NEPHROLLOGY AND UROLOGY IN THE AGED PATIENT

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Volume 34

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Nephrology and Urology in the Aged Patient

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Preface

The master tool of logic is the syllogism. If $A > B$ and $B > C$, then it must follow as the night the day that $A > C$. If the major and minor premises are true or scientifically correct by current knowledge, the conclusion is true or at least scientifically correct by current knowledge.

The demographer of today beams a clear message, which if not true is at least scientifically correct by current knowledge. In the first 80 years of the Twentieth Century, the 'over-65' population of Americans increased eight-fold. By century's end it will have increased 12-fold and shortly thereafter will include one in five Americans. While initially a fact of the developed world, the pace of similar graying is accelerating even more rapidly in the Second and Third Worlds. This gray delta constitutes about 35 million living Americans, who may use one-half or more of the health care resources. *A* would have to be a lot more foolish than *B* if they failed to recognize that in the coming decade the causation, case-mix, and area of the gray delta demands a change from early, mid-or even later-century medicine.

If Homer Smith was right in saying, "We are what we are because we have the kind of kidneys we have" and "The kidneys make the stuff of philosophy", then the who, what, where, when, and why the gray delta will be cared for must focus on the stuff of geriatric nephrology.

This book is timely. This book is a boundary setter. And Drs Oreopoulos, Michelis and Herschorn are true boundary-riders. This book is also a vista with a prospect of the fields where geriatric nephrology might be seen in the future. How will we manage the aged man or woman?

The very concept of an aging kidney, i.e., a 'change with time', is a semantic and conceptual trap for the nephrologist, focused as he is on the biology of one of our most adaptive and regenerative organs. The Aristotelian concept of vital force has merged with the notion of adaptation and the exhibition of growth and differentiation. In transplantation the cadaver kidney adapts to the abrupt cessation of blood and adapts to its new organism belying Pope's identification of life with blood, "the warm life came issuing through the wound". After live donation, each kidney subsumes almost the

total function of the previous pair. The sum of the two in separate bodies is greater than in the original donor. They have adapted. They have grown.

The rate of the slope of declining renal function with age (approximately 1 ml/min C cr/year) probably pertains only to the segment of the population studied with its potential later-life diseases and environmental hazards. Some cultures have a life expectancy less than one-half that of the US. It is unlikely that the slope of decline of GFR would be identical. It seems more likely that kidneys adapt to life and injury just as they do to death and transplantation. 'Aging', then, can be seen as a vector of the sum of the injuries for a person or a definable population.

This book explores the specifics of this process, especially in the section on aging, the pathophysiology of risk factors and progressive decline in renal function, the progression of parenchymal disease and whether it needs progress. In specifically designated chapters, it examines the special problems of the elderly in the ministration of transplantation, hemo and peritoneal dialysis and the immunologic changes induced by the new lipid chemotactic factor, the infections, the incontinence, the sexual dysfunction, the effect of other systematic disease such as diabetes, and the impact on ethics and other aspects of health-care delivery.

Nephrology as a spin-off of internal medicine has a well-defined, sister science – urology – a spin-off of general surgery. As in many specialties, there are actively defining 'gray' areas in their 'territoriality', affected by personality traits and the influence of training programs. On a practical plane, these are best navigated by teamwork. In the gray delta of the population, these 'gray' areas have widened and deepened. Standard surgical procedures such as lithotomy and prostatectomy, which occupied major urologic energy are declining. After all the stones have been 'tripsed' or prevented, and prostate shrunk by hormones, or microwave – who will care for the aftermath of obstruction.

Nephrology is clearly a post-World War II specialty. Initially and transitionally, geriatric nephrologists are being drawn largely from the ranks of aging adult and even pediatric nephrologists. As a solution, this cannot endure. The ranks of graying and broadly experienced nephrologists are fast declining as the elderly population is soaring.

If we are to cope with the special renal needs of the gray delta – the huge and risking wave of living and functioning elderly – this challenge requires nothing less than a serious realignment of our nephrology fellowship programs. A (the demand) $> C$ (the supply) of geriatric nephrologists. It is time to begin, time to build. This book offers just that – a template, a beginning.

"Grow old along with me – the best is yet to be!"

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Introduction

The present volume provides essential information presented at the Third International Conference on Geriatric Nephrology and Urology held in Toronto, Canada from April 3 to April 5, 1992. The editor and the contributors believe that geriatric nephrology and urology represent unique areas of medicine and surgery and that these specialties will not be practiced successfully without cooperation and mutual support. This international meeting embraced the related disciplines of transplantation medicine, nutrition, geriatric nursing, related areas of hypertension and fluid and electrolyte disorders, with input from individuals specializing in medical philosophy and medical ethics.

The Third International Conference on Geriatric Nephrology and Urology presented contributions from these related areas of geriatric care in a way that allowed those who attended to benefit from this rich variety. The present volume provides overviews of aging and changes in renal function over time, it devotes chapters to renal parenchymal disease and urinary tract infections and the sections on geriatric urology cover urinary incontinence and urinary-tract neoplasm, including prostatic cancer. It summarizes current information on renal replacement therapy in the elderly and reviews such important topics as hemodialysis, peritoneal dialysis, fluid and acid-base abnormalities as they are seen in older patients, and transplantation in the elderly.

Concerning medical care of older nephrology patients, the contributors have reviewed the management of hypertension in the elderly, current understanding of glomerular disease in older patients, current approaches to the elderly diabetic with renal disease, and use of antineoplastic and antimicrobial therapy in these special patients. They discuss the prevention of renal failure in older patients, both in diagnostic and therapeutic aspects, and examine sexual dysfunction and indications for surgery in the older patient with obstruction. Finally, the text examines such ethical issues as the use of advanced directives and the allocation of scarce resources.

For colleagues who could not attend the conference, the current volume provides an overview of the important topics discussed at the Third International Conference on Geriatric Nephrology and Urology. For those who

attended the conference, this collection will permit them to review the material and so enhance a valuable educational experience. The success of this meeting underscored the importance of the discipline of geriatric nephrology and emphasizes the value of an interdisciplinary approach to these patients. The editors of this volume hope that the reader will find the contents memorable and enlightening.

The editors wish to express their gratitude to the staff of Congress Canada, who organized the conference and to all participants, both lecturers and registrants. The enthusiasm and commitment of all concerned made this conference an outstanding success and promises to make these Proceedings a valuable resource.

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PART ONE

The aging process

CHAPTER 1

The aging process and geriatric principles

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Aging is a life-long process. Unfortunately, many persons do not think of their aging until they have diseases that otherwise may never have developed or have advanced their 'years' beyond what their genetics had predestined. Although we cannot change our gene pool, the most important factor in how well we will age, we can control other environmental factors capable of accelerating our aging process and even causing disease.

The aging process can be divided into three phases: a period of growth and development, maturation, and senescence. However, there is no clear demarcation showing where one of these periods ends and the other begins. More importantly, we age in two ways: chronologically and physiologically. While we can prove that we are of a certain age based on documents of our date of birth (chronological age), it is more difficult to quantitate physiological age – the way our bodies function.

With normal aging, physiological changes affect every cell, organ, and tissue in the body. Those processes that affect a single physiological function, such as the way a single nerve conducts an impulse, change little, if any, with increasing age and appear not to influence one's day-to-day functioning. If a disease, for example diabetes mellitus, interferes with a process, such as nerve conduction velocity, the 'curve' of normal aging will become accentuated and one's functional status will be affected earlier than if age alone were the only influencing factor. As processes become more complex and integrated, such as kidney function, change becomes more dramatic and can affect daily functioning. Renal function, for example, mandates that tubules, nephrons, and glomeruli work together. Obviously the body has a harder time keeping up with this integration because as a product of 'normal aging', renal function declines approximately 0.6% per year after maturity. This is not readily apparent because serum creatinine remains constant throughout life; it does not change because, at the same time that creatinine clearance declines, so does muscle mass. The processes most dramatically affected by increasing age are those functions that require a full integration of systems, for example, our ability to maintain our normal body temperature in a cold environment or to run in a marathon. Persons, even in their 80s and 90s,

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can run a marathon; the record is 3 hours and 45 minutes for an 80-year-old. However, with an equal amount of training, this same person will never be able to reproduce the time he/she had earlier in life or achieve world-class status. Because of normal aging, a man cannot increase his heart rate to the same degree as he ages, therefore he achieves less cardiac output. Also integration of the neuromuscular and cardiovascular systems becomes more difficult. There is an age-related reduction in vital capacity and an increase in residual volume and the lung's dead-space. The healthy aging process coupled with diseases that occur at increasing frequency with age produces an even more dramatic change. In brief, as we age, we face a decrease in physiological reserve. In fact, the aging process might be defined as a series of losses: physiological reserve; economic stability; support services; family and friends; self-esteem; etc.

A human has the maximal number of brain cells in the first trimester *in utero* and loses some of these cells every day of one's life thereafter, and suffers similar loss of cells in the heart, kidneys, and other vital organs; thus it becomes increasingly apparent that, as we age, we are becoming more frail and vulnerable. Even medical treatment may present an increasing risk, for example, hypotension and hypoglycemia, both potential side-effects of medications used to treat age-prevalent hypertension and diabetes mellitus, respectively, now may result in greater morbidity. Among other devastating problems, dementia, stroke, myocardial infarction, occur with greater frequency and are less reversible. Functional decline may make necessary assistance in simple activities of daily living such as transferring, toileting, mobility, and even feeding. For many institutionalization becomes a real threat; it is estimated that by the year 2000 as many as 5 million people will be institutionalized in the U.S. alone.

Today more people are living to an advanced age than ever before. Women still outlive men, although the increase in life-span is leveling off and, in certain parts of the world, a decline has been noted. While socioeconomic advances are responsible for the increased average life expectancy, there has been little change in the maximum life-span. As has been noted, some cave men lived to over 100 years, although the average life-expectancy was less than 35. This type of theoretical aging curve is referred to as a 'first-order chemical reaction' curve; a classic example is a bomb that explodes in a movie theater. The explosion has the same likelihood of killing someone whether they are 10 or 100 years of age. Another theoretical way that populations age is the 'rectangular' curve; under this curve, in ideal circumstances, persons in a given society live until such time that age alone determines that the systems can function no longer and death ensues. This aging curve resembles a rectangle. Clearly, no one ages in a pure form and multiple factors enter into one's longevity. While the theoretical 'rectangle' appears to be unattainable, we have as a society, become more rectangular. Changes in the ozone layer threaten the very existence of our aging society. Not only is UV light a potent accelerator of the aging process, it is also a potential

cause of increases in such diseases as skin cancer. Also UV light has been shown to affect the immune system. Pollution, carcinogens, malnutrition, etc. are other real threats to our aging and must be reckoned with if mankind is to attain the age that we were once destined to achieve.

Proper preventive health care can accomplish much. First, we need to be able to recognize normal age-related change (Table I) and to distinguish it from the various sequelae of disease. Secondly, recognizing that certain diseases occur more frequently with age (Table II), we must be able to recognize early warning signs and third, we must remember that, in the elderly, many diseases present in a non-specific and otherwise atypical manner (Table III). These guiding principles can help us provide the best care for our aging patients. We must become more proactive in regard to environmental issues if we are to help more persons to live to their full potential in a healthy and functional state. Today, approximately one-third of our remaining years after the age of 70 are spent in a dependent state in at least some area of daily care. This can be reduced if we start paying attention to our aging early enough. Life-long attention to the prevention of osteoporosis, for example, can keep bone mass sufficiently strong so that old age is not so frequently accompanied by fractures, a leading cause of morbidity and even mortality for persons over 80.

Table I. Age-related physiologic changes

System	Effect of age	Consequences
Central nervous system	– Decline in the number of neurons and the weight of the brain – Reduced short-term memory – Takes longer to learn new information – Increased speed of reaction time	– May result in problems with independent living
Spinal cord/ Peripheral nerves	– Decline in nerve conduction velocity – Diminished sensation – Decline in the number of fibers in the nerve trunks	– Slowness of 'righting' reflexes – Muscle wasting – Dimished sensory awareness – Reduced vibratory sensation
Cardio-vacular system	– Reduced cardiac output (normal?) – Valvular sclerosis of the aortic valves (common) – Reduced ability to increase the heart rate in response to exercise	– Reduced exercise tolerance
Respiratory system	– Decline in vital capacity – Reduced lung compliance – Reduced ciliary action – Increased residual volume – Increased AP chest diameter	– Diminished oxygen uptake during exercise – Reduced pulmonary ventilation on exercise – Increased risk of pulmonary infection – Reduced exercise tolerance

Table I. Continued

System	Effect of age	Consequences
Gastro-intestinal tract	– Decrease in number of taste buds – Loss of dentition – Reduced gastric acid secretion – Reduced motility of large intestine	– Reduced taste sensation – Possible difficulty in mastication – Potential cause of iron deficiency anemia – Constipation
Kidneys	– Loss of nephrons – Reduced glomular filtration rate and tubular reabsorption – Change in renal threshold	– Decreased creatinine clearance – Reduced renal reserve may lead to reduced glycosuria in the presence of diabetes mellitus
Musculo-skelletal system	– Osteoarthritis – Loss of bone density (normal?) – Diminished lean muscle mass	– Poor mobility; pain – Decreased vertical height – May predispose to fractures – Change in posture – Reduced caloric requirements – Reduced strength
Endocrine/ Metabolism	– Reduced basal metabolic rate (related to reduced muscle mass) – Reduced glucose tolerance	– Reduced caloric requirements – Must distinguish from true diabetes mellitis
Reproductive men	Delayed penile erection Infrequent orgasm Increased refractory period Decreased sperm motility and altered morphology	Diminished sexual response Decreased reproductive capacity
Reproductive women	Decreased vasocongestion Delayed vaginal lubrication Diminished orgasm Ovarian atrophy	
Skin	Loss of elastic tissue Hair loss Atrophy of sweat glands	Increased wrinkling Senile purpura Difficulty in assessing dehydration Reduced sweating
Sensory		
(a) Eye	Arcus senilis Lentricular opacity Decreased pupillary size Contraction of visual fields	– Increased risk of falls and fracture – Poor vision – Presbyopia
(e) Ears	Atrophy of external auditory meatus Atrophy of cochlear hair cells Atrophy of ossicles	Presbycusis (loss of hearing of high frequencies) Gradual loss of hearing
(c) Taste	Reduced number of taste buds Poor taste sensation	Loss of interest in food Malnutrition and weight loss
(d) Smell	Decline in the sensation of smell	Increased risk of gass poisoning; decreased apetite

Table II. Age-prevalent disease

System	Disease
Central nervous system	Dementia Depression Parkinsonism Subdural hematoma Transcient ischemic attack Trigeminal neuralgia
Eyes	Poor vision (cataract, macular degeneration)
Ears	Poor hearing
Cardiovascular system	Hypertension Ischemic heart disease Arrhythmia Cardiac failure Peripheral vascular disease Varicose veins
Respiratory system	Chronic obstructive pulmonary disease Pneumonia Pulmonary tuberculosis
Endocrine/Metabolic	Diabetes Mellitus Hypothyroidism Hypokalemia/hyponatremia Gout
Gastrointestinal trace	Hiatus hernia Dysphagia Constipation Fecal incontinence Diarrhea Malabsorption syndrome Ischemic colitis Irritable bowel syndrome Rectal prolapse Carcinoma of colon
Genitourinary system	Urinary tract infection Urinary incontinence Prostatism Renal insufficiency Prostatic carcinoma
Musculoskeletal system	Osteoporosis Osteoarthrosis Osteomalacia Polymyalgia rheumatica Paget's disease of bone
Blood	Anemia Multiple myeloma Myelofibrosis

Table II. Continued

System	Disease
Autonomic nervous system	Hypothermia Postural hypotension
Oral pharanx	Edentulous; Periodontal disease
Miscellaneous	Dehydration Foot problems Fractures Immobility Iatrogenic illness Malnutrition Cancer Pressure sores

Table III. Examples of atypical presentation of illness in old age

Disease	Examples of atypical presentation
Pneumonia	Anorexia Acute confusional state Normal pulse rate No elevation of body temperature No rise in white cell count Falls common
Pulmonary embolism	'Silent' embolism nonspecific symptoms
Myocardial infarction	Anorexia Absence of chest pain General deterioration Falls Weakness Shortness of breath common
Congestive cardiac failure	Non-specific symptoms
Acute abdomen	Absence of rigidity and tenderness
Urinary tract Infection	Acute confusional state Absence of pyrexia No rise in white cell count Incontinence
Parkinsonism	General slowness Recurrent falls
Transient Ischemic Attacks	Acute confusional state Falls

Table III. Continued

Disease	Examples of atypical presentation
Polymyalgia Rheumatica	Non-specific symptoms Poor general health Aches/pains Lethargy
Hyperthyroidism	Angina Atrial fibrillation Heart failure Absence of eye signs No increase in appetite Appetite may be poor Goiter commonly not palpated Bowel movements rarely increased
Hypothyroidism	Non-specific deterioration Confusional state Depression Anemia Vaginal bleed
Depression	May mimic dementia
Malignancy	Non-specific symptoms

The elderly persons of today are survivors. They have outlived their cohorts by living beyond their life-expectancy. At the turn of the century, the average life-span was 48 for men and 52 for women. Clearly the current life-expectancy of 74.7 years is a major accomplishment, which becomes even more impressive when one considers that today a 70-year-old woman has a 50% statistical chance of living an additional 17 years. The 70-year-old man of today can expect 12.5 years, which places each in their 80's at the time of expected death. On average, the 80-year-old of today can expect to live another 5 years; this population has the fastest growth of any age group. By the year 2040, in the U.S. alone we will have almost as many persons over the age of 80 than are over the age of 65 today. When one realizes that the 80-year-old has more normal age-related changes, has a higher incidence of age-prevalent diseases, and that diseases become even more atypical in their presentation as one ages, we must plan now through education and practice for the 'demographic imperative' we face. Whether we will ever become a purely 'rectangularized' society will rest in the hands of aging persons of today. We cannot be complacent but must face the challenges ahead with a clear understanding that any additional progress in prolonging functional life-span will not be an easy one. It is, however, a flight that is well worth the effort.

