In any case, apart from the quantitative differences, which essentially have epidemiological significance, the most important fact from a clinical point of view is that the reduction of renal function in elderly people may depend on two distinct types of lesions, which are quite different in terms of both their course and their prognosis.

Because of this dual renal pathology with advancing age, one of the problems the nephrologist is faced with every time he takes care of an elderly person is that of distinguishing patients with a "simple" aging kidney from those who are affected as well by a true renal "disease." The aim of such a distinction is to focus therapeutic efforts on the patients with real need of slowing down the progression of renal insufficiency. This goal may be certainly shared; however, the initial step, namely the diagnosis upon which the therapy should be based, is not to be taken lightly.

Renal biopsy could be a useful tool in ascertaining the presence of a parenchymal renal disease and to define its characteristics. Nevertheless, the potential of renal biopsy is rarely fully exploited in practice. First, many general practitioners fail to refer all the elderly patients who are possibly in need of a biopsy to a nephrologist; in addition, many nephrologists are reluctant to perform a renal biopsy in the elderly patients under their care. On the other hand, the biopsy by itself cannot provide the solution to such a complex problem, whereas it can be more useful when it is looked at in a wider perspective, including some clinical and epidemiological aspects besides the histomorphological picture.

This chapter examines the difficulties commonly encountered in the diagnosis of elderly renal diseases and reviews suitable ways of overcoming those difficulties. In particular, this chapter also focuses on the possible role of renal biopsy within a logical sequence of investigations using, step by step, the various diagnostic means available today.

The Need for a Stepwise Diagnostic Process

First Step: Patient Referral

A nephrologist is a secondary care specialist. Her ability to formulate a plan of diagnosis, prognosis, and therapy depends on the patient's first being referred from general practitioners, or from other specialists, so that

patients with nephrological problems always suffer from some "upstream" selection. One of the main factors affecting such a selection is the *age of the patient*: Usually, younger adults (20–65 years of age) are referred to a nephrologist at the onset of disease and without any particular limitations, whereas more elderly ones are often only referred when the disease has already progressed, or, even more frequently, they are not referred at all.

The referral of elderly patients compared to that of adult ones seems to be affected more by the presence or absence of overt symptoms. It is not rare that, at the onset of symptoms, an elderly person suffering from gross hematuria is referred to a urologist while those with ankle edema are referred to an angiologist or cardiologist; these very evident cases sooner or later tend to undergo a nephrological consultation. On the other hand, the destiny of asymptomatic patients is much more uncertain. It is a well-known fact that most renal lesions do not manifest themselves clinically before the appearance of late complications, and therefore their early detection may only result from an incidental finding on laboratory testing for a concurrent illness or nonspecific health status monitoring. The true problem of elderly patients is that their abnormal laboratory findings do not draw the attention of physicians and do not induce them to ask for a specialist's opinion. An epidemiological investigation, recently carried out in the UK, demonstrated that of all the subjects of all ages with some signs of renal disease at a laboratory level during one year, only 15% had been referred to a nephrologist, while 85% remained unknown to renal services. The different sizes of these two patient groups were related to their different demographic composition: The smaller group consisted of nearly equal parts of elderly and younger patients, whereas the second (unreferred) group, which was six times larger than the referred group, was almost entirely composed of elderly people [8].

The frequent underestimation of the significance of elderly patients´ laboratory reports in part depends on the use of serum creatinine as a marker of renal function. The problem is that muscle mass diminishes with age, and consequently the serum creatinine tends also to decrease, thus masking the eventual increase due to renal insufficiency [9]. For this reason, interest is growing in the mathematical formulas, which allow a more precise estimation of renal function by utilizing the value of serum creatinine after standardization for some factors known to affect the muscle state: gender, race, body weight, and, above all, age. The question of which is the best formula to calculate the renal function is still being debated; yet it seems that the simplified version of the formula derived from the MDRD study is more suitable in younger adult subjects, while there is some evidence that in the elderly, the older Cockcroft–Gault formula is preferable [10]. A consensus is growing about the idea that at least one of these formulas should be included in routine laboratory reports, so as to draw the physician's attention to the level at which the kidney is actually working, and avoiding the assumption that all elderly people have the same normal renal function as younger subjects [9]. Moreover, in both the United States [11] and Europe [12], some initiatives are being studied that aim to involve general practitioners in detecting those community dwellers who should benefit from referral to a nephrologist's care.

Second Step: The Clinical Assessment

The elderly person undergoing nephrological observation requires a special attention aimed at comprehending the complexity and the specificity of his or her problems [13].

History

The differences between elderly patients and younger adults are evident from the moment of history taking. Often, elderly people tend to emphasize nonspecific symptoms while underreporting those problems that could be of clinical importance. To overcome this difficulty, it may be useful to obtain the cooperation of the family and others involved in the care of the subject. These people can often give some valuable information on both past laboratory investigations and medications currently taken by the patient. It frequently occurs that we discover that some signs of renal disease had been already reported in the past, and this allows us to at least date the onset of disease. Moreover, it is not rare for an elderly patient to be taking a complex "cocktail" of medications, which can cause or at least contribute to the development of the renal problem affecting the patient.

Physical Examination

As with history taking, the physical examination also is more time-consuming and requires more patience in the elderly than in the adult. Before pursuing the often misleading symptoms complained of by the patient, it is necessary that inspection, palpation, percussion, and auscultation are aimed at looking for those signs that have a high probability of being present in an elderly person. In particular, inspection can reveal some signs of a skin infection, vasculitis, or diabetic foot. The abdominal palpation can reveal an enlarged urinary bladder, signs of prostatic hypertrophy or tumor, or an aortic aneurysm. The percussion of bony segments can cause pain suggestive of the presence of metastases or multiple myeloma, while the auscultation of a para-umbilical bruit can indicate the existence of a renal artery stenosis. Furthermore, in the elderly, even evaluating the most common parameters requires careful thinking: A BMI calculation can give an incorrect appraisal of nutritional state, as the increase in fatty body mass can conceal a decrease in lean body mass; in the same way, blood pressure measurement may be biased by the presence of arrhythmias, congestive heart failure, and vascular rigidity from calcification.

Laboratory Investigations

Both when ordering laboratory tests and when interpreting their results, we have to take into account the differences existing between elderly and young-adult patients. First of all, renal function should be assessed by measuring the *BUN* and *serum creatinine*, while an estimation of either *creatinine clearance* or *GFR* by proper formulas is mandatory [10]. Furthermore, since urea and creatinine arise from different metabolic pathways and undergo different renal handling, the ratio between the two substances can provide some useful information: A BUN level disproportionately high as compared to that of serum creatinine can raise suspicion of some clinical scenarios particularly common in elderly people, such as dehydration, urinary tract obstruction, and hypercatabolism.

Renal function is not the only aspect of pathophysiology in the elderly requiring a specific approach. The age-related problems deserving particular

attention are numerous, such as the derangement of *plasma electrolytes*. Though these changes are frequently induced by drugs, other causes cannot be excluded, such as hypercalcemia, which may be due to neoplastic or myelomatous bone erosions, as well as hypophosphatemia, which may be caused by malnutrition.

In elderly people with renal insufficiency, *malnutrition* is more widespread than commonly thought [14]. Its background presence should always be borne in mind, as it can make the clinical picture of renal diseases less clear. In fact, malnutrition not only lowers the serum concentration of urea, creatinine, and phosphate, but it can also affect other parameters, such as serum albumin, cholesterol, C3 complement factor, and lymphocyte count. Furthermore, malnutrition-associated iron deficiency contributes to the genesis of anemia, and this could be one of the reasons why anemia is more frequent in the elderly than in adults [15].

Another test that is often abnormal in the elderly population is the *serum protein electrophoresis*. When a monoclonal component appears, it is necessary to characterize the paraprotein by means of immunofixation on both serum and urine. A urine test has to be performed in every patient, since light chains may be present in the urine even in the absence of any changes in the serum pattern, as they are so readily excreted.

Besides disclosing the existence of paraproteins, urine provides a wide range of information, which is still being expanded thanks to advancing knowledge. In the last few years, studies in the field of proteomics have led to the discovery of some urinary proteins, with every one of them being consistent with the presence of a certain disease, as in the case of diabetic nephropathy, urinary tract malignancies, or tubular interstitial diseases. The progress in this field is so rapid that, in the near future, disease-specific urinary biomarkers are expected for all renal disorders [16]. At the moment, these investigations are still in a preliminary phase and require some rather complex technologies [17]. However, it is worth noting that the methods currently used, such as immunonephelometry, already allow the isolation of some urinary proteins, which possess diagnostic and prognostic properties. For example, *IgG* reveals a loss of selectivity in glomerular filtration, while *α1-microglobulin* indicates a saturation of tubular reabsorption [18]. Apart from the interest generated by these new developments, the *quantitation of proteinuria* remains one of the key components of urine analysis, as well as the characterization of *hematuria.* In the younger adult, hematuria is not a special problem from a diagnostic point of view, since up to the age of 50 or more, the bleeding nearly always arises from glomerular capillaries. In the elderly, the matter is more complex, as in addition to glomerular hematuria, some bleeding from elsewhere in the urinary tract frequently occurs. For this reason, some tool helping to detect the origin of hematuria, such as the erythrocyte morphology examined by phase contrast microscopy [19], is even more important in the elderly than in the adult.

Finally, it is impossible to leave out *urine culture*. Urinary tract infections occur at a maximum rate in advanced age and, even when they are asymptomatic, they are, however, associated with reduced survival [20]. The causes of such an association have been not explained as yet. Nevertheless, it is possible that in elderly people the link between the occurrence of urinary infections and the increase in mortality rate is the activation of an

inflammatory process; infections stimulate inflammation, and inflammation in turn is involved in the genesis of both cachexia and cardiovascular damage. The possibility that in elderly people a connection exists linking urinary infections, mortality, and inflammation seems to be supported by a recent epidemiological investigation showing high serum levels of various inflammatory factors in a sample of an elderly U.S. population [21]. It has been hypothesized that such factors, once produced, are not sufficiently cleared by the aging kidney and, consequently, they remain in the bloodstream for an abnormally long time [21]. According to this hypothesis, when renal function tends to decrease with aging, the only way to reduce the risk connected with the accumulation of inflammatory factors is to prevent the synthesis of those factors. Therefore, simply treating the acute episodes of urinary infections may be not sufficient. It seems more useful to detect and remove the causes that allow the infections to become chronic. A major cause, which is rather frequent in the elderly, is urinary tract obstruction, which nowadays can be easily detected by means of sonography.

Imaging Techniques

In the last decade, *sonography* and *duplex sonography* have definitively demonstrated their safety and reliability. Their use in the geriatric field is supported by two main circumstances: First, the lack of potentially nephrotoxic contrast media makes these techniques specifically indicated in investigating frail patients, such as the elderly with impaired renal function; second, these methods are particularly suitable in detecting some diseases that are commonly found in advanced age. Consequently, sonography has now come into clinical practice as a routine investigation of obstructive uropathy, renal cysts, and malignancies. Moreover, as sonography may display long-term changes in the density of the renal cortex, this investigation may direct the diagnosis, as in the case of parenchymal damage [22]. As to this aspect of sonography utilization, further improvements are expected from the setup of some new techniques that may provide a quantitative appraisal of renal sclerosis by computer-assisted counting of reflected echoes [23]. Finally, as to duplex sonography, it is currently impossible to avoid this investigation in the diagnosis of renal vascular diseases. Its uses range from the macroscopic renal vascular diseases such as atherosclerosis of main renal artery, to the microscopic ones such as arteriosclerosis of thin intra-renal branches [24].

Diagnostic Hypotheses

At the end of the first phase of clinical assessment, it is possible to classify the problem affecting the kidney of an elderly patient into one of the main nephrological syndromes:

acute renal failure
chronic renal insufficiency
nephrotic syndrome and
urinary abnormalities.

However, each one of these syndromes may be the manifestation of many different diseases. The whole clinical picture sometimes allows the formulation of a diagnostic hypothesis, but the clinical approach by itself is not always sufficient to reach diagnostic certainty.

Acute renal failure, as well as the sudden worsening of a preexisting chronic renal insufficiency, offers the opportunity of making a diagnosis exclusively on clinical grounds. In fact, it is usually easy to detect a pre-renal cause, such as dehydration and hypotension, or a postrenal cause such as urinary tract obstruction by prostatic enlargement, tumors, or calculi. In the same way, it is not difficult to hypothesize on a tubular obstruction by paraproteins, uric acid crystals, and myoglobin or a toxic tubulopathy due to drugs or radio-contrast media. Finally, it is usually possible to demonstrate the occlusion of either the renal artery or vein, as well as an imbalance in glomerular hemodynamics, induced by drugs affecting the renin-angiotensin system.

On the other hand, sometimes the clinical picture of the elderly is so unclear that it is difficult to detect the signs of an atheroembolism, or an allergic interstitial nephritis, or an acute pyelonephritis; as a consequence, many of these cases remain undiagnosed. The clinical diagnosis may be even more difficult when the acute renal failure is heralded by hematuria, mimicking the picture of nephritic syndrome, or when it is accompanied by proteinuria and it shows a rapidly progressive course.

In the cases of a nephritic syndrome, the first hypothesis may be that of a postinfectious acute glomerulonephritis. In spite of this, in the elderly, especially if the patient is in poor hygienic and nutritional condition, the clinical picture is often different from the classic one, thus inducing doubt in the interpretation of both signs and symptoms [25]. Moreover, other renal diseases, such as membranoproliferative glomerulonephritis, may present in the same way, therefore contributing to the uncertainties of diagnosis.

Regarding the cases with a rapidly progressive course, the presence of respiratory or skin manifestations directs the diagnosis toward an anti-GBM glomerulonephritis or a systemic vasculitis. Some types of vasculitis exist that are renal-limited and, consequently, are lacking those extra-renal symptoms directing the diagnosis [26]. In these cases, detecting the presence of ANCA may help substantially; however, laboratory tests may be negative in about 15% of vasculitides, as well as sometimes being positive in cases without vasculitis, as is sometimes the case with primitive or secondary glomerulonephritis, interstitial nephritis, and sometimes even unrelated infections (see Chapter 20). Furthermore, other renal diseases may exhibit a rapidly progressive course, independently of the presence of any vasculitis, as is the case with some severe cases of IgA nephropathy.

The influence that all these confounding factors may exert on the diagnosis of acute renal failure has been carefully examined by a recent study of clinical-histological comparison [27]. In a large study of elderly people with acute renal failure, clinical assessment, as compared to the histological characterization, gave a correct diagnosis in no more than one-third of cases; in another third of patients, the clinical picture only raised some suspicion about the underlying renal disease, so inducing us to consider such a disease just within the limits of differential diagnosis; finally, in the last third of patients, the simple clinical data were insufficient to make the diagnosis. Although these results may appear unsatisfactory, they are among the best achievable at this level of investigation. In other clinical settings, different from acute renal failure, the success of a clinical diagnosis may be even more uncommon.

Chronic renal insufficiency holds diagnostic difficulties that are even greater than those of acute renal failure. Very often, elderly patients are

referred when the disease is so advanced [27]that the only diagnostic possibility is to search for renal artery stenosis, whose dilatation sometimes allows dialysis to be postponed. However, even less advanced cases usually offer few possibilities of tracing back the nephropathy underlying the renal damage: Most nephropathies, after a first phase of activity, lose any specific features and show only a uniform clinical aspect of impaired renal function, hypertension, and urinary abnormalities. Except for the cases in which a nephropathy is self-evident (such as polycystic kidney disease), nothing even remains in the memories of the patients and their families to help the reconstruction of some relevant clinical facts, except the recovery of past laboratory reports to obtain some significant data.

The *nephrotic syndrome* is the most extensively studied among the modalities of presentation of elderly renal diseases; nevertheless, its diagnosis is still burdened by a number of unsolved problems [29]. The main difficulty is that this same symptomatology is provoked and shared by many diseases, so clinical reasoning has to go on a process of exclusion.

This diagnostic course usually starts by a search for the presence of a systemic disease. In positive cases, a secondary nephrotic syndrome may be hypothesized. However, great care should be taken, as the reality can be very different from how it appears. A typical example is that of a diabetic patient, in whom the "obvious" diagnosis of a diabetic nephropathy could be too hasty. In reality, such a diagnosis has a high probability of being correct only if the metabolic derangement has been present for about 10 years or more, and only if other characteristic signs such as proliferative retinopathy are present. In all other cases, it is probable that another nephropathy, different from diabetes, is present coincidentally in a diabetic patient [30]. The frequency of degenerative and obstructive disease of major and minor renal arteries in diabetes must not be forgotten.

A further example is that of the patient with myeloma, in whom both AL-type amyloidosis and light-chain deposition disease have to be taken into account. Bone marrow aspiration shows an abnormal appearance more frequently in the first case than in the second one. However, some transitional forms may be seen. Furthermore, faced with bone marrow with nonspecific changes in the presence of a serum electrophoresis with a small gamma spike, it is possible to consider a "monoclonal gammopathy of undetermined significance," which may be more accurately attributed to the aging immune system than to a true plasma cell dyscrasia [31]. In this case, nephrotic syndrome might be dependent upon some nephropathy not related to the presence of paraproteins.

These diagnostic uncertainties, which may be encountered in a patient affected by diabetes or myeloma, are the most frequent but not the only ones. In the patient suffering from rheumatoid arthritis or other chronic inflammatory diseases, the most probable hypothesis is that nephrotic syndrome is caused by an AA-type amyloidosis. However, it is also possible that some drugs, taken by the patient to fight the inflammatory disease, have effectively prevented the occurrence of amyloidosis, while inducing at the same time another nephropathy. This possibility may occur with the use of golden salts and NSAIDs, which can induce a membranous nephropathy or a minimal change disease, respectively.

Finally, in elderly patients showing some serological signs of SLE, before making a diagnosis of lupus nephritis, it is necessary to verify whether the increase in circulating levels of auto-antibodies is not a nonspecific phenomenon, as frequently found in the aged [32] and in Sjogren's syndrome, which is more common in the elderly than SLE. Ultimately, the diagnosis of secondary nephrotic syndrome should not be automatic. Nonetheless, the existence of a systemic disease at least offers a starting point to the clinical reasoning.

In the case of the patient without any evidence of systemic disease, the diagnostic dissection of a primary nephrotic syndrome is certainly more problematic. In fact, on a plain clinical ground, the only way to distinguish one nephropathy from the other is based on detection of some accompanying signs. Still, it is difficult to estimate the real weight of those signs: Even though their association with a particular nephropathy is significant at the level of a whole series, their discriminating power in the single patient may be weak indeed. For example, when primitive amyloidosis is suspected, it is possible to look for deposits of amyloid substance in both the skin and heart, by periumbilical fat aspiration and echocardiography, respectively. However, while the finding of those deposits may be considered an unmistakable sign, a negative result does not exclude the diagnosis.

The same type of ambiguity makes nearly all the diagnostic hypotheses uncertain. Given the suspicion of a membranous nephropathy, it is possible to investigate the presence of tumors, mainly in the lungs and bowel, by chest x-ray and by searching for occult blood in the stool, respectively. However, the association between membranous nephropathy and tumors does not exceed 10% of cases and, conversely, tumors may be associated with other nephropathies, different from membranous ones [33]. Consequently, both positive and negative results are not conclusive diagnostically. Similar considerations are valid for the association between minimal change disease and lymphomatous disorders. Even more problematic is the link between focal segmental glomerulosclerosis and so-called permeability factors, whose nature has been not clarified as of yet and whose measurement is much too complicated for routine practice [34].

After having examined the more frequent causes of primitive nephrotic syndrome and having attempted to make a differential diagnosis by a critical appraisal of accompanying signs, the search for renal disease causing the nephrotic syndrome is not yet over, as other less common causes remain to be considered. In particular, nephrotic syndrome might be the expression of rarer diseases, such as membranoproliferative glomerulonephritis. It might also be the rare manifestation of diseases usually exhibiting a different clinical picture, such as IgA nephropathy.

Urinary abnormalities are the most representative cases of the whole field of geriatric nephrology. Although they are extremely diffuse in advanced age, they are still the least frequently studied among renal syndromes in the elderly. The current neglect of this valuable diagnostic aid demonstrates that some old prejudices have not been overcome yet. Many physicians are still convinced that, after the age of 60, hematuria exclusively pertains to the urologist and that subnephrotic proteinuria is an expression of the aging kidney.

Actually, the clinical significance of urinary abnormalities is much more complex. There is no doubt that, in the aged, most isolated hematurias

arise from urinary tract neoplasia; nevertheless, hematuria may herald from a number of diseases, such as thin basement membrane nephropathy and papillary necrosis, which are typical nephrological diseases. Regarding isolated proteinuria, although the excretion of small, usually subclinical, amounts of protein does increase with age, its supposed connection with the aging kidney is not supported by any pathophysiological findings. In contrast, it is commonly the first sign of renal damage induced by diabetes, hypertension, or other causes [36]. Finally, when considering the combination of hematuria with proteinuria, it should not be forgotten that in adults this is the most common sign of most glomerulonephritides, especially IgA nephropathy. In the elderly, a sufficient number of studies demonstrating the same clinical-histological correlation are still lacking; however, there is no reason to suspect that in the aged, a clinical manifestation absolutely identical to that of younger adults may be induced by a cause different from that seen in the adult.

A valuable epidemiological investigation carried out in Japan demonstrated that both proteinuria and proteinuria associated with hematuria must not be considered as innocent by-products of the physiological aging process, since they may be the sign of some pathological change of the kidney, showing a high predictive power for the progression to end-stage renal disease [37].

Third Step: The Histological Characterization

Although renal diseases exhibit a short inventory of symptoms, this brief list conceals a wide range of morphological changes. A certain number of elementary lesions, alone or combined with each other, define about 50 main nosographic entities, which in turn are divided into various subgroups and severity levels. Since every one of these entities carries a different prognostic and therapeutic direction, it is important that the histological characterization is as precise as possible. Therefore, it is necessary to have mastery of all histopathological techniques available today and specific competence in renal histopathology [38]. At the same time, the clinical state of the patient must never be forgotten, so that useful clinical-histological correlations can be made. Renal biopsy should be performed whenever the indication exists, regardless of the patient's age.

The Renal Biopsy

Thus, advanced age does *not* fall within the acknowledged contraindications to renal biopsy [39]. Therefore, the existence of biopsy series dealing with patients aged 80 years and older should be not be surprising [40]. On the contrary, it should be surprising that those series are still so rare. The reasons for such a shortage have to be sought in a certain way of thinking, fairly common even among specialists. Even today some nephrologists wonder whether is it more proper to perform the biopsy or to refrain from this investigation in patients aged over 65 years [41]. Furthermore, another view exists that even asserts that the utility of performing a biopsy is a simple "myth," only deserving to be disproved [42]. This distrust in renal biopsy is often explained by the worry that, in the elderly, this investigation offers low benefits but creates high risks. In particular, there is a widespread suspicion that the background sclerosis of all aging kidneys will confuse the histological picture of any renal disease, therefore compromising the reliability of

diagnosis. Even more widespread is the fear that the risks connected with the invasiveness of a procedure are increased due to the frailty of elderly people.

However, experiences gathered in last three decades do not support any of these worries. Serious diagnostic difficulties due to excessive sclerosis of the aging kidney have been not reported in any known series. As to the risks connected with biopsy technique, the examination of two very large studies allowed the analysis of adverse events to be made separately according to the age of the patients: The frequency of postbiopsy complications occurring in patients older than 60 years was even lower than that observed in patients younger than 60 years: 7.9% vs. 8.1% in the first series [43], and 7.7% vs. 10.1% in the second [44]. It is possible that the low frequency of complications evident in these representative series was the consequence of some selection processes performed on biopsy candidates, excluding those elderly subjects considered at higher risk. Therefore, it is possible that a widening of selection criteria, however desirable, might be burdened by some increase in the frequency of complications. However, it is also possible that such an untoward occurrence may be counterbalanced by diffusion of some technical improvements allowing a reduction of risks connected with biopsy [45]. For example, in last few years, real-time ultrasound guidance and the use of automatic needles to draw the sample of renal tissue have definitely improved the safety of biopsies. The advantage these devices yield is proven by the fact that their adoption allowed a biopsy to be performed even in some people with a solitary kidney [46]. Therefore, if the taboo of the biopsy in the patient with a solitary kidney is already teetering, it is difficult to understand why the concerns regarding biopsies in elderly patients still persist in some quarters.

Refraining from renal biopsy in elderly patients is even more incomprehensible when it is compared to the rising popularity of other kinds of procedures, such as renal artery dilatation. Yet the comparison between the two procedures demonstrates that biopsy is less dangerous than angioplasty. In fact, a recent review of nearly 10,000 percutaneous renal biopsies recorded a total complication rate of 7.4% and a mortality rate of 0.06% [47]. On the other hand, a meta-analysis of nearly 1,500 percutaneous transluminal angioplasties showed a total complication rate of 12% and a mortality rate of 1% [48]. Therefore, a biopsy seems to present a complication risk around half that of angioplasty, with a mortality as little as 20 times less. However, as a rule, such a comparison should be not made, since the two kinds of procedures are not directly comparable: Biopsy only provides a diagnosis, which in its turn has to be utilized to set a therapy, whereas angioplasty is already a therapy by itself.

On the other hand, the therapeutic effect of angioplasty is still far from proven. As a matter of fact, the above-mentioned meta-analysis demonstrated that renal angioplasty is a definitive therapy in 25% of cases, induces some partial improvements in 45% of patients, and is ineffective in the remaining 30% [48]. These results are considered to be fairly good by some people, whereas they are not so convincing for others. However, most physicians seem to share the opinion that without renal angioplasty patients would experience a worsening of their condition. Actually, there is no evidence to support this last opinion, since none of the studies considered in the meta-analysis had a control group of patients. This aspect of the problem has been taken into account by a randomized prospective study: A plain pharmacological

therapy, administered to the patients included in control arm of the study, was able to obtain the same results as angioplasty, which was performed in the patients assigned to the principal arm of the study [49]. Taken together, all these observations suggest that the patients undergoing an angioplasty may run remarkable risks while obtaining no substantial benefits. In spite of this, many nephrologists do not hesitate to schedule their elderly patients for a renal angioplasty, whereas they are more reluctant to perform a renal biopsy.

The different attitudes toward these two procedures, which are both equally invasive, show how important the therapeutic perspective is in a physician´s decision making: Angioplasty at least offers some lingering hope of improvement, while the biopsy is just the starting point for a long therapeutic course. Therefore, it is possible that most doubts on the usefulness of a biopsy just reflect the perplexity of those therapeutic decisions that should be taken as a consequence of histological diagnosis.

Still, some controlled studies exist, though retrospective and nonrandomized, demonstrating that therapies for glomerulonephritis usually administered to younger adult patients are effective in the elderly, too. As is to be expected, these studies display a high frequency of drug-induced side effects; however, the same studies also display the more worrying outcomes observed in the control cases, not receiving the therapy. One of the more enlightening studies regarding this issue concerns the use of steroids alternated with chlorambucil in the treatment of membranous nephropathy [50]. In elderly patients treated according to this regimen, a therapeutic success, more frequently partial than total, was reached in 73% of cases, while no appreciable result was observed in 14% of patients and a worsening occurred in the remaining 13%. This result was not significantly different from that obtained by the same regimen in patients younger than 65 years. However, the price to be paid, in terms of drug-induced side effects, was much higher in elderly patients than in adult ones: 60% vs. 25%. The alarming frequency of iatrogenic complications could attenuate the fairly positive judgment on therapeutic effects of treatment. However, both milder treatments and refraining from any treatment worsened outcomes fairly. In the control group of patients, treated by a simple supportive therapy, membranous nephropathy spontaneously went into remission in 8% of cases, remained in a steady state in 34%, while progressing to end-stage renal disease in the remaining 58% of patients. By comparing the different therapeutic options, the data on mortality appeared even more concerning: Deaths that were probably connected with drug-induced side effects occurred in 7% of treated cases, whereas deaths directly caused by the renal disease occurred in 25% of the nontreated cases.

In the few published studies dealing with the therapy of renal diseases in the elderly, a risk–benefit ratio similar to that observed in the treatment of membranous nephropathy has been reported in the treatment of some other nephropathies, such as focal segmental glomerulosclerosis [51]. Such encouraging results have been obtained by using in each disease a proper therapeutic scheme, specifically indicated for that disease. This is an incentive to characterize the nephropathy by means of histology before undertaking appropriate therapy. On the contrary, a “blind” treatment, theoretically given to avoid the biopsy complications [42], has the same risks of drug-related side effects, without offering those benefits offered by a therapy specifically “tailored” according to the type of histological diagnosis [52].

The advantage of histological diagnosis does not only provide the basis for the right treatment. Even when a therapy of proven effectiveness is still lacking, the knowledge of an exact diagnosis presents some positive aspects: First of all, it allows useless therapies to be avoided; furthermore, it allows the patient follow-up to be scheduled in view of a future treatment, when it is available; finally, diagnosis is essential to direct the prognosis, as the various renal diseases do not show the same rates of progression [53].

Since the risks connected with the biopsy procedure are smaller than commonly assumed and, on the other hand, the benefits of histological diagnosis are greater than thought, it seems that the arguments in favor of renal biopsy in the elderly should prevail. In any case, to further improve the already positive risk–benefit ratio, it is necessary that biopsy candidates undergo a careful preliminary evaluation, aimed at investigating the presence of those clinical conditions known to be more frequently associated with postbiopsy bleeding: renal function impairment, hypertension, and taking of drugs with anticoagulant properties [45, 47].

In contrast to acute renal failure and rapidly progressive renal disease, severe chronic renal insufficiency is normally a clear-cut contraindication to renal biopsy. In fact, the excess of sclerotic tissue characteristic of the advanced phases of nephropathies, besides hampering the histological diagnosis, hampers hemostasis as well. In younger adults, a renal biopsy is usually avoided when the serum creatinine is higher than 3–4 mg/dL or when the kidney length is shorter than 8–9 cm. These limits may be not appropriate in the elderly, as both serum creatinine [9] and kidney dimensions [54] lose their connection with the severity of renal failure with aging. For this reason, it is more appropriate to calculate the creatinine clearance according to the Cockcroft–Gault formula [10] as discussed above and exclude from the biopsy those patients showing a value below about 30 mL/min, although it must be kept in mind that data to help determine what figure should be used are lacking.

Also, hypertension is usually considered to be a contraindication to renal biopsy; however, high blood pressure may be lowered before proceeding to the invasive procedure. The main problem is that an antihypertensive treatment may need more than one week before obtaining some result of clinical importance. Adjourning the biopsy for some weeks does not entail relevant consequences in patients with mild to moderate chronic renal insufficiency or in those with urinary abnormalities. Delay begins to become problematic in patients with nephrotic syndrome, as the late outcomes are directly related to the time spent by the body in this highly risky condition. Finally, every time delay is a serious concern in patients with either acute or rapidly progressive renal failure in whom a timely diagnosis and a timely therapy are essential for survival, even in a short period of time.

In these cases, a rapid lowering of blood pressure is indicated, according to the modalities currently used in hypertensive emergencies. As to the choice of antihypertensive drugs, calcium-entry blockers should possibly be avoided, since an increase of hemorrhagic risk in patients taking this kind of drug has been reported [55].

Besides calcium-entry blockers, all the drugs the patient takes have to be carefully evaluated under the aspect of hemorrhagic risk. Usually, elderly persons frequently use NSAIDs, predominantly to subdue musculoskeletal

pain, almost to the point of abuse; moreover, many elderly people take a low-dose (75 mg/24 hr) aspirin to prevent an arterial thrombosis at the level of carotid, coronary, or leg vessels; similarly, other elderly people are taking warfarin to prevent a thromboembolism from their fibrillating atria or mechanical heart valves. The importance of giving up NSAIDs, in the week preceding the biopsy and in the following one, has to be repeatedly explained to the patient and his family, since the hemorrhagic risk connected with these drugs is generally underestimated. As much patience is needed to convince the patient to withdraw from aspirin for the same two weeks; actually, such a temporary withdrawal is not harmful. On the contrary, withdrawal from warfarin deserves greater caution. In patients showing a high risk of thromboembolism, warfarin may be replaced by a preparation of heparin, according to the schemes recommended in the perioperative period of elective surgery [56]. In this case, performing a percutaneous biopsy is no longer possible, while an open biopsy becomes indicated, as this is the only way to warrant careful hemostasis [45]. In any case, postbiopsy bleeding remains the most dreaded complication. Consequently, many preventive strategies have been studied, such as the measuring of bleeding time and the administration of drugs with some antihemorrhagic action [45]. Nevertheless, the real effectiveness of these measures is still under debate and, at the moment, their validity seems to be more acknowledged in the United States than in Europe [57].

Once all practical and theoretical problems have been overcome, and the biopsy has finally been performed, it is possible to appraise the usefulness of histological investigation. As the single biopsy is helpful in solving the diagnostic doubts in a single patient, the databases collecting large series of biopsies are essential to understand the epidemiology of renal diseases. This is particularly important in the case of the elderly with renal diseases, who are still being burdened by a lot of old prejudices.

Renal Diseases in Elderly Patients

Elderly people may be affected by any kind of renal disease, exactly as adults and children are. This seems an obvious observation nowadays; however, only some years ago, the leading opinion was that elderly people were mainly prone to vascular and interstitial nephropathies, while glomerulonephritis occurred more frequently in young people. Reconciling the ideas commonly accepted in the past with today's reality is very difficult indeed. Theoretically, it is possible that renal diseases have changed their incidence pattern with time; it is also possible that the current diagnostic tools such as renal biopsy have finally displayed an epidemiological situation underestimated for a long time.

Misconceptions about the elderly renal diseases had probably risen from a too strict interpretation of some necroscopy data presented by the "fathers" of modern nephrology. In 1836, Richard Bright described the macroscopic appearance of the organs belonging to patients who died of albuminuric disease [58]. The age was only recorded in 74 of the 100 reported cases; of these, no more than 4 were older than 60 years, and their contracted kidneys testified that some disease occurred many years before, during the juvenile or adult age. The author observed that, although his series included patients aged between 8 and 73 years, disease had cut off the greater part of its victims before middle age was attained.

A century later, in 1942, Arthur Ellis described, also in the UK, a series of some 600 patients affected by "Bright's disease," grouping under this name every renal disease accompanied by hypertension [59]. The age was only reported in those 318 patients whose nephropathy was more precisely indicated as glomerulonephritis; 173 cases had experienced an abrupt onset of their disease, while 145 had suffered from an insidious onset. Only 5 patients were older than 60 years in the whole series, and all were to be found within the group of chronic cases. Actually, the author suspected that during the period between the two world wars, when he was collecting his series, many acute patients were not admitted to the hospital.

Anyway, the double misconception, about the low frequency of glomerulonephritis in elderly people and about the chronic nature of those rare glomerulonephritides eventually occurring in the elderly, began to be disproved when some more recent necroscopy data were made known. In 1960, a report was published on a study of more than 11,000 necroscopies performed between 1945 and 1956 [60]; of these, more than 1,000 showed a picture consistent with a pyelonephritis and nearly 100 revealed the signs of glomerulonephritis. From this latter group, 74 cases had been selected whose clinical records allowed the disease to be precisely reconstructed; surprisingly, 26 patients were older than 60 years: that is, more than one-third of the total. Another surprise involved the types of glomerulonephritis. As a matter of fact, among the elderly patients, the acute type, taken together with the "subacute" type [a confusing term used at that time to indicate crescentic (rapidly progressive) glomerulonephritis], was more frequent as compared to the chronic type: 65% vs. 35%; on the contrary, among the patients younger than 60 years, acute and subacute types showed a frequency lower than that of the chronic type: 46% vs. 54%. The authors warned against the errors that can possibly occur when only necroscopy data or only clinical data are considered: The former ones cannot account for all those cases not undergoing a post-mortem, while the latter ones can frequently induce a misdiagnosis, as was demonstrated in 45% of examined cases, by comparing the clinical records to the histological reports.

Some of these concepts were confirmed by another necroscopy study, performed between 1956 and 1972 and published in 1974 [61]. Of the 44 elderly patients who had died from glomerulonephritis, 64% showed a picture of rapidly progressive focal necrotizing nephritis, 18% exhibited acute postinfectious nephritis, and 18% had miscellaneous chronic nephritides.

If, in the period between 1960 and 1974, some research based on necroscopic investigations had subverted the original ideas about Bright's disease, biopsies in the following years helped define the emerging concepts in a more detailed way. Renal biopsy had already come into clinical practice from the second half of the 1960s; however, at the beginning, it was mainly performed in younger adults and children. The first large study entirely consisting of elderly patients with renal diseases was only published in 1980 [62]: The 115 patients older than 60 years corresponded to 10% of the authors' whole study. Glomerulonephritis was found in 68% of elderly patients, a renal involvement secondary to a systemic disease in 23%, and a tubular interstitial nephropathy in 9%. In patients younger than 60 years, a different proportion among the various diagnoses had been previously found: 55%, 30%, and 15%, respectively. Moreover, in any group of renal diseases, some differences in the

distribution of single nephropathies were evident, according to whether the patients were older or younger than 60 years; for example, among the primary glomerular diseases, elderly patients as compared to the younger ones had a higher frequency of extracapillary nephritis (16.5% vs. 4%) and a lower frequency of mesangial nephritis (6% vs. 10.5%). At the same time, among the nephropathies secondary to systemic diseases, elderly patients as compared to the younger ones had a higher frequency of vasculitides (8% vs. 3.2%) and a lower frequency of lupus nephritis (1.7% vs. 13.8%). The unique role of biopsy in defining a correct diagnosis was stressed by comparing histological and clinical features: The clinical presentation of most cases with the same nephropathy was as different as possible, thus being unsuitable for diagnosis.

After that report, many others followed in the next few years, and in 1985 about 30 studies were pooled together [63]. Based on these pooled data, a scheme had been constructed representing the whole spectrum of glomerulonephritis with age. The graph showed a bimodal trend, with a first peak of frequency around the age of 10 years and a second peak just corresponding to the age of 65 years. The graph showed as well that some types of nephropathy tended to be more frequent at the two extremes of life: Minimal change disease and membrano-proliferative glomerulonephritis were more common in children and young people, whereas pauci-immune rapidly progressive glomerulonephritis and membranous nephropathy were more common in elderly patients. Apart from these results, that article mainly deserves to be remembered because it showed the importance of a certain kind of methodological approach: To perform a detailed analysis of the distribution of the various renal diseases, according to all the different periods of a lifetime, it is necessary to have sample sizes so large that they can only be collected by pooling the data coming from many centers performing renal biopsies. The Registries of Renal Biopsy, which are organized at a regional or national level, are now dealing with this task, and some of these registries have recently presented their data on elderly renal disease.

The Danish Registry collected some 2,400 cases of primary glomerulonephritis diagnosed by means of biopsies performed between 1985 and 1997 [64]. The incidence of glomerulonephritis in the whole of Denmark (5.2 million people) was calculated to be nearly 39 cases per million per year. The incidence was also calculated according to the age of patients, provided that they were matched with the population being the same age. Interestingly, a graph was obtained mimicking that shown in the article cited above. A double peak of incidence was found: The first one between 20 and 30 years, the second one between 60 and 70 years; by comparing those peaks, glomerulonephritis clearly appeared to be more diffuse in the elderly than in young people. This evidence was allowed to emerge only thanks to the method used to express the data: incidence per million of population, rather than a percent frequency.

Using the same method of calculation, some similar results were obtained by the Italian Registry [65]. Among the biopsies performed in 1996, more than 2,500 cases were collected: Primary glomerulonephritis accounted for 59% of diagnoses, while secondary glomerulonephritis, nonglomerular renal diseases, and undiagnosed renal diseases were found in 20%, 11%, and 10% of cases, respectively. Among the patients undergoing biopsy, those older than 65 years accounted for 23% of the total. At first sight, this seems to

be a minority, as compared to the patients younger than 65 years; however, elderly patients included in the biopsy series were more numerous than the proportion of elderly people in the general population, who made up just 16%. This disproportion severely affected the results. When the frequency of renal diseases was expressed as a percentage rate, renal diseases occurring in the elderly always appeared to be as a negligible minority. On the contrary, when the incidence of renal disease was assessed by considering the composition of the general population, a different reality immediately appeared. The incidence of primary glomerular diseases, secondary glomerular diseases, and nonglomerular renal diseases, expressed as the number of cases per million of population, was greater in elderly patients (30.8, 16.2, and 9.8, respectively) than in adults (28.3, 8.4, and 4.5, respectively) and in children (8.7, 3.1, and 2.1, respectively). Even the total count of biopsies expressed in the same way was greater in elderly patients than in adults and children (61.9, 45.8, and 15.7, respectively). Italian nephrologists had performed a biopsy more frequently in elderly patients than in younger ones, probably without realizing it, since most of them still continue to consider the elderly patients as only making up only a marginal 23% of their biopsy patients. Finally, the incidence of the single types of primary glomerulonephritis, when expressed as the number of cases per million of population, appeared in a different light: Membranous nephropathy, crescentic nephritis, membrano-proliferative glomerulonephritis, minimal change disease, and acute post-streptococcal glomerulonephritis were all found to be more frequent in elderly patients than in younger patients. Only focal segmental glomerulosclerosis, non-IgA mesangioproliferative nephritis, and IgA nephropathy were found to be less common in elderly patients than in younger ones. The low frequency of IgA nephropathy occurring in elderly patients shown in the Italian Registry, as well as by most biopsy series, probably reflected a double-selection bias: Urinary abnormalities were considered too trivial to induce general practitioners to refer the elderly patients to a nephrologist and to induce nephrologists to perform a renal biopsy in those patients. This particular issue has been dealt with by a French regional registry.

The Registry of "Côtes d'Armor," in northwestern France, collected more than 1,700 biopsies performed between 1976 and 2002 [66]. Interestingly, this registry showed that the percentage of elderly patients who underwent biopsy increased from less than 10% before 1980 to more than 30% after 1996. As more and more elderly patients were accepted into the biopsy program, the annual incidence of renal disease, expressed as the number of cases per million of population, appeared to be changing. The most evident case concerned the incidence of IgA nephropathy. Before 1996, the occurrence of IgA nephropathy in elderly patients appeared to be one-third of that seen in younger patients (12 vs. 37). After 1996, the occurrence of IgA nephropathy was demonstrated to be similar in both elderly and young patients (27 vs. 25). Since it is difficult to believe that IgA nephropathy has changed its epidemiological pattern in only a few years, it is more likely that the increasing confidence toward renal biopsy in elderly patients has finally disclosed an epidemiological situation that had remained concealed for a long time.

Besides these Danish, Italian, and French registries, the British [67] and Spanish [68] collections have also made interesting contributions to the current understanding of elderly renal diseases. However, these last registries, as well

as another report from an Italian registry [69], expressed their data only as a percent frequency, rather than as an incidence per million of population, thus showing a clinical-histological appraisal rather than an epidemiological approach to the problem. Nevertheless, all the registries contributed to expanding the awareness that renal disease in the elderly is not a marginal issue.

Conclusion

Dialysis rooms are full of elderly patients, and more patients are continuously arriving. All healthcare professionals are worried; however, the measures taken to slow down the patient flow do not seem strong enough. Elderly patients should be offered the same chance of diagnosis, prognosis, and therapy that adult patients are usually given; however, many old-fashioned ideas are still hampering a correct approach to elderly renal disease.

Renal biopsy is an excellent tool to discover which nephropathy underlies nonspecific clinical pictures. This chapter has demonstrated how useful the biopsy may be in understanding the renal problem of the individual patient; it has also shown how much the Registries of Renal Biopsy can contribute to the understanding of the spread of renal disease through the communities. A wider use of biopsy in elderly patients, as recently seen in northwestern France, could be an important step toward both clinical and epidemiological objects.

References

1. D'Amico, G., Striker, G., eds. *Proceedings of Symposium on Renal Replacement Therapy Throughout the World: The Registries*, Milan, Italy, December 9-11, 1993. *Am. J. Kidney Dis*. 1995; 25:113–205.
2. Coresh, J., Astor, B., Greene, T., et al. Prevalence of chronic kidney disease and decreased kidney function in the adult U.S. population: Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis*. 2003; 41:1–12.
3. Foley, R., Murray, A., Li, S., et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement and death in the United States Medicare population, 1998 to 1999. *J. Am. Soc. Nephrol*. 2005; 16:489–495.
4. Keith, D., Nichols, G., Gullion, C., et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large Managed Care Organization. *Arch. Intern. Med*. 2004; 164:659–663.
5. Lindeman, R., Tobin, J., Shock, N. Longitudinal studies on the rate of decline in renal function with age. *J. Am. Geriatr. Soc*. 1985; 33:278–285.
6. Blejer, A., Shemanski, L., Burke, G. Tobacco, hypertension and vascular disease: Risk factors for renal functional decline in an older population. *Kidney Int*. 2000; 57:2072–2079.
7. Hemmelgarn, B., Zang, J., Manns, B., et al. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int*. 2006; 69:2155–2161.
8. John, R., Webb, M., Young, A., et al. Unreferred chronic kidney disease: A longitudinal study. *Am. J. Kidney Dis*. 2004; 43:825–835.
9. Duncan, L., Heathcote, J., Djurdjev, O., et al. Screening for renal disease using serum creatinine: Who are we missing? *Nephrol. Dial. Transplant* 2001; 16:1042–1046.

10. Lamb, E., Webb, M., Simpson, D., et al. Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: Is the Modification of Diet in Renal Disease formula an improvement? *J. Am. Geriatr. Soc*. 2003; 51:1012–1017.
11. Weinstock-Brown, W., Peters, R., Ohmit, S., et al. Early detection of kidney disease in community settings: The Kidney Early Evaluation Program (KEEP). *Am. J. Kidney Dis*. 2003; 42:22–35.
12. Gambaro, G., D'Angelo, A., Conte, M., et al. Silent chronic kidney disease epidemic seen from Europe: Designing strategies for clinical management of the early stages. *J. Nephrol*. 2005; 18:123–135.
13. Kaiser, F. Principles of geriatric care. *Am. J. Kidney Dis*. 1990; 16:354–359.
14. Garg, A., Blake, P., Clark, W., et al. Association between renal insufficiency and malnutrition in older adults: Results from the NHANES III. *Kidney Int.* 2001; 60:1867–1874.
15. Hsu, C., McCulloch, C., Curhan, G. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: Results from the third National Health and Nutrition Examination Survey. *J. Am. Soc. Nephrol*. 2002; 13:504–510.
16. Thongboonkerd, V., Malsit, P. Renal and urinary proteomics: Current applications and challenges. *Proteomics* 2005; 5:1033–1042.
17. Vidal, B., Jr., Bonventre, J., I-Hong Hsu, S. Towards the application of proteomics in renal disease diagnosis. *Clin. Sci*. 2005; 109:421–430.
18. D'Amico, G., Bazzi, C. Urinary protein and enzyme excretion as markers of tubular damage. *Curr. Opin. Nephrol. Hypertens*. 2003; 12:639–643.
19. Köhler, H., Wandel, E., Brunck, B. Acanthocyturia. A characteristic marker for glomerular bleeding. *Kidney Int*. 1991; 40:115–120.
20. Dontas, A., Kasviki-Charvati, P., Papanayiotou, P., et al. Bacteriuria and survival in old age. *N. Engl. J. Med*. 1981; 304:939–943.
21. Shlipak, M., Fried, L., Crump, C., et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 2003; 107:87–92.
22. O'Neill, C. Sonographic evaluation of renal failure. *Am. J. Kidney Dis*. 2000; 35:1021–1038.
23. Manley, J., O'Neill, C. How echogenic is echogenic? Quantitative acoustics of renal cortex. *Am. J. Kidney Dis*. 2001; 37:706–713.
24. Pearce, J., Edwards, M., Craven, T., et al. Renal duplex parameters, blood pressure and renal function in elderly people. *Am. J. Kidney Dis*. 2005; 45:842–850.
25. Montseny, J., Meyrier, A., Kleinknecht, D. The current spectrum of infectious glomerulonephritis. *Medicine* 1996; 74:63–73.
26. D'Amico, G., Sinico, R., Ferrario, F. Renal vasculitis. *Nephrol. Dial. Transplant* 1996; 11(Suppl. 9):S69–S74.
27. Haas, M., Spargo, B., Wit, E., et al. Etiologies and outcome of acute renal insufficiency in older adults. *Am. J. Kidney Dis*. 2000; 35:433–447.
28. Jungers, P., Chauveau, P., Descampes-Latscha, B., et al. Age and gender-related incidence of chronic renal failure in a French urban area: A prospective epidemiologic study. *Nephrol. Dial. Transplant* 1996; 11:1542–1546.
29. Cameron, S. Nephrotic syndrome in the elderly. *Semin. Nephrol*. 1996; 16:319–329.
30. Mazzucco, G., Bertani, T., Fortunato, M., et al. Different patterns of renal damage in type 2 diabetes mellitus: A multicentric study on 393 biopsies. *Am. J. Kidney Dis*. 2002; 39:713–720.
31. Kyle, R., Therneau, T., Rajkumar, V., et al. Prevalence of monoclonal gammopathy of undetermined significance. *N. Engl. J. Med*. 2006; 354:1362–1369.
32. Ruffatti, A., Rossi, L., Calligaro, A., et al. Autoantibodies of systemic rheumatic diseases in healthy elderly. *Gerontology* 1990; 36:104–111.
33. Eagen, J., Lewis, E. Glomerulopathies of neoplasia. *Kidney Int*. 1977; 11:297–306.

34. Ghiggeri, G., Carraro, M., Vincenti, F. Recurrent focal glomerulosclerosis in the era of genetics of podocyte proteins: Theory and therapy. *Nephrol. Dial. Transplant* 2004; 19:1036–1040.
35. Yamagata, K., Yamagata, Y., Kobayashi, M., et al. A long term follow-up study of asymptomatic hematuria and/or proteinuria in adults. *Clin. Nephrol*. 1996; 45:281–288.
36. Jones, C., Francis, M., Eberhardt, M., et al. Microalbuminuria in the U.S. population: Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis*. 2002; 39:445–459.
37. Iseki, K., Iseki, C., Ikemiya, Y., et al. Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int*. 1996; 49:800–805.
38. D'Amico, G. Why opening an Educational Corner in JN and starting with a histopathological atlas. *J. Nephrol*. 2004; 17:349–350.
39. Health and Public Policy Committee, American College of Physicians. Clinical competence in percutaneous renal biopsy. *Ann. Intern. Med*. 1988; 108:301–303.
40. Nair, R., Bell, J., Walker, P. Renal biopsy in patients aged 80 years and older. *Am. J. Kidney Dis*. 2004; 44:618–626.
41. Rifle, G., Ronco, P. Pour ou contre la biopsie rénale après 65 ans. [in French] *Néphrologie* 1990; 11:301–306.
42. Levey, A., Lau, J., Pauker, S., et al. Idiopathic nephrotic syndrome. Puncturing the biopsy myth. *Ann. Intern. Med*. 1987; 107:697–713.
43. Diaz-Buxo, J., Donadio, J. Complications of percutaneous renal biopsy: An analysis of 1,000 consecutive biopsies. *Clin. Nephrol*. 1975; 4:223–227.
44. Parish, A. Complications of percutaneous renal biopsy: A review of 37 years' experience. *Clin. Nephrol*. 1992; 38:135–141.
45. Stiles, K., Yuan, C., Chung, E., et al. Renal biopsy in high-risk patients with medical diseases of the kidney. *Am. J. Kidney Dis*. 2000; 36:419–433.
46. Mendelssohn, D., Cole, E. Outcomes of percutaneous kidney biopsy, including those of solitary native kidneys. *Am. J. Kidney Dis.* 1995; 4:580–585.
47. Korbet, S. Percutaneous renal biopsy. *Semin. Nephrol*. 2002; 22:254–267.
48. Leertouwer, T., Gussenhoven, E., Bosh, J., et al. Stent placement for renal arterial stenosis: Where do we stand? A meta-analysis. *Radiology* 2000; 1:78–85.
49. van Jaarsveld, B., Krijnen, P., Pieterman, H., et al. The effect of balloon angioplasty on hypertension in atherosclerothic renal artery stenosis. *N. Engl. J. Med.* 2000; 342:1007–1014.
50. Passerini, P., Como, G., Viganò, E., et al. Idiopathic membranous nephropathy in the elderly. *Nephrol. Dial. Transplant* 1993; 8:1321–1325.
51. Nagai, R., Cattran, D., Pei, Y. Steroid therapy and prognosis of focal segmental glomerulosclerosis in the elderly. *Clin. Nephrol*. 1994; 42:18–21.
52. Richards, N., Darby, S., Howie, A., et al. Knowledge of renal histology alters patient management in over 40% of cases. *Nephrol. Dial. Transplant* 1994; 9:1255–1259.
53. Locatelli, F., Del Vecchio, L., Andrulli, S., et al. The role of underlying nephropathy in the progression of renal disease. *Kidney Int*. 2000; 57(Suppl 75): S49–S55.
54. Burkhardt, H., Hahn, T., Gladisch, R. Is kidney size a useful predictor of renal function in the elderly? *Clin. Nephrol*. 2003; 59:415–422.
55. Pahor, M., Gurarlnik, J., Furberg, C., et al. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; 347:1061–1065.
56. Kearon, C., Hirsh, J. Management of anticoagulation before and after elective surgery. *N. Engl. J. Med*. 1997; 336:1506–1511.
57. Mattix, H., Singh, A. Is the bleeding time predictive of bleeding prior to a percutaneous renal biopsy? *Curr. Opin. Nephrol. Hypertens*. 1999; 8:715–718.

58. Brigh, R. Tabular view of the morbid appearance in 100 cases connected with albuminous urine, with observations. *Guy's Hosp. Rep*. 1836; 1:380–400.
59. Ellis, A. A natural history of Bright's disease. Clinical, histological and experimental observations. (First part) *Lancet* 1942; *i*:1–7; (Second part) *Lancet* 1942; *i*:34–36; (Third part) *Lancet* 1942; *i*:72–76.
60. Nesson, R., Robbin, S. Glomerulonephritis in older age groups. *Arch. Intern. Med*. 1960; 105:23–32.
61. Potvliege, P., De Roy, R., Dupuis, F. Necroscopy study on glomerulonephritis in the elderly. *J. Clin. Path*. 1975; 28:891–898.
62. Moorthy, A., Zimmerman, S. Renal disease in the elderly: Clinicopathologic analysis of renal disease in 115 elderly patients. *Clin. Nephrol*. 1980; 14:223–229.
63. Abrass, C. Glomerulonephritis in the elderly. *Am. J. Nephrol*. 1985; 5:409–418.
64. Heaf, J., Lokkegaard, H., Larsen, S. The epidemiology and prognosis of glomerulonephritis in Denmark 1985–1997. *Nephrol. Dial. Transplant* 1999; 14:1889–1897.
65. Vendemia, F., Gesualdo, L., Schena, F., et al. Epidemiology of primary glomerulonephritis in the elderly. Report from the Italian Registry of Renal Biopsy. *J. Nephrol*. 2001; 14:340–352.
66. Simon, P., Ramee, M., Boulahrouz, R., et al. Epidemiologic data of primary glomerular diseases in western France. *Kidney Int*. 2004; 66:905–908.
67. Davison, A., Johnston, P. Idiopathic glomerulonephritis in the elderly. In *Glomerulonephritis in the Elderly*, A. Sessa, M. Meroni, and G. Battini, eds. Contrib. Nephrol., Basel: Karger. 1993; 105:38–48.
68. Rivera, F., Lopez-Gomez, J., Perez-Garcia, R. Clinicopathologic correlations of renal pathology in Spain. *Kidney Int*. 2004; 66:898–904.
69. Gesualdo, L., Di Palma, A., Morrone, L., et al. The Italian experience of the national registry of renal biopsies. *Kidney Int*. 2004; 66:890–894.

18

Diabetic Nephropathy

Alessia Fornoni, Carlos Leon, and Leopoldo Raij

Introduction

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in the United States, accounting for 53% of incident patients and 45% of the prevalent ESRD population [1]. This percentage of incident patients is rather less in Europe, varying from 15 to 50% in different countries. These high figures are due primarily to the increased prevalence of type 2 diabetes in older subjects (20% of patients over age 65 have diabetes as defined by glucose tolerance tests), the longer life expectancy of patients with type 2 diabetes, and the acceptance of diabetics with ESRD in treatment programs today, from which they had formerly been excluded [2]. The great majority of elderly subjects (>70 years of age) with DN have this as a complication of type 2 diabetes.

DN is a syndrome characterized by the appearance of abnormal urine albumin excretion (>30 mg/24 hr or >20 μg/min or >30 μg/mg creatinine) or diabetic glomerular lesions and loss of glomerular filtration rate (GFR) in the absence of albuminuria. Among patients with type 1 diabetes, 17–28% progressed from normoalbuminuria to microalbuminuria after 10 years of follow-up, although 30% may revert back to normoalbuminuria [3,4]. Among patients with type 2 diabetes, microalbuminuria is already present in 30% of patients at time of diagnosis [1]. Without specific intervention, initial reports suggested that 80% of subjects with type 1 diabetes and microalbuminuria will progress to proteinuria (>300 mg/24 hr or > 200 ug/min or >300 μg/mg creatinine) over 6 to 14 years [5]. However, more recent studies showed that the overall risk for progression from microalbuminuria to proteinuria is 30% for patients with type 1 diabetes as well as those with type 2 diabetes [3]. Among the patients with overt nephropathy, ESRD will develop in 75% of type 1 diabetic patients and 20% of type 2 diabetic patients at 20 years [2]. Since the prevalence of type 2 diabetes is 10–15 times higher than type 1 and continues to rise in both North American and European populations [1,6], patients with type 2 diabetes now represent the largest single disease group requiring renal replacement therapy. In addition, since the greater risk of dying in the population with type 2 diabetes is from cardiovascular disease (CVD), and therapies and interventions for CVD continue to improve, a further increase in the number of patients with type 2 diabetes reaching ESRD is expected to occur. Thus, the healthcare burden of patients with diabetes and

ESRD requiring renal replacement therapy is expected to rise even though, among patients who require dialysis, those with diabetes have a 22% higher mortality at 1 year and a 15% higher mortality at 5 years than patients without diabetes [7].

Risk Factors

The early identification of those patients at risk of developing DN is the subject of an intense research effort. Among the known risk factors for the development of DN, both modifiable and non-modifiable risk factors have been identified (Table 18.1).

Nonmodifiable Risk Factors

Ethnicity

Race is a strong independent risk factor for DN. DN rates are much higher in African-American, Native American, and Hispanic compared with white populations [1]. Studies of Pima Indians show a cumulative incidence of ESRD of 40% at 10 years and 61% at 15 years following the onset of proteinuria, compared to a cumulative incidence of 17% ESRD at 15 years following the onset of proteinuria in Caucasian type 2 diabetics. For diabetes-related ESRD, Mexican Americans have an incidence ratio of 6, while African Americans have a ratio of 4 compared to Caucasian populations. Within the UK, the incidence of ESRD again is significantly higher among South Asians and African-Caribbean populations [8].

Family History

Clustering of DN in families has been convincingly demonstrated in several studies, and both heritability and segregational genetic analysis have suggested a role for genetic background in the pathogenesis of DN [9]. In fact, similar patterns of glomerular involvement were observed in family members with diabetes even in the absence of clinical nephropathy [10]. In addition, multiple studies support familial aggregation of albuminuria, GFR, and creatinine clearance [11]. This genetic clustering has led to a substantial development of genome-wide expression analysis for the identification of susceptibility genes [12]. The first genome scan that searched for nephropathy loci was performed in Pima Indians. Among this group, a strong familial clustering of nephropathy has been reported: 14.3% of diabetic offspring if neither parent

Table 18.1 Risk Factors for the Development of Diabetic Nephropathy. Risk Factors Can Be Divided Among Those That Can Be Modified by Intervention and Those That Are Not Amenable to Intervention.

Modifiable Risk Factors	Nonmodifiable Risk Factors
Hyperglycemia	Ethnic background
Hypertension	Family history
Cigarette smoking	Presence of retinopathy
Dyslipidemia	Altered GFR at presentation

had proteinuria; 22.9% if at least one parent had proteinuria; and 45.9% if both parents had nephropathy. More recently, Turkish kindreds and African-American families were also analyzed. As a result, susceptibility loci on chromosomes 3, 7, and 18 were identified. However, as DN is an example of a complex rather than Mendelian disease, no gene has yet been uniquely associated with susceptibility to DN in either human populations or animal models. Finally, when collecting family history from patients with diabetes, it is important to consider that parental hypertension is a risk factor for the development of DN among offspring [3].

Elevated GFR

It remains controversial whether hyperfiltration predicts the appearance of DN in patients with type 1 diabetes. While some found that GFR > 140 mL/min/1.73 m^2 predicted higher risk of progression to microalbuminuria [5], other studies were unable to confirm these findings [13]. A similar controversy exists for patients with type 2 diabetes [3].

Reduced GFR

Loss of GFR can be the initial manifestation of DN. In fact, in women with type 1 diabetes, a low GFR despite normoalbuminuria was associated with worse DN than women with normoalbuminuria and high GFR. Similarly, in patients with type 2 diabetes, particularly older women, a low GFR with normoalbuminuria was observed in up to 23% of the patients and was associated with a trend toward more rapid progression than in patients with microalbuminuria [14].

Presence of Retinopathy

The presence of diabetic retinopathy (DR) usually antedates the development of microalbuminuria in patients with type 1 diabetes, and the severity of DR lesions usually correlates with DN glomerular lesions even in the absence of renal functional abnormalities [15]. Patients with normoalbuminuria and proliferative DR have a 9-fold risk for microalbuminuria [4] when compared to the only 1.3-fold risk in the presence of stage 1 DR. The relationship between DR and DN is much less clear for type 2 diabetes [3,4]. However, when DN is defined by the presence of histological glomerulopathy (mesangial expansion and GBM thickening) and not solely by the presence of microalbuminuria, a strong concordance between DN and DR is observed [3].

Modifiable Risk Factors

Glycemia

The DCCT trial offers the best evidence that strict glycemic control was associated with lower likelihood of microalbuminuria at 6.5 years [16]. In addition, even after the discontinuation of intensive treatment that led to equal A1c value among groups, the long-term follow-up of the same patients

showed that there was a 59% risk reduction of developing microalbuminuria in those patients who were initially assigned to intensive treatment [17]. Similarly, in the UKPDS study on a patient population with type 2 diabetes, intensive glucose control reduced the risk for microalbuminuria [18]. Once microalbuminuria has developed, a correlation between A1c and reversal from microalbuminuria to normoalbuminuria has been established in patients with type 1 diabetes [19] as well as in those with type 2 diabetes [20]. In addition, higher A1c levels predicted progression from microalbuminuria to proteinuria in the EURODIAB study [21].

Hypertension

In the population of patients with type 1 diabetes and normoalbuminuria, ambulatory blood pressure measurements revealed that nocturnal blood pressure values and dipper status were predictors of progression to microalbuminuria [22]. In addition, data from the Steno Diabetes Center showed that before the onset of microalbuminuria, a 4 times higher number of patients who later developed microalbuminuria were receiving antihypertensive treatment when compared to those patients who maintained normoalbuminuria [4]. Similarly, prediabetic blood pressure predicted the development of microalbuminuria in a selected population of patients with type 2 diabetes, i.e., the Pima Indians [23]. In addition, blood pressure often predicts which patients with microalbuminuria may revert to normoalbuminuria in patients with type 1 [4, 16] and type 2 [20] diabetes. These data suggest that ambulatory BP monitoring may need to be performed annually in normotensive normoalbuminuric diabetic patients as an additional criterion to assess the risk of developing DN. In type 2 diabetics, the prevalence of hypertension is 30–50% at diagnosis, increasing to 90% with the development of abnormal urinary albumin excretion. The degree of hypertension after the diagnosis of diabetes is often related to the degree of albuminuria.

Cigarette Smoking

Cigarette smoking is an independent risk factor for the development of microalbuminuria as well as for the progression to ESRD in patients with type 1 diabetes [24] as well as for patients with type 2 diabetes [25]. When cigarette smoking and elevated A1c are concomitantly present, a synergistic effect is observed. Interestingly, analysis of renal biopsies of patients with type 2 diabetes shows that cigarette smoking is an independent determinant of GBM thickening [25].

Dyslipidemia

Among patients with type 1 diabetes and normoalbuminuria, serum cholesterol was higher in those patients who progress to microalbuminuira when compared to those who remained normoalbuminuric [4]. Similarly, low serum cholesterol levels also predicted return from microalbuminuria to normoalbuminuria in both the above Steno Study as well as the Joslin Clinic Study [19]. Although a recent strong association among lipids, inflammatory biomarkers, and renal function has been established in a cross-sectional study of 732 men with diabetes [26], there is no definitive evidence yet that lipid lowering may reduce progression of DN.

Clinical Manifestation of Diabetic Nephropathy

Clinical DN results from glomerular, tubular, interstitial, and vascular lesions, which become severe when normal glomerular membrane permselectivity, filtration function, and glomerular autoregulation of blood pressure are impaired. The natural history of renal involvement has been better defined in type 1 than type 2 diabetes. Mogensen [27] has identified five distinct stages of renal dysfunction in this population, and it has been assumed that a similar sequence of events occurs in type 2 diabetics. After an earlier functional phase (stages 1 and 2) in which hyperglycemia is accompanied by an increased GFR and microalbuminuira, persistence of high glomerular flows and pressures plus poor control of glycemia eventually fosters renal damage, which results in the progression of microalbuminuira to proteinuria accompanied with a decline in GFR (stage 3). This is followed by the development of hypertension (stage 4) and progression to ESRD (stage 5). However, not all patients follow this pattern, since a quite large subset of patients is characterized by worsening GFR despite normoalbuminuria in both type 1 and type 2 diabetes [3]. It is interesting to note that this pattern of presentation is more characteristic in the subpopulation of elderly females. In the third NHANES survey, Kramer et al. [28] noted that retinopathy and albuminuria (spot urine albumin/creatinine ratio) were absent in 30% of elderly type 2 diabetic patients with eGFR < 60 mL/min/1.73 m^2 (Modification of Diet in Renal Disease, MDRD, formula). These findings certainly do not invalidate the use of urine analysis for albumin/protein, but clearly suggest that complementary pathogenetic mechanisms operate in a small segment of elderly type 2 diabetic patients such as the possibility of premature senescence of the kidney or excessive sensitization of renal vasculature to blood pressure.

Screening for Diabetic Nephropathy

Screening for DN is based on the detection of microalbuminuria and can be performed by albumin-to-creatinine ratio in a random spot collection (preferred method), or by measurement of albumin in a timed urine collection (24 hours or less). Screening for microalbuminuria should be performed with diabetes duration more than 5 years in type 1 diabetics and in all type 2 diabetic patients. The analysis of a spot sample for the albumin-to-creatinine ratio is strongly recommended by most authorities such as the National Kidney Foundation (NKF) and American Diabetes Association (ADA) [2,29]. Measurement of a spot urine for albumin only, whether by immunoassay or by using a dipstick test specific for albumin, without simultaneously measuring urine creatinine, is less expensive than the recommended methods but is susceptible to false-negative and -positive determinations as a result of variation in urine concentration due to hydration and other factors. Screening for microalbuminuria should consist of at least two samples within six months (Figure 18.1). Presence of microalbuminuria in addition to level of GFR may be used to stage CKD according to the current National Kidney Foundation classification [30]. In addition, serum creatinine should be measured annually for the estimation of GFR in all adults with diabetes regardless of the degree of urine albumin excretion. The GFR can be easily estimated using the MDRD

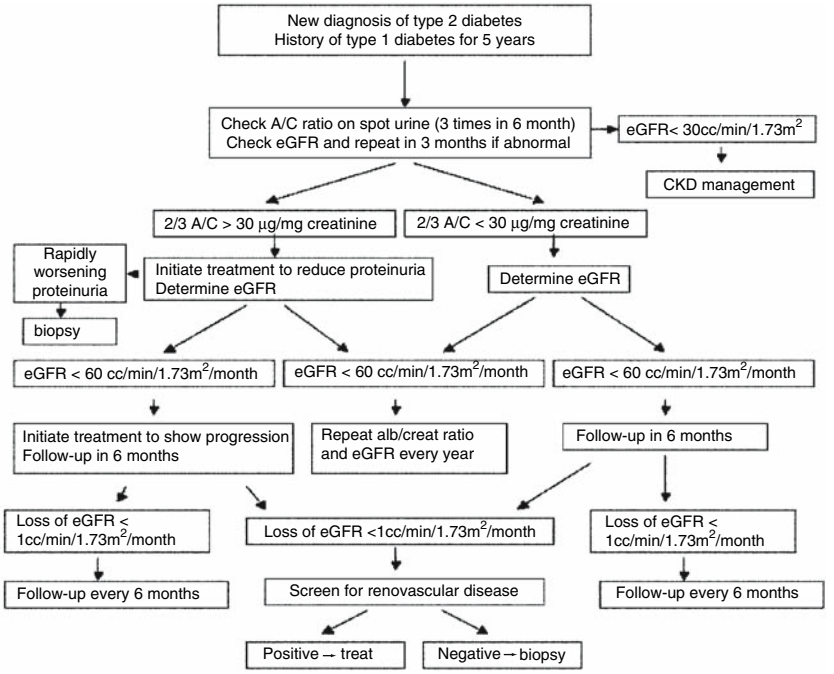

Fig. 18.1 Algorithm for the screening and management of diabetic nephropathy.

formula [30], although an overestimation of GFR can be expected in nephrotic patients with increased tubular secretion of creatinine. Nephrologist referral should be considered either when the GFR has fallen to <30 mL/min/1.73 m^2 or if GFR <60 mL/min/1.73 m^2 and difficulties occur in the management of hypertension or hyperkalemia. Early referral of such patients has been found to reduce cost and improve quality of care and keep people off dialysis longer. Screening for microalbuminuria is also essential to estimate the cardiovascular morbidity and mortality of the population of patients with diabetes. After 40 years of diabetes, only 10% of those with proteinuria are alive compared to 70% of those without, the main cause of mortality being cardiovascular disease. In type 2 diabetes mellitus, the UKPDS provides compelling evidence of the link between varying levels of proteinuria and mortality rates (1.4%/year for normoalbuminuria; 3.0% for microalbuminuria; 4.6% for proteinuria; and 19.2% in the presence of abnormal renal function).

Renal Pathology

Macroscopic Changes

The kidneys of patients with DN are, on average, larger than those of nondiabetic control subjects. Following the onset of diabetes, kidney weight increases by an average of 15% with parallel increases in the protein and RNA content of the kidney and an increase in DNA synthesis. In diabetics with microalbuminuria, renal volume continues to increase as urinary albumin excretion rises to the level of overt proteinuria. Thus, renal size remains increased until overt nephropathy is established. In most patients with type 1 diabetes,

glomerular hypertrophy develops and may be the expression of compensatory growth in the face of progressive glomerular loss. Similarly, hypertrophy of the interstitium occurs, which accounts for a large proportion of the overall renal weight.

Light Microscopy

It is well known that in early stages of renal disease, the renal histology is much less uniform in type 2 than in type 1 diabetes, with a high frequency of atypical patterns including tubulointerstitial lesions, advanced glomerular hyalinosis, or global sclerosis. In patients with type 1 diabetes, light microscopy findings such as arteriolar hyalinosis and global glomerulosclerosis are closely related and are associated with GFR loss, and the degree of GBM width as evaluated by EM is a predictor of the development of MA. Structural predictors of progression have instead not clearly been identified in patients with type 2 diabetes, although podocytopenia has been proposed as a predictor of progressive albuminuria in selected populations and in experimental models of type 2 diabetes. Both a nodular and a diffuse pattern of glomerular lesion can be observed. Diffuse glomerular lesions are more frequent than the nodular lesion, with an incidence of over 90% for patients with type 1 diabetes of over 10 years' duration and an incidence of 25–50% in patients with type 2 diabetes. It includes uniform thickening of the GBM, mesangial matrix expansion, hyalinosis (accumulation of plasma protein in the subendothelial space), increased number of mesangial cells, and accompanying periglomerular fibrosis [31]. The distribution of the diffuse lesions is irregular, both among lobules of the same glomerulus and between different glomeruli (Figure 18.2a). Nodular glomerular intercapillary lesions in the diabetic kidney were described in 1936 by Kimmelstiel and Wilson and can be found in the late stages of DN in type 1 and type 2 diabetics. They are periodic acid-Schiff (PAS) positive masses that are irregular in size and distribution, both within and between glomerular loops, but more likely in the peripheral part of the glomerulus. These large aggregates of extracellular matrix contain a number of mesangial cells and possibly macrophages. When

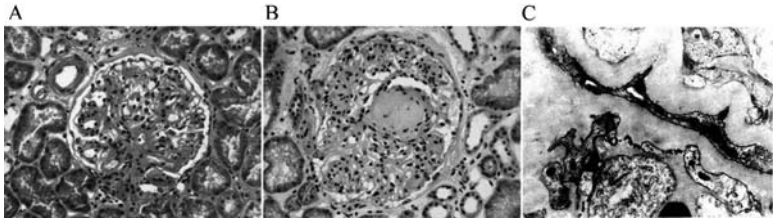

Fig. 18.2 (a)Diffuse glomerulosclerosis. The whole glomerulus shows increased mesangial matrix and increased thickness of several GBM tracts and of Bowman's capsule. Hyaline material is deposited at the vascular pole, as well as in a small vessel besides the glomerulus. Trichrome staining, 200X. (b)Nodular glomerulosclerosis. An acellular rounded accumulation of translucent material is present, where the remaining parts of the tuft show diffuse mesangial matrix deposition and increased thickening of the GBM. Deposition of hyaline material is present along the Bowman's capsule. Trichrome staining, 200X. (c) Electron microscopy: The dishomogeneous increased thickness of the GMB is evident. Uranil acetate-lead citrate, 13,000X. (Courtesy of Dr. Maria Pia Rastaldi.).

present, they are pathognomonic for diabetes, but they are not a universal finding and are reported in only 12–46% of biopsies in both type 1 and type 2 diabetes (Figure 18-2b). Nodules are also seen in amyloids, where they are unevenly distributed, and in light-chain deposition disease. In these conditions, specific stains and immunofluorescence findings, respectively, will clarify the diagnosis. In the arterioles, hyaline material progressively replaces the entire wall of both the afferent and efferent vessels. Although afferent arteriolar hyalinization occurs in other conditions, involvement of the efferent vessel is highly specific for diabetes and can be independent of the presence of hypertension. In the tubular and interstitial space, beside thickening and reduplication of the GBM, a variety of nonspecific findings characterize DN and have no diagnostic utility but have prognostic utility, since kidney survival rates diminish if interstitial fibrosis is present. Although aging per se can cause fibrointimal hyperplasia and up to 10% of glomerulosclerosis, most of the diabetic nephropathy-induced changes are not observed in normal aging.