CHAPTER 2

Changes in renal function with age

ROBERT D. LINDEMAN

Introduction

This presentation provides an overview of the changes in renal function and morphology during adult life, and a discussion of adaptive mechanisms responsible for the regulation of volume and composition of the extracellular fluid as they are affected by age. Kidney function can be easily, accurately, precisely, and non-invasively quantified using clearance techniques that require only the collection of timed urine samples and blood samples obtained at the midpoints of the urine collection periods. Such tests have made the kidney a model system for studies of aging in man.

Changes in glomerular filtration rate with age

Cross-sectional studies have shown a consistent age-related decline in renal function after age 30–40 years [1–3]. Wesson [2], in his review of 38 studies that recorded individual inulin clearances and age found an accelerating decrease in glomerular filtration rate with increasing age in both males and females. The rate of decline was more rapid in males (Fig. 1). According to Rowe *et al.* [3], the results from the Baltimore Longitudinal Study on Aging showed a similar decline in mean creatinine clearances in normal subjects followed over a 10-year period. A subsequent report from this study [4] showed that the mean decrease in creatinine clearance in 446 normal volunteers followed over a 23-year period was 0.87 ml/min/year, close to that observed in cross-sectional analyses. One third of these subjects, however, had no decline in creatinine clearances (Fig. 2) as illustrated by six subjects followed 15 to 21 years. These observations suggest that the decline in renal function observed with age in the cross-sectional analyses is not due to chronic involutional changes, which occur in all persons probably at different rates, but more likely is due to intervening pathology, e.g. undetected glomerulonephritis or interstitial nephritis secondary to infections, immunologic

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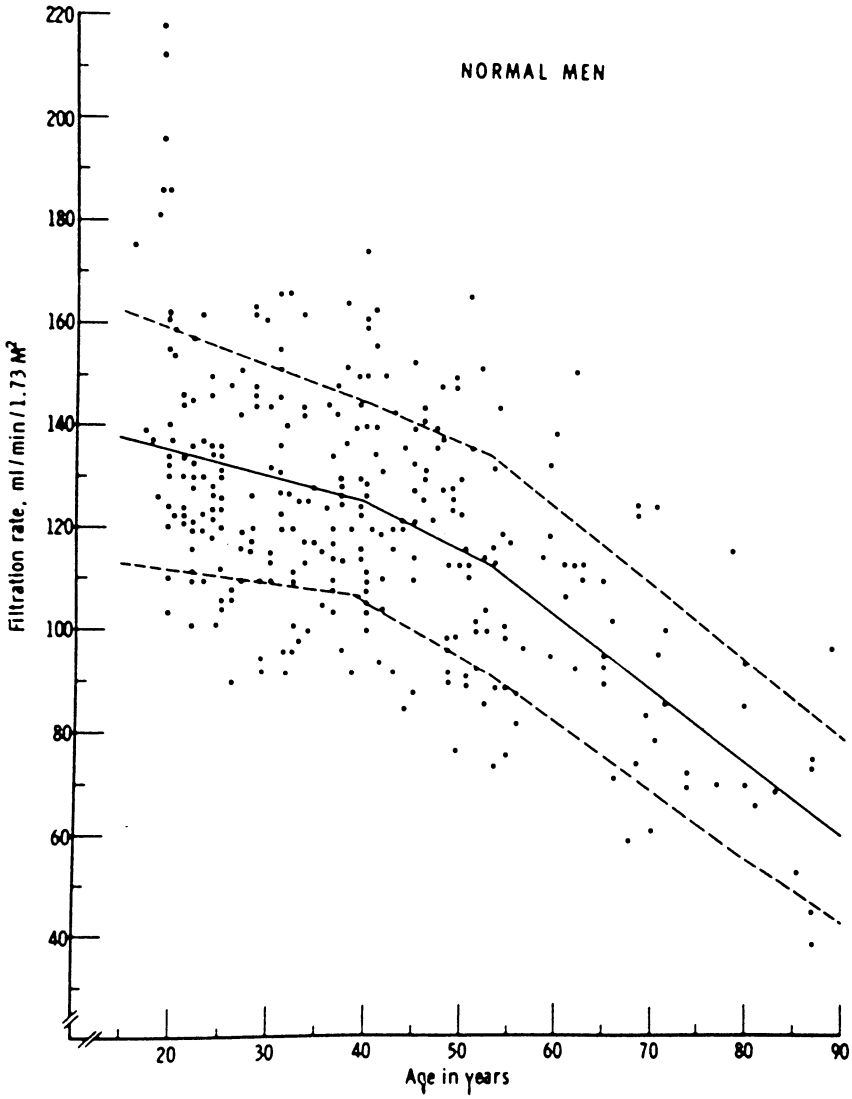

Fig. 1. Glomerular filtration rates (inulin clearances) per 1.73 m^2 in normal male volunteers plotted against age from 38 studies compiled by Wesson [2]. Solid and broken lines represent mean ± one standard deviation. Reprinted by permission.

insults, drugs, or other toxic exposures, vascular occlusions with resultant ischemic injury, or urinary tract infections or obstruction. The terms 'successful' vs. 'usual' aging have been used to distinguish between individuals who age without loss of organ function and the usual cross-section changes of any aging population, which are based on mean values [5]. The latter

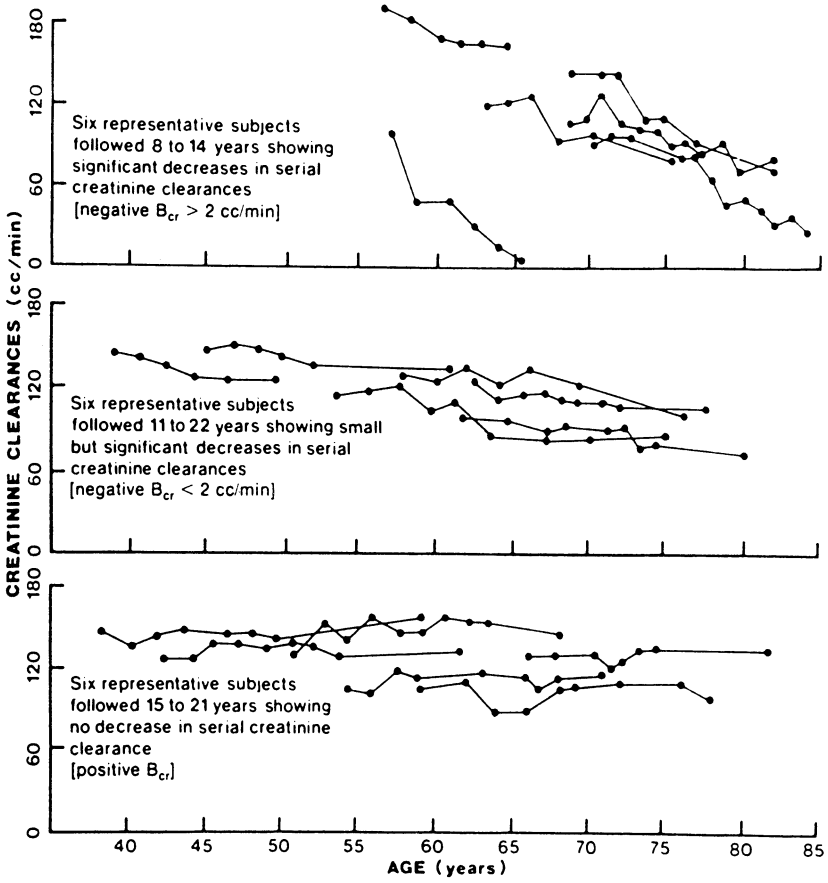

Fig. 2. Individual longitudinal displays of serial creatinine clearances plotted against age in years for representative subjects from the Baltimore Longitudinal Study on Aging. Especially note the six subjects in the bottom panel, representative of nearly one-third of the subjects followed, who had no decrease in creatinine clearances over periods up to 21 years. Reprinted by permission from Ref [4].

includes individuals with pathology, often asymptomatic, or at least undetected or unreported.

In the Baltimore Longitudinal Study of Aging, although mean true creatinine clearances fell from 140 ml/min/1.73 m^2 at age 25–34 years to 97 ml/min/1.73 m^2 at age 75–84 years, mean serum creatinine concentrations rose insignificantly from 0.81 to 0.84 mg/dl [3]. This indicates that mean creatinine production falls at nearly the same rate as the mean renal clearance of creatinine, reflecting the decrease in body muscle mass that occurs with age (Table I). In the older patient, the serum creatinine concentration must be interpreted with this in mind when it is used to determine or modify dosages of drugs cleared totally, e.g. the aminoglycoside antibiotics, or partially, e.g. digoxin, by the kidney.

Table I. Cross-sectional age difference in creatinine clearances, serum creatinine concentrations and 24-hour urine creatinine excretions (adapted from [3])

Age	No. subjects	Creatinine clearances ml/min/1.73 m^2	Serum creatinine concentrations mg/100 ml	Creatinine excretions mg/24 hr.
25–34	73	140.1	0.81	1862
35–44	122	132.6	0.81	1746
45–54	152	126.8	0.83	1689
55–64	94	119.9	0.84	1580
65–74	68	109.5	0.83	1409
75–84	29	96.9	0.84	1259

Changes in renal blood and plasma flow with age

The effective renal plasma flow (ERPF), generally estimated by measuring paraminohippuric acid (PAH) clearance, decreases from a mean of 649 ml per minute during the fourth decade to a mean of 289 ml per minute during the ninth decade [1]. The ERPF decreases more rapidly than the GFR. Since the extraction ratio (ERPF/RPF) at low arterial PAH concentrations is not influenced by age (92% in both young and old subjects), one can use PAH clearances to gain an accurate reflection of changes in renal blood flow with age [6].

The decrease in renal blood flow with age (without a parallel decrease in blood pressure) could be due to intraluminal vascular pathology (atheromata, sclerosis), or an increased renal vascular resistance caused by arteriolar vasoconstriction. McDonald *et al.* [7] reported that, compared to younger subjects, administration of a pyrogen produced a greater percentage increase in ERPF (91 vs. 71%) in older subjects, suggesting a greater resting vasoconstriction in the latter.

Using xenon-washout techniques, Hollenberg *et al.* [8] found that perfusion of the outer cortical nephrons declined more with age than did perfusion of corticomedullary nephrons. They did further studies to determine if this selective decrease in cortical-nephron perfusion was due to sclerotic changes in the small arcuate arterioles, or to a selective vasoconstriction of these vessels. The vasodilator, acetylcholine, increased renal blood flow in both young and old subjects but the effect was much more striking in younger subjects. In contrast, the vasoconstrictor response to angiotensin was similar in both young and old. This study suggests that the renal vasculature in the aged subjects is in a relatively greater state of baseline vasodilatation than that of young subjects. Since only these two investigations have addressed this question and since the results are contradictory, we need additional studies to resolve this issue.

Because the cortical component of renal blood flow decreases more rapidly than does mean renal flow rate, it appears that cortical nephrons are more

severely affected by age than are juxtamedullary nephrons. Since the juxtamedullary nephrons have a higher filtration fraction than do cortical nephrons, a selective loss of the latter might explain the increase in filtration fraction (GFR/ERPF) observed with age [1, 2, 7, 9]. An alternative explanation for the age-related increase in filtration fraction is that later in life the efferent arteriole is disproportionately vasoconstricted compared to the afferent arteriole, thereby increasing the filtration pressure in the glomerular capillary bed.

Correlations with renal morphology

Both kidney mass and function decrease after the third or fourth decade of life at a rate approximating nearly 1% per year. The principal loss of renal mass is from the cortex, and is primarily vascular; the most significant changes occur at the capillary level. Both the number of glomerular tufts per unit area and the number of glomerular and tubular cells decrease, while the size of the individual cell increases with age [10].

Normal aging is associated with sclerotic changes in the walls of the larger renal arteries, but generally these lesions do not encroach on the lumen sufficiently to produce functional changes [11]. In non-hypertensive elderly subjects, smaller vessels are relatively spared and only a small percentage of senescent kidneys show arteriolar changes. The incidence of sclerotic glomeruli increases with advancing age, from less than 5% of the total at age 40 to 10–30% of the total by the eighth decade [12]. Kasiske [13] found a strong direct correlation between the number of sclerotic glomeruli and the severity of atherosclerotic disease. He also found that, when the percentage of sclerosed glomeruli was less than 5%, the distribution between cortex and medulla was relatively uniform, but as it exceeded this level, the sclerosis became predominantly cortical.

Several investigators [14, 15] have provided detailed descriptions of ischemic obsolescence in cortical vs. juxtamedullary glomeruli. Initially, there is a progressive collapse of the glomerular tuft with wrinkling of the basement membranes, followed by a simplification and reduction in the vascular channels. Hyaline is deposited within the residual glomerular tuft and in the space of Bowman's capsule. Identifiable structures rapidly disappear. The obsolete glomerulus may be reabsorbed and disappear entirely. Reabsorption is suggested by the scantiness of the cellular response and by the residual scar. This process can leave a single vessel in place of the glomerular capillary bed, thus producing a shunt between the afferent and efferent arterioles (juxtamedullary glomeruli) or atrophy can produce an abrupt termination of the arteriole (cortical glomeruli).

Pathophysiology of the decrease in renal function with age

No one knows whether the decrease in renal function observed with age is due to a progressive involutional process with loss of nephron units and a decline in cellular function, or to various pathologic processes, often undetected, which produce acute and chronic injuries. Examples of such injuries include glomerulonephritis or interstitial nephritis due to infections, drugs, toxins, and immunologic insults, vascular occlusions with resultant ischemic injury, and urinary tract infection and/or obstruction. The Baltimore Longitudinal Study on Aging [4] has shown that over one-third of the male volunteers followed, some up to over 20 years, showed no decrease in renal function. These data suggest that there is no progressive involutional change, at least not in all persons, and support the concept that the decrease in renal function with age observed in cross-sectional studies is due to superimposed pathology. Elsewhere [16, 17] I have discussed a number of examples of undetected pathology as potential causes of reduced renal function in the elderly. An alternative explanation would be that, with any involutional changes (sclerosis of glomeruli, tubulointerstitial scarring), there is a compensatory increase in the function of remaining nephron units related to a release of a variety of growth factors, e.g. epidermal growth factor (EGF) or insulin-like growth factor I (IGF-I), as demonstrated in early insulin-dependent diabetes mellitus.