Immunofluorescence Microscopy

Staining for the IgG, albumin, and fibrinogen can be found in the GBM in patients with diabetic nephropathy. These proteins probably reach such sites passively as the result of increased capillary permeability, rather than through more specific interactions. There are also increases of type IV collagen, laminin, and fibronectin in the mesangium; type I and type VI collagen may accumulate late in the course of the disease, mainly in nodular lesions [31]; IgM, fibrin products, and C3 can be found in the arteriolar deposits of hyalin and may suggest a role for the coagulation pathway activation in the genesis of glomerulosclerosis.

Electron Microscopy

Thickening of the glomerular basement membrane is the earliest and more prominent feature of diabetic kidney disease (Figure 18-2c). Up to an 80% increase in the area of the capillary wall can be found within months of the onset of type 1 diabetes. Excessive irregular thickening of the basement membrane is associated with nodular renal disease. In all stages of DN, there are no electron-dense deposits. The foot processes of the epithelial cells remain discrete until renal function has declined to 20% of normal, when they become wider in cross-section with shortening of the filtration slits. Eventually, podocyte fusion and effacement are noted. The mesangial fraction (i.e., the volume of the glomerulus occupied by the mesangium) may double when compared with controls. In arterioles, the hyalin deposits appear as uniform densities and spread from a subintimal location toward the media and then to its near replacement.

Pathogenesis of Diabetic Nephropathy

A complete discussion of the pathogenesis of DN is beyond the scope of this chapter and will be limited to concepts that have influenced current therapeutic directions. Several contributing factors of either hemodynamic or metabolic origin have been identified, but an extensive research effort

is urgently needed to identify a unifying mechanism that could represent a new and more definitive therapeutic target. Since diabetes causes selective tissue damage (capillary endothelial cells in the retina, neurons and Schwan cells in peripheral nerves, and mesangial cells in the glomerulus), and these cells are vulnerable to hyperglycemia because of their inability to reduce intracellular transport of glucose when they are exposed to hyperglycemia, it has been suggested that several pathways activated by intracellular hyperglycemia may all contribute to the development of the complication [32]. Among them are the increased polyol pathway flux, the increased formation of advanced glycation end products (AGEs), and the increased hexosamine pathway flux. These metabolic derangements almost invariably result in activation of protein kinase C (PKC) and production of reactive oxygen species (ROS), finally leading to TGF-β upregulation and collagen production [33]. However, long-term inhibition of PKC or of ROS production does not prevent the chronic lesions associated with DN [34]. Similarly, strict glycemic control slows but does not prevent the progression of DN [16, 18], suggesting that other factors are involved and/or that hyperglycemia results in a "glucose memory," as suggested by clinical trials [17] and supported by our experimental findings of glucose-induced genetic modifications in mesangial cells [35]. In fact, hemodynamic mechanisms, of which activation of the renin-angiotensin-aldosterone (RAAS) axis is the most prominent feature, also plays an important role and is responsible for some of the metabolic findings observed in DN via its direct interaction with nitric oxide and ROS [7]. More recently, glomerular hypertension was found to be associated with mesangial overexpression of GLUT-1, clearly linking the hemodynamic and metabolic pathogenesis of diabetic nephropathy [36]. Coupling of hemodynamic and metabolic changes in DN is bidirectional, since hyperglycemia inhibits voltage-gated calcium channels, resulting in dilatation of glomerular afferent arterioles and impaired glomerular blood flow autoregulation [37]. More recent data also suggest that the complex interplay among metabolic, biochemical, and hemodynamic abnormalities may be explained by the unifying hypothesis that diabetic nephropathy is a chronic inflammatory disease [38].

Differential Diagnosis

The incidence of nondiabetic causes for proteinuria in diabetes ranges from 4–25%, usually higher in type 2 than type 1 diabetic patients. It is not clear whether most of these reports merely represent the coexistence of the two conditions rather than a specific association. Inevitably, the perceived incidence of nondiabetic glomerular disease will depend on the frequency with which renal biopsy is performed and the clinical criteria used to select patients for renal biopsy. It has been reported that in type 2 diabetic patients, the incidence of other renal disease may exceed 25%. A kidney biopsy should be considered in the following cases: absence of retinopathy (especially for patients with type 1 diabetes), sudden onset and rapid progression of proteinuria particularly with known disease duration of less than 5 years and/or abnormal evolution, presence of macroscopic hematuria or urinary sediment suggestive of active glomerulonephritis, and rapid decline of renal function. Membranous nephropathy is the primary glomerular disease most commonly

reported in association with diabetes. In most cases, patients present between the ages of 40 to 60 years after 10 or more years of diabetes. Diabetes can also manifest in the kidney as papillary necrosis, which is observed at autopsy in 4.4% of diabetic kidneys, more common in females, especially when recurrent urinary tract infections occur. The incidence and severity of papillary necrosis is decreasing with early antibiotic treatment but tends to occur in those with long-standing diabetes. If initially unilateral, it will often affect the contralateral kidney over subsequent years and will eventually be bilateral in 65% of patients. Presentation can be asymptomatic, following an indolent course. Tubular proteinuria is often accompanied by microscopic hematuria and sterile pyuria. Among other causes of renal disease in patients with diabetes, renovascular disease needs to be considered. Renovascular disease is recognized with increasing frequency in diabetics, especially in association with peripheral vascular disease. Typically, renal impairment may develop in the context of microalbuminuria or mild proteinuria. Hypertension is common but is not a universal feature. When suspected, the diagnosis should be sought by duplex scanning or magnetic resonance angiography, followed by conventional angiography if possible. Other kidney-related problems in diabetics include pyelonephritis, where Gram-negative organisms most commonly infect the parenchyma; another problem in diabetics is emphysematous pyelonephritis, a rare and severe complication of pyelonephritis, which usually affects diabetic patients and requires nephrectomy of the affected kidney. Renal tuberculosis should be suspected when there is azotemia with modest proteinuria and sterile pyuria in the absence of papillary necrosis. Although renal imaging may be suggestive and a tuberculin test may be positive, the diagnosis requires culture of Mycobacteria species in the urine. Finally, diabetic patients are at increased risk of contrast nephropathy.

Prevention and Treatment of Diabetic Nephropathy

General Considerations

According to the last position statement of the American Diabetes Association [2], the first goals in the prevention and treatment of DN are optimization of glucose and blood pressure control. In addition, a reduction in protein intake has been recently added with level of evidence B (supportive evidence) to the general recommendations. Finally, a strong preventive effort has been instituted by the National Kidney Disease Education project (http://www.nkdep.nih.gov), which has implemented a community-based strategy to educate individuals at highest risk for development of kidney disease. Thus, a new approach to DN based on the identification of new predictors and of new preventive measures is needed (Figure 18.3).

Glycemic Control

Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to delay the onset of MA and the progression of MA to proteinuria in patients with type 1 [16] and type 2 diabetes [18]. However, although these large studies demonstrate the importance of strict glycemic control for primary prevention of

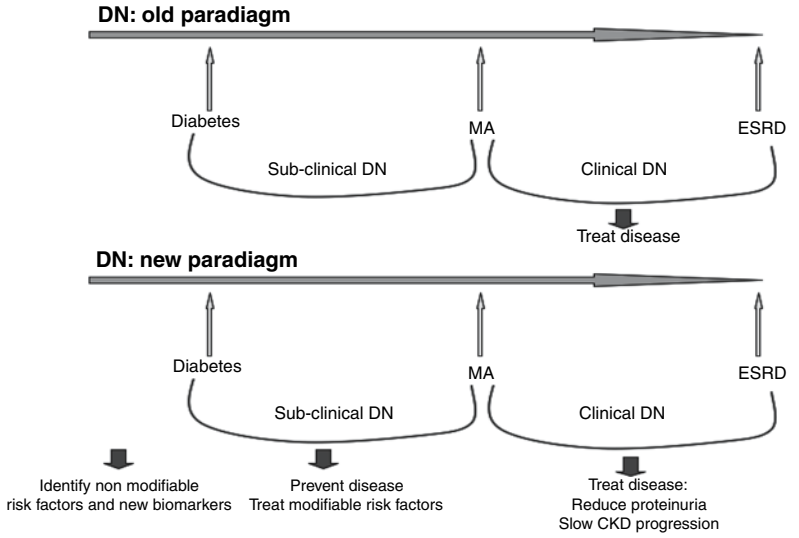

Fig. 18.3 New approach to DN. A schematic representation of the new paradigms for diagnosis and intervention in DN.

microvascular complications, there is no clear evidence that glycemic control can affect the progression of CKD in the population of patients with diabetes.

Blood Pressure Control

Large prospective randomized studies in patients with type 1 diabetes have demonstrated that treatment using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) provides a selective benefit over other antihypertensive drug classes in the primary prevention of DN and in delaying the progression from microalbuminuria to proteinuria [39–42]. More interestingly, a direct association between ARB use and decreased loss of renal function as a primary endpoint was observed in the Reduction of Endpoints in NIDDM with the Angiotensin II antagonist–Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT) [43, 44]. The safety and efficacy of ACEi in patients with more advanced renal failure have been reported more recently as well [45]. In addition to their beneficial effect in primary and secondary prevention of diabetic nephropathy, ACEi have been shown to reduce the incidence of CVD (i.e., myocardial infarction, stroke, death) independently of blood pressure control, further supporting the use of these agents in patients with microalbuminuria [41]. Although hyperkalemia has been a issue of concern with the use of ACEi-ARB, pooled data from clinical trials suggest that the risk is low [43, 44], and this also applies when ACEi are administered to patients with more advanced CKD [45]. Older age is not a contraindication to the use of ACE/ARB. In a population of type 2 diabetics with early DN, ARB are similar to ACEi in providing long-term renoprotection [46]. Smaller studies have been performed concerning protection of renal function with ACEi compared to other antihypertensive agents, but no agent has been found to be equal or superior to ACEi/ARB. In fact, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood

Pressure (JNC 7) recommended ACEi/ARB as a first-line agent in patients with diabetes. As additional therapy or in patients unable to tolerate ACEi and/or ARBs, the use of beta-blockers, diuretics, or calcium channel blockers for the management of blood pressure should be considered [47]. There have been variable results relating to the efficacy of ACEi or ARBs for the primary prevention of DN in patients with type 2 diabetes. Among several studies in normotensive normoalbuminuric patients, the largest was the BENEDICT trial [48], which showed a lower rate of progression to microalbuminuria in patients treated with trandolapril when compared to verapamil or placebo. More recent data also suggest that adding spironolactone to the recommended antihypertensive treatment may offer additional renoprotection in patients with either type 1 or type 2 diabetes.

Protein Restriction

The American Diabetes Association recommends restriction of protein intake to 0.8 g/kg in diabetic patients with any degree of CKD [2], although this issue remains controversial. Protein restriction may be of benefit in slowing the progression of albuminuria, GFR decline, and occurrence of ESRD. Protein restriction should be considered particularly in patients whose nephropathy seems to be progressing despite optimal glucose and blood pressure control and the use of ACEi/ARBs.

Combined Therapy

The optimal therapeutic approach to the treatment of DN may be intensive combined therapy, thereby targeting the many factors underlying the disease, including hyperglycemia, hypertension, and dyslipidemia. The potential efficacy of intensive combined therapy in patients with type 2 diabetes and microalbuminuria was examined in the Steno type 2 trial [49]. In this prospective study, 160 patients were randomly assigned to standard or multifactorial intensive therapy. The intensive regimen consisted of behavioral therapy (including advice concerning diet, exercise, and smoking cessation) and pharmacological intervention (consisting of the administration of an ACEi and multiple other agents to attain several aggressive clinical therapeutic goals). At a mean follow-up of 7.8 years, intensive therapy reduced both microvascular and macrovascular disease [49]. With respect to DN, there were significant improvements in albumin excretion and in progression to overt nephropathy. However, the study did not produce any evidence that intensive treatment may delay loss of GFR.

Novel Therapeutic Approaches

While a plethora of novel therapeutic agents are currently being tested in phase 1 and 2 clinical trials and offer very interesting novel therapeutic strategies, their use is beyond the objective of this chapter and has been recently reviewed elsewhere [34].

Care of the Elderly Patient with Diabetes

Evidence-based guidelines for the care of elderly patients with diabetes have been recently generated by the American Geriatric Society [50]. Unfortunately, there are no long-term studies in individuals over 65 years of age demonstrating the benefits of tight glycemic, blood pressure, and lipid control. Although there is clinical and functional heterogeneity in the population of older patients with diabetes, patients who can be expected to live long enough and who are active, cognitively intact, and willing to undertake the responsibility of self-management should be encouraged to do so and be treated using the goals for younger adults with diabetes. Although control of hyperglycemia is important, greater reductions in morbidity and mortality can be achieved in this population from control of all CV risk factors rather than from high glycemic control [3]. Even though the elderly represent the majority of diabetic patients with ESRD, some conclusion can be drawn from larger studies where elderly patients were included. The Irbesartan Diabetic Nephropathy Trial (IDNT) included elderly Caucasian patients (up to 70 years, mean age of 58 years) and showed benefits of delaying progression of decline in GFR with escalating doses of ARB [42]. In addition, the DETAIL trial (Diabetics Exposed to Telmisartan and Enalapril) included patients up to 80 years (mean age of 61 years in the treatment arms) and showed that telmisartan was as effective as enalapril in slowing the decline in GFR in patients with DN [46]. A similar mean age of 60.7 years characterizes the population studied by Brenner et al. [43] in a multicentered randomized clinical trial where losartan treatment was shown to be effective in reducing the rate of progression to ESRD when compared to placebo. Similar results were obtained after treatment with irbesartan in a patient population with a mean age of 69 years [39]. Thus, we can conclude that a nephroprotective effect using either ARBs or ACEi can be appreciated independently of age. However, none of the above-mentioned trials reported a specific subgroup analysis of the elderly population.

Management of End-Stage Renal Disease in Diabetes

Since the different modalities of renal replacement therapy are reviewed in Chapters 24 and 25, we will briefly review the topic by paying specific attention to issues related to diabetic patients.

Predialysis Care

A recent National Institutes of Health (NIH) consensus statement stressed the importance of early medical intervention in predialysis patients. Ideally, patients should be referred at an early stage of their disease to a multidisciplinary diabetic clinic comprising nephrologists, diabetologists, ophthalmologists, podiatrists, and dietitians [2]. Initially, attention must be directed toward delaying the rate of progression of renal disease, improving diabetic control, and preventing other diabetic complications. In view of the high death rate from CVD in diabetic patients, attention should focus on control of cardiovascular risk factors including smoking, hypertension, and hyperlipidemia. As CKD advances, attention must also be given to treatment of

anemia, hyperparathyroidism, and nutritional status. Patients can be counseled regarding future dialysis with full consideration of the medical and social implications of treatment once the GFR is less than 25 mL/min/1.73 m^2, at which point a plan for access placement should be made. Similarly, referral for pre-emptive transplantation should be made once the GFR is less than 20 mL/min/1.73 m^2. Dialysis access should be organized in good time before it needs to be utilized, which is particularly important in diabetics. It may also be the time to offer pre-emptive transplantation in selected cases.

Renal Replacement Therapy

Patients with ESRD due to DN require renal replacement therapy with higher GFRs than ESRD patients due to other etiologies, since patients with DN reaching ESRD appear to be more vulnerable to uremic symptoms, fluid retention, anemia, and hyperkalemia at an earlier stage than nondiabetic subjects. Current KDOQI guidelines recommend considering initiation of dialysis in diabetic patients when the GFR has reached 15 mL/min/1.73 m^2 [30]. Whether hemodialysis (HD) or peritoneal dialysis (PD) has a better survival in diabetic patients is controversial. While initial reports suggested that PD was associated with a better outcome [51], data from the USRDS case-mix study suggest that mortality may actually be increased in diabetic patients treated with PD rather than HD. Interestingly, the increase in risk with PD was limited to elderly diabetic patients [52]. In a subsequent very large study utilizing data from 398,940 patients who initiated dialysis between the years 1995 to 2000, mortality risk was significantly higher on HD than PD among younger diabetics with no co-morbidities, while HD was associated with a lower mortality risk in older diabetics independently of the presence or absence of co-morbidities [53]. Patient survival in diabetics on maintenance dialysis is lower (25% at 5 years) than that seen in nondiabetics with ESRD due to chronic glomerular disease or hypertension [1]. Survival also varies inversely with age, being best in young patients with good blood pressure control and no clinically evident cardiac disease. CVD is the most common cause of death, accounting for more than one-half of cases [1, 54]. The adequacy of dialysis and a decrease in nutritional status may also account for the worse outcome in diabetics. Diabetic patients appear to be more sensitive than nondiabetics to inadequate dialysis prescriptions, with a 7% increase in mortality for every 0.1 unit decline in Kt/V. Death by withdrawal from dialysis is also more likely to occur in diabetics. Renal transplantation is another option: In one USRDS report relating to diabetics with ESRD, patient survival at 5 years after renal transplantation in diabetics ranged from 75 to 83 % [1], far above that observed with either hemodialysis or peritoneal dialysis, which is approximately 25% at 5 years. The following are our recommendations concerning renal replacement therapy in diabetic patients: Renal and renal-pancreas transplantation should be offered to any suitable diabetic patient with ESRD. For those requiring dialysis, PD seems to be a good choice, in particular for diabetics who have adequate manual dexterity and visual acuity to perform this technique, although there is no consensus to support this recommendation. Home HD is also an option that is associated with the highest survival rates. Given the problems with HD access due to

vascular disease, early and close attention must be paid to the development of the vascular access in diabetic patients with CKD. As with nondiabetics, the preferred type is a native arteriovenous fistula. The optimal dose of PD or HD in diabetic patients is uncertain. We suggest aiming for the same goals in diabetics as in nondiabetics (see Chapter 24).

In the United States, only 15% of the incident patients with end-stage renal disease initiated HD using an arteriovenous fistula compared with 65% and 67% in Japan and Europe, respectively. Information from the U.S. Renal Data System showed that in 2000, 27% of patients had an arteriovenous fistula, approximately 23% were using a catheter for hemodialysis, and approximately 47% had a synthetic graft [1]. A variety of factors, such as diabetes and older age, have been proposed to contribute to the low incidence of fistulae. Previous reports have highlighted the elderly and diabetic patients as two groups with poor fistulae outcomes, blaming the culprit to a higher incidence of peripheral vascular disease and atherosclerosis. However, recent data emphasize that these populations of patients should not be excluded from fistulae creation since good outcome in these patients have been reported by many investigators in recent years. Konner et al. [55] reported on the successful creation of arteriovenous fistulae in 748 consecutive patients with ESRD; 181 of these patients (24%) had diabetes and 311 patients (42%) were elderly (65 years). Finally, the concomitant presence of other complications of diabetes, such as severe peripheral vascular disease leading to limb amputation and blindness, may affect the choice for the modality of renal replacement therapy and may affect the overall mortality of this specific patient population, although it is remarkable to note that blind diabetic patients who receive specific PD training suffer from fewer complications than non-blind controls. No matter what approach is chosen for the patient with diabetes, one should not forget that diabetics have a 22% higher mortality at 1 year and a 15% higher mortality at 5 years than patients without diabetes (see Chapter 25).

Concluding Remarks

DN is an increasing epidemic problem mainly related to the growing population of elderly patients with type 2 diabetes. Although specific recommendations in the elderly population are not available, we believe that recommendations from studies in the general population may apply to the elderly as well. While we wait for translation of the basic scientific advances to the clinical setting, we need to maintain an approach to ensure that glycemia, blood pressure, and CV risk factors are seriously addressed for each patient with a personalized approach [12].

References

1. USRDS. USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2005.
2. Standards of medical care in diabetes—2006. *Diabetes Care* 2006; 29(Suppl 1): S4–42.
3. Caramori, M.L., Fioretto, P., Mauer, M. Enhancing the predictive value of urinary albumin for diabetic nephropathy. *J. Am. Soc. Nephrol*. 2006; 17(2):339–352.

4. Hovind, P., Tarnow, L., Rossing, P., et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: Inception cohort study. *BMJ* 2004; 328(7448):1105.
5. Mogensen, C.E., Christensen, C.K. Predicting diabetic nephropathy in insulin-dependent patients. *N. Engl. J. Med*. 1984; 311(2):89–93.
6. Tognoni, G. Report on management of renal failure in Europe, XXVI, 1995. A conceptual and practical framework for interactive use of the ERA-EDTA Registry. *Nephrol. Dial. Transplant* 1996;11(Suppl)7:1–3.
7. Leon, C.A., Raij, L. Interaction of haemodynamic and metabolic pathways in the genesis of diabetic nephropathy. *J. Hypertens*. 2005; 23(11):1931–1937.
8. Lightstone, L., Rees, A.J., Tomson, C., Walls, J., Winearls, C.G., Feehally, J. High incidence of end-stage renal disease in Indo-Asians in the UK. *Quar. J. Med.* 1995; 88(3):191–195.
9. Rich, S.S. Genetics of diabetes and its complications. *J. Am. Soc. Nephrol*. 2006; 17(2):353–360.
10. Fioretto, P., Steffes, M.W., Barbosa, J., Rich, S.S., Miller, M.E., Mauer, M. Is diabetic nephropathy inherited? Studies of glomerular structure in type 1 diabetic sibling pairs. *Diabetes* 1999; 48(4):865–869.
11. Langefeld, C.D., Beck, S.R., Bowden, D.W., Rich, S.S., Wagenknecht, L.E., Freedman, B.I. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *Am. J. Kidney Dis.* 2004; 43(5):796–800.
12. Susztak, K., Bottinger, E.P. Diabetic nephropathy: A frontier for personalized medicine. *J. Am. Soc. Nephrol.* 2006; 17(2):361–367.
13. Jones, S.L., Wiseman, M.J., Viberti, G.C. Glomerular hyperfiltration as a risk factor for diabetic nephropathy: Five-year report of a prospective study. *Diabetologia* 1991; 34(1):59–60.
14. Caramori, M.L., Fioretto, P., Mauer, M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: An indicator of more advanced glomerular lesions. *Diabetes* 2003; 52(4):1036–1040.
15. Klein, R., Zinman, B., Gardiner, R., et al. The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: The Renin-Angiotensin System Study. *Diabetes* 2005; 54(2):527–533.
16. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. The Diabetes Control and Complications (DCCT) Research Group. *Kidney Int*. 1995; 47(6):1703–1720.
17. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: The Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003; 290(16):2159–2567.
18. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352(9131):837–853.
19. Perkins, B.A., Ficociello, L.H., Silva, K.H., Finkelstein, D.M., Warram, J.H., Krolewski, A.S. Regression of microalbuminuria in type 1 diabetes. *N. Engl. J. Med.* 2003; 348(23):2285–2293.
20. Araki, S., Haneda, M., Sugimoto, T., et al. Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes. *Diabetes* 2005; 54(10):2983–2987.
21. Giorgino, F., Laviola, L., Cavallo Perin, P., Solnica, B., Fuller, J., Chaturvedi, N. Factors associated with progression to macroalbuminuria in microalbuminuric type 1 diabetic patients: The EURODIAB Prospective Complications Study. *Diabetologia* 2004; 47(6):1020–1028.

22. Lurbe, E., Redon, J., Kesani, A., et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N. Engl. J. Med*. 2002; 347(11):797–805.
23. Nelson, R.G., Pettitt, D.J., Baird, H.R., et al. Pre-diabetic blood pressure predicts urinary albumin excretion after the onset of type 2 (non-insulin-dependent) diabetes mellitus in Pima Indians. *Diabetologia* 1993; 36(10):998–1001.
24. Chase, H.P., Garg, S.K., Marshall, G., et al. Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA* 1991; 265(5):614–617.
25. Baggio, B., Budakovic, A., Dalla Vestra, M., Saller, A., Bruseghin, M., Fioretto, P. Effects of cigarette smoking on glomerular structure and function in type 2 diabetic patients. *J. Am. Soc. Nephrol*. 2002; 13(11):2730–2736.
26. Lin, J., Hu, F.B., Rimm, E.B., Rifai, N., Curhan, G.C. The association of serum lipids and inflammatory biomarkers with renal function in men with type II diabetes mellitus. *Kidney Int.* 2006; 69(2):336–342.
27. Mogensen, C.E., Schmitz, A., Christensen, C.K. Comparative renal pathophysiology relevant to IDDM and NIDDM patients. *Diabetes Metab. Rev*. 1988; 4(5):453–483.
28. Kramer, H.J., Nguyen, Q.D., Curhan, G., Hsu, C.Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 2003; 289(24):3273–3277.
29. Eknoyan, G., Hostetter, T., Bakris, G.L., et al. Proteinuria and other markers of chronic kidney disease: A position statement of the National Kidney Foundation (NKF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). *Am. J. Kidney Dis*. 2003; 42(4):617–622.
30. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am. J. Kidney Dis*. 2002; 39(2 Suppl 1):S1–266.
31. Striker LJS, G., D' Agati, V. *The Renal Biopsy*, 3rd ed. Philadelphia: W.B. Saunders Company. 1997.
32. Brownlee, M. The pathobiology of diabetic complications: A unifying mechanism. *Diabetes* 2005; 54(6):1615–1625.
33. Ziyadeh, F.N., Sharma, K., Ericksen, M., Wolf, G. Stimulation of collagen gene expression and protein synthesis in murine mesangial cells by high glucose is mediated by autocrine activation of transforming growth factor-beta. *J. Clin. Invest.* 1994; 93(2):536–542.
34. Williams, M.E., Tuttle, K.R. The next generation of diabetic nephropathy therapies: An update. *Adv. Chronic Kidney Dis*. 2005; 12(2):212–222.
35. Fornoni, A., Lenz, O., Striker, L.J., Striker, G.E. Glucose induces clonal selection and reversible dinucleotide repeat expansion in mesangial cells isolated from glomerulosclerosis-prone mice. *Diabetes* 2003; 52(10):2594–2602.
36. Gnudi, L., Viberti, G., Raij, L., et al. GLUT-1 overexpression: Link between hemodynamic and metabolic factors in glomerular injury? *Hypertension* 2003; 42(1):19–24.
37. Carmines, P.K., Ohishi, K., Ikenaga, H. Functional impairment of renal afferent arteriolar voltage-gated calcium channels in rats with diabetes mellitus. *J. Clin. Invest*. 1996; 98(11):2564–2571.
38. Galkina, E., Ley, K. Leukocyte recruitment and vascular injury in diabetic nephropathy. *J. Am. Soc. Nephrol.* 2006; 17(2):368–377.
39. Lewis, E.J., Hunsicker, L.G., Bain, R.P., Rohde, R.D. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N. Engl. J. Med*. 1993; 329(20):1456–1462.
40. Bakris, G.L., Williams, M., Dworkin, L., et al. Preserving renal function in adults with hypertension and diabetes: A consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am. J. Kidney Dis.* 2000; 36(3):646–661.

41. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000; 355(9200):253–259.
42. Parving, H.H., Lehnert, H., Brochner-Mortensen, J., Gomis, R., Andersen, S., Arner, P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N. Engl. J. Med.* 2001; 345(12):870–878.
43. Brenner, B.M., Cooper, M.E., de Zeeuw, D., et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N. Engl. J. Med.* 2001; 345(12):861–869.
44. Lewis, E.J., Hunsicker, L.G., Clarke, W.R., et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N. Engl. J. Med*. 2001; 345(12):851–860.
45. Hou, F.F., Zhang, X., Zhang, G.H., et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N. Engl. J. Med*. 2006; 354(2):131–140.
46. Barnett, A.H., Bain, S.C., Bouter, P., et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N. Engl. J. Med.* 2004; 351(19):1952–1961.
47. Chobanian, A.V., Bakris, G.L., Black, H.R., et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42(6):1206–1252.
48. Ruggenenti, P., Fassi, A., Ilieva, A.P., et al. Preventing microalbuminuria in type 2 diabetes. *N. Engl. J. Med*. 2004; 351(19):1941–1951.
49. Gaede, P., Vedel, P., Larsen, N., Jensen, G.V., Parving, H.H., Pedersen, O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N. Engl. J. Med*. 2003; 348(5):383–393.
50. Brown, A.F., Mangione, C.M., Saliba, D., Sarkisian, C.A. Guidelines for improving the care of the older person with diabetes mellitus. *J. Am. Geriatr. Soc.* 2003; 51(5 Suppl Guidelines):S265–280.
51. Wolfe, R.A., Port, F.K., Hawthorne, V.M., Guire, K.E. A comparison of survival among dialytic therapies of choice: In-center hemodialysis versus continuous ambulatory peritoneal dialysis at home. *Am. J. Kidney Dis.* 1990; 15(5):433–440.
52. Held, P.J., Port, F.K., Turenne, M.N., Gaylin, D.S., Hamburger, R.J., Wolfe, R.A. Continuous ambulatory peritoneal dialysis and hemodialysis: Comparison of patient mortality with adjustment for comorbid conditions. *Kidney Int*. 1994; 45(4):1163–1169.
53. Vonesh, E.F., Snyder, J.J., Foley, R.N., Collins, A.J. The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. *Kidney Int.* 2004; 66(6):2389–2401.
54. Brunner, F.P., Selwood, N.H. Profile of patients on RRT in Europe and death rates due to major causes of death groups. The EDTA Registration Committee. *Kidney Int. Suppl.* 1992; 38:S4–15.
55. Konner, K., Hulbert-Shearon, T.E., Roys, E.C., Port, F.K. Tailoring the initial vascular access for dialysis patients. *Kidney Int.* 2002; 62(1):329–338.

19

Renal Cystic Disease in the Elderly

Roser Torra Balcells

Introduction

Cystic diseases of the kidney are a very heterogeneous group of disorders which have in common the presence of renal cysts (from the Greek *kystis*, "bladder"), that is, saclike structures containing fluid or semisolid material. The pathogenesis of these diseases is incompletely understood. Some cysts develop during embryogenesis, others late in life; some cysts arise from a genetic abnormality and are regarded as hereditary, while others are not. As most cysts look alike, classifications of renal cystic disorders have usually been based on the number and distribution of the cysts, microdissection characteristics, and genetic and clinical patterns. These are provisional classifications to clarify and organize the current knowledge, but they will eventually become obsolete when more is learned of the etiology and pathogenesis of these disorders.

A classification of the renal cystic diseases that can be seen in elderly patients is shown in Table 19.1. Some renal cystic diseases are excluded from this classification because they are not compatible with a normal life expectancy or are seen exclusively in neonates, infants, children, or young adults. Bilateral multicystic dysplasia, infantile polycystic kidney disease, phakomatosis, and renal cystic disorders in syndromes of multiple malformations will not be further discussed in this chapter.

Despite being the focus of a large amount of clinical and laboratory investigation during the past decade or more, there is a surprising lack of information on cystic diseases as they appear in an older population.

Diagnostic Tools

The diagnostic tools we use nowadays to diagnose cystic diseases of the kidney are the same at all ages and include the following:

Excretory urography (IVP): With the advent of newer modalities, it has become apparent that the sensitivity of IVP for small renal masses is limited. Findings suspicious for a mass effect in the kidney on IVP should prompt further radiographic evaluation.

Ultrasonography: Ultrasound is the recommended follow-up examination to a renal cystic disease. Its strength is the reliable identification of simple renal cysts. Increased through transmission, an anechoic internal component of the cyst, an imperceptible extrarenal wall, and a sharply demarcated

Table 19.1 Classification of Renal Cystic Disorders in the Elderly.

Unilateral multicystic kidney
Multilocular cyst
Simple cysts
Autosomal dominant polycystic kidney disease
Acquired cystic disease of the kidneys
Adult medullary cystic disease
Medullary sponge kidney
Cystic disease of the renal sinus
Pelvicaliceal diverticula
Neoplastic cysts
Inflammatory cysts

intrarenal wall allow confident diagnosis. Only when these criteria are not met is further imaging indicated. The sensitivity of ultrasound for renal cell carcinoma 3 cm or smaller is 79% [1], although the addition of Doppler technology may improve the accuracy of ultrasound determination of malignancy [2].

Computed tomography (CT): The current gold standard for the evaluation of renal masses is CT. Helical scanning has the advantages of minimal motion artifact, exact duplication of cuts before and after contrast administration, and the ability to reconstruct images retrospectively at any level.

Magnetic resonance imaging (MRI): For the routine evaluation of renal cysts, MRI currently carries no significant advantage over CT. In certain situations, however, such as a patient with contrast material allergy, or a hyperdense renal cyst, MRI is either safer or more accurate than CT. Additionally, MRI can assess venous involvement by renal cell carcinoma and renal volume in certain diseases such as ADPKD.

Dimercaptosuccinic acid (DMSA) renal scintigraphy: DMSA scintigrams, which differentiate parenchymal lobulations from space-occupying lesions, largely have been replaced by CT. Evolving single photon emission tomography (SPECT) techniques may enhance the usefulness of DMSA [3].

Angiography: The angiographic findings of hypervascularity and hypovascularity, although suggestive of renal cell carcinoma and renal cyst, respectively, are not conclusive. This fact and the invasiveness of angiography have led to its general replacement by CT or MRI in most cases.

Percutaneous aspiration or biopsy: Except for specific indications, percutaneous renal biopsy is not recommended for otherwise healthy patients with a renal mass. Situations in which fine needle sampling of a renal mass may be useful include clinical or radiographic suspicion of a diagnosis other than renal cell carcinoma (lymphoma, suspected nonrenal cancer metastatic to the kidney, abscess, or infected cyst, etc.).

"Simple" Cysts

Simple cysts are the most common renal disorder, and they are especially frequent in elderly patients. Over 50% of people over 50 years old have at least one cyst on post-mortem examination. The Mayo Clinic experience of 100 post-mortem examinations over the age of 90 indicated that one or more

cysts are present in almost 100% of cases. Twenty-four percent of patients over the age of 40 have cysts detectable by computed tomography of the abdomen obtained for reasons unrelated to the kidney. They can be single or multiple, are usually asymptomatic, and rarely lead to complications. Their clinical significance resides in the fact that they need to be differentiated from hypernephroma and, when very numerous, autosomal dominant polycystic kidney disease (ADPKD).

Pathology

Simple renal cysts are usually lined by a single layer of epithelial cells and filled with a clear, serous fluid. They are usually small and grow slowly, but huge cysts up to 30 cm in diameter have been described. The inner surface of these cysts is glistening and usually smooth, but some cysts may be trabeculated by partial septa that divide the cavity into broadly interconnecting locules. These septate simple cysts should not be confused with multilocular cysts.

Pathogenesis

Many clinical and pathological studies suggest that most, if not all, simple renal cysts are acquired. As opposed to the cysts in autosomal dominant polycystic kidney disease, the composition of cystic fluid in renal simple cysts usually resembles that of interstitial fluid [4], the difference being that small molecular tracers, such as inulin, paraaminohippuric acid, sodium o-iodohippurate, and sodium pertechnetate, are not found in the cystic fluid aspirated from patients to whom these drugs have been administered intravenously. Therefore, renal simple cysts do not appear to be in communication with the tubular lumina. It is possible that renal simple cysts result from progressive dilatation of saccular tubular diverticula with increasingly narrow necks, which are eventually completely cut off from the tubule.

Clinical Manifestations

Simple renal cysts occur equally in both kidneys and are found more frequently in the lower pole, followed by the upper pole and then the midsection of the kidney. Most frequently, the cysts are asymptomatic, but they may be discovered at the time of a nephro-urologic evaluation for some unrelated problem. It is therefore important that the presence of these cysts does not distract from the diagnosis of other more important intrarenal or extrarenal lesions. Large renal cysts may cause abdominal or flank discomfort, usually described as a sensation of weight or a dull ache. More frequently, however, this pain can be explained by another coincident lesion such as nephrolithiasis. Simple cysts in the upper pole of the right kidney can produce pain in the right upper abdominal quadrant, under the costal margin, and in the right side of the back and should be considered in the differential diagnosis of right upper quadrant abdominal pain.

Rare cases of gross hematuria due to vascular erosion by an enlarging cyst have been well documented [5], but another cause of macrohematuria or microhematuria is usually found in the great majority of patients with simple renal cysts who have hematuria.

When the simple cysts lie at or near the hilus, a urographic pattern of caliceal obstruction or hydronephrosis is frequently found [6]. In most but not all cases, these apparent obstructive changes seen on the excretory urogram are of no functional significance. A dynamic hippuran/DTPA radioactive renal scan before and after administration of frusemide is helpful to assess the degree of functional obstruction [7].

Rare cases of renin-dependent hypertension caused by solitary intrarenal simple cysts have been described [8]. The proposed mechanism is arterial compression by the cyst, causing segmental renal ischemia. These cases have been well documented by renal vein renin studies and cure of the hypertension following surgical or percutaneous drainage of the cyst. A rare but dramatic complication is that of infection of a renal cyst. The usual presentation is with high fever, flank pain and tenderness, and frequently a sympathetic pleural effusion. Most patients are females, and the most common pathogen is *Escherichia coli*. Urine cultures are frequently negative. Ultrasonography is helpful in making the diagnosis. As opposed to uncomplicated simple cysts, infected cysts have irregular borders with internal echoes. The distinction between an infected simple cyst and a primary abscess of the kidney, however, may be difficult and depends on the recognition of a smooth contour to the inner surface of the lesion at ultrasound.

Imaging and Differential Diagnosis

Ultrasound is the recommended imaging modality for reliable identification and follow-up of cystic lesions. Equivocal cysts raising the possibility of malignancy can be further evaluated with CT, but, if any doubts remain regarding the nature of the lesion, percutaneous aspiration or biopsy is advocated to provide a definitive answer. The ultrasound features that permit the diagnosis of benign simple cysts are lack of internal echoes, smooth walls, and enhancement of echoes deep to the lesion . If all of these criteria are met, accuracy approaches 100%. The computed tomography criteria that permit the diagnosis of benign simple cysts are a density that is near that of water, thin or imperceptible wall, sharp interface with renal parenchyma, and no significant increase in density after the administration of intravenous contrast material . The cysts in MRI are defined by low signal intensity in T1-weighted images and high signal intensity in T2-weighted images.

Based on CT evidence, Bosniak [9] has classified renal cysts into four categories:

Type I: This simple cyst is the most common and generally requires no treatment, although, rarely, a large simple cyst causes symptoms or obstruction and requires intervention.

Type II: This homogenous hyperdense cyst has thin septations and fine calcification that do not enhance after intravenous injection of contrast medium.

Type III: This multiloculated cystic mass or cyst has thick irregular calcifications, a thick wall, or nodularity.

Type IV: A cyst associated with a solid component; such lesions are considered to be cystic malignancies and should be managed with radical nephrectomy.

Simple renal cysts frequently are not solitary, and one or more additional cysts may be present in the same or contralateral kidney. Occasionally, however,

simple cysts may be very numerous and cause parenchymal and pyelocaliceal distortion. When both kidneys are extensively and diffusely involved, differentiation from autosomal dominant polycystic kidney disease may be difficult. Because of the obvious implications, it is important that the diagnosis of ADPKD is not made in this situation unless a familial history consistent with autosomal dominant transmission can be documented. In presence of renal failure, ADPKD always shows kidneys that are increased in size, whereas kidneys with renal failure and simple cysts are usually small but for the cysts.

There are few data on the numbers of renal cysts to be expected in normal individuals as an incidental finding, which is an important topic if an individual is at risk (for example, from family history) of having adult polycystic disease. Ravine et al. [10] suggest that while two cysts in total is sufficient to make a diagnosis of PKD under the age of 30, over the age of 60, in contrast, at least four cysts are required distributed within both kidneys. Simple cysts are more frequently detected with increasing age if more sophisticated imaging techniques are employed [11]. Pointers in favor of a few cysts being "simple" are that the kidneys are of normal size and that there are no associated liver cysts, which should be checked.

Treatment

The improvement of the diagnostic techniques during the past decade has dramatically reduced the indications for surgery in the management of benign simple cysts. At present, surgery is only indicated in the rare cases where there is still doubt about the precise diagnosis after using less invasive investigations, in the rare complicated cysts that cannot be adequately treated percutaneously, and in the symptomatic cysts that recur rapidly after percutaneous drainage. Drainage of the infected simple cyst is essential. The penetration of antibiotics into the cyst is poor. Percutaneous drainage is the most widely used technique to drain these cysts. Percutaneous aspiration of a renal cyst is easily accomplished and should be done for a diagnostic purpose whenever the cyst might be responsible for pain, obstruction, or hypertension. The recurrence rate of cysts following aspiration alone has exceeded 90%, prompting the use of sclerosing agents [12–14]. Successfully treated cysts resolve completely ultrasonographically, but a persistent defect still may be seen on CT. Alcohol appears to be the most effective agent (85% success). Of patients treated with alcohol, 50% experience a feeling of intoxication, nausea, flank pain, or hot flashes.Because of concern about collecting system obstruction if peripelvic cysts are present, this therapy should not be used. For most other simple cysts, aspiration and sclerosis are recommended as the first-line treatment. However, sclerosis may make radiographic follow-up of a lesion difficult, and so it should be avoided in complicated cysts.

Autosomal Dominant Polycystic Kidney Disease

While benign simple cysts are the most prevalent renal cystic disorder, autosomal dominant polycystic kidney disease (ADPKD) is undoubtedly the most important. This is also true in the geriatric population, especially with the recognition that survival of patients with this disease into old age is not as rare as initially thought and that significant pathology may result from associated

extrarenal disorders. The existence of polycystic kidneys has been known for centuries. Nevertheless, ADPKD did not become a well-defined entity, clearly separated from other renal cystic disorders, until the 20th century. During the early part of that century, reports of large series of patients helped to define its clinical characteristics and hereditary pattern. Among these early reports, the initial description by Lejars (1888) and the classical work by Dalgaard [15] deserve special mention.

Because of the natural history of ADPKD detailed below, the elderly with this disease are likely to differ from the population of younger patients in a number of respects, although very few comparisons or data analyses have, in fact, been made. Data from a number of series in the 1970s and 1980s suggest that the majority of ADPKD patients would have entered ESRD by the age of 65. The elderly population with ADPKD thus includes an increasing number of "survivors," who will have been selected for relatively benign disease in terms of rate of evolution. One factor in this will almost certainly be a relative excess of the somewhat more benign mutation PKD2 (see below), however many elderly PKD1 patients have been reported.

Epidemiology

There have been two population-based epidemiological studies of polycystic kidney disease in the adult. The first is a classical study by Dalgaard [15] in Copenhagen between 1920 and 1953. The second is a study by Iglesias et al. [16] in Olmsted County, Minnesota, between 1935 and 1980. Based on the Olmsted County data, the calculated lifetime risk of having a diagnosis of ADPKD is approximately 1 per 1000. This is a conservative value, since it does not include the autopsy cases. Up to 50% of patients with ADPKD may have escaped detection during life in the Olmsted County study. Comparison of these two epidemiological studies of ADPKD covering two different time periods suggests that ADPKD is becoming recognized earlier and more often during life and that milder cases are compatible with a normal life expectancy [16–18]. Approximately 6% of the total end-stage renal disease enrollment in the United States and 8% in Europe are due to ADPKD.

Pathology

The kidneys in ADPKD are almost always enlarged, to massive proportions in advanced cases. Characteristically, there is bilateral and diffuse involvement of the renal cortex and medulla with numerous small and larger cysts. Although the external surface of the kidney is distorted by innumerable cysts, the kidneys retain their characteristic reniform shape. Islands of normal renal parenchyma can be seen between the cysts. The contents of the cysts range from clear, straw-colored fluid to dark-reddish gelatinous material.

Pathogenesis

ADPKD (McKusick's online Mendelian inheritance in man [OMIM], 173900) is the most common genetic renal disease. It is genetically heterogeneous caused by mutations in the *PKD1* or *PKD2* genes. The PKD1 gene is located on the short arm of chromosome 16 (16p.3.3), codes for a protein, polycystin 1, which is involved in cell-cycle regulation and intracellular calcium transport,

and localizes in the primary cilia of renal epithelial cells. The PKD2 gene is located on the long arm of chromosome 4 (4q.21.2), codes for polycystin 2, which is a member of the family of voltage-activated calcium channels, and colocalizes to the primary cilia of renal epithelial cells [19]. A third gene, PKD3, is suspected but not yet identified. The gene penetrance of ADPKD is 100%; PKD1 is the most commonly implicated, affecting approximately 85% of patients, PKD2 approximately 15% [20].

Clinical Manifestations

The clinical diagnosis of ADPKD may be made at any time during infancy, childhood, or adulthood, but it is more frequently made during the third, fourth, and fifth decades of life. The diagnosis is usually made during the evaluation for abdominal or flank pain, hematuria, or hypertension. Nowadays a very common way of diagnosing the disease is family screening. Less frequently, the diagnosis is made during the work-up of a urinary tract infection or renal insufficiency, or because the patient has become aware of an abdominal mass. Although not necessarily the presenting complaints, many of these symptoms or manifestations are already present at the time of the initial evaluation, or they develop later on during the course of the disease [21].

Pain located in the abdomen, flank, or back is the most common initial complaint and it is almost universally present in patients with ADPKD. The pain can be caused by enlargement of one or more cysts, bleeding, either confined inside the cyst or leading to gross hematuria with passage of clots, or a perinephric hematoma; urinary tract infection (acute pyelonephritis, infected cysts, perinephric abscess); nephrolithiasis and renal colic; rarely, a coincidental hypernephroma. In addition, patients with ADPKD may have abdominal pain related to definitively or presumably associated conditions. Dull aching and an uncomfortable sensation of heaviness may result from a large polycystic liver. Although rare, hepatic cysts may become infected, especially after renal transplantation. Abdominal pain can also result from diverticulitis, which has been reported to occur with increased frequency in patients with ADPKD maintained on dialysis [22]. ADPKD patients may also be at a higher risk of developing thoracic aortic aneurysms [23]. But abdominal aortic aneurysms are not increased among these patients [24]. Of course, these patients may also develop pain for reasons completely unrelated to their underlying disease. It goes without saying that abdominal pain in a patient with polycystic kidneys may be a diagnostic challenge.

Hypertension

Hypertension is one of the most common early manifestations of ADPKD [25]. Even when renal function is normal, hypertension has been found in 50–75% of patients. In fact, the clinical course of hypertension in ADPKD is very unlike that of hypertension in chronic glomerulonephritis or tubulointerstitial nephropathies. In ADPKD, the hypertension is usually more severe early in the course of the disease and becomes less of a problem with the progression of the renal insufficiency. Studies of the renin-angiotensin-aldosterone system (RAS) have not convincingly demonstrated that it plays an important role in its pathogenesis. Moreover, Doulton et al. [26] have demonstrated that activation of the classic circulating RAS is no greater in

hypertensive ADPKD patients than in individuals with essential hypertension. In spite of this evidence, ACEi and ARBs are still the most indicated drugs to treat hypertension in ADPKD [27].

In patients with polycystic kidneys and normal renal function, the natriuretic response to an acute saline expansion is blunted as compared to controls, whereas in patients with polycystic kidneys and renal insufficiency, the natriuretic response is exaggerated [28]. This may explain why ADPKD patients develop hypertension early before the deterioration of renal function, at which time they are sodium retainers, whereas the hypertension tends to become less severe with the development of renal insufficiency, at which time they are sodium wasters.

Nephrolithiasis and Obstruction

The incidence of nephrolithiasis appears to be increased in ADPKD [29, 30]. The true incidence, however, is difficult to assess since the passage of stones is frequently not documented and renal colic in these patients may also be due to passage of blood clots. In addition, cyst wall calcification may be falsely taken for opaque renal calculi. All this considered, the frequency of nephrolithiasis in some series has ranged between 18 and 34%. The composition of the renal calculi does not appear to be different from the general stone population. Calcium oxalate, calcium phosphate, and uric acid stones have been reported. No metabolic abnormalities predisposing to stone formation have been identified so far. It is possible that the high incidence of stones in these patients is accounted for by the anatomical distortion with stagnation of the urine.

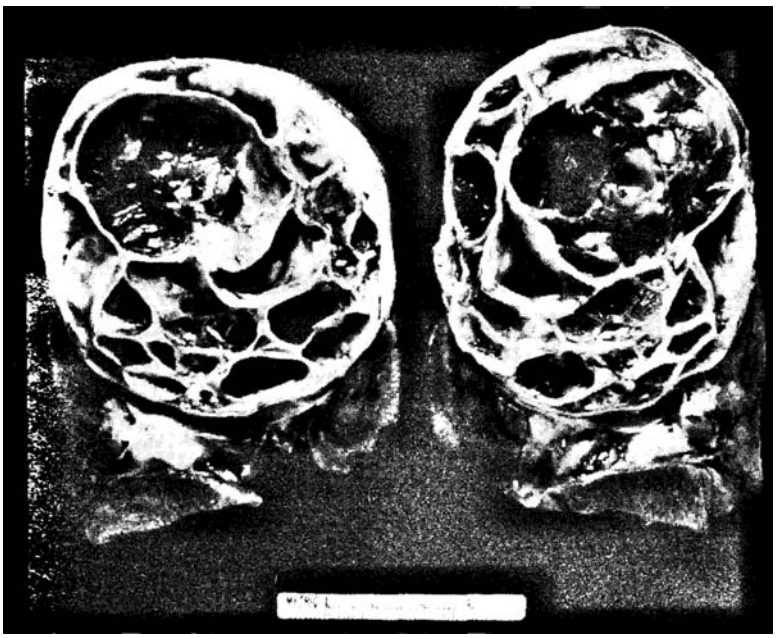

Fig. 19.1 Multilocular cyst. Well-circumscribed, encapsulated renal mass composed of multiple noncommunicating cysts.

Ureteral obstruction is not infrequent in ADPKD. It can be caused by a calculus, clot, or compression by a cyst. Because of the nonspecific symptoms and the caliceal distortion present in ADPKD, the obstruction may be difficult to detect. Unilateral or bilateral renal shutdown may rarely occur as a result of intracystic bleeding, with compression and obstruction of the renal pelvis.

Laboratory Findings

In addition to the microhematuria and mild degrees of proteinuria, sterile pyuria is very common. Hyperuricemia and erythrocytosis are also found with increased frequency. There is a decreased maximal urine concentrating capacity, whereas the capacity to dilute the urine is normal. Inability to acidify the urine and reduced ammonium formation have been described in some patients, but these defects may not be different from those encountered in other patients with moderate to severe renal disease.

Diagnosis

Ultrasonography has displaced excretory urography as the main screening test for polycystic kidney disease (Figure 19.2). It is more sensitive than excretory urography and avoids radiation exposure. It is less sensitive, however, than computed tomography. When the result of ultrasonography is questionable, computed tomography should be performed to rule out an early stage of development of the disease (Figure 19.3). Computed tomography has taken the place of renal arteriography in the early diagnosis of polycystic kidneys. MRI is the most precise tool to follow up kidney volume in ADPKD according to the CRISP study [Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP), sponsored by the National Institutes of Health (NIH)] [31]. The CRISP study was designed to include patients with normal

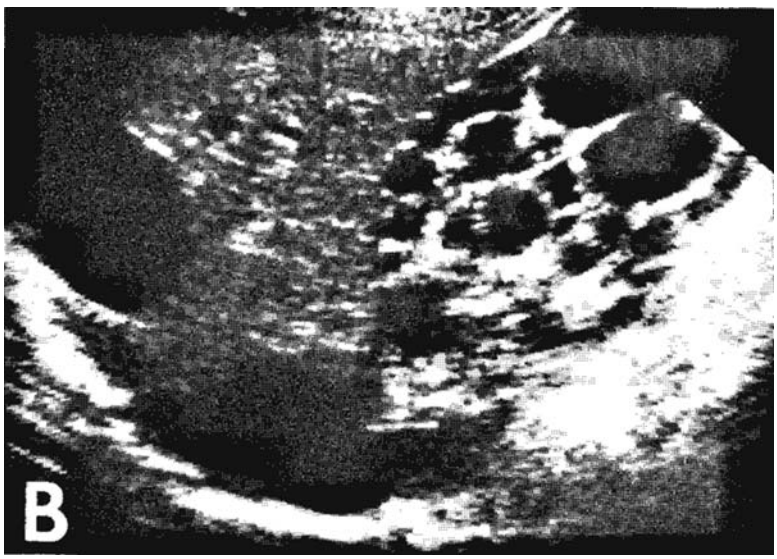

Fig. 19.2 Ultrasound scan of ADPKD kidneys.

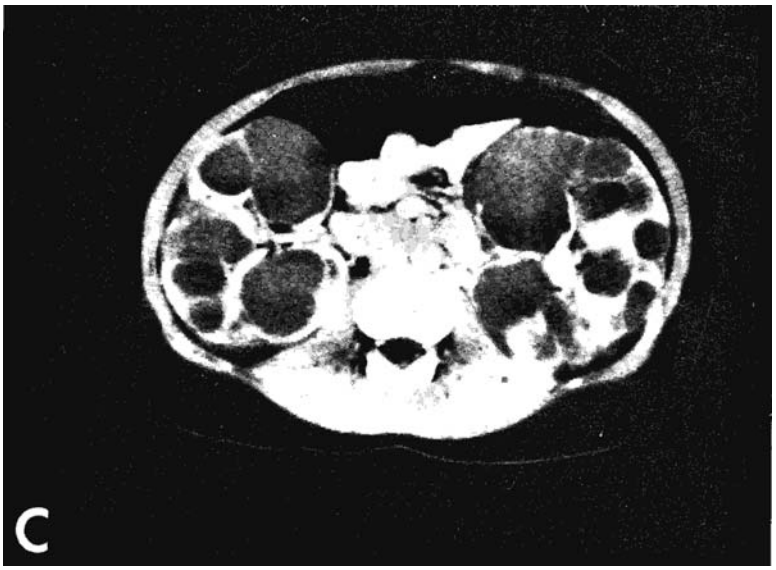

Fig. 19.3 CT scan of ADPKD kidneys.

function who were at high risk for renal insufficiency in order to demonstrate a clear-cut reduction in the glomerular filtration rate at some point during the study. Indeed, the study found a strong relationship between kidney volume at the beginning of the study and the subsequent change in the glomerular filtration rate. This information, when analyzed together with data from several longitudinal and cross-sectional studies, provides support for the view that enlarging cysts have an important role in promoting the ultimate decline in glomerular filtration rate [32]. However, at present, quantitative assessment of kidney volume with the use of MRI remains a research procedure, albeit a substantial potential addition to the ability to determine the effect of therapeutic interventions on renal progressionin this challenging disease.

Genetic testing is a diagnostic tool available nowadays. Either linkage analysis or mutation detection can be carried out for PKD1 and PKD2. The main indications for genetic testing are doubtful cases in adults and ruling out the disease for a living donor. Presymptomatic testing, prenatal diagnosis, and testing to know whether the disease is PKD1 or PKD2 are questionable. Although PKD2 disease is milder, it has been reported that most patients entering ESRD at an advanced age are still PKD1 [33].

Associated Conditions

ADPKD has been associated with a variety of extrarenal disorders. As previously mentioned, patients with this disease now survive longer. Because of the improved survivorship, the morbidity and mortality related to these associated disorders are likely to become more important.

Hepatic Cysts

The first report of polycystic liver disease (PLD) in association with autosomal dominant polycystic kidney disease (ADPKD) was made by Bristowe in 1856. Subsequently, PLD has become a well-recognized association in patients with ADPKD. Rarely symptomatic, patients with PLD usually require little intervention. However, the prevalence of ADPKD has undoubtedly contributed to the large number of cases of symptomatic hepatomegaly reported in the medical literature. Until recently, the existence of PLD and polycystic kidney disease was thought to represent the same autosomal dominant inherited genetic disorder. Advances in the field of genetics have now prompted the discovery of an autosomal dominant polycystic liver disease (ADPLD) distinct from ADPKD [34]. The number of ADPKD patients with hepatic involvement appears to be rising, likely as a result of longer life expectancy from improved renal replacement therapy and renal transplantation. The prevalence of hepatic cysts in ADPKD patients has climbed to 75–90% [35, 36].

In the cases of PLD with either ADPKD or ADPLD, hepatic complications typically occur only in the setting of significant hepatomegaly. However, even with massive organ enlargement, significant hepatic complications remain fairly uncommon. Symptomatic cases usually present with an abdominal mass, abdominal pain or sensation of abdominal fullness, dyspnea, and early satiety although patients may complain of more severe pain after meals or if a hepatic cyst ruptures, hemorrhages, or becomes infected. Abdominal wall hernias and uterine prolapse secondary to increased abdominal pressure from massive liver involvement or ascites may also occur. Hepatic insufficiency or failure has been reported very rarely as a complication of long-standing polycystic involvement of the liver.

Cyst infection poses a serious problem for the patient with PLD and has been reported to have morbidity and mortality rates of 3% and 2%, respectively, in the ADPKD patient with end-stage renal disease (ESRD). Liver-associated enzymes and bilirubin may be mildly elevated, but the diagnosis of cyst infection cannot be disregarded if these lab tests are normal. Classically, these patients will present with fever, leukocytosis, and right upper quadrant pain. This acute presentation can progress to sepsis and death if cyst infection is not diagnosed and treated aggressively, particularly in those patients with ESRD requiring hemodialysis. Bacteremia as documented by positive blood cultures is reported to occur in 63% of cases. When both blood and cystic fluid are cultured, identification of an organism can be made in up to 86% of cases. Published data suggest that the cyst infections are usually monomicrobial, with Gram-negative organisms such as *E. coli* being the most common offending organism. On CT scanning, the findings of fluid-fluid levels within cysts, cyst wall thickening, intracystic gas bubbles, cyst wall calcification, and heterogeneous or increased density have all been correlated with infection of a hepatic cyst. Ultrasound imaging may show changes such as indistinct cyst margins or cystic wall changes as well as echogenic fluid. Ultimately, drainage of the suspected cyst provides the definitive answer as to the presence of infection.

Prior to the development of laparoscopic techniques, laparotomy with fenestration was considered the standard of therapy for uncomplicated hepatic cysts. The combination of fenestration with hepatic resection is also a favored procedure for the highly symptomatic PLD patient. A low mortality rate

(3–11%) for those patients undergoing the procedure supports its use when necessary, although the relatively high morbidity rates (20–100%) must be considered [37]. Liver transplantation as a means of treating advanced PLD, while seemingly more accepted in recent literature, continues to have a very limited role in the management of the polycystic liver patient. This intervention should be reserved for those patients whose quality of life has become significantly affected [38].

Intracranial Aneurysms

The association of intracranial aneurysms and ADPKD has been established on the basis of large retrospective autopsy studies. In two prospective studies of patients with ADPKD screened by cerebral MR angiography, no association was found between the presence of ICA and age, gender, presence of hypertension, and reduced renal function [39]. The only characteristic clearly associated with the presence of ICA is a family history of ICA or SAH: In three large prospective studies, an ICA was detected in 15.6% of 77 patients with a positive family history versus only 5.9% of 186 patients without such a history [40]. Therefore prevalence of asymptomatic ICA in patients with ADPKD is about 6% in the absence of a familial history of ICA or SAH and about 16% in patients with such history.

The natural history of ICA in ADPKD remains largely unknown. We fortunately do know that all ICA do not rupture. When they do, this event entails a 35–55% risk of combined case fatality and morbidity.

MR angiography is the most convenient test to screen for the presence of intracranial aneurysms and carries essentially no risk, because it does not require intravascular administration of contrast material. Nowadays it is accepted that only patients with positive family history or related symptoms should be screened.

Other Cardiovascular Complications

Several case reports of associations of ADPKD and cardiovascular abnormalities have appeared in the literature. Dilatation of the aortic root, bicuspid aortic valve, mitral valve prolapse, and coarctation of the aorta were the most frequent abnormalities. Of these, dissecting thoracic aortic aneurysms were the most common. The observed frequency of coexisting polycystic kidney disease and dissecting thoracic aortic aneurysm in these autopsy series was 7.3 times higher than that expected by chance association alone.

Carcinoma in Polycystic Kidneys

Focal cellular hyperplasia of the tubular epithelium is a common abnormality in ADPKD, but it seems not to constitute a pre-neoplastic state. Many case reports of the association between ADPKD and renal cell carcinoma have been published, but these do not prove the existence of an association, since chance association of two relatively common disorders can be expected in a considerable number of patients. In many large series of patients, the association between renal cell carcinoma and ADPKD has not been found. Furthermore, development of renal cell carcinoma in polycystic kidney patients on hemodialysis or after renal transplantation has been reported rarely

and does not appear to be a common problem. When ADPKD and renal cell carcinoma coexist in the same patient, the diagnosis is challenging. Pain in association with fever, weight loss, anemia, or a striking change in the configuration of the kidney and the presence of mottled calcifications within a renal cyst should raise the suspicion of coexisting renal cell carcinoma. In this situation, MRI and renal arteriography are the most helpful diagnostic tests.

Clinical Course

A decline of renal function occurs in most, but not all, patients with ADPKD diagnosed during life if they are followed for sufficiently long periods of time. These patients have a prolonged period of stable renal function followed by a slow decline of renal function. A diversion from the initial slope in these patients should alert the physician to the possibility of an intercurrent renal disease, a reaction to a medication, or the development of obstruction. It is important to avoid undue pessimism when assessing the prognosis of ADPKD in an individual patient . Kidney survival is better in the patients diagnosed more recently. In a 1992–2001 cohort, the mean age at entry to ESRD was 63 years in men and 61 in women [41] and was associated with a lower mean blood pressure, possibly from improved management. A similar improved prognosis is seen as well in patients who at the time of the diagnosis are normotensive, have a normal serum creatinine or plasma urea, and have no proteinuria on the urinalysis. One of the most outstanding prognostic factors is kidney size [31].

Also, the genotype confers a different prognosis, with PKD2 patients having a better outcome than PKD1. The mean age of onset of ESRD for PKD1 is 53 years, while it is 69 for PKD2 patients [20]. A higher proportion of patients aged 60 or over should have PKD2 mutations than the usually quoted overall 14%, but data are not available on this point. It is therefore important, when assessing the prognosis of polycystic kidney disease in an individual patient, to take into consideration multiple factors peculiar to this patient rather than extrapolating from large clinical series.

Cardiovascular pathology and infections account for approximately 90% of the deaths of these patients treated by hemodialysis or peritoneal dialysis and after renal transplantation.

Treatment

There is as yet no specific therapy for ADPKD, although several promising lines of investigation are active at the moment [42] such as tolvaptan and octeotride. The goal of treatment is to prevent complications and, if possible, slow down the rate of progression of the renal disease. The patients should be advised against the use of constrictive belts and the practice of contact sports, as well as caution against narcotic or analgesic abuse for frequently occurring chronic pain. Cyst decompressive procedures are of no proven value. Hypertension should be strictly controlled. The best antihypertensive treatment for these should be provided. Reduction of dietary protein intake may be of value to slow down the rate of progression of renal insufficiency. Unnecessary urinary tract manipulation should be avoided; when absolutely necessary, antimicrobial prophylaxis should be prescribed.

The treatment of infected renal cysts poses special problems because of the variable penetration of different antibiotics into the cysts. Most antibiotics enter the proximal cyst to some extent. Lipid-soluble antibiotics with an alkaline pK, such as clindamycin, enter the distal cyst well. Other lipid-soluble antibiotics that may be useful in the treatment of these infected cysts are chloramphenicol, tetracycline, trimethoprim, erythromycin, and ciprofloxacin. Because of the reported increased risk for diverticulitis, prevention of constipation is important. In cases of unilateral or bilateral ureteral obstruction by a cyst, surgical relief of the obstruction is frequently necessary to relieve the pain and preserve renal function. Percutaneous draining of a compressing large renal cyst can be successful in rare cases. When end-stage renal disease occurs, dialysis and renal transplantation are indicated. Patients with ADPKD on maintenance hemodialysis do well compared with other types of renal disease, probably because they have fewer associated disorders. Bleeding secondary to heparinization during dialysis occurs only rarely, and usually these cases can be satisfactorily managed by using low or regional heparinization.

Finally, the discovery of ADPKD in an elderly patient raises the question of genetic counseling. We believe that relatives at risk, children and siblings, benefit from screening, but repercussions on insurability and employability should be considered in each individual case. The benefits from screening are early treatment and prevention of complications, choice of alternative family planning for those with ADPKD, and reassurance of those without ADPKD. Recommendations for screening include blood pressure measurements at age 10 and 15 and ultrasonography at age 20 (earlier in special circumstances, e.g., contact sports).

Unilateral Multicystic Kidneys

Unilateral multicystic kidneys are a rare form of noninheritable renal dysplasia that needs to be considered in the differential diagnosis of a nonvisualized kidney in the adult.

Pathology

These kidneys consist of a grape-like cluster of cysts held together by connective tissue and have lost the typical reniform outline. The composition of cystic fluid resembles plasma in regards to sodium, potassium, creatinine, urea, and sugar. The ureter is characteristically absent, rudimentary, or atretic.

Pathogenesis

The cause of multicystic renal dysplasia is uncertain, but a primary defect in the ureteric development is strongly suspected. Experimentally, a typical multicystic kidney can be produced by transient ureteric obstruction during renal development.

Clinical Manifestations

Multicystic dysplastic kidneys are the most common cause of an abnormal mass in the newborn and, when bilateral, are incompatible with life. Unilateral

multicystic kidneys, however, may not be detected until adulthood or may go completely undetected during life and be discovered at autopsy. Multicystic kidneys are most commonly found in the adult as an incidental finding during the evaluation of hypertension, nephrolithiasis, or urinary tract infection. Occasionally, however, the diagnosis of multicystic kidney will be associated with the presence of abdominal or flank discomfort due to the mass effect of the lesion.

Imaging

The diagnosis of this condition requires lack of visualization of the kidney by excretory urogram and the inability to obtain a retrograde pyelogram because of partial or complete absence or obliteration of the ureter. Very frequently, calcified cysts are shown on x-ray by the presence of ring-like calcifications of various sizes.

Treatment

Nephrectomy is not necessary except in those few patients who have abdominal or flank discomfort.

Multilocular Renal Cysts

Multilocular renal cysts consist of a well-circumscribed, encapsulated renal mass composed of multiple noncommunicating cysts of varying size (Figure 19.1).

Pathology

Histologically, two types of multilocular cysts have been described. In both types, no fully developed nephrons or segments of nephrons can be found in the septa of the cysts, while the remaining kidney tissue outside the cyst is normal. The first type of multilocular cysts is most frequently found in adults; the septa in this type are composed of fibrous tissue. The second type of multilocular cysts is found in infants and young children only and is considered by some authors to be a benign equivalent of a nephroblastoma.

Pathogenesis

The pathogenesis of multilocular cysts is unknown. Recent reviews suggest that multilocular cysts are neoplasms, usually benign but occasionally harboring histologic malignancy. A few cases have been reported where development of a multilocular cyst has occurred in a kidney previously normal by excretory urography. There is also evidence that these lesions increase in size, resulting in compression and damage of the surrounding normal renal parenchyma. It is possible, however, that not all multilocular cysts have a singular pathogenesis; some multilocular cysts, especially in children, may be congenital and dysplastic.

Clinical Manifestations

Multilocular cysts are less rare than initially suspected. Approximately half of the cases reported have occurred in children and half in adults. The ages of the adult patients at diagnosis have ranged from 18 to 72 years old, with a peak incidence in the sixth decade. Multilocular cysts are typically solitary and unilateral. Bilateral multilocular renal cysts are very rare and have been described only in children. The presenting symptoms are usually an abdominal mass, pain, or hematuria.

Imaging and Differential Diagnosis

Multilocular cysts are usually first detected on ultrasound. Multilocular cysts are complex masses with well-defined cysts mixed with highly echogenic stroma. Central and peripheral calcification occurs more commonly than initially reported. On angiography, these lesions are generally avascular or sparsely vascular, rarely being moderately vascular or hypervascular. The angiographic appearance is, therefore, insufficient to rule out a renal cell carcinoma. Cyst puncture reveals clear fluid with benign cytology. Only one or a few cysts are filled with contrast media if this is instilled, while the bulk of the multilocular cyst remains unopacified. CT is also a very good techinque to visualize this type of cyst.

Treatment

If technically possible, partial nephrectomy is the treatment of choice for multilocular cysts. The occurrence of renal cell carcinoma in multilocular cysts is not frequent enough to justify routine nephrectomy in these cases. However, thorough tissue sampling for histologic studies and use of frozen sections should be done at the time of surgery to rule out the presence of a renal adenocarcinoma, which would necessitate complete nephrectomy. A preoperative diagnosis of multilocular cysts free of renal adenocarcinoma is difficult to establish. On the other hand, atypical hyperplasias in multilocular cysts may on occasion be erroneously interpreted as low-grade adenocarcinomas. In any case, the biological course of multilocular cysts is usually benign, even in those cases with associated renal cell carcinoma with no reports of local or metastatic recurrence following nephrectomy for a multilocular cyst with adenocarcinoma.

Acquired Cystic Disease of the Kidneys

The terms “acquired cystic disease of the kidneys” and “acquired polycystic kidney disease” have been used to describe the cystic degeneration of the renal parenchyma that occurs in end-stage kidneys probably as a result of prolonged uremia. However, as said previously, the term “polycystic” should just be used for ADPKD or the recessive form of the disease.

It appears that the cystic changes can start prior to the initiation of dialysis and that they develop regardless of the type of dialysis being used. This phenomenon is therefore likely to be related to the uremic state rather than being a consequence of the dialysis procedures. The role of uremia is also

supported by the regression of those cystic changes that can occur after successful renal transplantation [43, 44].

Pathology

The kidneys are frequently larger than expected for an end-stage kidney, but true renal enlargement is rarely observed (Figure 19.4). The cysts,which are usually much smaller than in autosomal dominant polycystic kidney disease, tend to occur in the renal cortex but also involve the renal medulla . They may be lined by a simple cuboidal epithelium or by a hyperplastic multilayered epithelium with papillary projections. The continuity between the cysts and the renal tubules has been confirmed by microdissection studies, and they seem to originate from the proximal tubules [45]. Deposition of oxalate crystals

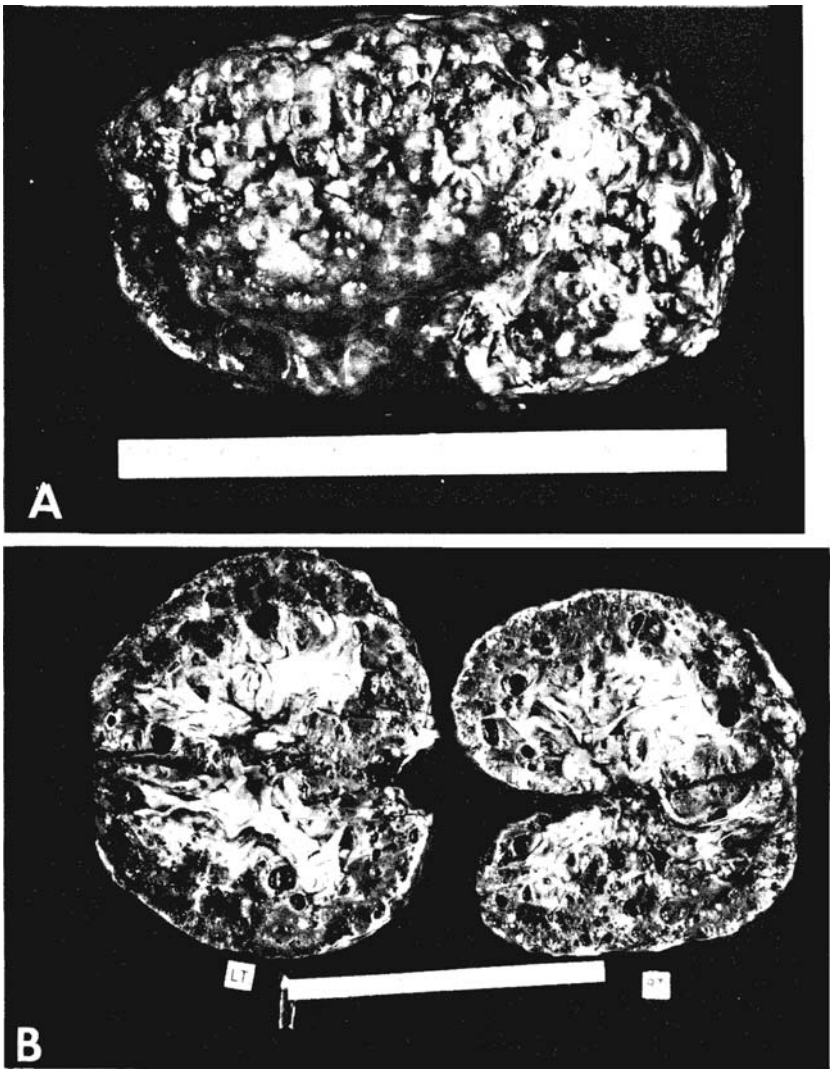

Fig. 19.4 Acquired cystic disease of the kidneys: (a) external surface; (b) cut surface.

is frequently observed in the renal interstitium surrounding the cysts, in the walls of the cysts, and in the lumen.

Pathogenesis

Tubular obstruction by interstitial fibrosis or deposition of oxalate, ischemia, and accumulation of toxic metabolites have all been proposed to play a role. It is possible that biologically active substances that are retained in uremia and not removed by dialysis, such as the mitogenic polyamines, could stimulate epithelial and smooth muscle cell proliferation and result in a variety of abnormalities in end-stage kidneys, including atypical cysts, renal cell tumors, and nodular formation in the intrarenal arteries and arterioles. Nevertheless, the evidence to support these hypotheses is sparse, and much more needs to be learned about pathogenesis and the biological and clinical significance of this disorder.

Clinical Manifestations

In most patients, the cystic degeneration of the renal parenchyma that occurs on long-term dialysis is a silent process. The number of patients with cysts, as well as the number and size of the cysts, increases with duration of the dialysis. Using sensitive computed tomography techniques, multiple renal cysts may be observed in approximately 80% of patients who have been on hemodialysis for more than 3 years. With the increasing number and size of the cysts, the kidney volume also increases. Determinations of kidney volume by computed tomography suggest that the volume of the kidney decreases during the first 3 years of dialysis and then increases as the result of cyst formation. It has been reported that the cysts occur more frequently in dialyzed patients who are anuric than in those who maintain some urine output. The frequency of these cystic changes does not appear to be influenced by the efficiency of dialysis, as reflected by blood chemistry parameters [46].

Complications of acquired cystic disease of the kidneys have included intracystic bleeding, gross hematuria, retroperitoneal hemorrhage, and malignant transformation.

Intracystic bleeding can be the cause of unexplained flank or back pain in hemodialysis patients. The hemorrhagic cysts can rupture into the pelvis, giving rise to gross hematuria, or into the retroperitoneum, causing a retroperitoneal hemorrhage. Retroperitoneal hemorrhage is a life-threatening complication that usually has a dramatic outcome. Heparinization during hemodialysis and the use of anticoagulants to prevent the clotting of arteriovenous fistulae may play a contributory role. The typical presentation of these patients is with severe abdominal and flank or back pain, distended abdomen, hypoactive or absent bowel sounds, and a palpable abdominal mass. In some cases, fever, femoral nerve compression, and obstructive jaundice have been observed. Spontaneous retroperitoneal bleeding has been estimated to occur in 1–3% of all chronic hemodialysis patients. In many of these cases, the retroperitoneal hemorrhage results from the rupture of a sclerotic artery in the wall of the cyst.