Once individuals with kidney injury from any cause, reach a critical level of renal functional deterioration, the disease progresses, even if the initiating event or condition is resolved. This is due to a progressive glomerular sclerosis. A vast literature has been generated on the role of hyperperfusion and hyperfiltration in the progression of declining renal function. Brenner and colleagues [18, 19] suggest that the protein-rich diet characteristic of modern Western society induces chronic renal hyperperfusion and hyperfiltration, thereby contributing to the structural and functional deterioration of the aging kidney. Presumably, with age alone as with primary renal disease, diabetes mellitus, hypertension and renal ablation, the high glomerular pressures and plasma flow rates created by the high-protein intake contribute to the development of glomerular sclerosis resulting in a progressive decline in renal function. Not all evidence supports this theory because long-term followup of patients undergoing nephrectomy for unilateral renal disease or kidney transplant donation do not show deteriorating renal function or evidence of glomerular sclerosis. The evidence that a high protein diet contributes to a deterioration in renal function in the elderly is reviewed elsewhere [20], but it does not appear that this is a significant factor unless there is also some pathology that diminishes renal function.

Unilateral nephrectomy causes compensatory hypertrophy in the normal remaining kidney, however, compared to the young, the rates of enlargement and increased function are much lower in the old. There is no increase after birth in the number of nephrons. Cellular hyperplasia is the predominant

response to nephrectomy in the young whereas cellular hypertrophy is the chief response in the elderly [21]. Even though the kidneys of older animals enlarge primarily by hypertrophy, the rate of hypertrophy is less than that observed in younger animals. A recent symposium [22] describes the role of the growth factors in cellular hyperplasia and hypertrophy and their impact on recovery of the kidney from injury and on the development of glomerulosclerosis. It appears that the processes of glomerular hypertrophy and glomerular sclerosis are closely linked.

The effect of age on other renal functions

Maximum tubular transport capacity

The tubular maximum for PAH secretory transport decreases with age at a rate paralleling the decrease in inulin clearance [1, 23]. The tubular maximum for glucose reabsorption also decreases at a rate closely paralleling the decrease in inulin clearance [24].

Although reductions with age in the secretory and reabsorptive tubular maxima could be explained simply by a progressive loss of functioning nephrons, animal studies suggest that the old, tubular cells have fewer energy-producing mitochondria [25], lower enzyme concentrations [25–27], lower concentrations of total or sodium-potassium activated adenosine triphosphatase (ATPase) [28], decreased sodium extrusion and oxygen consumption [29], and decreased tubular transport capacity [25]. Because these studies were performed on tissue slices, it is difficult to be sure that all these decreases are attributable to a true decrease in renal tubular-cell function and are not due to a higher proportion of non-tubular mass in old *versus* young kidneys.

Concentrating and diluting ability

A decrease in concentrating ability with age is well documented [9, 30–33]. Twelve hours of water deprivation increased mean urine osmolality to 1109 mOsm/L in young subjects (mean age 33 years), 1051 mOsm/L in middle-aged subjects (mean age 49 years), and 882 mOsm/L in old subjects (mean age 68 years). The decrease in concentrating ability could not be related strictly to an increase in solute load in surviving functional nephrons [9, 33]. Rowe *et al.* [33] suggested that the relative increase in medullary blood flow per nephron with age, as shown by Hollenberg *et al.* [8], would result in enhanced removal of medullary solute (washout), and thus decrease maximum urinary osmolality.

Similarly, maximum urine osmolality following infusions of large doses of pitressin is decreased in older subjects undergoing a water diuresis [31]. The

kidneys of elderly subjects, in contrast, respond normally to graded doses of pitressin insufficient to maximally concentrate the urine [9]. This suggests that the decrease in concentrating ability of older subjects is due to a decrease in medullary hypertonicity rather than to any defect in the tubule's ability to respond to pitressin.

Maximum diluting ability, as measured by minimum urine osmolality achieved with water loading, also decreases with age [9]. However, when one compares maximum free-water clearance per unit of nephron mass (GFR), there is little difference between young and old subjects, suggesting that there is no basic defect in the ability of the individual tubule to produce a dilute urine [9, 34, 35].

Excretion of hydrogen ions

To maintain systemic acid-base balance, the kidney must excrete a quantity of hydrogen ion equal to that quantity of fixed acid generated by metabolism. Under basal conditions, the blood pH, pCO_2, and bicarbonate of older persons without significant renal disease do not differ from the values observed in young subjects [36, 37]. However, the decreases in blood pH and bicarbonate concentrations following ingestion of an acid load persist longer in elderly persons [37, 38]. The minimum urine pH achieved after an acid load is similar in young and old subjects. In younger subjects a much larger percentage of the ingested acid load, as measured by total acid excretion (ammonium *plus* titratable acid *minus* bicarbonate), was excreted over an eight hour period. However, if total acid excretion in 8 hours is factored by GFR, similar rates of excretion are obtained. The young subjects excrete a greater percentage of their total acid as ammonium, presumably because older subjects have an increase in urinary buffers responsible for titratable acid, e.g. phosphate, creatinine, per unit of GFR. Agarwal and Cabebe [38] found that elderly subjects showed a small pH gradient defect and in them ammonium excretion was reduced even after correction for GFR. Adler *et al.* [37] reported that, in older subjects, the administration of glutamine, the major substrate for renal ammoniagenesis, did not correct the defect in ammonium excretion suggesting that the defect was not due to a lack of substrate. In older persons, a limitation of the kidney's ability to excrete acid may predispose to the development of and delayed recovery from metabolic acidosis.

Glomerular permeability

Functional studies of glomerular filtration show no changes in membrane permeability. Glomerular permeability to free hemoglobin and a spectrum of different-molecular-weight dextrans do not differ between young and old

subjects [39, 40]. This is true even though, as one ages, the mesangium of the individual glomerulus takes up a greater percentage of total glomerulus volume and the glomerular basement membrane thickens [41].

Renal control of fluid and electrolyte homeostasis

Under normal circumstances, age has no effect on serum sodium and potassium concentrations, or the body's ability to maintain normal extracellular volumes. However, the extrarenal mechanisms responsible for maintaining volume and composition of the extracellular fluids, often become impaired in the elderly, especially when stressed by acute and/or chronic illness.

Epstein and Hollenberg [42] found that older subjects did not conserve sodium as efficiently as do younger subjects. The half-time for reduction of urinary sodium excretion after rigid salt restriction was 17.6 hours in the young compared to 30.9 hours in older subjects. Elderly subjects consistently have lower plasma-renin activities and plasma or urinary aldosterone excretions, both on restricted and unrestricted salt diets, and in the supine and upright positions [43, 44]. In the elderly, these decreased plasma-renin activities and plasma concentrations or urinary excretions of aldosterone may be related to an impaired responsiveness to β-adrenergic stimulation because one of the effects of β-adrenergic stimulation is to increase levels of circulating renin and aldosterone. The decrease in aldosterone at least partially explains the elderly's decreased ability to conserve sodium, when challenged with a low salt diet.

Two other factors may operate in the elderly to explain this relative inability to conserve salt. First, circulating atrial natriuretic factor (ANF) levels, while variable in the elderly, are substantially higher than those observed in healthy young adults [45, 46]. These elevated levels may play a role in the salt-losing tendency of the aging kidney, both directly by its natriuretic effect, and indirectly by suppressing renin and aldosterone synthesis and release. Secondly, as renal function decreases in the older person, assuming food and salt intake are reasonably well maintained, the solute load per residual functioning nephron increases thus producing an osmotic diuresis and impairing ability to conserve sodium.

The low renin and aldosterone levels also would account for the greater tendency of older individuals to develop hyperkalemia when receiving supplemental potassium [47]. The combination of a decreased glomerular filtration rate and this impaired renin-aldosterone response leaves older individuals 'at risk' for the development of hyperkalemia. Because the distal nephron has such a large capacity for secreting potassium even in patients with severely reduced renal function, hyperkalemia generally develops only when one or more additional factors, e.g. oliguria, or an excess endogenous or exogenous potassium load, is introduced into the body. Drugs that interfere with this aldosterone-dependent tubular secretion of potassium in the distal

tubule include the potassium-sparing diuretics, e.g., spironolactone, triamterene and amilorilde, the β-adrenergic blockers, the angiotensin-converting enzyme (ACE) inhibitors, and the non-steroidal anti-inflammatory drugs. Elderly persons with interstitial nephritis, especially diabetics, develop a more pronounced hyporeninemic hypoaldosteronism referred to as a Type IV renal-tubular acidosis.

The increased tendency of the older person to lose both salt and water (concentrating defect) undoubtedly contributes to the more rapid development of dehydration and hypernatremia in them. More important, however, is the impairment in the thirst mechanism that develops with age. Phillips *et al.* [48] who studied the thirst response, and pituitary and renal responses to 24 hours of water deprivation in young vs. old subjects, showed increased serum osmolalities and plasma arginine vasopressin (AVP) levels and decreased urine osmolalities in the older group after water deprivation. The younger subjects, however, reported much more thirst after water restriction, and, at the end of the study, rapidly drank water to restore plasma osmolality to normal, whereas the older individuals drank little water and still had not corrected the hyperosmolality after 2 hours. If older persons had a normal thirst response to water deprivation, they would compensate for the inability to conserve salt and to concentrate their urine by increasing fluid intake.

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CHAPTER 3

Renal consultations in hospitalized very old people

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Summary

Renal consultations between January 1, 1987 and March 31, 1991 were reviewed to assess the etiology and outcome of renal disorders in patients ≥ 85 years old. Of 2491 consultations, 41 (2%) were in these very old patients. A sample of 23 charts (56%) at Kings County Hospital Center (KCHC) were compared with 20 'control' charts selected randomly as equivalent in age and service, but not related to kidney disease. In addition, we reviewed all KCHC admissions to the medical and surgical services during the study period ($n = 50{,}991$) to ascertain admission diagnoses and death rates sorted by age.

There were 15 deaths in the renal consultation group (65%) but only 2 in 20 control very old patients (10%) ($p < 0.0007$). Patients ≥ 85 years old, who had a renal consultation, died at a significantly higher rate than those in the same age range who did not have an identified renal problem. Kidney patients had significantly higher blood urea nitrogen and serum creatinine levels than did the controls. In these very old kidney patients, death was attributed to common medical problems including hypertension, diabetes, stroke, cardiac disease, and pneumonia. Only two patients died from acute renal failure. The two deaths in control patients were due to extensive burns and pneumonia-septicemia. An analysis of reasons for admission to KCHC, when sorted by age, showed a progressive rise in kidney disorders, from 7.5% of admissions in those aged 18 to 44 years to 28.6% in the very old group aged ≥ 85 years old.

We have concluded that a request for a nephrologic consultation must be taken seriously in very old patients. From the current data, we cannot distinguish the exact contribution of intrinsic renal disease from prerenal azotemia as an agonal event in extrarenal disease. With respect to the subset of patients with azotemia due to renal disease, any reduction in the two-thirds mortality in the very old patients seen in renal consultation may be contingent – in part – on earlier introduction of dialytic therapy at lower levels of azotemia.

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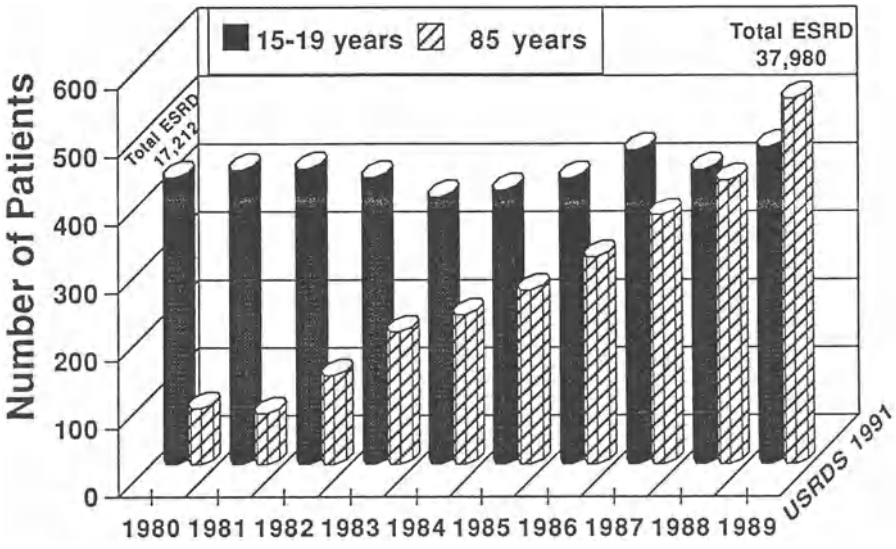


Fig. 1. Incidence of ESRD by age. Growth over the last decade in the number of new ESRD patients who were ⩾ 85 years old is contrasted with the constant number of new ESRD patients in the 15 to 19 year old age group. Data are from the United States Renal Data System 1991 report [2].

Introduction

Old age, like a hazy horizon, is located just beyond those attempting its definition. For the nephrologist, the geriatric patient is someone older than those usually accepted for long-term care. Wing illustrated this point when he remarked that his two dialysis patients 'over 70' were sufficiently unusual to warrant proud introduction to the Secretary of State [1]. In the six years since his report, aggressive expansion of the United States renal failure program has extended to those 85 years and older (Fig. 1 of the U.S. Renal Data System) [2]. To identify the medical conditions present in these *very old* kidney patients, we did a retrospective analysis of patients admitted by our renal service or referred for evaluation by other services.

Our service assists in the management of hospitalized patients manifesting renal insufficiency, acid-base imbalance, fluid and electrolyte disorders, hypertension, and direct manifestations of intrinsic renal disease. Since January 1, 1987, we have entered every renal consultation into a computerized data base that permits retrieval and sorting of data by demographic criteria. To determine the type and severity of disorders prompting renal consultation in the very old – defined as those aged 85 years or older – we recalled all records of patients whose date of birth indicated an age of at least 85 on admission. This paper provides a summary of these records, and a retrospec-

Table I. Diagnosis on consultation requests in very old patients

Unexplained azotemia	9
Hypertensive nephropathy	8
Congestive heart failure	5
Diabetic nephropathy	5
Hemodialysis complication	4
Acute renal failure	4
Pneumonia	2
GI hemorrhage	2
Urinary obstruction	1
Stroke	1
Total	**41**

tive analysis of admissions to the medical and surgical services of a large municipal hospital, arranged by age.

Methods

The Renal Division of the Department of Medicine provides consultations to Kings County Hospital Center (KCHC), a large municipal hospital, and University Hospital of Brooklyn (UHB), a state institution that includes the care of private patients. Between January 1, 1987 and March 31, 1991, there were 2491 renal consultations and direct renal admissions. Of these, 41 patients (2% of all consultations) were $\geqslant 85$ years old (Table I). After the patients were discharged, one of us compared the initial renal diagnoses assigned by the consulting renal fellow for computer entry at the time of admission with diagnoses for the same illness in the same patient determined by chart review. After discovering a strikingly high death rate in elderly renal consultation patients evaluated at KCHC, we extended the study, from the computer grouping of contemporaneous medical and surgical admissions, to include a control population by randomly and sequentially selecting charts of patients who were $\geqslant 85$ years old when admitted to the medical and surgical services during the same interval, but who had not had a renal consultation.

Each of these charts was also reviewed. The purpose of this control group was to assess the significance of mortality rates discovered in those who had had renal consultations. To gain perspective of the number and significance of very old kidney patients, we compiled all admissions to KCHC during the time of our kidney study by age, gender, race, diagnosis, and death rate. Statistical analysis of variance between groups and patient subsets was performed using the EPISTAT program for *t* tests, chi square tests, and the Fisher Exact test.