Whether acquired cystic disease of the kidneys should be regarded as a premalignant state is controversial [47]. In their original description, Dunnill et al. [43] described three types of renal tumors associated with acquired cystic

disease. These were papillary tumors, tumors exhibiting tubular differentiation, and solid tumors. They were frequently multicentric. A major problem is how to assess their malignant potential. The distinction between renal cell adenomas and carcinomas is frequently made on the basis of size; if the renal cell tumor is less than 3 cm in diameter, the risk of metastasizing is usually small. Whether renal cell carcinomas will become a major medical problem in the long-term maintenance of the hemodialysis population is uncertain.

Imaging and Treatment

Only the complications of acquired cystic disease of the kidneys may require treatment. Until more information becomes available, it seems reasonable to follow small (<3 cm) renal tumors by serial computed tomography, MRI, or ultrasound examinations . Surgical intervention would be indicated for large solid tumors with invasive features or when there is evidence of progressive tumor enlargement. The treatment of retroperitoneal bleeding is usually conservative, but therapeutic embolization or nephrectomy may become necessary in some cases.

Adult Medullary Cystic Disease

Juvenile nephronophthisis (JNPHP) and *medullary cystic kidney disease* (MCKD) are two diseases with common pathological features represented by the presence of small cysts located at the corticomedullary junction and deeper in the renal medulla, arising from the distal convoluted and collecting tubules, along with some tubulointerstitial damages. JNPHP and MCKD usually lead to end-stage kidney disease (hence the alternative term of *uremic medullary sponge kidney* to refer to the entire JNPH/MCKD group). JNPHP, an autosomal recessive condition, is linked to mutations in more than one gene. As JNPHP is a condition affecting young people, only MCKD is within the scope of this chapter.

MCKD usually occurs in the third to fourth decades of life, sharing the same clinical renal presentation with JNPHP, except for the growth retardation and extrarenal malformations, which are absent in MCKD, and for the later age of occurrence of uremia. Two forms of MCKD are recognized, MCKD1 (OMIM 174000) and MCKD2 (OMIM 603860), which are transmitted as autosomal dominant traits, the corresponding genes of which have been identified and mapped to chromosome 1q [48] and chromosome 16p [49], respectively. Uremia supervenes after 60 years of age in MCKD type 1 and around 30 years in MCKD type 2. MCKD type 2 is often associated with hyperuricemia and gout, and on occasion hyperuricemia has been also observed in association with JNPHP, with this latter phenotype being considered a likely allelic variant of MCKD type 2 in that its responsible gene, which encodes uromodulin, is apparently located on chromosome 16p in a region overlapping with the locus of MCKD2 [50]. In approximately 15% of the cases of JNPHP/MCKD complex, no family history is found, possibly representing a new mutation.

Pathology

The kidneys are small, and the characteristic pathological change is the presence of multiple cysts most commonly seen at the cortical medullary junction and along the medullary collecting ducts. Nevertheless, these cysts are not universally present and, when present, are not necessarily confined to the medulla. For this reason, some authors object to the term *medullary cystic disease*.

Clinical Manifestations

MCKD is usually recognized during the second to fifth decades of life, has an insidious onset, and progresses rapidly to end-stage renal failure. A late onset of the disease, during the seventh and eighth decades of life, has been observed in some families, and, therefore, medullary cystic disease should be considered in the differential diagnosis of chronic renal failure even in the elderly. In some of these elderly patients, the clinical course has been unusually prolonged. Inability to concentrate urine and wasting of sodium are usually present. The urinary sediment is characteristically benign and the proteinuria is usually mild, below 1 g per 24 hours. Anemia is a very frequent finding, but there is no evidence to support that the degree of anemia is out of proportion to the degree of insufficiency. Hypertension may be present but is not a prominent feature of this disease. Extrarenal disorders, such as retinitis pigmentosa, metaphyseal chondrodysplasia, cerebellar ataxia, and hepatic fibrosis, which are frequently associated with JNPHP, are not observed in the adult form. Osteodystrophy is less frequent.

Imaging

Detection of the cysts by radiographic procedures is frequently unsuccessful, since these are usually small (1 mm to 1 cm in diameter). Ultrasound may show increased echogenicity of kidneys with a density comparable to the liver, diminished corticomedullary demarcation, and presence of multiple cysts at the corticomedullary junction.

Treatment

The treatment of medullary cystic disease is merely supportive. Because of the tendency to salt wasting, volume contraction, and renal azotaemia, unnecessary sodium restriction or the use of diuretics should be avoided.

Medullary Sponge Kidney

Medullary “sponge” kidney (MSK) is a medical condition characterized by the congenital ectasia of the distal collecting tubules with enlargement of the affected pyramids, either diffusely throughout both kidneys, only in one kidney, or variably in different papillae.

The exact pathogenesis of MSK is not known. It is generally assumed to be congenital in origin, although no clear inheritance pattern has been found. The global incidence of MSK is estimated to be around 0.5%, and in the elderly population, in specific, this incidence is thought to be minute.

MSK has been associated with several other medical conditions. These include hemihypertrophy, hepatic fibrosis, and autosomal dominant poly kidney disease. Hemihypertrophy is probably the most significant one as it can be found in up to 25% of MSK patients. MSK, as such, is usually symptomless, but complications such as urinary tract infection and calculi cause renal colic to be the most frequent presenting symptom. Microscopic hematuria is an expected finding in MSK, while gross hematuria is found in 10–20% of patients.

The diagnosis of MSK is confirmed radiographically with the radiological features on antegrade visualization of the papillae ranging from a blush in mild cases to the outline of cystic dilatation of the collecting ducts in the most obvious cases.

The clinical course of MSK is usually benign and does not progess to renal failure, although some patients may reach ESRD. Most commonly, patients suffer from recurrent UTI as well calculus-related renal colic and urinary tract obstruction [51].

Pathology

Precaliceal canalicular ectasia may involve one or more renal papillae in one or both kidneys. These dilated tubules may be surrounded by an apparently normal medullary interstitium or, in cases of more prominent cystic disease, inflammatory cell filtration and interstitial fibrosis. The renal size is usually normal or slightly enlarged.

Pathogenesis

MSK is usually regarded as a nonhereditary disease, despite rare reports of familial cases. It is more controversial whether it should be considered a congenital or acquired disorder. Although there have been cases of MSK diagnosed in childhood, others remark that the rarity of this disorder in children favors the interpretation that this is an acquired disease. Progression of the tubular ectasia and development of new tubular dilatation and medullary cysts have been documented in some patients. It is possible that MSK is only a structural abnormality and results from a variety of different physical, chemical, or genetic factors.

Clinical Manifestations

The prevalence of MSK by age, gender, and race is unknown. The frequency in different clinical series has varied widely between 0.5 and 21%, depending not only on the type of population being studied but also on the different diagnostic criteria used to identify MSK. Early reports suggest a male predominance, but both genders probably are equally involved. In fact, females with idiopathic calcium nephrolithiasis have underlying MSK more frequently than males. Most patients are diagnosed in their fourth or fifth decade, but infrequently the diagnosis is not made until the sixth, seventh, or eighth decade.

Although MSK may be silent, its anatomical characteristics and association with functional alterations mean that it is frequently complicated by nephrolithiasis and pyelonephritis. Other, less frequent manifestations are

gross and include microscopic hematuria, renal failure, and primary hyperparathyroidism.

Recurrent calcium nephrolithiasis and nephrocalcinosis are the most common signs. The association with renal hypercalciuria, distal tubular acidosis, and hypocitraturia (in conjunction with urinary stasis in the papillary duct ectasias) triggers the formation of calcium phosphate and/or calcium oxalate stones.

Hyperparathyroidism is frequently associated and was thought to cause MSK and also trigger stone formation in these patients [52]. However, in most patients, hypercalciuria, nephrocalcinosis, and renal stones clearly precede the onset of hyperparathyroidism by many years. It was also suggested that renal hypercalciuria triggers the parathyroid gland stimulation, leading to hyperplasia. Nevertheless, we now believe that both hyperparathyroidism and stones might be secondary to common disorders. In addition to the morphological abnormalities of the precalyceal ducts, MSK is associated with other abnormalities of the lower tubule, such as a defective urinary concentration, distal renal tubular acidosis, and hypocitraturia, and also of the upper nephron (in the proximal tubule), that is, maximum reabsorption of glucose (TmGlucose) and maximum secretion of P-aminohippurate (TmPAH) [53]. The risk of renal failure seems to be modest in MSK and related to renal infections and the formation of struvite stones. Familial cases have been reported, sometimes associated with renal agenesia, other renal malformations, or abnormalities in the urinary tract.

Imaging

The diagnosis of MSK is made by excretory urography that characteristically reveals the anterograde visualization by contrast media of dilated collecting tubules [54]. Medullary sponge kidneys are commonly bilateral, but they may be unilateral in up to one-fourth of the cases. The degree of tubular dilatation is highly variable, and the wide range of reported frequencies of this abnormality is in part due to the variable degrees of collecting duct dilatation that different observers have decided to consider abnormal. Mild cases of precaliceal ectasia can easily be overlooked if the excretory urography is not of high quality, clearly outlining most caliceal fornices, or if the images are obscured by overlying bowel. A definite diagnosis of MSK can be made when the dilated collecting ducts are visualized on early and delayed films without the use of compression and in the absence of ureteral obstruction. Deposition of calcium salts within these dilated tubules may give the radiographic appearance of renal calculi or nephrocalcinosis. The distribution of the renal calculi in these patients is characteristic, in clusters fanning away from the calyx. Although MSK can occasionally be detected by ultrasonography or computed tomography, the contribution of these techniques to the diagnosis of this condition is very limited.

Treatment

There is no specific treatment for MSK. The treatment of nephrolithiasis and urinary tract infection, when present, is the same as it would be in the general population. Thiazides and inorganic phosphates have been found to

be effective in preventing stones in these patients. Extensive or repeated unnecessary investigations for hematuria should be avoided.

Cystic Disease of the Renal Sinus

Less is known about the cystic disorders involving the renal sinus than of those involving the renal parenchyma. The differential diagnosis of mass-occupying lesions in the area of the renal sinus is difficult, and many different processes may look the same on excretory urography [55].

Parapelvic cysts originate in the renal parenchyma extending into, and primarily expanding within, the renal sinus. Peripelvis cysts originate in sinus structures, which presumably represent mostly lymphatic collections.

Clinical Manifestations

Parapelvic cysts are most frequently diagnosed after the fourth decade of life and are usually asymptomatic. They are usually discovered in the course of evaluations for conditions such as urinary tract infections, nephrolithiasis, hypertension, and prostatism. Despite considerable distortion of the calices and infundibuli, the pressure in these lymphatic cysts is low and not likely to result in significant functional obstruction. Indeed, renal function in patients with bilateral multiple parapelvic cysts is usually normal. The evidence that supports a pathogenetic role of these cysts in the hypertension or nephrolithiasis of these patients is not convincing. Occasionally, parapelvic cysts are the only finding in the course of evaluations for otherwise unexplained lumbar or flank pain.

Treatment

The therapeutic approach to parapelvic cysts should be conservative, since this is a benign condition.

Pelvicaliceal Diverticula

These are cystic cavities that contain urine and are lined by transitional epithelium [56]. They may be contained in the renal parenchyma and originate from the fornix of a minor calyx by a narrow isthmus (caliceal diverticulum) or be extrarenal and in direct communication with the renal pelvis (pelvic diverticulum). It is uncertain whether these diverticula are of congenital or acquired origin. They are usually better demonstrated by retrograde pyelography than by excretory urography. They are usually asymptomatic unless complicated by nephrolithiasis or infection. The frequency of stone formation in the caliceal diverticulum has been reported to be between 10 and 50%. Surgical intervention is indicated rarely when conservative management of these complications fails.

Neoplastic Cysts

These have been covered in previous sections.

Inflammatory Cysts

Medullary cavities resulting from analgesic-related papillary necrosis or from mycobacterial or other bacterial infections sometimes need to be considered in the differential diagnosis of medullary sponge kidney and caliceal diverticula. Detailed discussion of these disorders is not in the scope of this chapter.

References

1. Amendola, M.A., Bree, R.L., Pollack, H.M., et al. Small renal cell carcinomas: Resolving a diagnostic dilemma. *Radiology* 1988; 166(3):637–641.
2. Kier, R., Taylor, K.J., Feyock, A.L., Ramos, I.M. Renal masses: Characterization with Doppler US. *Radiology* 1990; 176(3):703–707.
3. Cook, G.J., Lewis, M.K., Clarke, S.E. An evaluation of 99Tcm-DMSA SPET with three-dimensional reconstruction in 68 patients with varied renal pathology. *Nucl. Med. Comm*. 1995; 16(11):958–967.
4. Brickner, N.S., Patton, J.F. Cystic disease of the kidneys; a study of dynamics and chemical composition of cyst fluid. *Am. J. Med*. 1955; 18(2):207–219.
5. Brown, C.D. Massive spontaneous renal cyst hemorrhage. *JAMA* 1978; 239(14):1418–1419.
6. Hinman, F., Jr. Obstructive renal cysts. *J. Urol*. 1978; 119(5):681–683.
7. Roth, J.K., Jr., Roberts, J.A. Benign renal cysts and renal function. *J. Urol*. 1980; 123(5):625–628.
8. Mang, H.Y., Markovic, P.R., Chow, S., Maruyama, A. Solitary intrarenal cyst causing hypertension, with plasma renin activity study before and after cyst aspiration. *NY State J. Med.* 1978; 78(4):654–656.
9. Bosniak, M.A. The current radiological approach to renal cysts. *Radiology* 1986; 158(1):1–10.
10. Ravine, D., et al. Evaluation of ultasonographic criteria for autosomal dominant polycystic kidney disease. *Lancet* 1994; 343:824–827.
11. Nascimento, A.R., et al. Rapid MR imaging detection of renal cysts. *Radiology* 2001; 221:628–632.
12. Ozgur, S., Cetin, S., Ilker, Y. Percutaneous renal cyst aspiration and treatment with alcohol. *Int. Urol. Nephrol*. 1988; 20(5):481–484.
13. Hobarth, K., Kratzik, C. [Percutaneous sclerosing of kidney cysts with alcohol.] *Urologe A* 1991; 30(3):189–190.
14. Aboutaieb, R., Joual, A., Ousehal, A., el Mirini, M. Benjelloun, S. [Percutaneous alcoholization of simple serous cysts of the kidney.] [in French] *Ann. Urol. (Paris)* 1995; 29(5):280–283.
15. Dallgaard, O.Z. Bilateral polycystic disease of the kidneys; a follow-up of two hundred and eighty-four patients and their families. *Acta Med. Scand. Suppl.* 1957; 328:1–255.
16. Iglesias, C.G., Torres, V.E., Offord, K.P., Holley, K.E., Beard, C.M., Kurland, L.T. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935–1980. *Am. J. Kidney Dis.* 1983; 2(6):630–639.
17. Fick, G.M., Johnson, A.M., Hammond, W.S., Gabow, P.A. Causes of death in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol*. 1995; 5(12):2048–2056.
18. Gabow, P.A. Autosomal dominant polycystic kidney disease. *N. Engl. J. Med*. 1993; 329(5):332–342.
19. Sutters, M. The pathogenesis of autosomal dominant polycystic kidney disease. *Nephron Exp. Nephrol*. 2006; 103(4):e149–e155.

20. Hateboer, N., Dijk, M.A., Bogdanova, N., et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. *Lancet* 1999; 353(9147):103–107.
21. Milutinovic, J., Fialkow, P.J., Agodoa, L.Y., Phillips, L.A., Rudd, T.G., Sutherland, S. Clinical manifestations of autosomal dominant polycystic kidney disease in patients older than 50 years. *Am. J. Kidney Dis*. 1990; 15(3):237–243.
22. Scheff, R.T., Zuckerman, G., Harter, H., Delmez, J., Koehler, R. Diverticular disease in patients with chronic renal failure due to polycystic kidney disease. *Ann. Intern. Med.* 1980; 92(2 Pt 1):202–204.
23. Chapman, J.R., Hilson, A.J. Polycystic kidneys and abdominal aortic aneurysms. *Lancet* 1980; 1(8169):646–647.
24. Torra, R., Nicolau, C., Badenas, C., et al. Abdominal aortic aneurysms and autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* 1996; 7(11):2483–2486.
25. Chapman, A.B., Gabow, P.A. Hypertension in autosomal dominant polycystic kidney disease. *Kidney Int. Suppl*. 1997; 61:S71–S73.
26. Doulton, T.W., Saggar-Malik, A.K., He, F.J., et al. The effect of sodium and angiotensin-converting enzyme inhibition on the classic circulating renin-angiotensin system in autosomal-dominant polycystic kidney disease patients. *J. Hypertens.* 2006; 24(5):939–945.
27. Nutahara, K., Higashihara, E., Horie, S., et al. Calcium channel blocker versus angiotensin II receptor blocker in autosomal dominant polycystic kidney disease. *Nephron Clin. Pract*. 2005; 99(1):c18–c23.
28. D'Angelo, A., Mioni, G., Ossi, E., Lupo, A., Valvo, E., Maschio, G. Alterations in renal tubular sodium and water transport in polycystic kidney disease. *Clin. Nephrol*. 1975; 3(3):99–105.
29. Grampsas, S.A., Chandhoke, P.S., Fan, J., et al. Anatomic and metabolic risk factors for nephrolithiasis in patients with autosomal dominant polycystic kidney disease. *Am. J. Kidney Dis*. 2000; 36(1):53–57.
30. Torres, V.E., Wilson, D.M., Hattery, R.R., Segura, J.W. Renal stone disease in autosomal dominant polycystic kidney disease. *Am. J. Kidney Dis*. 1993; 22(4):513–519.
31. Grantham, J.J., Torres, V.E., Chapman, A.B., et al. Volume progression in polycystic kidney disease. *N. Engl. J. Med.* 2006; 354(20):2122–2130.
32. Rule, A.D., Torres, V.E., Chapman, A.B., et al. Comparison of methods for determining renal function decline in early autosomal dominant polycystic kidney disease: The consortium of radiologic imaging studies of polycystic kidney disease cohort. *J. Am. Soc. Nephrol*. 2006; 17(3):854–862.
33. Torra, R., Badenas, C., Perez-Oller, L., et al. Increased prevalence of polycystic kidney disease type 2 among elderly polycystic patients. *Am. J. Kidney Dis.* 2000; 36(4):728–734.
34. Li, A., Davila, S., Furu, L., et al. Mutations in PRKCSH cause isolated autosomal dominant polycystic liver disease. *Am. J. Hum. Genet.* 2003; 72(3):691–703.
35. Grunfeld, J.P., Albouze, G., Jungers, P., et al. Liver changes and complications in adult polycystic kidney disease. *Adv. Nephrol. Necker Hosp.* 1985; 14:1–20.
36. D'Agata, I.D., Jonas, M.M., Perez-Atayde, A.R., Guay-Woodford, L.M. Combined cystic disease of the liver and kidney. *Sem. Liver Dis.* 1994; 14(3): 215–228.
37. Soravia, C., Mentha, G., Giostra, E., Morel, P., Rohner, A. Surgery for adult polycystic liver disease. *Surgery* 1995; 117(3):272–275.
38. Pirenne, J., Aerts, R., Yoong, K., et al. Liver transplantation for polycystic liver disease. *Liver Transplant.* 2001; 7(3):238–245.
39. Huston, J., III, Torres, V.E., Sullivan, P.P., Offord, K.P., Wiebers, D.O. Value of magnetic resonance angiography for the detection of intracranial aneurysms

in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol*. 1993; 3(12):1871–1877.
40. Chapman, A.B., Rubinstein, D., Hughes, R., et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. *N. Engl. J. Med*. 1992; 327(13):916–920.
41. Schrier, R.W., McFann, K.K., Johnson, A.M. Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease. *Kidney Int.* 2003; 63:678–685.
42. Torres, V.E. Therapies to slow polycystic kidney disease. *Nephron Exp. Nephrol.* 2004; 98(1):e1–e7.
43. Dunnill, M.S., Millard, P.R., Oliver, D. Acquired cystic disease of the kidneys: A hazard of long-term intermittent maintenance haemodialysis. *J. Clin. Pathol*. 1977; 30(9):868–877.
44. Choyke, P.L. Acquired cystic kidney disease. *Eur. Radiol.* 2000; 10(11): 1716–1721.
45. Costa, M.Z., Bacchi, C.E., Franco, M. Histogenesis of the acquired cystic kidney disease: An immunohistochemical study. *Appl. Immunohistochem. Mol. Morphol*. 2006; 14(3):348–352.
46. Levine, E., Grantham, J.J., Slusher, S.L., Greathouse, J.L., Krohn, B.P. CT of acquired cystic kidney disease and renal tumors in long-term dialysis patients. *Am. J. Roentgenol*. 1984; 142(1):125–131.
47. Truong, L.D., Choi, Y.J., Shen, S.S., Ayala, G., Amato, R., Krishnan, B. Renal cystic neoplasms and renal neoplasms associated with cystic renal diseases: Pathogenetic and molecular links. *Adv. Anat. Pathol*. 2003; 10(3):135–159.
48. Christodoulou, K., Tsingis, M., Stavrou, C., et al. Chromosome 1 localization of a gene for autosomal dominant medullary cystic kidney disease. *Hum. Mol. Genet*. 1998; 7(5):905–911.
49. Scolari, F., Puzzer, D., Amoroso, A., et al. Identification of a new locus for medullary cystic disease, on chromosome 16p12. *Am. J. Hum. Genet*. 1999; 64(6):1655–1660.
50. Rampoldi, L., Caridi, G., Santon, D., et al. Allelism of MCKD, FJHN and GCKD caused by impairment of uromodulin export dynamics. *Hum. Mol. Genet*. 2003; 12(24):3369–3384.
51. Cameron, J.S. Medullary sponge kidney. In *Oxford Textbook of Clinical Nephrology*, A. Davison, J.S. Cameron, J.P. Grünfeld, C. Ponticelli, E. Ritz, C.G. Winearls, and C. Van Ypersele, eds. Oxford: Oxford University Press. 2005; pp. 2495–2501.
52. Tessitore, G..,, D'Angelo, A., et al. Medullary sponge kidney and hyperparathyroidism—A puzzling association. *Am. J. Nephrol*. 1982; 2(2):77–84.
53. Pabico, R.C., McKenna, B.A., Freeman, R.B. Renal tubular dysfunction in patients with cystic disease of the kidneys. *Urology* 1998; 51(5A Suppl):156–160.
54. Gambaro, G., Feltrin, G.P., Lupo, A., Bonfante, L., D'Angelo, A., Antonello, A. Medullary sponge kidney (Lenarduzzi-Cacchi-Ricci disease): A Padua Medical School discovery in the 1930s. *Kidney Int*. 2006; 69(4):663–670.
55. Nahm, A.M., Ritz, E. The renal sinus cyst—The great imitator. *Nephrol. Dial. Transplant* 2000; 15(6):913–914.
56. Timmons, J.W., Jr., Malek, R.S., Hattery, R.R., Deweerd, J.H. Caliceal diverticulum. *J. Urol.* 1975; 114(1):6–9.

20

Renal Vasculitis in the Elderly

David Jayne

Introduction

Vasculitis in the kidney typically presents with the syndrome of rapidly progressive glomerulonephritis and results in 4% of the cases of renal failure in those over 60 years old [1]. The typical renal lesion of vasculitis is a glomerular capillaritis leading to a segmental, necrotizing glomerulonephritis with epithelioid crescent formation [2]. Less frequently, this lesion occurs with arteritis of extra-glomerular vessels in the kidney, while a large-vessel arteritis of the renal artery is rare. It has become increasingly clear that renal vasculitis is more common with age and that this disease is probably the most common primary cause of renal failure in the elderly. Because untreated renal vasculitis progresses to end-stage renal disease, and steroid and immunesuppressive therapy can improve the outcome, early diagnosis and institution of therapy are particularly important. A major current dilemma is the toxicity of this treatment and its contribution to morbidity and mortality, which are increased in the elderly. There is a clear advantage in early diagnosis when less intense treatment is effective, on careful monitoring of therapy to minimize adverse recent risk, and in the evaluation of safer alternative drugs.

Classification of Renal Vasculitis

Vasculitis occurs as a primary disease or secondary to drug reactions, infections, or malignancy. It may also occur as a component of another auto-inflammatory disease such as rheumatoid arthritis, systemic lupus erythematosus (SLE), or Behcet's disease. This situation is complicated because apparent primary systemic vasculitic disorders, especially microscopic polyangiitis associated with autoantibodies to neutrophil cytoplasmic antigens (ANCA), may be triggered by causes of secondary vasculitis. This has been well described for both infective endocarditis and rheumatoid arthritis. Reports of secondary renal vasculitis frequently involve the elderly, but this has not been systematically studied [3].

The terminology of the primary vasculitic disorders has been defined by consensus statements, which have been classified according to the predominant vessel size involved and the presence or absence of ANCA (Table 20.1) [4]. Renal vasculitis is a common feature of the small vessel vasculitides, whether or not ANCA is present. Wegener's granulomatosis and microscopic

Table 20.1 The Classification of Primary Systemic Vasculitis According to the Predominant Size of Blood Vessel Involvement and the Presence or Absence of ANCA.

Predominant Size of Vessel Involved	Usually ANCA-Positive	Usually ANCA-Negative
Small	Wegener's granulomatosis Microscopic polyangiitis Renal-limited vasculitis	Henoch–Schönlein purpura Cryoglobulinaemia
Medium	Churg–Strauss angiitis	Polyarteritis nodosa Kawasaki disease
Large		Giant cell arteritis Takayasu's arteritis

polyangiitis have been grouped together as "ANCA-associated vasculitis"; a category of renal-limited vasculitis has also been described either alone or as a subgroup of microscopic polyangiitis. When it occurs in Churg–Strauss angiitis, the features are similar to those in microscopic polyangiitis; in polyarteritis nodosa, a glomerulonephritis would reassign the diagnosis to microscopic polyangiitis and significant. Both giant cell arteritis and Takayasu's arteritis involve the aorta and its major branches, but the latter is rarely described in the elderly. Large-vessel arteritis in the elderly is ascribed to giant cell arteritis, but when renal involvement has occurred, there has usually been evidence of a concurrent small-vessel vasculitis [5].

For patients presenting with the syndrome of rapidly progressive glomerulonephritis, deteriorating renal function, and a crescentic glomerulonephritis on biopsy, classification depends on the nature of the glomerular immune deposits and the presence of circulating antibodies (Table 20.2). Linear immune fluorescence and anti-glomerular basement membrane antibodies are characteristic of anti-GBM disease; speckled deposits of immunoglobulin and complement imply an immune complex process such as SLE or Henoch–Schönlein purpura, while a pauci-immune appearance is associated with circulating ANCA and a diagnosis of vasculitis. An overlap syndrome with both anti-GBM disease and ANCA-associated vasculitis is found in 30% of anti-GBM positive patients and is more common in older patients with anti-GBM disease [6]. Up to 30% of renal biopsies in ANCA vasculitis have speckled immune deposits of uncertain diagnostic significance. Finally, some 10% of pauci-immune crescentic nephritis patients are ANCA-negative, and this group has previously been termed as having "idiopathic rapidly progressive or crescentic glomerulonephritis" [7].

Epidemiology of Vasculitis

The incidence of primary systemic vasculitis is approximately 40/million/year, with the ANCA-associated group comprising 15–20/million/year [8]. An apparent increasing incidence has been explained by improved detection, especially in the elderly; where long-term epidemiology studies have been performed, no increase in incidence has been seen. Prevalence rates of ANCA vasculitis range from 90–200/million. Both Wegener's granulomatosis and microscopic polyangiitis have an increased incidence with age, being very

Table 20.2 The Classification of Rapidly Progressive Glomerulonephritis According to Renal Immune Fluorescence Findings and Circulating Serological Abnormalities

	Renal Immunofluorescence	Compatible Serology	Diagnosis
Type 1	Linear	Anti-GBM antibodies	Anti-GBM disease
Type II	Granular	ANA, anti-dsDNA antibodies	Systemic lupus erythematosus
		Cryoglobulins	Cryoglobulinaemia
		Low complement levels	Henoch–Schönlein purpura
Type III	"Pauci-immune" (absent, or scanty deposits)	ANCA	Vasculitis

rare in children. Where the association with age in Wegener's granulomatosis is similar for those aged 50–60 and in older age groups, the incidence of microscopic polyangiitis continues to rise and is highest in the oldest age groups (Figure 20.1). Renal involvement is more common in microscopic polyangiitis, at over 90%, and in Wegener's granulomatosis the proportion with renal involvement increases with age [9]. An analysis from patients entered into prospective therapeutic trials has indicated that renal function at diagnosis is lower in older patients, indicating that not only is renal involvement more frequent, but it is more aggressive (Figure 20.2) [10]. The age association implies an etiological contribution of an aging immune system and the possible involvement of environmental factors. Silica exposure

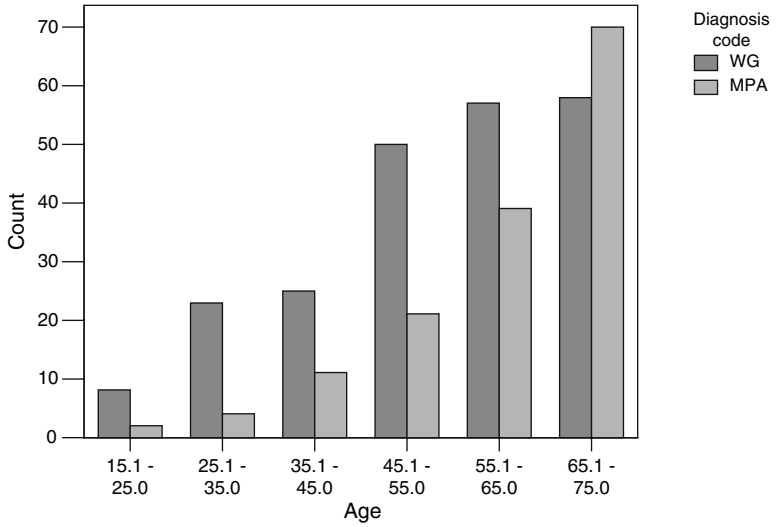

Fig. 20.1 Frequency of Wegener's granulomatosis and microscopic polyangiitis according to the patient's age at diagnosis. Number of patients for each decade enrolled into three clinical trials.
(*Source:* Data from the European Vasculitis Study Group [26].)

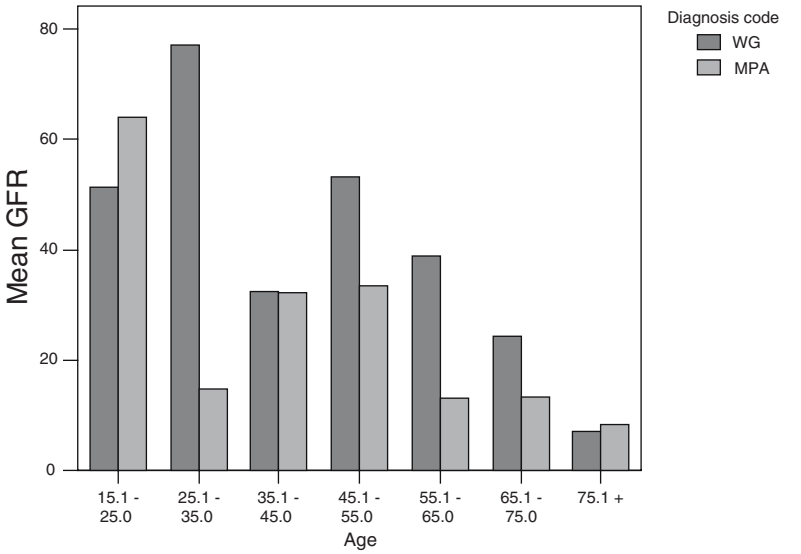

Fig. 20.2 Glomerular filtration rate (mean) at diagnosis according to the patient's age. (*Source:* Data from the European Vasculitis Study Group [26].)

increases the incidence of microscopic polyangiitis, and an association with farming, especially with animals, has also been demonstrated. The relative frequencies of Wegener's granulomatosis and microscopic polyangiitis are influenced by latitude, with Wegener's granulomatosis being more frequent in colder climates in both the North and South hemispheres [8]. In addition, there are ethnic differences, with Wegener's granulomatosis being less common in eastern Asian and black populations. The lack of a major immunogenetic contribution and the late age of onset differentiate ANCA-associated autoimmunity from other autoantibody-associated autoimmune diseases.

As a consequence of the increased incidence with age, the proportion of kidney biopsies displaying a crescentic nephritis rises from 5% in those under 60 years to over 11% in those over 60 years of age [11].

Pathogenesis

ANCA-associated vasculitis predominantly affects small blood vessels, with glomerular and alveolar capillaritis accounting for renal and pulmonary vasculitis, the most common manifestations in the elderly. The pathogenetic role of ANCA remains controversial, because this pathology can occur without circulating ANCA, immune deposits are rarely present, and ANCA can persist without disease activity. Experimental studies have demonstrated unequivocally that ANCA can induce neutrophil activation and cytokine release and mediate endothelial cytotoxicity [12]. Both spontaneous and induced animal models have confirmed the pathogenicity of ANCA [13]. ANCA with specificity for myeloperoxidase (MPO-ANCA) is more common in the elderly than proteinase 3 ANCA [14]. MPO-ANCA is also found in vasculitis associated with environmental exposure or occurring secondary to chronic infections. This points to a greater role of environmental stimuli for vasculitis occurring

in the elderly. In contrast, genetic factors may be less important in the elderly, as the association of polymorphisms of alpha 1 anti-trypsin and Fc gamma R III with vasculitis is only found with PR3-ANCA-positive patients. Dysregulated antigen presentation occurs in Wegener's granulomatosis, and persistent circulating T cell and B cell activation are typically present [15]. Bacterial antigens have been proposed to play a role in Wegener's granulomatosis, possibly through molecular mimicry, but the lack of an immunogenetic association implies that environmental drives are likely to be numerous and varied between patients. The inflammatory infiltrate at vasculitic foci is neutrophil-rich, and interventions that deplete neutrophils, including experimental chemokine blockade or the drugs cyclophosphamide and deoxyspergualin, are effective therapies [16]. Autoantibodies to endothelial antigens are found in over 50% of vasculitis patients, but their targets have not been defined and their contribution to pathogenesis is unclear [17]. Wegener's granulomatosis is characterized by poorly formed granulomata in a perivascular distribution with frequent giant cells. Granulomatous disease appears less common in the elderly and capillaritis predominates [9].

Presentation and Diagnosis of Renal Vasculitis

The absence of specific symptoms of renal disease results in diagnostic delay, and patients with renal limited vasculitis present with more advanced renal failure than those with extrarenal disease [18, 19]. However, there is usually a prodromal phase of several months with constitutional symptoms such as fever, night sweats, polymyalgia, and weight loss. During this phase, urinary abnormalities will be present and should be sought in all elderly patients with unexplained illness. Without early detection, for patients presenting with symptoms and signs of uremia, the average delay from onset of symptoms is 6 to 9 months and may be longer in the elderly [14, 19]. Glomerular hematuria and proteinuria are always present in renal vasculitis but may be confused with prostatic disease or urinary tract infection. Atypical presentations including "failure to thrive" and unexpected, asymptomatic renal impairment may be more common in the elderly.

The diagnosis depends on the triad of clinical features, serology, and histology. ANCA positivity confirmed by a positive proteinase 3 ANCA or myeloperoxidase ANCA has a high predictive value for the diagnosis of vasculitis in the absence of another chronic inflammatory process. A negative ANCA does not exclude the diagnosis of vasculitis; immune-complex causes including SLE should be considered, as they may be missed in the elderly. Renal histology is essential in the absence of ANCA positivity in order to make a secure diagnosis. There is a debate as to the diagnostic value of renal biopsy when the ANCA is positive and clinical presentation is typical. However, false-positive ANCAs have been reported in myeloma, atheroembolic disease, and chronic infections, so the absence of biopsy confirmation increases the risk of an incorrect diagnosis. In practice, the start of treatment need not be delayed for a biopsy result.

The typical renal biopsy feature in ANCA-associated vasculitis is a pauci-immune necrotizing glomerulonephritis with crescent formation [2]. The proportion of affected glomeruli in a biopsy is predictive of outcome as is the severity of tubulointerstitial fibrosis [20]. Microscopic polyangiitis is

associated with more severe biopsy changes, with more evidence of chronicity and scarring [2]. In Wegener's granulomatosis, acute tubular changes are more frequent, scarring is less apparent, and the prognosis is better. There has been debate as to whether treatment should be guided by histological features and over the suggestion that those with advanced, chronic changes should receive less aggressive treatment in view of a poorer prognosis. This has not been examined in an interventional study, and the relatively poor correlation between histological changes and renal outcome for individual patients argues against adjusting treatment according to the biopsy's severity.

Attempts have been made to subgroup patients with vasculitis according to the extent and severity of disease, and several systems have been developed. They include the "five-factor score," which identified factors predictive of a poor prognosis, and comprised proteinuria, impaired renal function, cardiac or gastrointestinal vasculitis, and central nervous system vasculitis; the disease extent index, a numerical score of the number of systems involved; generalized or limited Wegener's granulomatosis based on the presence of predefined "major" items of vasculitis activity using an adapted Birmingham Vasculitis Activity Score (BVAS) [21]. The European Vasculitis study group (EUVAS) has subclassified ANCA vasculitis at presentation into three groups: early systemic, generalized, and severe, according to the presence and severity of renal disease. In three concurrent studies, the average age of each group rose with the severity of the vasculitis: early systemic at 51 years; generalized at 56 years; and severe renal at 66 years [22, 23]. Elderly patients with Wegener's granulomatosis are more likely to have atypical or delayed presentations, have less severe ear nose and throat disease, and are less likely to develop endobronchial disease, yet renal vasculitis is more aggressive [9,24]. Renal vasculitis is more common in the elderly, with ANCA-associated vasculitis being present in 95% of the cases [14]. Pulmonary involvement, typically with radiological infiltrates, both in Wegener's granulomatosis and in microscopic polyangiitis, is also more frequent in the elderly, occurring in 50–76%, probably reflecting alveolar capillaritis [14,19]. An overlap between microscopic polyangiitis and idiopathic pulmonary fibrosis has recently been described, and unusual vasculitic presentations in the elderly diagnosed as pulmonary fibrosis have been reported [25].

Approaches to Therapy

Without therapy, renal vasculitis in ANCA vasculitides will usually progress to end-stage renal disease. Progression of renal disease in rarer vasculitides, such as in Henoch–Schönlein purpura, has been less well studied and the role of therapy less established. Current regimens aim to suppress manifestations of disease activity and achieve a "remission" in order to avoid further vital organ damage, rescue renal function, and reduce constitutional disturbance [26]. The toxicity of high corticosteroid doses and cyclophosphamide has been accepted to achieve this aim, with lower steroid doses and an alternative immunesuppressive, such as azathioprine, used to maintain remission [23]. The major early risk of this treatment is sepsis, often associated with neutropenia, which increases the septic risk more than fourfold [19]. A causal sequence of cyclophosphamide-induced neutropenia, sepsis, and death has been established and cyclophosphamide protocols amended to minimize the risk of

neutropenia [18,26]. Elderly patients are much more susceptible to the myelosuppressive effects of cyclophosphamide and consequently have a higher rate of severe infection and infective death [19]. Impaired neutrophil function in the elderly also contributes to susceptibility to infection. Furthermore, elderly patients are less tolerant of steroid-related side effects including fluid retention, hypertension, diabetes, and steroid-induced bone disease.

The combination of more severe disease and higher rates of treatment toxicity in the elderly presents the physician with a major challenge. If treatment of renal vasculitis is unsuccessful and the patient progresses to end-stage renal failure, mortality is particularly high, over 50% after one year [18,19]. The use of intravenous pulsed cyclophosphamide appears safer than daily oral cyclophosphamide, with a lower incidence of neutropenic sepsis and lower cumulative cyclophosphamide exposure [27]. In retrospect, a mistake that has previously been made is to use higher cyclophosphamide doses, 2–5 mg/kg/day of oral cyclophosphamide, for those with more severe disease [28]. Results in the elderly, with advanced renal disease, were particularly poor with this approach, and recent protocols have reduced dosage for age and renal impairment, in view of the renal excretion of active metabolites, and have reduced severe adverse event rates, even in the elderly, to below 20% [19,26,29]. Corticosteroid dosing has not been examined in the elderly, and current protocols still use prolonged high-dose oral prednisolone. When used in combination with cyclophosphamide, steroid dose appears closely related to infective risk, and there is a trend toward the use of short-term, high-dose intravenous pulsed methylprednisolone and more steeply tapering oral corticosteroid usage.

Plasma exchange has been shown, in small studies, to improve chances of renal recovery for patients with ANCA-associated vasculitis presenting in renal failure [30]. Common complications relate to the need for intravenous access, which would already be in place for patients requiring renal support. There does not appear to be particular problems with using plasma exchange in the elderly, and this intervention offers the opportunity of a rapid therapeutic effect. Whether plasma exchange permits reduced steroid or cyclophosphamide exposure or is useful in less severe renal, or severe nonrenal, presentations is not known.

For less aggressive presentations, methotrexate has been demonstrated to be as good as cyclophosphamide for remission induction and is probably safer [22]. Both azathioprine and methotrexate are routinely used to prevent relapse after induction therapy with cyclophosphamide, and their efficacy appears equivalent. The duration of induction therapy depends on the speed of response; some 75% remit by 3 months and 90% by 6 months. True refractoriness to cyclophosphamide is rare; more commonly it is not tolerated or is withdrawn due to sepsis.

Although cyclophosphamide can be withdrawn when disease control is achieved, the duration of subsequent immunesuppressive therapy that is required to prevent relapse is not known. Some 50% of patients with renal vasculitis will relapse by 5 years, and relapse of renal vasculitis increases the risk of progression to end-stage renal disease: This risk needs to be balanced against the anticipated complications of long-term therapy [18]. Factors predictive of relapse include reduction or withdrawal of therapy, diagnosis of Wegener's granulomatosis as compared to microscopic polyangiitis, and ANCA status

after remission induction therapy [31]. There has been controversy as to how useful the ANCA test is in disease monitoring; this is due in part to differences in ANCA testing methodology and to the fact that immunesuppressive therapy dissociates disease activity from ANCA levels. However, it has now been clearly shown that ANCA positivity six months after the onset of therapy, or the presence of a positive ANCA when treatment is withdrawn, is strongly predictive of relapse [32]. This association is of particular value in the elderly when it is more desirable to minimize therapy and should allow safer withdrawal of therapy within 1 year in over 50% of elderly patients.

Alternative Therapies for Renal Vasculitis

The high risk of severe adverse events of current therapy in the elderly has focused attention on the evaluation of alternative therapies. Intravenous immunoglobulin reduces levels of vasculitic activity in persisting or relapsing vasculitis, reduces ANCA production, and, as sole therapy, has led to initial disease control in new patients with ANCA-associated vasculitis presenting with rapidly progressive glomerulonephritis [33, 34]. Tumor necrosis factor (TNF) blockade with the soluble 75kd TNF receptor etanercept was not effective at preventing relapse in Wegener's granulomatosis in a placebo-controlled trial, but the addition of infliximab to induction protocols for renal vasculitis has been safe, has permitted reduced steroid exposure, and requires further evaluation to assess whether it improves renal recovery [35, 36]. T cell depletion with anti-thymocyte globulin or alemtuzumab (CAMPATH 1-H) has led to remissions in refractory disease but carries a high risk of infective mortality in those over 60 years or those with uremia. Rituximab is a monoclonal antibody targeting CD20 on B cells developed for non-Hodgkin's lymphoma. It has shown surprising efficacy in several small prospective studies in refractory vasculitis and appears safe [37]. Immunesuppressives have been safely withdrawn after rituximab, and retreatment at the time of ANCA rise or relapse is effective. Thus, B cell depletion carries the hope of improving control in vasculitis while reducing the risks associated with immune suppression. It is unclear to what extent this will benefit the elderly with renal vasculitis when much of the treatment-related mortality occurs in the first 3 months. The therapeutic effect of rituximab is delayed, and initial therapy with high-dose steroids and cyclophosphamide may still be required.

Alternative immunesuppressives including mycophenolate mofetil, leflunomide, and deoxyspergualin have been assessed for remission maintenance or the treatment of refractory disease. Current data with mycophenolate mofetil and leflunomide are inconclusive, but both agents may be useful alternatives to azathioprine or methotrexate for specific patients. Deoxyspergualin has a novel and incompletely understood mode of action and appears in preliminary studies to be at least as effective as cyclophosphamide [16].

The Outcome of Renal Vasculitis

Creatinine at presentation remains the strongest predictor of both patient and renal survival for vasculitis in the elderly [20, 38]. Those presenting in renal failure have a particularly poor outcome, and earlier diagnosis is likely

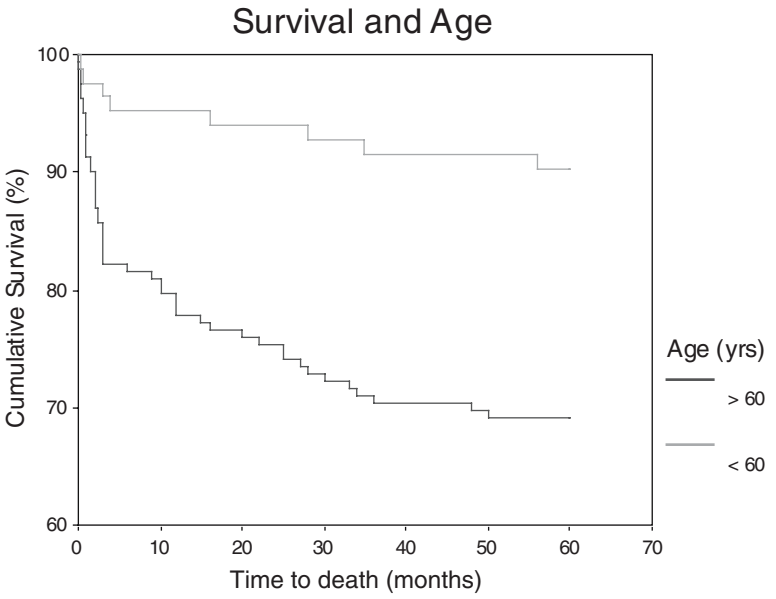

Fig. 20.3 Patient survival according age above or below 60 years for patients presenting with renal vasculitis in London between 1995 and 2000.
(*Source:* Booth, A.D., Almond, M.K., Burns, A., et al. Outcome of ANCA-associated renal vasculitis: A 5-year retrospective study. *Am. J. Kidney Dis.* 2003; 41:776–784.)

to improve outcome more than improved therapies. Elderly patients have considerably higher early mortality, with rates of 36% and 50% reported in the early 1990s. In a large audit of renal vasculitis between 1995 and 2000, mortality at 1 year was 5% for those under 60 and 23% for those over 60, and rose to 44% for those over 70 (Figure 20.3) [18]. In part this is due to more advanced renal disease with more chronicity on renal biopsy, but intolerance of therapy and infections are major contributors. Dual positive presentations of anti-GBM disease and vasculitis are more common in the elderly and are associated with particularly aggressive pulmonary and renal disease and poor outcomes [39].

There have been fewer long-term studies of renal vasculitis, but there is the impression that once renal vasculitis is controlled and provided relapse is avoided, renal function can remain stable for many years [18]. There is probably an increased cardiovascular risk during longer follow-up, which may relate to more widespread vascular injury at the time of active vasculitis or the consequences of chronic renal failure and long-term medication. Angiotensin-converting enzyme antagonists may improve renal outcome, but they require further study. Malignancy rates at 5 years are 10–15%. It is unclear whether this is a genuine increase from the expected risk or a consequence of the disease or its therapy. Vasculitis can also occur in the context of malignancy. It has recently been appreciated that thromboembolic disease is particularly common in the few months after diagnosis of vasculitis, occurring in 15% in one study [35].

Relapse of vasculitis is less common in the elderly than in younger patients, possibly due to the lower proportion of patients with Wegener's granulomatosis and granulomatous disease that is more refractory to therapy [9].

Consequently, immune suppression does not necessarily have to be so prolonged once remission has been achieved. Follow-up should remain lifelong because late relapse occurs with potentially devastating consequences.

Summary

Vasculitis is increasingly being recognized as a disease of the elderly and is now a common primary cause of renal failure. Diagnosis is often delayed with severe consequences on the risks of death and end-stage renal failure. Strategies to improve early detection of vasculitis, using urine testing and the ANCA assay, are required in combination with increased awareness among primary care physicians. The treatment of vasculitis in the elderly differs little from that of younger age groups, yet the morbidity and mortality associated with therapy are considerably higher. Treatment protocols have been better evaluated by randomized controlled trials supported by collaborative research networks in Europe and the United States [26, 35]. There have been modest improvements in reducing the toxicity of therapy with recent protocols that reduce cyclophosphamide dosing according to age, but newer, safer, agents are required. B cell depletion is the most promising approach to improve medium- to longer-term therapy, but with the possible exception of TNF alpha blockade and intravenous immunoglobulin, there are no new approaches for induction therapy. Elderly patients with vasculitis tolerate end-stage renal failure particularly poorly, which places an emphasis on rapid, effective induction therapy, and plasma exchange is attracting renewed interest for this indication. Ongoing cohort studies are exploring the late consequences of vasculitis, and strategies to reduce the increased cardiovascular and malignancy risks are likely to be evaluated in the future.

References

1. Kohli, H.S., Bhat, A., Aravindan, et al. Spectrum of renal failure in elderly patients. *Int. Urol. Nephrol*. 2007; 23:23.
2. Hauer, H.A., Bajema, I.M., van Houwelingen, H.C., et al. Renal histology in ANCA-associated vasculitis: Differences between diagnostic and serologic subgroups. *Kidney Int.* 2002; 61:80–89.
3. Ulm, S., Hummel, M., Emig, M., et al. Leukocytoclastic vasculitis and acute renal failure after influenza vaccination in an elderly patient with myelodysplastic syndrome. *Onkologie* 2006; 29:470–472. Epub 2006 Sep 27.
4. Jennette, J.C., Falk, R.J., Andrassy, K., et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* 1994; 37:187–192.
5. Muller, E., Schneider, W., Kettritz, U., Schmidt, W.A., Luft, F.C., Gobel, U. Temporal arteritis with pauci-immune glomerulonephritis: A systemic disease. *Clin. Nephrol*. 2004; 62:384–386.
6. Jayne, D.R., Marshall, P.D., Jones, S.J., Lockwood, C.M. Autoantibodies to GBM and neutrophil cytoplasm in rapidly progressive glomerulonephritis. *Kidney Int*. 1990; 37:965–970.
7. Eisenberger, U., Fakhouri, F., Vanhille, P., et al. ANCA-negative pauci-immune renal vasculitis: Histology and outcome. *Nephrol. Dial. Transplant* 2005; 20: 1392–1399. Epub 2005 Apr 26.
8. Watts, R.A., Scott, D.G. Epidemiology of the vasculitides. *Sem. Respir. Crit. Care Med.* 2004; 25:455–464.

9. Krafcik, S.S., Covin, R.B., Lynch, J.P., III, Sitrin, R.G. Wegener's granulomatosis in the elderly. *Chest* 1996; 109:430–437.
10. Vassallo, M., Shepherd, R.J., Iqbal, P., Feehally, I. Age-related variations in presentation and outcome in Wegener's granulomatosis. *J. Roy. Coll. Phys. Lond*. 1997; 31:396–400.
11. Rychlik, I., Jancova, E., Tesar, V., et al. The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994–2000. *Nephrol. Dial. Transplant* 2004; 19:3040–3049. Epub 2004 Oct 26.
12. Hewins, P., Savage, C.O. ANCA and neutrophil biology. *Kidney Blood Press. Res.* 2003; 26:221–225.
13. Xiao, H., Heeringa, P., Hu, P., et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J. Clin. Invest*. 2002; 110:955–963.
14. Wang, Y., Zhao, M.H., Yu, J., et al. The clinical and pathological characteristics of Chinese elderly patients with anti-neutrophil cytoplasmic autoantibodies associated small vessel vasculitis. *Exp. Gerontol.* 2004; 39:1401–1405.
15. Abdulahad, W.H., van der Geld, Y.M., Stegeman, C.A., Kallenberg, C.G. Persistent expansion of CD4+ effector memory T cells in Wegener's granulomatosis. *Kidney Int*. 2006; 70:938–947. Epub 2006 Jul 12.
16. Birck, R., Warnatz, K., Lorenz, H.M., et al. 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: A six-month open-label trial to evaluate safety and efficacy. *J. Am. Soc. Nephrol*. 2003; 14:440–447.
17. Frampton, G., Jayne, D.R., Perry, G.J., Lockwood, C.M., Cameron, J.S. Autoantibodies to endothelial cells and neutrophil cytoplasmic antigens in systemic vasculitis. *Clin. Exp. Immunol*. 1990; 82:227–232.
18. Booth, A.D., Almond, M.K., Burns, A., et al. Outcome of ANCA-associated renal vasculitis: A 5-year retrospective study. *Am. J. Kidney Dis*. 2003; 41:776–784.
19. Harper, L., Savage, C.O. ANCA-associated renal vasculitis at the end of the twentieth century—A disease of older patients. *Rheumatology* (Oxford) 2005; 44:495–501. Epub 2004 Dec 21.
20. Hauer, H.A., Bajema, I.M., Van Houwelingen, H.C., et al. Determinants of outcome in ANCA-associated glomerulonephritis: A prospective clinico-histopathological analysis of 96 patients. *Kidney Int*. 2002; 62:1732–1742.
21. Merkel, P.A., Seo, P., Aries, P., et al. Current status of outcome measures in vasculitis: Focus on Wegener's granulomatosis and microscopic polyangiitis. Report from OMERACT 7. *J. Rheumatol*. 2005; 32:2488–2495.
22. De Groot, K., Rasmussen, N., Bacon, P.A., et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 2005; 52:2461–2469.
23. Jayne, D., Rasmussen, N., Andrassy, K., et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N. Engl. J. Med*. 2003; 349:36–44.
24. Le Thi Huong, D., Wechsler, B., Piette, J.C., et al. [Wegener's granulomatosis in elderly subjects. 37 cases.] [in French] *Presse Med.* 1988; 17:2379–2382.
25. Nada, A.K., Torres, V.E., Ryu, J.H., Lie, J.T., Holley, K.E. Pulmonary fibrosis as an unusual clinical manifestation of a pulmonary-renal vasculitis in elderly patients. *Mayo Clin. Proc.* 1990; 65:847–856.
26. Jayne, D.R., Rasmussen, N. Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: Initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. *Mayo Clin. Proc*. 1997; 72:737–747.
27. de Groot, K., Adu, D., Savage, C.O. The value of pulse cyclophosphamide in ANCA-associated vasculitis: Meta-analysis and critical review. *Nephrol. Dial. Transplant* 2001; 16:2018–2027.

28. Hoffman, G.S., Kerr, G.S., Leavitt, R.Y., et al. Wegener granulomatosis: An analysis of 158 patients. *Ann. Intern. Med.* 1992; 116:488–498.
29. Haubitz, M., Bohnenstengel, F., Brunkhorst, R., Schwab, M., Hofmann, U., Busse, D. Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. *Kidney Int.* 2002; 61:1495–1501.
30. Pusey, C.D., Rees, A.J., Evans, D.J., Peters, D.K., Lockwood, C.M. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int.* 1991; 40:757–763.
31. Boomsma, M.M., Stegeman, C.A., van der Leij, M.J., et al. Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: A prospective study. *Arthritis Rheum.* 2000; 43:2025–2033.
32. Sanders, J.S., Huitma, M.G., Kallenberg, C.G., Stegeman, C.A. Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatology* (Oxford) 2006; 45:724–729. Epub 2006 Jan 6.
33. Jayne, D.R., Chapel, H., Adu, D., et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *Quar. J. Med*. 2000; 93:433–439.
34. Ito-Ihara, T., Ono, T., Nogaki, F., et al. Clinical efficacy of intravenous immunoglobulin for patients with MPO-ANCA-associated rapidly progressive glomerulonephritis. *Nephron Clin. Pract*. 2006; 102:c35–42. Epub 2005 Sep 19.
35. Etanercept plus standard therapy for Wegener's granulomatosis. *N. Engl. J. Med*. 2005; 352:351–361.
36. Booth, A., Harper, L., Hammad, T., et al. Prospective study of TNF alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J. Am. Soc. Nephrol*. 2004; 15:717–721.
37. Smith, K.G., Jones, R.B., Burns, S.M., Jayne, D.R. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. *Arthritis Rheum*. 2006; 54:2970–2982.
38. de Lind van Wijngaarden, R.A., Hauer, H.A., Wolterbeek, R., et al. Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. *J. Am. Soc. Nephrol.* 2006; 17:2264–2274. Epub 2006 Jul 6.
39. Rutgers, A., Slot, M., van Paassen, P., van Breda Vriesman, P., Heeringa, P., Tervaert, J.W. Coexistence of anti-glomerular basement membrane antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis. *Am. J. Kidney Dis.* 2005; 46:253–262.

21

Acute Renal Failure in the Aged

Carlos G. Musso, José M. López-Novoa, José Carlos Fernandez
and Juan-Florencio Macías-Núñez

Acute Renal Failure: Its Definition and Physiopathology

Acute renal failure (ARF) the generic term for an abrupt and sustained decrease in renal function resulting in inability to maintain the equilibrium of the internal milieu. Despite the absence of a universal definition, it is reasonable to define ARF as an acute and sustained increase in serum creatinine of 0.5 mg/dL if the baseline is less than 2.5 mg/dL, or an increase in serum creatinine by more than 20% if the baseline is more than 2.5 mg/dL [1].

Three mechanisms are involved in the appearance of ARF: diminution of the renal blood flow with preservation of renal *parenchymal* integrity (pre-renal ARF), acute lesions of the renal parenchyma (intrinsic renal ARF), and obstruction of the urinary flow (post-renal ARF) [2]. Pre-renal ARF can be induced by the following situations: intravascular volume depletion, decreased cardiac output, renal vasoconstriction, and impaired autoregulation induced by drugs. Intrinsic ARF can be caused by the compromise of renal vasculature, glomeruli, acute tubular necrosis (ATN), or tubulointerstitial damage.

The pathophysiology of ATN can be divided into three phases: initial, maintenance, and recovery. The initial phase of ischemic ATN refers to a hypothetical period of time during which renal perfusion is compromised to the extent that precipitates intrarenal events that are responsible for persistence of renal dysfunction long after the original cause has been resolved. Maintenance refers to the period of ongoing renal failure that is usually followed by a recovery phase during which the renal injury is repaired and baseline renal function is re-established [3]. Although many of the theories that explain the reduction of GFR in ARF have been known for 50 years, the exact pathogenesis of this syndrome, especially the means by which oligoanuria is sustained, remains unresolved; however, it is clearly multifactorial [4,5]. The current consensus opinion is that three major factors contribute to the profound reduction in GFR that characterizes ATN: tubule injury, *hemodynamic* abnormalities, and intrarenal inflammation. Tubular injury leads to insufficiency by causing "back-leakage" of glomerular filtrate and intratubular obstruction. Intrarenal vasoconstriction and reduction of the ultrafiltration coefficient (Kf) can also directly impair GFR. Most of our knowledge about these factors has been derived from experimental models of ARF, mainly in rodents. These models can be divided into two groups: the hemodynamic models,

which are based on *ischemia* derived from occlusion of the renal artery, and intramuscular injection of glycerine; and the nephrotoxic ones based on the administration of uranile nitrate (UN), mercury bichloride ($HgCl_2$), or aminoglycosides [6].

The main physiopathological aspects of the ARF learned from the above-mentioned studies are the following (Figure 21.1):

1. Reduction of renal blood flow (RBF): The initial phase of $HgCl_2$-induced ARF has a minimal impact upon RBF se RBF undergoes only a 20% reduction while GFR decreases by a further 50% [7]. Moreover, clinical evidence from animals administered UN indicates that, while RBF might return to its original levels within 48 hours, GFR remains depressed and can even diminish further. Ischemic damage provokes vacuolization of endothelial cells and reduces the diameter of renal arterioles, thereby increasing the vascular resistance. However, classical studies indicate that the cellular vacuolization affects the epithelial tubules more than the endothelial vasculature [8]. All these findings suggest that other factors apart from vasoconstriction contribute to the decrease in GFR.
2. Reduction of the ultrafiltration coefficient (Kf): The glomerular Kf decreases during the initial phase of UN-induced ARF. This indicates that changes in glomerular permeability can justify, at least in part, the observed descent of the GFR. Mesangial cell concentration probably contributes to Kf reduction in ARF [9]. It seems that this phenomenon could be secondary to the intrarenal generation of angiotensin II [10].
3. Tubular obstruction: There is some morphological evidence of obstruction of the proximal segment of the nephron during the initial phase of UN-induced ARF. There exists strong morphological evidence of intratubular obstruction after 1 hour of ischemia. It is known that obstruction induces changes in the resistance of preglomerular, glomerular, and postglomerular

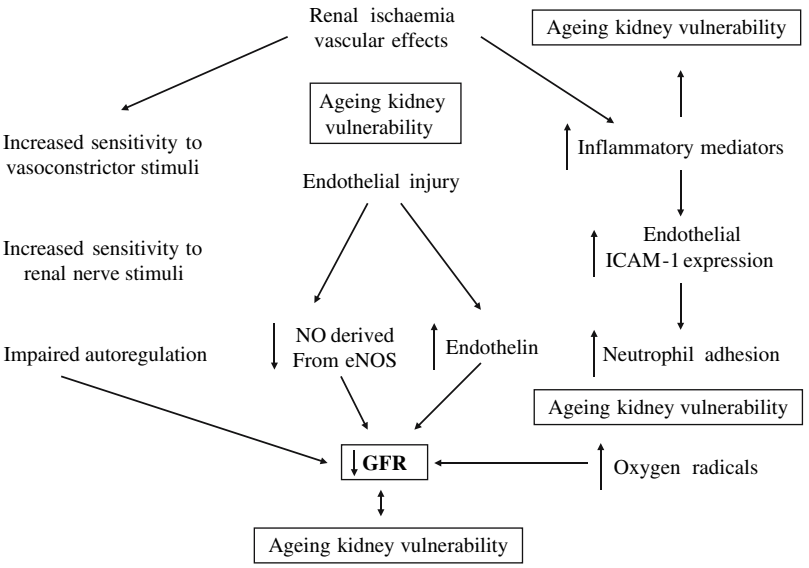

Fig. 21.1 Possible relationships between the instauration of acute tubular necrosis (ATN) and the changes that accompany the physiological aging process.

vessels, which thereby results in an acute increase of glomerular pressure. It is more probable that intratubular obstruction plays a role in the suppression of filtration in the initial phase of ARF than during the maintenance phase [11, 12].

4. Integrins and their role in tubular obstruction: Tubular cells redistribute the integrins on their membranes when they are subjected to oxidative stress; they relocate them from the basal to apical surface. This phenomenon contributes to tubular obstruction in two ways: First, the basal cell surfaces are no longer securely attached to the basement membrane, so cells detach and are shed. Second, once free, the cells are not effectively cleared, as the apical surfaces, full of translocated integrins, adhere inappropriately to other cells that are still fixed in their normal positions. Tamm–Horsfall proteins have also been implicated in tubular obstruction. They contain an amino acid sequence that cell surface integrins use to recognize and bind to other cells. Therefore, they have the ability to bind desquaminated cells and so contribute to tubule cast formation and hence tubular obstruction [13].
5. Interstitial inflammation-leukocyte infiltration and adhesion molecules: Injury due to ischemia and subsequent reperfusion is via an interstitial inflammatory process that involves leukocyte infiltration, edema, and the resultant compromise of microvascular blood flow. The expression of certain adhesion molecules is increased in response to cytokines released by ischemic tissues. These adhesion molecules are necessary for the infiltration of leucocytes. Chemokines, which are involved in the attraction and activation of leucocytes (such as interleukin-1 and TNF-a), have also been implicated in ischemic-reperfusion injury [13].
6. Alterations in intracellular calcium: An increase in the level of unbound intracellular calcium has been noted in the proximal tubules of rat kidneys subjected to hypoxia. Furthermore, cells of this region can be protected from hypoxic damage using calcium chelators to reduce the concentration of free intracellular calcium [13].
7. Calpain enzyme: Levels of intracellular calcium influence the actions of many important enzymes; one of these is calpain, a calcium-dependent cysteine protease. When activated, calpain is involved in the destruction of proteins that play a key role in the interaction between the cytoskeleton of the cells and plasma membrane [13].
8. Oxidant mechanisms: Significant evidence implicates reduced oxygen metabolites in ischemic noxious and immune-mediated tissue damage in ARF [13].
9. Insulin-like growth factors (IGF): After damage to the kidney, whether ischemic or noxious (e.g., radiocontrast dye), production of IGFs is increased, enhanced by both growth hormone and epidermal growth factor (EGF). Exogenous IGF-I has been shown to improve recovery time in rat kidneys following ischemia [13].
10. Epidermal growth factors (EGF) and transforming growth factor-α (TGF-α): They act on the same receptor, and EGF has been shown to be a mitogen for proximal tubule cells *in vitro*. Administration of EGF following renal injury enhances proliferation and speeds the recovery of proximal tubules *in vivo* [13].

11. Transforming growth factor-βs (TGF-βs): This may regulate wound repair and tissue reconstruction, by stimulating synthesis of extracellular matrix (ECM) proteins as well as promoting cell differentiation and proliferation. Following ischemic damage, upregulation of TGF-β1 appears to regulate synthesis of various ECM proteins in the proximal tubules. Nevertheless, such activity could also contribute to excessive fibrosis and sclerosis during tissue repair [13].
12. Hepatocyte growth factor (HGF): This is also implicated in the response of the injured kidney, being increased following both ischemia and toxic damage. HGF seems to play a major role in tubular re-epitheliazation [13].
13. Retrodiffusion (back-leak): Following an intense ischemia, obstruction may exist without any detectable increase in intratubular pressure due to the retrodiffusion mechanism. During the maintenance phase, there is evidence to suggest that this mechanism plays an important role, alongside other factors, in the continuing reduction of GFR [14].

Mediators Implicated in ARF

It has been clearly shown that a substantial part of the reduction in RBF and GFR is based upon an active and reversible process of renal arteriolar vasoconstriction and contraction of the glomerular mesangial cells. There is sufficient evidence that the ARF process involves a series of vasoconstrictors: angiotensin II, platelet-activating factor, adenosine, endothelin, and vasoconstrictor prostanoids. In addition, the absence of vasodilators such as nitric oxide (NO) and vasodilator prostanoids can play an important role (Figure 21.1).

The Renin-Angiotensin System

In experimental models of rats with renal ischemia, activation of the intrarenal renin-angiotensin system (RAS) was observed after 15 minutes of ischemia, and it continued for 24 hours following the removal of the obstruction. With $HgCl_2$-induced ARF models, plasma levels of renin and angiotensin II increase during the initial phase; however, this does not take place during maintenance, in which their levels are diminished. In the model of UN-induced ARF, levels of circulating and renal renin increase following the injection of the toxin, yet they remain elevated for 96 hours [11]. The model of the RAS activated by injections of glycerine has been heavily studied: During the initial phase, some studies demonstrated an increase in the activity of plasma and renal renin levels, whereas others showed both increase and inhibition. In the maintenance phase of ARF, there is more homogeneity, and all the studies demonstrate an increase in circulating and renal levels of renin and angiotensin II [15]. The mechanisms by which angiotensin II reduces GFR and RBF are multiple. First, it produces vasoconstriction, diminishing the RBF. Second, angiotensin II reduces the Kf and thereby glomerular filtration, a mechanism most likely to be mediated by mesangial contraction. Third, angiotensin II is a basic mediator of the tubular-glomerular feedback system, thereby contributing to the reduction in RBF and subsequently GFR during ARF [16].

Platelet-Activating Factor

Platelet-activating factor (PAF) is a vasoactive agent with important effects on renal function. The administration of PAF in animal studies produces

some effects that imitate ARF. There is evidence to demonstrate that the administration of PAF inhibitors protects against the reduction in GFR and RBF in animals with renal ischemia. The known mechanisms by which PAF induces ARF are by contracting smooth muscle and also inducing contraction of the glomerular and mesangial cells, reducing the RBF [17].

Prostanoids

Prostanoids are involved in the regulation of renal function on multiple levels: They have hemodynamic effects and modulate the action of different hormones, vasoconstrictors, and vasodilators. They participate in the tubulo-glomerular feedback and regulate the glomerular Kf since they are likely to mediate the regulation of mesangial contraction. The evidence for the role of ecosanoids in the genesis or maintenance of ARF is extensive. It has been suggested that the decrease in renal prostaglandins could be implicated in glycerine-induced ARF as well as in the increase in TXA_2 in hemodynamic and nephrotoxic models [18]. The administration of prostaglandins has a protecting effect on noradrenaline and glycerine-induced ARF [19] but not on UN-induced ARF. It can be concluded that the increase in the production of renal prostaglandins protects hemodynamic ARF; however, the effect upon the nephrotoxic variety of this syndrome is much less clear. Perhaps within the hemodynamic models there is an increased production of the vasodilating PGE_2 and PGI_2, while in toxic models the production of vasoconstrictor (TXA_2) is augmented [20].

Endothelin

Endothelin (ET) is formed by a family of peptides (ET-1, ET-2, ET-3) that function via two different types of receptors, ET-A and ET-B, that have vasoconstrictor/proliferative and vasodilator effects, respectively [21]. The administration of small quantities of ET-1 induced a very important reduction in the GFR and RBF. The mechanism by which endothelin decreases the glomerular filtration rate seems to be, in part, the increase in the renal vascular resistance and thus the sensitization of the renal vascular bed to the endothelium. The role of endothelin in the evolution of ARF is based upon the fact that treatment with antiendothelin antibodies improves the outcome of renal failure [22]. Antagonists of the receptors ET-A also improve the renal function in rats that have been injected with glycerine or have renal ischemia [23].

Adenosine

Adenosine (ADO) is produced by the cells of an organism when the hydrolysis of ATP is greater than the synthesis of ATP. This situation occurs during ischemia or nephrotoxic ARF. ADO is a vasodilator in the majority of the vascular beds of an organism; in the kidney, however, it acts as a vasoconstrictor and thereby produces a marked decrease in RBF and GFR [24]. There is evidence that ADO A-1-receptor antagonists improve renal function in diverse experimental models of ARF [25].

Nitric Oxide

Nitric oxide (NO) is an endogenous vasodilator with a very important role in the physiology and pathophysiology of diverse renal illnesses. Today, we know that the modulation of the vascular tone, in part mediated by NO, represents a local system that effectively controls blood flow to many vital

organs, thereby playing a fundamental role in intraglomerular hemodynamics. It has also been suggested that the observed vasoconstriction in post-ischemic ARF is associated with a reduction in the capacity of the endothelium to produce NO. Various studies suggest that NO is involved in the maintenance of RBF and GFR in rats with ARF [26].

Acute Renal Failure in the Elderly: Its Particular Characteristics

Many aspects of ARF are basically the same between young and old patients, while many others are rather different, and such knowledge gives the clues for mastering this syndrome in the aged group. These geriatric clues are described in this section.

High Susceptibility to Renal Failure

True incidence of acute renal failure in seniors is hard to define, but it is estimated to be around 950 cases per million population in those aged 80–89 [28–30]. The increased incidence of ARF in this age group is favored by certain factors. First, there are histological and functional changes of the aged kidney that make this organ susceptible to developing acute tubular necrosis (ATN): disturbance in the autoregulatory vascular defense [31], reduction in the number of glomeruli and glomerular capillaries [31, 32], renal tubular frailty [33], and salt and water wasting secondary to a reduced tubular reabsorption capability of these substances [34,35]. Second, there are extrarenal factors that make old people prone to ARF: reduced capability to metabolize drugs, exposure to polypharmacy and surgical procedures, errors in following medical prescriptions due to reduced cognitive capability and hearing or visual acuity, susceptibility to infection secondary to diminution of immunity against bacterial agents [2], predisposition to dehydration due to environmental factors (e.g., hot weather) and individual ones (e.g., primary hypodypsia, immobility syndrome, etc.), high prevalence of systemic diseases that can induce renal damage or dysfunction (e.g., diabetes mellitus, hypertension, heart failure, etc,) [28, 30].

Particular and Prevalent Causes of ARF in the Elderly

Hydroelectrolytic imbalance is the most common etiology of ARF in the elderly population [36], affecting approximately 1% of all community hospital admissions in elderly individuals and up to 25% of non-ambulatory geriatric patients [28]. The main causes of dehydration in the elderly are primary hypodypsia, gastrointestinal losses (vomiting, diarrhea), heat stroke, fever, and renal losses due to glucosuria or diuretics [28].

Other prevalent causes of pre-renal failure in the elderly are bleeding, cardiac insufficiency, sepsis, renovascular compromise, hemodynamically mediated pharmacological damage, and cirrhosis [2, 37].

Autoregulatory mechanisms of renal blood flow and glomerular filtration rate are usually altered in the elderly; then some drugs commonly prescribed to the elderly, which can impair renal autoregulation or interfere with vasodilatory capacity, may lead this population to ARF. Among these

drugs are prostaglandin-synthesis inhibitors [nonsteroidal anti-inflammatory drugs (NSAIDs)], angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor antagonists. If it is essential to treat with these drugs, the patient's renal function should be monitored closely and frequently [28, 30].

Pre-renal acute renal failure can easily lead to acute tubular necrosis in this population. *Tubular frailty* is a senile kidney condition that predisposes aged people to develop ATN easily, even after a mild renal insult. Aging tubular cells may be more vulnerable to ischemia because cellular antioxidant defenses decline with age, and oxidant injury may be a critical determinant of ischemic acute renal failure. Besides, the increased propensity to vasoconstriction may enhance the aged kidney's susceptibility to toxic substances [38]. Moreover, the tubular recovery from the established tubular necrosis is very slow. It may take more than the usual two weeks compared to younger patients, even though these aged patients may necessitate dialysis well before their tubular recovery [28, 32].

The most frequent causes of parenchymal ARF are post-ischemic and postnephrotoxic ATN [39, 40]. Nephrotoxic insults that characteristically cause ATN in the old include aminoglycosides and radiocontrast [41, 42]. Furthermore, the interaction between renal hypoperfusion and nephrotoxins is at least additive and probably synergistic [43].

Other frequent causes of renal ARF in the old population are acute glomerulonephritis (e.g., rapidly progressive: idiopathic crescentic glomerulonephritis, anti-GBM-associated glomerulonephritis, etc.), acute interstitial nephritis (e.g., NSAIDs, allopurinol, etc.), and intratubular deposition (e.g., rhabdomyolysis) [2, 28, 44–46].

Among the vascular causes that lead to intrinsic renal failure in the elderly are vasculitis (e.g., microvascular polyarteritis nodosa, Wegener), atheroembolic disease, and acute renal artery thrombosis [28, 46, 47].