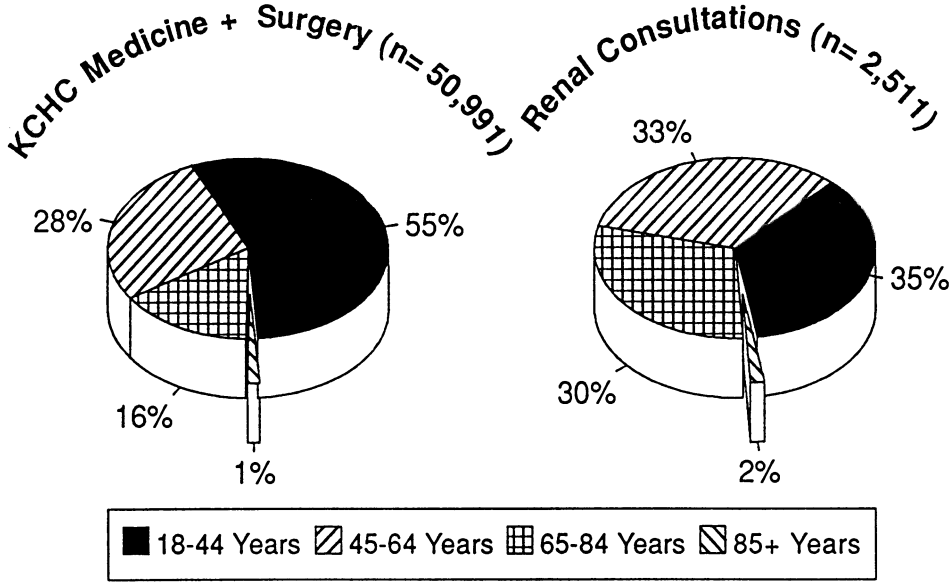


Fig. 2. Very old patients (85+ years) admitted 1/1/87–3/31/91. Contrasting age-group analyses for admissions to the Medical and Surgical Services at Kings County Hospital Center (left) and consultations by the Renal Division over the interval January 1, 1987 to March 31, 1991 (right). Note that while patients 85 years or older constituted 1% of admissions, they required 2% of all consultations.

Results

Renal consultations were twice as frequent in patients who were ≥ 85 years old (2%) than might have been predicted from the proportion of hospital admissions for this very old age group (1%) at Kings County Hospital Center (Fig. 2). Table I lists the diagnoses recorded by the renal fellow in response to 41 consultations in patients aged 85 years or older – 27 derived from KCHC and 14 from UHB. The most prevalent disorders were unexplained azotemia (9 patients), hypertensive nephropathy (8), congestive heart failure (5), diabetic nephropathy (5), acute renal failure (4), and complications of hemodialysis (4). Of 27 consultations listed for KCHC, the hospital record was available in 23 patients. The remaining 4 charts were lost or were in use somewhere within the hospital. Table II shows the prevalence of major medical illnesses recorded in the charts of the consultation and control patients. In those who had had a kidney consultation, the key finding was the extremely high death rate (65%) during the admission in which consultation was requested. No single factor explains these deaths, although severe prerenal azotemia was noted in 7 of the renal patients (30.4%) and none of the controls. The disorders of old age – stroke, cardiac failure, and pneumonia – were insufficient to separate the renal patients from the controls (Table III). Only two of the renal patients had acute renal failure (one had acute

Table II. Chart review of consultation and control patients

Condition	⩾ 85 Year old Consultations ($n = 23$)	⩾ 85 Year old Control patients ($n = 20$)	p Value
Hypertension	17	9	0.10
Stroke	7	4	0.67
Diabetes	7	2	0.2
Septicemia, pneumonia	6	6	–
Cardiac disease	6	3	–
Prerenal azotemia	7	0	–
Acute renal failure	2	2	–
Malignancy	1	2	–
Obstructive uropathy	1	0	–
Trauma (burn)	0	4	–
GI hemorrhage	1	1	–
Death	15	2	< 0.0007

Table III. Comparison of consultation and control groups

	Consultations ($n = 23$)	Controls ($n = 20$)	p values
Men : women	12 : 11	4 : 16	0.06
Mean age	88.7 ± 3.6 yrs	88.5 ± 2.4 yrs	0.83
Blood urea nitrogen	100.5 ± 56 mg/dl	21.3 ± 8.9 mg/dl	< 0.0007
Serum creatinine	5.6 ± 2.9 mg/dl	1.1 ± 0.3 mg/dl	< 0.0002
Deaths	15 (65%)	2 (20%)	< 0.0007

Table IV. Cause of 15 deaths in 23 very old renal patients

Chart finding	Number of patients
Cerebrovascular accident	1
Diabetic complications	4
Heart disease – myocardial infarction, failure	3
Hypertension complications	2
Pneumonia, septicemia	4
Acute renal failure – subdural hematoma, myocardial infarction	4
Total	**15**

myocardial infarction, the other subdural hematoma). Both died despite repeated hemodialyses. It was difficult to ascribe a single or main cause of death to the fifteen kidney patients who died; in nearly all instances, the patient entered with a single illness, such as pneumonia or myocardial infarction, and then had a sequence of multisystem complicationss inducing multiorgan failure. Thus, although Table IV lists 18 causes of death for the 15 renal patients who died, the list could have been expanded to 30 causes. In

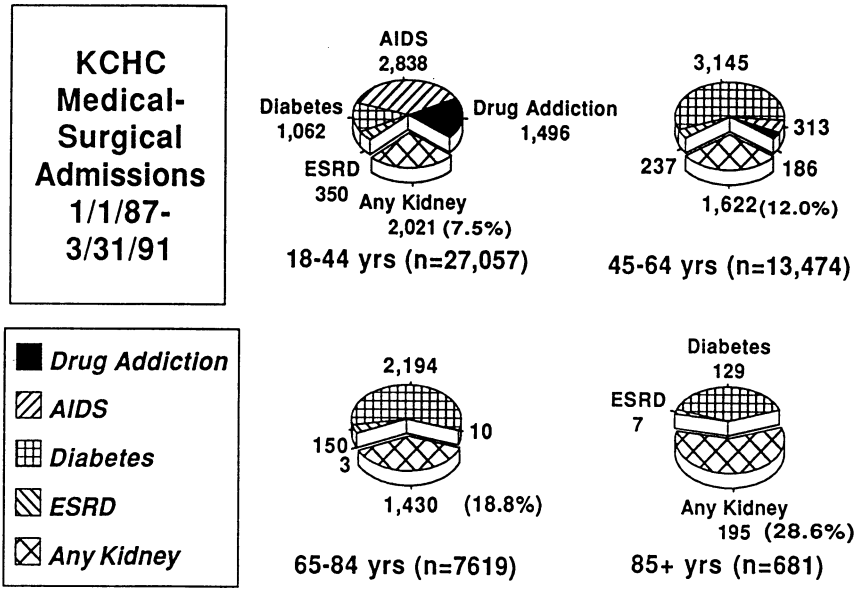
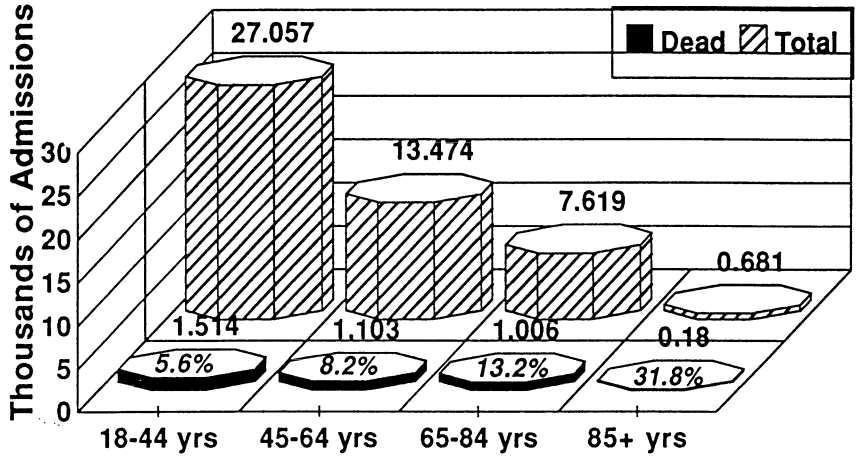


Fig. 3. Admissions to the medical and surgical services at Kings County Hospital Center between January 1, 1987 and March 31, 1991 grouped by age and diagnosis. Note that not all causes of admission are shown. The percent of renal admissions reflects the ratio of kidney disorders to all admissions in the denominator (not just those shown in the pie wedges). There is a progressive rise in the proportion of kidney-related admissions with increasing age.

the two control patients, death was easier to categorize because each person had been well until an acute illness (burn, pneumonia), the complications of which led to death.

Figure 3 reviews the relative frequency of renal disorders among hospital admissions – sorted by age. We divided adult admissions to the medical and surgical services of KCHC between January 1, 1987 and March 31, 1991, into four groups according to age. Those in the 18- to 44-year-old group had a renal diagnosis in 2021 of 27,057 (7.5%) admissions. The proportion of admissions with a renal diagnosis increased progressively to 12.0% in the 45 to 65-year-old group, 18.8% of the 65- to 84-year-old group, and finally to 28.6% of admissions in those ≥ 85 years old. It was also impressive that diabetes persisted into very old age as a cause of hospitalization. In fact, of 681 hospitalized patients 85 years or older, 47.6% were listed as having diabetes and/or a kidney disorder as their principal diagnosis.

Figure 4 analyzes the cause of death of hospitalized patients grouped by the same age ranges used to study admission rates. Not surprisingly, the case fatality rate increases sharply with increasing age. Of 27,057 admissions aged 18 to 44 years, 1514 (5.6%) died during their hospitalization. The case fatality rate rose to 8.2% for patients 45 to 64 years old, 13.2% for those 65 to 84 years old, and finally 31.8% for those ≥ 85 years old. The 65% death rate



Total	27.057	13.474	7.619	0.681
Dead	1.514	1.103	1.006	0.18

Fig. 4. Medical + surgical admissions (KCHC) deaths by age: 1/1/87–3/31/91. Deaths during admission to Kings County Hospital Center's Medical and Surgical services in four age groups. There is a progressive increase in the death rate with increasing age.

in the 23 renal consultations was significantly higher than that for all patients $\geqslant 85$ years of age ($p = 0.0001$).

Discussion

The main finding of our study is the ominous consequences of renal malfunction considered serious enough to provoke a renal consultation in $\geqslant 85$-year-old patients hospitalized in a municipal hospital. Nearly two-thirds of these patients die during the hospitalization in which consultation is requested. While death is a fellow traveller with advanced age in the seriously ill, some question whether such a generalization is sound. For example, Rich *et al.* asked whether age is an independent predictor of mortality after myocardial infarction and concluded that: "Even after statistical adjustment for numerous baseline and therapeutic differences between younger and older patients, age remains a potent independent predictor of adverse outcome" [3]. Using Rich *et al.* as a basis to ask: "Should age be used as a criterion for initiating or withholding therapy after acute infarction?", Manolio and Furberg advise that: "As physicians, we must discipline ourselves to look beyond a patient's age to consider his or her medical condition and potential for benefit, as well as the desires of patients and their families" [4]. That most clinicians agree that age *per se* ought not to be an exclusion criterion from most medical treatments is substantiated by the growing number of patients accepted for

Table V. Cause of 2 deaths in 20 very old control patients

Chart finding	Number of patients
Pneumonia, septicemia	1
Third-degree burns, sepsis	1
Total	**2**

ESRD treatment throughout the world. As is true for a younger patient, management of the very old with a 'renal problem' requires a renal diagnosis, a listing of options in therapy, and, lastly, a prognosis.

Only sketchy information exists, however, concerning what is normal or abnormal in terms of kidney function after the age of 85. Multiple cross-sectional studies have compared kidney structure and function in the elderly to that in young subjects. Typically, a small number of elderly subjects (frequently defined as over 60 years of age) without obvious illness are compared to a group of healthy young subjects.

Aging is accompanied by a reduction in renal blood flow [5], reduced GFR [6], impairment of sodium conservation [7], impairment of urinary concentration [8], and reduced excretion of an acid load [9]. In a rare longitudinal study, Lindeman *et al.* [10] measured GFR over time and concluded that it falls by 0.75 ml/min/year in healthy subjects. It should be appreciated, however, that 35% of the subjects in the study of Lindeman *et al.* showed no deterioration in GFR over the course of many years.

The structural changes that accompany the functional decrements of aging include a reduction in total renal mass, loss of glomeruli, and an increase in interstitial tissue [11, 12]. Within glomeruli, there is increased mesangial matrix, thickening of the basement membrane, and loss of lobulation in the glomerular tuft [13], while tubules develop increasing numbers of diverticuli that may represent the origins of retention cysts [14]. Concerning vascular changes of aging, Takazakura *et al.* [15] found two distinct changes: Obliteration of cortical afferent arterioles with atrophy of glomeruli, and spiralling of medullary afferent arterioles, that bypass the glomeruli and shunt blood directly to efferent arterioles.

Information about renal disease in the elderly comes from three main sources: Series of patients with acute renal failure, biopsy series, and statistics on causes of ESRD in various age groups. The most common cause of acute renal failure in elderly patients appears to be prerenal azotemia, followed by acute tubular necrosis [16]. However, in our present report, only two of 15 deaths were attributed to acute tubular necrosis (Table IV). In one of the rare studies that specifically identified a sub-group over 80 years of age, Druml *et al.* [17] found no influence of age on mortality from acute renal failure. We cannot determine the significance of age as a prognostic factor in the mortality of acute renal failure until we compare the outcome of subgroups of older and younger patients in a controlled prospective study.

Although a number of studies show a higher mortality among elderly patients [18–20], just as many show no difference in mortality between patients older and younger than 65 [21–23].

Several workers have studied the etiology of biopsy proven renal disease in the elderly in retrospective reviews of their pathology records. Moorthy *et al.* [24] compared 455 patients younger than 60 to 115 patients between 60 and 84. Rapidly progressive glomerulonephritis (16%), membranous nephropathy (13%), amyloidosis (4%), and diffuse proliferative glomerulonephritis (4%) were *more than twice as common* among the elderly. Nephrosclerosis was diagnosed not only in 13% of the elderly, but also in 10% of the younger group. Rakowski *et al.* [25] studied 83 individuals between 55 and 85, in whom the most common diagnoses were membranous nephropathy (12%), nephrosclerosis (13%), and diabetes (16%). In 143 patients between 60 and 80 years of age, Kingswood *et al.* [26] reported that the leading diagnoses were membranous nephropathy (17%), focal proliferative glomerulonephritis (13%), and amyloid (13%).

Studies of the distribution of causes of ESRD in old and young populations, suggest that, in the elderly, hypertension and urinary tract obstruction become more important causes of renal failure, while diabetes becomes less common [27]. Among the very old in the present report, however, diabetes and hypertension persisted into the ninth decade of life as management problems. In data from the Medicare ESRD program, hypertension was the leading cause of renal failure (37%), followed by glomerulonephritis (13%), diabetes (10%), obstruction (6%), and cystic disease (2%) in those 75 years of age or older. The cause of renal failure was 'unknown' in 15% [28].

It might be argued that our sample size ($n = 23$) is too small to permit generalizations about all very old people. Although our sample size is small and the population represents a select, often very ill subgroup of very ill people, the grave prognosis associated with azotemia in those $\geqslant$ 85-year-old hospitalized patients was not present in an age-matched group of contemporaneous patients with nonrenal illnesses. The high mortality noted in very old azotemic patients may reflect multiorgan failure, as well as an underappreciation of the severity of renal failure because of lower levels of serum creatinine, based on a decreased muscle mass, than would be found in younger patients with the same degree of renal insufficency.

An evaluation that starts a renal consultation paints a picture of an unstable subset of our population awaiting disaster – which is exactly what awaits them when hospitalized. This view of the very old may be too harsh. Indeed, a recent editorial in the Lancet, that asked 'What is it like to be very old?', depicted the prospect of those over 90 years old as follows: "Nearly half of them have not been to hospital for the past 5 years and most of the remainder have only attended once over that period. Just a third have regular contact with their family doctor. Over 90% of those living at home are fully continent; two-thirds never have trouble sleeping; only two-fifths take analgesics. Over 70% report that they are in good spirits, never feel

lonely, and are free from worries. Most lead lives of dignity and contentment" [29]. These inferences are drawn from what appears to be a middle class population, rather than the population of inner-city poor served by KCHC.