Another important cause of ARF in the elderly is extrarenal urinary obstruction [48]. ARF develops only with bilateral obstruction or obstruction in a solitary functioning kidney. Among the causes of lower urinary tract obstruction, the most common is prostatic enlargement due to benign prostatic hyperplasia or to prostatic adenocarcinoma.

Prostatic carcinoma usually invades the ureterovesical junctions and causes bilateral hydronephrosis with progressive renal insufficiency. The second most common cause of urethral obstruction in males is urethral stricture disease [49]. In females the most common cause of postrenal failure is ureteral obstruction due to pelvic malignancy—invasive carcinoma of the cervix. Such an obstruction is especially common after radiation therapy. One form of retroperitoneal fibrosis that may occur mainly in older patients may be due to leakage from atheromatous lesions in the aorta. The inflammation that attends such slow retroperitoneal leakage from aortic aneurysms may obstruct the ureters [50,51]. An uncommon but classic manifestation of urinary tract obstruction is alternating anuria and polyuria; usually, this is caused by fluctuating accumulation and release of urine behind a stone that changes its position. In rare cases, unilateral obstruction can lead to anuria and ARF; loss of function in the non-obstructed kidney may be due to vascular or ureteral spasm, mediated by autonomic activation [52] (Tables 21.1, 21.2, and 21.3).

Table 21.1 Total Number of Patients with ARF in the Renal Unit of the University Hospital of Salamanca. 2000–2005.

Total number of patients	**386**
Male:	245(63.5%)
<65:	62(25.3%)
65–79:	107(43.7%)
>80:	76(31.0%)
Female :	141(36.5%)
<65:	25(17.7%)
65–80:	57(40.4%)
>80:	59(41.8%)
Stratification by age:	
Youngest: 21 years	
Oldest: 97 years	
<65 years:	82(21.2%)
65–79 years:	163(42.2%)
>80 years	141(36.5%)

Source: Courtesy of Dr. J.A. Menache.

"Atypical" Presentation of the Condition

In the elderly, diseases usually have patterns of presentation different from those observed in the young population. Signs and symptoms are frequently less defined in the aged group. Diseases usually present with few symptoms (paucisymptomatic) or just as general weakness or loss of appetite. Moreover, any disease could present merely as one of the entities known as the *geriatric giants:* confusional syndrome, falls, immobility syndrome, and acute urinary or fecal incontinence. These presentation patterns are called "atypical," but they could actually be regarded as "typical" in this population [53, 54].

Unreliable Physical Examination

Some physical signs found in the physical examination in an old patient may make physicians arrive at misinterpretations. For instance, dry mouth and skin, orthostatic hypotension, and persistence of skin folding are all signs frequently present in the healthy elderly, not necessarily implying a clinically significant state of dehydration. Moreover, the finding of edema in immobilized patients

Table 21.2 Total Number of Etiological Factors.

Etiology:	
One etiological factor:	313(81.1%)
<65:	21 (4%)
65–79:	141(45.0%)
80–96:	105(33.5%)
Multiple:	73.(18.9%)
<65:	9(12.3%)
65–79:	30(41.1%)
80–96:	34(46.6%)
Etiological agents: 487	

Table 21.3 Factors in Pre-renal ARF or Acute Reversible Renal Hypoperfusion: 267 (54.8 %).

Hypovolemia:			202(75.65%)
Fluid restriction (low intake):			114(56.43%)
Age (years) Cases	<65: 29 (14.4%)	65–79: 77 (38.1%)	>80: 96 (47.5%)
Fluid loss: Diarrhea:			202(75.7%) 48 (23.8%)
Age (years) Cases	<65: 15 (31.3%)	65–79: 13 (27.1%)	>80: 20 (41.7%)
Vomiting:			20 (9.9%)
Age (years) Cases	<65: 3 (15%)	65–79: 13 (65%)	>80: 4 (20%)
Sepsis:			30 (11.2%)
Age (years) Cases	<65: 7 (23.3%)	65–79: 14 (46.7%)	>80: 9 (30%)
Hypotension:			18 (6.7%)
Age (years) Cases	<65: 3 (16.7%)	65–79: 10 (55.6%)	>80: 5 (27.8%)
Cardiac failure:			9 (3.4%)
Age (years) Cases	<65: 0	65–79: 6 (66.7%)	>80: 3 (33.3%)
Febrile syndrome:			4 (1.5%)
Age (years) Cases	<65: 4 (100%)	65–79: 0	>80: 0
Renal artery thrombosis: 65–79:			1 (0.4%)
Stent re-stenosis: 65–79:			1 (0.4%)
Aorta clamping: <65:			1 (0.4%)
Renal or intrinsic ARF:			144 (29.6%)
Drugs:			113 (78.5%)
ACEi, AII-receptor blockers:			44 (38.9%)
Age (years) Cases NSAID: Age (years) Cases Contrast media: Age (years) Cases Aminoglycosides: Age (years) Cases	<65: 5 (11.4%) <65: 9 (36%) <65: 5 (26.3%) <65: 1 (25%)	65–79: 18 (40.9%) 65–79: 6 (24%) 65–79: 14 (73.7%) 65–79: 3 (75%)	>80: 21 (47.7%) 25 (22.1%) >80: 10 (40%) 19 (16.8%) >80: 0 4 (3.5%) >80: 0
Cis-platin: 65–79: Opioids: <65: Lithium: <65: Influenza vaccination: 65–79 Unknown: <65:			1 (0.9%) 1 (0.9%) 1 (0.9%) 1 (0.9%) 3 (100%)
Rhabdomyolysis:			9 (6.3%)
Age (years) Cases	<65: 4 (44.4%)	65–79: 1 (11.1%)	>80: 4 (44.4%)

(Continued)

Table 21.3 *(Continued)*

Malignant hypertension:			2 (1.4%)
Age (years)	<65:	65–79:	>80:
Cases	1 (50%)	1 (50%)	0
Acute hepatitis: <65:			1 (0.7%)
Multiple myeloma: >80:			1 (0.7%)
Hypercalcemia: <65:			1 (0.7%)
Severe hyperglycemia: >80:			1 (0.7%)
Acute tubular necrosis (unknown etiology): 65–79:			1 (0.7%)
Interstitial nephropathy: 65–79:			1 (0.7%)
Glomerulopathies:			9 (6.3%)
Hemolytic uremic syndrome:			4 (44.4%)
Age (years)	<65:	65–79:	>80:
Cases	3 (75%)	1 (25%)	0
Schölein–Henoch purpura: 65–79:			1(11.11%)
Polyarteritis nodosa: <65:			1 (11.11%)
SLE: <65:			1 (11.11%)
Wegener granulomatosis: <65:			1(11.11%)
Chronic lymphatic leukemia GN: 65–79:			1(11.11%)
Obstructive renal failure:			76 (15.6 %)
Age (years)	<65:	65–79:	>80:
Cases	18 (23.7%)	28 (36.8%)	30 (39.5%)
Worsening of pre-existing CRF:			4 (0.8%)
Age (years)	<65:	65–79:	>80:
Cases	2 (50%)	1 (25%)	1 (25%)

Causes of ARF stratified by age. Young = <65 years, old = 65–79 years, and Old-Old = 80–97 years.

does not mean volume overload, just as the lack of thirst does not signify an absence of dehydration [55]. Among the most reliable signs of dehydration in the elderly is axillary dryness [2].

Unreliable Urinary Indexes

The urinary indexes—urinary osmolality, urinary sodium, urea-to-creatinine ratio, fractional excretion of sodium, and fractional excretion of urea—are useful markers for distinguishing between pre-renal and renal ARF in young people (Table 21.4). These indexes reflect the presence of sodium and urea and the water reabsorption state that characterizes pre-renal ARF (or its lack in the parenchymal state) [2].

In the elderly, many urinary indexes such as urinary sodium, FE_{Na}, fractional excretion of urea (FE_U), and urinary osmolality should be interpreted carefully, as renal physiological changes secondary to the aging process make the expected values of these urinary indexes completely different from those in the young population. Taking a closer look, the characteristic reduced sodium and urea reabsorption and the reduced urinary concentration capability of this population make the FE_{Na} and FE_U higher and the urinary osmolality lower in respect to the values achieved by young people in renal hypoperfusion states. These altered index patterns can lead to an incorrect interpretation, making an acute pre-renal failure resemble a parenchymal one [55]. However, during situations of extreme renal hypoperfusion (e.g., severe hypernatremic states), some aged patients reach low fractional excretion of urea values, as young patients normally do [56, 57].

The Intermediate Syndrome

Due to the combined influence of the senile tubular frailty and tubular dysfunction, the so-called intermediate syndrome is frequently observed in the elderly. This means a patient suffering from a pre-renal acute renal failure resembles a parenchymal failure, since this aged patient usually has not only high plasma urea and creatinine but also urinary indexes compatible with acute tubular necrosis. However, the renal failure can resolve with volume expansion, as is the case with pre-renal insufficiency. Contrary to the classical pre-renal failure recovery time of 24–48 hours after rehydration, the intermediate syndrome resolves in about a week [33, 58].

Uremic Syndrome with Mild Uremia

Uremic symptoms can appear in the aged population despite the presence of a not-so-elevated plasma urea level, since this value overestimates the patient's glomerular filtration rate. This phenomenon can be justified by two particular characteristics of the urea handling in the elderly group: a reduced urea production secondary to a low protein intake and an increased urea renal excretion probably secondary to a reduced tubular reabsorption. Due to the aforementioned reasons, it should not rule out the presence of a uremic syndrome only because of the absence of very elevated urea plasma levels.

Furthermore, the uremic syndrome may present not by showing its classic symptoms such as nausea, vomiting, etc., but as one of the geriatric giants: confusion, gait disorders, immobility syndrome, and /or incontinence [59–61].

Prophylaxis of ARF

Avoiding situations that could damage the kidney is the best strategy against the consequences of ARF in the elderly. The following principles summarize these concepts [32]: Avoid dehydration before imaging studies based on contrast media and surgical procedures, avoid nephrotoxic substances, avoid polypharmacy, prescribe low doses of drugs (the lowest desired dose of drugs), use drugs for the shortest time, adjust drug doses to the expected functional reduction of the senile kidney, and assess renal function before and after the introduction of some drugs that could be potentially nephrotoxic [62–64]. The concept of these maneuvers is to prevent situations that can lead the aged kidney to ischemic and/or toxic tubular damage.

Table 21.4 Classical Urinary Indexes (in Young People).

	Pre-Renal ARF	Renal ARF
Nau (mmol/L)	< 20	> 40
FENa (%)	< 0.5	> 1
FEU (%)	< 35	> 50
UO (mOsm/L)	> 550	< 350

ARF = acute renal failure.
NaU = urinary sodium.
FENa=fractionalexcretion of sodium.
FEU = fractional excretion of urea.
UO = urinary osmolality.
Source: Miller et al. *Ann. Intern. Med*. 1878; 89:47.

Diagnosis of ARF: Particular Aspects

Principles and means for etiological diagnosis and ARF treatment are the same in both the young and the aged population. Renal biopsy does not carry a greater risk in the older patient compared to the younger, and adequate renal tissue can be obtained in 80–95% of cases, with a complication rate of 2.2–9%. However, because of complex changes in the aged kidney or concomitant diseases such as arteriosclerosis or global sclerosis, the interpretation of the histological finding may be more difficult.

Retrograde pyelography, nuclear medicine imaging techniques, and computed tomography also can help in patients who have an unidentified cause of obstruction in whom ultrasound has been unsatisfactory [65–67].

Treatment of ARF: Particular Aspects

As in practically any case of acute renal failure (irrespective of age), rehydration is crucial as the first therapeutic maneuver. This fact becomes more important in aged people, since they are more prone to volume contraction. It is crucial to highlight the importance of rehydration as the first therapeutic approach, since it is not always easy to distinguish, based on laboratory

Table 21.5 Patients with ARF of Either Etiology with the Need for Hemodialysis.

	Total:	63
	Men:	40 (63.5%)
	Women:	23 (36.5%)
	<65:	18 (28.6%)
	65–79:	28 (44.4%)
	>80:	15 (23.8%)
Causes:		
	Identified etiologic factors:	76
	Pre-renal:	33 (43.4%)
	Dehydration:	22 (66.6%)
	Hypotension:	4 (12.1%)
	Sepsis:	3 (9.1%)
	Cardiac failure:	2 (6.1%)
	Thrombosis of renal artery:	1(3.1%)
	Malignant hypertension:	1(3.1%)
Renal:		33(43.4%)
	Nephrotoxicity:	21(63.6%)
	ACEi + AII RA:	8 (38.1%)
	NSAIDs:	5(23.8%)
	Contrast media:	5(23.8%)
	Aminoglycosides:	2(9.5%)
	Unknown:	1(4.8%)
	Rhabdomyolysis:	4(12.1%)
	Glomerulonephritis:	3 (9.1%)
	Hemolytic uremic syndrome:	2(6.1%)
	Toxic hepatitis:	1(3.0%)
	Vaccination:	1(3.0%)
	Interstitial nephropathy:	1(3.0%)
	Obstructive:	9(11.8%)
	Unidentified etiological agent:	1(1.3%)

tests, between pre-renal and parenchymal ARF. However, since old people usually have rigid cardiac walls (presbycardia) and a reduced glomerular filtration rate, they should be rehydrated cautiously, because they are prone to develop pulmonary edema during aggressive volume infusion [68].

In parenchymal ARF, if there's no contraindication to their use, loop diuretics can be safely used, since they can convert an oliguric situation to a non-oliguric one and facilitate therapeutic interventions and caloric/water ingestion [69, 70]. Low-dose dopamine, on the other hand, is of no proven benefit [68,71]. Prompt recognition of acute interstitial nephritis secondary to drugs may lead to stopping its inducing drug, early intervention with steroids, and more rapid recovery of renal function [45].

Because of the potential for reversing ARF in some forms of glomerulonephritis and vasculitis, one should not hesitate to perform a renal biopsy [72]. In rapidly progressive glomerulonephritis, the same principles are usually applied to treat adults and old patients, but one should take into account that the relative risk of death is 5.3 times higher in older (>60 years) patients compared to younger ones [73] following aggressive immunosuppression.

In post-renal ARF, the ideal treatment for its resolution is by urological desobstruction.

The indications for dialysis in the elderly are the same as in the younger adult. One does not select a mode of dialysis (i.e., hemodialysis, hemofiltration, or peritoneal dialysis) on the basis of the patient's age; rather the mode is chosen on the basis of a number of patient- and/or disease-specific factors, including the presence of hemodynamic instability, severe hypervolemia, hypercatabolism, compromised pulmonary function, bleeding potential, vascular access difficulties, and others [28]. Most elderly patients respond well to either peritoneal dialysis or hemodialysis [74–76] (Table 21.5).

Table 21.6 Rates for Patients with ARF.

Total:		62 (16%)
Male:		38(61.3%)
Female:		24(38.7%)
<65:		9(14.5%)
65–79:		18(29.0%)
>80:		35(56.5%)
Etiology:		
Total number:		62
Pre-renal:		47 (75.8%)
Dehydration:		20(42.5%)
Septic shock:		17(36.2%)
Cardiac failure:		5(10.6%)
Hypotension:		3(6.3%)
Rhabdomyolysis:		2 (4.3%)
Renal:		6 (9.7%)
	NSAIDs:	3(50%)
	IECA, ARA-II:	1(16.6%)
	Contrast media	1(16.6%)
	Unidentified etiological agent:	1(16.6%)
Obstructive:		9(14.5%)

Survival rates differ from center to center and between studies, due mainly to different study methods and patient selection; the survival rate is estimated to be around 40% [77, 78] (Table 21.6).

Preliminary data suggest that most of these patients died from a cause related to the disease responsible for the ARF. Recent studies have concluded that, in the elderly, the outcome has improved over the years. From current evidence it seems that old age is not by itself an independent indicator of poor prognosis in ARF [28, 79, 80].

References

1. Lameire, N. Recent advances in clinical acute renal failure. *Rev. Port. Hipert*. 2005; 19(1):15–30.
2. Macías-Núñez, J.F., Sanchez Tomero, J.A. Acute renal failure in old people. In *Renal Function and Disease in the Elderly*, J.F. Macías-Núñez and S. Cameron, eds. London: Butterworth. 1987; pp. 461–484.
3. Brady, H.R., Clarckson, M.R., Lieberthal, W. Acute renal failure. In *The Kidney,* B. Brenner, ed. Philadelphia: Saunders. 2005; pp. 1215–1292.
4. Racusen, L.C. The morphologic basis of acute renal failure. In *Acute Renal Failure: A Comparison to Brenner and Rector´s The Kidney,* B.A. Molitoris and W.F. Finn, eds. Philadelphia: W.B. Saunders. 2001; pp. 1–12.
5. Stein, J.H., Lifschitz, B.D., Barnes, L.D. Current concepts on the pathophysiology of acute renal failure. *Am. J. Physiol*. 1978; 234:F171–181.
6. Solez, K. The morphology of acute renal failure. In *Acute Renal Failure,* J.M. Lazarus and B.M. Brenner, eds. New York. Churchill Livingstone. 1993; pp. 33–51.
7. Solez, K., Altman, J., Rienhoff, H., et al. Early angiographic and renal blood flow changes after $HgCl_2$ or glycerol administration. *Kidney Int.* 1976; 10:S153–S159.
8. Rodriguez Mañas, L. Aging and the vascular wall. *Circulation* 2000; 104: 2638–2640.
9. Avasthi, P., Evan, A.P., Hay, D. Glomerular endothelial cells in uranyl nitrate-induced acute renal failure in rats. *J. Clin. Invest*. 1980; 65:121–127.
10. Schor, N., Ichikawa, I., Rennke, H.G., et al. Pathophysiology of altered glomerular function in aminoglycoside-treated rats. *Kidney Int.* 1981; 19:288–296.
11. Flamenbaum, W., McNeil, J.S., Kotchen, T.W., Saladino, A.J. Experimental acute renal failure induced by uranyl nitrate in the dog. *Circ. Res.* 1972; 31:682–698.
12. Venkatachalam, M.A., Bernard, B.D., Donohoe, J.F., Levinsky, N.G. Ischemic damage and repair in the rat proximal tubule: Differences among the S_1, S_2 and S_3 segments. *Kidney Int*. 1978; 14:31–49.
13. Lameire, N.H., Vanholder, R.C. Acute renal failure: Pathophysiology and prevention. In *Oxford Textbook of Clinical Nephrology*, A. Davison, J.S. Cameron, J.P. Grünfeld, C. Ponticelli, E. Ritz, C.G. Winearls, and C. Van Ypersele, eds. Oxford: Oxford University Press. 2005; pp. 1445–1464.
14. Donohoe, J.F., Venkatachalam, M.A., Bernard, D.B., Levinsky, N.G. Tubular leakage and obstruction after renal ischemia: Structure-function correlations. *Kidney Int*. 1978; 13:208–222.
15. Goormaghtigh, N. Existence of an endocrine gland in the arteriolar media of renal arterioles. *Proc. Soc. Exp. Biol. Med*. 1939; 42:688–689.
16. López-Novoa, J.M., Casado, S., Hernando, L. Protection by propanolol against
17. glycerol-induced acute renal failure. Role of extracellular volume expansion. *Biomedicina* 1978; 29:303–306.
18. López-Novoa, J.M. Potential role of platelet activating factor in acute renal failure. *Kidney Int.* 1999; 55:1672–1682.

19. Martínez-Salgado, C., Rodríguez-Barbero, A., Rodríguez-Puyol, D., Pérez de Lema, G., López-Novoa, J.M. Involvement of phospholipase A2 in gentamicin-induced rat mesangial cell activation. *Am. J. Physiol.* 1997; 273:F60–F66.
20. Werb, R., Clark, W.F., Lindsay, R.M., et al. Protective effect of prostaglandin (PGE2) in glycerol-induced acute renal failure in rats. *Clin. Sci. Mol. Med.* 1978; 55:505–507.
21. Mauk, R.H., Patak, R.V., Fadem, S.Z., et al. Effect of prostaglandin E administration in a nephrotoxic and a vasoconstrictor model of acute renal failure. *Kidney Int.* 1977; 12:122–130.
22. Perez del Villar, C., Garcia Alonso, C.J., Feldstein, C.A., Juncos, L.A., Romero, J.C. Role of endothelin in the pathogenesis of hypertension. *Mayo Clin. Proc*. 2005; 80:84–96.
23. Garcia, R.E. Therapeutic strategies in the prevention of acute renal failure. *Ren. Fail*. 1997; 19:231–235.
24. Tsau, Y.K., Tsai, W.S., Chen, C. Urinary entothelin-1 in children with acute renal failure of tubular origin. *J. Fromo. Med. Assoc*. 1998; 97:387–391.
25. Macías-Núñez, J.F., García Iglesias, C., Santos, J.C., Villamediana, L.M., López-Novoa, J.M. Influence of plasma renin content, intrarenal angiotensin II, captopril and calcium channel blockers on the vasoconstriction and renin release promoted by adenosine in the kidney. *J. Lab. Clin. Med*. 1985; 106:562–567.
26. Kolonko, A., Wiecek, A., Kokot, F. The nonselective adenosine antagonist theophylline does prevent renal dysfunction induced by radiographic contrast agents. *J. Nephrol*. 1998; 11:151–156.
27. Valdivielso, J.M., Rivas Cabañero, L., Perez-Barriocanal, F., López-Novoa, J.M. Effect of nitric oxide synthesis modification on renal function in gentamicin-induced nephrotoxicity. *Env. Toxicol. Pharmacol*. 1997; 3:123–128.
28. Musso, C.G. Acute renal failure in the elderly: Pearls for its assessment and treatment. biomed.uninet.edu/2005/.
29. Lameire, N., Nelde, A., Hoeben, H., Vanholder, R. Acute renal failure in the elderly. In *Nephrology and Geriatrics Integrated,* D. Oreopoulos, W. Hazzard, and R. Luke, eds. Dordrecht: Kluwer Academic Publishers. 2000; pp. 93–111.
30. Fillit, H., Mayer, L., Bona, C.A. Immunology of aging. In *Textbook of Geriatric Medicine and Gerontology*, J.C. Brocklehurst, R.C. Tallis, and H. Fillit, eds. New York: Churchill-Livingstone. 1992; pp. 71–90.
31. Pascual, J., Ordónez, O., Liaño, F. Fracaso renal agudo en el anciano. In *Fracaso Renal Agudo*, F. Liaño and J. Pascal, eds. [in Spanish] Barcelona: Masson. 2002; pp. 369–382.
32. Beck, L.H. Changes in renal function with aging. *Clin. Geriatr. Med*. 1998; 11:199–209.
33. Hernando Avendaño, L., López-Novoa, J. Glomerular filtration and renal blood flow in the aged. In *Renal Function and Disease in the Elderly*, J.F. Macías-Núñez and S. Cameron, eds. London: Butterworth. 1987; pp. 27–48.
34. Musso, C.G. Geriatric nephrology and the "nephrogeriatric giants." *Int. Urol. Nephrol*. 2002; 34:255–256.
35. Macías-Núñez, J.F., García Iglesias, C., Bondía Román, A., Rodríguez Commes, J.L., et al. Renal handling of sodium in old people: A functional study. *Age and Ageing* 1978; 7:178–181.
36. Macías-Núñez, J.F., Musso, C.G. Renal physiology in the oldest old: The Sphinx remakes her question. *Int. Nephrol. Urol*. (in publication).
37. Macías-Núnez, J.F., López-Novoa, J.M., Martinez-Maldonado, M. Acute renal
38. failure in the aged. *Sem. Nephrol*. 1996; 16:330–338.
39. Spangler, P.F., Risley, T.R., Bilyew, D.D. The management of dehydration and incontinence in non-ambulatory geriatric patients. *J. Appl. Behav. Anal*. 1984; 17:397–401.

40. Jerkic, M., Vojvodic, S., López-Novoa, J.M. The mechanism of increased renal susceptibility to toxic substances in the elderly. Part I. The role of increased vasoconstriction. *Int. Urol. Nephrol*. 2001; 32(4):539–547.
41. Lameire, N., Matthys, E., Vanholder, R., De Keyser, K., Pauwels, W., Nachtergaele, H., Lambrecht, L., Ringoir, S. Causes and prognosis of acute renal failure in the elderly. *Nephrol. Dial. Transplant* 1987; 2:316–322.
42. Lameire, N., Verspeelt, J., Vanholder, R., Ringoir, S. A review of the pathophysiology, causes and prognosis of acute renal failure in the elderly. *Geriatr. Nephrol. Urol*. 1991; 1:77–91.
43. Dixon, B.S., Anderson, R.J. Nonoliguric acute renal failure. *Am. J. Kidney* 1985; 6:71–80.
44. Musso, C.G. Aminoglycosides and nephropathy. biomed.uninet.edu. 2004; 2(2): 1–3.
45. Musso, C.G. Clinical catastrophic events in geriatrics: Its physiopathological bases. *Int. Nephrol. Urol*. (in publication).
46. Musso, C.G., Pidoux, R., Mombelli, C., et al. Acute renal failure secondary to rhabdomyololysis induced by influenza vaccine in n old patient. www.biomed.uninet.edu. 2005; (3).
47. Lou, L.M., Boned, B., Gomez Sanchez, R. Characteristics of acute renal failure in elderly patients admitted to a small town hospital. *Nefrologia* 2002; 22(6): 547–554.
48. Musso, C.G., Macías-Núñez, J.F. Renal diseases. In *Principles and Practice of Geriatric Medicine*, J.M.S. Pathy, A.J. Sinclair, and J.E. Morley, eds. Chichester: John Wiley & Sons. 2006; pp. 1495–1508.
49. Liaño, F., Gamez, C., Pascual, J., Teruel, J.L., Villafruela, J.J., Orte, L., Ortuno, J. Use of urinary parameters in the diagnosis of total acute renal artery occlusion. *Nephron* 1994; 66:170–175.
50. Pascual, J., Orofino, L., Liano, F., Marcen, R., Naya, T., Orte, L., Ortuno, J. Incidence and prognosis of acute renal failure in older patients. *J. Am. Geriatr. Soc*. 1990; 38:25–30.
51. Walsh, P.C. Benign prostatic hyperplasia. In *Campbell's Urology*, 5th ed., P.C. Walsh, R.F. Gittes, A.D. Perlmutter, T.A. Stamey, and W.B. Saunders, eds. Philadelphia: 1986; pp. 1248–1265.
52. Serra, R.M., Engle, J.E., Jones, R.E., Schoolwerth, A.C. Perianeurysmal retroperitoneal fibrosis: An unusual cause of renal failure. *Am. J. Med*. 1980; 68:149–153.
53. Wagneknecht, L.V., Hardy, I.C. Value of various treatments for retroperitoneal fibrosis. *Eur. Urol*. 1981; 7:193–198.
54. Maletz, R., Berman, D., Peelle, K., Bernard, D. Reflex anuria and uremia from unilateral ureteral obstruction. *Am. J. Kidney Dis.* 1993; 22:870–873.
55. Perez Almeida, E., Blanco Pascual, E. The patient with immobility syndrome. In *Geriatría desde el Principio,* J.F. Macías-Núñez, F.G. Guillén Llera, and J.M. Ribera Casado, eds. [in Spanish] Barcelona: Editorial Glosa. 2000; pp. 135–152.
56. Gil Gregorio, P. The patient with psychiatric alterations. In *Geriatría desde el Principio*, J.F. Macías-Núñez, F.G. Guillén Llera, and J.M. Ribera Casado, eds. [in Spanish] Barcelona: Editorial Glosa. 2000; pp. 183–202.
57. Musso, C.G., Macías-Núñez, J.F. The aged kidney: Structure and function. Main nephropathies. In *Geriatría desde el Principio,* A. Salgado, F.G. Guillén Llera, and I. Ruipérez, eds. [in Spanish] Barcelona: Masson. 2000; pp. 399–412.
58. Musso, C.G., Caceres, J.M., Luque, K., et al. Fractional excretion of urea in severe dehydrated elderly. biomed.uninet.edu. 2005; (1).
59. Musso, C.G., Jauregui, R., et al. Low fractional excretion of urea in hypothyroidism-induced hyponatremia. biomed.uninet.edu. 2005; (1).
60. Musso, C.G., Luque, K., Reynaldi, J., et al. Intermediate syndrome: A typical pattern of pre-renal acute renal failure in the elderly. biomed.uninet.edu. 2004; (3).

61. Musso, C.G., Giordani, C., Stonski, E. Acute renal failure with normal plasma urea levels: A marker of proximal tubular dysfunction with diabetes insipidus. biomed.uninet.edu. 2004; (2).
62. Musso, C.G., Vilas, M., Fernandez Otero, L., Jauregui, R., Imperiali, N.,
63. Algranati, L. Acute renal failure with normal plasma urea level secondary to acute pyelonephritis in a single kidney patient. biomed.uninet.edu. 2006; (1).
64. Musso, C.G. El riñón del anciano, nefropatías más frecuentes y tratamiento dialítico. In A. Cusumano and O. Hermida, eds. [in Spanish] Buenos Aires. 2000.
65. Solomon, R., Werner, C., Mann, D., D'Elia, J., Silva, P. Effects of saline, mannitol and furosemide on acute decreases in renal function by radiocontrast agents. *N. Engl. J. Med.* 1994; 331:1414–1416.
66. Pfaffle, A.E., Moses, J.W., Chan, R., Gleim, G.W., Zabetakis, P.M., Stugensky, K., Michelis, M.F. Negative fluid balance and the occurrence of radiocontrast associated acute renal failure. *Geriatr. Nephrol. Urol*. 1994; 4:71–77.
67. Piper, S.N., Kumle, B., Boldt, J. Diltiazem may preserve renal tubular integrity after cardiac surgery. *Can. J. Anaesth.* 2003; 50(3):285–292.
68. Amis, E.S., Cronan, J.J., Pfister, R.C., Yoder, I.C. Ultrasonic inaccuracies in diagnosing renal obstruction. *Urology* 1982; 19:101–105.
69. Rascoff, J.H., Golden, R.A., Spinowitz, B.S., Charytan, C. Non-dilated obstructive nephropathy. *Arch. Intern. Med*. 1983; 143:696–698.
70. Lalli, A.F. Retroperitoneal fibrosis and inapparent obstructive uropathy. *Radiology* 1977; 122:339–342.
71. Musso, C., Liakopoulos, V., Ioannidis, I., Stefanidis, I. Acute renal failure in the elderly: Particular characteristics. *Int. Nephrol. Urol*. (in publication).
72. Cantarovich, F., Fernandez, J.C., Locatelli, A., Perez Loredo, J. Furosemide in high dose in the treatment of acute renal failure. *Postgrad. Med. J*. 1971; 47(Suppl): 13–17.
73. Cantarovich, F., Rangoonwala, B., Lorez, H., et al. High-dose furosemide for established ARF: A prospective, randomized, double blind, placebo controlled, multicenter trial. *Am. J. Kidney Dis*. 2004; 44:402–409.
74. Firedrich, J.O., Adhikari, N., Herridge, M.S., Beyene, J. Meta-analysis: Low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann. Intern. Med*. 2005; 142:505–524.
75. Rakowski, T.A., Winchester, J.F. Renal biopsy in the elderly patient. In *Geriatric Nephrology,* M.F. Michelis and H.G. Preuss, eds. New York: Field Rich. 1986; pp. 37–39.
76. Keller, F., Michaelis, C., Biitner, P., Bennhold, I., Schwarz, A., Distler, A. Risk factors for long-term survival and renal function in 64 patients with rapidly progressive glomerulonephritis (RPGN). *Geriatr. Nephrol. Urol*. 1994; 4:5–13.
77. Baraldi, A., Ballestri, M., Rapana, R., Lucchi, L., et al. Acute renal failure of medical type in an elderly population. *Nephrol. Dial. Transplant* 1998; 13(Suppl 7):25–29.
78. Van de Noortgate, N., Verbeke, F., Dhondt, A., Colardijn, F., et al. The dialytic management of acute renal failure in the elderly. *Semin. Dial*. 2002; 15(2): 127–132.
79. Mandal, A.K., Baig, M., Koutoubi, Z. Management of acute renal failure in the elderly. Treatment options. *Drugs Aging* 1996; (4):226–250.
80. Klouche, K., Cristol, J.P., Kaaki, M., Turc-Baron, C., et al. Prognosis of acute renal failure in the elderly. *Nephrol. Dial. Transplant* 1995; 10(12):2240–2243.
81. Santacruz, F., Barreto, S., Mayor, M.M., Cabrera, W., et al. Mortality in elderly patients with acute renal failure. *Ren. Fail*. 1996; 18(4):601–605.
82. Pascual, J., Liano, F. Causes and prognosis of acute renal failure in the very old. *J. Am. Geriatr. Soc*. 1998; 46(6):721–725.
83. Sesso, R., Roque, A., Viciosos, B., Stella, S. Prognosis of ARF in hospitalized elderly patients. *Am. J. Kidney Dis*. 2004; 44(3):410–419.

22

Multiorganic Dysfunction Syndrome in the Elderly Critically Ill Patient

Monica Bonello, Zaccaria Ricci, Dimitris Petras, Nereo Zamperetti, and Claudior Ronco

Introduction

An evolving ability to support vital organ system function during a period of otherwise lethal physiological insufficiency changed the process of hospital care over the last half of the 20th century. Over a relatively short period, the development of techniques such as positive pressure ventilation, hemodialysis, invasive monitoring, and cardiovascular support transformed life-threatening illness from a rapidly lethal event to a chronic state that was, potentially, survivable. Furthermore, since a substantial proportion of patients admitted into the ICU are over 65 years old, a peculiar discipline arose within critical care medicine: critical care of the elderly patient. Moreover, this new discipline has created an entirely unprecedented spectrum of clinical problems, arising in the wake of the profound physiological derangements of critical illness and the relatively heroic interventions applied to reverse them. For example, the intensive care unit (ICU) made possible a spectrum of disorders that are characterized by their strong association with inflammation and described by their effects on the function of individual organ systems: acute respiratory distress syndrome, acute renal failure, disseminated intravascular coagulation, septic shock, and stress gastrointestinal bleeding, to name a few. Yet it is not simply that any one of these organ system derangements is the cause of all the others. Rather, all share common features that justify their consideration as manifestations of a common process—initially described as *multiple organ failure (MOF)* [1, 2], and more recently termed *multiple organ dysfunction syndrome (MODS)* [3]. Indeed, it is not yet at all clear whether MODS is a single pathological process with a highly variable clinical expression or simply the limited phenotypic expression of a large number of pathologically divergent processes.

Finally, the use of such advanced treatments in elderly patients raises many general issues, particularly in the field of ethics. Surprisingly, perhaps, we shall see that chronological age turns out *not* to be the most important determinant of outcome in patients with MODS, which undermines attempts to treat them in a manner significantly different to younger patients in the same situation.

The Epidemiology of Critical Illness in the Elderly

Elderly patients are frequently admitted in intensive care units, and an increasing proportion of patients in ICUs are over the age of 65. Of the 17,440 patients in medical and surgical ICUs from 40 institutions in the United States in the 1980s, the proportion of patients who were over age 65 was 48% [4]. Twenty-five percent were age 65 to 74, 17.2% were age 75 to 84, and 5.3% were 85 or older. The incidence of acute respiratory failure, a diagnosis that almost uniformly requires ICU admission, increases almost exponentially with age (Figure 22.1). According to a cohort drawn from 904 hospitals in the United States, the incidence of acute respiratory failure in the 65- to 84-year age group is almost twice that of the 55- to 64-year age group and is more than three times that of younger age groups [5].

In a prospective cohort of 15,757 consecutive adult patients admitted to 361 ICUs in 20 countries in 1998, the median age of patients receiving mechanical ventilation was 63 years (interquartile range: 48 to 73) [6]. Furthermore, the proportion of elderly patients admitted to ICUs may be increasing. In Sweden, the proportion of patients who were over age 70 admitted to a medical-surgical adult ICU increased from 19% in 1980 to 28% in 1995 ($p < 0.001$) [7]. During the same period, the proportion of patients admitted to the ICU under age 60 decreased from 58% to 41% ($p < 0.001$). The number of elderly patients who will require intensive care services is going to increase substantially in the near future as the world's population ages.

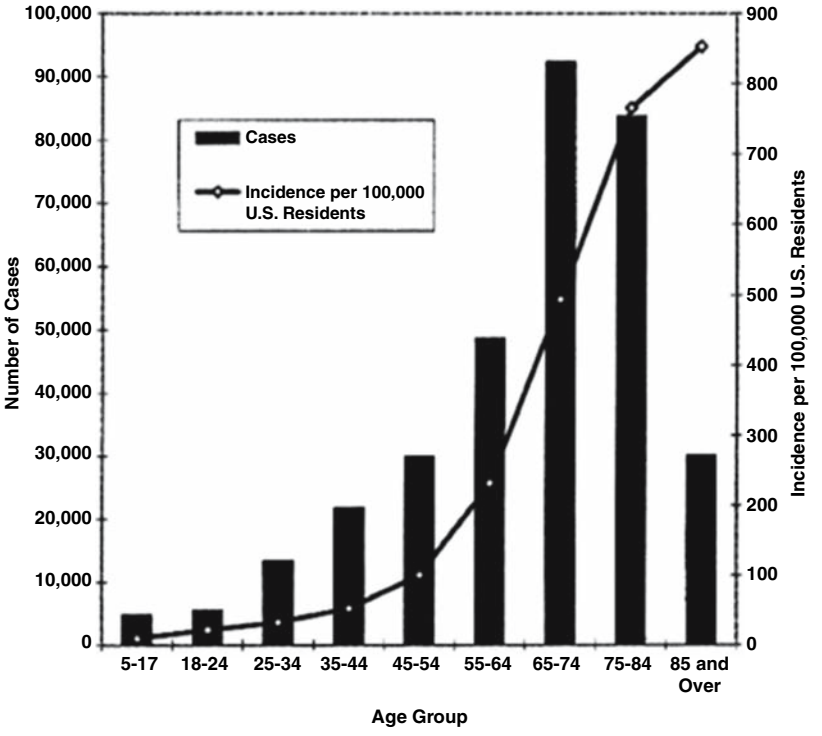

Fig. 22.1 Cases and incidence of acute respiratory failure in the United States, 1994, by age. Bars denote the numbers of acute respiratory failure cases; diamonds indicate incidence per 100,000 U.S. residents [5].

Hospital survival for all elderly patients admitted to ICUs ranged from 60% to 85% during the 1980s, depending on the type of ICU and enrollment criteria [8–10], while survival of patients with acute respiratory failure ranged from 33% to 60% [11–14]. Most studies indicated that survival for patients older than age 65 was significantly lower than for younger patients, and some suggested that age is a risk factor for death due to critical illness. However, more recent studies have taken the important step of using illness-severity models to adjust for other important risk factors including severity of acute illness, underlying co-morbidities, and pre-admission functional status. Adjusting for these variables, age accounts for only 3–5% of the explanatory power for interpatient differences in risk of death. Using data from a cohort of patients enrolled in an intervention study related to liberation from mechanical ventilation, Ely et al. [15] compared the in-hospital mortality rate between patients age 75 or older and patients under age 75. Mortality rates were 38.1% for patients 75 years or older and 38.8% for patients younger than 75 years ($p > 0.2$). Among covariates including gender, ethnicity, APACHE II score, and group assignment for the intervention, only APACHE II score was independently associated with risk for in-hospital death. Similar results were obtained by using age cut-offs of 65 years and 80 years and by performing analyses with APACHE II scores calculated without points for age. Duration of mechanical ventilation was similar between groups (median 4.2 days for older patients versus 6.4 days for younger patients; $p = 0.14$).

Focusing on specific causes of respiratory failure provides some insight into the question of age and the outcome of respiratory failure. Seneff et al. [16] examined hospital and 1-year survival for patients in the APACHE III database who were admitted with an acute exacerbation of chronic obstructive pulmonary disease. Hospital mortality for patients younger than age 65 years was 10.2%, compared with 32.9% for those aged 65 years or older ($p < 0.001$). However, age accounted for less than 4% of explanatory power for hospital mortality, while nonrespiratory organ dysfunction accounted for 53%. Age was a somewhat more significant factor in 1-year mortality, but again, its explanatory power was minor compared with respiratory and nonrespiratory physiology. Acute lung injury and ARDS are more severe forms of respiratory failure that carry a higher overall burden of illness for patients. Two recent studies suggest that age is an important factor in survival with these conditions [17, 18]. In a series of 107 patients admitted to a medical ICU with acute lung injury, being over 65, co-morbid conditions, and sepsis were found to be significant risk factors for mortality after controlling for illness severity by APACHE II scores and presence of acute organ failures [17]. Ely et al. [18] assessed the effect of age on survival from acute lung injury by examining data on 902 patients enrolled in the ARDS Network. Most of the patients were randomized to management with tidal volumes of either 6 mL/kg of ideal body weight or 12 mL/kg ideal body weight, and other ventilator management was by protocol. Patients were excluded if they had co-morbid conditions with an estimated 6-month mortality rate greater than 50%. Mutivariable Cox regression analysis adjusted for covariates, including APACHE III score, indicated that an age greater than 70 years was a strong predictor of in-hospital death, with a hazard ratio for death of 2.5 (CI: 2.0 to 3.2) relative to patients younger than 70. Older patients also had a longer duration of mechanical

ventilation and were more likely to require reintubation. Using age cut-offs of 65 or 80 years did not change these results. In a prospective cohort of 256 patients with ARDS studied from 1987 to 1990, investigators observed that mortality was significantly higher for patients over 55 compared with those 55 years or younger (64% versus 45%; $p = 0.002$) [19]. In a multivariate analysis including age, sepsis, APACHE II score, acute organ failure, and variables for gas exchange, age was the only independent variable predicting mortality.

Patients over 55 were more likely to have support withdrawn, even in the absence of a chronic health impairment. In their discussion, the authors raised the issue of age bias in decisions to withdraw support. In a larger study to determine whether provision of less aggressive care is a factor in the higher short-term mortality for seriously ill elderly patients, the SUPPORT investigators examined survival over 180 days for 9105 patients who were enrolled in the SUPPORT study [20]. Patients in the five participating institutions were enrolled based upon having one of nine serious diagnoses and an expected 6-month mortality of 50% or less. Adjusting for gender, ethnicity, income, baseline functional status, severity of illness, and aggressiveness of care, each additional year of age increased the hazard of death by 1.0% for patients 18 to 70 years of age and by 2.0% for patients older than 70 years of age. For SUPPORT patients with average severity of illness and treatment intensity, estimates of age-specific 6-month mortality rates were 44% for 55-year-old patients, 48% for 65-year-old patients, 53% for 75-year-old patients, and 60% for 85-year-old patients. It should be noted again, however, that severity of acute physiological abnormalities and diagnosis were much stronger contributors to prognosis than age. Aggressiveness of care was assessed by measuring scores on the Therapeutic Intervention Scoring System (TISS), the presence of a do-not-resuscitate order on day 1, and decisions to withhold major surgery, dialysis, tube feeding, transfer to the intensive care unit, blood transfusion, and vasopressors. Based upon these measures, elderly patients received less aggressive care than younger patients, but this had no bearing on the age effect for mortality. The authors speculate that this outcome may be related to younger patients receiving additional invasive treatments that did not significantly improve their outcome.

Age is a well-known risk factor in trauma patients, too. Pre-existing medical conditions in older age and impaired age-dependent physiological reserve contributing to a worse outcome in multiple injured elderly patients are hypothesized as reasons for increased mortality. A recent retrospective clinical study of a statewide trauma data set from 1993 through 2000 [21] included 5375 patients with an Injury Severity Score (ISS) over 16 who were stratified by age. Mortality in this series increased beginning at age 56 years, and that increase was independent of the ISS. The mortality rate increased from 7.3% (patients 46–55 years of age) to 13.0% (patients 56–65 years of age) in patients with ISS 16–24; from 23.8% to 32.1% in those with ISS 25–50; and from 62.2% to 82.1% in those with ISS 51–75 ($p < 0.05$). Severe traumatic brain injury was the most frequent cause of death, with a significant peak in patients older than 75 years. The incidence of lethal multiple organ failure increased significantly beginning at age 56 years ($p < 0.05$), but it showed no further increase in patients aged 76 years or older. In contrast, the incidence of lethal shock showed a significant increase from age 76 years ($p < 0.05$),

but not at age 56 years. However, beginning at age 56, mortality increased significantly in patients who sustained multiple trauma—an increase that was independent of trauma severity.

Physiopathology of Multiple Organ Dysfunction Syndrome (MODS)

The first descriptions of MODS emphasized its common association with occult or poorly controlled infection [22], frequently either peritonitis or pneumonia [23]. However, more recent reports indicate that infection, although common in patients with MODS, is not necessarily present [24] and frequently follows, rather than precedes, the development of the syndrome [25]. Indeed, nosocomial infection may be better considered a manifestation of MODS than a cause of it.

Although infection commonly triggers MODS, the evidence that infection plays an important role in the evolution of the syndrome is not compelling. Meta-analyses of the effects of infection prophylaxis using the techniques of selective digestive tract decontamination show a striking reduction in rates of such infections as pneumonia, wound infection, and bacteremia but a much more modest (albeit statistically significant) reduction in mortality [26, 27]. Moreover, peritonitis and pneumonia are frequent causes of MODS, but the evidence that successful treatment of either alters outcome is far from compelling [28–31]. Although it is difficult to differentiate the clinical manifestations of inflammation from the infections that are commonly their cause, it can be shown that the severity of the clinical inflammatory response, rather than the presence or absence of infection, is the more important determinant of ICU survival [32]. Other mechanisms, such as tissue hypoxia and microvascular coagulopathy, have been suggested as pathophysiological factors leading to MODS and as potential targets of new therapeutic options: early goal-directed therapy (EGDT) [33] and activated protein C (APC) [34, 35]. Nonetheless, MODS is a prototypical example of the application of complex theories to an understanding of the pathophysiology of critical illness [36,37]. It arises through the interactions of a network of physiological insults including infection, the host inflammatory response, tissue ischemia, injury, and the interventions used to sustain organ function during a time of otherwise lethal insufficiency. Its mediators are many and interdependent, with the activity of one inducing the expression of others that amplify, inhibit, or otherwise modify the expression of the process. The clinical syndrome that emerges reflects the state of dynamic balance that exists between each of the component mediators and can be considered an emergent system. Strategies directed against events early in the process may be effective as prophylaxis but are unlikely to have a significant effect on a process whose expression, at least from the perspective of the element targeted, has become autonomous. For example, although the prevention of infection in critical illness may reduce morbidity and mortality [38], once such downstream events as proinflammatory mediator release have been activated, their persistence is not necessarily dependent on continuing infection. Similar considerations may help to explain the relatively modest impact of neutralization of early proinflammatory mediator release in patients with sepsis [39]. In contrast, activation of coagulation is a relatively late consequence of the inflammatory response and, therefore, conceptually a more attractive therapeutic target. In reality,

the disparate biological processes that comprise inflammation are intimately interrelated, and strategies directed at one manifestation may have significant and unexpected consequences for others. Unfortunately, these processes are not demonstrated particularly well in small-animal models, and the elucidation of the richness of these interactions emerges only slowly, as data from trials of a variety of interventional strategies accumulate.

According to a recent proposed hypothesis [40], this perceived "failure" of organs might instead be interpreted as a potentially protective mechanism, because reduced cellular metabolism could increase the chances of survival of cells, and thus organs, in the face of an overwhelming insult. Multiple organ failure induced by critical illness might be primarily a functional, rather than a structural, abnormality. Indeed, it may not be failure as such, but a potentially protective, reactive mechanism. The decline in organ function would be triggered by a decrease in mitochondrial activity and oxidative phosphorylation, leading to reduced cellular metabolism. This effect on mitochondria might be the consequence of acute-phase changes in hormones and inflammatory mediators.

Conclusion

MODS is a complex syndrome whose pathophysiological mechanisms are poorly understood, and multiple pathways lead to organ failure. Differences among different ages have not been deeply evaluated yet. What seems to arise from retrospective studies is that if age is an established mortality risk factor for MODS patients, its proportional impact is probably blunted when adjusted with other co-factors (mainly severity scores), especially for older (>75) patients. Age per se is not a reliable prognostic factor in elderly critically ill patients.

Acute Renal Failure in the Setting of MODS

Introduction

Acute renal failure (ARF) affects 5–7% of all hospitalized patients [41–43] and continues to be associated with poor outcomes [44–50]. This syndrome is common in the intensive care unit, with a reported incidence of 1–25% [51, 52] depending on the population being studied and the criteria used to define its presence. ARF, a manifestation of single organ (kidney) failure—for example, isolated acute renal tubular necrosis, drug toxicity, urinary tract obstruction, etc. (see Chapter 21)—can usually be managed outside the ICU setting and carries a good prognosis even in the elderly, with mortality rates less than 5–10% [53]. In contrast, ARF complicating nonrenal organ system failure in the ICU setting is associated with mortality rates of 50–70%, which have remained relatively constant over the last several decades [54–59]. It is generally accepted that ARF in the ICU setting is associated with a high mortality rate [60, 61] and that ICU patients who develop ARF have a higher mortality than those who do not [62–64]. Furthermore, evidence exists that ARF is a specific independent risk factor for poor prognosis in the critically ill patient [61].

It is interesting that, despite the many improvements in dialytic technology, including the development and refinement of continuous renal replacement therapies for the most critically ill patients, we have seen no effective change in the high mortality rates associated with complex ARF in a setting of multiorgan failure. A possible explanation of this finding may include a change in the population of patients, the differences between the causes of ARF in the past and nowadays, and more complexity in the pathophysiology of ARF. Another possibility is that patients who would previously have died before they could long enough to develop ARF, and the older patients who are more susceptible to ARF make up an increasing percentage of the ICU population.

A final explanation might be that the same pathophysiological factors involved in the development of ARF are also incriminated in the failure of other organs, so that ARF is generally part of MODS [59]. It is evident that patients with ARF as part of MODS have the highest mortality rate. Additionally, critically ill patients and especially elderly critically ill patients are affected by variously combined causes and risk factors for ARF, including all conditions reducing an effective circulating volume and leading to a further decrease in mean arterial pressure and thus also renal perfusion pressure, such as hypovolemia, hypotension, hypoxia, sepsis [65], rhabdomyolysis [66], pre-existing renal, hepatic, or cardiac dysfunction, diabetes mellitus, positive pressure ventilation, and exposure to nephrotoxins. In the perioperative setting, ARF risk factors include prolonged aortic clamping [67], emergency rather than elective surgery, use of higher volumes (>100 mL) of intravenous contrast media, and raised intraabdominal pressure.

Over the last three decades, several experimental models have identified pathophysiological mechanisms associated with ARF and have enhanced our understanding of the disease [68–70]. These mechanisms are the same in the young and in the elderly. It is evident that ARF can result from alterations in renal perfusion, changes in glomerular filtration, and tubular dysfunction and that correction of these factors can ameliorate the effects of ARF [71, 72]. It is well known that, in the elderly patient, renal perfusion and glomerular filtration and tubular function are impaired and that ischemic injury can occur more easily. The elderly usually have reduced renal blood flow, and GFR autoregulation may be lost; thus, hypoxia in the cortex and medulla can occur in the early onset of MODS (see Chapter 5).

On the basis of the identification of the underlying mechanisms, several new potential interventions have been developed that have been shown to alter the course of incipient and established ARF in experimental models [73–75]. Nonetheless, no effective therapy in the early management of ARF has been found yet. Interventions that have been deemed ineffective (or potentially harmful) include the following: loop and osmotic diuretic agents [76, 77], "renal dose" dopamine [78, 79], atrial natriuretic peptide [80, 81], insulin-like growth factor-1 [82], and endothelin-receptor antagonists [83]. It is therefore very important for physicians to have an appreciation of what is known and not known about the pathophysiology of ARF in order to implement rational therapies.

Pathogenesis of Septic Acute Renal Failure

Sepsis and septic shock are very often associated with MODS, remain the most important cause of acute renal failure in critically ill patients, and account for more than 50% of cases of ARF in the ICU. Despite our increasing ability to support vital organs and resuscitate patients, the incidence and mortality of septic ARF remain high [84, 85]. A possible explanation of why, despite treatment, ARF is so common in severe sepsis and septic shock and why mortality has remained high might relate to our minimal understanding of septic ARF and its pathogenesis. It is therefore very important for critical care physicians to have an appreciation of what is known and not known about this condition in order to implement rational therapies.

A dominant and worldwide paradigm derived from observations in animals and humans with hypodynamic or hypovolemic shock (hemorrhagic, cardiogenic, or even septic shock) is based on a belief that ARF is due to renal ischemia/underperfusion [85]. This construct implies that restoration of an adequate renal blood flow should be the primary means of renal protection in critically ill patients. Led by a paradigm of what the "organ resuscitation" should be and how flow should be increased, the school of "fill and spill" ("fill" the circulation and urine will "spill" into the bucket) developed, with a common therapeutic response to oliguria in a septic patient being to "fill the circulation" [86]. Surprisingly, no randomized controlled trials (RCTs) exist to either support or negate this paradigm in septic patients.

The second approach of "squeeze and diurese" for septic ARF treatment is still based on the concept that ischemia/underperfusion is the major pathophysiological mechanism. The protagonists of this approach hold that once adequate filling has been achieved (typically RAP > 10 mmHg in a patient without cardiac disease) and the cardiac output has been confirmed to be preserved or increased, more is to be gained by increasing the mean arterial pressure, the driving force to renal blood flow, with vasopressors ("squeeze") [87, 88]. This is often accompanied by the administration of loop diuretics, in order to "paralyze the medulla, avoid ischemia and induce polyuria" ("diurese"): This way, fluid management should be simplified, as the antibiotics take effect and the septic state abates. Interestingly, this approach is considered dangerous in North America but is reasonably popular in Australia. As with the "fill-and-spill" paradigm, no RCTs exist to either support or negate the "squeeze and diurese" paradigm in septic patients.

In the presence of sepsis, the belief that renal blood flow (RBF) decreases significantly remains controversial. Some studies have concluded that RBF in sepsis might, in fact, increase [89, 90], and so the effect on RBF in each case of hyperdynamic human sepsis is largely unknown. It is possible that, even though there is preserved or increased global renal blood flow in hyperdynamic sepsis, intrarenal redistribution of blood flow favoring the cortex may occur. Unfortunately, no studies with technology that allows continuous measurements of both medullary and cortical blood flow in humans with hyperdynamic sepsis have been performed. In a recent investigation using laser Doppler flowmetry to continuously monitor medullary and cortical blood flow in hyperdynamic septic sheep [91], we found that both medullary and cortical blood flows remain unchanged and that the administration of norepinephrine induced a significant increase in flows to both regions. These

observations challenge the view that the medulla is ischemic during hyperdynamic sepsis, although it highlights that hemodynamic factors are indeed at work, which can be modified by interventions that affect systemic blood pressure and cardiac output. Nevertheless, even though hemodynamic changes are important, they are likely to represent only part of the mechanisms responsible for loss of renal function.

In conclusion, renal hypoperfusion might be important in hypodynamic states, but persistent renal underperfusion is unlikely to play a key role in the continued development of ARF during hyperdynamic resuscitated sepsis (i.e., the state seen in the majority of critically ill, septic patients with severe ARF).

From the above discussion, we know that neither global nor intrarenal hemodynamic changes can consistently be shown to be the sole contributor to sepsis-induced ARF. There must, therefore, be other mechanisms at work that are not hemodynamic in nature but may be immunological or toxic in nature. Sepsis is characterized by the release of a vast array of inflammatory cytokines, arachidonate metabolites, vasoactive substances, thrombogenic agents, and other biologically active mediators. A large body of experimental data suggests that these mediators and neuroendocrine mechanisms might be involved in the pathogenesis of organ dysfunction in sepsis [92]. How they injure the kidney remains unknown, although one such mechanism might be apoptosis.

Apoptosis is a form of cell death that is mediated by a genetically determined biochemical pathway and characterized morphologically by cell shrinkage, plasma membrane blebbing, chromatin condensation, and nuclear fragmentation [93, 94]. Cells can die by one of two pathways: necrosis or apoptosis. Necrosis results from severe ATP depletion and leads to rapid uncoordinated collapse of cellular homeostasis. Apoptosis is an energy-requiring and genetically directed process.

There is now evidence to show that renal tubular cells die by apoptosis as well as necrosis in experimental models of acute ischemic and toxic renal injury [93]. Jo and colleagues [94] have recently shown that apoptosis of tubular cells by lipopolysaccharide and inflammatory cytokines is a possible mechanism of renal dysfunction in endotoxemia. Unfortunately, TNF blockade with monoclonal antibodies fails to protect the animal or kidney from apoptosis during endotoxemia [95]. Preliminary experimental observations in septic sheep also show that, after only 3 hours of sepsis, induced by an intravenous injection of *E. coli*, there is strong expression of early-phase pro-apoptotic proteins such as Bax (the pro-apoptotic protein responsible for mitochondrial injury) [94]. Clearly, it would be attractive to have therapies that can favorably modulate the development of apoptosis. A new paradigm might need to be considered and tested.

Attenuating or blocking apoptosis in sepsis and ARF might sound far-fetched, but it is not as far away from the bedside as clinicians might think. Bernard and colleagues [96] showed a significant decrease in the 28-day mortality rate (30.8% in the placebo group and 24.7% in the treatment group) in 1690 sepsis patients treated with recombinant human activated protein C (rhAPC). The efficacy of rhAPC in septic patients may be due to its anticoagulation effect. However, a recent study by Joyce et al. [97] showed that rhAPC directly modulated patterns of endothelial cell gene expression clustering into anti-inflammatory and cell survival pathways and modulated several genes

in the endothelial apoptosis pathway, including the Bcl-2 homologue protein (an inhibitor of apoptosis). More recently, Cheng and co-workers [98] have shown that APC blocks p53-mediated apoptosis of human brain endothelium *in vitro* as it normalized the Bax/Bcl-2 ratio and reduced caspase-3 signaling. This study creates a new link among coagulation, inflammation, apoptosis, and cell death and provides some insight into the molecular basis for the efficacy of rhAPC in systemic inflammation and sepsis.

Caspases are enzymes that play a key role in apoptosis, and caspase inhibitors have been developed as anti-apoptotic agents. Fauvel et al. [99] developed an animal model that showed myocardial dysfunction after endotoxin administration. These investigators successfully used a broad-spectrum caspase inhibitor (z-VAD.fmk) and a specific caspase-3-inhibitor (z-DEVD.fmk) and demonstrated decreased myocardial dysfunction, reduced caspase activation, and reduced nuclear apoptosis 2 hours after experimental endotoxaemia. Neviere et al. [100] also used z-VAD.fmk from 4 to 14 hours after endotoxin administration in rats and showed that not only was there a reduced caspase activity and nuclear apoptosis, but also endotoxin-induced myocardial dysfunction could be completely prevented. As myocardial dysfunction can be prevented by anti-apoptotic treatment, it is possible that future studies will show that the kidney is another organ that may benefit from caspase inhibitors. However, the complexity of the balance of factors involved in apoptosis and the response to sepsis are highlighted by the possibility that caspase inhibition may actually cause harm [101].

The use of aggressive insulin therapy aimed at achieving euglycemia in critically ill patients has been shown to reduce mortality significantly in a single-center study of critically ill patients [102]. Among the important findings of this trial was a dramatic reduction in the development of severe ARF. A possible explanation for this finding may relate to the immunomodulating effects of insulin [103], including a powerful anti-apoptotic effect [104], and conversely to the fact that a high glucose concentration induces oxidative stress-mediated apoptosis in tubular epithelial cells [105].

Ventilation of patients with the acute respiratory distress syndrome by means of a low-tidal volume strategy has been shown to reduce mortality [106]. The mechanisms for such reduced mortality, however, remain unknown. In a fascinating series of studies, Imai et al. [107] recently demonstrated that low-tidal volume ventilation might protect from ventilation-induced renal epithelial cell apoptosis by reducing Fas ligand-dependent pro-apoptotic activity in plasma.

N-acetylcysteine has been shown to attenuate contrast-induced renal injury in many randomized controlled studies [108].However, its mechanism of action remains unknown. Its effect on oxygen radical-induced inflammation and apoptosis may offer the correct explanation [109] and suggest yet another pathway to the attenuation of sepsis-/inflammation-associated apoptosis.

Conclusions

Although hemodynamic factors are likely to play an important role in the pathogenesis of sepsis-induced ARF, other mechanisms are also at work, which include immunological, toxic, and inflammatory elements. Among these mechanisms, apoptosis may be important. Indeed, organ-protective

strategies recently reported in animal and human studies could work by inhibiting the development of the apoptotic cascade. Although the importance of prompt and adequate resuscitation with rapid and carefully monitored restoration of intravascular filling, cardiac output, and blood pressure must not be neglected, it is possible that, as evidence accumulates for apoptosis as a major mechanism of organ injury, the paradigms currently used to explain ARF in sepsis will shift from acute tubular necrosis to acute tubular apoptosis (ATA) and our therapeutic approach will change accordingly.

Renal Replacement Therapy in MODS

Introduction

Renal replacement therapy (RRT) has evolved from the concept of "we need to treat the dysfunction of a single organ" (the kidney). As intensive care units have become more and more complex, it has become clear that the majority of patients with acute renal failure often have dysfunction of several other organs. In order to facilitate single organ support in this setting, continuous renal replacement therapy (CRRT) techniques have been developed. It is now time to move from the simple goal of achieving adequate renal support. The proper goal of extracorporeal blood purification in ICU should be *multi-organ support therapy (MOST)*. MOST represents the best logical future conceptual and practical evolution of CRRT: Its biological rationale is provided by animal and clinical evidence that confirms the need to move rapidly in this direction theoretically, practically, and technologically.

The picture of MODS is a devastating clinical entity leading to death in the majority of cases. The superimposed condition of sepsis further increases illness severity and worsens the prognosis. In these circumstances, treatment of ARF becomes complicated and the concept of adequate treatment requires deeper understanding. The probability of death is directly correlated to the number of failing organs, other than the kidney and the severity of physiological disorders. A clinically sensitive approach should try to broaden the spectrum of physiological endpoints targeted by extracorporeal therapy and attempt to reduce the number of dysfunctioning organs, degree of severity, loss of homeostasis, and ultimate effect on outcome. Since the severity of physiological disorder (score) in the first 24 hours after admission to the ICU "drives" prognosis at hospital discharge, early and adequate correction of disorders is critical for outcome. The adequacy of any artificial organ support is, therefore, measured by how closely it mimics the flexibility, versatility, and efficacy of the organ system(s) it seeks to substitute or support.

The Multiple Potentials of MOST

Kidneys

Extracorporeal therapies have traditionally been employed to replace lost renal function in ARF. This is definitely the most common utilization of CRRT in the ICU. In the last 20 years, evidence has accumulated to support the concept that CRRT is efficient, safe, and well tolerated [110]. Evolution from the arteriovenous circulation to venovenous pumped systems has improved efficiency and increased clearance to 2 or even 3 L/hr. This results in values

of daily Kt/V ranging from 1 to 1.5. Disregarding for a moment the concept that dose and outcome are correlated, the end result of an efficient therapy such as CRRT is blood purification similar to that obtained by the native kidney.

Temperature

With the extracorporeal fluxes used for CVVH and CVVHD, negative thermal balance of up to –100 kJ/hr can be obtained depending on the length of the blood lines, the room temperature, and the dialysate/replacement fluid temperature. This might contribute to modulating the inflammatory response as well as oxygen demand in several organs with the possibility of using such a mechanism for specific clinical targets.

Acid Base and Electrolytes

Most imbalances of sodium and other electrolyte imbalances can be corrected by increasing or restricting free water intake. Other electrolyte imbalances can be medically corrected. When disorders are life-threatening or refractory to medical corrections, extracorporeal therapy is the treatment of choice. The use of convection applied to the extracorporeal circulation is the same used by the human glomerulus. The ultrafiltrate contains crystalloids in the same concentration as in plasma water, but not cells or colloids. This mechanism is guaranteed by the use of a highly permeable membrane mounted on the hemofilter with permeability characteristics similar to those of the human glomerulus. The function of the renal tubules and the interstitium is accomplished, during hemofiltration, by the reinfusion of a tailored replacement solution. With this mechanism, a final solute and electrolyte balance can be achieved according to the desired goals. The advantage of such a system in comparison to the use of diuretics is the possibility of dissociating the removal of water from that of sodium or other electrolytes. Because of the slow and gentle rate of fluid exchange, the treated blood operates in continuous equilibrium with peripheral tissues and organs, and the entire organism may benefit from a rapid and effective restoration of water, sodium, and electrolyte homeostasis. This restoration of homeostasis is particularly true for acid-base control (as administration of bicarbonate can be easily titrated to the necessary acid-base goals), intra- and extracellular potassium and phosphate equilibrium, and water fluxes between the interstitium and the intracellular space.

Heart

Cardiac support can be achieved by the optimization of fluid balance, the reduction of organ edema, and the restoration of desirable levels of preload and afterload. Furthermore, the continuity of the extracorporeal therapy allows remarkable cardiovascular stability with maintenance of hemodynamic parameters including mean arterial pressure, heart rate, and systemic vascular resistance. Such stability, which is achieved through slow continuous ultrafiltration and continuous refilling of the intravascular volume from the interstitium, allows stability of circulating blood volume and the preservation of organ perfusion.

Brain

Cerebral edema is a consequence of rapid solute movement during intermittent hemodialysis [111]. The arrival of CRRT has eliminated this risk. The accumulation of uremic toxins from inadequate blood purification is a

known cause of encephalopathy. This is not the case during the use of CRRT in the ICU. The development of hypotension can induce brain injury. As we showed, the use of CRRT with its associated hemodynamic stability has decreased this risk. The accumulation of amino acid derivatives might be responsible for the encephalopathy of sepsis. By removing such excessive soluble derivatives and decreasing imbalances between amino acids, CRRT may also have an effect on the encephalopathy of sepsis. Acidemia induces changes in the function of cerebral enzymes involved in glucose utilization and may be responsible for changes in consciousness [112]. The correction of acidemia by CRRT might also be another way of protecting the brain from injury. Thus, a significant degree of brain protection is provided.

Liver

The ideal blood purification system for liver support should have a blood flow of at least 600–800 mL/min; it should be capable of removing lipid-soluble toxins, water-soluble toxins, and protein-bound toxins; and it should achieve clearances of the above toxins of at least 600–700 mL/min. A complete liver support system should include a detoxification component and a secretory component, possibly capable of metabolic activity. While the first component can be accomplished by an inert mechanical system, the second one can only be performed by a hybrid artificial organ containing a mixture of synthetic materials and living hepatocytes. Nevertheless, the first detoxifying component can be sufficient to perform liver support and to bridge the patients toward recovery of the native organ or transplantation. To perform such a task, a combination of membrane separation processes and adsorption mechanisms must be utilized. Different systems are available today for liver support [113]. Some of them utilize the direct contact of blood with absorbent materials. This approach can be utilized in series with standard hemofiltration procedures, but it has limitations imposed by the partial absorptive capacity of the sorbents. In fact, in order to place the sorbent in contact with blood, the material must be coated to improve biocompatibility; this process of coating often reduces the efficiency of the absorptive process. On the other hand, more effective sorbent materials can be utilized and placed in contact with plasma, if the blood cells are previously separated through a plasma filter. The final expected physiological effects can be an improved neurological state, clearance of unconjugated bilirubin at 20–40 mL/min or more, clearance of some aromatic amino acids, decrease in serum ammonia, and removal of some cytokines.

Sepsis and Septic Shock

The issue of whether hemofiltration can remove inflammatory mediators has been controversial for some time. Numerous *ex vivo* as well as animal and human studies have shown that synthetic filters can extract nearly every substance involved in sepsis to a certain degree [114]. Prominent examples are complement factors, TNF, IL-1, IL-6, IL-8, and PAF [115–118]. Regarding plasma cytokine levels, their decrease appears minor in host defenses against infection, while high levels need to be modulated by anti-inflammatory feedback. As sepsis does not fit a one-hit-model but shows the complex behavior of mediator levels that change over time, neither single-mediator-directed nor one-time interventions seem appropriate. Some studies showed no influence on cytokine plasma levels by CRRT [119]. On the other hand,

significant clinical benefits in terms of hemodynamic improvement have been achieved even without measurable decreases in cytokine plasma levels ("the peak concentration hypothesis"). The removal of substances other than the measured cytokines might have been responsible for the achieved effect. However, several mediators may act together to alter the functional responses of the circulating leukocytes. When the response to sepsis is viewed in a network perspective, absolute values seem to be less relevant than relative ones. Within an array of interdependent mediators, even small decreases could induce major balance changes.

In spite of some encouraging results as already mentioned, the extent of achievable clinical benefit with conventional CRRT (using conventional filters and flow rates) in sepsis has generally been disappointing [120]. Consequently, attempts have been made to improve the efficiency of soluble mediator removal in sepsis by increasing the amount of plasma water exchange, i.e., increasing ultrafiltration rates. Animal studies provide great support to this concept. These studies established that a convection-based treatment can remove substances with hemodynamic effects resembling septic shock, when sufficiently high ultrafiltration rates are applied. More relevant to human sepsis was the finding that ultrafiltration dosage is correlated to outcome in critically ill patients with ARF. In a large randomized, controlled study including 425 patients, an ultrafiltration dosage of 35 mL/kg/hr increased survival rate from 41% to 57% compared to a dosage of 20 mL/kg/hr [121]. Eleven to 14% (per randomization group) of the patients had sepsis. In these subgroups, there was a trend to have a direct correlation between treatment dosage and survival even above 35 mL/kg/hr in contrast to the whole group where a survival plateau was reached.

Of note, there was no increase in adverse effects even with the highest ultrafiltration dosage. Impressive clinical results were obtained in an evaluation of short-term HVHF in 20 patients in catecholamine-refractory septic shock [122] comprising a patient cohort with very poor expected survival. A control group was not defined. Only one 4-hour session of HVHF removing 35 L of ultrafiltrate replaced by bicarbonate-containing fluid was applied as soon as mean blood pressure could not be stabilized above 70 mmHg with dopamine, norepinephrine, and epinephrine after appropriate volume resuscitation. HVHF was followed by conventional CVVH. Endpoints were the increase in cardiac index, mixed venous oxygen saturation and arterial pH, and decrease in norepinephrine requirements. Eleven patients reached all predefined endpoints and showed impressively good survival (9 out of 11) at 28 days. Nine patients did not reach all endpoints and had a 100% mortality rate. Apart from responding to HVHF, only time from ICU admission to start of HVHF and body weight were survival-associated factors in the analysis. Patients with higher body weight did worse possibly because they received a smaller ultrafiltration dosage per body weight, as the authors speculated [122]. These trials still need cautious interpretation with respect to their limited design, but they certainly deliver evidence of feasibility and efficacy to set the stage for a large-scale trial on HVHF in sepsis.

A further step to increase mediator removal has been achieved with plasma filtration coupled with absorption and followed by dialysis or filtration (CPFA) [123]. The use of a plasma filtration membrane coupled with an absorption device (as in CPFA) could enhance unselective removal and

improve hemodynamic stability compared to CRRT: In a recent cross-over trial, CPFA was indeed associated with the restoration of a stable hemodynamic state, particularly related to an increase in MAP [124]. This change in blood pressure led to a significant reduction in norepinephrine requirement. CPFA also restored *in vitro* leukocyte responsiveness to LPS. The magnitude of this effect was significantly greater with CPFA than with CVVHDF alone [124].

Conclusions

Multi-organ dysfunction remains the paramount challenge in the care of critically ill patients with ARF. We need to change our conceptual framework of reference from renal replacement therapy to general extracorporeal blood purification and then to multi-organ support therapy. The evolution from RRT to MOST is going to be technically and scientifically complex and will need strong scientific evidence to be confirmed and routinely utilized in the future.

MODS in the Elderly: Bioethical Problems

Caring for elderly patients with MODS can pose important bioethical questions, which must be carefully addressed and appropriately managed.

The most important features of the situation can be summarized as follows:

1. The pathological insult is very severe by definition, and the prognosis is usually worsened by different coexisting chronic pathologies (diabetes, hypertension, COPD, etc.) and multi-organ subclinical derangements.
2. When the importance of the acute illness and the need for intensive care become apparent, such patients are seldom sufficiently competent to be effectively involved in planning the course of care. Furthermore, they can be affected by pre-existing depression, which can condition their decision about care: A survey comparing depressed and nondepressed older veterans suggests that depression is associated with treatment refusal in situations with a good medical prognosis [125].
3. Again, very elderly patients can be already beyond the physiological limits of life expectancy and thus near the natural end of their life.
4. Finally, the overall standard of care they need can be extremely burdensome, long, painful, and, in addition, very expensive.

The consequent core question is, how intensive and prolonged should the care for elderly patients with MODS be? Do existing published data help make a correct decision?

As for the results of intensive care, data from the SUPPORT study show a modest independent association between patient age and survival of serious illness. Each additional year of age increased the hazard of death by 1.0% for patients 18–70 years old and by 2.0% for patients >70 years of age. Such an effect was not explained by the less aggressive care provided to elderly patients [20]. In a recent prospective, observational cohort study, Chelluri and co-workers [126] demonstrated that in critical patients receiving prolonged mechanical ventilation, long-term mortality rate is associated with older age and poor pre-hospitalization functional status. Many survivors needed assistance after discharge from the hospital, and more than half still required

caregiver assistance at 1 year. More data are needed on the longer-term post-hospital courses of elderly patients who survive MODS, as many of them had, and still have, underlying major health problems that may have contributed to the episode that precipitated their stay in the ICU.

Other data, again from the SUPPORT study, demonstrate that seriously ill older patients were on average treated less aggressively than younger patients. Yet, such diminished aggressiveness of treatment does not seem responsible for the modest survival disadvantage associated with older age; on the contrary, it could be the consequence of an excessive provision of ineffective treatment to younger patients [127].

Another prospective observational study of patients receiving prolonged mechanical ventilation showed that daily and total hospital costs were lower in older patients in nearly all cost departments examined, probably because of preferences for less aggressive care by older patients and their families or by healthcare providers [126]. A further, retrospective analysis on patients with acute respiratory failure demonstrated that for patients with relatively good short-term prognoses, ventilator support and aggressive care were economically worthwhile, even for patients 75 years of age and older. Not surprisingly, for patients with poor short-term prognoses, ventilator support and aggressive care were much less cost-effective for adults of all ages [128]. Equally, in a prospective cohort study, Montuclard and co-workers [129] showed a reasonable hospital survival in elderly patients ($\geq$70 years old) after prolonged (>30 days) mechanical ventilatory support. The authors believe that, in spite of a moderate disability (perceived quality-of-life scores remained nonetheless acceptable), their data justify prolonged ICU stays for elderly patients [129].

Again regarding quality of life of survivals, data from Udekwu and co-workers [130] demonstrated that in elderly patients surviving surgical intensive care, rates of full dependency rose only slightly and perceived quality of life was high. According to the authors, the undoubtedly high hospital and post-discharge mortality should not motivate restriction of care for elderly patients requiring surgical intensive care, given their high post-illness subjective quality-of-life measures.

As for patients' preferences regarding intensive care, data from the SUPPORT study show that patient age may influence decisions to withhold life-sustaining treatments. For ventilator support, surgery, and dialysis, the rate of decisions to withhold therapy increased 15%, 19%, and 12%, respectively, with each decade of age [20]. In a previous study, most very old hospitalized patients who could be interviewed were unwilling to trade much time for excellent health, but preferences varied greatly. These authors underlined that—whenever possible—health values of the very old should be elicited directly from the patient [131]. Also, a recent prospective cohort study demonstrated a wide variation in preference for aggressive care. Predicted quality of life appears to be as important as estimates of intensive care unit survival in decision making. When confronted with extended mechanical ventilation and associated care, a significant proportion of patients would accept this care only for an improved prognosis [132].

As for the usefulness of knowing patients' preferences, data from a prospective cohort study on patients over 80 demonstrate that the use of life-sustaining treatments was prevalent in those patients who died, despite the fact that the majority had a preference for comfort care. Most patients

who died had refused aggressive care; 70% wanted their care focused on comfort care, and 80% had a do-not-resuscitate order. However, 63% received life-sustaining treatments before death [133].

So it is not surprising that the published data are too heterogeneous to draw easy conclusions in this area, particularly because of the great variability among patients. In real life, biology and biography very seldom coincide: "75 years of age" can have totally different meanings in two patients who may have quite different biological status, from virtually normal for age in all respects, to the presence of multiple incapacitating coexisting morbid conditions.

In addition, the biographical data can change, and so preferences about quality of life, acceptability of prognosis, and consequently intensity of care can change, even in the same patient at different times. Yet, the patient remains of central and fundamental importance in the decision. A good policy would be to plan a timely course of treatment for every patient, involving him and his relatives as soon as possible in the decision-making process. Ideally, every patient should be admitted to the ICU with a clear plan of action, in which the patient's wishes, attitudes, and moral/religious beliefs are clarified and the intended therapeutic goal is specified. In this way, it is possible give the right sense to every intended intervention and to make sound decisions even in case of unexpected/unplanned situations. Of course, as the clinical conditions change, the therapeutic goal can be updated; yet, the goal should always be clear, well known, and shared by everybody involved in the patient's care. Unfortunately, all of this happens very rarely in the real world. Yet, decisions have to be made every day.

For an appropriate decision to be made, at least three key factors are relevant:

1. The clinical data: The diagnosis and the prognosis should be ascertained as reasonably as possible. A decision based on wrong or incomplete data is both clinically and morally questionable.
2. The patient: The person's wishes about intensity of care should be clarified, hopefully before starting intensive care. If competence is questionable, advance directives—when available—can help. In case of refusal of possibly meaningful nonfutile care, the patient's position should be carefully evaluated and weighed against the patient's view of life and moral and religious beliefs (as witnessed by the patient's relatives and friends), in order to assess its acceptability and to do what the patient really wants to be done.
3. The environment: The presence and the position of a careful and loving family are usually a key factor in order to make a correct decision. Indeed, the patient's relatives can play a fundamental role in the decision process, supporting the conscious patient and helping the clinicians assess the wishes of the unconscious one. After at least the partial failure of large and expensive trials such as the SUPPORT study, the "La Crosse" experience deserves great attention [134]. Two of the most important features of this pre-hospital, community-based study were that the focus of end-of-life decision making was facilitating discussion about values and preferences, not completing documents, and that such a discussion was refocused away from autonomy toward family relationships [135].

In practice, the best decision is the one that best promotes the patient's dignity, keeping in mind that excellence in ICU care is measured by the quality of ICU survivals and of ICU deaths as well. Obviously, the patient's position, as to the definition of an acceptable level of care and of (residual) life, is mandatory [136]. Regardless of the final decision, every patient has the right to be protected against pain and any form of physical and psychological suffering.

References

1. Eiseman, B., Beart, R., Norton, L. Multiple organ failure. *Surg. Gyn. Obstet*. 1977; 144:323–326.
2. Fry, D.E., Pearlstein, L., Fulton, R.L., et al, Multiple system organ failure: The role of uncontrolled infection. *Arch. Surg*. 1980; 115:136–140, 278–283.
3. Bone, R.C., Balk, R.A., Cerra, F.B., et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: ACCP/SCCM Consensus Conference Committee. *Chest* 1992; 101:1644–1655.
4. Knaus, W.A., Wagner, D.P., Draper, E.A., et al. The APACHE III prognosis system: Risk prediction of hospital mortality for critically III hospitalized adults. *Chest* 1991; 100:1619– 1636.
5. Behrendt, C.E. Acute respiratory failure in the United States: Incidence and 31-day survival. *Chest* 2000; 118:1100–1105.
6. Esteban, A., Anzueto, A., Frutos, F., Alia, I., Brochard, L. Characteristics and outcomes in adult patients receiving mechanical ventilation. A 28-day international study. *JAMA* 2002; 287:345–355.
7. Jakob, S.M., Rothen, H.U. Intensive care 1980–1995: Change in patient characteristics, nursing workload and outcome. *Intensive Care Med*. 1997; 23:1165–1170.
8. McLean, R.F., McIntosh, J.D., Kung, G.Y., Leung, D.M., Byrick, R.J. Outcome of respiratory intensive care for the elderly. *Crit. Care Med*. 1985; 13:625–629.
9. Nicolas, G., Le Gall, J.R., Alperovitch, A., Loirat, P., Villers, D. Influence of patients' age on survival, level of therapy and length of stay in intensive care units. *Intensive Care Med*. 1987; 13:9–13.
10. Chelluri, L., Pinsky, M.R., Grenvik, A.N. Outcome of intensive care of the "oldest-old" critically ill patients. *Crit. Care Med.* 1992; 20:757–761.
11. Campion, E.W., Mulley, A.G., Goldstein, R.L., et al. Medical intensive care for the elderly. A study of current use, costs, and outcomes. *JAMA* 1981; 246: 2052–2056.
12. Fedullo, A.J., Swinburne, A.J. Relationship of patient age to cost and survival in a medical ICU. *Crit. Care Med*. 1983; 11:155–159.
13. Witek, T.J., Jr., Schachter, E.N., Dean, N.L., Beck, G.J. Mechanically assisted ventilation in a community hospital: Immediate outcome, hospital charges, and follow-up of patients. *Arch. Intern. Med*. 1985; 145:235–239.
14. O'Donnell, A., Bohner, B. Outcome in patients requiring prolonged mechanical ventilation: Three-year experience. *Chest* 1991; 100:295.
15. Ely, E.W., Evans, G.W., Haponik, E.F. Mechanical ventilation in a cohort of elderly patients admitted to an intensive care unit. *Ann. Intern. Med*. 1999; 131:96–104.
16. Seneff, M.G., Wagner, D.P., Wagner, R.P., Zimmerman, J.E., Knaus, W.A. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995; 274: 1852–1857.
17. Zilberberg, M.D., Epstein, S.K. Acute lung injury in the medical ICU: Comorbid conditions, age, etiology, and hospital outcome. *Am. J. Resp. Crit. Care Med*. 1998; 157(4 Pt 1):1159– 1164.

18. Ely, E.W., Wheeler, A.P., Thompson, B.T., et al. Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. *Ann. Intern. Med.* 2002; 136:25–36.
19. Suchyta, M.R., Clemmer, T.P., Elliott, C.G., Orme, J.F., et al. Increased mortality of older patients with acute respiratory distress syndrome. *Chest* 1997; 111: 1334–1339.
20. Hamel, M.B., Davis, R.B., Teno, J.M., Knaus, W.A., Lynn, J., Harrell, F., Jr., Galanos, A.N., Wu, A.W., Phillips, R.S. Older age, aggressiveness of care, and survival for seriously ill, hospitalized adults. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *Ann. Intern. Med.* 1999 Nov. 16; 131(10):721–728.
21. Kuhne, C., Ruchholtz, S., Kaiser, G.M., Nast-Kolb, D., Working Group on Multiple Trauma of the German Society of Trauma. Mortality in severely injured elderly trauma patients—When does age become a risk factor? *World J. Surg.* 2005; 29:1–7.
22. Maclean, L.D., Mulligan, W.G., Mclean, A.P.H., et al. Patterns of septic shock in man: A detailed study of 56 patients. *Ann. Surg.* 1967; 166:543–562.
23. Bell, R.C., Coalson, J.J., Smith, J.D., et al. Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann. Intern. Med.* 1983; 99: 293–298.
24. Tran, D.D., Groeneveld, A.B., van der Meulen, J., et al. Age, chronic disease, sepsis, organ system failure, and mortality in a medical intensive care unit. *Crit. Care Med.* 1990; 18:474–479.
25. Marshall, J.C., Christou, N.V., Horn, R., et al. The microbiology of multiple organ failure: The proximal gastrointestinal tract as an occult reservoir of pathogens. *Arch. Surg.* 1988; 123:309–315.
26. D'Amico, G., Pifferi, S., Leonetti, C., et al. Effectiveness of antibiotic prophylaxis in critically ill adult patients: Systematic review of randomized controlled trials. *Br. Med. J.* 1998; 316:1275–1285.
27. Nathens, A.B., Marshall, J.C. Selective decontamination of the digestive tract (SDD) in surgical patients: A systematic review of the evidence. *Arch. Surg.* 1999; 134:170–176.
28. Norton, L.W. Does drainage of intraabdominal pus reverse multiple organ failure? *Am. J. Surg.* 1985; 149:347–350.
29. Nathens, A.B., Rotstein, O.D., Marshall, J.C. Tertiary peritonitis: Clinical features of a complex nosocomial infection. *World J. Surg.* 1998; 22:158–163.
30. Wunderink, R.G. Attributable mortality of ventilator-associated pneumonia. *Sepsis* 1997; 1:211–221.
31. Markowicz, P., Wolff, M., Djedaini, K., et al. Multicenter prospective study of ventilatorassociated pneumonia during acute respiratory distress syndrome: The ARDS Study Group. *Am. J. Resp. Crit. Care Med.* 2000; 161:1942–1948.
32. Marshall, J.C., Sweeney, D. Microbial infection and the septic response in critical surgical illness: Sepsis, not infection, determines outcome. *Arch. Surg.* 1990; 125:17–23.
33. Rivers, E., and The Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N. Engl. J. Med.* 2001; 345:1368–1377.
34. Bernard, G.R., Hartman, D.L., Helterbrand, J.D., et al. Recombinant human activated protein C (rhAPC) produces a trend toward improvement in morbidity and 28-day survival in patients with severe sepsis. *Crit. Care Med.* 1999; 27: A33–118.
35. Bernard, G.R., Vincent, J.-L., Laterre, P.-F., et al. Efficacy and safety of recombinant activated protein C for severe sepsis. *N. Engl. J. Med.* 2001; 344: 699–709.

36. Seely, A.J.E., Christou, N.V. Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. *Crit. Care Med*. 2000; 28: 2193–2200.
37. Marshall, J.C. Complexity, chaos, and incomprehensibility: Parsing the biology of critical illness. *Crit. Care Med*. 2000; 28:2646–2648.
38. Nathens, A.B., Marshall, J.C. Selective decontamination of the digestive tract in surgical patients: A systematic review of the evidence. *Arch. Surg*. 1999; 134:170–176.
39. Marshall, J.C. Clinical trials of mediator-directed therapy in sepsis: What have we learned? *Intensive Care Med*. 2000; 26:S75–S83.
40. Singer, M., De Santis, V., Vitale, D., Jeffcoate, W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004; 364:545–548.
41. Albright, R.C. Acute renal failure: A practical update. *Mayo Clin. Proc*. 2001; 76:67–74.
42. Hou, S.H., Bushinsky, D.A., Wish, J.B., et al, Hospital acquired renal insufficiency: A prospective study. *Am. J. Med.* 1983; 74:243–248.
43. Nash, K., Hafeez, A., Hou, S. Hospital-acquired renal insufficiency. *Am. J. Kidney Dis.* 2002; 39:930–936.
44. Behrend, T., Miller, S.B. Acute renal failure in the cardiac care unit: Etiologies, outcomes, and prognostic factors. *Kidney Int*. 1999; 56:238–243.
45. Bennett, W.M. Posttransplant acute renal failure. *Ren. Fail*. 1997; 19:225–226.
46. DuBose, T.D., Jr., Warnock, D.G., Mehta, R.L., Bonventre, J.V., Hammerman, M.R., Molitoris, B.A., Paller, M.S., Siegel, N.J., Scherbenske, J., Striker, G.E. Acute renal failure in the 21st century: Recommendations for management and outcomes assessment. *Am. J. Kidney Dis*. 1997; 29:793–799.
47. Clermont, G., Acker, C.G., Angus, D.C., Sirio, C.A., Pinsky, M.R., Johnson, J.P. Renal failure in the ICU: Comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. *Kidney Int*. 2002; 62:986–996.
48. Metcalfe, W., Simpson, M., Khan, I.H., Prescott, G.J., Simpson, K., Smith, W.C., MacLeod, A.M. Acute renal failure requiring renal replacement therapy: Incidence and outcome. *Quar. J. Med*. 2002; 95:579–583.
49. Liano, F., Junco, E., Pascual, J., Madero, R., Verde, E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. *Kidney Int*. 1998; 66:S16–S24.
50. Pruchnicki, M.C., Dasta, J.F. Acute renal failure in hospitalized patients: Part I. *Ann. Pharmacother*. 2002; 36:1261–1267.
51. De Mendonca, A., Vincent, J.-L., Suter, P.M., et al. Acute renal failure in the ICU: Risk factors and outcome evaluated by the SOFA score. *Intensive Care Med*. 2000; 26:915–921.
52. Chertow, G.M., Levy, E.M., Hammermeister, K.E., Grover, F., Daley, J. Independent association between acute renal failure and mortality following cardiac surgery. *Am. J. Med*. 1998; 104:343–348.
53. Shusterman, N., Strom, B.L., Murray, T.G., Morrison, G., West, S.L., Maislin, G. Risk factors and outcome of hospital-acquired acute renal failure. *Am. J. Med.* 1987; 83:65–71.
54. Silvester, W., Bellomo, R., Cole, L. Epidemiology, management, and outcome of severe acute renal failure of critical illness in Australia. *Crit. Care Med*. 2001; 29:1910–1915.
55. Vincent, J.L. Incidence of acute renal failure in the intensive care unit. *Contrib. Nephrol.* 2001; 132:1–6.
56. Liano, F., Pascual, J. Outcomes in acute renal failure. *Semin. Nephrol*. 1998; 18:541–550.
57. Abernethy, V.E., Lieberthal, W. Acute renal failure in the critically ill patient. *Crit. Care Clin*. 2002; 18:203–222.

58. Bates, D.W., Su, L., Yu, D.T., Chertow, G.M., Seger, D.L., Gomes, D.R., Platt, R. Correlates of acute renal failure in patients receiving parenteral amphotericin B. *Kidney Int*. 2001; 60:1452–1459.
59. Brivet, F.G., Kleinknecht, D.J., Loirat, P., Landais, P.J. Acute renal failure in intensive care units: Causes, outcome, and prognostic factors of hospital mortality—A prospective, multicenter study. French Study Group on Acute Renal Failure. *Crit. Care Med.* 1996; 24: 192–198.
60. Butkus, D.E. Persistent high mortality in acute renal failure. *Arch. Intern. Med.* 1983; 143:209–212.
61. Chertow, G.M., Christiansen, C.L., Cleary, P.D., Munro, C., Lazarus, J.M. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch. Intern. Med.* 1995; 155:1505–1511.
62. Menashe, P.I., Ross, S.A., Gottlieb, J.E. Acquired renal insufficiency in critically ill patient. *Crit. Care Med*. 1988; 16:1106–1109.
63. Mangano, C.M., Diamondstone, L.S., Ramsay, J.G., Aggarral, A., Herskowitz, A., Mangano, D.T. Renal dysfunction after myocardial revascularization: Risk factors, adverse outcome, and hospital resource utilization. *Ann. Intern. Med.* 1998; 128:194–203.
64. Vivino, G., Antonelli, M., Moro, M.L., Cottini, F., Conti, G., Bufi, M., et al. Risk factors for acute renal failure in trauma patients. *Intensive Care Med*. 1998; 24:808–814.
65. Wiecek, A., Zeier, M., Ritz, E. Role of infection in the genesis of acute renal failure. *Nephrol. Dial. Transplant* 1994; 9(Suppl 4):40–44.
66. Ward, M.M. Factors predictive of acute renal failure in rhabdomyolysis. *Arch. Intern. Med*. 1988; 148:1553–1557.
67. Myers, B.D., Moran, S.M. Hemodynamically mediated acute renal failure. *N. Engl. J. Med*. 1986; 314:97–100.
68. Lieberthal, W., Nigam, S.K. Acute renal failure. II. Experimental models of acute renal failure: Imperfect but indispensable. *Am. J. Physiol. Ren. Physiol*. 2000; 278:F1–F12.
69. Rosen, S., Heyman, S.N. Difficulties in understanding human "acute tubular necrosis": Limited data and flawed animal models. *Kidney Int*. 2001; 60: 1220–1224.
70. Ueda, N., Kaushal, G.P., Shah, S.V. Apoptotic mechanisms in acute renal failure. *Am. J. Med.* 2000; 108:403–415.
71. Heyman, S.N., Lieberthal, W., Rogiers, P., Bonventre, J.V. Animal models of acute tubular necrosis. *Curr. Opin. Crit. Care* 2002; 8:526–534.
72. Sutton, T.A., Fisher, C.J., Molitoris, B.A. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney Int*. 2002; 62: 1539–1549.
73. Wang, S., Hirschberg, R. Role of growth factors in acute renal failure. *Nephrol. Dial. Transplant* 1997; 12:1560–1563.
74. Meyer, M., Richter, R., Forssmann, W.G. Urodilatin, a natriuretic peptide with clinical implications. *Eur. J. Med. Res*. 1998; 3:103–110.
75. Lieberthal, W. Biology of ischemic and toxic renal tubular cell injury: Role of nitric oxide and the inflammatory response. *Curr. Opin. Nephrol. Hypertens*. 1998; 7:289–295.
76. Venkataram, R., Kellum, J.A. The role of diuretic agents in the management of acute renal failure. *Contrib. Nephrol*. 2001; 132:158–170.
77. Solomon, R., Werner, C., Mann, D., D'Elia, J., Silva, P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N. Engl. J. Med.* 1994; 331:1416–1420.
78. Kellum, J.A., Decker, J.M. Use of dopamine in acute renal failure: A meta-analysis. *Crit. Care Med*. 2001; 29:1526–1531.

79. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: A placebo controlled randomized trial. *Lancet* 2000; 356:2139–2143.
80. Allgren, R.L., Marbury, T.C., Rahman, S.N., Weisberg, L.S., Fenves, A.Z., Lafayette, R.A., Sweet, R.M., Genter, F.C., Kurnik, B.R., Conger, J.D., Sayegh, M.H. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. *N. Engl. J. Med*. 1997; 336:828–834.
81. Lewis, J., Salem, M.M., Chertow, G.M., Weisberg, L.S., McGrew, F., Marbury, T.C., Allgren, R.L. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. *Am. J. Kidney Dis*. 2000; 36: 767–774.
82. Hirschberg, R., Kopple, J., Lipsett, P., Benjamin, E., Minei, J., Albertson, T., Munger, M., Metzler, M., Zaloga, G., Murray, M., Lowry, S., Conger, J., McKeown, W., O'Shea, M., Baughman, R., Wood, K., Haupt, M., Kaiser, R., Simms, H., Warnock, D., Summer, W., Hintz, R., Myers, B., Haenftling, K., Capra, W., et al. Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure. *Kidney Int*. 1999; 55: 2423–2432.
83. Wang, A., Holcslaw, T., Bashore, T.M., Freed, M.I., Miller, D., Rudnick, M.R., Szerlip, H., Thames, M.D., Davidson, C.J., Shusterman, N., Schwab, S.J. Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. *Kidney Int*. 2000; 57:1675–1680.
84. Marshall, J.C. Inflammation, coagulopathy, and pathogenesis of multiple organ dysfunction syndrome. *Crit. Care Med*. 2001; 29(S9):S99–S106.
85. Jorres, A. Acute renal failure. Extracorporeal treatment strategies. *Minerva Med*. 2002; 93:329–334.
86. Mehta, R., Clark, W.C., Schetz, M. Techniques for assessing and achieving fluid balance in acute renal failure. *Curr. Opin. Crit. Care* 2002; 8:535–543.
87. Martin, C., Papazian, L., Perrin, G., Saux, P., Gouin, F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103:1826–1831.
88. Bellomo, R., DiGiantomasso, D. Noradrenaline and the kidney: Friends or foes? *Crit. Care* 2001; 5:294–298.
89. Ravikant, T., Lucas, C.E. Renal blood flow distribution in septic hyperdynamic pigs. *J. Surg. Res*. 1977; 22:294–298.
90. Brenner, M., Schaer, G.L., Mallory, D.L., Suffredini, A.F., Parrillo, J.E. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. *Chest* 1990; 98:170–179.
91. DiGiantomasso, D., Morimatsu, H., May, C.N., Bellomo, R. Intra-renal blood flow distribution in hyperdynamic septic shock: effect of norepinephrine. *Crit. Care Med*. 2003; 31:2509–2513.
92. Knotek, M., Rogachev, B., Wang, W., et al. Endotoxemic renal failure in mice: Role of tumor necrosis factor independent of inducible nitric oxide synthase. *Kidney Int*. 2001; 59:2243–2247.
93. Liberthal, W., Levine, J.S. Mechanisms of apoptosis and its potential role in renal tubular epithelial cell injury. *Am. J. Physiol*. 1996; 271:F477–F488.
94. Jo, S.K., Cha, D.R., Cho, W.Y., et al. Inflammatory cytokines and lipopolysaccharide induce Fas-mediated apoptosis in renal tubular cells. *Nephron* 2002; 91:406–415.
95. Rodriguez-Wilhelmi, P., Montes, R., Matsukawa, A., et al. Tumour necrosis factor-alpha inhibition reduces CXCL-8 levels but fails to prevent fibrin generation and does not improve outcome in a rabbit model of endotoxic shock. *J. Lab. Clin. Med*. 2003; 141:257–264.
96. Bernard, G.R., Vincent, J.-L., Laterre, R.-F., et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N. Engl. J. Med*. 2001; 344:699–709.

97. Joyce, D.E., Gelbert, L., Ciaccia, A., et al. Gene expression profile of antithrombotic protein C defines new mechanisms modulating inflammation and apoptosis. *J. Biol. Chem*. 2001; 276:11199–11203.
98. Cheng, T., Liu, D., Griffin, J.H., et al. Activated protein C blocks p53-mediated apoptosis in ischemic human brain endothelium and is neuroprotective. *Nat. Med*. 2003; 9:338–342.
99. Fauvel, H., Marchetti, P., Chopin, C., Formastecher, P., Neviere, R. Differential effects of caspase inhibitors on endotoxin-induced myocardial dysfunction and heart apoptosis. *Am. J. Physiol. Heart Circ. Physiol*. 2001; 280: H1608–H1614.
100. Neviere, R., Fauvel, H., Chopin, C., Formstecher, P., Marchetti, P. Caspase inhibition prevents cardiac dysfunction and heart apoptosis in a rat model of sepsis. *Am. J. Resp. Crit. Care Med*. 2001; 163:218–225.
101. Cauwels, A., Janssen, B., Waeytens, A., Cuvelier, C., Brouckaert, P. Caspase inhibition causes hyperacute tumous necrosis factor-induced shock via oxidative stress and phospholipase A2. *Nat. Immunol*. 2003; 4:387–393.
102. Van den Berghe, G., Wouters, P., Weekers, F., et al. Intensive insulin therapy in critically ill patients. *N. Engl. J. Med*. 2001; 345:1359–1367.
103. Hansen, T.K., Thiel, S., Wouters, P.J., et al. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J. Clin. Endocr. Metab*. 2003; 88:1082–1088.
104. Augustin, R., Pocar, P., Wrenzycki, C., Niemann, H., Fischer, B. Mitogenic and anti-apoptotic activity of insulin on bovine embryos produced *in vitro. Reproduction* 2003; 126:91–99.
105. Allen, D.A., Harwood, S., Varagunam, M., Raftery, M.J., Yaqoob, M.M. High glucose-induced oxidative stress causes apoptosis in proximal tubular epithelial cells and is mediated by multiple caspases. *FASEB J*. 2003; 17:908–910.
106. The ARDS Network. Ventilation with low tidal volumes as compared to traditional tidal volumes for acute lung injury and acute respiratory distress syndrome. *N. Engl. J. Med*. 2000; 342:1301–1308.
107. Imai, Y., Parodo, J., Kajikawa, O., et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA* 2003; 289:2104–2112.
108. Birck, R., Krzossok, S., Markowetz, F., et al. Acetylcysteine for prevention of contrast nephropathy: Meta-analysis. *Lancet* 2003; 362:598–603.
109. Ozdulger, A., Cinel, I., Koksel, O., et al. The protective effect of N-acetylcysteine on apoptotic lung injury in a cecal ligation and puncture-induced sepsis model. *Shock* 2003; 19:366–372.
110. Bellomo, R., Ronco, C. Indications and criteria for initiating renal replacement therapy in the intensive care unit. *Kidney Int*. 1998; 53(Suppl 66):S106–109.
111. Ronco, C., Bellomo, R., Brendolan, A., Pinna, V., La Greca, G. Brain density changes during renal replacement therapy in critically ill patients with acute renal failure. Continuous hemofiltration versus intermittent hemodialysis. *J. Nephrol*. 1999; 12:173–178.
112. Guisado, R., Arieff, A.I. Neurologic manifestations of diabetic comas: Correlation with biochemical alterations in the brain. *Metabolism* 1975; 24:665–679.
113. Sussman, N.L., Kelly, J.H. Extracorporeal liver support and the kidney. In *Critical Care Nephrology*, C. Ronco and R. Bellomo, eds. Dordrecht: Kluwer Academic Publishers. 1998; pp. 959–967.
114. Silvester, W. Mediator removal with CRRT: Complement and cytokines. *Am. J. Kidney Dis*. 1997; 30(Suppl 4):S38–43.
115. Hoffmann, J.N., Hartl, W.H., Deppisch, R., et al. Hemofiltration in human sepsis: Evidence for elimination of immunomodulatory substances. *Kidney Int*. 1995; 48:1563–1570.

116. Gasche, Y., Pascual, M., Suter, P.M., et al. Complement depletion during haemofiltration with polyacilonitrile membranes. *Nephrol. Dial. Transplant* 1996; 11:117–119.
117. Bellomo, R., Tipping, P., Boyce, N. Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. *Crit. Care Med*. 1993; 21:522–526.
118. Ronco, C., Tetta, C., Lupi, A., et al. Removal of platelet-activating actor in experimental continuous arteriovenous hemofiltration. *Crit. Care Med*. 1995; 23:99–107.
119. Cole, L., Bellomo, R., Journois, D., et al. Aphase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit. Care Med*. 2002; 30:100–106.
120. De Vriese, A.S., Vanholder, R.C., Pascual, M., et al. Can inflammatory cytokines be removed efficiently by continous renal replacement therapies? *Intensive Care Med*. 1999; 25:903–910.
121. Ronco, C., Bellomo, R., Homel, P., et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 2000; 356:26–30.
122. Honore, P.M., Jamez, J., Wauthier, M., et al. Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit. Care Med*. 2000; 28:3581–3587.
123. Tetta, C., Cavaillon, J.M., Schulze, M., et al. Removal of cytokines and activated complement components in an experimental model of continuous plasma filtration coupled with sorbent adsorption. *Nephrol. Dial. Transplant* 1998; 13:1458–1464.
124. Ronco, C., Brendolan, A., Lonnemann, G., et al. A pilot study of coupled plasma filtration with adsorption in septic shock. *Crit. Care Med*. 2002; 30: 1250–1255.
125. Lee, M., Ganzini, L. Depression in the elderly: Effect on patient attitudes toward life-sustaining therapy. *J. Am. Geriatr*, *Soc*. 1992; 40(10):983–988.
126. Chelluri, L., Mendelsohn, A.B., Belle, S.H., Rotondi, A.J., Angus, D.C., Donahoe, M.P., Sirio, C.A., Schulz, R., Pinsky, M.R. Hospital costs in patients receiving prolonged mechanical ventilation: Does age have an impact? *Crit. Care Med*. 2003; 31(6):1746–1751.
127. Hamel, M.B., Lynn, J., Teno, J., Covinsky, K.E., Wu, A.W., Galanos, A., Desbiens, N.A., Phillips, R.S. Age-related differences in care preferences, treatment decisions, and clinical outcomes of seriously ill hospitalized adults: Lessons from SUPPORT. *J. Am. Geriatr. Soc*. 2000; 48(5 Suppl):S176–182.
128. Hamel, M.B., Phillips, R.S., Davis, R.B., Teno, J., Desbiens, N., Lynn, J., Tsevat, J. Are aggressive treatment strategies less cost-effective for older patients? The case of ventilator support and aggressive care for patients with acute respiratory failure. *J. Am. Geriatr. Soc*. 2001; 49(4):382–390.
129. Montuclard, L., Garrouste-Orgeas, M., Timsit, J.F., De Jonghe, B., Carlet, J. Outcome, functional autonomy, and quality of life of elderly patients with a long-term intensive care unit stay. *Crit. Care Med*. 2000; 28(10):3389–3395.
130. Udekwu, P., Gurkin, B., Oller, D., Lapio, L., Bourbina, J. Quality of life and functional level in elderly patients surviving surgical intensive care. *J. Am. Coll. Surg*. 2001 Sept; 193(3):245–249.
131. Tsevat, J., Dawson, N.V., Wu, A.W., Lynn, J., Soukup, J.R., Cook, E.F., Vidaillet, H., Phillips, R.S. Health values of hospitalized patients 80 years or older. HELP Investigators. Hospitalized Elderly Longitudinal Project. *JAMA* 1998; 279(5):371–375.
132. Lloyd, C.B., Nietert, P.J., Silvestri, G.A. Intensive care decision making in the seriously ill and elderly. *Crit. Care Med.* 2004 Mar; 32(3):649–654.

133. Somogyi-Zalud, E., Zhong, Z., Hamel, M.B., Lynn, J. The use of life-sustaining treatments in hospitalized persons aged 80 and older. *J. Am. Geriatr. Soc*. 2002; 50(5):930–934.
134. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). *JAMA* 1995; 274: 1591–1598.
135. Hammes, B.J., Rooney, B.L. Death and end-of-life planning in one Midwestern community. *Arch. Intern. Med*. 1990; 158:383–390.
136. Prendergast, T.J. Advance care planning: Pitfalls, progress, promise. *Crit. Care Med*. 2001; 29(2-Suppl):N34–N39.

23

Etiology, Diagnosis, and Management of Chronic Renal Insufficiency in the Aged

Jordan L. Rosenstock and Michael F. Michelis

Demographics

In 2003, out of a total of approximately 450,000 end-stage renal disease (ESRD) patients in the United States, there were close to 90,000 patients aged 65–74 and just under 70,000 older than 75 years of age. The growth in the elderly ESRD population has been rising faster than the rate of increase of ESRD for the population as a whole. The prevalence rate (in patients per million population) of the ESRD population 65–74 years of age has grown 66% between 1993 and 2003 and has nearly doubled for patients older than 75. This is in contrast to an increase in all patients of 47% during the same time period [1].

According to National Health and Nutrition Examination Surveys (NHANES), approximately 4% of the U.S. population in 2000, or 7.7 million people, had chronic renal insufficiency (CRI) as defined by a glomerular filtration rate (GFR) less than 60 mL/min. Among those older than 65 years, close to 20% of the population were estimated to have CRI [2].

Etiologies

Epidemiological Data

What are the causes of ESRD and CRI in the elderly? In the USRDS database, for 2003, diabetes and hypertension were the most common causes of ESRD for all patients, at 44% and 28% of the incident ESRD patients, respectively, followed by glomerulonephritis at 8%. When the data for patients 65 years of age and older are analyzed, hypertension, although still less frequent than diabetes, becomes an even more common diagnosis, making up 35% of elderly patients with ESRD. Diabetes decreases to 42%, and glomerulonephritis falls to only 5% [1].

The NHANE surveys did not identify the specific etiology of renal disease but evaluated the presence of associated diseases. Among the elderly

population with a history of hypertension, the proportion of patients with CRI was more than 20%. If the population had diabetes, the proportion was close to 30% [2]. Considering this association among diabetes, hypertension, and CRI in the elderly and the dominance of these as causes of ESRD, it would be reasonable to attribute a major proportion of CRI in the elderly to diabetes and hypertension.

The prevalence of type 2 diabetes increases with age [3], as do concomitant hypertension and vascular disease (see Chapter 18) [4]. The prevalence of hypertension also increases with age (see Chapter 11) [5]. Older patients are much more likely to have isolated systolic hypertension than younger patients. Elderly hypertensives may also have lower plasma renin activity, more ventricular hypertrophy, and lower cardiac output than younger patients (see Chapter 1) [6]. Secondary forms of hypertension, especially renovascular hypertension, are more common in elderly patients, and secondary hypertension should be suspected with new-onset hypertension in someone older than 60 or in those in whom the blood pressure becomes more difficult to control.

Renal Biopsy Databases

Evaluating the reports of renal biopsy diagnoses in elderly patients with CRI is useful to help characterize the causes of CRI in the elderly. The use of renal biopsy to diagnose the etiology of renal disease in the elderly has become common (see Chapter 17). In the UK MRC Registry, the proportion of biopsies undertaken in elderly patients increased from 6% to 21% from 1978 to 1990 [7]. It has become clear that glomerular diseases (aside from diabetic glomerulopathy) are at least as common, if not more so, in the elderly as in younger patients. In studies where glomerular disease incidence was compared head to head with younger patients, some patterns emerge [7–12]: IgA nephropathy and lupus nephritis are much more frequent in younger patients, while crescentic glomerulonephritis and amyloid are more common in the elderly. However, most of the patients in biopsy series were biopsied for diagnoses other than CRI, and data on renal biopsy findings in elderly patients with CRI as the predominant abnormality are limited. In fact, the only diagnosis that approximates chronic renal insufficiency in the published literature is “chronic renal failure” (CRF). The term “CRF” is not precisely defined in most of these studies but generally implies renal insufficiency that has lasted for a prolonged period—usually for weeks to months.

The three largest biopsy reports were published in the early 1990s (one in the United States and the other in France, and the third more recently in Italy) (see Chapter 17). Preston and colleagues [12] found that CRF was the diagnosis in 57 patients 65 years or older, or 17% of the elderly biopsy population. As many as 25 of the 57 had a primary glomerular disease most commonly of a “proliferative sclerosing” or “crescentic” type. Twelve of the 57 had a secondary glomerular disease (diabetes in 7 of these), and 7 had chronic interstitial nephritis. The most common individual diagnosis was nephrosclerosis, which was found in 10 of 57 cases. Modesto-Segonds and co-workers [9] found that CRF made up 46 of 211 (22%) in a French biopsy series. The most common diagnosis was again primary glomerular disease (30/46), although they did not find any crescentic GN in this group.

Nephrosclerosis was again common and seen in 5 of the 46 cases. The most recent report [8] contained only 26 elderly patients with CRF. It found that nephrosclerosis was the diagnosis in the overwhelming majority of these patients (21/26). Table 23.1 summarizes the biopsy studies in elderly patients with CRF.

It seems reasonable to conclude that, based on epidemiological data, diabetes and hypertension are likely the most important causes of CRI in the elderly. When biopsy data are considered, chronic primary glomerular diseases may be important as well. It must be remembered, however, that besides being limited in numbers, biopsy data are likely skewed to patients with atypical presentations. This most likely exaggerates the prevalence of glomerular diseases, other than those that are diabetes-related. It is telling that in this elderly biopsy population, nephrosclerosis is still a predominant finding. Nephrosclerosis implies extensive sclerosis or scarring of glomeruli and interstitium on biopsy. While nephrosclerosis could result from advanced chronic glomerular disease, it may more likely reflect the burden of hypertensive or vascular disease.

Ischemic Nephropathy

Ischemic nephropathy, or renal dysfunction due to renovascular disease, is likely a significant cause of CRI in the elderly. Indeed, in a subgroup analysis of the USRDS data for 2003, renal arterial disease is implicated as the cause of ESRD in the greatest number of elderly patients after diabetes, primary hypertension, and "renal failure of unknown etiology" [1]. Renal vascular lesions are present in up to 25% of patients with CRI above the age of 70 [13]. Ischemic nephropathy may coexist with other forms of nephropathy, such as nephrosclerosis or diabetic nephropathy [14]. Renovascular disease should be suspected in elderly patients with new-onset or worsening hypertension, especially if there is evidence of atherosclerotic disease elsewhere.

Table 23.1 Biopsy Findings Reported in Elderly Patients with CRF.

	Nephroscl		Primary GL	Secondary GL	DM	CIN
Other						
Nair (2004) (n = 26)	80	4	4	8	—	4
Modesto-Segonds(1993) (n = 46)	11	65	22	4	—	—
Preston (1990) (n = 57)	18	44	9	12	12	—
Kingswood (1984) (n = 20)	15	35	10	—	—	40
Moorthy(1980) (n = 12)	50	—	—	—	17	—

Values expressed as percentages of patients in study.
Nephroscl = nephrosclerosis.
Primary GL = primary glomerulopathy.
Secondary GL = secondary glomerulopathy other than diabetes.
DM = diabetic nephropathy.
CIN = chronic interstitial nephropathy.

Asymmetric kidney size on sonogram may be a clue. A number of noninvasive tests can be used to identify renovascular disease if suspected. Duplex ultrasound of the renal arteries or gadolinium-enhanced magnetic resonance arteriography (MRA) are generally recommended as screening tests if there is a suspicion of renovascular disease [15]. MRA might be preferable at a center that does not have significant experience with duplex imaging, as the latter technique is quite operator-dependent [15].

Other Causes of CRI

Other important causes of chronic kidney disease (CKD) in the elderly include obstructive nephropathy, which is more common in males. The principal cause is prostatic hypertrophy and chronic bladder outlet obstruction, but could also be due, in men or women, to genitourinary malignancies or functional bladder disease (see Chapter 14). The prevalence of chronic renal disease due to nonsteroidal anti-inflammatory drugs and analgesics is somewhat controversial [16–20] but likely also plays a role, especially in the elderly, who are more prone to medication toxicity. Classic analgesic nephropathy may be identified by the finding of small, irregularly shaped kidneys with papillary calcifications on computed tomography (CT) scan or sonogram and is usually associated with a history of chronic daily ingestion of analgesic mixtures [20].

A history of colonoscopy with a phosphorus-containing oral purgative preparation has recently been implicated as a cause of renal damage. This was identified in a series of 21 patients who developed renal failure following a colonoscopy and were found to have nephrocalcinosis on renal biopsy [21]. All patients had ingested a phosphorus oral purgative, which can cause hyperphosphatemia and resultant precipitation of calcium-phosphate in the kidney. This purgative has recently become very popular for use prior to colonoscopies, and it is possible that renal failure related to colonoscopies will be seen with increasing frequency.

Light-chain-related diseases, especially multiple myeloma and amyloidosis, should also be considered in elderly patients. Monoclonal gammopathy occurs in up to 5% of those older than 75 [22], and the risk of transformation to a malignant disorder is about 1% per year [23]. Myeloma kidney or amyloidosis should be considered in a patient with renal failure, anemia, and a monoclonal protein in the blood or urine, especially if large kidneys are identified on sonogram or CT scan. Chronic glomerulosclerosis due to aging is likely also an important contributing cause and is discussed in earlier chapters of this book. Table 23.2 lists the common causes of CRI in the elderly.

Table 23.2 Frequent Causes of CRI in the Elderly.

Diabetes mellitus
Hypertension
Ischemic/vascular
Obstructive
Medication-related (NSAIDs, analgesics)
Chronic glomerular disease
Bone marrow dyscrasia-related (Multiple myeloma, amyloidosis)
Age-related sclerosis

Diagnosis: An Algorithm

In practice, an algorithm for evaluating elderly patients with CRI seems appropriate. In addition to taking a general history of medical illnesses that could contribute to CRI, taking a careful history of medication use, with special attention to nephrotoxic agents, such as antibiotic use, nonsteroidal anti-inflammatory agents, and analgesics, is necessary. One should also inquire about a history of colonoscopy done after a phosphorous-containing bowel preparation was used. Estimation of the patient's volume status to rule out a chronically volume-depleted or overloaded state is essential. Also, looking for evidence of malignancy, including inquiring about a history of weight loss, is useful. A patient with a history of diabetes should have an ophthalmologic examination to rule out diabetic retinopathy, which frequently coexists with nephropathy. The absence of retinopathy does not rule out diabetic nephropathy, however, as up to 45% of type 2 diabetic patients with nephropathy may not have retinopathy [24]. The presence of retinopathy, however, is an important predictor of progression of renal disease [24].

Other objective data such as a sonographic study of the kidneys and bladder are important. Sonography can diagnose obstructive disease and cystic disease as well as evaluate for the presence of renal asymmetry, which can indicate renovascular disease. A sonogram might also reveal large kidneys in the setting of renal failure, which can be seen in amyloidosis or myeloma kidney. A blood test should include a complete blood count (CBC), and a serum chemistry should incorporate a serum calcium level, which, if elevated, could be a sign of the presence of a malignant disorder involving the bone. A low serum potassium and metabolic alkalosis might indicate renin and aldosterone activation, which could be seen in renovascular disease. A urine specimen should be obtained for assessment of proteinuria and sediment findings that could indicate the presence of a glomerular disease. A serum and urine electrophoresis to rule out a monoclonal gammopathy is important. Table 23.3 lists the recommended studies in an elderly patient with CKD. If the etiology of renal dysfunction is unclear, or if the progression of the renal disease seems especially rapid, or if there is evidence of an active glomerular disease, a renal biopsy should be considered. Before performing a renal biopsy, one should make certain there are adequately preserved renal size and cortical thickness on the sonogram. Table 23.4 summarizes the indications for renal biopsy.

In summary, CRI is widespread in the elderly. There is a definite association with diabetes and hypertension, which themselves are increased in the elderly population. Renovascular disease and medication toxicities are likely more important in elderly patients than younger patients. Nephrosclerosis is

Table 23.3 Recommended Studies in Evaluation of Elderly CRI Patient.

Serum chemistry including serum calcium and potasium
Complete blood count
Urinalysis with microscopy
Urine protein-to-creatinine ratio (or 24-hour urine protein)
Serum and urine electropheresis
Renal sonogram/post-void bladder sonogram
Ophthalmologic exam for retinopathy (especially in a diabetic patient)

Table 23.4 Indications for Renal Biopsy*.

Unexplained decreased renal function
Unexplained acceleration of chronic renal dysfunction
Unexplained proteinuria
Active urinary sediment

* Patient should have adequate renal cortex on imaging study.

frequently seen on renal biopsies, which likely reflects the burden of hypertension or vascular disease. Glomerular diseases are seen with a frequency similar to younger patients, but elderly patients are more likely to have amyloid or crescentic glomerulonephritis, while younger patients are more likely to have IgA nephropathy or lupus nephritis. An elderly patient with CRI should be evaluated thoroughly for specific, and perhaps treatable, causes of renal disease.

Estimating the GFR

An important issue, and one much discussed in the contemporary renal literature, is the problem of assessing renal function clinically (see Chapter 5) [25–27]. Alternative measures such as serum cystatin C levels have been suggested [28, 29]. Recently, cystatin C levels have been shown to predict cardiovascular outcomes in elderly patients better than creatinine-based equations [30–32], but it remains to be seen whether this measurement will gain widespread acceptance and use (see Chapter 5).

Management

Identifying the etiology for the renal disease in the elderly is important for more than academic interest. If renal disease due to nephrotoxic medications is identified, the patient can be advised to avoid those medications. Elderly patients with a number of glomerular diseases may be candidates for treatment with immunosuppressive or other therapy. Patients with renal disease related to a blood dyscrasia should be referred to a hematologist and may benefit from treatment for bone marrow disease. The presence of renovascular disease would necessitate caution in the use of angiotensin inhibitors; in some cases, the patient may benefit from revascularization.

In all elderly patients with CRI, one must pay special attention to dosing of medications in the presence of reduced GFR and be vigilant in avoiding nephrotoxic insults. A number of other areas require attention in all patients with CRI. Theses include optimal blood pressure control, glycemic control, lipid management, and consideration of the use of inhibitors of the renin-angiotensin system. Also important is attention to anemia, hyperphosphatemia, hyperuricemia, obesity, and smoking cessation. These areas are all crucial not only because the CRI population is at increased risk for cardiovascular complications but also because there is growing evidence that almost all of these areas are important in influencing the progression of renal disease.

Blood Pressure

Uncontrolled hypertension (see Chapter 11) is well established to increase the progression of chronic kidney disease to ESRD [33]. But what is the optimal blood pressure in CKD? Epidemiological and observational data have shown the patients who can attain a systolic blood pressure under 130 mmHg have less progression of renal disease [33, 34], which seems most important in patients with proteinuria [33]. However, the few trials that have randomized patients with CRI to more versus less intensive blood pressure control are less clear. The MDRD study initially showed better outcomes only in the subgroup of patients with more than 1 g of proteinuria per day who were randomized to a blood pressure of less than 125/75 mmHg versus under 140/90 mmHg. Subsequently, longer-term follow-up showed a difference in all patients randomized to a lower blood pressure, regardless of proteinuria [35]. The AASK study, however, did not show a benefit of a blood pressure of less than 125/75 mmHg as opposed to less than 140/90 mmHg [36]. The fact that the AASK study enrolled patients with less proteinuria (median 0.08 g/day versus 0.35 g/day in the MDRD study) could explain the difference.

One must keep in mind that observational data have recently found that in patients with coronary artery disease (CAD), lower blood pressure, especially a diastolic blood pressure under 70 mmHg, appears to be a marker for mortality [37]. A recent report found that in a cohort of Dutch patients older than 85 years of age, a diastolic blood pressure of less than 70 was actually associated with more rapid progression of CKD [38]. Also, analysis of a large study of diabetics with CKD (the IDNT trial) found increased mortality for those with a systolic blood pressure less than 120 mmHg [34].

The latest Joint National Committee (JNC) guidelines recommend a blood pressure of less than 130/80 in all patients with renal disease [39]. This is probably most important in patients with proteinuria, as discussed above. However, one might advise caution in elderly patients, especially those with known or suspected CAD. As we mentioned, elderly patients are more likely to have isolated systolic hypertension with a normal or low diastolic pressure, so one should be cognizant of the diastolic pressure when titrating antihypertensive therapy in such patients.

Use of Renin-Angiotensin Inhibition

The relative importance of specifically using an inhibitor of the renin-angiotensin system (see Chapters 11 and 12) as opposed to other agents for blood pressure control was recently questioned in a meta-analysis in *Lancet* [40]. The study showed that the incidence of ESRD was not decreased by the use of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin-receptor blocker (ARB), especially when differences in blood pressure were taken into account. However, this study was heavily weighted by the ALLHAT study, which did not enroll patients with kidney disease and did not check for proteinuria [41]. Multiple studies geared to patients with proteinuric renal diseases showed specific benefit of ACEi or ARB. Patients should be evaluated for proteinuria and given an ACEi or ARB if possible, especially if the patient has more than 1 g/day of proteinuria. This seems to be beneficial even in advanced CKD. Indeed, a recent study in the *New England Journal of Medicine* [42] found that patients with advanced CRI (serum creatinine

between 3.1 and 5.0) who were randomized to benazepril had a significant decrease (43%) in progression to doubling of serum creatinine, ESRD, or death. This was a population of mostly patients with chronic glomerular diseases who had a mean proteinuria of 1.5 g/day, who would be more likely to benefit from ACEi or ARB treatment than those with less proteinuria. It must be emphasized that it is critical to monitor creatinine and potassium in patients with CRI who are started on an angiotensin-inhibiting agent, especially if there is any possibility of renovascular disease. The aforementioned study only randomized patients who did not have a rise in serum creatininine greater than 30% and whose potassium did not rise above 5.6 mmol/L on initiation of the medication; it would be prudent to stop the medication or adjust the dosage in patients who do develop significant acute rises in creatinine or hyperkalemia.

Cholesterol

Hyperlipidemia is well established as a CVD risk factor and should be kept at an optimal level in patients with CKD because of their CVD risk. Studies in animal models have suggested that hyperlipidemia is also associated with progression of renal disease. Hyperlipidemia has also been associated with worsening nephropathy in observational studies in various renal diseases in humans. Two recent meta-analyses of randomized trials found that the use of statins was able to decrease proteinuria [43] and also slow the progression of renal insufficiency [44]. It remains to be seen whether this is a specific effect of statins, which have other physiological effects in addition to simply lowering lipids. It also is unknown what the optimal lipid levels should be in those with renal disease, but considering the CVD risk in such patients, it would be reasonable to aggressively treat hyperlipidemia as one would for all patients with high CVD risk, who are now targeted to a goal low-density lipoprotein (LDL) less than 100 mg/dL or even lower.

Uric Acid

Hyperuricemia is very common in CRI patients. It is associated with hypertension and also with progressive renal disease. Experimental data have suggested that lowering uric acid levels may decrease renal damage in moderate hyperuricemia. A recent study was the first to randomize patients with CRI and hyperuricemia to allopurinol versus placebo [45]. The allopurinol dose was adjusted with a goal to attain a normal uric acid level. The study found a significant decrease in the proportion of patients who had deterioration of renal function over a year in the patients given allopurinol, whose uric acid levels decreased from a mean of 9.75 mg/dL to 5.88 mg/dL. This was a small study (54 patients) and should be considered preliminary, but it is clear that a uric acid level should be checked in patients with CKD and uric acid lowering therapy considered in patients with an elevated level.

Glucose

Epidemiological studies have shown that uncontrolled diabetes is associated with an increased occurrence of nephropathy. The landmark DCCT trial established the importance of intensive glucose control in preventing the

development of nephropathy in type 1 diabetes [46]. The UKPDS study [47] randomized over 3800 type 2 diabetic patients to more or less intensive therapy and achieved median HgbA1c levels of 7.0% versus 7.9%. Aside from significant decreases in progression of retinopathy, the study found reductions in microalbuminuria, proteinuria, and doubling of serum creatinine in patients with better control, though the reductions were only clearly apparent after 9 years. The most likely reason that it took so long to show benefit is that both groups had reasonable control. A follow-up analysis of the UKPDS population [48] found that for each reduction of HgbA1c by 1%, there was a 37% decrease in microvascular complications, which included retinopathy and nephropathy. The American Diabetic Association (ADA) currently recommends a target HgbA1c level of <7.0% in all diabetics. Unfortunately, over 50% of diabetics in the United States did not meet this goal according to the most recent NHANES data [49].

Anemia

Anemia is very common in CKD patients due to deficiency of endogenous erythopoietin (EPO). Correction of anemia with exogenous EPO is associated with improved quality of life and better exercise tolerance and may reduce cardiac hypertrophy. Three relatively small studies (73–88 patients) [50–52] suggested that treatment of anemia with EPO can decrease the progression of CRI. The goal hemoglobin in CRI remains uncertain. A recent meta-analysis found that increasing the hemoglobin to greater than 13 g/dL might increase the risk of death in patients with CVD and CRI when compared with a hemoglobin level lower than 12 g/dL. However, most patients included in the analysis were on dialysis, so it remains unclear if non-ESRD CRI patients behave differently. The largest trial undertaken to answer this question was terminated early due to concern about red cell aplasia from the particular formulation of EPO used in the trial (Eprex) [53]. Two hundred forty-one patients with CRI were randomized to high-hemoglobin (13–15 g/dL) or low-hemoglobin (11–12 g/dL) groups. No significant differences in outcomes were seen in either renal disease progression or cardiovascular events. At present, EPO should be initiated when the hemoglobin falls below 11 g/dL, and the target level should be a hemoglobin between 11 and 12 g/dL. Careful attention to blood pressure is important when initiating EPO, as the blood pressure may rise as the hemoglobin is corrected.

Smoking/Obesity

Both obesity and smoking are well established to be detrimental to good health. It is not well recognized, however, that they may also contribute to the progression of renal disease. Orth [54] clearly established that smoking is a risk for progression to ESRD in patients with IgA nephropathy and polycycstic kidney disease [54]. Previously, a number of studies had shown that smoking was associated with the onset and progression of diabetic nephropathy [54]. It seems that elderly men may be most susceptible to the detrimental effects of smoking on the kidney, according to a study in patients with various glomerular diseases [55].

Obesity has also been shown to be associated with risk of CKD [56] and ESRD [57]. Mechanistically, both obesity and smoking may have

similar effects on the kidney. Both are associated with hyperfiltration of the glomerulus, systemic hypertension, and activation of the sympathetic and renin-angiotensin-aldosterone systems [54, 58]. Patients who have CKD can be given an additional motivation to stop smoking and lose weight: It may help defer or avoid the onset of ESRD.

Phosphate/Calcium/Parathyroid

As CRI progresses, alterations in calcium, phosphorus, and bone metabolism occur due to phosphate retention, decreases in 1,25-dihydroxycholecalciferol, and secondary hyperparathyroidism. These abnormalities are associated with bone disease as well as vascular and soft tissue calcifications. Even mild hyperphosphatemia has been associated with increased mortality in ESRD patients. One should monitor phosphate levels in CRI patients and treat the patients with dietary phosphate restriction and oral phosphate binders as soon as one detects even mild hyperphosphatemia. Current guidelines recommend a phosphorus level under 4.7 mg/dL for all patients with predialysis CKD. Once phosphorus levels are controlled, one can start therapy with an activated vitamin D preparation if the patient has hypocalcemia or hyperparathyroidism. New agents such as calcimimetic medications, which directly suppress the parathyroid gland by binding to calcium-sensing receptors, have recently come into use and will likely play a larger role.

Current State

According to a recent study [59], physicians may be remiss in properly recognizing, assessing, and treating patients with CKD. A group of patients with CRI at an academic primary care center were identified. The mean age of the patients was 71 years. Only 19% had a quantification of proteinuria. Incredibly, only 54% had a urinalysis. Close to half of the patients had mean systolic blood pressures greater than 140 mmHg. Hopefully, due to recent efforts by various organizations to energize physicians regarding awareness and diagnosis of CKD, early referral to nephrologists will become the norm, and the care of such patients should improve. Specific attention to the various available therapies described above should help limit or slow the progression of CKD.

References

1. U.S. Renal Data System, USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2004.
2. Coresh, J., Byrd-Holt, D., Astor, B.C., et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J. Am. Soc. Nephrol.* 2005; 16:180–188.
3. Harris, M.I., Flegal, K.M., Cowie, C.C., et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. *Diabetes Care* 1998; 21:518–524.
4. Wilson, P.W.F., Anderson, K.M., Kanel, W.B. Epidemiology of diabetes mellitus in the elderly: The Framingham Study. *Am. J. Med.* 1986; 80:S5A, 3–9.

5. Fields, L.E., Burt, V.L., Cutler, J.A., et al. The burden of adult hypertension in the United States 1999 to 2000: A rising tide. *Hypertension* 2004; 44:398–404.
6. Schmeider, R.E., Frohlich, E.D., Messerli, F.H. Pathophysiology of hypertension in the elderly. *Cardiol. Clin*. 1986; 4:235–243.
7. Davison, A., Johnston, P.A. Idiopathic glomerulonephritis in the elderly. In *Contributions in Nephrology*. Basel: Karger. 1993; pp. 38–48.
8. Nair, R., Bell, J.M., Walker, P.D. Renal biopsy in patients aged 80 years and older. *Am. J. Kidney Dis*. 2004; 44:618–626.
9. Modesto-Segonds, A., Ah-Soune, M.F., Durand, D., et al. Renal biopsy in the elderly. *Am. J. Nephrol.* 1993; 13:27–34.
10. Moorthy, A.V., Zimmerman, S.W. Renal disease in the elderly: Clinopathologic analysis of renal disease in 115 elderly patients. *Clin. Nephrol*. 1980; 14:223–229.
11. Colombo, V., Confalonieri, R., Minola, E., et al. Renal biopsies in the elderly. In *Contributions in Nephrology*. Basel: Karger. 1993; pp. 102–105.
12. Preston, R.A., Stemmer, C.L., Materson, B.J., et al. Renal biopsy in patients 65 years of age or older: An analysis of the results of 334 biopsies. *J. Am. Geriatr. Soc*. 1990; 38:669–674.
13. Coen, G., Manni, M., Giannoni, M.F., et al. Ischemic nephropathy in an elderly nephrologic and hypertensive population. *Am. J. Nephrol*. 1998; 18:221–227.
14. Textor, S.T. Ischemic nephropathy: Where are we now? *J. Am. Soc. Nephrol*. 2004; 15:1974–1982.
15. Safian, R., Textor, S.C. Renal-artery stenosis. *N. Engl. J. Med*. 2001; 344:431–442.
16. Perneger, T.V., Whelton, P.K., Klag, M.J. Risk of kidney failure associated with the use of acetaminophen, aspirin and nonsteroidal anti-inflammatory drugs. *N. Engl. J. Med.* 1994; 331:1675–1679.
17. Fored, C.M., Ejerblad, E., Lindblad, P., et al. Acetaminophen, aspirin, and chronic renal failure. *N. Engl. J. Med.* 2001; 345:1801–1808.
18. McLaughlin, J.K., Lipworth, L., Chow, W.H., et al. Analgesic use and chronic renal failure: A critical review of the epidemiological literature. *Kidney Int*. 1998; 54:679–686.
19. Ibanez, L., Morlans, M., Vidal, X., et al. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end stage renal disease. *Kidney Int*. 2005; 67:2393–2398.
20. De Broe, M.E., Elseviers, M.M. Analgesic nephropathy. *N. Engl. J. Med*. 1998; 338:446–452.
21. Markowitz, G.S., Stokes, M.B., Radhakrishnan, J., et al. Acute phosphate nephropathy following an oral sodium phosphate bowel purgative: An underrecognized cause of chronic renal failure. *J. Am. Soc. Nephrol*. 2005; 16: 3389–3396.
22. Kyle, R.A., Therneau, T.M., Rajkumar, S.V., et al. Prevalence of monoclonal gammopathy of undetermined significance. *N. Engl. J. Med*. 2006; 354: 1362–1369.
23. Kyle, R.A., Therneau, T.M., Rajkumar, S.V., et al. A long term study of prognosis in monoclonal gammopathy of undetermined significance. *N. Engl. J. Med*. 2002; 346:564–569.
24. Trevisan, R., Vedovato, Mazzon, C., et al. Concomitance of diabetic retinopathy and proteinuria accelerates the rate of decline of kidney function in type 2 diabetic patients. *Diabetes Care* 2002; 25:2026–2031.
25. Levey, A.S., Bosch, J.P., Lewis, J.B., et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann. Intern. Med*. 1999; 130:461–470.
26. Levey, A.S., Coresh, J., Balk, E., et al. National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Ann. Intern. Med*. 2003; 139:137–147.

27. Lamb, E.J., Webb, M.C., Simpson, D.E., et al. Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: Is the modification of diet in renal disease formula an improvement? *J. Am. Geriatr. Soc*. 2003; 51:1012–1017.
28. Dharnidharka, V.R., Kwon, C., Stevens, G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. *Am. J. Kidney Dis*. 2004; 43:861–867.
29. Shlipak, M.G., Sarnak, M.J., Katz, R., et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N. Engl. J. Med.* 2005; 352: 2049–2060.
30. Sarnak, M.J., Katz, R., Stehman-Breen, C., et al. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann. Intern. Med.* 2005; 142:497–505.
31. Shlipak, M.G., Katz, R., Sarnak, M.J., et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann. Intern. Med.* 2006; 145:237–246.
32. Fliser, D., Ritz, E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am. J. Kidney Dis*. 2001; 37:79–83.
33. Jafar, T.H., Stark, P.C., Schmid, C.H., et al. Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient level meta-analysis. *Ann. Intern. Med*. 2003; 19:244–252.
34. Pohl, M.A., Blumenthal, S., Cordonnier, D.J., et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: Clinical implications and limitations. *J. Am. Soc. Nephrol.* 2005; 16:3027–3037.
35. Sarnak, M.J., Greene, T., Wang, X., et al. The effect of lower target blood pressure on the progression of kidney disease: Long term follow-up of the Modification of Diet in Renal Disease Study. *Ann. Intern. Med*. 2005; 142:342–351.
36. Wright, J.T., Bakris, G., Greene, T., et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 2002; 20:2421–2431.
37. Messerli, F.H., Mancia, G., Conti, R., et al. Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann. Intern. Med.* 2006; 144:884–893.
38. van Bemmel, T., Woittiez, K., Blauw, G.J., et al. Prospective study of the effect of blood pressure on renal function in old age: The Leiden 85-Plus Study. *J. Am. Soc*. *Nephrol*. 2006; 17:2561–2566.
39. Chobanian, A., Bakris, G.L., Black, H., et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA* 2003; 289:2560–2571.
40. Casas, J.P., Chua, W., Loukogeorgakis, S., et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. *Lancet* 2005; 366:2026–2033.
41. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288:2981–2997.
42. Hou, F.F., Zhang, X., Zhang, G.H., et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N. Engl. J. Med*. 2006; 354:131–140.
43. Douglas, K., O'Malley, P.G., Jackson, J.L. Meta-analysis: The effect of statins on albuminuria. *Ann. Intern. Med.* 2006; 145:117–124.
44. Sandhu, S., Wiebe, N., Fried, L.F. Statins for improving renal outcomes: A meta-analysis. *J. Am. Soc. Nephrol*. 2006; 17:2006–2016.
45. Siu, Y.P., Leung, K.L., Tong, M.K.H., et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower the uric acid level. *Am. J. Kidney Dis*. 2006; 47:51–59.

46. DCCT Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus the Diabetes Control and Complications Trial. *N. Engl. J. Med*. 1993; 329:978–986.
47. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837–853.
48. Stratton, I.M., Adler, A.I., Neil, A.W., et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *Br. Med. J*. 2000; 12:405–412.
49. Resnick, H.E., Foster, G.L., Bardsley, J., et al. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999–2002, the National Health and Nutrition Examination Survey. *Diabetes Care* 2006; 29:531–537.
50. Roth, D., Smith, R.D., Schulman, G., et al. Effects of recombinant human erythropoietin on renal function in chronic renal failure predialysis patients. *Am. J. Kidney Dis*. 1994; 24:777–784.
51. Kuriyama, S., Tomonari, H., Yoshida, H., et al. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. *Nephron* 1997; 77:176–185.
52. Gouva, C., Nikolopoulos, P., Ioannidis, P., et al. Treating anemia early in renal failure patients slows the decline in renal function: A randomized controlled trial. *Kidney Int*. 2004; 66:753–760.
53. Rossert, J., Levin, A., Roger, S.D., et al. Effect of early correction of anemia on the progression of CKD. *Am. J. Kidney Dis*. 2006; 47:738–750.
54. Orth, S.R. Effects of smoking on systemic and intrarenal hemodynamics: Influence on renal function. *J. Am. Soc. Nephrol*. 2004; 15:S58–63.
55. Stengel, B., Couchoud, C., Cenee, S., et al. Age, blood pressure and smoking effects on chronic renal failure in primary glomerular nephropathies. *Kidney Int*. 2000; 57:2519–2526.
56. Fox, C.S., Larson, M.G., Leip, E.P., et al. Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004; 291:844–850.
57. Hsu, C.Y., McCulloch, C.E., Iribarren, et al. Body mass index and risk for end-stage renal disease. *Ann. Intern. Med*. 2006; 144:21–28.
58. Bosma, R.J., Krikken, J.A., van der Heide, H., et al. Obesity and renal hemodynamics. *Contrib. Nephrol*. 2006; 151:184–202.
59. Israni, A., Korzelius, C., Townsend, R., et al. Management of chronic kidney disease in an academic primary care clinic. *Am. J. Nephrol*. 2003; 23:47–54.
60. Kingswood, J.C., Banks, R.A., Tribe, C.R., et al. Renal biopsy in the elderly: Clinicopathologic correlations in 143 patients. *Clin. Nephrol*. 1984; 22:183–187.

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Substitutive Treatments of End-Stage Renal Diseases in the Elderly: Dialysis

Nada Dimkovic and Dimitrios G. Oreopoulos

Introduction

The number of elderly patients who need renal replacement therapy (RRT) for end-stage renal disease (ESRD) grows steadily coincident with the overall aging of the Western population and with the increasing frequency with which elderly patients are accepted for such treatment. According to the U.S. Renal Data System (USRDS) 2000 Annual Data Report, the mean age at initiation of dialysis was 61 years; other Western countries have reported a similar trend. Individual countries show a marked variation in their trends in the use of renal replacement therapies, possibly reflecting the variable accessibility to health care worldwide. Since 1978, the median age of the incident ESRD population in the United States has increased from 54 to 65 years. In the United States, rates of new ESRD cases have consistently been the highest in the over-75 age group; prevalent rates have increased 86% for the entire population, 110% for the 65- to 74-year age group, and 153% for those 75 and over [1]. Similar trends are also observed in Canada: While in 1994 the elderly represented 14% of all patients receiving treatment for kidney failure, on December 31, 2003, 27% of dialysis patients were 75 years or older [2]. In the UK, the median age of patients starting RRT has risen from 64.4 years in 2000 to 65.5 years in 2002 [3]. Similarly striking increments of the older patients with ESRD were observed in Japan as well [4]. In New Zealand, the "epidemic" of elderly patients with dialysis requiring end-stage renal disease has been described, raising important issues pertaining to planning and provision of RRT [5]. All the data mentioned above suggest that ESRD has become a geriatric illness and that, in the 21st century, nephrologists will be forced to practice mainly geriatric medicine.

Elderly patients with ESRD are specific in many ways. They are less likely than younger patients to have ESRD secondary to glomerulonephritis but more likely to have renal failure due to type 2 diabetes and/or hypertension and to renal vascular disease [6, 7]. Such patients have many co-morbid conditions that make therapy considerably more difficult and require multidisciplinary work and a special knowledge of geriatric medicine. Canadian data show that 65.4% of patients age 65 years or over who are on RRT have two or more co-morbid conditions (excluding diabetes), and 80% of them have at least one

chronic illness; at the time of initiation of RRT, 30% of them have three or more chronic illnesses [8]. This may be the reason for late referral/nonreferral of the elderly to a nephrologist. Indeed, older age seems to be an important factor for nonreferral. In Saõ Paolo, Brazil, 26% of patients who reached ESRD in 1991 died without receiving dialysis, and the likelihood of acceptance for dialysis was 12-fold lower among patients over 60 years of age than among patients in their third decade [9]. In Scotland, among 304 patients with chronic renal failure identified during a 12-month period, 64% were not referred for dialysis; their average age was 76 years, compared with 62 years among those who were referred [10]. From a mailed survey regarding referral for dialysis sent to randomly selected family physicians/general practitioners and internists in Ontario, Canada, it appears that physicians are less likely to refer patients to a nephrologist as age and co-morbidity increase [11]. On the other hand, among a large cohort of American dialysis patients, elderly persons and those with co-morbid conditions were actually more likely to begin dialysis at higher levels of kidney function [12].

The treatment of choice for the elderly ESRD population is a very important issue, and one may ask whether the elderly population is being denied a treatment choice from which they may benefit. To answer this question, it is necessary to review what is known about how elderly patients cope with dialysis and why they may benefit from peritoneal dialysis or hemodialysis. Experience with elderly patients with renal diseases and uremia is still limited. For ethical reasons, there are only very few comparative studies and no randomized, prospective studies have been conducted. Also, existing studies are based on populations that differ considerably in both medical and social characteristics. Concerning the elderly who need dialysis, we face such challenges as accurate diagnosis, requirements for special care, mode of therapy, quality of life, and social and ethical issues.

Diagnostic Challenges in the Predialysis Period

In elderly patients, chronic renal failure is characterized by an absence of classic symptoms, the nonspecific nature of the presenting symptoms, the presence of co-morbid conditions, and interference of the aging process with the interpretation of findings.

These patients require regular screening for co-morbid conditions; screening for cancer (PSA, Pap smear, mammography, renal ultrasound or CT, chest x-ray, bone density); review of medications, with emphasis on over-the-counter medications, the possibility of drug interactions, dosing; adequate vaccinations; examination of feet; and, if necessary, psychiatric and social intervention. Only a team that includes a variety of specialists can succeed in this approach.

The elderly show a poor correlation between serum Cr and GFR probably due to differences in muscle mass associated with age, gender, race, nutrition, and activity. Therefore, it is preferable to monitor creatinine clearance measured or calculated for serum creatinine using the Cockroft–Gault method. This method gives agreement with GFR in mild degree of renal failure but overestimates it by up to 100% when GFR is 10 mL/min or less. This is presumably due to malnutrition and inactivity, which are particularly relevant in elderly patients [13]. Therefore, some authors suggest the MDRD-derived

equation for determination of GFR in advanced renal failure [13]. In addition, one should emphasize symptom control and regular monitoring of fluid overload and/or dehydration. Salt intake should be limited to 4–5 g/L. Severe constipation, which is frequent in the elderly, may exacerbate hyperkalemia. In the predialysis phase, the use of erythropoietin (rh-EPO) may improve the quality of life (QL.) and prevent left ventricular hypertrophy. Strict dietary protein restriction often is unnecessary (acceptable ingestion: 60–70 g protein/day). Also, to avoid acidosis, special attention should be paid to serum bicarbonate levels.

Initiation of Dialysis

The timing of initiation of dialysis is controversial, and there is no definitive evidence on this issue. The issue over whether dialysis should be initiated at "full dose" or in an incremental manner with dose adaptation according to progressive decrease of residual renal function remains open. Numerous studies have suggested that survival is reduced in patients starting dialysis after a GFR of 6 mL/min has been reached compared to starting dialysis earlier [14–16]. It has been recognized widely that early mortality (first 90 days) is high among the elderly ESRD population (even 27% for age over 85) and that co-morbid factors and late referral to nephrology units are significantly related to early death [17]. Late referral is associated with a longer initial hospitalization and greater frequency and longer duration of subsequent hospital admissions [18, 19]. On some occasions, it is not that the elderly are not referred early, but that the nephrologist may have delayed initiation of dialysis due to misleading serum creatinine levels. Therefore, NKF-DOQI guidelines suggest that we should perform regular calculations of creatinine clearance to avoid late initiation of dialysis [20]. An early referral may avoid subclinical uremic manifestations and malnutrition and enable the team to provide better salt and water balance, to better control anemia, and to minimize overall morbidity and mortality [21]. A low serum albumin level, a dietary protein intake less than 0.7 g/kg/day, weight loss, and a decrease in muscle mass indicate the need for dialysis [22].

Hemodialysis

In most countries, hospital hemodialysis (HD) is the principal form of RRT in the elderly [23, 24]. According to recent data, the elderly are more frequently treated by HD than by peritoneal dialysis (81% vs. 19%) when compared to their younger counterparts (65 vs. 35%) [25]. Hemodialysis offers many advantages for the elderly such as dialysis performance by nurses, shorter treatment time, socialization with staff and other patients, and continuous follow-up by medical team. Although it is used rarely, home HD is a highly successful therapeutic option [26], and individuals on home HD have few dialysis-related complications [27].

For a variety of reasons, many of the usual hemodialysis complications occur with increased frequency in elderly subjects. These complications include vascular access-related complications, intradialytic/postdialysis hypotension, malnutrition, infection, and gastrointestinal bleeding. Withdrawal from dialysis is also more frequent among the elderly compared with younger patients.

Vascular Access-Related Complications

Crucial to successful hemodialysis is the presence of functional vascular access. In comparison to a younger cohort, elderly patients are more likely to have poor-quality (or absent) forearm or leg veins because of prior medical interventions and are more likely to have atheroma or medial calcifications affecting their radial or brachial arteries [28]. Diabetes and hypertension, the most frequent causes of ESRD in the elderly [6, 7], are associated with atherosclerotic blood vessels. Proper planning for such access requires comprehensive evaluation with respect to earlier placement of vascular catheters, presence of cardiac pacemaker or a prosthetic cardiac valve, presence of enlarged axillary lymph nodes, and past radiation therapy. National Kidney Foundation (NKF) DOQI vascular access practice guidelines recommend that at least 40% of patients should use an arteriovenous (AV) fistula. In 1999, only 23% of prevalent patients older than 64 years of age used a native AV fistula, compared to nearly one-third of patients aged 45–54 years. Regarding the success rate of AV fistulae, reports vary from a very high success rate [29] to less satisfactory results [30]. Both radial-cephalic and brachial-cephalic fistulae provide excellent patency rates, lower complication rates, and improved performance compared to other types of vascular access. The wrist AV fistula preserves more proximal vessels for future access placements; potential disadvantages in elderly patients include slow maturation and inadequate blood flow rates due to atherosclerosis of the radial artery. In such instances, the elbow fistula may be preferred, or the transposed brachial-basilic fistula may have a higher incidence of arm swelling and steal syndrome [31].

The tendency has been to place an artificial graft (Gore-Tex, Impra), even though failure rates of grafts are higher than those of fistulae [32] and lead to more frequent hospitalization and higher mortality [33]. An AV graft provides a large surface area for easy canulation and a much shorter time to mature compared to an AV fistula. The specific location will be primarily determined by each patient's anatomic restriction, but antecubital loop graft or the upper arm curved graft is preferable. Potential sites for venous outflow include the median antecubital vein, proximal and distal cephalic vein, basilica vein at the elbow or the upper arm, axillary artery, and femoral vein [31]. By reviewing the results of 494 new vascular accesses in 348 HD patients older than 65 years over 29 years, Berardinelli and Vegeto [34] have shown better results with 221 elbow fistulae compared with 32 forearm fistulae (78% vs. 57.2% at 3 years; $p < 0.05$). Among various vascular substitutes, the same authors confirmed that homologous saphenous vein grafts, alone or mixed, have the best patency in comparison with other organic, semiorganic, or synthetic grafts [34]. In elderly patients, Didlake et al. [35] found no difference in the frequency of thrombosis, infection, flow problems, or pseudoaneurysm formation between elderly and young patients; but Dobkin et al. [36] confirmed a fourfold increase in deaths due to vascular access-related infections. Vascular-access thrombosis associated with recombinant human erythropoietin (rh-EPO) therapy was more common in elderly patients, for both native AV fistulae and grafts [37].

In cases of late referral, "trial dialysis," and a failed AV fistula [31], both cuffed and noncuffed catheters may provide suitable vascular access. The preferred location for a dialysis catheter is the right internal jugular vein.

Catheters of both types have higher rates of infection and malfunction than fistulae or grafts [31].