From our preliminary exploration of the very old kidney patient, we are dismayed over their high death rate and stimulated to pursue a much more intensive and aggressive course in management, which will include early resort to dialytic therapy. We will emphasize that a request for renal consultation in very old patients should alert the consultant to our finding that, in two-thirds of those $\geqslant 85$ years or older, renal consultation is followed by death in days.

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PART TWO

Progression of renal diseases

CHAPTER 4

Progression of glomerular diseases: risk factors and clinical overview

GEORGE E. SCHREINER

The great renal physiologist, Homer Smith, once wrote, "We are what we are because we have the kind of kidneys we have". Thus, the important questions in nephrology are those which deal with a chemical milieu consistent with a high quality of life. When that milieu is optimal or tolerable, the nuances of social decisions become highly relevant. However, when that chemical milieu is suboptimal or intolerable due to declining kidney function, the actions of society become almost irrelevant to the patient except those actions directed toward making metabolic improvement possible.

In this context our most important questions become: Do kidneys of necessity age? When does aging begin? Is there an inevitable rate? Is aging a condition or disease or sum of multiple injuries? Is the rate variable? Is it genetically determined, and if so, is this mutable or immutable? Can we prevent progressive loss of kidney function? As time goes by, can we lower the rate of loss and thus prolong the quality of life? Can we reverse the decline and can we realistically hope for improvement if some decline has already been seen?

Demography

Currently close to 200,000 Americans live on various forms of dialysis or transplantation over 500,000 people worldwide. Thus, the possibility of an inevitable decline of kidney function with age is not a trivial medical or economic problem. The end results of this process in the U.S. alone annually may cost 9 billion dollars, and the inevitability of increase is already in the human biological plan. From the beginning of this century up to the 1981 census, Americans over 65 increased by more than 8-fold, from 3.1 million in 1900 to 26 million in 1980. The US census bureau projects 33 to 36 million persons over 65 by the end of century. This will represent 15% of the population and, by the end of the first quarter of the new century in 2025, there will be 60 million and one out of every 5 Americans will be over the age of 65.

D.G. Oreopoulos, M.F. Michelis and S. Herschorn (eds), Nephrology and Urology in the Aged Patient, 37–48.

The classical study of Davies and Shock [1] indicated that the glomerular filtration rate (GFR) declines at roughly the rate of 1 ml/min/yr between the ages of 40 and 80. This value was derived from 70 presumably normal males drawn from the environment of Baltimore City Hospital. Wesson [2] added data drawn from 36 different studies and found an accelerating decline with age in GFR in both men and women (greater in men). In a 20 year hospital study of 884 community volunteers in the same Baltimore environment, Rowe, Tobin and Shock [3] found Ccr declining from 140 (25–34) to 97 (95–84), a 31% decline. In a later study [4] of individuals followed sequentially, 1/3 of subjects including some elderly showed no decline over 20 years.

Unfortunately, the early studies persuaded most clinicians and many clinical nephrologists that it is normal to have a 50% GFR at the age of 70 and derivatively a serum creatinine on a multiple blood screen of 1.6 to 2.4 mg/dl. With the standard deviations encountered in clinical automated techniques, this is a coarse screen indeed and will miss early kidney disease in the older age groups and also mild kidney disease, which can be slowly progressive in the elderly.

Therefore, it is reasonable to ask whether the socioeconomic environment of early studies contained people with underdiagnosed hypertension, diabetes, obstructive disease and infections of the urinary tract. Many Americans in this socioeconomic group are smokers, significantly overweight and noted for nutritional deficiencies, high-lipid diets and considerable environmental stress. It would be difficult, but fascinating, to determine whether retrospective followup in later decades would reveal segments of this 'normal' population who had been prehypertensive, prediabetic or prepremature atherosclerotic. The epidemiologic fact that functional measurements in some subjects remain at a plateau and that many nonagenarians and centenarians have low normal GFRs when adjusted for muscle and skeletal mass, suggest that progressive decline of kidney function with age *is not* inevitable.

Perhaps a better concept is that progressive decline of kidney function with age is a *clinically acquired situation* and could be diagrammed as a vector of the sum of injuries produced by multiple risk factors varying tremendously in different genetic, ethnic and environmental populations (Fig. 1).

While some risk factors for the progressive decline in kidney function may be unknown, the clinical data suggest that most of them have already been identified (Table I). The most visible histopathologic changes from the operation of these risk factors are focal or segmental sclerosis, often leading to global sclerosis. Table II lists the diseases and clinical situations in which focal sclerosis is prominent on renal biopsy. Experienced clinicians will realize that many of the risk factors in Table I are present in the diseases and clinical states in Table II.

Because these clinical situations are so disparate, they almost demand a final common pathway to explain this shared histopathology. In basic principles of human biology, we would expect that common pathway to include

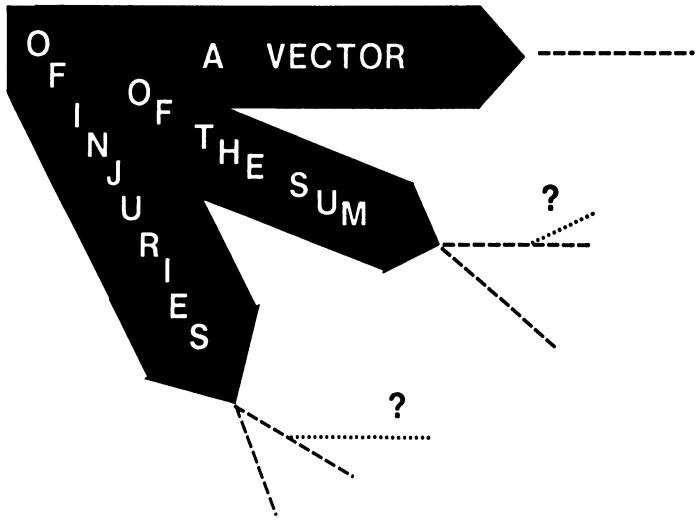

Fig. 1. Renal insufficiency: a measurable reduction in kidney function.

Table I. Progression of renal disease risk factors

Proteinuria	Undiagnosis
↑ Blood Pressure	Focal Sclerosis
Hyperfiltration	Nephrotoxins
Lipids	Ischemia
Atherosclerosis	Summation – minor insults
Obstruction	

Table II. Clinical causes of focal glomerulosclerosis leading to global sclerosis

1. Systemic diseases – e.g. diabetes, amyloid, nephrosis of pregnancy, etc.
2. Vascular lesions – hypertension, intravascular thrombosis, falciparum malaria, DIC, microangiopathy, etc.
3. Lipid storage disease – Fabry's disease, familial lecithin-cholesterol acetyl transferase deficiency, etc.
4. Vasculitis – SLE, Wegener's etc.
5. Obstruction with reflux
6. Infection especially ascending bacterial, sub-active bacterial endocarditis, hepatitis B and C, iganephropathy, aids (HIV) nephropathy
7. Immune glomerular disease – lipoid nephrosis, Schoenlein-Henoch, membranous, mesangioproliferative, membranoproliferative, crescentic iganephropathy
8. Nephrotoxins, including snake and other venoms, drugs, etc.

a chemical messenger, chemotactic factor, one or more cell species to respond to the chemotactic factor, a pattern of response, the local production of mediators of injury and inflammation, such as the interleukins and other kinins. In such a basic biologic system, the presence of both amplifiers and/or inhibitors is likely.

Historically, the conceptual framework for progressive decline in kidney function has focused predominantly on vascular physiology because the endothelial surface area per gram of kidney is the highest of any organ in the body. Its microanatomy is unique in having two capillary beds in series and a visible high-pressure capillary filtration system called the glomerulus. In addition, the high degree of autoregulation of pressure and flow in the kidney suggests the teleologic concept of hydraulic protection. However, a vascular framework does not explain many of the known risk factors that have been correlated by clinicians.

Recently immunologic mechanisms have been given greater attention as a possible explanation for the clinical risk factors. Klahr, Schreiner and Ishikawa [5] have demonstrated that obstruction of the ureter in the rodent is followed within hours by rapid invasion of the kidney by macrophages. This occurs most rapidly in the cortex but also in the medulla and continues for at least 24 hours and perhaps days after release of obstruction. These cells arrange themselves in a necklace around the tubules as if in response to a chemotactic factor elaborated locally. They release a number of cytokines including interleukin, which may affect glucose and salt transport across the epithelial cells. This may lead to sodium retention during the initiating phase of obstruction and the well-known, post-release saluresis. If the kidneys are radiated or macrophages are inhibited from entering the kidneys, the post-release saluresis is obliterated. These invading cells mediate immunologically active events in the medulla, which may account for some of the features of tubular interstitial nephritis; in the cortex, these cells may enter the mesangium and, with other kinins, may initiate the inflammatory events that lead to early stages of focal sclerosis.

Hypertension

More than 60 million Americans between the ages of 25 and 74 have hypertension and are at special risk for stroke, coronary disease, left-ventricular hypertrophy, progressive nephrosclerosis and vascular damage to organ systems. There are specially high risks for blacks, the elderly, urban dwellers and certain occupations. Argy *et al.* [6] compared the hypertension on hemodialysis in Hawaii and Washington. Blacks are highly represented in Washington and in the Georgetown CAPD population and are virtually absent from the Hawaiian. Dramatic differences exist between the populations and the risk for nephrosclerosis. The risks are so different that the progressive loss of kidney function with age could not be the same in the two environments. In

Table III. Hypertension and nephrosclerosis effect of *age* (M ±SD)

Mean DBP	Stable function	Reduced function	Total
< 90 MM	49.4 ±11.8	58.9 ± 11.1	50.9 ± 11.7
> 90 MM	46.4 ± 12.3	36.8 ± 13.6	42.2 ± 12.6

N Eng J Med 1989; 320:684.

this context it is not surprising that Washington, DC (statistically urbanized by reporting as a city-state) has the highest crude death rate from kidney disease in the entire nation. There is, of course, a special kind of interaction between age and blood pressure in the effects of hypertension on kidney function. Table III is taken from a study reported in Rostand *et al.* [7]. A group of hypertensive subjects were divided into those with mean pressures over and under 90, and those with stable and reduced function. The age of patients with stable function was similar to that of those with both moderate and severe levels of blood pressure. However, those with mild hypertension were a full decade older than those with reduced renal function. On average those with severe hypertension were a decade younger. This table makes clear that severe hypertension damages the young kidney but mild or moderate hypertension takes its toll more gradually in the elderly and is often overlooked.

Proteinuria

In recent years proteinuria has been overlooked as a risk factor for the progressive decline of kidney function. Schreiner [8] originally defined the nephrotic syndrome in modern terms: "The nephrotic syndrome is a clinical entity having multiple causes and characterized by increased glomerular permeability that is manifested in massive proteinuria and the excretion of fat bodies. There is a variable tendency toward edema, hypoproteinemia and lipemia. Usually protein excretion rates are in excess of 3.5 g/24 hr/1.73 square meters of body surface in the absence of depressed glomerular filtration rates". This definition was based on a study of 183 patients with a nephrotic syndrome at Georgetown between 1952 and 1960 of whom 92 were male and 68 Caucasian. Quantitative aspects were based on a study of Berman and Schreiner [9]. This quantitative definition of nephrotic-range proteinuria has been reproduced in many textbooks usually without the qualification that it should be corrected for filtration rate. If protein clearance is factored by the GFR, it can be expressed as a permeability factor and serve as a true physiologic measurement independent of body size or the filtered load of protein. In that review [8, p. 350] we constructed a scattergram (Fig. 2) plotting the serum albumin in grams per deciliter against cholesterol and commented [8, p. 355] "the paucity of patients in the right

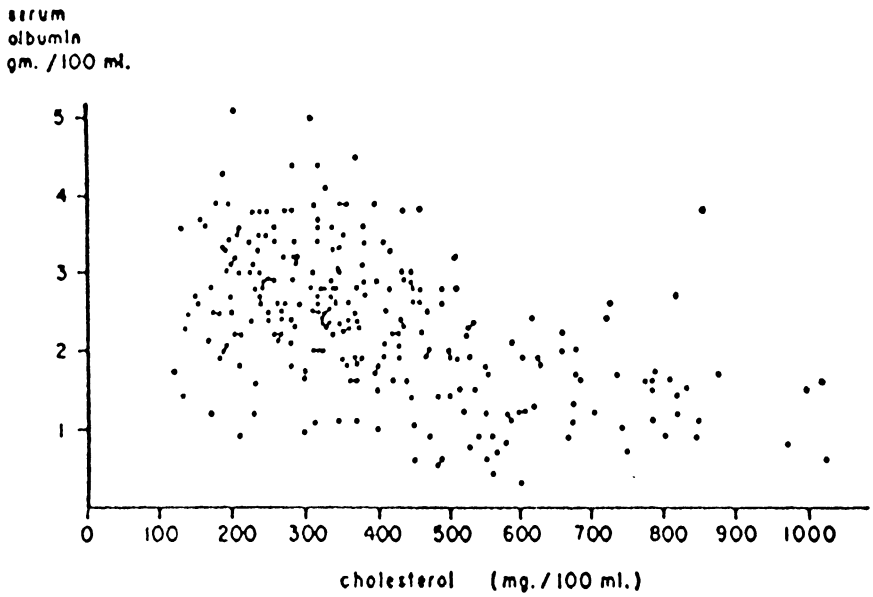

Fig. 2. Scattergram of serum albumin (gldl) vs. cholesterol (mg/100 ml). Reproduced with permission from Ref. [8], p. 350.

upper quadrant emphasizes the relatively rare occurrence of a markedly elevated cholesterol in the presence of normal serum albumin. There are, however, many instances of low levels of cholesterol in the presence of hypoalbuminemia. Several clinical entities marked by protein deficiency such as nutritional deficit, kwashiorkor cirrhosis, idiopathic hypoproteinemia, may *not* have associated hyperlipemia". Therefore, we proposed a relation to proteinuria *per se*. At that time, almost one-third of a certury ago, there was little data that even experimental nephrosis was an autoimmune disease, although, there were some singular, suggestive experiments. Hess, Ashworth and Ziff [10] transferred experimental nephrosis by the transplant of lymph nodes into a paired animal rendered susceptible to tissue transplantation by previous injection of spleen cells during the neonatal period, a technique used today to develop transplant tolerance. We also commented that convincing evidence of an active immunologic factor lay in the demonstrated transmission of periarteritis and subacute glomerulonephritis to human renal transplants and we asked the question [8, p. 355] "Are plasma lipids actually synthesized in the diseased kidney?" "Are metabolic consequences of nephrosis, such as lipidemia due to the same . . . reaction which affects the kidney, but in this instance also effects an extrarenal site of lipid synthesis?"