Intradialytic/Postdialysis Hypotension

Hypotension occurs in 20–30% of dialysis treatments. Some investigators reported more frequent episodes of hypotension during dialysis in elderly patients, while others have found no difference [38]. In elderly patients, hypotension may be the consequence of autonomic dysfunction, low cardiac reserve, and rapid ultrafiltration. When compared to younger patients, the elderly have an increased impairment of cardiopulmonary-/pressor-receptor reflex function [39], especially in the presence of coexisting diabetes, left ventricular hypertrophy, severe congestive heart failure, or the ingestion of certain drugs (clonidine, propranolol, diltiazem). This autonomic defect can impair the patient's ability to maintain an adequate systemic blood pressure following a large degree of fluid removal via ultrafiltration. Additional factors include intake of antihypertensive medications before HD, lower sodium concentration in the dialysate, intake of food during HD, severe hypocalcemia, and release of adenosine during organ ischemia. Also, the incidence of arrhythmias increases progressively with age and in such patients could be a risk factor for a cardiac death [40].

Among older HD patients there is a high incidence of symptoms that could be due to hypotension between HD sessions. Most importantly, the presence of orthostatic hypotension is a major risk factor for syncope and falls [41]. Not only orthostatic hypotension but also a fall in systolic blood pressure on standing between 10–20 mmHg may still have clinical relevance in the elderly. There are other, more subtle problems related to frequent falls; thus, after a fall, patients lose confidence and as a consequence may experience a reduced quality of life [42].

It is important to identify those older HD patients whose treatment strategies should be modified. A number of possible interventions may reduce the frequency of intradialytic hypotension: frequent assessment of dry weight, avoidance of net ultrafiltration rates above 1 L/hr, and correction of anemia. In some patients, tight blood pressure control is of less concern than reducing the risk of falls and addressing quality-of-life issues. The use of drugs such as midodrine together with nonpharmacological measures including compression hosiery may improve the symptoms of orthostatic hypotension [43].

Malnutrition

Approximately 10% of patients undergoing hemodialysis have moderate to severe malnutrition. The incidence is even higher in the elderly, possibly occurring in up to 20% of individuals, and is associated with decreased survival [44]. A variety of causes have been implicated in the development of malnutrition in elderly dialysis patients, including low income, social isolation, malabsorption and gastrointestinal motility disorders, ill-fitting dentures, depression, drug effect, impaired taste and anorexia, chronic constipation, frequent and prolonged hospitalizations, and underdialysis. Although protein requirements may be slightly reduced in elderly dialysis patients, dialytic losses of amino acids as well as the catabolic effects of the dialysis itself may result in protein malnutrition. Therefore, it is important to prescribe a diet adequate in protein and energy and to use oral supplements to normalize the serum bicarbonate level. The NKF-DOQI Adult Nutrition Work Group

recommendations for dietary protein intake in the elderly do not differ from those for younger patients: 1.2 g protein/kg body weight/day for HD patients and 1.2 or 1.3 g protein/kg body weight/day for PD patients [45]. They also recommend a slight reduction in energy intake from 35 to 30 kcal/kg body weight/day because of their slightly lower energy needs [45]. Multivitamin preparations are also recommended. No formal studies have been carried out to determine whether micronutrient needs are different for elderly dialysis patients, but it seems prudent to describe water-soluble vitamins as well as micronutrients in at least the same amounts as those prescribed for younger dialysis patients [46]. Special attention should also be paid to calcium intake, as the risk of bone loss is high in the older population [46]. Since dietary calcium intake is generally associated with phosphorus intake, calcium supplements should be prescribed.

Infections

The elderly are at increased risk for infections due in part to aging of the immune system and the effect of poor nutrition on immune function. Death from infection is the second leading cause of death among hemodialysis patients over the age of 64 [47]. The most frequent life-threatening infections among elderly HD patients arise from infected vascular access and from the gastrointestinal and genitourinary tracts. In the hospital setting, significantly higher annual incidences of seroconversion rates in those aged 55 to 74 during a shorter dialysis period suggest the greater susceptibility of the middle-aged and elderly patients to acquisition of hepatitis C (HCV) infection than the younger (15- to 24-year) group [48].

Gastrointestinal Bleeding

The elderly are at higher risk of gastrointestinal disorders including gastritis, ulcer disease, diverticulosis, angiodisplasia, and carcinoma. Therefore, they are at particular risk of bleeding while on hemodialysis. Hemorrhagic gastritis in elderly HD patients is the consequence of uremia and therapy with NSAIDs. Angiodysplasia is a frequent finding and can occur anywhere along the gastrointestinal tract. The lesions are usually multiple. Perforation of colonic diverticulosis may arise in part because of the constipating effects of calcium- or aluminum-based phosphate binders [49].

Effective dialysis, better platelet function, H2 blockers, photocoagulation/electrocautery, tight heparinization or citrate anticoagulation, and, finally, peritoneal dialysis are usual measures in those with bleeding disorders on HD.

Peritoneal Dialysis

Increasingly authors are citing chronic peritoneal dialysis (CPD) as the treatment of choice in elderly patients with ESRD. Such dialysis offers many advantages including good control of hypertension, independence from hospitals, simplicity of access, better cardiovascular stability (less hypotension and fewer arrhythmias), and slow solute removal (Table 24-1). A family member may perform such dialysis, and the patient does not need transportation to the hospital [50]. On the other hand, the elderly are at risk of some complications that are more frequent in them than in younger PD patients.

Table 24.1 Advantages and Disadvantages of Hemodialysis and Peritoneal Dialysis in the Elderly.

Hemodialysis	
Advantages:	Technique independence
	Less time on treatment
	Socialization
	Continuous follow-up
Disadvantages:	Vascular access problems
	Infection related to permanent catheter/graft
	Dependence of transport
Peritoneal dialysis	
Advantages:	Simplicity of access
	Better cardiovascular stability (less of hypotension risk and arrhythmia)
	Good control of hypertension
	Well tolerated due to slow solute removal
	Ease of travel
	Independence of the hospital
	Can be performed by a family member
	No need for transportation
Disadvantages:	Not suitable for all patients*
	Difficulty in learning*
	Social isolation
	Family burn-out

*Problem could be overcomes with family/social support.

Modality-Related Complications

Peritonitis and exit-site infection are the most common complications of peritoneal dialysis but also are the leading causes of morbidity and technique failure. The elderly are at increased risk of infection for a variety of reasons such as immunodeficiency due both to aging of the immune system and to malnutrition. However, we do not fully understand the role of immunodeficiency in the development of peritonitis in these patients. Peritonitis rates in the elderly are variable and depend on the reporting center, the year of publication, the system used, and the patient's ability to perform exchanges [51]. A broad spectrum of results exists, ranging from those who did not find any significant difference in peritonitis rate between age groups (elderly vs. younger) [52, 53] to those who found peritonitis to be more frequent in the elderly [54, 55] or less frequent in the elderly [56]. No differences in peritonitis rates were found between those doing PD with assistance and those who did "self"-PD [57]. However, bedridden patients tended to have a higher peritonitis rate, but it is not clear whether these episodes were related to contamination or to some bowel dysfunction [52]. Causative micro organisms are similar to those in younger patients [54], but some differences were confirmed; for example, some authors found a lower incidence of culture-negative peritonitis in the elderly [58]; others described a higher incidence of peritonitis due to Staphylococcus epidermidis [59, 60]. These discrepancies could be explained by the diminished manual dexterity of the elderly and a higher degree of contamination during bag exchanges. The higher incidence of Gram-negative peritonitis described by some authors has been explained by the higher incidence of gastrointestinal pathology in the elderly—constipation,

diverticulosis, and bowel perforation [61]. The incidence of yeast peritonitis ranged from 2% to 33% [62, 63]. Peritonitis, when present, caused a higher fatality among patients over 65 (2.3%) and 75 (3.2%) than among those younger than 65 (1.4%) [64].

Although some authors have reported a higher incidence of catheter-related complications among the elderly [59], others did not confirm this finding [58].

Most authors agree that exit-site and tunnel infections were less frequent in the elderly than in younger patients on PD, perhaps because older patients are less active than the younger [60, 62]. The incidence of hernias in the elderly is similar to that in younger patients [65] but sometimes is more frequent due to the well-known weakness of the abdominal musculature [66].

Malnutrition

There is evidence that malnutrition is more frequent in the elderly than in younger patients on CPD [57, 67], and this complication is highly correlated with mortality [67]. Also, low initial albumin levels correlate with mortality among the elderly on Continuous Ambulatory Peritoneal Dialysis (CAPD) [17], and cachexia is a frequent cause of death [58]. There is no significant difference in the incidence of malnutrition between elderly patients on CPD and those on HD [68].

Elderly patients on CPD rarely suffer from malnutrition alone: They often have a primary disorder or illness that is the cause of this malnutrition and that plays a major part in the outcome. Furthermore, malnutrition in the elderly may reflect such factors as low income, social isolation, depression, dental problems, malabsorption, or drug effects. The mode of dialysis per se often makes its own contribution because these patients may lose 20–50 g of protein and up to 15 g of free amino acids weekly, even in the absence of peritonitis. Also, abdominal fullness, glucose absorption, diminished appetite, and inadequate dialysis, once the residual renal function has declined, may contribute to anorexia and malnutrition.

Because of the many factors that can produce malnutrition in the elderly on CPD, these patients should be examined carefully to identify any underlying cause since many of these factors are reversible. Thus, routine measurement and follow-up of all nutritional parameters are of pivotal importance in the elderly on CPD. The renal dietician should have a central role in the diagnosis and treatment of malnutrition in these patients [69].

Hospitalization

Hospitalization rates are higher among elderly than among younger patients, especially among blacks and diabetics [70, 71]; the duration of stay varies between 5.5 [72] and 23.1 in-hospital days [73]. The most common cause of hospitalization is peritonitis [11, 36, 39]. No differences were reported in hospitalization rates between elderly patients on PD and HD [74].

Survival

Different results have been described on the survival of the elderly on RRT, an important parameter of the success of treatment. Those differences may be explained by differences in criteria for acceptance. Data presented by Lawping et al. [75] have shown that the 1-year survival rates for patients aged 70 years or over compare very favorably with survival rates reported in

a UK study of patients of all ages who were 15 years younger (71% for all elderly who started dialysis and 81% for those who survived 90 days vs. 63% and 85% for younger patients, respectively) [76]. Cox regression analysis confirmed that mortality was significantly associated with age 80 years and older and peripheral vascular disease but not with diabetes, ischemic heart disease, cerebrovascular disease, chronic obstructive airway disease, gender, or treatment method. These authors pointed out that these unexpected findings about the lack of association between mortality and co-morbidity need to be interpreted with caution since the level of severity of these co-morbidities was unknown. Another report has shown that more than 50% of patients older than 75 years died within 2 years after starting dialysis; their mean survival was 31 months and, according to a multivariate logistic regression model, risk factors for increased mortality were the number of hospitalization days during the past 3 months and lower weight [77]. In the same study, mortality rates in HD and PD patients were similar.

Advanced age is associated with shorter survival on PD [78, 60, 79]. The elderly have many co-morbid conditions, and most elderly patients die of diseases that were present at the start of dialysis [80]. Also associated with these high-risk co-morbid conditions was early mortality—within 90 days—which is included in some papers and not in others. Compared to those younger than 65 years, the elderly had a significantly greater chance of dying within 90 days after treatment withdrawal [81].

Comparison of survival rates on PD vs. HD have shown varied results. Some studies have shown better survival on PD than on HD [82], except for female diabetics [83] or those on hemofiltration [23]. Others show a survival equal to that on HD [84, 71, 85, 86] or, in one report, worse than HD [87]. Recently, Collins et al. [88] reported that PD patients in the United States were slightly younger, with slightly fewer females, a greater percentages of whites, and a comparable percentage of patients with diabetes and lower Charleston co-morbidity index (3.1 vs. 3.6) than HD patients. Even so, they had a lower survival than their counterparts on HD even after adjusting for basic demographics, co-morbidity, and residual renal function. Winkelmayer et al. [89] studied the 1-year survival of all patients >65 years who began RRT between January 1991 and June 1996 (2503 incident patients); 21.5% of them were on PD and 78.5% were on HD. Patients who initially were assigned to PD had a higher overall mortality rate than those initially assigned to HD (1.24; 95% CI, 1.09–1.41). The survival pattern between treatment modalities changed over time: Patients starting PD were 16% more likely to die during the first 3 months; between 3 to 6 months after beginning PD, the mortality rate among them was similar to that on HD; between 6 to 12 months, patients who started PD had a 45% (6 to 9 months) and 57% (9 to 12 months) higher mortality rate than HD patients. Previously, the excess death rate observed between 6 to 12 months was attributed to the presence of patients with diabetes. However, these authors did not consider clinical and biological parameters, patient compliance with treatment, dose of dialysis, quality of life, access and availability, and associated cost of treatment. Also, during the 5 years of the above-noted retrospective analysis, the techniques of both HD and PD were being improved. Data from the Netherlands Cooperative Study on the Adequacy of Dialysis 2 have shown that after 2 years on dialysis, there was an increase in mortality for PD

patients; this tendency was observed especially among patients above 60 years of age and was not influenced by censoring strategy [90]. More recent data [91] regarding the gender effect on mortality rate for HD and PD patients starting dialysis between 1990 and 1998 in Canada found that for HD patients there was no difference in adjusted mortality rate ratio (RR) between genders irrespective of diabetic status, while females ≥65 years on PD had significantly higher adjusted mortality rates than males. Moreover, diabetic females on PD had significantly higher mortality rates than males in both age groups.

Risk factors for mortality on PD include peripheral vascular disease [92], chronic obstructive pulmonary disease [23], cardiomyopathy, systemic disease [87], depression [93], diabetes, and low initial serum albumin level [94]. Also, those "forced" to begin CAPD had a 25% survival at 2 years compared to those who chose CAPD, who had a 25% survival at 5 years [71]. The greatest cause of mortality among the elderly, as among younger dialysis patients, is cardiac disease. In various series, withdrawal from dialysis was the cause of death in up to 40% of patients [95, 96]. More recent studies have shown a significant improvement in the survival of the elderly on PD [97].

To evaluate the effectiveness of automated PD in the elderly, Kadambi et al. [98] compared the outcomes of three groups of patients of different ages (<50 years, 50–64 years, and >65 years). This large retrospective study, which included 192 patients over 65 years old, found a higher mortality rate in the elderly than in younger patients. However, technique failure rates were not different than for younger patients [98].

Quality of Life

Quality of life (Q.L.) is an important issue for the elderly, as for all dialysis patients. Conclusions about Q.L. are influenced by the way in which Q.L. is defined and measured. Sickness Impact Profile (SIP) [99] and the Medical Outcome Study (MOS) Short Form-36 (SF-36) [100] are used frequently to define patient-assessed functioning and well-being. The most meaningful group for Q.L. comparison with the elderly on dialysis may be elderly persons without renal failure. Differences between the former and the latter were less marked than comparable differences between young patients on dialysis and not on dialysis on virtually every SF-36 scale [101]. However, compared to their peers of similar age and not on dialysis, elderly dialysis patients were more likely to have compromised physical function [102]. Data from the North Thames Dialysis Study confirmed lower scores on the physical component score of the SF-36 in older than in younger patients [75]. However, mental quality of life in elderly dialysis patients was similar to that of elderly people in the general population. Adjusted analysis also showed no significant differences in quality of life between PD and HD patients. In a multicenter survey of almost 2500 patients, Gutman et al. [103] reported that Karnofsky scores indicated that only 40% of patients older than 60 years were able to do more than self-care. More optimistic data from National Kidney Dialysis and Kidney Transplantation Study (NKDKTS) showed almost one-half of patients older than 65 years had a reasonable degree of ability to perform normal activities [104].

Comparisons of psychosocial issues in older and younger patients suggest more frequent suicidal tendencies in elderly dialysis patients [105], more evident depressive symptoms [106, 107], and more loneliness [108]. Recently, it has been reported that the elderly on dialysis have higher scores on the psychosocial and physical dimensions in the Sickness Impact Profile (SIP) [109]. Both univariate and multivariate analyses indicated that advancing age was associated with lower SF-36 physical functioning scores in a multicenter cohort of Dutch patients studied 3 months after beginning dialysis [110]. Another study from the United States reported that older patients had lower levels of physical functioning but higher SF-36 mental health scores than younger patients [111]. In addition, older patients were less likely than younger patients to be disturbed by the effects of kidney disease on their daily lives [111].

Westlie et al. [112] and Rotellar et al. [113] have found a positive association between advancing age and life satisfaction among dialysis patients. Patients older than 70 years were active socially, enjoyed life [112], and perceived life to be less stressful than did younger patients [114, 115]. Data from NKDKTS have shown that patients $\geq$65 reported greater functional impairment than younger patients. At the same time, however, patients $\geq$65 years had a higher well-being index, more positive feelings, and greater satisfaction with their marriages, family life, savings, standard of living, investments, and life in general [105].

It is important to recognize that, in elderly dialysis patients, enhanced functional independence may significantly improve their Q.L. Asai et al. [116] and Ota et al. [117] have concluded that low-intensity physical exercise may significantly improve a patient's functional status scores and deficits in balance, range of motion, and flexibility. An inner-city HD clinic [117, 118] offered elderly patients a physical therapy program and an individual approach after initial assessment. When elderly patients are rehabilitated in specialized geriatric units, they have less need for subsequent nursing home placement [119]. An integrated program at a chronic care and rehabilitation services center has been shown to improve Q.L. and lower the cost of care [120].

With respect to Q.L. and the modality of treatment of elderly uremics, it has been shown that transplanted elderly patients had a better Q.L. than did similar HD patients, as measured by SF-36 scores [121]. The benefits of chronic PD as compared to HD for the elderly including a greater sense of well-being, lower illness- and modality-related stress, fewer mood disturbances, and fewer dialysis-related symptoms [122]. According to a recent meta-analysis that compared emotional distress and psychological well-being across renal replacement therapies, elderly patients on CAPD had a greater sense of well- being than did those on in-center HD [123].

The Q.L. of elderly patients may be improved significantly by attending to all the reversible influences such as anemia, inadequate dialysis, malnutrition, and co-morbid conditions (including anemia).

Social Issues

PD is not used extensively among the elderly, because they are unable to perform dialysis by themselves: About 61.2% of very old patients (above 80) need help with dialysis exchanges, exit-site care, and medication [70]. Many

patients older than 65 suffer from such co-morbid conditions as depression, dementia, impaired vision, and decreased physical and mental activity, all of which significantly impair their health, and these factors are problematic for any dialysis modality. However, given a network of medical and social support, the elderly can perform dialysis (especially automated PD) successfully.

Home Care Nursing

Experience with such care was based mainly on the experience of the French investigators who started CAPD, where the home care was performed by trained home care nurses. Such nurses may provide the elderly with comfortable and safe home dialysis without reliance on family members. Also, the low rate of infection and hospitalization and the avoidance of transportation in this high-risk population achieve significant savings that affect the nurses' salaries. The rates of peritonitis and exit-site infection were not significantly different between those who had "assisted dialysis" by a home care nurse and those on "self-dialysis" [70]. The home care nurse may assist in the treatment of peritonitis episodes and other complications, thereby contributing to a total hospitalization rate lower than that usually reported [94].

Rehabilitation and Chronic Care Dialysis Units (RCDU)

Such units may provide dialysis, physiotherapy, a rehabilitation program, and occupational therapy for those patients who cannot return home or who cannot be placed in a nursing home. Such units achieve significant reduction in costs compared to hospital treatment, and this cost reduction is not accompanied by any deterioration in the elderly person's quality of life [124].

Dialysis in the Nursing Home

More and more elderly will live in a nursing home in the future. The 1997 National Nursing Home Survey found that there were nearly 1.5 million residents >65 years old living in nursing homes in the United States [125]. Of these nursing home patients, 0.3% were on dialysis; approximately 90% of these were on hemodialysis and 10% were on peritoneal dialysis [126]. A substantial number of nursing homes refused to introduce dialysis into everyday care, because (1) of a perception that the ESRD elderly population is difficult to care for, (2) the homes lack knowledge about dialysis and renal diet, (3) they lack adequate storage space for machine and supplies, and (4) there is poor communication with the renal team [127].

Although HD is the mode most often used in nursing homes, the published data are limited. As in the overall dialysis population in the United States [128], HD patients in the nursing homes have better survival than those on PD [127]. However, there is very little additional data and, until now, there have been no control trials. Nursing home residents on HD spend about 15 hours in the dialysis unit per week, which takes away from rehabilitation and social activities. In addition, their need for transportation may be overcome by building the dialysis center within or adjacent to a skilled nursing facility.

Peritoneal dialysis in nursing homes offers many advantages and allows flexibility of exchange schedules for patients and for staff. In this regard, automated PD (APD) or nightly PD keeps the patient's daytime free for nursing home activities, increases socialization, and enables better rehabilitation, which improves a patient's quality of life. Patients on PD in nursing

homes and day care centers have lower survival than the general CAPD population; this is probably a reflection of patient selection because those in nursing homes are significantly older and have many co-morbid conditions. Anderson et al. [129, 130] did a retrospective analysis initially of 44, and later of 109, nursing home patients on CAPD over a 10-year period. Survival rates at 6 and 12 months were 51.7% and 37.2%, respectively. Risk factors for death included age greater than 75 years, activities of daily living score less than 8, coronary artery disease, decubitus ulcer(s), and malnutrition (serum creatinine less than 680 ∘mol/L). Carey et al. [131], who studied the outcomes of 93 CAPD patients in 10 community extended-care facilities over a 5-year period, observed 6- and 12-month survival rates of 50% and 40%, respectively. The same authors concluded that, when compared to age-matched patients in the community who experienced 1 peritonitis episode per 13.5 patient-months, nursing home patients have a higher risk of peritonitis, 1 episode per 9.6 patient-months [129, 130, 131]. Whether the high rate of peritonitis reflects patient-specific susceptibility factors or just poor technique remains to be elucidated. On the contrary, elderly patients in nursing homes have been treated successfully for months without an excessive rate of peritonitis. Thus, Lima Memorial Hospital reported a peritonitis rate of 1 episode per 14.6 patient-months, and the University of Wisconsin had a peritonitis rate of 1 episode per 17 patient-months. These rates do not differ significantly from those in the overall non-institutionalized elderly [132].

Withdrawal from dialysis was more frequent among nursing home dialysis patients; according to some authors [133], "living in a nursing home" was the main risk factor for termination of dialysis. However, this high discontinuation rate among the elderly is not due to dialysis per se but rather to associated social and medical circumstances [134].

We can improve dialysis services in nursing homes through workshops about kidney diseases, hemodialysis, peritoneal dialysis, and renal diet; by better communication between nursing staff and the renal team; and with "nursing home dialysis" manuals. These measures will improve staff confidence and will contribute to better morale and better performance.

Ethical Issues

Dialysis as a life-extending treatment may offer life to the elderly; for many of these elderly patients, these are lives of quality. However, some older individuals elect to cease dialysis because of Q.L. issues [135, 136]. For this reason, we should be completely honest when educating patients and their families regarding the burdens associated with living on dialysis. Healthcare professionals cannot make this decision for others but should share their knowledge and experience and advise patients without projecting their own prejudices. With respect to the decision-making process, the first published guidelines that appeared in 1993 [137] were personal and did not reflect the majority opinion. A set of consensus guidelines, published by the National Kidney Foundation in 1996 [138], allowed all patients to explore their own opinions. Finally, the American Society of Nephrology and the Renal Physicians Association published evidence-based guidelines in 2000 [139]. All of these publications emphasize that they are just guidelines and not rules; they emphasize the difficulties of the decision-making process that arise from

the heterogeneous nature of both providers and patients. None of the guidelines recommends mandatory standards for the determination of the patient's candidacy for dialysis. Sometimes neither the medical team nor the patient or family members find it easy to reach a decision. In such cases, the patient should be offered a 30- to 90-day trial period of dialysis. All guidelines recommend against offering dialysis to patients with a known terminal illness or to patients who have serious mental impairment as a result of stroke, Alzheimer's disease, or neurological dysfunction. Also, patients on dialysis who develop a terminal illness or become demented should be offered the choice to discontinue dialysis. The same recommendation is made for those patients who have serious mental impairment as a result of stroke, Alzheimer's disease, or neurological dysfunction.

References

1. U.S. Renal Data System. Bethesda, MD: National Institutes of Health. 2003.
2. Canadian Institute for Health Information, June 29, 2005.
3. The Renal Association. UK Renal Registry Report 2003, Bristol: The Renal Association. 2003.
4. Yamagata, K., Takahashi, H., Suzuki, S., Mase, K., Hagiwara, M., Shimizu, Y., et al. Age distribution and yearly changes in the incidence of ESRD in Japan. *Am. J. Kidney Dis*. 2004; 43(3):433–443.
5. Madhan, K. The epidemic of elderly patients with dialysis-requiring end-stage renal disease in New Zealand. *N. Zeal. Med. J*. 2004; 117(1195). Available online at http://www.nzma.org.nz/journal/117-1195/912/.
6. Blagg, C.R. Chronic renal failure in the elderly. In *Geriatric Nephrology*, D.G. Oreopoulos, ed. Boston: Martinus, Nijhoff. 1986; p. 117.
7. Porush, J.G., Faubert, P.F. Chronic renal failure. In *Renal Diseases in the Aged*, J.G. Porush and P.F. Faubert, eds. Boston: Little Brown Co. 1991; p. 285.
8. Canadian Institute for Health Information: Annual Report 1999, Dialysis and Transplantation, Canadian Organ Replacement Register. Ottawa: Canadian Institute for Health Information. 1999.
9. Sesso, R., et al. Acceptance for dialysis treatment: Insufficient and unequal. *Nephrol. Dial. Transplant* 1996; 11:982–986.
10. Khan, I.H., et al. Chronic renal failure: Factors in influencing nephrology referral. *Quar. J. Med*. 1994; 87:559–564.
11. Mendelson, D.C., Singer, P.A. Referral for dialysis in Ontario. *Arch. Intern. Med*. 1995; 155:2473–2478.
12. Kausz, A.T., Obrador, G.T., Arora, P., Ruthazer, R., Levey, A.S., Pereira, B.J.G. Late initiation of dialysis among women and ethnic minorities in the United States. *J. Am. Soc. Nephrol*. 2000; 11:2351–2357.
13. Levey, A.S. et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann. Intern. Med*. 1999; 130:461–470.
14. Tattersall, J., et al. Urea kinetics and when to commence dialysis. *Am. J. Nephrol*. 1995; 15:283–289.
15. Ruggenenti, P., et al. In chronic nephropathies prolonged ACE inhibition can induce remission: Dynamic of time-dependent changes in GFR. Investigators of the GISEN Group. Gruppo Intaliano Studi Epidemiologici in Nefrologia. *J. Am. Soc. Nephrol*. 1999; 10:997–1006.
16. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. Adequacy of dialysis and nutrition in continuous ambulatory peritoneal dialysis: Association with clinical outcomes. *J. Am. Soc. Nephrol*. 1996; 7(2):198–207.

17. Mignon, F., Siohan, P., Legallicier, B., Khayat, R., Vitron, B., Michel, C. The management of uremia in the elderly: Treatment choices. *Nephrol. Dial. Transplant* 1995; 10(Suppl 6):55–59.
18. DeOreo, P.B. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization and dialysis-attendance. *Am. J. Kidney Dis*. 1997; 30:204–212.
19. Jassal, V.S., Roscoe, J.M. Dialysis in old age: Are we really doing all we should? *Age and Ageing* 1999; 28:503–504.
20. National Kidney Foundation Inc. Dialysis outcomes quality initiative: Clinical practice guidelines for hemodialysis adequacy. *Am. J. Kidney Dis*. 1997; 10(Suppl 2):S17–S63.
21. Tattersall, J., Greenwood, R., Farrington, K. Urea kinetics and when to commence dialysis. *Am. J. Nephrol*. 1995; 15:283–289.
22. Hakim, R., Lazarius, J.M. Initiation of dialysis. *J. Am. Soc. Nephrol*. 1995; 6: 1319–1328.
23. Mandigers, C.M.P.W., de Jong, W., van den Wall Bake, A.W.L., Gerlag, P.G.G. Renal replacement therapy in the elderly. *Netherlands J. Med*. 1996; 49:135–142.
24. Salomone, M., Piccoli, G.B., Quarello, F., Borca, M., Cesano, G., Torazza, M.C., Grott, G., Gonella, M., Cavagnino, G., Triolo, G., Piccoli, G. Dialysis in the elderly: Improvement of survival results in the eighties. *Nephrol. Dial. Transplant* 1995; 10(Suppl 6):60–64.
25. Letourneau, I., Ouimet, D., Dumont, M., Pichette, V., Leblanc, M. Renal replacement in end-stage renal disease patients over 75 years old. *Am. J. Nephrol*. 2003; 23:71–77.
26. McDonald, M., McPhee, P.D., Walker, R.J. Successful self-care home dialysis in the elderly: A single center experience. *Perit. Dial. Int.* 1995; 15:33–36.
27. 2000 Annual Report of the ESRD Clinical Performance Measures Project. Washington, DC: Department of Health and Human Services, Health Care Financing Administration Office of Clinical Standards and Quality. 2000.
28. Roake, J. Dialysis in the elderly. *N. Zeal. Med. J*. 2004; 117(1195):1–4.
29. Wings, O.E., Wolma, F.J. Complications of vascular access for hemodialysis. *Southern Med*. 1985; 78:513.
30. Hindsale, J.G., Lipcouritz, G.S., Hoover, E.L. Vascular access in the elderly: Results and perspectives in a geriatric population. *Dial. Transplant* 1985; 14:560.
31. Latos, D.L. Hemodialysis in the elderly: Vascular access and initiation of renal replacement therapy. *Sem. Dial*. 2002; 15(2):91–93.
32. Woods, J.D., Turenne, M.N., Strawdernam, R.L., et al. Vascular access survival among incident hemodialysis patients in the United States. *Am. J. Kidney Dis*. 1997; 30:50.
33. Feldman, H.I., Held, P.J., Hutchinson, J.T., et al. Hemodialysis vascular access morbidity in the United States. *Kidney Int*. 1993; 43:1091.
34. Berardinelli, L., Vegeto, A. Lessons from 494 permanent access in 348 haemodialysis patients older than 65 years of age: 29 years of experience. *Nephrol. Dial. Transplant* 1998; 13(Suppl 7):73–77.
35. Didlake, R., Raju, S., Rhodes, R.S., Bower, J. Dialysis access in patients older than 65 years. In *Vascular Access for Hemodialysis II*, B.G. Sommer and M.L. Henry, eds. Boston: Wall Gore and Associates, Inc. 1991; p. 166.
36. Dobkin, J.F., Miller, M.H., Steigbigel, N.H. Septicemia in patients on chronic hemodialysis. *Ann. Intern. Med.* 1978; 88:28.
37. Tang, I.Y., Vrahnos, D., Valaitis, D., Lau, A.H. Vascular access thrombosis during recombinant human erythropoietin therapy. *ASAIO J*. 1992; 38:M528.
38. Jacobs, C., Diallo, A., Bales, E.H., Nectoux, M., Etienne, S. Maintenance haemodialysis treatment in patients aged over 60 years. Demographic profile, clinical aspects and outcome. *Proc. Eur. Dial. Transplant Assoc.* 1984; 21:477.

39. Cleroux, J., Giannottasio, C., Grassi, G., et al. Effects of aging on the cardiopulmonary receptor reflex in normotensive humans. *J. Hypertens*. 1988; 6:S141.
40. Niwa, A., Taniguchi, K., Ito, H., Nakagawa, S., Takeuchi, J., Sasaoka, T., Kanayama, M. Echocardiographic and Holter findings in 321 uremic patients on maintenance hemodialysis. *Japan Heart J*. 1985; 26:403.
41. Russell, G.R., Kenny, R.A., Brierly, E.J. Are elderly haemodialysis patients at risk of falls and postural hypotension? *Int. Urol. Nephrol*. 2003; 35:415–421.
42. Tinetti, M.E., Mendes de Leon, C.E., Doucette, J.T., Baker, D.I. Fear of falling and fall-related efficacy in relationship to functioning among community-living elders. *J*, *Gerontol*, 1944; 49:M140–M147.
43. Agrawal, A., Saran, R., Khanna, R. Management of orthostatic hypotension from autonomic dysfunction in diabetics on peritoneal dialysis. *Perit. Dial. Int*. 1999; 19:415–417.
44. Chauveau, P., Combe, C., Laville, M., et al. Factors influencing survival in hemodialysis patients aged older than 75 years: 2.5-year outcome study. *Am. J. Kidney Dis*. 2001; 37:997.
45. Clinical practice guidelines for nutrition in chronic renal failure. *Am J. Kidney Dis*. 2000; 35(Suppl 2).
46. Blumberg, J. Nutritional needs of seniors. *J. Am. Coll. Nutr*. 1997; 16:517–523.
47. U.S. Renal Data System. 1991 Annual Data Report. Bethesda, MD: The National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases. 1991.
48. Saxena, A.K., Panhotra, B.R. The vulnerability of middle-aged and elderly patients to hepatitis C virus infection in a high-prevalence hospital-based hemodialysis setting. *JAGS* 2004; 52:242–246.
49. Zuckerman, G.R., Comette, G.L., Clouse, R.E., Harter, H.R. Upper gastrointestinal bleeding in patient with chronic renal failure. *Ann. Intern. Med.* 1985; 102:588.
50. Nissensen, A.R., Diaz-Buxo, J.A., Adock, A., Nelms, M. Peritoneal dialysis in the geriatric patients. *Am. J. Kidney Dis*. 1990; 16:335–338.
51. Benevent, D., Benzakour, M., Peyronnet, P., Legarde, C., Leroux-Robert, C., Charmes, J.P. Comparison of continuous ambulatory peritoneal dialysis and hemodialysis in the elderly. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl):68–71.
52. Nolph, K.D., Lindblad, A.S., Novak, J.W., Steinberg, S.M. Experiences with the elderly in the National CAPD Registry. *Adv. Perit. Dial*. 1990; 6:33–38.
53. Baek, M.Y., Kwon, T.H., Kim, Y.L., Cho, D.K. CAPD, an acceptable form of therapy in elderly ESRD patients: A comparative study. *Adv. Perit. Dial.* 1997; 13:158–161.
54. De Vecchi, A., Maccario, M., Braga, M., Scalamogna, A., Castelnovo, C., Ponticelli, C. Peritoneal dialysis in nondiabetic patients older than 70 years: Comparison with patients aged 40 to 60 years. *Am. J. Kidney Dis*. 1998; 31: 479–490.
55. Ross, C.J., Rutsky, E.A. Dialysis modality in the elderly patients with end-stage renal disease: Advantages and disadvantages of peritoneal dialysis. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl): 11–18.
56. Gokal, R. CAPD in the elderly—European and UK experience. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl):38–41.
57. Issad, B., Benevent, D., Allounache, M., Durand, P.Y., Aguilera, D., Milongo, R., et al. 213 Elderly uremic patients over 75 years of age treated with long-term

peritoneal dialysis: A French multicenter study. *Perit. Dial. Int*. 1996; 16 (Suppl I): S414–S418.
58. Segoloni, G.P., Salomone, M., Piccoli, G. CAPD in the elderly: Italian multicentric study experience. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl):41–46.
59. Jagose, J.T., Afthentopoulos, I.E., Shetty, A., Oreopoulos, D. Successful use of continuous ambulatory peritoneal dialysis in octogenarians. *Geriatr. Nephrol. Urol*. 1996; 5:135–141.
60. Holley, J.L., Bernardini, J., Perlmutter, J.A., Piraino, B. A comparison of infection rates among older and younger patients on continuous peritoneal dialysis. *Perit. Dial. Int*. 1993; 14:66–69.
61. Wakeen, M.J., Zimmerman, S.W., Bidwell, D. Viscous perforation in PD patients: Diagnosis and outcome. *Perit. Dial. Int*. 1994; 14:371–377.
62. Nissenson, A.R., Gentile, D.E., Soderblom, R. CAPD in the elderly: Southern California/Southern Nevada experience. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)* A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl):51–55.
63. Joglar, F., Saade, M. Improved overall survival of elderly patients on peritoneal dialysis. *Adv. Perit. Dial*. 1991; 7:63–67.
64. Piccoli, G., Quarello, F., Salomone, M., Bonello, F., Paciffiti, A., Beltrame, G., et al. Dialysis in the elderly: Comparison of different dialysis modalities. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl): 72–81.
65. Gentile, D.E., and Geriatric Advisory Committee. Peritoneal dialysis in geriatric patients: A survey of clinical practises. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl):29–32.
66. Bargman, J.M. Complication of peritoneal dialysis related to increased intra-abdominal pressure. *Kidney Int*. 1993; 43(Suppl 40):S75–S80.
67. De Vecchi, A.F., Maccario, M., Ponticelli, C. Peritoneal dialysis in the ninth decade of life experience in a single center. *Geriatr. Nephrol. Urol*. 1996; 6: 75–80.
68. Dombos, N.V., Oreopoulos, D.G. Nutritional aspects of patients on CAPD. In *Peritoneal Dialysis. Proceedings of Third International Course on Peritoneal Dialysis*, Vicenza, Italy, G. La Greca, S. Chiamonte, A. Fabris, M. Feriani, and C. Ronco, eds. Milan: Wichtig. 1988; pp. 113–118.
69. Lowrie, E.G., Lew, N.L. Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am. J. Kidney Dis*. 1990; 15:458.
70. Jagose, J.T., Afthentopoulos, I.E., Shetty, A., Oreopoulos, D. Successful use of continuous ambulatory peritoneal dialysis in octogenarians. *Geriatr. Nephrol. Urol*. 1996; 5:135–141.
71. Gokal, R. CAPD in the elderly—European and UK experience. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl): 38–41.
72. Holley, J.L., Bernardini, J., Perlmutter, J.A., Piraino, B. A comparison of infection rates among older and younger patients on continuous peritoneal dialysis. *Perit. Dial. Int.* 1993; 14:66–69.
73. Nolph, K.D., Lindblad, A.S., Novak, J.W., Steinberg, S.M. Experiences with the elderly in the National CAPD Registry. *Adv. Perit. Dial.* 1990; 6:33–38.
74. Brown, E.A. Peritoneal dialysis versus hemodialysis in the elderly. *Perit. Dial. Int*. 1999; 19:311–312.

75. Lamping, D.L., Constatinovici, N., Roderick, P., Normand, C., Henderson, L., Harris, S., et al. Clinical outcomes, quality of life and costs in the North Thames dialysis study of elderly people on dialysis: A prospective cohort study. *Lancet* 2000 Nov. 4; 356:1543–1550.
76. Chandna, S.M., Schulz, J., Lawrence, C., Greenwood, R.N., Farrington, K. Is there a rationale for rationing chronic dialysis? A hospital-based cohort study of factors affecting survival and morbidity. *Br. Med. J.* 1999; 318:217–223.
77. Letourneau, I., Ouimet, D., Dumont, M., Pichette, V. Renal replacement in end-stage renal disease patients over 75 years old. *Am. J. Nephrol*. 2003; 23:71–77.
78. De Vecchi, A., Maccario, M., Braga, M., Scalamogna, A., Castelnovo, C., Ponticelli, C. Peritoneal dialysis in nondiabetic patients older than 70 years: Comparison with patients aged 40 to 60 years. *Am. J. Kidney Dis*. 1998; 31: 479–490.
79. Stack, A.G., Messana, J.M. Renal replacement therapy in the elderly: Medical, ethical and psychosocial consideration. *Adv. Renal Repl. Ther*. 2000; 7(1):52–62.
80. Issad, B., Benevent, D., Allonache, M., Durand, P.Y., Aguilera, D., Milongo, R., et al. 213 Elderly uremic patients over 75 years of age treated with long-term peritoneal dialysis: A French multicenter study. *Perit. Dial. Int*. 1996; 16(Suppl I):S414–S418.
81. Tsakiris, D., Jones, E.H.P., Briggs, J.D., Elinder, C.G., Mehls, O., Mendel, S. Deaths within 90 days from starting renal replacement therapy in the ERA-EDTA registry between 1990–1992. *Nephrol. Dial. Transplant* 1999; 14:2343–2350.
82. Fenton, S.S.A., Schaubel, D.E., Desmeules, M., Morrison, H.I., Mao, Y., Copleston, P., et al. Hemodialysis versus peritoneal dialysis: A comparison of adjusted mortality rates. *Am. J. Kidney Dis.* 1997; 30(3):334–342.
83. Collins, A.J., Hao, W., Xia, H., Ebben, J.P., Everson, S.E., Constatini, E.G., Ma, J.Z. Mortality risks of peritoneal dialysis and hemodialysis. *Am. J. Kidney Dis.* 1999; 34(6):1065–1074.
84. Benevent, D., Benzakour, M., Peyronnet, P., Legarde, C., Leroux-Robert, C., Charmes, J.P. Comparison of continuous ambulatory peritoneal dialysis and hemodialysis in the elderly. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients*), A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl):68–71.
85. Piccoli, G., Quarello, F., Salomone, M., Bonello, F., Paciffiti, A., Beltrame, G., et al. Dialysis in the elderly: Comparison of different dialysis modalities. In *Advances in Peritoneal Dialysis (Peritoneal Dialysis in the Geriatric Patients)*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6(Suppl): 72–81.
86. Winchester, J.F. Peritoneal dialysis in older individuals. *Geriatr. Nephrol. Urol*. 1999; 9:147–152.
87. Malberti, F., Conte, A.L., Marcelli, D., Spotti, D., Lonati, F., Locatelli, F. Ten years' experience of renal replacement treatment in the elderly. *Geriatr. Nephrol. Urol*. 1997; 7:1–10.
88. Collins, A.J., Wienhandl, E., Snyder, J.J., Chen, S.C., Gilbertson, D. Comparison and survival of hemodialysis and peritoneal dialysis in the elderly. *Sem. Dial*. 2002; 15(2):98–102.
89. Winkelmayer, W.C., Glynn, R.J., Mittleman, M.A., Levin, R., Pliskin, J.S., Avorn, J. Comparing mortality of elderly patients on hemodialysis versus peritoneal dialysis: A propensity score approach. *J. Am. Soc. Nephrol*. 2002; 13:2353–2362.
90. Termorshuizen, F., Korevaar, J.C., Dekker, F.W., Van Manen, J.G., Boeschoten, E.W., Krediet, R.T. Hemodialysis and peritoneal dialysis: Comparison of adjusted mortality rates according to the duration of dialysis: Analysis of the Netherlands cooperative study on the adequacy of dialysis. *J. Am. Soc. Nephrol*. 2003; 14:2851–2860.

91. Krishnan, M., Schaubel, D., Bargman, J.M., Oreopoulos, D.G., Fenton, S.A. Gender differences in outcome for patients on HD and PD: A Canadian perspective. *J. Am. Soc. Nephrol*. 2001; 12:218A.
92. Brown, E.A. Peritoneal dialysis versus hemodialysis in the elderly. *Perit. Dial. Int*. 1999; 19:311–312.
93. Devins, G.M., Mann, J., Mandin, H., Paul, L.C., Hons, R.B., Burgess, E.D. Psychosocial predictors of survival in end-stage renal disease. *J. Nerv. Ment. Dis*. 1990; 178:127–133.
94. Gokal, R., Jabukowski, C., King, J., Hunt, L., Bogle, S., Baillord, R., et al. Outcome in patients on CAPD and haemodialysis: 4-Year analysis of a prospective multi centre study. *Lancet* 1987; 2:1105–1109.
95. Husebye, D.G., Kjellstrand, C.M. Old patients and uremia: Rates of acceptance to and withdrawal from dialysis. *Int. J. Artif. Organs* 1987; 10:166–172.
96. Port, F.K. Death and survival in patients with end-stage renal failure. *Am. J. Kidney Dis*. 1990; 15:215–217.
97. Moran, J. Changes in the dose of peritoneal dialysis: Have these independently affected outcomes? *Am. J. Kidney Dis*. 1998; 32:S52–S57.
98. Kadambi, P., Troidle, L., Gorban-Brennan, N., Kliger, A.S., Finkelstein, F.O. APD in the elderly. *Sem. Dial*. 2002; 15:430–433.
99. Bergner, M., Bobbitt, R.A., Carter, W.B., Gilson, B.S. The sickness impact profile. Development and final revision of a health status measure. *Med. Care* 1981; 19:787–805.
100. Ware, J.E. Jr., Sherbourne, C.D. The MOS 36-item short-term health survey (SF-36). *Med. Care* 1992; 30:473–483.
101. Mingardi, G., Cornalba, L., Cortinovis, E., Ruggiata, R., Mosconi, P., Apolone, G., for the DIA Q.L. group. Health-related quality of life in dialysis patients. A report from an Italian study using the SF-36 Health Survey. *Nephrol. Dial. Transplant* 1999; 14:1503–1510.
102. Kutner, N.G., Brogan, D., Fielding, B., Hall, W.D. Older renal dialysis patients and quality of life. *Dial. Transplant* 1991; 20:171–175.
103. Gutman, R.A., Stead, W.W., Robinson, R.R. Physical activity and employment status of patients on maintenance dialysis. *N. Engl. J. Med*. 1981; 304:309–313.
104. U.S. Congress Office of Technology Assessment. Life-sustaining technologies and the elderly; excerpts of congressional OTA study. *Nephrol. News Issues* 1989; 3(10):21–22, 31–34.
105. Czackes, J.W., Kaplan De-Nour, A. *Chronic Hemodialysis as a Way of Life*. New York: Brunner/Mazel. 1978.
106. Kutner, N.G., Cardenas, D.D. Rehabilitation status of chronic renal disease patients undergoing dialysis: Variations by age category. *Arch. Phys. Med. Rehabil*. 1981; 62:626–631.
107. McKevitt, P.M., Jones, J.F., Marion, R.R. The elderly on dialysis: Physical and psychosocial functioning. *Dial. Transplant* 1986; 15:134–137.
108. Oreopoulos, D.G. Geriatric nephrology. *Perit. Dial. Bull*. 1984; 4:197–198.
109. Moreno, F., Lopez Gomez, J.M., Sanz-Guajardo, D., Jofre, R., Valderrabano, F., on behalf of the Spanish Cooperative Real Patients Quality of Life Study Group. Quality of life in dialysis patients. A Spanish multicenter study. *Nephrol. Dial. Transplant* 1996; 11(Suppl 2):125–129.
110. Merkus, M.P., Jager, K.J., Dekker, F.W., Boeschoten, E.W., Stevens, P., Krediet, R.T., and the Necosad Study Group. Quality of life in patients on chronic dialysis: Self-assessment 3 months after the start of treatment. *Am. J. Kidney Dis*. 1997; 29:584–592.
111. Kutner, N.G., Zhang, R., McClellan, W.M. Patient-reported quality of life early in dialysis treatment: Effects associated with usual exercise activity. *Nephrol. Nurs*. 2000; 27:357–367.

112. Westlie, L., Umen, A., Nestrud, S., Kjellstrand, C.M. Mortality, morbidity and life satisfaction in the very old dialysis patients. *Trans. Am. Soc. Artif. Intern. Organs* 1984; 30:21–30.
113. Rotellar, E., Lubelza, R.A., Rotellar, C., Martinez-Camps, E., Alea, M.V., Valls, R. Must patients over 65 be haemodialysed? *Nephron* 1985; 41:152–156.
114. Stout, J.P., Gokal, R., Hiller, V.F., et al. Quality of life of high-risk and elderly dialysis patients in the UK. *Dial. Transplant* 1987; 16:674–677.
115. Schultz, K.O'K., Powers, M.J. Adjustment of older patients to hemodialysis. *Dial. Transplant* 1987; 16:234–242.
116. Asai, K., Kawahara, H., Takenaka, R., Toriyama, T., Hori, R., Takhashi, H., Yoshimine, N. Hemodialysis and the elderly patients: Retrospective analysis of morbidity and mortality. *Geriatr. Nephrol. Urol*. 1993; 3:139–144.
117. Ota, S., Takahasi, K., Suzuki, H., Nishimura, S., Makino, H., Ota, Z., Tania, K., Kaneshige, T. Exercise rehabilitation for elderly patients on chronic hemodialysis. *Geriatr. Nephrol. Urol*. 1995; 5:157–165.
118. Pianta, T.F., Kutner, N.G. Improving physical functioning in the elderly dialysis patient. Relevance of physical therapy. *Am. Nephrol. Nurse Assn. J*. 1999; 26: 11–14.
119. Harris, R.E., O'Hara, P.A., Harper, D.W. Functional status of geriatric rehabilitation patients: A one-year follow-up study. *J. Am. Geriatr. Soc*. 1995; 43:51–55.
120. Jassal, S.V., Brissenden, J.E., Roscoe, J.M. Specialized chronic care for dialysis patients: A five-year study. *Clin. Nephrol*. 1989; 50:84–89.
121. Rebollo, P., Ortega, F., Baltar, J.M., Diaz-Corte, C., Navascues, R.A., Naves, M., Urena, A., Badia, X., Alvares-Grande, J. Health-related quality of life (HRQOL) in end-stage renal disease (ESRD) patients over 65 years. *Geriatr. Nephrol*. 1998; 8:85–94.
122. Nissenson, A.R. Quality of life in elderly and diabetic patients on peritoneal dialysis. *Perit. Dial. Int*. 1996; 16(Suppl 1):S406–S409.
123. Cameron, J.I., Whiteside, C., Katz, J., Devins, G. Differences in quality of life across renal replacement therapies: A meta-analysis comparison. *Am. J. Kidney Dis*. 2000; 35(4):629–637.
124. Jassal, S.V., Brissenden, J.E., Raisbeck, A., Roscoe, J. Comparative cost-analysis of two different chronic care facilities for end-stage renal disease patients. *Geriatr. Nephrol. Urol*. 1988; 8:69–76.
125. Centers for Disease Control And Prevention/National Center for Health Statistics: The National Nursing Home Survey: 1997 Summary. Atlanta: Centers for Disease Control. 1998.
126. Anderson, J.E., Kraus, J., Sturgeon, D. Incidence, prevalence and outcome of end-stage renal disease patients placed in nursing homes. *Am. J. Kidney Dis*. 1993; 21:619–629.
127. Tong, E.M., Nissenson, A. Dialysis in nursing homes. *Sem. Dial*. 2002; 15(2):102–106.
128. Bloembergen, W., Port, F., Maugher, E., Wolfe, R. A comparison of mortality between patients treated with HD and PD. *J. Am. Soc. Nephrol*. 1995; 6:177–183.
129. Anderson, J.E., Kraus, J., Sturgeon, D. Incidence, prevalence and outcomes of end-stage renal disease patients placed in nursing homes. *Am. J. Kidney Dis*. 1993; 21:619–627.
130. Anderson, J.E. Ten years' experience with CAPD in a nursing home setting. *Perit. Dial. Int.* 1997; 17:255.
131. Carey, H.B., Chorney, W., Pherson, K., Finkelstein, F.O., Kliger, A.S. Continuous peritoneal dialysis and the extended care facility. *Am. J. Kidney Dis*. 2001; 37:580–587.
132. Schleifer, C.R. Peritoneal dialysis in nursing homes. In *Advances in Peritoneal Dialysis*, A.R. Nissenson, ed. Toronto: Peritoneal Dialysis Bulletin Inc. 1990; 6:86–91.

133. Husebye, D.G., Kjellstrand, C.M. Old patients and uremia: Rates of acceptance to and withdrawal from dialysis. *Int. J. Artif. Organs* 1987; 10:166–172.
134. Kjellstrand, C.M. Giving life-giving death: Ethical problems of high-technology medicine. *Acta Med. Scand*. 1988; 725(Suppl):1–88.
135. Neu, S., Kjellstrand, C.M. Stopping long-term dialysis: An empirical study of life-supporting treatment. *N. Engl. J. Med*. 1986; 314:14–20.
136. Casel, C.K., Moss, A.H., Retting, R.A., Levinsky, N.G. Ethical issues. In *Kidney Failure and the Federal Government*, R.A. Retting and N.G. Levinsky, eds. Washington, DC: National Academy Press. 1991; pp. 51–61.
137. Lowance, D.C. Factors and guidelines to be considered in offering treatment to patients with end-stage renal disease: A personal opinion. *Am. J. Kidney Dis*. 1993; 21:679–683.
138. National Kidney Foundation: 1996 Summary and Recommendation in Initiation of Withdrawal of Dialysis in End Stage Renal Disease: Guidelines for the health Care Team. New York: National Kidney Foundation. 1996; pp. III–IV.
139. Renal Physicians Association and American Society of Nephrology. Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis. Clinical practice guideline no. 2. Washington, DC: Renal Physicians Association. 2000.

25

Substitutive Treatments of End-Stage Renal Diseases in the Elderly: Renal Transplantation

Ali Alobaidli and Sarbjit V. Jassal

Introduction

Renal transplantation is the only current therapy for patients with end-stage renal disease (ESRD) that offers freedom from daily or alternate-day dialysis therapy. In younger patients, studies have repeatedly shown that transplantation offers a better quality of life, at less cost, in comparison to dialysis therapy. Although emerging evidence from nocturnal dialysis suggests an equivalent outcome, transplantation is still considered the treatment of choice for those with end-stage renal disease.

Two limitations to transplantation exist, however: One is the discrepancy between the number of organs available and the number required across the world; and the other is the allocation of these relatively scarce organs in an equitable manner. Until relatively recently, transplantation was only offered to healthy young patients; however, transplantation is now increasingly being offered, with good success, to older individuals. The objective of this chapter is to review some of the literature about the demographics and outcome with transplantation in those aged over 65 years and to discuss some practical problems that can arise.

In the early 1980s, nephrologists and demographers saw a rise in the number of patients starting renal replacement therapy (RRT). This growth was initially attributed to the increased availability of dialysis, the use of dialysis in those with other severe co-morbid conditions, and the lifting of age-related restrictions across the developed world. Over the next 10 or 20 years, the numbers of patients starting dialysis continued to rise at fairly high rates. Despite the expectation that a plateau will be reached, current trends continue to show an increase in numbers.

Strikingly, the growth rate differs widely across different age bands. While the rate per million population (pmp) of younger patients starting dialysis appears to be stabilizing, the growth rate in the older population starting dialysis (i.e., either those in the age band of 65–74 years old or those $\geq$75 years) has continued to rise. Worldwide trends appear to be similar, with only small differences. Canadian and American data, for example, show the most

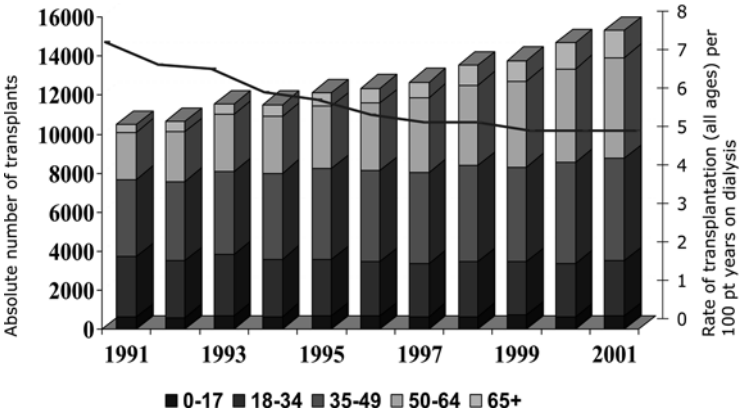

Fig. 25.1 The trend of the number of patients undergoing kidney transplantation in the United States over the 10-year period 1991–2001. The different age bands are also shown. Although the absolute number of transplants has increased over time, the rate of transplantation (i.e., the number of transplants per 100 dialysis patients per year) has decreased dramatically.

dramatic increases for those >75 years, while data from Europe, Australia, and Japan show the most growth in those >60 years of age [1–6].

The statistics for kidney transplantation differ from those of dialysis. Overall, the rate of kidney transplantation, regardless of age, has declined (Figure 25.1: shown as thick line), though the absolute number of transplants has grown, albeit slowly (bars). The largest increase in the absolute numbers of transplants is seen in the group of older patients, suggesting a worldwide acceptance of the benefits of transplantation in seniors (Figure 25.1). Limited organ availability has led to political and medical debates to rage over the appropriateness of transplantation in this age group, and this is briefly discussed in a subsequent section.

Demographic Changes in Transplantation Rates

Both dialysis and transplant demographics are dependent on a variety of factors. Among them are the baseline rate of renal disease, the availability of dialysis, and the rate of organ procurement. As a result, there is a wide variation across the world in both the numbers and the reporting methods used (Table 25.2). As a result, it is important to distinguish between the number of transplants and the rate of transplantation. In the United States, for example (where there is a high prevalence of diabetes), there is a high incidence of patients starting renal replacement therapy. Most patients are maintained on hemodialysis (in 2001, 485,950 patients were on either peritoneal or hemodialysis in the United States), and only a relatively small proportion are transplanted (in 2001, 2.9% of prevalent dialysis patients got a kidney transplant). However, when reported as the overall rate of kidney transplantation per million population, the rate of transplantation was 50 pmp. In contrast, the total number of patients on dialysis in Saudi Arabia is small (7687 in the year 2002; personal communication), with a higher percentage (4%) undergoing transplantation in any one year. However, when transplantation statistics are reported as per million population, the rates appear lower

Table 25.1 Summary Table Showing Observed Patient and Graft Survival Rates in Older Patients Undergoing Kidney Transplantation from Selected Publications.

Source of Data	Year	N	Age	Survival rates				CyA use
				Patient		Graft		
				1 yr	5 yr	1 yr	5 yr	
Ost et al. [52]	1980	34	60+	60		49	45	n
Sommer et al. [53]	1981	62	50+	55	40	57		n
Lundgren et al. [54]	1982	94	55+	66		52		n
Jordan et al. [55]	1985	54	50+	89	72	67	55	n
Jordan et al. [55]	1985	13	50+	84	80	82	70	n
Sommer et al. [56]	1986	52	50+	88*		82*		y
Sommer et al. [56]	1986	198	55-60	89		55		y
			60-64	79		67		y
			65+	100		76		y
Pirsch et al. [57]	1989	30	60-73	91	91†	74	74†	y
Morris et al. [58]	1991	45	60+	75	58	72	52	y
USRDS [15] CD	2003		50-64	91.4	74.5	86.3	63.6	y
			65-69	87.5	61.7	82.9	54.4	y
USRDS [15] LD	2003		50-64	96.2	83.3	93.9	75.6	y
			65-69	93.7	78.1	91.3	72	y
Andreu et al. [16]	1992	70	55+	97	82-94	94	72–88	y
Deluca et al. [17]	1992	119	55+	87	78	75		y
Tesi et al. [59]	1994	133	60+		68.1		62	y
Alberchtson [60]	1995	106	70+	80	54	78	52	y
Alberchtson [60]	1995	20	70+	80	74	80	74	y
A.I. Sanchez [18]	1998	511	55+	91.5	76	83.4	70.1	?
Basar [19]	1999	230	60+	90	76	84	64	Y
Doyle [66]	2000	206	60+	90	68	86	60	y
Saudan [61]	2001	49	60+	98	78	93	65	y
Fabrizii [21]	2004	335	50-59		83.6		93≈	y
		141	60-64		75.9		91≈	y
		151	65+		75.5		89≈	y
UNOS [62]	2004	6603	65+		73.5		68.5	y
Oniscu [65]	2005	75	65+	91	66	88 (93^{Ω})	63 (81^{Ω})	y

Patient and graft survival rates for living donor transplantation are shown in *italics*.

* Reported survival at 18 month.

† Survival reported at 3 years.

≈ Censored graft survival estimated from graph.

Ω Censored graft survival.

than in the United States (13 transplants pmp). Unlike U.S. data (most transplants in the United States, Canada, and Australia are with cadaveric organs [1,7–9]), most transplants in Saudi Arabia are from living related or unrelated donors. To further contrast how demographics vary across the world because of healthcare policies, the recent introduction of government-funded and—controlled living unrelated donor programs in Iran have resulted in very high rates of successful transplantation, with 95% of all transplants being done using organs from living donors (related and unrelated), and 79% from living unrelated donors. At the present time, there is no waiting list in Iran. As a result of the new policy, however, Ghods et al. [10] report that at least 84% of donors and >50% of recipients come from a low socioeconomic class.

Table 25.2 Demographic Data for End-Stage Renal Disease Across Selected Countries of the World.

Country	Year	Dialysis Patients	% Dialysis Patients Transplanted	Number on TWL	Total Transplants (% of TWL)	Tx Rate pmp	Cadaveric (%)	Living (%)
United States [7, 15]	2001	485, 950	2.9	47, 830	14, 244(30)	50	58	42
Canada [1]	2001	15, 974	6.3	2, 423	1, 010(42)	32	62	38
Australia [8]	2001	6, 812	7.9	1, 702	540(32)	28	61	39
New Zealand [8]	2001	1, 460	7.5	295	110(37)	29	61	39
Saudi Arabia	2002	7, 687	4	2, 687	308(11)	13	19	81
Iran [10]	2000	8, 300	17	0	1, 422(n/a)	21.6	< 5	> 95

Tx Rate pmp = transplant rate quoted as per million population. TWL = transplant waiting list.

Patient Survival

Patient survival rates with transplantation remain impressive across all age groups (Table 25.1). In patients aged 65+ years, recent USRDS data show 1-, 3-, 5-, and 10-year patient survival rates of 87.9%, 76.1%, 61.7%, and 24.5%, respectively. The data show a gradual improvement in both patient and graft survival over time, particularly since the advent of cyclosporine and newer immunosuppressive therapies.

The observational data reported in Table 25.1 are useful but do not answer the question, "how much better than dialysis is transplantation for older individuals?" Direct comparisons are difficult—for example, the comparison of the survival of a 65+-year-old person to the survival of younger patients is fraught with difficulties—younger patients, regardless of co-morbidity, can be expected to have a longer life expectancy by virtue of their age. Comparisons to older patients who remain on dialysis are equally unsatisfactory, as clinicians screen out patients and usually only offer transplantation to those with no or few co-morbidities. As a result, researchers have struggled to compare dialysis and transplantation outcomes using innovative mathematical models. Two such methods are described here.

Probably the best-known method is that published first by Port et al. [12], and subsequently by Wolfe et al. [14], Rabbatt et al. [13]. and Oniscu et al. [66]. By selecting only patients who were currently being treated with dialysis but who had been screened and placed on a waiting list for a cadaveric transplant, they assumed that any selection bias that may have occurred was minimized and the dialysis and transplant cohorts were comparable at baseline. This selected dialysis population was then compared to those who actually received a transplant. The data were reported both as estimated life expectancy and as the relative risk of death for patients on the waiting list for transplantation compared to those receiving a transplant. The disadvantage of this method is that patients who actually get a transplant have survived their time on the waiting list on dialysis (patients who would have died would not have been transplanted!), and the methodology therefore results in a "survivorship bias." The results showed that dialysis patients had a stable risk of death equal to 6.3 per 100 ptyrs. [ptyrs (ptyrs) are best interpreted using an example, e.g., a total of 100 ptyrs can be collected either by following 2 patients for 50 years each, by following 10 patients for 10 years each, or, as is more commonly done, by following 100 patients for an average of 1 year each]. Transplant patients had a higher immediate post-operative risk of death (17.9 per 100 ptyrs), falling with time to a baseline mortality rate of 3.8 per 100 ptyrs. The higher perioperative mortality risk fell rapidly such that by 159 days the risk of death was equal in dialysis and transplant patients. In diabetic patients, this time to equal risk was lower (89 days) because of a higher baseline risk of death with diabetes. Specific death rates for patients aged $\geq$60 years (per 100 ptyrs) were estimated at 23.2 for those on dialysis, 10.0 for those on the waiting list, and 7.4 for those with a transplant. Life expectancy estimates differed greatly between the two modeled treatment strategies; however, the calculated life expectancies are higher than those currently observed (Table 25.3).

An alternative method that has been used also showed transplantation to be superior to dialysis. Using decisional analysis, a mathematic model of

Table 25.3 Summary of Results from Papers That Compare Survival of Patients Remaining on Dialysis with Survival After Kidney Transplantation.

Age Group (Years)	Relative risk of death 18 months' post-transplant	Time at which likelihood of survival equals reference group(days post-transplant)	Projected years of life without transplant	Projected years of life with transplant	Ref
60–74 (overall)	0.39	369	6	10	Wolfe [14]
60–74 (nondiabetic)	0.37	442	7	12	"
60–74 (diabetic)	0.46	247	5	8	"
All ages (nondiabetic)	0.25	n/a	n/a	n/a	Rabbatt [13]
All ages (all causes)	0.36	325	n/a	n/a	Port [12]
65 years old (no wait time)	n/a	n/a	6.6	8.2	Jassal [63]
75 years old (no wait time)	n/a	n/a	4.3	5.9	Unpublished Jassal et al.

probability, patients on the waiting list for transplantation were compared with those who would receive a transplant. Survivorship bias was removed by making the assumption that the time of transplantation could be controlled, and the models built to reflect scenarios where patients underwent transplantation immediately (as with living donor transplants) or after a waiting period of 2 or 4 years. The models were validated against registry data, to ensure that predicted life expectancies matched those actually observed (Figures 25.2 a and b), and the population characteristics varied to reflect patients of different ages and co-morbidity profiles. The results showed that transplantation offered significant life-expectancy benefits in patients of all ages, but that the overall advantages decreased with increased age and longer waiting times (Table 25.3).

Subsequent publications continue to show benefits for those seniors undergoing transplantation (summarized in Table 25.1) [15–23]. Recently, Fabrizii et al. [21] described a single-center retrospective cohort of 627 patients >50 years who underwent kidney transplantation between 1993 and 2000. Although a younger cohort (patients recruited included mostly those <65 years), the study results are notable for four points:

1. In comparison to younger individuals, seniors (defined as those over 65 years of age) have lower rates of hypertension and an increased prevalence of coronary artery disease.
2. In this center, older organs were preferentially allocated to older patients. This is a common practice but may adversely affect overall patient and graft survival rates (see the section on practical issues).
3. Patients in the 60–64 age group and those aged ≥65 years have similar patient and graft outcomes.
4. Perioperative mortality and hospital stay lengths were similar across all ages. Of note, the study includes much detailed information on

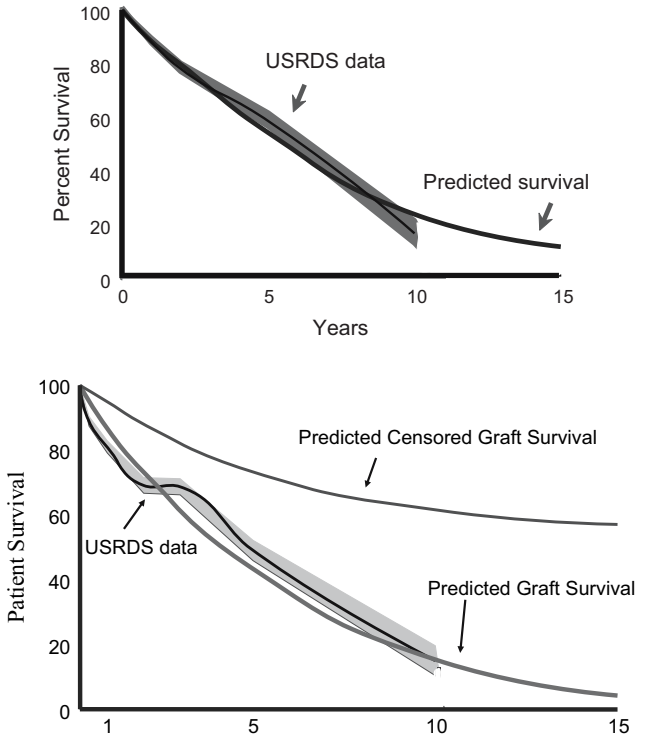

Fig. 25.2 Graphs showing validation data supporting the results published by Jassal et al., *JASN* 2003. These show that both predicted patient and predicted graft survival were similar to observed data. In both graphs the fine black line with surrounding shaded area represents the USRDS mean survival +/- the standard error. Predicted survival rates are shown in the heavy black lines.

patient demographics, co-morbidities, the standardized and explicit work-up process required in recipient evaluation, and complete data on immunological and donor characteristics. In contrast, however, only 151 patients over 65 years were included, making it possible that they had insufficient power to detect small but clinically significant differences in survival and hospitalization outcomes across the age groups.

Graft Survival

Graft survival rates are shown in Table 25.1. Graft survival rates are traditionally defined as the number of patients with a functioning graft at a particular time (e.g., 1 year after transplantation) divided by the number of patients who underwent kidney transplantation. Consequently, populations with a high mortality rate who die with a functioning renal allograft appear to have unexpectedly low graft survival rates. Data from the early 1970s tended to demonstrate disappointing graft survival rates in older individuals, with average 1-year graft survival rates of 50–60% for those aged $\geq$50 years while those <50 years had rates of 70% or more (Table 25.1). Although newer immunosuppressive regimes have had a great impact on graft survival rates, the data still remain disappointing if one considers absolute graft survival rates alone.

More recently, an increasing number of centers are reporting censored graft survival rates where patients who died with a functioning renal allograft are censored at the time of death. Using this methodology, graft survival rates appear to be equal to, or possibly better in, older individuals than in younger persons [21, 24–26, 64].

Problems Seen Commonly Post-transplantation in the Elderly

Increased Infections

Previous studies in healthy individuals have shown a decrease in immunocompetence with age. In the dialysis and transplant population, patients are at risk of further immunocompromise because of uremia and, in transplant patients, antirejection protocols. In an elegant study, using data from USRDS transplant and waitlisted patients, Meier-Kreische et al. [27] showed an exponential increase in the risk of infectious death in those over 55 years of age, with a corresponding decrease in the risk of acute rejection with age (28% in patients 18–29 years, 19.7% in patients older than 65 years). As survival studies show a benefit from transplantation despite the higher rate of infectious death, further research in the field of immunomodulation may be most beneficial for seniors with a transplant.

Immunotherapy Protocols for the Elderly

Specifically tailored immunotherapy may help modify the risk of infectious complications in seniors. Furthermore, it seems reasonable to assume the elderly would be at higher risk of falls, fractures, and proximal myopathy than younger individuals. Thus, it seems wise, though unproven, to reduce the exposure to prednisone. In the pre-cyclosporine era, most physicians prescribed a combination of azathioprine and low-dose prednisone. The subsequent introduction of cyclosporine led to decreases in the doses of prednisone used, with a corresponding improvement in patient and graft survival rates and the number of sepsis-related complications. Studies advocating cyclosporine monotherapy have been successful in highly selected patient populations, but little data are available specifically for seniors [28–30]. Xenos et al. [31] showed, in an observational study of 21 patients over 60 years, that the use of tacrolimus, steroid, and either mycophenolate mofetil or azathioprine was associated with reduced rates of acute rejection and superb patient and graft survival at 1 year. No specific recommendations can be made, as there are insufficient data from randomized controlled trials in older patients.

Drug pharmacology and metabolism are altered with age. One commonly seen example is the gradual age-related decline in cytochrome P450 activity. Cytochrome P450 is responsible for the removal of both steroid and cyclosporine and a decreased volume of distribution for lipid-soluble drugs [32]. Consequently, older patients are more prone to the side effects of calcineurin inhibitors, and dose modification may be required. Mycophenolate mofetil (MMF) is a powerful immunosuppressive drug that inhibits the proliferation of T and B cells by blocking the enzyme inosine monophosphate dehydrogenase. Retrospective, observational studies suggest older patients

may be at increased risk of hospitalization secondary to infections, especially those caused by cytomegalovirus and fungus, with MMF therapy [33, 34]. Although the results of these studies are of concern, the observed higher infection rates need to be balanced against the proven benefits of less rejection and better graft survival. Data in regard to the use of IL-2 or antilymphocyte induction therapy are conflicting, and further work is required [35–37]. Suggested new immune suppression protocols specifically tailored to the older individual include either the use of anti-IL2R Mo antibody, steroid, sirolimus, and MMF or anti-IL2R Mo antibody, steroid, sirolimus, and low-dose calcineurin inhibitor. Neither of these regimes, however, has been evaluated in randomized controlled trials [61].

Functional Independence

Seniors are at higher risk of increased dependency for simple activities associated with healthy living. For example, a substantial proportion of older individuals requires help with housework or shopping or may have difficulties with managing their own financial affairs. In the geriatric literature, functional independence measured using performance indicators predicts the need for institutional care and survival. In the transplant literature, Nyberg et al. [38] studied a small subset of patients of all ages before and after kidney transplantation. Patients were tested for handgrip strength, the ability to step up onto a chair, and quadriceps strength. Younger patients showed an improvement in handgrip and quadriceps strength. In contrast, older individuals had a decrease in all functional measures, even 1 year after transplantation.

Effects of Waiting Times

Within Canada, and particularly within our own transplant service, the number of donor kidneys (both cadaveric and living) has remained stable over the past 10 years [1]. In contrast, the number of individuals waitlisted for transplant continues to increase. The result—as in many transplant centers across the world—is an increase in the time from initial waitlisting to organ transplantation. More recent studies have shown that the outcome of kidney transplantation is poorer in those with a longer period pre-transplantation on dialysis [39]. Recent studies have suggested the cost-effectiveness for older individuals and the overall quality of life benefits from transplantation are highest if older patients can be encouraged to find a willing live organ donor (Figure 25.3) [63].

Quality of Life Post-renal Transplantation

There is little doubt that successful renal transplantation improves overall quality of life (QoL) of patients with ESRD. Older individuals report improved QoL scores post-transplantation with higher functional autonomy, less comorbidity, and improved rehabilitation as compared to patients on continued hemodialysis [40–42]. In a recent meta-analysis, Cameron et al. [43] compiled the results of 49 studies that looked at differences in QoL across different renal replacement therapy modalities. Using rigorous meta-analytical tools,

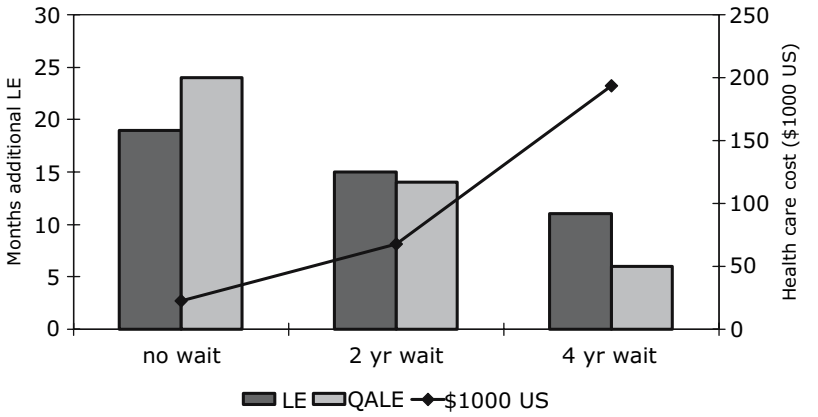

Fig. 25.3 The average increase in life expectancy (LE), quality-adjusted life expectancy (QALE), and the additional resources required by the healthcare system when a 65-year-old nondiabetic patient is transplanted immediately, after a 2-year waitlisted time or after 4 years (adapted from Jassal et al.).

they found that successful renal transplantation was associated with lower distress and greater well-being than in center hemodialysis or continuous ambulatory peritoneal dialysis patients. Sadly, study validity was compromised by significant case-mix variation across the three treatment groups, a factor commonly seen in cross-sectional studies comparing transplantation to dialysis.

Practical Issues

Patient Selection and Pre-transplant Assessment

In general, older patients have more co-morbid conditions than younger patients. The Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that patients aged 18–44 years old had on average 2.2 co-morbid conditions, while those aged >70 years had 4.1 co-morbid conditions [44]. Based on these observations we believe the utility of a thorough pre-transplant work-up is even higher in seniors. In our own unit, older patients undergo thorough routine pre-transplant assessment adapted from numerous guidelines and reports [45–47]. We place special emphasis on the cardiovascular assessment, as well as including a thorough screening process for malignancy and infections. Here we have summarized some pre-transplant screening tests that may be particularly relevant to older patients.

Cardiac Evaluation

A full history and physical examination is imperative. Baseline electrocardiogram, echocardiogram, and cardiac stress testing (for example, using thallium or dipyridamole-thallium scans) are necessary. Although no strong clinical evidence is available to support the following practice, cardiac catheterization is usually recommended only if one or more of these noninvasive tests are abnormal or if the patient is symptomatic. It is recommended that asymptomatic patients with diabetes also undergo cardiac catheterization given the high prevalence of silent cardiac disease.

Peripheral Vascular Disease

Doppler studies and arteriography to detect peripheral ischemia are usually advised. As older patients may not have the same exercise demands as younger individuals, a simple reliance on history is not felt to be adequate.

Gastrointestinal Evaluation and Screening for Malignancy

Gastrointestinal work-up is controversial. In our own center, colonoscopy is recommended to exclude active diverticulitis or occult colonic malignancy for those >50 years old. Under the Canadian periodic health examination, patients should be screened annually for occult rectal bleeding, and if over 50 years with sigmoidoscopy. In males, routine digital rectal examination and a prostatic-specific antigen are recommended. Women should undergo routine mammography as part of their work-up for transplantation.

It is our practice to request routine abdominal ultrasound evaluation for the exclusion of gallstones (although there are no data to support treatment of the asymptomatic patient with cholelithiasis, there is increased concern that infection related to gallstones may be significant—this remains highly debated) [47]. Screening for gastric ulceration or *H. pylori* is likewise controversial, particularly in an asymptomatic patient [47]. In support of the argument are data published by Fabrizii et al. [21] showing that the presence of gastrointestinal co-morbidity was highly associated with both patient death and graft loss.

Screening for Infection

This remains one of the most unstudied areas in the area of transplantation in seniors. Many seniors have had potential exposure to tuberculosis, and therefore screening seems appropriate. However, the ideal method of screening in patients on dialysis remains unknown. Within our own center, we continue to screen using Purified Protein Derivative (PPD) and/or chest x-ray evaluation, although we recognize that this may be limited by a high incidence of anergy.

Frequency of Screening Reevaluation

Although no clear recommendations can be made, older patients on the waiting list for transplantation should probably be reevaluated more frequently. An abbreviated screening system at more frequent intervals than typical for younger patients may be considered, though the cost-utility of this policy remains unknown**.**

Factors Limiting Kidney Transplantation for Seniors: Issues and Possible Solutions

Organ shortage is the most limiting factor in the number of transplants done worldwide. Ethical debates rage about the ethical implications of allocating a scarce resource, such as a cadaveric or living donor kidney, to an individual with a limited life span. Both sides have valid arguments—those in favor cite the fact that many of these individuals are survivors, who have contributed to society over the years, and now are deserving of societal resources, while those against cite the limited life span of the individual and naturally of the transplanted organ. It is neither the premise nor the objective of this review to

enter into this debate. Suffice to say, all measures should be taken to increase the number of cadaveric organs available and to improve living donation rates, particularly in Europe and North America.

In the ideal setting, all older recipients should identify a living donor. This would not only reduce the burden on an already-restricted organ pool but would also offer a clear survival benefit [63]. However, failing that, the use of other methods to maximize organ retrieval is imperative. Recent interest has focused on the use of less-than-perfect organs [48–50], so-called extended-criteria donor (ECD) or marginal donor kidneys. [Marginal donor kidneys are defined as those taken from a donor over 55 years; from a donor with a 10-year history of diabetes or hypertension; from a donor who died from a cerebral vascular accident (stroke); or organs procured from a non-heart-beating donor.] More recently, the use of double cadaveric kidney transplants was described to limit the discard rate of ECD kidneys coming from marginal donors. "Double" or "two-kidney transplants" describe transplant surgeries where two kidneys, both with higher levels of scarring, are transplanted into one individual. These are increasingly being commonly used, in an attempt to close the gap between the supply and demand for organs. Optimal kidneys undoubtedly show superior graft and patient survival than ECD kidneys. However, when compared to remaining on dialysis, the use of marginal kidneys was still preferential (in terms of survival benefit) for older patients (Table 25.4) [51].

Adjusted mortality estimates, the days to equal risk, and the time to equal survival were reported for recipients aged 18–29 years, 30–44 years, 44–55 years, 55–64 years, and >65 years (Table 25.4). Although the projected extra lifetime decreased with increasing recipient age, marginal organs still offered a survival benefit above that from dialysis alone. Consequently, in our own center, we encourage those without a living donor to accept marginal donor organs.

Table 25.4 Reported Mortality Risks in Marginal Donor Kidney Recipients Relative to Waitlisted Dialysis Patients.

	Annual Death Rate for Waitlisted Patients(%)	Time Until Risk of Death Equal in Both dx and tx Patients (Days)	Time Until Survival Probability Equal in Both dx and tx Patients (Days)	Relative Risk	Projected Extra Lifetime if Transplanted (year)
All ages (years)	63	185	531	0.75	5.1
18–29	2.2	163	547	NS	6.4
30–44	5.4	134	309	NS	4.9
44–54	6.5	196	521	0.70	6.3
55–64	6.5	193	580	0.66	7.3
>65	10.0	171	475	0.71	3.8

Dx = dialysis.

Tx = transplantation.

Source: Ojo, A.O., Hanson, J.A., Meier-Kriesche, H., Okechukwu, C.N., Wolfe, R.A., Leichtman, A.B,, Agodoa, LY., Kaplan, B., Port, F.K. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J. Am. Soc. Nephrol*. 2001; 12(3):589–597.

Summary

This review summarizes the data available, to date, on the role of transplantation in seniors. Increasing amounts of data continue to emerge supporting the role of transplantation across all age groups. Acknowledging the importance of the ongoing debate about organ allocation strategies, and assuming societal acceptance, we recommend that seniors be encouraged to consider kidney transplantation if surgically suitable. In our opinion, living donor transplantation is significantly preferable to cadaveric organ transplantation or dialysis.

References

1. Canadian Organ Replacement Register (CORR). Annual Report 2001.
2. U.S. Renal Data System. USRDS Annual Data Report 2005.
3. Agodoa, L.Y., Eggers, P.W. Renal replacement therapy in the United States: Data from the USRDS. *Am. J. Kidney Dis*. 1995; 25:119–133.
4. Fenton, S., Desmeules, M., Copleston, P., Arbus, G., Froment, D., Jeffery, J., Kjellstrand, C. Renal replacement therapy in Canada: A report from the Canadian Organ Replacement Register. *Am. J. Kidney Dis*.1995; 25:134–150.
5. Disney, A.P. Demography and survival of patients receiving treatment for chronic renal failure in Australia and New Zealand: Report on dialysis and renal transplantation treatment from the Australia and New Zealand Dialysis and Transplant Registry. *Am. J. Kidney Dis*. 1995; 25(1):165–175.
6. Disney, A.P.S., Russ, G.R., Walker, R., Sheil, A.G.R. Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) Report. 1997.
7. The U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients OPTN/SRTR Annual Report. 2001.
8. Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) Annual Report. 2001.
9. http://secure.cihi.ca/cihiweb. CORR inSITES, April 2003. A Decade of Organ Donation in Canada: 1993 to 2002: Figure 7: Distribution of kidney transplants by donor type, Canada 1993–2002.
10. Ghods, A.J. Renal transplantation in Iran. *Nephrol. Dial. Transplant* 2002; 17(2):222–228.
11. Ghods, A.J. Changing ethics in renal transplantation: Presentation of Iran model. *Transplant. Proc*. 2004; 36(1):11–13.
12. Port, F.K., Wolfe, R.A., Mauger, E.A., Berling, D.P., Jiang, K. Comparison of survival probabilities for dialysis patients vs. cadaveric renal transplant recipients. *JAMA* 1993; 270(11):1339–1343.
13. Rabbat, C.G., Thorpe, K.E., Russell, J.D., Churchill, D.N. Comparison of mortality risk for dialysis patients and cadaveric first renal transplant recipients in Ontario, Canada. *J. Am. Soc. Nephrol*. 2000; 11(5):917–922.
14. Wolfe, R.A., Ashby, V.B., Milford, E.L., Ojo, A.O., Ettenger, R.E., Agodoa, L.Y., Held, P.J., Port, F.K. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N. Engl. J. Med*. 1999; 341(23):1725–1730.
15. USRDS Annual Data Report 2003. Reference tables. http://www.usrds.org/2003/pdf/g_03.pdf.
16. Andreu, J., de la Torre, M., Oppenheimer, F., Campistol, J.M., Ricart, M.J., Vilardell, J., et al. Renal transplantation in elderly recipients. *Transplant. Proc*. 1992; 24(1):120–121.
17. DeLuca, L., Cardella, C.J. How can the care of elderly dialysis patients be improved? *Sem. Dial*. 1992; 5:28–29.

18. Sanches-Fructuso, A.I., Naranjo, D.P., Fernandez, C., Aviles, B., Barrientos, A. Renal transplantation in elderly patients. *Transplant. Proc*. 1998; 30:2277.
19. Basar, H., Soran, A., Shapiro, R., Vivas, C., Scantlebury, V.P., Jordan, M.L., Gritsch, H.A., McCauley, J., Randhawa, P., Irish, W., Hakala, T.R., Fung, J.J. Renal transplantation in recipients over the age of 60: The impact of donor age. *Transplantation* 1999; 67(8):1191–1193.
20. Doyle, S.E., Matas, A.J., Gillingham, K., Rosenberg, M.E. Predicting clinical outcome in the elderly renal transplant recipient. *Kidney Int*. 2000; 57:2144.
21. Fabrizii, V., Winkelmayer, W.C., Klauser, R., Kletzmayr, J., Saemann, M.D., Steininger, R., Kramar, R., Horl, W.H., Kovarik, J. Patient and graft survival in older kidney transplant recipients: Does age matter? *J. Am. Soc. Nephrol*. 2004; 15(4):1052–1060.
22. Moreso, F., Ortega, F., Mendiluce, A. Recipient age as a determinant factor of patient and graft survival. *Nephrol. Dial. Transplant* 2004; 19(Suppl 3):16–20.
23. Roodnat, J.I., Zietse, R., Mulder, P.G., Rischen-Vos, J., van Gelder, T., Ijzermans, J.N., Weimar, W. The vanishing importance of age in renal transplantation. *Transplantation* 1999; 67(4):576–580.
24. Herrero, J.C., Gutierrez, E., Martinez, A., Gonzalez, E., Morales, E., Munoz, M.A., Valentin, M., Bueno, B., Praga, M., Hernandez, E., Morales, J.M., Rodicio, J.L., Andres, A. Results of kidney transplantation in recipients over 70 years of age: Experience at a single center. *Transplant. Proc*. 2003; 35(5):1675–1676.
25. Saudan, P., Berney, T., Leski, M., Morel, P., Bolle, J.F., Martin, P.Y. Renal transplantation in the elderly: A long-term, single-centre experience. *Nephrol. Dial. Transplant* 2001; 16(4):824–828.
26. Moosa, M.R. Impact of age, gender and race on patient and graft survival following renal transplantation—Developing country experience. *S. Afr. Med. J*. 2003; 93(9):689–695.
27. Meier-Kriesche, H.U., Ojo, A.O., Hanson, J.A., Kaplan, B. Exponentially increased risk of infectious death in older renal transplant recipients. *Kidney Int*. 2001; 59(4):1539–1543.
28. Morales, J.M., Munoz, M.A., Campo, C., Andres, A., Araque, A., Alamo, C., Praga, M., Ortuno, T., Hernandez, E., Rodicio, J.L. Renal transplantation in older patients with double therapy with optional change to cyclosporine monotherapy: Long-term results. *Transplant. Proc*. 1994; 26(5):2511–2512.
29. Andreu, J., de la Torre, M., Oppenheimer, F., Campistol, J.M., Ricart, M.J., Vilardell, J., Talbot, R., Carretero, P. Renal transplantation in elderly recipients. *Transplant. Proc*. 1992; 24(1):120–121.
30. Spanish Monotherapy Study Group. Cyclosporine monotherapy versus OKT3 and cyclosporine versus prednisone and cyclosporine as induction therapy in older renal transplant patients: A multicenter randomized study. *Transplant. Proc*. 1994; 26(5):2522–2524.
31. Xenos, E.X., Ciancio, G., Burke, G.W., Roth, D., Miller, J. The use of tacrolimus as induction and maintenance immunosuppression in renal cadaveric transplant recipients over the age of 60. *Clin. Transplant*. 1997; 11(5 Pt 2):497–499.
32. Hardman, J.G., Limbird, L.E. eds. *The Pharmacological Basis of Therapeutics*. New York: McGraw Hill & Co. 1996.
33. Meier-Kriesche, H.U., Friedman, G., Jacobs, M., Mulgaonkar, S., Vaghela, M., Kaplan, B. Infectious complications in geriatric renal transplant patients: Comparison of two immunosuppressive protocols. *Transplantation* 1999; 68(10):1496–1502.
34. Johnson, D.W., Nicol, D.L., Purdie, D.M., Preston, J.M., Brown, A.M., Hawley, C.M., Campbell, S.B., Wall, D., Griffin, A.D., Isbel, N.M. Is mycophenolate mofetil less safe than azathioprine in elderly renal transplant recipients? *Transplantation* 2002; 73(7):1158–1163.

35. Lundgren, G., Fehrman, I., Gunnarsson, R., Lindholm, B., Tillegard, A., Ost, L., Groth, C.G. Cadaveric renal transplantation in patients over 55 years of age with special emphasis on immunosuppressive therapy. *Transplant. Proc*. 1982; 14(3):601–604.
36. Jordan, M.L., Novick, A.C., Steinmuller, D., Braun, W., Buszta, C., Mintz, D., Goormastic, M., Streem, S. Renal transplantation in the older recipient. *J. Urol*. 1985; 134(2):243–246.
37. Emparan, C., Laukotter, M., Wolters, H., Dame, C., Heidenreich, S., Senninger, N. Calcineurin-free protocols with basiliximab induction allow patients included in "old to old" programs achieve standard kidney transplant function. *Transplant. Proc*. 2003; 35(4):1326–1327.
38. Nyberg, G., et al. Physical performance does not improve in elderly patients following successful kidney transplantation. *Nephrol. Dial. Transplant* 1995; 10:86–90.
39. Okechukwu, C.N., Lopes, A.A., Stack, A.G., Feng, S., Wolfe, R.A., Port, F.K. Impact of years of dialysis therapy on mortality risk and the characteristics of longer term dialysis survivors. *Am. J. Kidney Dis*. 2002; 39(3):533–538.
40. Bonal, J., Cleries, M., Vela, E. Transplantation versus haemodialysis in elderly patients. Renal Registry Committee. *Nephrol. Dial. Transplant* 1997; 12(2): 261–264.
41. Jofre, R., Lopez-Gomez, J.M., Moreno, F., Sanz-Guajardo, D., Valderrabano, F. Changes in quality of life after renal transplantation. *Am. J. Kidney Dis*. 1998; 32(1):93–100.
42. Laupacis, A., Keown, P., Pus, N., Krueger, H., Ferguson, B., Wong, C., Muirhead, N. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int*. 1996; 50(1):235–242.
43. Cameron, J.I., Whiteside, C., Katz, J., Devins, G.M. Differences in quality of life across renal replacement therapies: A meta-analytic comparison. *Am. J. Kidney Dis*. 2000; 35(4):629–637.
44. Dialysis Outcomes and Practice Patterns Study (DOPPS) 2005. http://www.dopps.org.
45. Steinman, T.I., Becker, B.N., Frost, A.E., Olthoff, K.M., Smart, F.W., Suki, W.N., Wilkinson, A.H.; Clinical Practice Committee, American Society of Transplantation. Guidelines for the referral and management of patients eligible for solid organ transplantation. *Transplantation* 2001; 71(9):1189–1204.
46. Ismail, N. Renal transplantation and the elderly. *UpToDate* 2004.
47. Kasiske, B.L., Cangro, C.B., Hariharan, S., Hricik, D.E., Kerman, R.H., Roth, D., Rush, D.N., Vazquez, M.A., Weir, M.R.; American Society of Transplantation. The evaluation of renal transplantation candidates: Clinical practice guidelines. *Am. J. Transplant* 2002; 1(Suppl 2):1–95.
48. Andres, A., Morales, J.M., Herrero, J.C., Praga, M., Morales, E., Hernandez, E., Ortuno, T., Rodicio, J.L., Martinez, M.A., Usera, G., Diaz, R., Polo, G., Aguirre, F., Leiva, O. Double versus single renal allografts from aged donors. *Transplantation* 2000; 69(10):2060–2066.
49. Remuzzi, G., Grinyo, J., Ruggenenti, P., Beatini, M., Cole, E.H., Milford, E.L., Brenner, B.M. Early experience with dual kidney transplantation in adults using expanded donor criteria. Double Kidney Transplant Group (DKG). *J. Am. Soc. Nephrol*. 1999; 10(12):2591–2598.
50. Remuzzi, G., Ruggenenti, P. Renal transplantation: Single or dual for donors aging > or =60 years? *Transplantation* 2000; 69:2000–2001.
51. Ojo, A.O., Hanson, J.A., Meier-Kriesche, H., Okechukwu, C.N., Wolfe, R.A., Leichtman, A.B,, Agodoa, LY., Kaplan, B., Port, F.K. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J. Am. Soc. Nephrol*. 2001; 12(3):589–597.

52. Ost, L., Groth, C.-G., Lindholm, B., Lundgren, G., Magnusson, G., Tillegard, A. Cadaveric renal transplantation in patients of 60 years of age and above. *Transplantation* 1980; 30:339–340.
53. Sommer, B.G., Ferguson, R.M., Davin, T.D., Kjellstrand, C.M., Fryd, D.S., Simmons, R.L., et al. Renal transplantation in patients over 50 years of age. *Transplant. Proc*. 1981; 13:33–35.
54. Lundgren, G., Fehrman, I., Gunnarsson, B., Lindholm, B., Tilligard, A., Ost, L., et al. Cadaveric renal transplantation in patients over 55 years of age with special emphasis on immunosuppressive therapy. *Transplant. Proc*. 1982; 14:601–604.
55. Jordan, M.L., Novick, A.C., Steinmuller, D., Braun, W., Buszta, C., Mint, Z.D., et al. Renal transplantation in the older recipient. *J. Urol*. 1985; 134:243–246.
56. Sommer, B.G., Mandelbaum, D.M., Henry, M.L., Ferguson, R.M. Renal transplantation in the middle-aged and elderly uremic patient. In *Geriatric Nephrology*, D.G. Oreopoulos, ed. Dordecht: Martinus Nijhoff. 1986; pp. 157–168.
57. Pirsch, J.D., Stratta, R.J., Armbrust, M.J., D'Alessandro, A.M., Sollinger, H.W., Kalayoglu, M., et al. Cadaveric renal transplantation with cyclosporine in patients more than 60 years of age. *Transplantation* 1989; 47:259–261.
58. Morris, G.E., Jamieson, N.V., Small, J., Evans, D.B., Calne, S.R. Cadaveric renal transplantation in elderly recipients: Is it worthwhile? *Nephrol. Dial. Transplant* 1991; 6:887–892.
59. Tesi, R.J., Elkhammas, E.A., Davies, E.A., Henry, M.L., Ferguson, R.M. Renal transplantation in older people. *Lancet* 1994; 343:461–464.
60. Albrechtson, D., Leivestad, T., Sodal, G., Bentdal, O., Berg, K.G., Brekke, I., et al. Kidney transplantation in patients older than 70 years of age. *Transplant. Proc*. 1995; 27(1):86–88.
61. Baid-Agrawal, S., Reinke, P., Schindler, R., Tullius, S., Frei, U. Congress Report WCN 2003 Satellite Symposium on Kidney Transplantation in the Elderly, Weimar, Germany, June 12–14, 2003. *Nephrol. Dial. Transplant* 2004; 19:43–46.
62. Peddi, V.R., Katznelson, S., Halukurike, V., Baker, T.J., McBride, M.A. State of renal transplantation in older Americans: An analysis of the UNOS database. American Transplant Congress Meeting, May 18, 2004.
63. Jassal, S.V., Krahn, M.D., Naglie, G., Zaltzman, J.S., Roscoe, J.M., Cole, E.H., Redelmeier, D.A. Kidney transplantation in the elderly: A decision analysis. *J. Am. Soc. Nephrol*. 2003; 14(1):187–196.
64. Matas, A.J., Gillingham, K.J., Sutherland, D.E.R. Half-life and risk factors for kidney transplant outcome: Importance of death with function. *Transplantation* 1993; 55:757–761.
65. Oniscu, G., Brown, H., Forsyth, J.L. How old is old for transplantation? *Am. J. Transplant*. 2004; 4:2067–2074.
66. Oniscu, G., Brown, H., Forsyth, J.L. How great is the survival advantage of transplantation over dialysis in elderly patients? *Nephrol. Dial. Transplant* 2004; 19:945–951.

26

Pharmacokinetics in the Geriatric Population

Alfonso Dominguez-Gil Hurlé, M.J. García Sánchez, M.M. Fernández De Gatta, and Ampara Sánchez Navarro

Introduction

Because of the aging process, as well as other superimposed factors (i.e., comorbidity, polypharmacy, frailty, noncompliance, etc.), the elderly differ from other adults in their response to drugs. Aging is accompanied by nonpathological alterations in the structure and function of many organs, which may affect physiological processes and therefore drug disposition. The physiological changes inherent to aging occur at different rates among individuals and even among various organs in the same individual. This accounts for increasing interindividual variability—a feature of advancing age—and hence individuals of the same chronological age may show significant differences in the kinetic profile of drugs. Accordingly, we could optimize therapy if we had a categorization of the elderly on the basis of biological age and the consequent probability of functional decline.

Absorption

With respect to the oral administration of drugs, the absorption process is of special relevance because this route is most widely used. Bioavailability (F) governed by the fraction of the dose absorbed (F_{abs}) and the fraction that escapes from intestinal (F_{GI}) or hepatic (F_{H}) metabolism, known as intestinal and hepatic first-pass effect, respectively [1].

To measure the oral absorption of drugs, we must know whether the absorption process is limited by the blood flow or by membrane permeability. These factors in turn are affected by the physicochemical properties of the drug, the formulation used for its administration, and the physiological aspects of the gastrointestinal tract (GIT), such as stomach pH, motility, permeability, drug transporters (P-glycoprotein, organic peptide transporters, etc.), and gastrointestinal blood flow [1].

Generally, the elderly population has hypochloridria secondary to atrophic gastritis, although some studies report that acid gastric secretion is maintained during the normal process of aging. This contradiction may be explained by

the widespread use of proton-pump inhibitors and H_2-receptor antagonists in the elderly, which would probably be responsible for the greater reduction in the levels of hydrochloric acid observed in such individuals [2].

In the elderly, these changes in gastric pH levels affect absorption in various ways, depending on whether the drug requires an acid pH to become ionized and solubilized, as is the case with ketoconazole, ampicillin esters, or iron compounds; drugs that are labile in acid media, such as erythromycin; or prodrugs, which require such a medium to become hydrolyzed or biotransformed into the active form.

In general, the elderly display a slowing down of gastric emptying [3], although one study has reported a similar rate of emptying for elderly and young individuals [4]. The probable effect of this—a delay in gastric emptying—will depend on the physicochemical characteristics of the specific drug. In this sense, one can increase the bioavailability of sparingly soluble drugs because a longer dwell time in the gastrointestinal tract may allow a better solubilization if dissolution is the limiting step to absorption. In contrast, for drugs that are highly soluble and labile in acid medium, a delay in gastric emptying may produce a lower F_{abs}.

Although still controversial, it seems likely that the elderly undergo changes in intestinal motility. Firth and Prather [5] have reported modifications in gastrointestinal transit patterns, including decreased postprandial contractions and reductions in the frequency of peristaltic waves. Nevertheless, with some exceptions, these modifications should not affect the absorption profile of drugs to any significant extent. Some extended-release formulations may be sensitive to the prolongation of the transit time through the gastrointestinal tract (GIT), although the clinical significance of this remains unknown.

It is accepted that, for most drugs, intestinal permeability due to passive diffusion mechanisms remains unaltered with age [6, 7]. Drugs that are absorbed through an active transport mechanism are likely to be absorbed more slowly and in smaller quantities in elderly patients; this has been confirmed for certain nutrients such as glucose, calcium, iron, vitamin B_{12}, and leucine [8]. One type of drug transporter currently attracting much interest is P-glycoprotein, although we have no evidence concerning the effect of advanced age on it [9].

In geriatric patients, the decrease in hepatic clearance, especially for drugs that undergo metabolic phase I reactions (see metabolism section of this chapter) and/or flow-limited biotransformation, may have an important effect on F. Thus, this parameter increases for drugs with an extensive first-pass effect such as calcium antagonists, β-blockers, and statins. However, when prodrugs are used, such as enalapril and perindopril, their activation via the first-pass effect may be reduced.

In elderly individuals, conclusions concerning the bioavailability of drugs administered orally vary, depending on the drug. Thus, the absolute bioavailability of chlormethiazole, lidocaine, labetalol, verapamil, levodopa, and propranolol increases significantly with aging [10]. On the other hand, no differences from younger persons have been found for drugs such as imipramine, amitryptiline, metoprolol, morphine, meperidine, antiepileptics, salicylates, diazepam, lorazepam, penicillin, phenylbutazone, metronidazole, and bumetanide [7], whereas a reduction in intestinal absorption, measured as absolute bioavailability, has been found for indomethacine, prazosin, and

in the absorption rate of digoxin [6]. Despite this, it is clinically difficult to differentiate the effects attributable to an alteration in absorption itself from those due to a modification of the first-pass effect. Only when we have reliable data on the metabolites of a drug that undergoes an intestinal and hepatic first-pass effect can the influence of aging on absorption and metabolism be determined separately [1]. Unfortunately, such information is not available in most studies carried out on geriatric populations.

In summary, changes that occur during aging may increase or decrease the bioavailability of orally administered drugs. Although current pharmacokinetic data are still limited, such changes (generally an increase in F) may only be clinically significant in some cases [9]. Modifications in the absorption process may be more relevant with the concomitant administration of anticholinergic drugs or modifiers of stomach acidity, or when the patient has lesions of the GIT such as resections, ulcers, or stenosis.

When the drug is delivered through other routes that include absorption processes, such as subcutaneous, percutaneous, or intramuscular administration, a decline in tissue blood perfusion and associated age-dependent morphological and biochemical changes should allow us to predict a decrease in the absorption rate. Currently, however, only a few studies have been carried out and only some of them have reported a slower skin penetration of drugs in the elderly [7, 11].

Distribution

The distribution process is governed by the drug's physicochemical characteristics (mainly its lipophilic character), body composition, membrane permeability, tissue blood flow, and degree of binding to plasma proteins. As a result, a change in any of these age-associated physiological parameters may alter the process of distribution.

In geriatric patients, body fat increases between 20–40% and body water is reduced by 10–15% [12], which, with a reduction in lean body mass (LBM) and a greater frequency of dehydration, will give rise to a decrease in the apparent distribution volume (V_d) of water-soluble drugs, such as the aminoglycosides, or those that are distributed in muscle, such as digoxin. This situation may be exacerbated by the presence of cardiovascular disease, which is common in the elderly and compromises the flow of blood to organs and tissues. In contrast, the V_d is increased in lipophilic drugs [13]. Consistent with this, a linear relationship has been established between the log of the octanol–water partition coefficient (usual surrogate variable of drug permeability) and the quotient between the V_d in elderly and young individuals for different drugs, suggesting that the more lipophilic a drug is, the greater the probability of its V_d being higher in elderly subjects [9]. Modifications in body composition differ, depending on the patient's gender, and the increase in the V_d of liposoluble drugs tends to be greater in women, while the decrease in the V_d of water-soluble drugs tends to be greater in men. These changes suggest that we need to increase loading doses (by 10–15%) for highly lipophilic drugs and, by contrast, reduce by the same magnitude the loading dose for water-soluble drugs. However, when clearance is constant, changes in V_d lead to a proportional increase in the elimination half-life of the drug ($t_{1/2}$), we should counsel a decrease in the frequency of administration.

With age, changes also occur in cardiac output and in turn, these changes also affect the distribution process, although not all tissues are affected to the same extent. To this we should add changes in biomembrane permeability that, due to their degeneration, may facilitate the access of drugs to the different body structures. These two effects would work in opposite ways on the V_d, and this might justify why the literature has no data that relate such changes to significant modifications in the V_d of drugs. Nevertheless, a lower tissue perfusion may increase the time required for drugs to access tissues and hence increase the duration of the distribution phase. It has been reported in the elderly that blood flow to the brain does not decrease and that the relative fraction of the drug that reaches the brain may even be greater. This would account in part for the greater sensitivity of elderly patients to drugs that act on the central nervous system and even the need to use lower doses of induction anesthetics.

Although the total plasma protein concentration is not modified with age, their relative fractions do change. Thus, elderly individuals show a decrease in albumin concentrations of about 10% [14]. Turnheim [7] has related the decrease in the levels of serum albumin to an increase in the unbound fraction (f_u) of many drugs, although only in some of them does the change in f_u surpass 50% [15]. However, generally, the effect of age on f_u, reflected in an increase in V_d [7], is of little clinical significance [16, 17]. This is because an increase in f_u also elicits an increase in total plasma clearance (CL) (only the f_u is available for clearance from the organism) [13]. Therefore, f_u remains without significant change despite a decrease in total concentrations. Thus, in most cases, it is not necessary to correct the dosage regimen. One would only expect an increase in f_u to raise the drug effect in those drugs that have a small V_d, such as oral anticoagulants and oral antidiabetics [7], in which case a dosage adjustment could be necessary. In any event, the decrease in serum albumin associated with aging is of much less importance than those associated with pathological processes such as heart failure, renal disease, rheumatoid arthritis, hepatic cirrhoses, and certain malignancies. Therefore, low levels of serum albumin in the elderly often are related more to the presence of such disease than to aging itself [7].

The decrease in serum albumin is accompanied by an increase in α_1-acid glycoprotein, probably secondary to inflammatory processes associated with aging [16]. Accordingly, for drugs highly bound to this protein, f_u may decrease by almost one-third. In the case of lidocaine, f_u is reduced by approximately 40% in the elderly [16], which may give rise to a decrease in the CL of the drug [7]. Even in this situation, the area under the curve of the unbound fraction (f_u.AUC), the most relevant pharmacokinetic parameter from the clinical point of view, is not affected when these drugs are administered orally [17]. The changes in protein binding may alter the f_u.AUC in drugs that have a high hepatic extraction coefficient, have extensive binding to plasma proteins, and are administered intravenously, including some that are frequently used in geriatric therapy such as doxorubicin, fentanyl, haloperidol, midazolam, propofol, propanolol, and verapamil [17].

In summary, the changes associated with aging that have the greatest effect on the distribution process are modifications in body composition and plasma proteins (for drugs strongly bound to them), although all these modifications do not seem to have much clinical significance. Of greater relevance is

the increase in V_d that occurs with liposoluble drugs, such as thiopentone, lignocaine, chlormethiazole, and diazepam, because this increase prolongs the $t_{1/2}$, as far as the CL does not change, and leads to a greater accumulation of the drug, necessitating a reduction of the dose. However, a decrease in V_d, observed in most water-soluble drugs, tends to be balanced by a reduction in renal clearance and hence has a minimum net effect on $t_{1/2}$ [18].

Metabolism

The metabolism of drugs occurs mainly in the liver, whose capacity for biotransformation depends on the activity of the enzyme systems involved and on the blood flow it receives. Our knowledge of this kinetic process is broader and more specific than before, so that, for most drugs, we know not only the fraction eliminated by metabolism, the main metabolites, and the reactions involved, but also the enzyme or enzymes involved and their quantitative contribution. Figure 26.1 offers a scheme of the processes of hepatic biotransformation in humans, and Table 26.1 shows some examples of the metabolic process of representative drugs. Most of them are carried out by only 8 to 10 isoenzymes from the hepatic microsomial system known as cytochrome P-450 (CYP), which belongs to the CYP1, CYP2, and CYP3 families.

Aging leads to marked changes in the physiology of many organs, but in the absence of associated disease, an aged liver does not differ significantly from that of a younger adult. Nevertheless, a decrease occurs in biliary function, including the flow and secretion of bile acids. Although one might expect a decrease in the hepatic clearance of drugs excreted in the bile, to date we have no clinical evidence to confirm this point [19]. The two most outstanding features of liver function in the elderly are the changes that affect the metabolism of drugs and the increase in interindividual variability, which makes it difficult to detect the deterioration that accompanies aging. Therefore,

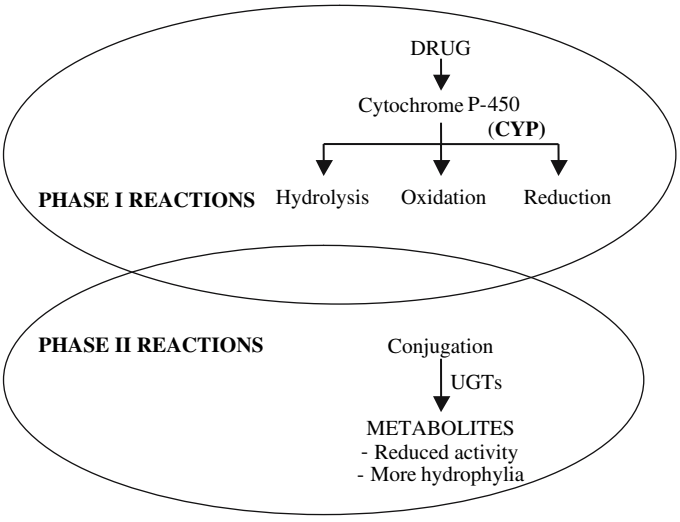

Fig. 26.1 Schematic representation of hepatic biotransformation processes in humans.

Table 26.1 Representative Drugs in Relation to Biotransformation Process.

Flow-Limited	Limited Capacity	Phase I Reactions	Phase II Reactions
Morphine	Antipirine	Antipirine	Isoniazide
Propanolol	Theophylline	Diltiazem	Oxazepam
Amitryptiline	Diazepam	Propanolol	Temazepam
Verapamil	Phenytoin	Lidocaine	Paracetamol
Lidocaine	Warfarin	Theophylline	Mizolastine
Nifedipine	Valproic acid	Ibuprofen	
		Rabeprazol	
		Citalopram	
		Zolpidem	

in the liver, the greatest clinical implication of aging is pharmacological and is related to the organ's biotransformation capacity, although considerable controversy continues concerning the effect of aging on drug metabolism.

Consistent with the notion that aging affects the intrinsic functions of the liver only slightly and then chiefly its response to extrahepatic factors, it has been reported that, at least with respect to metabolism, the pharmacokinetic alterations due to age per se are 20–40% vs. 50–300% for other characteristics, such as genetic factors, co-morbidity, frailty, or drug interactions [18]. Likewise, a recent analysis of the simultaneous influence of age and gender on the *in vivo* activity of CYP enzymes concluded that such factors have only slight relevance and clinical significance on interindividual variability [20]. Aging does not seem to affect the differences in the kinetic profile determined genetically for drugs metabolized by the enzyme CYP-2D6. In the case of omeprazol, a representative drug metabolized by the enzyme CYP-2C19, the evident differences between genotypes are clearly attenuated by age, and efficient metabolizers show clearance values similar to those considered to be deficient metabolizers [21].

When antipyrine is used as a marker of oxidative hepatic metabolism mediated by the CYP, the influence of aging is clear; other drugs have also shown a decrease in the hepatic clearance of elderly subjects as compared to younger adults [7]. On the other hand, phase II reactions, such as conjugation with glucuronides, glycine, or sulphates, do not change appreciably with aging. On the whole, the influence of age on the kinetic profile, studied in more than 46 drugs in 4500 individuals, has confirmed a decrease in clearance for people over 60; this reaches a value of 50% in individuals aged 80–85. With regards to the mechanism involved, Phase I metabolism, mediated by CYP, decreases with age, whereas conjugation processes do not seem to be affected [22].

With age, the clearance of drugs with a high hepatic extraction coefficient (flow-limited) is modified in proportion to the flow value, while in drugs of low extraction (capacity-limited), their intrinsic clearance, which depends on the content and activity of the enzymes involved, is the main determinant of drug clearance.

Various techniques have shown that aging causes a decrease in hepatic blood flow of approximately 40% and a similar or slightly smaller (25–35%) reduction in liver mass [23, 24]. In contrast, studies on the effect of age on the content and activity of hepatic enzymes have shown conflicting results, even for CYP. In general, most enzymes are not modified, but some

authors have described a decrease in their content or activity in elderly persons. Two reviews of studies carried out in humans concluded that the activity of most CYP enzymes, with the noteworthy exception of CYP-2D6, decreases with aging. Thus, we expect a decrease in the hepatic clearance of drugs that are eliminated mainly through biotransformation, both those of high hepatic extraction (flow-dependent) and those of low hepatic extraction (capacity-limited). Despite this, whereas the former aspect has been consistently confirmed and the observed decrease in clearance corresponds to that estimated flow, in capacity-limited drugs no obvious relationship has been shown between clearance and advanced age. Even though elderly subjects sometimes show a decreased clearance for capacity-limited drugs, the observed decrease does not correspond to that expected according to the size of the liver. A study of 226 liver biopsies in individuals in whom antipyrine clearance was quantified *in vivo* revealed a maximum decrease of 50% in the overall content of CYP and yet only a 30% reduction in its CL in persons over 70 years [25]. Dopa decarboxylase content seems to decline appreciably in the elderly, which accounts for the up to threefold increase in the bioavailability of levodopa in such individuals.

Thus, it seems that the different enzyme systems involved in the biotransformation of drugs show a different sensitivity to the aging process; in other words, the capacity of the liver to biotransform drugs does not decrease in the same way or to the same magnitude from drug to drug or from individual to individual. In addition, it seems that Phase II metabolic reactions are not age-dependent, whereas Phase I oxidative reactions are affected by the aging process. This apparent paradox can be accounted for by postulating that oxidative reactions are directly dependent on oxygen supply and that the structural changes that occur in the sinusoidal endothelium with aging (thickening and defenestration) decrease the oxygen availability [9, 19].

Analysis of the effect of aging on the induction of metabolism also provides conflicting results, and yet it appears that the inhibition of metabolism does not change appreciably with aging. Thus, for example, the inhibitory effects of fluoxetin on the activity of CYP-2C19 are evident regardless of age. Table 26.2 summarizes the evidence and the most important gaps in our information about the effect of aging on hepatic metabolism.

In conclusion, the elimination capacity due to biotransformation processes may be reduced in geriatric patients, although one cannot generalize or establish fixed criteria for dosing as a function of this change. Nevertheless, it has been suggested that the doses of highly extracted drugs can be reduced by 40%, while those subject to Phase I reactions could be reduced by 30%. It would not appear necessary to adjust the dosage of drugs whose metabolism involves conjugation processes. In geriatric patients, one should consider that other factors, such as drug interactions, cancer, hepatic impairment, etc., are common and that their effects on the biotransformation capacity may even surpass those of age. Thus, in frail, protein-malnourished elderly, their metabolism, including Phase II reactions, may be decreased compared to healthy, well-nourished elderly [7]. The decrease in hepatic blood flow secondary to heart failure or a β-adrenergic blockade may be superimposed on the effects of age and may strongly affect the hepatic clearance of high-extraction drugs. Also, renal impairment may lead to a general decline in CYP activity.

Table 26.2 Main Evidence and the Limitations of Literature About the Effect of Aging on Hepatic Metabolism.

Accepted Principles	Important Limitations
Reduction of clearance for high-extraction drugs	Controversy for capacity-limited drugs
Reduction of metabolism in Phase I, above all of oxidative type	Scant information about the relationship between genetic polymorphisms and age
Phase II reactions not affected	Discrepancies about the effect of age on inhibition/induction processes
Reduction of the hepatic first-pass effect	Scant application of the available information in the design of dosage regimens
Increased interindividual variability	
Noteworthy effect of additional factors: pathologies, frailty, interactions, etc.	

Renal Elimination

The kidney contributes the most to the elimination of drugs and their metabolites. Total renal excretion is the result of three main processes: glomerular filtration, active tubular secretion, and tubular reabsorption. Although less relevant, two other mechanisms are involved in the renal elimination of drugs: those mediated by the CYP system and those mediated by specific proteins that function as efflux pumps (P-glycoprotein). Table 26.3 shows the renal mechanisms and the processes involved in drug elimination.

In view of the elevated number of drugs using the renal system as their major route of elimination, the physiological changes that lead to a decline in renal clearance with age make it necessary to consider the changes in renal function in geriatric patients in order to establish efficient and safe doses in this population group.

The modifications in the renal system as a result of aging differ from those triggered by chronic or acute renal failure. In both cases, the final functional consequence is a decrease in the glomerular filtration rate (GFR) and/or a decrease in active transport processes in the tubules. Pharmacokinetically, both situations produce a reduction in renal clearance and a greater accumulation of drugs in the organism. Nevertheless, we should take care in choosing the methods used for the assessment of renal function and their application for

Table 26.3 Renal Processes and Corresponding Mechanisms Involved in Drug Elimination.

Glomerular Filtration	Tubular Secretion	Tubular Reabsorption	Metabolism	Protein-Mediated Transport
Dependent upon renal flow and the free drug fraction	Active transport mediated by anion/cation transporters	Active transport mediated by anion/cation transporters or passive diffusion influenced by pH and urinary flow	Mediated by the CYP 450 system	Active process mediated by P-glycoprotein

dosage adjustment, bearing in mind the particularities of this situation. Thus, to assess renal function, it is crucial to apply methods that will allow a correct estimation of that function.

The National Kidney Foundation Guidelines [26] recommend the use of equations that incorporate serum creatinine concentration (S_{cr}) and anthropometric variables (age, gender, ethnicity, body mass) to assess renal function. Chapter 5, which deals with this topic, offers a revision of available formulas, makes recommendations, and cites limitations for their application in clinical practice.

These equations, like other models based on the use of S_{cr}, do not apply in some circumstances, and we have serious doubts about the use of S_{cr} to estimate the glomerular filtration rate in geriatric patients. One study in which GFR was estimated from the clearance of iothalamate in patients aged between 65 and 85 indicated that no method based on the use of S_{cr} provides totally reliable results in this population group [27]. The Cockcroft–Gault (CG) formula [28] was derived from a retrospective study of men with a variety of disease states; in particular, some individuals between 60 and 79 years had significant renal pathology. This fact could account for the underestimation of the GFR when that formula is applied to geriatric patients without renal co-morbidity.

Currently, we recommend prospective studies that exclude individuals with co-morbidities when attempting to assess the changes in renal function due to age, because in more recent generations aging has become "healthier"; therefore, the decline in renal function may be less than that generally accepted, and some healthy elderly persons may have no relevant changes in renal function. Accordingly, the CG formula would reflect more the incidence of renal failure in patients of advanced age rather than changes due to aging itself, and hence its generalized use in elderly patients would not be appropriate. Cystatin C may be another potential biomarker of renal function [29]. However, in the elderly, levels of cystatin C are significantly lower than in younger subjects (0.84 mg/L vs. 0.69 mg/L) [30], and therefore its use cannot be recommended in this population.

Increasing evidence suggests that, in certain clinical situations, creatinine clearance (C_{cr}) estimated by the above methods (see Chapter 5) may correlate poorly with renal drug clearance, suggesting that the different mechanisms of renal excretion do not decline in parallel. Indeed, the renal removal of drugs is modified in a variety of ways, depending on the disease process that triggers the renal deterioration. Thus, as Tett proposed [31], we should reappraise the methods used to determine renal function and use new strategies that will allow us to assess the changes in each of the processes that individually contributes to renal excretion. Some drugs widely used in geriatric medicine depend on routes other than glomerular filtration for their renal elimination; in particular, active excretion [32] or metabolism [33]. In these cases, the methods of dose adjustment based only on the GFR are not appropriate.

In addition, in patients with decreased renal function, such as the elderly, we should not overlook changes in the renal excretion of metabolites that have pharmacological or toxicological activity. Representative examples are the active metabolites of meperidine and midazolam; in elderly patients, the former—normeperidine—can decrease the seizure threshold, while the accumulation of the latter—alpha-hydroxymidazolam—produces excessive

sedation. Even more alarming is the accumulation of the active metabolite of morphine (morphine-6-glucuronide); this moiety is more potent than the parent drug, and in renal-impaired patients its half-life may be increased up to 50 hours, as compared to 3–5 hours without such impairment. Severe toxicological effects have observed [34, 35] in patients over 65 who received 50 mg of morphine and who had co-morbidities (diabetes, angina, etc.) that produced a greater degree of renal dysfunction. These adverse effects were due to elevated levels of morphine-6-glucuronide. The anticancer agents that undergo a strong renal elimination are of special interest in the individualized selection of dosage regimens in elderly patients. In a retrospective study, Gelman and Taylor [36] emphasized the importance of considering a decrease in the GFR of elderly individuals treated with anticancer agents; they reported that, in women older than 65, the toxicity of cyclophosphamide, methotrexate, and fluoroacyl is reduced with no loss of efficacy when the dose is adjusted according to this renal excretion.

Dosage Regimens and Dose Adjustment

Many texts, manuals, and generalized empirical guides offer advice concerning drug dosage in moderate or severe renal impairment in elderly patients [37]. For example, McCormack et al. [38] make the following recommendations: Adjust the dosage as long as more than 75% of the drug and/or its active (or toxic) metabolites are eliminated in the urine and $C_{cr} < 60$ mL/min/72 kg; when the fraction excreted in urine (f_e) is in the 50–74% range, adjustment would only be necessary when the patient has a $C_{cr} \leq 45$ mL/min/72 kg.

Such recommendations are useful when one does not need a precise adjustment of the dose. However, empirical modifications of this type may not be appropriate if the drug has a narrow therapeutic range and the clinical situation demands maximum optimization of the response. In these cases, one must rely on dosage individualization based on the particular characteristics of the patient.

In geriatric patients who do not have associated co-morbidities, the loading dose does not require significant change from that used in other populations. Digoxin, however, is a particular case and, as noted above, reduction of the initial dose is recommended. There are two alternatives for the adjustment of the maintenance doses: [1] extending the dosing interval and/or [2] decreasing the maintenance dose. The first strategy is preferable if one wants to maintain the C_{max}/C_{min} ratio of an adult patient. If the aim is to maintain the mean concentrations in a balanced way, the second choice should be employed.

For drugs whose $f_e \geq 0.9$, the dosage can be adjusted as follows [33]:

1. Extending the dosage interval: dosage interval in the elderly = (standard C_{cr}/patient C_{cr}) × standard interval. With this strategy, one gets significant fluctuations in serum levels; this circumstance sometimes is associated with a decrease in toxic effects but also with a reduction in efficacy because of the possibility of subtherapeutic levels for a fraction of dosage interval.
2. Reducing the dose: dose in the elderly = (patient C_{cr}/standard C_{cr}) × standard dose. This method leads to fewer fluctuations in blood drug levels.

The decision to apply one strategy or the other depends on the clinical implications associated with each; sometimes it becomes necessary to combine both to minimize toxicity and maximize efficacy.

If $f_e \leq 0.9$, the following is proposed [37]: dose in the elderly = $[(1 - f_e)] + [f_e \times (\text{patient } C_{cr}/\text{standard } C_{cr})] \times$ standard dose.

A high proportion of hospitalized geriatric patients receive doses higher than those recommended for drugs excreted mainly through the kidney; for example, allopurinol and metformin because of their propensity to cause adverse effects. With the former, one of the active metabolites, oxypurinol, produces adverse effects and, in renal impairment, accumulates due to an increase in its half-life from 24 to 125 hours. One should avoid drugs with an elevated f_e and a narrow therapeutic margin in this type of patient. If there is no other therapeutic alternative, one should monitor serum drug levels to achieve dosage individualization.

The above strategies for dosage adjustment assume that the reduction in the renal clearance of the drug is proportional to the reduction in GFR or C_{cr} in the patient; in turn, this assumes (1) that there are no changes in other renal processes of elimination and (2) the maintenance of the remaining pharmacokinetic parameters (F, V_d, nonrenal clearance). Although these conditions may not be obtained in many clinical situations, they are likely in geriatric patients who do not have associated morbidities because age itself involves a progressive decrease in renal function, while the remaining kinetic processes are less affected. For drugs subject to active transport processes in the kidney, such proposed dosage strategies would be acceptable as long as this mechanism makes only a minor contribution to elimination.

References

1. Burton, P.S., Goodwin, J.T., Vidmar, T.J., et al. Predicting drug absorption: How nature made it a difficult problem. *J. Pharmacol. Exp. Ther*. 2002; 303:889–895.
2. Hurwitz, A., Brady, D.A., Schaal, S.E., et al. Gastric acidity in older adults. *JAMA* 1997; 278:659–662.
3. Orr, W.C., Chen, C.L. Aging and neural control of the GI tract: IV. Clinical and physiological aspects of gastrointestinal motility and aging. *Am. J. Physiol*. 2002; 283:G1226–G1231.
4. Gainsboroug, N., Maskrey, V.L., Nelson, M.L., et al. The association of age with gastric emptying. *Age and Ageing* 1993; 22:37–40.
5. Firth, M., Prather, C.M. Gastrointestinal motility problems in the elderly patient. *Gastroenterology* 2002; 122:1688–1700.
6. Saltzman, J.R., Kowdley, K.V., Perrone, G., et al. Changes in small intestine permeability with aging. *J. Am. Geriatr. Soc*. 1995; 43:160–164.
7. Turnheim, K. Drug dosage in the elderly. Is it rational? *Drugs & Aging* 1998; 13(5): 357–379.
8. Sacchi, V.F., Magagnin, S. Age-related modifications of leucine uptake in brush-border membrane vesicles from rat jejunum. *Mech. Ageing Dev.* 1992; 63:257–273.
9. McLean, A.J., Le Couteur, D.G. Aging biology and geriatric clinical pharmacology. *Pharmacol. Rev*. 2004; 56:163–184.
10. Wilkinson, G.R. The effects of diet, aging and disease-states on presystemic elimination and oral drug bioavailability in humans. *Adv. Drug. Deliv. Rev*. 1997; 27:129–159.
11. Roskos, K.V., Maibach, H.I., Guy, R.A. The effect of aging on percutaneous absorption in man. *J. Pharmacokinet. Biopharm.* 1989; 17:617–630.

12. Beaufrere, B., Morio, B. Fat and protein redistribution with aging: Metabolic considerations. *Eur. J. Clin. Nutr*. 2000; 54:S48–S53.
13. Bressler, R., Bahl, J.J. Principles of drug therapy for the elderly patients. *Mayo Clin. Proc*. 2003; 78:1564–1577.
14. Campion, E.W., deLabry, L.O., Glynn, R.J. The effect of age on serum albumin in healthy males: Report from the Normative Aging Study. *J. Gerontol*. 1988; 43:M18–M20.
15. Wallace, S.M., Verbeek, R.K. Plasma protein binding in the elderly. *Clin. Pharmacokinet*. 1987; 12:41–72.
16. Grandison, M.K., Boudinot, F.D. Age-related changes in protein binding of drugs: Implications for therapy. *Clin. Pharmacokinet*. 2000; 38:271–290.
17. Benet, L.Z., Hoener, B.A. Changes in plasma protein binding have little clinical relevance. *Clin. Pharmacol. Ther*. 2002; 71:115–121.
18. Mangoni, A.A., Jackson, S.H. Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. *Br. J. Clin. Pharmacol*. 2004; 57(1):6–14.
19. Schmucker, D.L. Liver function and phase I drug metabolism in the elderly. A paradox. *Drugs & Aging* 2001; 18:837–851.
20. Bebia, Z., Buch, S.C., Wilson, J.W., et al. Bioequivalence revisited: Influence of age and sex on CYP enzimes. *Clin. Pharmacol. Ther*. 2004; 76:618–627.
21. Ishizawa, Y., Yasui-Furukori, N., Takahata, T., et al. The effect of aging on the relationship between the cytochrome P450 2C19 genotype and omeprazole pharmacokinetics. *Clin. Pharmacokinet*. 2005; 44:1179–1189.
22. Ginsberg, G., Hattis, D., Russ, A., et al. Pharmacokinetic and pharmacodynamic factors that can affect sensitivity to neurotoxic sequelae in elderly individuals. *Environ. Health Perspect*. 2005; 113:1243–1249.
23. Zeeh, J., Platt, D. The aging liver. Structural and functional changes and their consequences for drug treatment in old age. *Gerontology* 2002; 48:121–127.
24. Kinirons, M.T., O´Mahony, M.S. Drug metabolism and ageing. *Br. J. Clin. Pharmacol*. 2004; 57:540–544.
25. Sotaniemi, E.A., Arranto, A.J., Pelkonen, O., et al. Age and cytochrome P450-linked drug metabolism in humans: An analysis of 226 subjects with equal histopathological conditions. *Clin. Pharmacol. Ther*. 1997; 61:331–339.
26. Levey, A.S., Coresh, J., Balk, E., et al. National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease. Evaluation, classification and stratification. *Ann. Intern. Med*. 2003; 139:137–147.
27. Bailie, G.R., Uhlig, K., Levey, A.S. Clinical practice guidelines in Nephrology: Evaluation, classification and stratification of chronic kidney disease. *Pharmacotherapy* 2005; 25:491–502.
28. Cockcroft, D.W., Gault, M.H. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31–41.
29. Burkhardt, H., Bojarski, G., Gretz, N., et al. Creatinine clearance, Cockcroft–Gault formula and cystatin C: Estimators of true glomerular filtration rate in the elderly? *Gerontology* 2002; 48:140–146.
30. Fliser, D., Ritz, E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am. J. Kidney Dis*. 2001; 37:79–83.
31. Tett, S.E., Kirkpatrick, C.M.J., Gross, A.S., et al. Principles and clinical application of assessing alterations in renal elimination pathways. *Clin. Pharmacokinet*. 2003; 6:45–65.
32. Matzke, G.R., Comstock, T.J. Influence of renal function and dialysis on drug disposition. In *Applied Pharmacokinetics and Pharmacodynamics*, M.E. Burton, L.M. Shaw, J.J. Schentag, and W.E. Evans, eds. London: Lippincott Williams and Wilkins. 2006; pp. 187–212.
33. Gabardi, S., Abramson, S. Drug dosing in chronic kidney disease. *Med. Clin. N. Am*. 2005; 89:649–687.

34. Conway, B.R., Fogarty, D.G., Nelson, W.E., et al. Opiate toxicity in patients with renal failure. *Br. Med. J*. 2006; 332:345–346.
35. Angst, M.S., Buhrer, M., Lotsch, J. Insidious intoxication after morphine treatment in renal failure: Delayed onset of morphine-6-glucuronide action. *Anesthesiology* 2000; 92:1473–1476.
36. Gelman, R.S., Taylor, S.G.T. Cyclophosphamide, metotrexate, and 5-fluorouracil chemotherapy in women more than 65 years old with advanced breast cancer: The elimination of age trend in toxicity by using dosed based on creatinine clearance. *J. Clin. Onc*. 1984; 2:1404–1413.
37. Pillans, P.I., Landsberg, P.G., Fleming, A.M., et al. Evaluation of dosage adjustment in patients with renal impairment. *Int. Med. J*. 2003; 33:10–13.
38. McCormack, J.P., Cooper, J., Carleton, B. Simple approach to dosage adjustment in patients with renal impairment. *Am. J. Health Syst. Pharm*. 1997; 54:2505–2509.

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Quality of Life in Elderly Patients with Renal Failure

Francisco Ortega and Pablo Rebollo

The Concept of Health-Related Quality of Life

The evaluation of quality of life has aroused great interest among doctors working in various clinical fields in the last 20 years. According to Testa [1], the number of scientific articles appearing on Medline in response to the keywords "quality of life" has shown a significant increase, starting with 5 articles in 1973 and reaching 1,252 articles in 1993. Far from being a passing fashion, however, evaluation of health-related quality of life (HRQoL) has continued to interest doctors, especially those dealing directly with the chronically ill, within the framework of a movement in medicine that attempts to return the prominence of the patient in the course of his illness. Thus, in the PUB MED database, on April 1, 2006, the same keywords "quality of life" gave 78,125 articles, 8,077 of which had been published in the previous year.

What Is "Quality of Life"?

But what exactly do we mean by "quality of life" (QoL)? The World Health Organization (WHO) defines quality of life as "the personal perception of an individual of his situation in life, within the cultural context and values in which he lives, and in relation to his objectives, expectations, values and interests" [2]. Physical health, psychological state, degree of independence, social relationships, relationship with the environment, and religious beliefs are dimensions included in this broad concept of quality of life. The WHO also affirms that quality of life is not the same as "state of health," "lifestyle," "satisfaction with life," "mental state," or "well-being," but is rather a multidimensional concept that incorporates the individual's perception of these and other aspects of life. When this multidimensionality is considered from the health point of view, two factors can be identified: one related directly to health, which constitutes what is referred to as the health-related quality of life (HRQoL), and the other not directly related to this, which is the nonmedical factor, comprising family, friends, religious beliefs, work, income, and other circumstances of life. These factors, medical and nonmedical, are related among themselves, as the illness, in addition to affecting the physical

domain, also has repercussions on the psychological state of the individual, her degree of independence, and her social relationships [3]. Nonmedical factors may also affect health, but these are outside the objectives of health care or medicine [4].

Why Should We Measure HRQoL?

The reasons why it is considered necessary to evaluate the HRQoL may be summarized as [1] the determination of the efficacy of a medical intervention, [2] improvement in clinical decision making, [3] evaluation of the quality of care, [4] estimation of the patient's needs, and [5] understanding of the causes and consequences of differences in health [5].

The main purpose of clinicians is to restore the health of their patients. Unfortunately, however, many conditions are incurable and chronic, and in them the conservation or restoration of quality of life represents an important therapeutic objective. Bearing in mind the progressive increase in the number of chronic illnesses in the developed world, the need to measure health status in those illnesses that affect the quality of life of the patients will be readily appreciated [6], especially when the illness or its therapy has dramatic effects on the patient's HRQoL [7].

The use of HRQoL measurements and the resulting data offer a means of monitoring the illness and the benefits of treatment in terms that are important for the patient, that is, in terms of quality of life [8]. Clinicians need information about the effects of an illness on their patients, as well as on the effects of a treatment, in order to be able to recommend it and evaluate their patient's progress [6]. Great interest exists at present in the use of HRQoL evaluation tools in clinical trials of new drugs in order to demonstrate improvement in terms of health as perceived by the patient. This interest in evaluating health in clinical trials has become compulsory in the United States and is required by the U.S. Food and Drug Administration (FDA). The European Organisation for Research and Treatment of Cancer (EORTC) also requires all proposals for new studies to include evaluation of the quality of life and of the cost-effectiveness.

A further point of the great interest in HRQoL measurement is its application in health economics, particularly in evaluating the results of healthcare interventions, establishing priorities, and examining and auditing health services and research programs [9–11]. The aim of this chapter is to provide more precise evaluations of the health of individuals or populations and of the benefits and harm that may result from provision of various health treatments.

HRQoL Evaluation Tools

Many clinicians, especially those caring for chronic patients, are interested in carrying out an evaluation of the HRQoL of the patients under their care. The first challenge they face, after an initial approach to the concept and the particular methodology these evaluations require, is the choice of an HRQoL evaluation tool that is appropriate for their purpose. Review of the bibliography concerning HRQoL evaluation in the specific field of medicine to be addressed will show that there are numerous general and/or specific questionnaires in use. Some of these questionnaires may be translated into

the language in question, and others not. It may be that none of them fits in with the aims of the evaluation proposed. Therefore, the clinician is faced with three possibilities for continuing his work: [1] to create a new HRQoL evaluation tool that will serve his specific goals; [2] to translate and adapt a tool that already exists in another language; or [3] to choose one of the various HRQoL evaluation tools already translated and adapted for his country by other authors.

If a tool that suits the investigator's purposes exists but is in another language, she should make a "transcultural adaptation." The simplest and most frequent case, however, is that there already exists a tool, adapted and validated, in that language that meets her requirements. From among these one should reject those that have poor psychometric properties and select from the remainder the one that best fits in with our objective. The psychometric properties to be evaluated in the HRQoL evaluation questionnaire are the same general properties that any measurement tool should possess: appropriateness, validity, reliability, and sensitivity to changes (Table 27.1). The "appropriateness" deals with ascertaining the degree to which the content of a specific measurement corresponds to the requirements of the investigator wishing to use it. It is also known as "content validity" and is evaluated by panels of experts and non-experts (patients). "Validity" is defined as the degree to which a measurement tool provides information about the phenomenon it is intended to measure and not of other phenomena. It is not easy to evaluate the validity of health measurements, as the phenomenon is a complex one and therefore permits different approaches. Criterion validity is the relationship it maintains with another measurement considered as a model or criterion, and it may be carried out using the two tools at the same time (convergent validity) or subsequent to the use of the tool that it is intended to examine (predictive validity). The "concept validity" represents the degree to which a particular measurement is related to others in a manner consistent with the theoretical hypotheses that define the phenomenon, concept, or construct that it is desired to measure. Often the analysis of the "concept validity" is the strategy used to evaluate the validity of HRQoL measurement questionnaires. It is established through correlation analysis. The study of "reliability" is intended to quantify the random error intrinsic to the measurement. It is the degree to which the measurement tool is free of random error. With regard to this psychometric property, a variety of approaches are possible. Cronbach's Alpha coefficient provides an estimate of reliability based on all the possible correlations between two series of items within a test. This coefficient evaluates the "internal consistency." Another approach is the study of the reproducibility of the questionnaire, through test-retest or inter-observers' correlation coefficients. Finally, "sensitivity to change" is simply defined

Table 27.1 Psychometric Properties of HRQoL Measurement Tools.

Property	Evaluation
Appropriateness	Panels of experts and non-experts
Validity of Criterion	Sensitivity, specificity, and predictive
Validity of Concept	power: correlation analysis
Reliabilty	Cronbach's alpha/test-retest reproducibility
Sensitivity to change	Comparison of scores before and after an intervention

as the capacity of a tool to detect changes. It is established by comparing the scores on the questionnaire before and after an intervention, measuring also the comparison of the changes in the scores on these scales with the changes in other, related measurements that are assumed to move in the same direction, and by the so-called effect of size, an estimate of the magnitude of change in the state of health. It is also often described as the minimum change considered significant by people with that health condition, people close to them, or that is important for them or their careers.

There are two types of quality-of-life measurements, generic and specific, and they have different advantages and disadvantages. The generic tools may be used in a large variety of populations; they evaluate dimensions relevant to a wide range of subjects and permit comparisons between different populations but are not sensitive to changes in health. The specific tools, on the other hand, are designed for a particular population and, therefore, incorporate dimensions more relevant to this population and are more sensitive to changes in state of health. However, they do not allow comparisons to be established between different populations.

Most of the generic tools were designed to evaluate the principal areas of quality of life. Tools of this type are highly valued in recent years because they do not suffer from clinical "contamination" and allow comparative analyses with other healthy populations (communities) and/or diverse pathologies with chronic evolution, for example, among populations of patients on renal function substitution therapy, whether dialysed or transplanted. Those most widely used are the following:

1. "Sickness Impact Profile" (SIP), developed by Bergner et al. [12, 13]
2. "Nottingham Health Profile," developed by Hunt et al. [14]
3. "EuroQoL" [15]
4. "Dartmouth COOP Functional Health Assessment Charts/Wonca" [16]
5. "SF-36 Health Survey," developed by Ware and Sherbourne [17].

Moreover, several specific HRQoL measurement questionnaires have been developed specifically for dialysis and renal transplant patients. Although one of the objectives for which specific tools in general are designed is to enable investigators to carry out individualized follow-up, the specific dialysis or renal transplant questionnaires do not allow such a follow-up when patients, as often happens in practice, change renal replacement therapy. Thus, if a transplant patient loses renal function and returns to dialysis, he cannot continue to be evaluated using the same questionnaire. However, in the case of transplanted patients, these questionnaires provide very detailed information regarding the side effects of immunosuppressive medication on their HRQoL and are, therefore, very useful, especially in the field of clinical trials. The three questionnaires of this kind developed to date and that meet minimum standards of quality are the "Kidney Transplant Questionnaire" of Laupacis et al. [18], the "End-Stage Renal Disease Symptom Checklist—Transplantation Module" of Franke et al. [19], and the "Life Satisfaction Index" of Hricik et al. [20]. In the case of dialysis patients, the recommended questionnaires are the Kidney Disease Questionnaire (KDQ) of Laupacis et al. [21] and the Kidney Disease Quality of Life Instrument (KDQoL) of Hays et al. [22].

HRQoL in Elderly Patients with End-Stage Renal Disease

HRQoL and Adaptation to Illness in the Elderly

When reviewing the scientific literature, one will find two groups of authors coming to different conclusions: One group finds that age worsens HRQoL, while the other finds the opposite. Several years ago, explanations for such a difference were ascribed to inappropriately low hemoglobin levels before the generalized use of erythropoietin, or to dialysis with acetate bath, or to inappropriate and nonstandardized methodology to evaluate HRQoL. But in recent times, explanations are not as evident as in the past. In a paper published in the *BMJ*, Carr et al. [23] related three problems with measuring HRQoL: (1) People have different expectations about their health, their illnesses, etc.; (2) people may be at different points of their illness trajectory when their HRQoL is measured; and (3) the reference value of their expectation may change over time.

To understand the problem, we should go back to the basics. Thus, it is a well-known fact that aging worsens HRQoL in the general population, but while decline in physical functioning is evident, mental health scores show little change. This pattern suggests that a process of psychological adjustment occurs with advancing age. An example of this can be seen in Table 27.2, where the normal scores of SF-36 Physical Functioning and Mental Health domains are derived from random samples of a general population in the United States [17], but also from samples of general populations of other countries such as Spain [24]. As this table shows, the scores in the domain of Physical Functioning decrease with age, but the scores in the Mental Health domain remain stable.

We know that there is a process of psychological adaptation in aging patients with chronic conditions, such as hip replacement, multiple sclerosis, urinary incontinence, COPD, AIDS, fibromyalgia, arthritis, diabetes mellitus, cancer, diseases of the skin, as well as end-stage renal disease on renal replacement therapy (RRT) [25]. The adaptation to and acceptance of the illness are factors that have a fundamental influence on the HRQoL of the chronically ill.

In order to eliminate the influence of age on HRQoL studies, the test scores are standardized, which means that they are compared with the results obtained in the general population for the same age and gender. One of the tests with which comparisons are possible is Ware's "SF-36 health survey," which has

Table 27.2 Scores in the Physical Function and Mental Health Dimensions of the SF-36 Health Questionnaire in the General Population.

	Age				
Domain	**35–44**	**45–54**	**55–64**	**65–74**	**75+**
PF (Physical Function)					
U.S. population	89.7	84.6	76.2	69.4	53.2
Spanish population	94.5	90.3	81.7	68.9	60.0
MH (Mental Health)					
U.S. population	75.1	75.3	75.0	76.9	74.0
Spanish population	77.7	77.9	75.4	75.3	70.3

been translated into many languages and adapted to multiple cultures and with which normal values have been established in many countries.

To conclude, with aging there is a decline in physical functions but not in mental ones, despite the presence of serious chronic illnesses. Compared to younger individuals, elderly patients appear to adapt better psychologically at least to RRT, as we will describe later.

HRQoL in Elderly Patients on Dialysis

The incidence of chronic renal failure rises dramatically with age [26], but paradoxically, while older age is no longer considered a contraindication to dialysis, there has been no corresponding increase in the number of renal transplants performed in patients over the age of 65 [27], with the exception of Norway [28]. The majority of elderly patients initiating RRT remain, therefore, on chronic dialysis treatment until death. Few studies exist that analyze their HRQoL. Our challenge is to provide this life-prolonging therapy to all patients who need it in such a way that improves their quality of life at a cost that society can afford.

Some time ago, Fletcher et al. [29] pointed out the existence of two populations of elderly patients on dialysis. One population encompasses those who are well-adapted and satisfied with their way of life, with an unexpectedly high degree of satisfaction in some cases. This is the product of greater social relationships and better treatment and care as a result of their inclusion in a dialysis program. The other population comprises those who, in contrast, undergo a rapid physical and emotional deterioration, often asking for dialysis withdrawal, who may have to abandon dialysis to hasten an early death.

For instance, Antoine et al. [30] studied a population of 35 hemodialysed patients aged 75 years and older, who answered a comprehensive questionnaire including a set of items defining the determinants of their quality of life, the prevalence of complaints among 35 predetermined symptoms, Folstein Mini Mental State Examination performance, scores on Katz Activities of Daily Living and Lawton (Instrumental Activities of Daily Living) independence scales, SF-36 health survey, and a score regarding their quality of life subjectively rated by the patients. The main results were that asthenia, a major complaint, reflected well the reduced physical capabilities of the patients (mean SF-36 physical score, measured with standard deviations with respect to the mean of the general population: –1.1 SD), but despite the high prevalence of incapacitating painful symptoms (42%) and psychological symptoms (23%), autonomy remained satisfactory. The levels of perceptual health and of quality of life remained satisfactory for the majority of patients (mean mental SF-36 score: –0.06 SD, and 84% of the patients scored their quality of life >5 out of 10). The authors concluded that these patients could mobilize considerable resources; they added, “The psychological reserve or resignation helps elderly people to tolerate dialysis and its constraints” [31]. However, they argued that maintaining functional autonomy while remaining independent with regards to decision making (particularly in controlling ways of receiving assistance) and preserving close relationships emerge as major determinant factors of the quality of life of very elderly dialysed patients.

Ethical questions arise about the benefits of dialysis when a patient appears unwilling or unable to comply with this treatment (see Chapter 28). Such

attitudes and behavior may be due to psychological factors, but these are not routinely assessed. Thus, in one study of older dialysis patients (>70 years) [32], 60% of the patients were depressed, according to psychological assessment and the score of a depression scale (MADRS), and between 30–47% had significant cognitive impairment. Almost half of the depressed patients were also cognitively impaired. The scores for HRQoL varied widely within the sample. These authors concluded that cognitive impairment and depressive mood are often overlooked and underestimated in this population. Regular assessments of depressive mood, cognitive ability, and quality of life are recommended, given the prevalence of problems in these domains for older dialysis patients.

Another study [33] of 169 older patients with ESRD starting on dialysis (mean age = 76.2) concluded that if the initiation of dialysis is planned in advance in older ESRD patients, then dialysis has no greater effect on HRQoL than other diseases. However, if dialysis is unplanned, it severely impairs HRQoL. These results represent an argument for improving the predialysis care of older renal failure patients by ensuring early referral and planning dialysis [33]. In this respect, we found that lack of an arteriovenous fistula at the start of chronic hemodialysis caused significant morbidity and mortality, with a substantial increase in costs, especially among elderly patients [34].

In order to characterize the HRQoL of Scottish dialysis patients at least 80 years of age and to compare it with that of patients with other serious illnesses (lung cancer and myocardial infarction), a retrospective study was performed of all older patients starting dialysis in Dumfries and Galloway between January 1, 1994, and December 31, 2003, and of all older patients with chronic renal failure starting dialysis in Scotland between January 1994 and December 2001. Quality-of-life assessment indicated a similar social functioning and mental health, but poorer physical health than their younger dialysis counterparts. Dialysis can be an effective treatment modality for a considerable proportion of octogenarians with end-stage renal failure [35], and age alone should not be used as a barrier to referral considering the benefits of dialysis in elderly people. Indicators of the ability to benefit from treatment, rather than chronological age, should be used to develop policies that ensure equal access to care for all [36].

Using the SF-36 Health Survey, scored and standardized for age and gender, we studied patients 65 years and older and compared them with the scores of those younger than 65; we found that the loss of HRQoL of patients on RRT (dialysis and renal transplant) aged 65 and over was lower than in younger patients [37].

HRQoL in Elderly Patients with a Renal Transplant

Survival of patients who receive a kidney transplant is higher compared to those on a waiting list (for a kidney transplant) [38]. Interest is now centered on long-term results and on HRQoL. Recently, the most important complications and side effects of drugs in renal transplant recipients have changed, as can be seen in Table 27.3. Thus, appearance of acute rejection has fallen from over 40% to 10–20% and has been accompanied by better long-term patient and graft survival [39]. However, the 10% rate of adverse gastrointestinal complications in 1996 has now risen to 40% or higher, and such complications

Table 27.3 Changes in the Immunosuppressive therapy, in the Frequencies of Acute Rejection, and Their Side Effects for Renal Transplant Patients in the Last Decade.

Year	1996	2004
Frequency of acute rejection	≥40%	10–20%
Frequency of gastrointestinal disorders	10% (1)	40%(2)

(1) Our own cross sectional study sample of 210 kidney transplanted patients, 21 of them with gastrointestinal disorders.
(2) European Cooperative Study sample (40): 40% with adverse gastrointestinal effects: 67% of these slight, 22% moderate, and 11% serious.

are more serious [40]. Nowadays the problem with renal transplants is not so much acute rejection but the long-term outcome; i.e., patient's survival, graft survival, and HRQoL. Prolongation of patients' survival can be achieved by the reduction of cardiovascular risk factors as well as by the reduction of the incidence of infections; prolongation of graft survival can be achieved by the reduction of chronic graft rejection; and HRQoL can be improved through, among other actions, a reduction in the adverse effects of the many drugs administered and to patients' improved information prior to transplantation regarding possible complications, thus avoiding exaggerated, or unrealistic, expectations, which assists the patients when faced with such complications.

Many studies now have demonstrated the improvement in HRQoL after transplantation [41–43], even among elderly patients [44, 45]. Today it is generally accepted that the HRQoL of successfully transplanted patients is superior to that of patients on hemodialysis or peritoneal dialysis. In 1997, Dew et al. [43] analyzed 66 studies on the HRQoL of 6726 patients with renal transplants. Most of the studies reported a statistically significant improvement after transplantation with respect to the pretransplant physical, mental, and social aspects of HRQoL. In over 70% of the studies, patients perceived the mental aspects of their HRQoL as equal or superior to those of the healthy population, and almost 100% of their overall HRQoL was considered equal or superior.

Problems with the Available Data and their Interpretation

The majority of the studies and their findings should be approached with caution, because only a small proportion of them corrected their findings for various variables such as age, gender, co-morbidity, and negative selection that usually characterize patients on dialysis and lead to poorer HRQoL among them, compared to transplanted patients.