We collected a great deal of clinical anecdotal evidence that proteinuria *per se* appeared to damage the tubules and kidney function with the exception of early childhood lipoid nephrosis. This hypothesis is represented in studies, one of which (Fig. 3 [11]) shows an actuarial plot of percentages of nephrotic

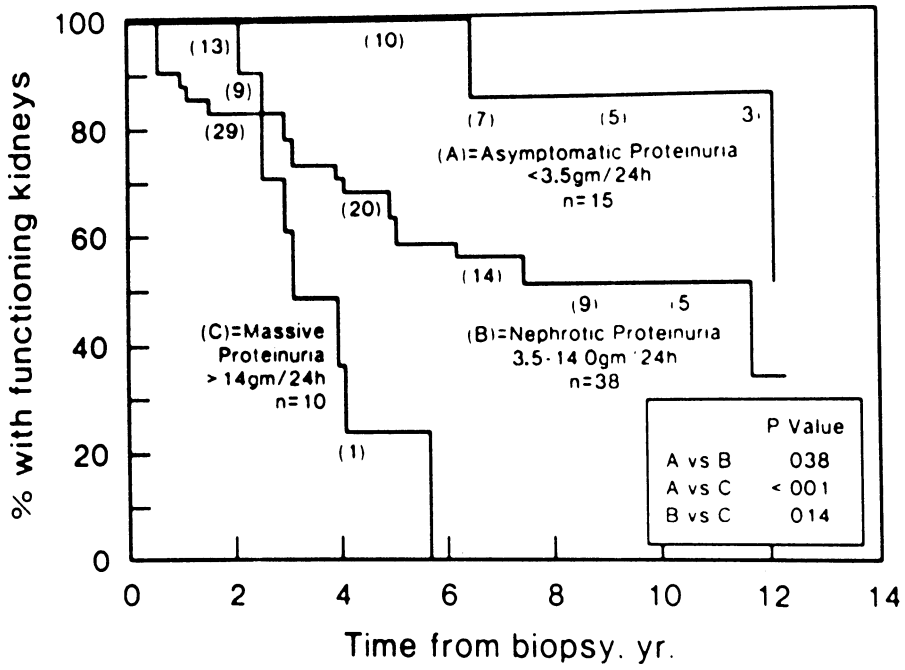

Fig. 3. Kidney survival curves for three groups of patients established on the basis of degree of proteinuria at time of renal biopsy. Estimated percentage of patients with functioning kidneys 2 years or more after renal biopsy is distinctly different for the three clinical groups. An inverse correlation was found between degree of proteinuria and kidney survival. Numbers in parentheses are patients followed up who had not reached end-stage renal failure at 2-year intervals after renal biopsy. From Ref. [11] with permission.

patients with functioning kidneys over a period of 6 to 14 years, patients in the group with more than 14 grams have a statistically significant bad prognosis. A great deal more data of this sort is scattered through the clinical literature. Mogansen and others have shown that microalbuminuria is often the earliest best sign and single best prognostic indicator in the early stages of diabetic glomerular sclerosis – a disease often characterized by progressively greater glomerular permeability for protein. Pabico [12] showed that, in 9 patients with minimal proteinuria, the maximum osmotic U/P ratio was 3.5 ± 0.17 whereas, in a group of 8 patients with massive proteinuria, the maximum osmotic U/P ratio was 2.33 ± 0.28. This suggests that proteinuria in the nephrotic range could produce tubular defects, presumably by facilitating injury.

These data suggested that progressive decline in kidney function was probably multifactorial but that, while we had made some significant advances in treating hypertension as a risk factor, we have been able to do little to affect the proteinuria except in lipoid nephrosis (by prednisone),

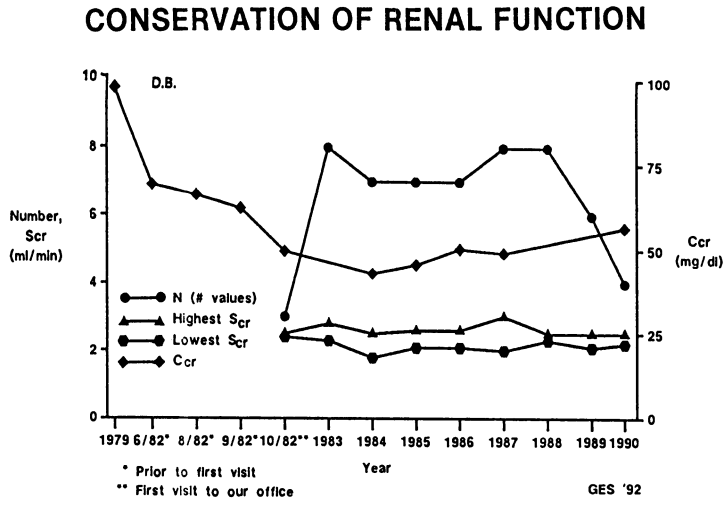

Fig. 4. Example of conservation of renal function.

the one disease where for unknown reasons, it didn't seem to matter. Also we did not have many ways of controlling lipidemia, which was subsequently demonstrated by Keane and others to be an independent risk factor.

Over a decade ago I began to use an holistic approach to fathom the risk factors in patients with progressive loss of kidney function so as to use the most effective way of improving or reversing each risk factor and to change that means as more effective ones appeared. The first such patient (Fig. 4) had lost almost 2/3 of his function in a few years at a hypertension clinic which treated only his blood pressure. By treating all the risk factors we hoped at best to slow the rate of decline. This happened and the patient plateaued for $2\frac{1}{2}$ years and then began to improve slowly. Figure 5 shows that even patients with membranous glomerulonephritis, who respond to the Ponticelli regimen using prednisone and chlorambucil, show a decline in proteinuria as the first obvious harbinger of improvement; the filtration rate may significantly improve even if it had been seriously depressed. This particular patient, who fell outside Ponticelli's selection criteria, had been bedridden by massive anasarca. The regimen was tried in desperation. Note that kidney function improved and the striking decline in proteinuria was maintained. Figure 6 shows another patient with membranous glomerulonephritis who had no response to three years of prednisone during which he became hypertensive. The holistic approach greatly reduced his proteinuria and to the time of this publication, has preserved his filtration rate. Figure 7 shows similar response in a 37-year-old woman with recurrent nephrotic syndrome of pregnancy and minimal change on renal biopsy.

Of course, such clinical experiences are anecdotal but double-blinded, tightly controlled, monotherapy clinical trials are useless in answering the

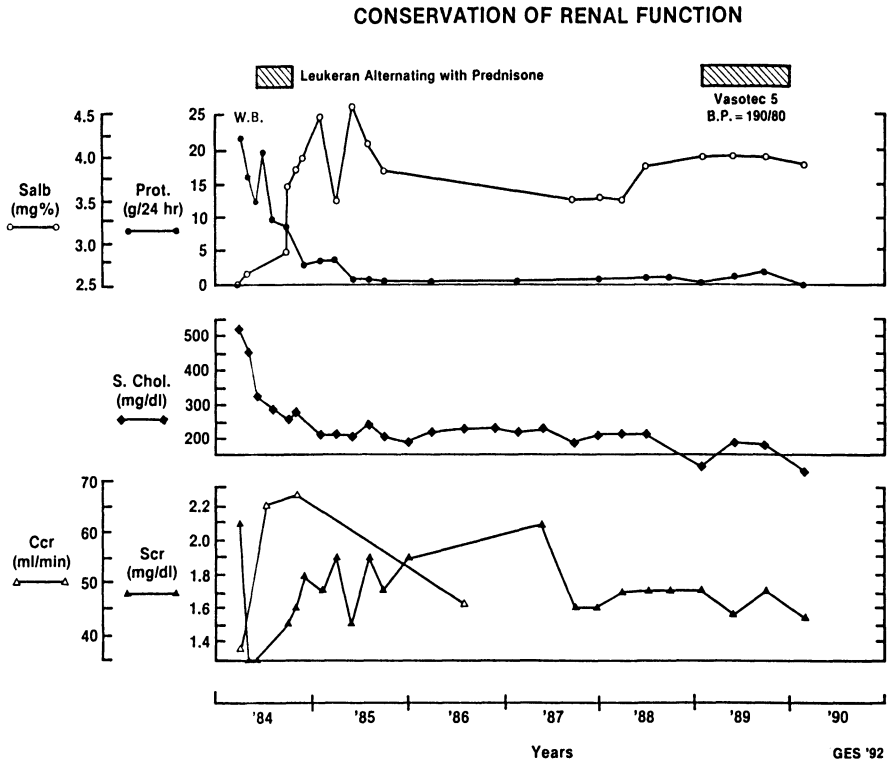

Fig. 5. Example of conservation of renal function.

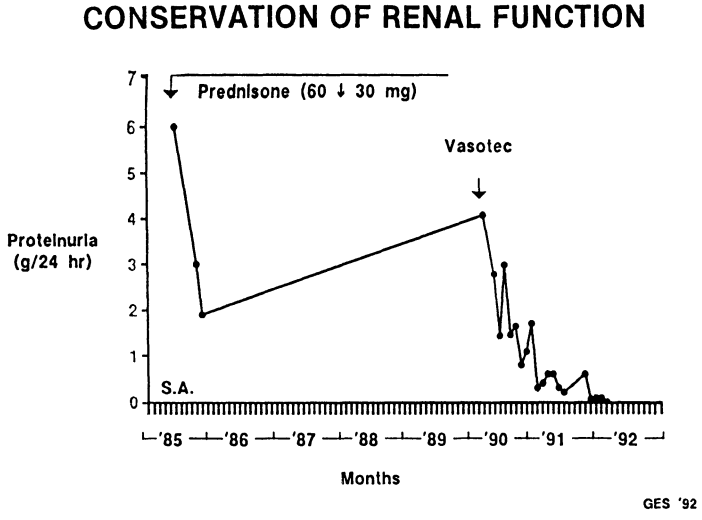

Fig. 6. Example of conservation of renal function.

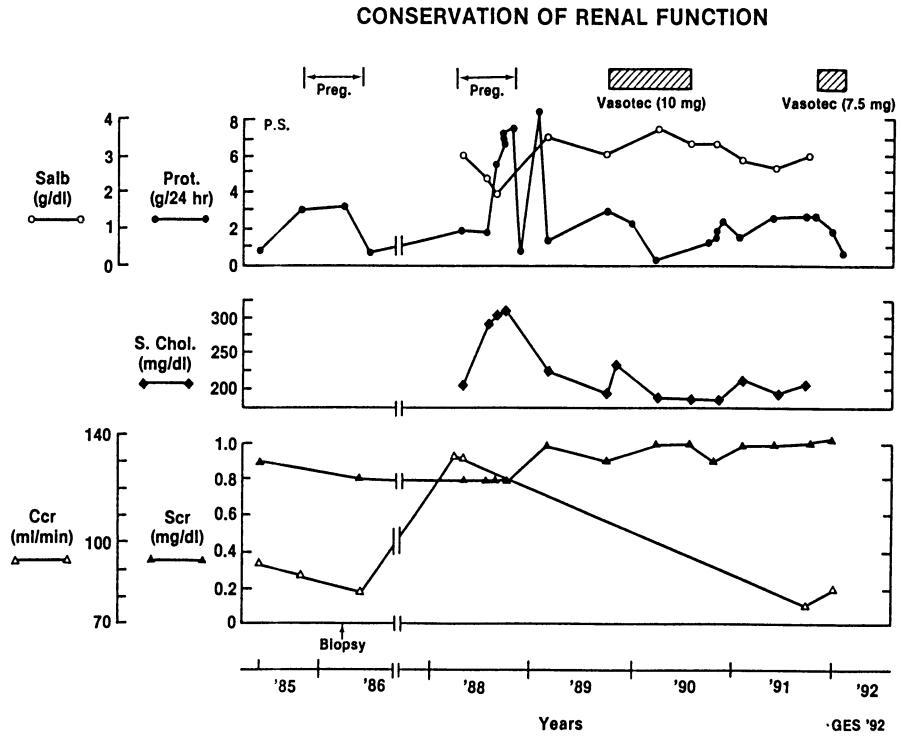

Fig. 7. Example of conservation of renal function.

key question, namely, What can we achieve by effective control of risk factors in a multifactorial pathogenesis? We want to know, if a patient has 10 risk factors, what will be the outcome if we control 6 or 7? What can we hope for if eventually we learn how to control all 10. In the case of proteinuria as a risk factor, GF Schreiner has given us fresh insights into the mechanism. Schreiner, who noted the influx of macrophages into the kidney in response to obstruction, also noted that infiltration and progressive decline of function were halted in fatty-acid deficient rats that apparently either lacked, or were deficient in, a chemotactic factor. Subsequently he has identified this factor as a small lipid bound to albumin and inactive in the serum but when proteinuria is present, is removed by the tubule cells. This chemotactic factor greatly enhances macrophage migration and activation.

Summary

In summary I believe the aging kidney is not aging. The progressive decline in kidney function is neither necessary nor inevitable. In fact, the kidney is one of the most regenerative organs of the body and in this regard, is a sort of a baby liver. After live-donor transplantation, each kidney takes over

Table IV. A lifelong quest

Undiagnosed and minor renal disease
Premature arteriosclerosis
Hypertension by middle age
Lipid abnormalities – genetic and dietary
Hyperfiltration – High protein diets
Smoking (?)
Subtle environmental nephrotoxins
Other

almost the total function previously supplied by a pair of kidneys. The sum of the two in separate bodies is much greater than the sum of the two in the initial donor. Furthermore, without proteinuria, the hyperfiltration that follows unilateral nephrectomy does not seem to produce progressive nephrosclerosis or progressive renal insufficiency in donors or recipients, who did not have a rejection reaction and were followed for many years.

I believe that progressive chronic renal insufficiency (Fig. 1) is a vector representing the sum of multiple injuries. Logically this should lead us into a holistic approach to prevent, treat or at least ameliorate all of the identifiable risk factors. It may be that new methods for separate control of blood pressure, lipidemia and proteinuria may be synergistic in decreasing the lipid chemotactic factor identified by Schreiner *et al.* (See next chapter in this book).

It is now the responsibility of the clinical nephrologist and the truly involved internist to undertake with his patient a lifelong quest (Table IV) to unearth and diagnose minor renal disease; to do what he can to prevent premature arteriosclerosis; to detect and treat hypertension by middle age and if possible to prevent its development; to treat lipid abnormalities, both genetic and dietary, by the most effective means; to pay attention to hyperfiltration from excessive protein diets, to treat proteinuria by whatever methods are available for that patient and the particular disease causing proteinuria; to eliminate subtle, environmental nephrotoxins and to pursue whatever measures he can to prevent, treat or at least ameliorate the risk factors to progressive sclerosis.

A new era of prevention and holistic nephrology is beginning. It will be far more satisfying and more economical than the dramatic therapies we have employed during the past generation of nephrology. We must continue both approaches in the best interests of our patients especially those who are aging and already on their way to progressive renal failure.

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CHAPTER 5

Progression of glomerular sclerosis: molecular and immunologic mechanisms

GEORGE F. SCHREINER

Abbreviations

EGF	Epidermal growth factor	PDGF	Platelet-derived growth factor
IGF	Insulin-like growth factor	TGF-β	Transforming growth factor-β
IL-1	Interleukin-1	TNF	Tumor-necrosis factor
LDL	Low-density lipoprotein	TxA_2	Thromboxane A_2

Introduction

The aging kidney is not inevitably caused by sclerosing kidney. While glomerular sclerosis is the final common pathway of many renal toxins, research over the last decade into the cell biology of the traumatized glomerulus has detailed the heterogeneous mechanisms that underlie its susceptibility to sclerosis. As the mechanisms have been defined, it has become clear that glomerular sclerosis is not the exclusive attribute of longevity; it happens to the young kidney, the hypertensive kidney, the proteinuric kidney, without age-specific predilection. The sclerosing glomerulus represents the vectorial sum of distinct pathways, many of them adaptive responses to trauma, many of them interdependent in their contributions to glomerular effacement (Fig. 1). The aging kidney may be susceptible and the target of multiple injurious vectors rather than of a single one. Nonetheless, in the absence of such vectors or in the presence of therapies that prevent the expression of these vectors, we have no reason to believe that the kidney would be unable to preserve its function and even adapt to serve the changing metabolic needs of its aging host. Therefore, the first step towards targeted therapy, which will protect both the 30- and 70-year-old kidney, is to delineate the pathways of glomerular sclerosis.