For this reason, as mentioned previously, HRQoL results should be standardized (corrected) for age and gender, within the constraints that this is only possible when the HRQoL questionnaire used has normal population score (i.e., scores from the general population). With the application of this standardization, however, it has been observed that transplanted patients still had a better HRQoL than those on dialysis [44]. For instance, in 2002, after comparing transplanted patients according to age, the "European best practice guidelines for renal transplantation" [46] affirmed that since renal transplantation may extend the duration and improve the quality of life in elderly

patients with end-stage kidney disease, transplantation should be considered for all patients, particularly if pretransplantation education programs are implemented among those considered for transplantation.

However, there are authors who, not using standardized SF-36 Health Survey scores, find that in renal transplant recipients, greater age is associated with a greater deterioration in the physical component of the score [47]. Similarly, Baiardi et al. [48] concluded that age and diabetes were inversely associated with the physical domains of HRQoL. Furthermore, a recent study found that age before transplant had no effect on HRQoL, but after transplantation patients 30 to 49 years old reported a better HRQoL than others [49]. Another study that compared patients over 65 years of age with younger ones found that the general benefit of transplantation is similar in both age groups, but the benefit in mental health is greater in the older group [50]. They analyzed, with the SF-36 questionnaire, both medical and psychosocial variables in a group of kidney transplant patients older than 65 years old and compared them with a younger group. They found that total benefit was similar in both groups, with general physical health being slightly greater than that in the normal population for both groups and that the benefits in mental health were more pronounced in the elderly group.

Other factors may also be involved. Thus, Siegel and his colleagues [51], using the Life Satisfaction Index, a tool specifically developed for the "Transplant Learning Center" program (the objective of which is to improve the education of and support for solid organ repcipients who have received one form or another of cyclosporin), found that among 3676 patients the mean satisfaction scores of patients aged more than 64 years—along with those of female, or those married, or with higher levels of education and income—were better than those of patients under 64 years, males, or those unmarried, or with lower levels of education and income. On the other hand, satisfaction was lower among those who had greater medical co-morbidity, those who reported more adverse effects due to the immunosuppressive medication, and those who did not take the medication correctly. It was interesting to observe how the patients' perception of health problems differed from that of their physician: The presence of hypertension and hypercholesterolemia did not affect the patients much, in contrast to articular and ocular problems, diabetes, and, especially, emotional and psychological problems, which occurred in only 14% of the sample.

Possible Effects of Age *per se*

We have reported earlier, with another questionnaire (the SF-36 Health Survey), similar findings of a lower loss of HRQoL in elderly transplanted patients compared to younger ones. We carried out a cross-sectional study [52], evaluating the HRQoL of 210 kidney transplant recipients u] sing two generic tools: the Spanish version of the Sickness Impact Profile and the SF-36 Health Survey. Factors independently associated with HRQoL were gender, education level, time on dialysis, time with the transplant, hospital admissions during the past year, co-morbidity, and functional state measured on the Karnofsky scale. We also made other interesting observations: When scores were standardized with respect to that of the general population, they showed that loss of HRQoL was minimal (some scores were even superior)

in transplanted patients over the age of 65 in comparison with those of the same age in the general population. The loss of HRQoL experienced by younger transplant patients was greater when compared with the HRQoL of healthy younger people in the general population. This finding, which, in essence, demonstrates an improved adaptation of the elderly patients to transplantation, when compared with the younger ones, was confirmed in another cross-sectional study designed specifically for this purpose [37]. In effect, we found that when standardized scores were used (that is, comparing patient scores with those of the age- and gender-matched persons), elderly kidney transplant patients had a better HRQoL than younger ones, and even a better HRQoL than that of the general age- and gender-matched population. Recently, we have conducted a prospective study of patients followed up for three years, with the aim of studying the variation in HRQoL according to age, and we confirmed the previous finding, that is, elderly transplant patients (compared to the general population of the same age and gender) had a better HRQoL than that of younger ones [53].

Recently Rosenberger et al. [54] found that age is the greatest predictor of the physical component (PCS) of SF-36, contributing 23.3% of this physical component, but only 4.4% of the mental component (MCS). Between age groups, differences were found in the HRQoL predictors, with serum creatinine being the most important for patients under 45 years of age and the number of hospital admissions being the most important for patients 45 years and older. These authors concluded that it is important to evaluate HRQoL by groups of age, since HRQoL predictors vary with age [54]. In the same line of research, and evaluating the variables associated with different aspects of HRQoL in patients receiving transplants from live as well as deceased donors, another study found that concern for the viability and functioning of the transplant predicted 15.1% of the variance in the Mental Component Summary score (MCS) of the SF-36, while age, income, co-morbidities, and time on dialysis explain 37.8% of the variance in the Physical Component Summary score (PCS) of the SF-36 in patients receiving transplants from live as well as cadaver donors. This study concluded that patients who receive transplants from live or cadaver donors might present differences in emotional response but not in HRQoL [55].

From all these studies, one can conclude that the physical component of the SF-36 score diminishes with age, but that just as this occurs in the population of renal patients, so it occurs in the general population, which means that a score comparison that does not take this into account cannot conclude that the benefit of transplant to HRQoL is lower in the elderly group compared to young patients. Furthermore, study of the mental component of the SF-36 shows an improved adaptation to the illness with age, which is perhaps logical, given the fact that, in younger patients, illness has a greater impact on HRQoL, in view of their higher expectations for their lives.

It has also been observed that certain renal transplant patients have developed emotional problems, associated with poor compliance with medication and negative impact on HRQoL. Using multivariate analysis, Baines et al. [56] demonstrated that age, gender, employment status, length on dialysis, etiology of the renal disease, and psychotherapy received before transplantation did not affect the results [56]. Similarly, Griva et al. [57] did not find an association between depression and age. Examining the prevalence

of sleep disorders among kidney transplant patients and HRQoL, Eryilmaz et al. [58] found that patients with most problems were the younger ones, those with a lower educational level, and those who were more depressed.

Effects of Immunosuppressive Drugs

In the majority of patients, the adverse effects of immunosuppression appear to have a negative impact on morbidity, mortality, and HRQoL. Changes in physical appearance, mood, and vitality have a direct negative effect on patients' well-being. Rosenberg et al. [59] explored the side effects of immunosuppressive drugs and sought to identify the patients most affected and the factors involved. They found that age, social support, mode of dialysis before transplant, time elapsed from transplant, and type of immunosuppression received did not affect the total score for stress induced by adverse effects.

Regarding immunosuppression and HRQoL according to age, an epidemiological study carried out in France attempted to estimate the HRQoL of renal transplant patients of over 74 years [60]. Using Karnofsky's scale, the study showed that this was between 80 and 100 in 78.4% of the patients. Mean age was 76 years with a mean post-transplantation time of 9.9 years. Renal function was good and HRQoL appeared excellent**.** However, Moloney et al. [61], evaluating the impact of skin disorders due to immunosuppression on HRQoL, found that this was most diminished among younger patients**.**

Cost-Benefit Analysis

Few data in this area have a bearing on transplantation in older subjects. In a decision analysis model to evaluate the costs and benefits of a kidney transplant versus continued dialysis for elderly patients with ESRD, Jassal et al. [62] used as reference a theoretical cohort of patients 65 years old, without co-morbidities or transplant contraindications, and who had been waiting for 2 years. Assuming 2 years on the waiting list, transplantation remained economically attractive for patients of 70 years but was less economically attractive for those aged 75 years. These authors concluded that transplantation, if available within a reasonable period of time, offers considerable clinical benefits for elderly patients at a reasonable economic cost. Prolonging the time these patients spend on the waiting list drastically reduces the attractiveness of the clinical and economic benefits of the transplant, suggesting that live, related transplantation may be a solution for this population.

In conclusion, in the majority of elderly patients on whom a kidney transplant can be performed, there is an improvement in the HRQoL.

Conclusions

Many conditions, especially in old people, are incurable and chronic and in which the conservation or restoration of quality of life represents an important therapeutic objective. The evaluation of health-related quality of life (HRQoL) has continued to interest doctors, especially those dealing directly with the chronically ill, within the framework of a movement in medicine that attempts to return the prominence of the patient in the course of his

illness. Aging worsens HRQoL in the general population, but while decline in physical functioning is evident, mental health scores show little change. This pattern suggests that a process of psychological adjustment occurs with advancing age.

Dialysis Patients

Two populations of elderly patients on dialysis exist: those who are well-adapted and satisfied with their way of life, with an unexpectedly high degree of satisfaction in some cases, and, in contrast, those who undergo a rapid physical and emotional deterioration, often asking for dialysis withdrawal, and who may have to abandon dialysis to hasten an early death.

Cognitive impairment and depressive mood are often overlooked and underestimated in this population. Regular assessments of depressive mood, cognitive ability, and quality of life are recommended. Unplanned dialysis severely impairs HRQoL, especially in old people.

Transplanted Patients

The incidence of chronic renal failure rises dramatically with age, but paradoxically, while older age is no longer considered a contraindication to dialysis, there has been no corresponding increase in the number of renal transplants performed in patients over the age of 65.

It is generally accepted that the HRQoL of successfully transplanted patients is superior to that of patients on either hemodialysis or peritoneal dialysis. The loss of HRQoL of patients on RRT (dialysis and renal transplant) aged 65 and over seems to be lower than in younger patients.

The physical component of HRQoL diminishes with age, but just as this occurs in the population of renal patients, so it occurs in the general population, which means that a score comparison that does not take this into account cannot conclude that the benefit of transplant to HRQoL is lower in the elderly group compared to younger patients. Furthermore, study of the mental component of HRQoL shows an improved adaptation to the illness with age.

References

1. Testa, M. Assessment of quality of life outcomes. *N. Engl. J. Med.* 1996; 334: 835–840.
2. World Health Organisation. Quality of Life Assessment. An annotated bibliography. Geneva: WHO (MNH/PSF/94.1). 1994.
3. Orley, J., Kuiken, W. *Quality of Life Assessment: International Perspectives*. Berlin: Springer-Verlag. 1994.
4. Guyatt, G.H., Feeny, D.H., Patrick, D.L. Measuring health-related quality of life. *Ann. Intern. Med.* 1993; 118:622–629.
5. Ware, J.E., Brook, R.H., Davies-Avery, A. Choosing measures of health status for individuals in general populations. *Am. Public Health* 1981; 71:620–625.
6. Patrick, D.L. Prologue. In *La Medida de la Salud. Guía de Escalas de Medición en Español* [in Spanish], X. Badía, M. Salamero, and J. Alonso, eds. Barcelona: Edimac. 2002.
7. Bungay, K.M., Ware, J.E. Medición y control de la calidad de vida relacionada con la salud [in Spanish]. Conceptos Actuales. Kalamazoo, MI: Upjohn Company. 1996.

8. Fernández-López, J.A., Hernández-Mejía, R., Siegris, J. Quality of life profile for the chronically ill (PECVEC): A method to evaluate well-being and functioning in clinical practice. *Aten. Primaria* 2001; 28:680–689.
9. Fitzpatrick, R., Fletcher, A., Gore, S., et al. Quality of life measures in health care. I: Applications and issues in assessment. *Br. Med. J*. 1992; 305:1074–1077.
10. Fletcher, A., Gore, S., Jones, D., et al. Quality of life measures in health care. II: Design, analysis, and interpretation. *Br. Med. J*. 1992; 305:1145–1148.
11. Spiegelhalter, D.J., Gore, S.M., Fitzpatrick, R., et al. Quality of life measures in health care. III: Resource allocation. *Br. Med. J*. 1992; 305:1205–1209.
12. Bergner, M., Bobbit, R.A., Pollard, W.E., et al. The Sickness Impact Profile: Validation of the health status measure. *Med. Care* 1976; 14:57–67.
13. Bergner, M., Bobbit, R.A., Carter, W.B., et al. The Sickness Impact Profile: Development and final revision of a health status measure. *Med. Care* 1981; 19:787–805.
14. Hunt, S.M., McKenna, S.P., McEwan, J., et al. The Nottingham Health Profile: Subjective health status and medical consultations. *Soc. Sci. Med*. 1981; 15: 221–229.
15. Euroqol Group. Euroqol, a new facility for the measurement of Health Related Quality of Life. *Health Policy* 1990; 16:199–208.
16. Landgraf, J.M., Nelson, E.C. Summary of the WONCA/COOP International Health Assessment Field Trial. The Dartmouth COOP Primary Care Network. *Aust. Fam. Phys*. 1992; 21:255–257, 260–262, 266–269.
17. Ware, J.E., Sherbourne, C.D. The MOS 36-item Short-Form Health Survey (SF-36): Conceptual framework and item selection. *Med. Care* 1992; 30:473–483.
18. Laupacis, A., Pus, N., Muirhead, N., Wong, C., et al. Disease-specific questionnaire for patients with a renal transplant. *Nephron* 1993; 64:226–231.
19. Franke, G.H., Reimer, J., Kohnle, M., et al. Quality of life in end-stage renal disease patients after successful kidney transplantation: Development of the ESRD symptom checklist—Transplantation module. *Nephron* 1999; 83:31–39.
20. Hricik, D.E., Halbert, R.J., Barr, M.L., et al. Life satisfaction in renal transplant recipients: Preliminary results from the Transplant Learning Center. *Am. J. Kidney Dis*. 2001; 38:580–587.
21. Laupacis, A., Muirhead, N., Keown, P., et al. A disease-specific questionnaire for assessing quality of life in patients on hemodialysis. *Nephron* 1992; 60:302–306.
22. Hays, R.D., Kallich, J.D., Mapes, D.L., et al. Development of the kidney disease quality of life (KDQOL) instrument. *Qual. Life Res*. 1994; 3:329–338.
23. Carr, A.J., Gibson, B., Robinson, P.G. Is quality of life determined by expectations or experience? *Br. Med. J*. 2001; 322:1240–1243.
24. Alonso, J., Regidor, E., Barrio, G., et al. Valores poblacionales de Referencia de la versión española del Cuestionario de Salud SF-36 [in Spanish]. *Med. Clin. Barcelona* 1998; 111:410–416.
25. Singer, M.A., Hopman, W.M., MacKenzie, T.A. Physical functioning and mental health in patients with chronic medical conditions. *Qual. of Life Res*. 1999; 8: 687–691.
26. Jager, K.J., van Dijk, P.C., Dekker, F.W., et al. The epidemic of aging in renal replacement therapy: An update on elderly patients and their outcomes. *Clin. Nephrol*. 2003; 60:352–360.
27. Ortega, F. Survival and HRQoL in elderly patients with end-stage renal disease on renal replacement therapy. Doctoral thesis. Universidad de Oviedo. June 1997.
28. Kafkia, T., De Vos, J.Y., Elseviers, M., et al. Transplant practice in Europe: Selection of patients. *EDTNA ERCA J*. 2006; 32:33–37.
29. Horina, J.H., Holzer, H., Reisinger, E.C., et al. Elderly patients and chronic hemodialysis. *Lancet* 1992; 339:183.
30. Antoine, V., Souid, M., Andre, C., et al. Symptoms and quality of life of hemodialysis patients aged 75 and over. *Nephrologie* 2004; 25:89–96.

31. Antoine, V., Edy, T., Souid, M., et al. Concerning aging, the beginning of dialysis, the beginning of dependence: Repercussions on the psychopathology of the very old dialysis patient. *Nephrologie* 2004; 25:83–88.
32. Tyrrell, J., Paturel, L., Cadec, B., et al. Older patients undergoing dialysis treatment: Cognitive functioning, depressive mood and health-related quality of life. *Aging Ment. Health* 2005; 9:374–379.
33. Loos, C., Briancon, S., Frimat, L., et al. Effect of end-stage renal disease on the quality of life of older patients. *J. Am. Geriatr. Soc*. 2003; 51:229–233.
34. Ortega, T., Ortega, F., Diaz-Corte, C., et al. The timely construction of arteriovenous fistulae: A key to reducing morbidity and mortality and to improving cost management. *Nephrol. Dial. Transplant* 2005; 20:598–603.
35. Ronsberg, F., Isles, C., Simpson, K., et al. Renal replacement therapy in the over-80s. *Age and Ageing* 2005; 34:148–152.
36. Lamping, D.L., Constantinovici, N., Roderick, P., et al. Clinical outcomes, quality of life, and costs in the North Thames Dialysis Study of elderly people on dialysis: A prospective cohort study. *Lancet* 2000; 356:1543–1550.
37. Rebollo, P., Ortega, F., Baltar, J.M., et al. Is the loss of health-related quality of life during renal replacement therapy lower in elderly patients than in younger patients? *Nephrol. Dial. Transplant* 2001; 16:1675–1680.
38. Wolfe, R.A., Ashby, V.B., Milford, E.L., et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N. Engl. J. Med*. 1999 Dec. 2; 341:1725–1730.
39. Ojo, A.O., Meier-Kriesche, H.U., Hanson, J.A., et al. Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. *Transplantation* 2000; 69:2405–2409.
40. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; 345:1321–1325.
41. Laupacis, A., Keown, P., Pus, N., et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int*. 1996; 50:235–242.
42. Evans, R.W., Manninen, D.R., Garrison, L.P., et al. The quality of life of patients with end-stage renal disease. *N. Engl. J. Med*. 1985; 312:553–559.
43. Dew, M.A., Switzer, G.E., Goycoolea, J.M., et al. Does transplantation produce quality of life benefits? *Transplantation* 1997; 64:1261–1273.
44. Rebollo, P., Ortega, F., Baltar, J.M., et al. Health related quality of life (HRQoL) in end-stage renal disease (ESRD) patients over 65 years. *Geriatr. Nephrol. Urol*. 1998; 8:85–94.
45. Hathaway, D., Winsett, R.P., Johnson, C., et al. Post kidney transplant quality of life prediction models. *Clin. Transplant*. 1998; 12:168–174.
46. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.12. Elderly (specific problems). *Nephrol. Dial. Transplant* 2002; 17:58–60.
47. Chiu, S.F., Wong, H.S., Morad, Z., Loo, L.H. Quality of life in cadaver and living-related renal transplant recipients in Kuala Lumpur hospital. *Transplant. Proc*. 2004; 36:2030–2031.
48. Baiardi, F., Degli Esposti, E., Cocchi, R., Fabbri, A., Sturani, A., Valpiani, G., Fusarol, M. Effects of clinical and individual variables on quality of life in chronic renal failure patients. *J. Nephrol.* 2002; 15:61–67.
49. Cetingok, M., Winsett, R.P., Hathaway, D.K. A comparative study of quality of life among the age groups of kidney transplant recipients. *Prog. Transplant*. 2004; 14:33–38.
50. Humar, A., Denny, R., Matas, A.J., Najarian, J.S. Graft and quality of life outcomes in older recipients of a kidney transplant. *Exp. Clin. Transplant*. 2003; 1:69–72.

51. Siegal, B., Halbert, R.J., McGuire, M.J. Life satisfaction among kidney transplant recipients: Demographic and biological factors. *Prog. Transplant*. 2002; 12: 293–298.
52. Rebollo, P., Bobes, J., González, M.P., Saiz, P., Ortega, F. Factors associated with health related quality of life in patients undergoing renal replacement therapy. *Nefrología* 2000; 20:171–181.
53. García-Mendoza, M., Valdés, C., Ortega, T., Rebollo, P., Ortega, F. Differences in health related quality of life between elderly and younger patients on haemodialysis. *J. Nephrol*. (in publication).
54. Rosenberger, J., van Dijk, J.P., Nagyova, I., Roland, R., Geckova, A.M., van den Heuvel, W.J., Groothoff, J.W. Do dialysis- and transplantation-related medical factors affect perceived health status? *Nephrol. Dial. Transplant* 2005; 20:2153–2158.
55. Akman, B., Ozdemir, F.N., Sezer, S., Micozkadioglu, H., Haberal, M. Depression levels before and after renal transplantation. *Transplant Proc*. 2004; 36:111–113.
56. Baines, L.S., Joseph, J.T., Jindal, R.M. Prospective randomized study of individual and group psychotherapy versus controls in recipients of renal transplants. *Kidney Int*. 2004; 65:1937–1942.
57. Griva, K., Ziegelmann, J.P., Thompson, D., Jayasena, D., Davenport, A., Harrison, M., Newman, S.P. Quality of life and emotional responses in cadaver and living related renal transplant recipients. *Nephrol. Dial. Transplant* 2002; 17:2204–2211.
58. Eryilmaz, M.M., Ozdemir, C., Yurtman, F., Cilli, A., Karaman, T. Quality of sleep and quality of life in renal transplantation patients. *Transplant Proc*. 2005; 37:2072–2076.
59. Rosenberger, J., Geckova, A.M., Dijk, J.P., Roland, R., Heuvel, W.J., Groothof, F.J.W. Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients. *Clin. Transplant*. 2005; 19:70–76.
60. Buchler, M., Halimi, J.M., Najjar, A.A., Giral, M., Hiesse, C., Giraudeau, B., Jacquelinet, C., Nivet, H., Lebranchu, Y. Living with a functioning kidney transplant at 74 years or older: A national epidemiological study. *Clin. Transplant*. 2004; 18:681–685.
61. Moloney, F.J., Keane, S., O'Kelly, P., Conlon, P.J., Murphy, G.M. The impact of skin disease following renal transplantation on quality of life. *Br. J. Dermatol*. 2005; 153:574–578.
62. Jassal, S.V., Krahn, M.D., Naglie, G., Zaltzman, J.S., Roscoe, J.M., Cole, E.H., Redelmeier, D.A. Kidney transplantation in the elderly: A decision analysis. *J. Am. Soc. Nephrol*. 2003; 14:187–196.

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Ethical Dilemmas in Geriatric Uremia Therapy

Eli A. Friedman and Amy L. Friedman

Introduction

The objectives of this chapter are to introduce and explore representative ethical problems generated by modern renal replacement therapy:

1. Review the historical origin of medical ethics with specific reference to nephrology.
2. Recognize the complex stresses surrounding assignment of a deceased donor renal transplant to a geriatric patient while young patients continue to wait for a donor kidney.
3. Appreciate the concept of futility and support for a geriatric patient's opting for death rather than further uremia therapy as the best in choice in coping with renal failure.

Birth of Nephrology and Recognition of Need for an Ethics Base in Medicine

At an organizational meeting of what was to become the International Congress (Society) of Nephrology in 1960, held at Eaux d'Evian, a resort on Lake Geneva, the Congress convened 20 invited clinicians and scientists who presented papers on renal tubular micropuncture, urine acidification, natuiretic factors, the mesangial cell discovered with the electron microscope, an inventory of glomerular lesions, Balkan nephritis, and initial outcome reports of chronic dialysis and kidney transplantation. Attendees concluded that there was need for a new specialty to be called nephrology. At that time, however, no recognition of the impact of ethics on the choices confronting kidney doctors was evident in any aspect of the program.

The United States lagged behind Europe in agreeing to establish the discipline of nephrology. Thus, 1966's Third International Congress of Nephrology meeting in Washington, DC, had to be sponsored by the Renal Section of the American Heart Association. Not until 1967 did the American Society of Nephrology conduct its initial meeting in Los Angeles. But, those involved in the practice of nephrology found themselves increasingly involved in devising means of treating a growing population of uremic patients seeking treatment. Of

the body's vital organ systems, only renal function can be replaced over the long term by either a bionic device or a solid organ transplant. Morning report on our newly established academic nephrology service in 1963 became a debate over the ethical correlates of making life-and-death decisions as to which patients would receive kidney transplantation, maintenance hemodialysis, or peritoneal dialysis. Although an ethical code binding physician conduct did not begin with Kolff's invention of a practical artificial kidney, the burden of fair allocation of life-saving treatment with this new device forced adoption of a transparent standard for nephrologists' life-or-death decisions [1]. This chapter reviews the genesis of nephrology's core beliefs and lists many recurrent problems that try the souls of both neophyte and experienced kidney doctors. Special emphasis on ethical questions generated by geriatric patients with kidney disease is the consequence of two realities: (1) While there were 33 million Americans aged 65 years or older in 2003, by the year 2030 this number is expected to increase to 70 million [2]. (2) More than 1 million Americans over the age of 65 years currently have advanced kidney disease, and provision for their expensive care has been incomplete and without an overall plan. Elderly patients often suffer extrarenal co-morbidity, forcing the question of whether or not to commence costly regimens such as maintenance dialysis or renal transplantation [3].

Medical Ethics Originates in China

Initial historical reference to any need for medical ethics probably occurred in China during the Zhou Dynasty when fees paid to physicians were contingent upon the degree of patient benefit attained [4]. Concepts that how doctors should treat patients was modulated by patient attitudes were proposed in seven Chinese schools of medicine between 770 and 221 B.C.E. Bian Que [5], a popular doctor of the era, proposed that medicine should withheld from individuals who

1. Expressed unreasonable arrogance and indulgence
2. Appreciated wealth more than life
3. Were unable to keep body and soul together
4. Suffered from an interlocking Yin and Yang
5. Were too weak to take prescribed medicines
6. Favored sorcery over medicine.

Early Indian culture also contributed extensively to the development of medical ethics. Among ancient surviving documents are the Caraka Samhita (approximately 500 B.C.E.) and Susruta Samhita (approximately 300 A.D.). Both allude to earlier works dating to 2000 B.C.E. and the foundation of a system of natural healing. Ayurveda Caraka Samhita expounded:

> He who practices medicine out of compassion for all creatures rather than for gain or for gratification of the senses surpasses all. No benefactor, moral or material, compares to the physician who by severing the noose of death in the form of fierce diseases, brings back to life those being dragged towards death's abode, because there is no other gift greater than the gift of life. He who practices medicine while holding compassion for all creatures as the highest religion is a man who has fulfilled his mission. He obtains supreme happiness. [6]

Constraints on physician behavior probably were initially recorded by Hippocrates, a Greek physician of about 400 B.C.E. [7]. His credo for

neophyte physicians, repeated to this day as many medical students graduate, as "The Hippocratic Oath," proclaims: "I will follow that system of regimes which, according to my ability and judgment, consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous." Conflicting interpretations of this oath are evident as physicians defend their decisions on treatment, exclaiming: "I have an ethical obligation never to cause the death of a patient," antiposed by the rejoinder that: "My ethical obligation is to relieve pain even if the patient dies."

Appreciating that physicians' behavior under the stresses and temptations of practice was imprecisely defined by the Oath Hippocrates [8], its structured "rules" required physicians to

1. Honor their medical instructors and their offspring.
2. Teach medicine only to those bound by the Oath.
3. Practice medicine for the benefit of patients. Do no harm.
4. Prescribe neither deadly medicine nor substance to produce abortion.
5. Abstain from mischief and corruption.
6. Maintain doctor-patient confidentiality.

In China, starting with the Han Dynasty (206 B.C.E.–24 A.D.), Confucianism emphasized patient care and benevolence (loving people), believing that the purpose of medicine was to save lives, an ultimate expression of love [9]. Zhong Zhang Jin (author of *Shang Han Lun*, the earliest systematic herbal text) stipulated that Confucians could love people provided that they grasped medical theories attentively [10]. Diagnoses must be rigorous and painstaking to avoid doing harm. Benevolence demanded a duty to respect patients as an ultimate expression of humanity. Demanding money or sex for care was proscribed. Furthermore, no patient's treatment was to be influenced on the basis of status, wealth, appearance, age, race, or mental ability. Amplifying Confucianism, Tianchen Li, a Ming Dynasty (1368 A.D.–1644 A.D.) physician, suggested. "We should treat patients as our mothers" [11].

Confucius believed everyone had a conscience, an inborn sense of right and wrong, that in physicians leads to the doctor's four senses:

1. Pity: Compassion and love for the patient.
2. Shame: The doctor would feel shame if he ever
   a. put his interests ahead of his patient
   b. diagnosed without all four physical examination methods
   c. abused medicines or
   d. deceived a patient.
3. Respect.
4. Right and wrong: Do not damage the patient's interests. Confucian physicians practiced self-cultivation through self-examination, self-criticism, and self-restriction. Confucius proposed that instead of trying to set up a universal code of behavioral guidelines, each person should subject himself to self-examination [12].

The Concept of Benevolence

From Hippocrates on, all guides to the ethical practice of medicine included a veneration of human life, today termed "benevolence." Mencius observed, "In medicine, benevolence means causing no harm to patients" [13]. We

can trace modern concerns about the ethical treatment of "patients" to the Nuremberg Military Tribunal, which followed the sadistic unscientific "research" performed under Nazi Germany during World War II. The tribunal findings were codified as the Nuremberg Code in 1947 [14]. Subsequent international efforts to define ethical conduct in medical investigation and practice at a conference in Geneva (1948) [15], followed by the initial Declaration of Helsinki (1964) of the World Medical Association, were subsequently revised and updated several times [16].

Medical Ethics in Research: The Belmont Report

Perhaps the single most important resource governing both the practice of medicine and the conduct of research involving human subjects is The Belmont Report (1979) [17, 18], which established

1. Boundaries between practice and research
2. Basic ethical principles
   a. Respect for persons
   b. Beneficence
   c. Justice
3. Applications
   a. Informed consent
   b. Assessment of risk and benefits
   c. Selection of subjects

Scribner's Seattle Success Introduces Rationing and Ethical Change

Medical discovery and research may instantaneously change "proper" medical practice. To illustrate, consider the impact of Scribner's 1960 report that convincingly documented the reality that irreversible renal failure, a prevalent cause of death, was a treatable disorder. *Life* magazine and other national news sources enthusiastically reported the success of "chronic dialysis." Lacking equipment, trained staff, and any funding, the renal community suddenly confronted a population seeking treatment for family members in the throes of uremia. A year of twice-weekly maintenance hemodialysis, as originally designed by Scribner's Seattle team, required more than $10,000 not including doctors' fees (about $250,000 in 2006 dollars). Obviously, demand dwarfed the capacity of Scribner's small hospital acute dialysis unit.

Forced by inadequate resources to turn away a growing number of patients, the Seattle team established an anonymous panel of volunteer community members acting as a "Who Shall Live Committee." Struggling with the enervating chore of screening applicants to select those most "deserving" of life-sustaining treatment, the Committee set criteria including an age range of 18 to 45 years [19]. When a 16-year-old high school student whose renal failure was caused by lupus nephritis rejected her exclusion (meaning certain death), a small and portable dialysis system termed the "minimonster" was designed by Dr. Albert "Les" Babb, the Seattle team's chief engineer within 4 months, permitting the first "home dialysis" in July 1964. His accomplishment

was listed as one of the "Ten Wonders of Biomedical Engineering" by the Biomedical Engineering Society in 1990. Dr. Babb subsequently was elected to the National Academy of Engineering, the National Academy of Sciences, and the Institute of Medicine. A decision in medical ethics became a defining moment in nephrology.

Questions generated by the need for fair allotment of insufficient life-saving resources forced nephrologists, hospital administrators, academic deans, and legislators to deal with a new kind of triage. Coping with dialysis rationing (and other high-cost regimens) ultimately sparked a change in thinking about accessibility of health care in the United States [20] that demarked the beginning of modern bioethics [21]. As aptly stated by Alber Jonsen, professor of biomedical history and ethics at the University of Washington, it was the "Committee" that forced open "a new era for the ethics of medicine," as the healthcare profession faced "an issue that the traditional ethics of medicine had not previously faced and for which it had no ready response" [22].

In a remarkable saga that included live performance of hemodialysis as a demonstration for the House of Representatives Ways and Means Committee, dialysis treatment for renal failure became a national legislative priority [23]. To its great credit, the U.S. Congress, in 1972, amended the Social Security Act disability requirement to permit reimbursement for long-term dialysis [24]. A further amendment in 1978 and related state legislation increased Medicare deductibles as well as co-payments to allow for home hemodialysis supplies. By these actions, Americans affirmed the principle that healthcare services should not be an exclusive right of the rich and privileged, of the white-collar worker, the breadwinner, or any other selected "profile" [25]. Reflecting on the national impact of his introduction of dialysis, Scribner remarked: "When the U.S. Congress enacted legislation in 1972 which made all patients with end-stage kidney disease eligible for Medicare, they set a precedent that led to Medicare funding of many of the very expensive technology-based treatments such as coronary bypass open heart surgery, and bone marrow transplantation." The ethical basis for universal dialysis in kidney failure became the foundation for "fair" organ allocation in kidney transplantation [26] and other forms of modern high-technology medicine. But does access to the donor kidney pool apply if the patient is very old, a non-citizen, or HIV-positive?

Ethical Concerns over Patient Adherence

A vexing recurrent problem in provision of ESRD services focuses on the extent of obligation to continue care (dialysis) to a nonadherent, hostile, and even combative patient [27]. Rarely, but importantly, a confrontational patient may threaten the viability of an ESRD program, demanding resolution by resort to the courts. A landmark case unfolded in Jackson, Mississippi, when, on December 21, 1987, in Civil Action No. 086–079 (B), in U.S. District Court, Southern District of Mississippi, Judge William H. Barbour ruled that Dr. John Bower, Director of Nephrology at the University Medical Center, had to continue dialysis of Michael Brown, who had a 10-year record of misconduct and staff abuse. Brown overtly injected narcotic drugs, missed dialysis treatments, and proffered verbal abuse to Dialysis Unit staff. A short time later, Brown died in a motor vehicle accident after a police chase at

100 miles per hour. Further details as to why Bower was unable to transfer Brown and the subsequent stress involved in retaining the patient are depicted in Bower's "Rest of the Story" [28] recounting of a senior nephrologist's unsuccessful dealing with a Court unable to help a renal program's plea for relief from a vindictive and hurtful patient.

There is no clear evidence that geriatric ESRD patients are more likely to be nonadherent to their regimen than are adults of younger age. The opposite may be true though no report lists rates of nonadherence by age cohorts. Although elderly ESRD patients gain added lifetime on dialysis that is satisfying and, as a group, show better psychosocial adjustment to dialysis than do younger patients, limitations in physical functioning characteristic of chronic dialysis patients such as arthritis and peripheral motor neuropathy increase with patient age [29].

Factors purportedly associated with poor adherence by geriatric ESRD patients include confusing "too" frequent drug dosing, inadequate patient's perception of treatment benefits, poor patient-physician communication, lack of motivation, poor socioeconomic background, and lack of family and social support [30]. Strategies advocated to improve regimen compliance lack scientific validation in dialysis and transplant patients, including simplifying the treatment regimen, establishing a partnership with the patient, and increasing awareness through education and feedback.

Recurrent Ethical Issues in Provision of Uremia Therapy

Table 28.1 lists recurrent ethical issues arising in the daily practice of proffering care for geriatric uremic patients. While each has been the subject of protracted discourse explored in depth in a Case Manual [31], two issues, the marketing of live donor kidneys and following a patient's wish to terminate dialysis, will be explored in depth as illustrative examples of the complexity of conjoined legal-ethical stresses to demonstrate the extent of controversy and the absence of a single truth. As will be evident upon conclusion of the essay, application of medical ethics is far removed from evidence-based science. Reaching and acting upon an "answer" may engender annoyance at best and outrage at worst. Nevertheless, there may be no escape from the reality that an ethical dilemma is presented by an active patient management problem demanding resolution beyond its passive recognition.

Illustrative Case 1: A Kidney Transplant for a Recipient of Advanced Age?

An 83-year-old married accountant, sustained by maintenance hemodialysis for 6 years, is a six-antigen "perfect match" for a deceased donor kidney shipped from Memphis, Tennessee, to Brooklyn at 2:00 on a Sunday morning. Still active as a fiscal consultant, and with no known extrarenal complications of his polycystic kidney disease, the accountant has been fully adherent to instructions and medications and is an independent, functional person, actively volunteering in the patient support group. A secondary potential recipient is a 23-year-old medical student who has been on dialysis for 3 months and is an incomplete three-antigen match for the available donor. The transplant coordinator insists that it is unethical to "waste" the kidney on an

Table 28.1 Ethical Stresses in Nephrology.

Patient selection for/exclusion from long-term renal replacement therapy	
a.	How old is too old for renal replacement therapy?
b.	Should young people be selected before old people for kidney therapy?
c.	Should "important" people (Politicians [President], Clergy [Pope], Affluent [Billionaire contributor to hospital]) be placed ahead of ordinary people in allotting renal replacement therapy?
d.	Are multiple deceased organ transplants ethical while a waitlist exists[i]
e.	Must non-citizens be treated when therapy is scarce or expensive?
f.	Are women to be assigned treatment on an equal basis as are men?
g.	Is it reasonable to take race and religion into account when determining who shall be treated?
h.	Is HIV infection a reasonable exclusion criterion?
i.	Does absent insurance coverage and being poor mean denial of therapy?
j.	Should prisoners be excluded from renal replacement therapy?
Who decides not to start life-sustaining dialysis in ESRD?	
a.	Patient
b.	Family
c.	Futility
d.	Financial
How should the medical staff cope with patient noncompliance,[ii] hostility, or criminality?	
a.	Withdraw renal replacement therapy with death an obvious consequence
b.	Consultation (psychiatry, social service, administration family, clergy, friends)
c.	Role of Ethics Committee
Is it okay to instill co-modification (buying and selling) of kidney transplants[iii]?	
a.	Payment to deceased donor families
b.	Concealed payment to donor
c.	Open marketing of kidneys legally
d.	Open marketing of kidneys concealed

i Piccoli, G.B., Soragna, G., Putaggio, S., Burdese, M., Longo, P., Rinaldi, D., Bergamo, D., Mezza, E., Consiglio, V., Novaresio, C., Gai, M., Motta, D., Malfi, B., Giacchino, F., Jeantet, A., Segoloni, G.P. How many organs should one patient receive? The ethics of transplantation in the medical school. *Transplant. Proc*. 2004; 36:444–445.

ii Williams, M.E., Kitsen, J. The involuntarily discharged dialysis patient: Conflict (of interest) with providers. *Adv. Chron. Kidney Dis*. 2005; 12:107–112.

iii Piccoli, G.B., Putaggio, S., Soragna, G., Mezza, E., Burdese, M., Bergamo, D., Longo, P., Rinaldi, D., Bermond, F., Gai, M., Motta, D., Novaresio, C., Jeantet, A., Segoloni, G.P. Kidney vending: Opinions of the medical school students on this controversial issue. *Transplant. Proc*. 2004; 36:446–447.

old person when society would benefit from facilitating the medical career of the student. The student's wife previously advised his nephrologist that she is concerned over a growing sense of depression and futility threatening continued attendance at medical school.

Because the mean wait for a deceased donor kidney in New York City exceeds 9 years, individuals seeking a kidney transplant face greater mortality on dialysis compared with that of a transplant recipient. It follows that denying a dialysis patient a donor kidney, in fact, is a form of a death sentence (for the duration of shortened survival on dialysis). Defense of the "too old" for a deceased donor kidney position requires that an upper age limit that is not "too old" be established [32]. If not 84 years, then 74 years? Or 64? What if a choice has to be made between a "young" 74-year-old and an "old" 64-year-old? Question upon question is provoked by almost any method of organ allocation. One recurrent issue raised by geriatric patients, who

appreciate their ephemeral existence, and are able to afford the cost, is whether a purchased kidney might be transplanted to truncate their death-defying delay while "suspended" on dialysis.

Selling Kidneys: Legal and Ethical Conundrum

It is broadly understood that continued growth of the ESRD population, with only a marginal increase in the number of deceased donor kidneys, has progressive lengthened the waiting time for a deceased donor transplant. As estimated by the U.S. Department of Health & Human Services: In early February 2006, as this was written, 65,000 candidates were listed in the United States by the Organ Procurement and Transplant Network as waiting for a deceased donor kidney (http://www.optn.org/latestData/rptData.asp) [33]: "17 people die each day waiting for transplants that can't take place because of the shortage of donated organs." One estimate calculates that an undefined but definite cohort of at least 3000 of those on the waitlist who will die each year might have survived had a suitable donor kidney been available [34]. Geriatric ESRD patients are especially vulnerable for protracted waits because of what many legislators and transplant teams view as the rational priority of giving a scarce commodity (solid organ transplants) to those who may attain the longest benefit (younger patients). Strategies to expand the donor pool—public relations campaigns and drivers' license designation—have not altered a relatively static rate of deceased organ donor consents.

Despite intensive public relations efforts including celebrity endorsements, National Kidney Foundation efforts, and state drivers' license advance permission, the number of deceased donor kidney transplants performed in the United States has been relatively static over the past decade. Thus, as listed by the United Network for Organ Sharing [35], while kidney transplants performed between 1988 (8,873) and 2004 (16,004) increased by 80.3%, deceased organ transplants in the same interval increased only 32.5% (from 7,061 to 9,357). To address this shortage of donor kidneys, acceptance of what previously have been termed "marginal" kidneys termed "expanded criteria donors" from geriatric [36], hypertensive, and even proteinuric donors has increased progressively [37].

Additionally, the potential questionable resource of purchasing kidneys from compensated donors, a highly controversial and evocative issue, has gradually evolved from an unmentionable practice performed secretly in developing (poor) countries to an openly debated topic in national societies such as the American Society of Nephrology and the American Transplantation Society. Clearly illegal in most nations, and viewed as unethical by professional medical organizations, the voluntary sale of purchased donor kidneys now accounts for thousands of black market transplants, accounting for an estimated one-quarter of all kidney transplants performed globally. Legalizing kidney purchase hinges on the key premise that individuals are entitled to control of their body parts even to the point of inducing risk of life.

Selling a human organ in the United States has been proscribed for over 20 years. As starkly stated in the National Organ Transplant Act (NOTA): "It shall be unlawful for any person to knowingly acquire, receive, or otherwise

transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce" [38]. Punishment for violation would be effected by fines up to $50,000 and/or 5 years in prison, but has never, to these authors' knowledge, been meted out. A year after the enactment of NOTA, the Ethics Committee of the Transplantation Society issued a supporting Policy Statement: "No transplant surgeon/team shall be involved directly or indirectly in the buying or selling of organs/tissues or in any transplant activity aimed at commercial gain to himself/herself or an associated hospital or institute" [39]. Within the next 5 years, several countries and the World Health Organization issued similar bans of organ marketing [40].

Broadly condemned by medical associations around the globe, the sale of human organs constitutes transactions deemed "morally and ethically irresponsible" or "inhumane and unacceptable." A key spokesperson, Berkeley anthropology professor Nancy Scheper-Hughes, who has studied actual conditions and consequences of kidney sales in Brazil and other countries, states that permitting legal solid organ sales would permit "one relatively privileged population [to] claim property rights over the bodies of the disadvantaged" [41].

International spokespersons for human ethics, at the highest level, have strongly condemned the practice of selling organs as unethical. The late Pope John Paul II wrote that buying and selling organs violates "the dignity of the human person" [42]. Similarly, American transplantation associations repeatedly endorsed the stance that paying donors for their organs was not only illegal but unethical. Furthermore, the American Society of Transplant Surgeons (ASTS) expounded the position that solicitation for organ donation is inappropriate, even absent the exchange of "valuable consideration": The ASTS is strongly opposed to the solicitation of organs (deceased) or organ donors (live) by recipients or their agents, whether this is through personal or commercial Websites, billboards, media outlets, or other forms of advertising when the intent of such solicitation is to redirect the donation to a specific individual rather than according to the fair policies of allocation (UNOS policy on organ allocation) by which all members on the waiting list abide [43].

Are there measures short of kidney selling that might alleviate the shortage of kidney donors? At one extreme, Congress has been urged to conduct a trial to assess the value of compensating deceased donor's families as well as to test some form of payment to live kidney donors. Testifying against this proposal at a Congressional hearing for consideration of permitting organ sales, Francis L. Delmonico, director of renal transplantation at Massachusetts General Hospital, speaking on behalf of the National Kidney Foundation, remarked:

> Congressional endorsement of a payment for organs … could propel other countries to sanction an unethical and unjust standard of immense proportions, one in which the wealthy readily obtain organs from the poor, justified by the citation of congressional sanction. In that reality, the poor person will remain poor but lose health and maybe more than one organ in the process of a government authorized abuse of the poor for the rich." [44]

At the other extreme of an increasingly polarized debate, some transplant surgeons now advocate the regulated sale of kidneys as a means of preventing the death of as many as 100,000 people annually. For example, at the most

recent American Transplantation Congress, Arthur Matas, of the University of Minnesota transplant team, remarked that nationwide waiting time for a deceased donor kidney transplant has risen to over 5 years, inducing death on the waiting list of 7%, underscoring the need for establishment of a regulated system of living kidney sales [45]. Containing regulatory and insurance incentives to safeguard the potential exploitation and ethical concerns raised by Dr. Scheper-Hughes, Matas proposed careful donor medical and psychosocial evaluations with a fixed tax-free payment to the donor plus an option of short- or long-term health and life insurance. Comparing the sale of a kidney to the now-legal uterine rental by surrogate mothers to advance medical technologies, Matas pointed out that there currently are individuals who benefit others without losing their dignity or becoming victims. Paid organ donors need not be victims who have not lost their right to determine what happens to their body.

In 2007, it is pertinent to review what was learned from the wild and extensive racketeering spawned by America's 1920s' "Prohibition" of alcoholic beverages. A key point is that legislation, *per se*, may not force human behavior compliance [46]. Thus, while the sale of human organs is against existing law in nearly every country, illegal kidney transplants are widely available through devious and often unsavory vendors in India, Turkey, China, Russia, and South Africa, as described in *The New York Times* [47]. Organs Watch, a nongovernment transplant monitoring organization, estimates that "… thousands of illegal transplants occur every year bought by patients from the Persian Gulf states, Japan, Italy, Israel, the U.S. and Canada supplied by 'donor' nations, including India, Pakistan, Turkey, Peru, Mexico, Romania and South Africa" [48]. Sustaining this allegation, the late Michael Friedlander, formerly a transplant nephrologist at Hadassah University Hospital in Israel, remarked: "What's happening now is absurd. Airplanes are leaving every week. I've seen 300 of my patients go abroad and come back with new kidneys … it's a free-for-all" [49]. Friedlander characterized today's kidney market as forcing potential kidney purchasers to be "exposed to unscrupulous treatment by uncontrolled free enterprise."

Responding to the unregulated and often tumultuous reality of under-the-counter marketed kidneys, voices favoring kidney sales are becoming more evident. For example, at sharp variance with the Catholic position stated above by the Pope, a surprisingly positive endorsement for the legalization of human organ sales was provided by Robert Berman of the Orthodox Jewish Halachic (*interpreted by orthodox rabbis*) Organ Donor Society, writing in the Jerusalem Post of August 9, 2005: "The choice before us in not between buying or not buying organs. This is happening regardless of the law. The choice is whether transplant operations and the sale of organs will be regulated or not" [50].

Distinguished scholars with active university appointments have spoken in favor of marketing kidneys. For example, Nobel Laureate (Economics) Gary S. Becker and his colleague Julio J. Elias constructed a fascinating analysis of the variables to be considered in establishing a "market price" for a live donor kidney if viewed as a commodity [51]. A sample calculation would assume that an American earning a mean of $40,000 annually has a life valued at $3 million, faces a risk of death from nephrectomy of 1% and a decrease of 5% in quality of life, and will lose $7,000 of income due to convalescence from

surgery; these investigators calculated a fair kidney purchase price of $45,000. Using a more probable death risk of 1 in 300 nephrectomies (the true reported risk is 3 in 10,000 [52]) reduces the kidney price to $20,000. Our present "non-system" promotes kidney purchase on a black market available only to wealthier individuals bearing the total expense for what may be inadequately screened, suboptimally matched organs inserted by unregulated (inferior?) surgeons. Regulating donor kidney purchase, according to Becker and Elias, would end the black market while eliminating advantages of wealth in organ acquisition since poorer individuals unable to afford the black market would bypass the wait by obtaining their kidneys via Medicaid or Medicare.

Both rich and poor are allowed to make lifestyle decisions and engage in risky behaviors (e.g., sky diving, volunteering for military service, working on oil rigs, and smoking cigarettes) (Table 28.2). Lacking wealth does not preempt making a rational decision. Prohibiting the poor from donating organs leaves them still poor; consequently, according to Matas, withholding the ability to be paid for donation eliminates one path to improve a person's financial situation. Why is it so ethically wrong? And how is it different, or any worse than selling one's sperm or egg cells, actions now legal and widely advertised in newspapers and magazines? In one context, commercialization of semen and ova is more morally questionable than organ sale because those cells, like stem cells, have the potential to create entirely new human beings, while an organ does not.

In his "Advice to the Ethics Committee of the Transplantation Society," A.S. Daar, director of the Program in Applied Ethics and Biotechnology at the University of Toronto, writes:

Table 28.2 Everyday Examples of Individual Jurisdiction and Authority over One's Body.

1. Consenting for federal (National Institutes of Health) studies that impart personal risk:
   a. biopsies of liver, kidney, muscle
   b. invasive procedures, bronchoscopy, cystoscopy
   c. participation in new drug trials
2. Engaging in behavior risking serious injury:
   a. working on oil rigs
   b. sky diving
   c. bungee jumping
   d. mountain climbing
   e. swimming with sharks
   f. Pamplona "Running of the Bulls"
   g. professional boxing and football
   h. ingesting high-calorie diet when obese
   i. cigarette smoking
   j. motorcycle riding without a helmet
3. Renting or selling body parts:
   a. selling semen
   b. selling ova
   c. surrogate uterus rental
   d. whole body rental (prostitution)
4. Enrolling in voluntary military service
5. Donating organs and portions of organs (pancreas, liver, lung) to relatives
6. Donating organs and portions of organs (pancreas, liver, lung) to friends

Table 28.3 Potential Positive Aspects of Legalizing Live Donor Kidney Sale.

1. Decreased deaths of ESRD patients on dialysis waiting list[iv]
2. Increased number of rehabilitated patients with irreversible kidney failure
3. Salvage of patients treated by dialysis who would otherwise die
4. Reduced acceptance of marginal donors in absence of medically suitable donor
5. Improved economic status of donor
6. Enhanced feeling of altruism and goodness in donor
7. Decreased cost of ESRD therapy for transplant modality

iv Gill, J.S., Tonelli, M., Johnson, N., Kiberd, B., Landsberg, D., Pereira, B.J. The impact of waiting time and comorbid conditions on the survival benefit of kidney transplantation. *Kidney Int*. 2005; 68:2345–2351.

The position of the Transplantation Society is that the buying and selling of organs is wrong, that we must base transplantation on altruism, that we must encourage legislation to ban commerce, and that any member of the Transplantation Society who participates in the buying and selling of organs will be expelled from the society. Adopting this position on its own has been totally useless in stopping the increase of the buying and selling of organs. [53]

The positive consequence of organ donation (Table 28.3) as well as the main objections to legalizing the marketing of donor kidneys (Table 28.4) have been thoroughly analyzed. It is time for innovative thinking and fresh approaches. Trong recently thoughtfully reviewed the ethics of accepting living donor organs [54].

Why Legalize the Marketing of Kidneys?

Introducing appropriate legalization to regulate and manage kidney sales through a national regulatory body would be a "natural" extension of the present end-stage renal disease (ESRD) network collaborating with UNOS and the OPTN. Eliminating black market brokers would divert funds to kidney sellers. Also, money saved from decreasing the number of prevalent dialysis patients might conceivably generate the total funding for additional kidney transplants. Recognition of the extent of limitations in current laws coupled with acknowledgment of the global sale of human kidneys would begin the

Table 28.4 Objections to Legalizing Live Donor Kidney Sale.

1. Permits inherently unethical medical practice
2. Exploitation of poor by relatively wealthy
3. Small but definite risk of death or complications in otherwise healthy individuals[v]
4. Against religious teaching (Catholic, Muslim)
5. May shorten life expectancy while inducing hypertension
6. Demeaning self-worth
7. Kidneydonors in India gained neither economic nor social benefit long-term[vi]

v Friedman, A.L., Peters, T.G., Jones, K.W., Boulware, L.E., Ratner, L.E. Fatal and nonfatal hemorrhagic complications of living kidney donation. *Ann. Surg*. 2006 Jan; 243:126–130.

vi Goyal, M., Mehta, R.L., Schneiderman, L.J., Sehgal, A.R. Economic and health consequences of selling a kidney in India. *JAMA* 2002 Oct 2; 288(13):1589–1593.

lifting of predictable mortality for thousands of dialysis patients haplessly entrapped on a waitlist extending to 10 years in some regions.

A fascinating though only partially described donor kidney allocation plan, adopted by Iran in 1998, permits a compensated and regulated living-unrelated donor renal transplant program [55]. According to the authors, by providing financial incentives to volunteer living donors, Iran is now the only developed nation that has eliminated a renal transplant waiting list. Regulations prevent "transplant tourism," meaning that foreigners are not allowed to undergo renal transplantation from Iranian living unrelated donors nor are they permitted to volunteer as kidney donors for Iranian patients. Of 17,718 renal transplants performed through the end of 2004, 3,196 were from living related donors, 13,920 were from living unrelated donors, and 602 were from deceased donors. By means of the Iran Plan, more than 50% of persons with ESRD now have a functioning kidney transplant. Much more will have to be detailed about the actual operation of the Iran Plan before advocating its extension to other nations, though the purported positive aspects are impressive.

Reservations that adoption of a federal organ marketing scheme necessitates further "socialization" of our healthcare system are reasonable. Insertion of yet another federal agency to "supervise" presently overregulated nephrologists and transplant surgeons is a less-than-attractive proposition. But the mandate underlying this essay is consideration of endorsement of a strategy for resolution of a problem that has grown into a serious conundrum. At the least, debating the controlled initiation and study of potential regimens that may increase donor kidney supply in the future in a scientifically and ethically responsible manner is better than doing nothing more productive than complaining about the current system's failure.

Illustrative Case 2: Withdrawal from Dialytic Therapy

A 91-year-old blind, diabetic, widowed housekeeper, unable to walk or care for herself because of a series of increasingly severe strokes, has been sustained by maintenance hemodialysis for 9 years. Progressive deafness—now profound—prevents the patient's use of talking books, a telephone, or a volume-enhanced radio. Distressed over worsening urinary and bowel incontinence that force the wearing of diapers, the patient requests that dialysis treatments be discontinued. Still lucid and oriented to time and place, the patient states that her decision is the result of months of thought and a discussion with her minister. The patient's son, a practicing attorney and only living relative, rejects the concept of withdrawing dialytic therapy until "the final spark of life is gone." He threatens court action against the renal team and the hospital should any action toward stopping dialysis be taken. Following an urgent meeting of the Hospital Ethics Committee, the hospital director orders the attending nephrologist to continue dialysis indefinitely.

Generalization about refusal of long-term dialysis therapy for ESRD is limited by differences in cultural attitudes. In Japan, for instance, "Refusal of dialysis is not uncommon in elderly patients with chronic renal failure" [56]. ESRD treatment rates that are half that of the United States in Europe, the United Kingdom, and Canada most probably result from medical and ethical standards pertaining to futility and life extension that sharply diverge from those obtained in the United States. Discussions with nephrology trainees

permitted formulation of a list of key issues that were generated by study of this case, including

1. Who determines the application of a life-sustaining therapy (patient, family, physician)?
2. Does a patient have the *right* to refuse a life-sustaining therapy?
3. Can a family override a patient's wish regarding life-sustaining therapy?
4. When family conflict is brought to a hospital administrator's attention, does the resolution shift from patient and physician to the administrator?

Legal Analysis

Based on consultation with medically oriented attorneys, and review of the concept of "Advanced Directives," it is reasonable to assert that a competent patient's decision to discontinue life-saving medical treatment (including dialysis) must be honored, despite objections from a responsible relative. The reverse would be true when all of the following apply: (1) A patient is *not* competent to make the decision to discontinue life-saving medical treatment; (2) there is insufficient evidence that she made such a decision when competent; (3) her son is her surrogate or legal representative; and (4) the son's decision to continue medical treatment is determined to be the substituted judgment of, or in the best interests of, the patient. These conditions are not met by the circumstances of this case.

Assuming the patient was competent when deciding to discontinue dialysis treatments, the hospital director risks liability by ordering continuation of dialysis. In a case that reached the U.S. Supreme Court, a competent, nonterminally ill person was found under the Due Process Clause of the 14th Amendment to have the right to refuse unwanted medical treatment—even if death will result [57]. Justice O'Connor wrote that there is a protected liberty interest in refusing unwanted medical treatment, including artificially delivered food and water. A federal appeals court stated that "a liberty interest in refusing medical treatment extends to all types of medical treatment, from *dialysis* or artificial respiration to the provision of food and water by tube or other artificial means" [58]. Subsequently, supreme courts in several states concluded that their state constitutional right of privacy encompasses the right to refuse life-saving medical treatment.

Other states have statutes providing that physicians need not accede to a patient's request to withdraw or withhold treatment if it would be against their beliefs to do so, but must try to or successfully transfer the patient to another healthcare provider willing to comply with the request. Whether a competent patient's decision to discontinue dialysis treatments must be honored was addressed by a New York State Court [59] decision that a dialysis patient who verbally and in a signed statement wished to discontinue dialysis treatments had made an informed, rational, knowing decision to forego the treatments.. After the patient lapsed into uremic coma, the court denied the hospital's petition to continue dialysis treatments.

Juggling and balancing state and individual interests in a dialysis context, Iowa determined that the state's interest in preserving life corresponds directly to the degree to which the patient's quality of life has diminished due to physical deterioration [60]. Noting that continued dialysis would permit the

patient to have "an otherwise normal and healthy life for perhaps twenty years," the court concluded that the state's interest in preserving life "weighs heavily in the balance." Because the patient had minor children, the court found that the state's interest in protecting innocent third parties from the impact of the patient's death was invoked, outweighing the patient's interest in discontinuing dialysis treatments.

Applying this balancing test to the hypothetical situation in Case 2, the hospital director would have a legal obligation to honor the patient's decision to discontinue dialysis treatments unless the state's interests outweighed that decision. It does not appear likely that the patient is terminally ill triggering the state interest in preserving life. Further, lacking the need to protect "innocent third parties" such as dependent children, the patient's competent decision to discontinue dialysis treatments would likely override any state interest in continuing the treatments.

Determining whether a patient is competent can be difficult. Patients who are senile, unconscious, traumatized, disoriented, excessively emotional, or minors may all be held incompetent. The general test for competency is the factual question of whether, "at the time and under the circumstances when his consent is required, the patient has the mental ability to make a rational, deliberate decision regarding the proposed treatment." Should a hospital director have uncertainty about a patient's competence, he must protect the hospital and himself legally by continuing dialysis treatments until a court can address the issue. Incompetent patients retain their right to make decisions about their care, but that right generally must be exercised on their behalf by their surrogate, usually a member of the patient's family. Even if the son is the patient's surrogate decision maker, that does not necessarily mean that the hospital director is legally required (or permitted) to follow his instruction to continue dialysis treatments. From the legal perspective, given that the patient was competent when she made the decision to discontinue dialysis treatments, the hospital director was legally obligated to honor that decision despite the son's objection and threat of a lawsuit.

Ethical Analysis

The hospital director has an ethical obligation to honor the patient's decision to stop dialysis treatments and thereby end her life. However, he also has an ethical obligation to make sure that discontinuation is the patient's own, sincere, fully informed, conclusive decision and that the son fully understands that decision.

Patients with decisional capacity have the moral right to either consent to or refuse any treatment intervention offered to them, even if as a consequence of such refusal their death may result. Such decision-making empowerment is based on the philosophic principle of autonomy and the legal principle of individual self-determination. What is critical in this case is the recognition that despite her increasingly debilitated condition, the patient continues to possess decision-making capacity to exercise such right of refusal, and her decision to discontinue treatment appears to be a well-considered, authentic reflection of her wishes. Since the patient still has decisional capacity, the son has neither the legal authority to insist on treatment continuance nor any

standing on which to sue the hospital and attending physician. Dialysis should be discontinued in accord with the choice of this capable patient.

Before authorizing discontinuation of the patient's dialysis treatments, the director should talk to the patient. He should find out if there are any additional reasons why she has decided to discontinue treatments. He should be certain that she understands the ramifications of her decision and has all the information necessary to make it. He should also make sure that she has reached her decision of her own accord, rather than being coerced by anyone else. For instance, the patient says she reached her decision after "months of thought and discussion with her minister." The director should confirm that the patient has adopted any advice she received as her own decision, not out of a sense of obligation to do whatever her minister says. He should also confirm that the patient's decision is sincere and carefully thought out—not something she blurted out in a moment of high emotion, but didn't really mean.

The director also should consider how the patient's decision is affecting her son. He should try to identify and clear up any misunderstandings or lack of information that may be causing the son to reject his mother's decision to discontinue treatments. He should probe the reason underlying the son's wish to have his mother's treatments continued. Perhaps the son simply does not want his mother to die. Or, maybe he fears guilt should he not do everything possible to keep his mother alive. Or, maybe the son mistrusts the director and nephrologist and thinks they are trying to get rid of his mother because of reimbursement problems. To facilitate better understanding between the patient and the son, the director should encourage discussion between them. All of these communications should take place as soon as possible. Every day that the patient's wish is not honored is another day she must suffer a potentially humiliating, undignified, low-quality, depressing, undesired life against her will.

Mildred (Barry) Friedman, a patient advocate reviewing this case, submitted the following:

> When the threat of legal action is more important than granting the wish of a patient, there is something wrong with our priorities. Unfortunately, the desire to allow life to end, is thought to be a result of mental incompetence. A decision to continue life, no matter how painful, embarrassing, or without pleasure that life is, is accepted as coming from a healthy mind. If the decision is to allow natural events to end life, mental ability and stability are questioned. Ceasing dialysis is not *pure suicide.* It is, rather, recognition of the inevitable end to life. Dialysis is not without pain, discomfort, and the expenditure of much energy. Consider only the effort of an outpatient to arrive at a dialysis unit.
>
> This woman is being pushed by her circumstances into what many people dread, an aware mind trapped in an incompetent body. She seems to regard her "quality of life" as negative. Her life belongs to her and just as we accepted her right to make many decisions (marriage, bearing children), so must we accept her right to make this decision.
>
> Wishes of a son or any other relative must be listened to but not allowed to override. If the mother was not competent, then the son's decisions would take control. We each are in charge of one life, our own. Recognition of this is inherent in the endorsement of Living Wills. The hospital director is wrong. Hospitals and physicians have been sued before. Hospitals must be patient friendly places not overly concerned with their perceived own well being.

Summary and Key Take-Home Points

Nephrology has increasingly morphed into a geriatric specialty. As reported by the U.S. Renal Data System (USRDS), the mean age of newly treated ESRD patients in the United States is 62.7 years [61]. Approximately 35.2% of prevalent ESRD patients on December 31, 2003, were 65 years or older. Yet both kidney transplantation (usually) and all forms of dialysis (frequently) are withheld from older patients, on the grounds that they are unsuitable candidates due to medical or psychological complications. Ethical concerns in excluding or including older patients can lead to vexing analyses especially when conflict between family and medical team wishes exists. When celebrities opt not to agree to dialysis, headlines usually follow, as was true for James A. Michener, the universally celebrated Pulitzer Prize–winning author, who, at the age of 90, stopped hemodialysis treatments in Austin, Texas [62]. Similarly, Australia's richest man, billionaire media "mogul" Kerry Packer, at age 68, decided not to extend his life by dialysis after a failed kidney transplant [63]. Packer's cardiologist said that Packer "knew he was on borrowed time. He could have opted for more dialysis, but he chose to go quickly and with dignity." By contrast, death in renal failure untreated by dialysis or a kidney transplant is the typical ESRD outcome for geriatric patients older than 65 outside the United States. Yet, substantive life prolongation in ESRD patients of advanced age is attainable with transplant recipients evincing best outcome. Of the USRDS cohort of incident ESRD patients from 1994 to 2000, aged 75 or older, 1-year survival on dialysis was 62.6% compared with 81.7% after a deceased donor transplant. After 5 years, 40.3% of deceased donor kidney grafts and 12.4% on dialysis were alive, connoting the substantive advantage of selecting the transplant option for uremia therapy. For the subset aged 70 to 70 years when given a deceased donor kidney, 34% were alive with a functional kidney graft 10 years later.

Nevertheless, bias against providing uremia therapy for the aged persists in nephrology practice in the United States. Illustrating this assertion, for ESRD patients age 80 or older, as reported by the USRDS, although survival permitted by a deceased donor allograft is astoundingly good, of 71,000 incident patients of age 80+ between 1994 and 2000, only 66 (1 in 1000) were waitlisted for a kidney transplant [60]. Overcoming negativism toward the elderly ESRD patient's prospects whether treated by dialysis or a transplant is a challenge, especially in developing nations with limited budgets for health care. There are no simple answers to devising a fair method of treatment allocation when the reality is that resources are insufficient to treat all who might benefit.

Lastly, the profound issue of whether marketing body parts including solid organs is an ethical option for physician, patient, and government is unlikely to yield to a simple answer. Recalling failed efforts to control other aspects of human behavior by legislation such as prostitution and consumption of alcohol, a mixture of wisdom and broad education will be needed to construct an equitable system to regulate who, under which circumstances, is able to donate a kidney to whom. Some grasp of the pressure driving the marketing of kidneys can be obtained by asking any group of medical personnel familiar with present uremia therapy whether the purchase of a kidney for a close

relative would be pursued in the absence of a familial donor. In the authors' experience, the response is uniformly positive.

References

1. Friedman, E.A. Kolff's contributions provoked the birth of ethics in nephrology. *Artif. Organs* 1998; 13:46–51.
2. Coresh, J., Astor, B.C., Greene, T., Eknoyan, G., Levey, A.S. Prevalence of chronic kidney disease and decreased kidney function in the adult U.S. population. Third National Health and Nutrition Examination Survey. *Am. J. Kidney Dis*. 2003; 41:1–12.
3. Hansberry, M.R., Whittier, W.L., Drause, W. The elderly patient with chronic kidney disease. *Adv. Chronic Kidney Dis*. 2005; 12:71–77.
4. Li, Benfu. *Medical Ethics*. Beijing: Peking Union Medical College and Beijing Medical University Press. 1996; pp. 41–42.
5. Li, Bocong. *On Bianque and the School of Bianque*. Xian: Shanxi Science and Technology Press. 1990.
6. Mukhopadhyaya, G. *History of Indian Medicine* (Three volumes: Containing Notices; Biographical and Bibliographical; Of the Ayurvedic Physicians and Their Works on Medicine—From the Earliest Ages to the Present Time). 2003. Munshiram Manoharlal Publishers Pvt. Ltd. ISBN 8121506603.
7. Chadwick, J., Mann, W.N. *Hippocratic Writings*. London: Penguin Books Ltd. 1950.
8. Miles, S.H. *The Hippocratic Oath and the Ethics of Medicine*. Oxford: Oxford University Press. 2003.
9. Sun, S. *Essential Prescriptions Worth a Thousand Gold in Hua Fan's History of Late Han Dynasty: Records of Craft*s. Beijing: People's Health Press. 1982; p. 476.
10. Zhou, Y., ed. *Famous Physicians' Addresses on Medical Ethics*. Changsha: Hunan Science and Technology Press. 1983; p. 212.
11. Liang, S. *Essence of Chinese Culture*. Shanghai: Xuelin Press. 1987; p. 69.
12. Zhang and Cheng. *Medicine Is a Human Art: The Basic Principles of Professional Ethics in Chinese Medicine*. Beijing: Medical History Research Center, Beijing Medical University.
13. Wu, J.S. Mencius. In *Great Thinkers of the Eastern World*, I.P. McGreal, ed. New York: HarperCollins. 1995.
14. Nuremberg Code [from Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10]. Nuremberg, October 1946–April 1949. Washington, DC: U.S.G.P.O. 1949–1953.
15. Declaration of Geneva. Adopted by the General Assembly of World Medical Association at Geneva, Switzerland, September 1948.
16. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.
17. The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical Principles and Guidelines for Research Involving Human Subjects. April 18, 1979.
18. Lemaire, F. Patient care versus research: Does clinical research provide individual benefit to patients enrolled in trials? *Curr. Opin. Crit. Care* 2004; 10:565–569.
19. Darrah, J.B. Moment in history. The Committee. *ASAIO Trans*. 1987; 33:791–793.

20. Childress, J. Who shall live when not all can live. *Soundings* 1970; 53: 339–355. Reprinted: *Intervention and Reflection: Basic Issues in Medical Ethics*, R. Munson, ed., Belmont, CA:Wadsworth Publishing Company. 1983; pp. 497–505.
21. Blagg, C.R The early years of chronic dialysis: The Seattle contribution. *Am. J. Nephrol*. 1999; 19:350–354.
22. Jonsen, A.R. *The New Medicine and the Old Ethics*. Cambridge: Harvard University Press. 1990.
23. Rettig, R.A., Levinsky, N.G., eds. *Kidney Failure and the Federal Government*. Committee for the Study of the End-Stage Renal Disease Program. Division of Health Care Services. Institute of Medicine. Washington, DC: National Academy Press. 1991.
24. Section 2991 of the Social Security Act Amendments (Publ. No. 92–603, October 30, 1972).
25. Jonsen, A.R. The Birth of Bioethics. Special Supplement, Hastings Center Report, 1993; 23(6):S1.
26. Friedman, E.A., Najarian, J., Starzl, T., Schreiner, G.E., Bonomini, V., Cameron, S., Gurland, H., Giordano, C., Migone, L., Lesavre, P.. Ethical aspects in renal transplantation. Discussions on ethics in transplantation. *Kidney Int*. 1983; 23 (S14):S90–93.
27. Kutner, N.G. Improving compliance in dialysis patients: Does anything work? *Sem. Dial*. 2001; 14:324–327.
28. Bower, J. Brown versus Bower. In *The Rest of the Story in Legal and Ethical Issues in Treating Kidney Failur* e. Case Study Manual. E.A. Friedman, ed. Dordrecht: Kluwer. 2000.
29. Loghman-Adham, M. Medication noncompliance in patients with chronic disease issues in dialysis and transplantation. *Am*, *J*, *Mgd. Care* 2003; 9:155–171.
30. Koveh, K., Kimmel, P.L Compliance in hemodialysis patients: Multidimensional measures in search of a gold standard. *Am. J. Kidney Dis*. 2001; 37:244–266.
31. Friedman, E.A., ed. *Legal and Ethical Issues in Treating Kidney Failure. Case Study Manual*. Dordrecht: Kluwer. 2000.
32. Oniscu, G.C., Brown, H., Forsythe, J.L. How old is old for transplantation? *Am. J. Transplant* 2004; 4:2067–2074.
33. Organ Procurement and Transplant Network. Website (www.optn.org), September 17, 2005. P.O. Box 2484, Richmond, VA 23218.
34. http://www.organdonor.gov, August 28, 2005, U.S. Department of Health & Human Services. 200 Independence Avenue, S.W. Washington, DC 20201.
35. United Network for Organ Sharing (UNOS) Website (www.unos.org), September 17, 2005.
36. Remuzzi, G., Cravedi, P., Perna, A., et al. Long-term outcomes of renal transplantation from older donors. *N. Engl. J. Med*. 2006; 354:343–352.
37. Baskin-Bey, E.S., Kremers, W., Stegall, M.D., Nyberg, S.L. United Network for Organ Sharing's expanded criteria donors: Is stratification useful? *Clin. Transplant*. 2005; 19:406–412.
38. National Organ Transplant Act Public Law 98–507. October 19, 1984.
39. Council of The Transplantation Society. Commercialization in transplantation: The problems and some guidelines for practice. *Lancet* 1985; 2:715, and *Transplantation* 1986; 41:1.
40. World Health Organization. Guiding principles on human organ transplantation. *Lancet* 1991; 337:1470.
41. Scheper-Hughes, N. Living kidney donation: Controversies and realities. Organs without borders: Open markets, closed systems and the global search for living donors. Program and abstracts of the American Transplant Congress 2005: 6th Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation; May 21–25, 2005, Seattle.

42. Pope John Paul II Evangelium Vitae. Encyclical Letter on the Value and Inviolability of Human Life. March 25, 1995.
43. American Society of Transplant Surgeons. Statement on Solicitation of Donor Organs, January 20, 2005. http://www.asts.org/donorsolicitation.cfm.
44. Delmonico, F.L. The House Committee on Energy and Commerce, Assessing Initiatives to Increase Organ Donations. Subcommittee on Oversight and Investigations, June 3, 2003.
45. Matas, A. Living kidney donation: Vontroversies and realities. The case for a regulated system of living kidney sales. Program and abstracts of the American Transplant Congress 2005: 6th Annual Joint Meeting of the American Society of Transplant Surgeons and the American Society of Transplantation; May 21–25, 2005, Seattle.
46. Behr, E. *Prohibition: Thirteen Years That Changed America*. New York: Arcade Publishing. 1996.
47. Finkel, M. This little kidney went to market. *New York Times Magazine*, May 27, 2001; p. 28.
48. Scheper-Hughes, N. A grisly global trade: A taboo tumbles: The market for "fresh" human organs is expanding worldwide, with the poor providing for the rich. *Los Angeles Times*, August 3, 2003.
49. Rifkin, J. *The Biotech Century: Harnessing the Gene and Remaking the World*. New York: Jeremy P. Tarcher/Putnam. 1998.
50. Berman, R. Selling organs should be legal. *Jerusalem Post*, August 9, 2005.
51. Becker, G.S., Elias, J.J. Introducing Incentives in the Market for Live and Cadaveric Organ Donations. Conference on Organ Transplantation: Economic, Ethical and Policy Issues, University of Chicago, May 16, 2003.
52. Matas, A.J., Bartlett, S.T., Leichtman, A.B., Delmonico, F.L. Morbidity and mortality after living kidney donation, 1999–2001: Survey of United States transplant centers. *Am. J. Transplant* 2003; 3:830–834.
53. Daar, A.S. Money and organ procurement: Narratives from the real world. In *Ethical, Legal and Social Issues in Organ Transplantation*, T. Gutmann, A. Daar, R.A. Sells, and W. Land, eds. Munich: Pabst Publishers. 2004.
54. Trong, R.D. The ethics of organ donation by living donors. *N. Engl. J. Med.* 2005; 353:444–446.
55. Ghods, A.J., Nasrollahzadeh, D. Transplant tourism and the Iranian model of renal transplantation program: Ethical considerations. *Exp. Clin. Transplant*. 2005; 3:351–354.
56. Fujimaki, H., Kasuya, Y., Kawaguchi, S., Hara, S., Koga, S., Takahashi, T., Mizuno, S. [Refusal of initiation of dialysis by elderly patients with chronic renal failure.] [in Japanese] *Nippon Ronen Igakkai Zasshi* 2005; 42:417–422.
57. *Cruzan v. Director, Missouri Department of Health* ("Cruzan"), 497 U.S. 261, 264 (1990).
58. *Compassion in Dying v. State of Washington* ("Compassion in Dying"), 79 F.3d 790, 815 (9th Cir. 1996).
59. *Lydia Hall Hospital*, 116 Misc. 2d 477, 455 N.Y.S. 2d 706 (1982).
60. *Polk County Sheriff v. Iowa Dist. Court*, 1999 Iowa Supp. LEXIS 105, *12 (Supreme Court of Iowa, April 28, 1999).
61. U.S. Renal Data System, USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. 2005.
62. Friedman, E.A. Legal and ethical aspects of vital organ substitution. *ASAIO J*. 2000; 46:375–377.
63. Skatssoon, J., Coomber, J., Hedge, M. Kerry Packer dies peacefully at home with family. December 27, 2005. News.com.au.

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