Glomerular sclerosis is a complex process which still is incompletely understood. The endpoint is the effacement of the glomerular capillary bed and

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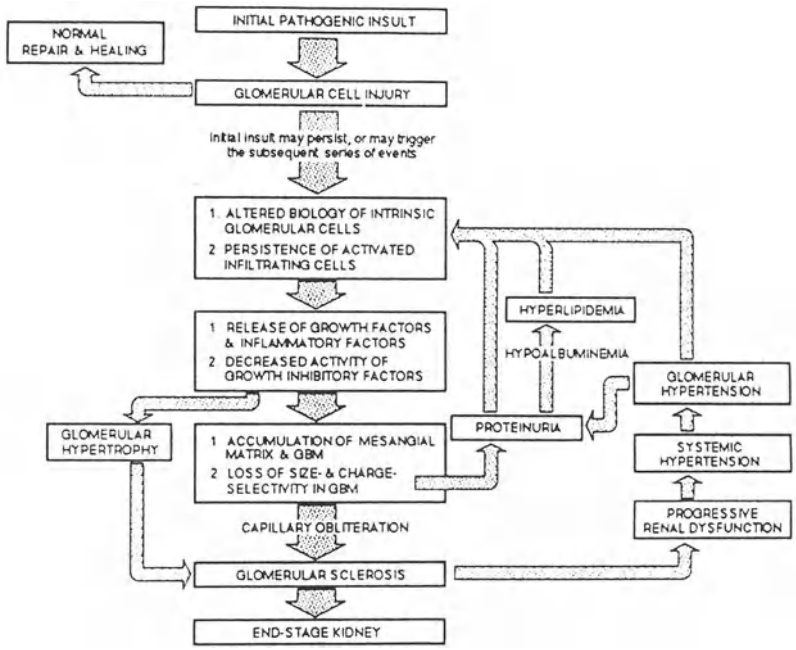

Fig. 1. Mechanisms by which glomerular injury may lead to glomerulosclerosis. Reprinted with permission from Ref. [1].

the loss of its capacity to form a plasma ultrafiltrate. Cellular changes in the sclerosing glomerulus include proliferation of endogenous glomerular cells, particularly endothelial and mesangial cells, inhibited function of epithelial cells, and infiltration by mononuclear leukocytes, principally macrophages. Extracellular changes in glomerular effacement include expansion of extracellular matrix, particularly in the glomerular mesangium with subsequent collapse of the adjacent capillary lumens [1].

The mesangium

The mesangium appears to be the locus of the earliest events in glomerular sclerosis. This structure is composed of contractile cells that resemble vascular smooth-muscle cells, whose state of activation determines the surface area of the glomerulus available for ultrafiltration. The mesangial matrix consists of a variety of glycoproteins and mucopolysaccharides [2]. The expanding mesangial matrix characteristic of sclerosis contains excess amounts of normally present mesangial proteins, including laminin, fibronectin, collagen, and decorin. Often increased numbers of mesangial cells can be found in the early phases of mesangial sclerosis; these cells represent an admixture of proliferating mesangial cells and infiltrating macrophages. As the glomeru-

lar capillary bed becomes ischemic secondary to the occlusion of the capillary lumens, these cells disappear, leaving an acellular scar as a residual mark of their presence [3]. As will be noted below, many of the peptide factors implicated in glomerular sclerosis induce either mesangial-cell proliferation or synthesis of extracellular mesangial matrix.

In addition, the circulation of macromolecules in the mesangium renders the glomerulus more vulnerable to injurious molecules. The fenestrated endothelium overlying the mesangium permits macromolecules to diffuse under the endothelium and into the mesangial region. This parallel circulation passes through the mesangial stalk, past the juxtaglomerular region, and out into the interstitium, from which it is drained by the renal lymphatics. Thus, toxic serum molecules or the secreted products of activated cells within the mesangium can affect the entire mesangial space and the structures of the juxtaglomerular region, which in turn regulate glomerular microcirculation [3].

Circulating paraproteins are examples of toxic macromolecules, which are deposited within the mesangium and contribute to glomerular sclerosis. Myeloma proteins, amyloid, cryoglobulins all are associated with mesangial deposition [1]. Recently it has been observed that lipoproteins, particularly low-density lipoproteins (LDL), are deposited in the mesangium in various experimental and human models of chronic glomerular injury [3]. Low-density lipoproteins can stimulate mesangial-cell proliferation in low dose or can actually be cytotoxic to mesangial cells in high dose, particularly when oxidized [4]. Deposition of toxic lipoproteins may be augmented by either metabolic alterations of the mesangium or intraglomerular hemodynamic changes. The non-enzymatic glycosylation of both mesangial matrix and serum proteins observed in diabetics enhances the binding of LDL to matrix and inhibits LDL catabolism, thus potentiating the effects of LDL on the microenvironment of the glomerulus [5]. Diabetic glomerulopathy is also associated with increased deposits of proinflammatory immune complexes within the mesangium [1], which may be due to hemodynamic effects. Infusions of angiotensin II enhance the deposition of immune complexes within the mesangium; the increased mesangial localization of immune complexes observed in experimental nephrosis is blocked by the angiotensin-II antagonist, saralesin [6]. Intraglomerular hypertension secondary to increased intrarenal production of angiotensin II, as seen in the Goldblatt model, is also associated with the increased mesangial deposition of filtered proteins, a process shown experimentally to accelerate the sclerosis of diabetic nephropathy [7].

Glomerular hypertension

Glomerular hypertension itself has been shown to be a risk factor for sclerosis. The progressive sclerosis seen in human and experimental models of reduced renal mass has been attributed to increased glomerular perfusion

and elevated pressure within the glomerular capillary bed [8]. Maneuvers that inhibit glomerular hypertension, such as inhibition of angiotensin I-converting enzyme or dietary restriction of protein inhibit glomerular sclerosis in both animals and man [1, 8]. In addition to increasing glomerular hypertension and promoting mesangial depositions of immune complexes and perhaps lipoproteins, angiotensin II also may serve as a growth factor, stimulating mesangial-cell proliferation as well as contraction [1]. Thus, angiotensin II may be a glomerular toxin on both physiological and metabolic levels. Systemic hypertension, whether or not it is angiotensin II-dependent, is also linked to the development of nephrosclerosis. It induces a series of potentially injurious responses within the kidney and glomerulus, including vascular-wall intimal hyperplasia, resulting in ischemic decrease of blood flow, direct mediation of glomerular and endothelial damage perhaps *via* the subcellular deposition of serum proteins [9].

Growth factors

Angiotensin II is not the only peptide that is thought to stimulate mesangial expansion. Other growth factors have been suggested from the observation that glomerular hypertrophy is the initial event in several models of progressive glomerular sclerosis, including diabetes, high-protein diets, and partial renal ablation [1]. The contribution of one particular protein growth factor was demonstrated when Doi and colleagues observed glomerular hypertrophy leading to sclerosis in mice rendered transgenic for growth hormone [10]. When combined, platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF), induce mesangial-cell proliferation [3]. Mesangial cells can stimulate themselves via production of a PDGF-like molecule; they are induced to synthesize this factor by other protein factors including epidermal growth factor (EGF) and tumor necrosis factor (TNF) [11]. Recently transforming-growth factor-β (TGF-β) has been shown to play a crucial role in expansion of the mesangium. TGF-β does not induce mesangial-cell proliferation but markedly stimulates its production of extracellular matrix [12]. An experimental model of glomerulonephritis induced by administration of antibody against a mesangial-cell antigen is associated with a marked influx of macrophages and a rapid expansion of the mesangium with respect to both mesangial cell proliferation and matrix synthesis. If the antibody is administered repeatedly, glomerular sclerosis develops eventually. The increase in mesangial matrix is due to increased synthesis of the proteoglycans biglycan and decorin. Their synthesis is regulated by TGF-β, which, in this model of sclerosis, is produced in markedly increased amounts within the glomerulus. Importantly, manipulating this model to block the glomerular synthesis of TGF-β interrupts the mesangial expansion normally observed in this model [13]. Another growth factor, interleukin 1 (IL-1), also is implicated in progressive glomerular effacement.

Lipids

Recently, we have had considerable evidence concerning the influence of hyperlipidemia on exacerbating the progression of glomerular sclerosis. In both a rat model of diabetic nephropathy and a model of partial renal ablation, the remnant kidney, hypercholesterolemia and hypertriglyceridemia correlated with the evolution of glomerular sclerosis; lowering of serum lipids, via mevinolin or clofibrate, markedly protected glomerular structure and function [14]. The results of human studies using lipid-lowering agents are not available yet. As noted earlier, hyperlipidemia may be toxic via direct effects of lipoproteins; alternatively, it may be associated with enhanced infiltration of the glomerulus by macrophages.

One lipid pathway implicated in chronic glomerular injury is the arachidonate metabolite, thromboxane A_2 (TxA_2). This highly vasoconstrictive metabolite of cyclo-oxygenase is released by both mesangial cells and infiltrating leukocytes. In animals with subtotal renal ablation, inhibition of TxA_2 synthesis improves renal blood flow and retards progressive sclerosis [15]. Several workers are evaluating the efficacy of thromboxane synthase inhibitors in human glomerular disease.

Intraglomerular coagulation

Support for the concept that activation of serum or cell-dependent coagulation pathways may contribute to nephrosclerosis arose from the observation that heparin or warfarin inhibits glomerular sclerosis in rats with partial nephrectomies. However, heparin has been shown to regulate mesangial-cell biology independently of its anticoagulant properties: it markedly inhibits proliferation of mesangial cells, and this may be the most important mechanism underlying its antisclerosis effect [1,13]. While many believe that platelet activation contributes to sclerosis, perhaps *via* the production of growth factors such as PDGF or via induction of thrombosis, no convincing effect of platelet antagonists has been demonstrated in human or animal examples of glomerulosclerosis [1].

Infiltrating leukocytes

Only recently have we appreciated that circulating immune cells may make a significant contribution to the chronicity of glomerular injury, even when the initial insult is not immunological. Macrophages are found in a wide variety of glomerular lesions, which are associated with progression to sclerosis, including the glomerulonephritis of systemic lupus erythematosus, membranoproliferative glomerulonephritis, rapidly progressive glomerulonephritis, diabetes, focal segmental sclerosis, and almost all other causes

of nephrotic proteinuria, excepting minimal change disease. Macrophages appear in the glomeruli of numerous experimental glomerulopathies leading to sclerosis, including experimental nephrosis and partial renal ablation. Indeed, hyperlipidemia *per se* is associated with increased glomerular macrophages in both rats and guinea pigs [3]. In an exhaustive series of statistical analyses of numerous parameters of systemic metabolism and renal function in the rat-renal-ablation model, Van Goor *et al.* identified serum cholesterol and proteinuria as the principal clinical determinants, and mesangial-cell proliferation and glomerular macrophage infiltration as the principal cellular correlates of glomerular susceptibility to focal sclerosis [17]. Prevention of macrophage influx into the glomerulus and interstitium of the kidney via sublethal irradiation or dietary restriction of essential fatty acids is highly effective in preventing the sclerosis seen in these models [18, 19]. The association between hyperlipidemia and glomerular sclerosis suggests that the cell biology of glomerular sclerosis is analogous to that of atherosclerosis, which begins with the infiltration of monocytes into subendothelial positions in the presence of hypertension and hyperlipidemia and the subsequent transformation of those monocytes into lipid-laden macrophages, the proliferation of vascular smooth-muscle cells and increase in intimal matrix – all similar to the events attending glomerular sclerosis. A causal link between hyperlipidemia and macrophages is supported by observations from our laboratory that glomerular and interstitial inflammation is associated with the release of a monocyte-specific chemotactic factor, which appears to be a neutral lipid. This factor is not produced in the dietary state of essential fatty acid deficiency, in which suppression of monocyte migration into the glomerulus protects against glomerulosclerosis and nephrosclerosis [16, 21]. Recently this factor has been identified in the urine of nephritic rats and in the urine of patients with renal diseases associated with proteinuria and declining renal function.

Finally, macrophages produce several protein growth factors that have been implicated in glomerular sclerosis, for example, a macrophage-derived factor IL-1, which is released by macrophages after a variety of stimuli, can alter glomerular structure and function on a chronic basis. Glomerulonephritis is associated with enhanced glomerular IL-1 release, both acutely and chronically, in both humans and rats. Removing macrophages from inflamed glomeruli *via* specific antiserum reduces proteinuria and diminishes mesangial-cell proliferation – a process driven by factors produced by infiltrating macrophages [22, 23]. IL-1 stimulates mesangial and endothelial-cell proliferation, and collagen production by glomerular epithelial cells [24–26]. In addition to IL-1, when activated, macrophages may release PDGF, TNF, and EGF, all of which have been implicated in mesangial-cell activation and/or injury [16].

Conclusion

Glomerular sclerosis may be linked to an array of etiologies *via* converging, often interdigitated pathways of chronic injury. Delineating these pathways is crucial to the design of therapeutic interventions directed at lesions that may combine one or more toxic mechanisms. The presence of more than one injurious pathway may have synergistic consequences in promoting glomerular scarring. Mesangial expansion, with or without hypercellularity and increased mesangial matrix, provides a unifying hypothesis for understanding the road to sclerosis. Therapeutic interventions intended to arrest glomerular sclerosis are currently underway with respect to dietary alterations of proteins and/or lipids, decreasing glomerular hypertension, and pharmaceutically lowering of serum lipids. Future initiatives will include blockade of the toxic effects of protein growth and differentiation factors, interruption of the lipid and perhaps protein-dependent mechanisms underlying macrophage infiltration of the glomerulus, and pharmacological modulation of the synthesis and degradation of mesangial matrix.

In the context of these efforts, age can be seen only as a variable that permits inclusion of additional factors of injury after a primary etiology of glomerular injury. Once lesions are classified according to their many pathogenic mechanisms and once we design therapeutic strategies to neutralize those pathways then we will abandon the concept of intrinsic disease of the kidney attributable to old age and we will see that the functional life span of the kidney is commensurate with the life span of its host.

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CHAPTER 6

Renal complications of non-steroidal anti-inflammatory drugs in older people

PAULA A. ROCHON

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs in the United States and the United Kingdom [1, 2]. They are largely used by people over the age of 60 suffering from arthritis. Although generally these drugs are seen as safe and effective, NSAIDs cause side effects in those who use them, particularly older patients who are more vulnerable to the adverse reactions to all drugs.

This chapter will examine the renal side effects of non-salicylate NSAIDs in older people. We will begin by describing why this is an important problem. Next the renal toxicity of NSAIDs will be reviewed and the few studies focusing on older people will be described. This will highlight the need for more age-specific studies in this important area affecting a large and growing segment of the population. Finally, based on the information available to us, we will offer a series of guidelines for clinicians considering the use of NSAIDs in their older patients.

Why is this important

Use

To give some idea of the impact of this problem, we should recognize that, in the United States in 1982, 10 years ago, more than 70 million prescriptions for NSAIDs were filled by pharmacies. In this country at that time, the wholesale cost of NSAIDs was estimated at 800 million dollars, and the cost to the consumer was about a billion dollars [3]. The use of NSAIDs has increased substantially in recent times primarily because these drugs now can be purchased over-the-counter without a prescription. While the impact of over-the-counter preparation of NSAID use in the United States has not been fully determined, it is likely to be substantial. In the United Kingdom during the first 6 months that over-the-counter ibuprofen was available, 18 million of 24-tablet bottles were sold [4]. Since 1982 additional NSAIDs have

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been approved for general use and placed on the market; the most recent, nabumetone, introduced in January 1992.

In the United States, a total of 16 NSAIDs are now available: diclofenac, diflunisal, fenoprofen, flubiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumetone, naproxen, phenylbutazone, piroxicam, sulindac and tolmetin. Based on information obtained from office physicians who report on their private patients, the National Disease and Therapeutic Index estimates that over 40% of fenoprofen, indomethacin and meclofenamate and over 50% of piroxicam and sulindac are used by people over the age of 60 [1]. Frequently these drugs are prescribed for the elderly because this group is prone to arthritis. In fact, 49% of people over age 60, report some form of this disorder [5].

Adverse effects of NSAIDs

NSAIDs toxicity has had an impressive impact. In the United Kingdom, the Committee for Safety of Medicines has shown that NSAIDs are responsible for almost one-quarter of all reported adverse drug reactions in that country [2].

Since older adults are the major users of NSAIDs and because they are more prone to side effects from all drugs, they experience a disproportionate number of these NSAID-attributed side effects and the most severe of these cases. Specifically, the Committee for Safety of Medicine reports 75% of all NSAID-associated gastrointestinal bleedings were in patients 60 years of age and over, and 90% of the associated fatalities were in patients over the age of 60 [2]. Similarly Griffin *et al.* reported a substantial risk of death related to peptic-ulcer disease in older patients using NSAIDs [6].

Although the most frequently reported NSAID side effects are gastrointestinal, renal side effects are likely to be underestimated [7]. Gastrointestinal disease often produces symptoms, thus they are easy to recognize and gastrointestinal 'bleeds' are often dramatic. In contrast, renal disease may produce no symptoms and thus go unrecognized unless tests for renal function are undertaken. The next most common NSAID-associated adverse reactions are skin lesions followed by central nervous system reactions [7].

Despite the frequency and seriousness of NSAID adverse reactions particularly in older people, NSAIDs continue to be overprescribed. A recent study of the acutely hospitalized elderly in England, showed that some 13% of them were on NSAIDs at the time of admission and most had adverse drug reactions attributed to these drugs. In 75% of these older patients, NSAIDs were discontinued and one-half of these people required no subsequent therapy with such drugs [8]. Given the potential high risk associated with these drugs, we should prescribe them only when clearly required.

The Ad Hoc Committee of the National Kidney Foundation outlined concerns about the potential impact on kidney function of ibuprofen release

as an over-the-counter preparation [4]. This committee identified several groups who were at high risk for renal complications, including those 65 years of age or over. The committee suggested that warnings be placed on or in the packages of these over-the-counter NSAIDs, warning these high risk groups about the adverse renal events caused by over-the-counter ibuprofen unless the substance is used under the supervision of a physician. In addition they identified other high-risk groups to whom this restriction should apply such as those with heart disease and hypertension and those on diuretics commonly used by older people [4]. However, in the United States, the package inserts in over-the-counter ibuprofen do not carry these specific warnings. Instead, a general warning that if the purchaser has a medical condition for which they are taking prescription drugs or are under a doctor's care, they should consult the physician before taking the product. However, this general warning may not be adequate and we continue to have deep concern about renal complications from over-the-counter NSAIDs [9–11].

Renal complications

Proposed mechanisms of NSAID-related renal impairment

NSAIDs block the production of cyclo-oxygenase, an enzyme necessary for prostaglandin production. Renal prostaglandins, prostaglandin E_2 and prostacyclin (prostaglandin I_2) are powerful vasodilatory hormones. In healthy young people with normal renal function, prostaglandins are less important; in fact a study of normal volunteer subjects [12] showed no change in renal blood flow or the glomerular filtration rate following the inhibition of prostaglandins by NSAIDs. However, older people with underlying renal impairment and limited renal reserve may depend on the compensatory effects of prostaglandins to maintain adequate renal blood flow and glomerular filtration rate. In addition, at baseline, there is some suggestion that renal prostaglandin synthesis decreases with advancing age [13]. When one gives NSAIDs to elderly patients with age-related renal impairment, it may tip the balance from adequate renal function to impaired function. To be specific, NSAID administration can unmask prostaglandin dependence of renal function in older people [14]; without its contribution to vasodilation, unopposed vasoconstriction may lead to renal failure.

The renal complications of NSAIDs can be divided into two groups: renal failure, and fluid and electrolyte abnormalities. NSAID-associated renal failure can be further subdivided into hemodynamic abnormalities, papillary necrosis and acute interstitial nephritis. Fluid and electrolyte abnormalities include sodium retention, hyperkalemia and impairment of water excretion [15]. Of these, hemodynamic disturbances are particularly relevant to older people.

Sodium retention and hyperkalemia are frequently reported in association

with NSAID use while papillary necrosis and interstitial nephritis are uncommon. We will review each of these NSAID-associated renal abnormalities with particular reference to their relevance to older people.

Renal failure

Hemodynamic factors are important in the development of NSAID-associated renal failure in older people. As noted earlier, older patients with diminished renal perfusion rely on the vasodilatory prostaglandins to maintain renal blood flow and are therefore likely to develop renal complications when prostaglandin production is blocked by the administration of NSAIDs. For example, an older person may have pre-existing renal impairment such as an age-related decline in glomerular filtration rate, atherosclerosis or hypertensive renal disease [7]. Superimposed on this renal dysfunction, an older patient may have hemodynamic impairment secondary to the use of diuretics or congestive heart failure, both of which lead to volume depletion.

When NSAIDs are given to an older person with pre-existing renal impairment and some form of hemodynamic impairment, it blocks the important compensatory contribution of prostaglandin-mediated vasodilation. The resulting renal vasoconstriction can lead to ischemia so it is not surprising that impaired renal function is common in older people taking NSAIDs.

Papillary necrosis

NSAIDs may cause chronic renal failure secondary to papillary necrosis. Unlike renal failure due to hemodynamic disturbance, papillary necrosis is relatively uncommon. Again the mechanism is likely related to the inhibition of prostaglandins and resultant vasoconstriction which lead to renal ischemia particularly of the medulla. This injury has been associated with phenacetin or aspirin taken alone or in combination [16]. However, papillary necrosis has been reported in association with NSAID use [15, 16].

Interstitial nephritis

Evidence concerning a relationship between interstitial nephritis and NSAID use is limited to case reports [16] of acute renal failure with nephrotic-range proteinuria, and of acute interstitial nephritis with proteinuria that is not in the nephrotic range. We have little information concerning this complication in the elderly.

Fluid and electrolyte abnormalities

Sodium retention

Sodium retention has been associated with almost all of the NSAIDs [16]. Normally, prostaglandins facilitate sodium excretion in two ways. As intrarenal vasodilators, prostaglandins promote increased renal blood flow and glomerular filtration rate, which increases the filtered load of sodium. In addition, prostaglandins decrease the amount of reabsorbed sodium [15]. NSAIDs block the production of prostaglandins, which decreases the kidney's ability to excrete sodium. The resulting sodium retention manifests itself as edema reported in as many as 25% of arthritis patients treated with fenoprofen, and 10% of those receiving ibuprofen [16].

Impairment of water excretion

NSAIDs seem to impair the kidney's ability to excrete free water. Prostaglandins play several roles in the urinary concentrating and diluting mechanism but their overall effect is to promote free-water excretion [15]. Although prostaglandins have numerous and complex actions, they are likely to facilitate water excretion through the following mechanism [15]. Through intrarenal vasodilation, prostaglandins increase renal blood flow and glomerular filtration rate and thus promote the delivery of filtrate to the distal nephron. In addition, increased medullary blood flow decreases papillary hypertonicity, which facilitates free water excretion by limiting the maximum concentrating ability. As well as playing other roles in maintaining water balance, prostaglandins also interfere with the action of antidiuretic hormone and thus limit water reabsorption by the collecting duct [15]. When administration of an NSAID interferes with prostaglandin synthesis, it impairs the complex process which maintain water balance, and as a result decreases the kidney's ability to excrete water.

Hyperkalemia

Hyperkalemia is another adverse effect of NSAIDs on kidney function related to renal prostaglandins, which enhance delivery of filtrate to distal sites and increase renin release [15]. For example, when prostaglandins are inhibited, less sodium is available for exchange in the distal tubules and therefore limiting the amount of potassium that can be excreted. In addition, inhibition of prostaglandins blunts the response of the renin-angiotesin-aldosterone system [15]. Almost all NSAIDs produce a decrease in plasma-renin levels [16]. Hyperkalemia secondary to prostaglandin inhibition is a serious side effect that may require medical intervention.

Table I. Qualitative summary of the seven published studies on renal complications of NSAID use in older people

Author (Year)	Sample size	Mean age	Renal outcome measure
Clinical Trials			
Gurwitz (1991)	7	72	Creat Cl[1]
Murray (1991)	6	72	Inulin Cl
Cummings (1988)	52	72	Bun/Creat[2]
Observational Studies			
Gurwitz (1990)	NSAID 114 comparison 45	87	Bun/Creat
Hale (1989)	NSAID 181 comparison 796	76	Estimated Creat Cl
Allred (1989)	NSAID 27 comparison 27	84	Bun/Creat
Sandler (1991)*	Chronic renal disease 554 control 516	62	Not applicable

* Case control study.
[1] Creat Cl = creatinine clearance.
[2] Bun = Blood urea nitrogen.

NSAIDs and renal function in older patients

Given the frequency of NSAIDs side effects and the likelihood that most of these reactions occurred in the elderly, it is surprising that the literature contains so little specific information about the renal complications of non-salicylate NSAIDs in older people. A review of the published literature in a MEDLINE search (key words: anti-inflammatory agents non-steroidal, not aspirin, English only, human only, renal) and a survey of personal files identified only seven studies [9, 11, 14, 17–20]. An additional three studies, not included in our sample, have been published. Two of these three studies, an observational study by Fox and Jick [21] and a clinical trial by Bonney *et al.* [22] included both young and old people. However, neither of these studies provide a separate analysis for the subgroup of older people. The third study, by Whelton *et al.* [23], evaluated 12 patients, half of whom were 65 years of age or over. However, this study evaluated patients with pre-existing asymptomatic renal failure and was therefore also excluded.

The literature on NSAID-associated renal complications in older people is small and relatively recent; the first paper in this area was published in 1988. Table I summarizes these seven papers and the following discussion reviews their content.

Three of the seven studies were clinical trials. In the first of these, a crossover trial of indomethacin followed by sulindac, Gurwitz *et al.* studied seven healthy older people (without any major comorbid disease) with a mean age of 72 [14]. Treatment with either of these NSAIDs brought signifi-

cant reduction in creatinine clearance. However, the authors suggest that their results be interpreted with caution. The sample size was small and the marked variation in estimates of creatinine clearance limited the study's ability to detect small changes in clearance after drug therapy. In addition, the therapy may have been too short to affect renal function.

Murray *et al.* studied six healthy older people (mean age 72 years) in a randomized crossover trial with three NSAIDs-ibuprofen, sulindac and piroxicam [18]. Using inulin clearance – a more precise measure of renal function, they found a statistically significant decline in inulin clearance after the first dose and after a month of treatment with each of the NSAIDs. This information was published as an abstract and more data is expected as additional subjects are studied [18].

The third study was a randomized trial which compared ibuprofen with aspirin in 52 patients (mean age 72) with arthritis and other comorbid medical conditions [20]. Using serum creatinine and blood urea nitrogen to reflect renal function, no deterioration was found after six weeks of therapy. However, seven of the 52 patients were dropped from the study in the first two weeks because of adverse, chiefly gastrointestinal, drug reactions. These seven patients were not included in the analysis.

Four of the seven studies were observational. Gurwitz *et al.* identified risk factors for NSAID-associated nephrotoxic effects in frail, older people (mean age 87 years) residing in a long-term care facility [17]. The 114 residents, who received a NSAID had a statistically significant increase in blood urea nitrogen compared to 45 people in the control group. Furthermore, blood-urea nitrogen was elevated after a short period on the NSAID, only 5–7 days of therapy. Fifteen patients receiving NSAIDs developed azotemia (defined as a 50% rise in blood urea nitrogen over baseline). Risk factors for azotemia included the use of a loop diuretic and a higher prescribed NSAID dose. This, the only study of the renal toxicity of NSAIDs in the frail 'old-old' (85 years and over), documents the frequency of renal dysfunction and azotemia following a short course of NSAIDs in this vulnerable group; it illustrates the need for caution when prescribing these agents.

Hale *et al.* [9] examined ambulatory older patients in an annual health screening program (mean age 76) and evaluated renal function in 181 patients who received non-salicylate NSAIDs and a comparison group of 796 patients who did not. They found a statistically significant decline in renal function, as estimated by a reduction in creatinine clearance in the group of men on NSAIDs. This study has been criticized because of the method used to estimate creatinine clearance and because the information about NSAIDs use was based on self reporting, which is known to be unreliable [17].

Sandler *et al.* [11] conducted a case-control study of the relationship between chronic renal disease and NSAID usage. They identified 554 patients between the ages of 30 and 79 hospitalized with a diagnosis of chronic renal disease and compared them to a group of 516 controls. Information on NSAID use was obtained from telephone interviews. They found a twofold

increase in chronic renal disease in association with daily use of NSAIDs – an increased risk that was seen predominantly in men 65 years of age and over.

Allred *et al.* [19] conducted a prospective cohort study of ambulatory patients admitted to their day hospital in England to look at the relationship between NSAID use and renal function. In 27 patients on NSAIDs and another 27 patients not on NSAIDs, renal function was evaluated using serum creatinine and urea. Neither group showed any decline in renal function as measured by blood urea nitrogen or serum creatinine.

Although each of these seven studies evaluated renal complications of NSAIDs in older people, they cannot be compared because they used different parameters. For example, using inulin clearance, Murray *et al.* [18] showed a decline in glomerular filtration after NSAID administration, which suggests that, when a precise measure is used, renal impairment can be demonstrated after NSAID administration even in healthy elderly people. However, techniques such as inulin clearance are not readily available to the clinician.

Because indices such as blood-urea nitrogen and serum creatinine levels are available, the clinician will use these to look for renal impairment in their older patients. In addition, studies of healthy older people cannot be generalized to the more usual frail older person with multiple comorbid illness. Therefore it is important to collect information on older patients more typical of those who may use the drug. For this reason, the study by Gurwitz *et al.* [17] is helpful because it used a renal outcome measure that is readily available and the frail older patients they studied are those most at risk for adverse renal complications of NSAIDs. There are only few studies of NSAIDs and of their renal complications in older patients relative to the huge volume of these drugs used by this segment of the population [24, 25].

Guidelines to prescribing NSAIDs to older patients

The available data on the relationship between NSAID use and renal impairment in older people indicate that no NSAID is totally safe in the elderly. Their risk/benefit ratio should be considered carefully before they are prescribed, particularly in frail older people and alternatives should be considered. Table II presents some guidelines to follow when considering prescribing NSAIDs.

First, is the NSAID really needed? They are overprescribed particularly in older people without adequate consideration of the risks and benefits in this vulnerable group [8]. Consider, therefore, alternative approaches.

Whenever possible, prescribe simple non-pharmacologic treatment. Patients for example have to be educated on how to protect their joints from further damage. Losing weight, using an adaptive aid such as a cane, and

Table II. Guidelines to consider before prescribing NSAIDs

NSAIDs	Are they needed?
Simple	Non-pharmacologic therapy may provide adequate benefit
Analgesic	Consider acetaminophen
If	NSAIDs are required use: minimum dose minimum duration of treatment
Do	Monitor for side effects
Stop	If side effects develop

following structured exercise programs all help the patient and reduce the symptoms of arthritis [7, 26].

If the patient requires a simple analgesic, acetaminophen may suffice and has minimal side effects; in the treatment of osteoarthritis of the knee, it is as effective as either analgesic or anti-inflammatory dose of ibuprofen [27]. When considering using NSAIDs in older patients, one should weigh the costs and benefits.

If NSAIDs are required, the minimum effective dose should be used because the literature suggests that higher NSAID doses are related to renal toxicity. Gurwitz *et al.* showed that, in the frail older patient, a higher NSAID dose was associated with the development of azotemia [17]. In addition, the NSAID should only be used for as long as treatment is indicated. A regular re-evaluation of the need for continued treatment should also be carried out.

Patients, particularly those in the vulnerable frail older group, taking NSAIDs should be monitored carefully for side effects. Concerning laboratory tests, blood urea nitrogen, serum creatinine and potassium levels must be particularly checked. History and physical exam should focus on evidence of adverse effects such as edema. Remember that renal impairment is often asymptomatic and must be anticipated in the older patient. NSAID therapy in patients who develop side effects should be discontinued.

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CHAPTER 7

Treatment of hyperlipidemia in the elderly

RUTH McPHERSON

Hypercholesterolemia is a major risk factor for coronary heart disease (CHD) and patients over age 65 show an increased incidence of both lipid abnormalities and clinical CHD. Although the positive association between low-density, lipoprotein (LDL) cholesterol and CHD incidence and the stronger negative relationship between high-density lipoprotein (HDL) cholesterol and CHD risk are well established, the predictive power of LDL-cholesterol decreases with age [1]. Hence, many have questioned the benefit of lipid treatment in the elderly.

Effects of age on the LDL-C/CHD risk relationship

There may be many reasons for the decline in the slope of the LDL-C versus CHD curve with age [2, 3]. The elderly have other risk factors for CHD, such as hypertension, impaired glucose tolerance, and obesity and these may intervene in the cholesterol/CHD relationship [2]. Generally, older individuals have more advanced atherosclerotic disease and the acute coronary event may be due to plaque rupture or thrombosis and hence the event is less dependent on LDL-mediated changes in plaque size. In addition, other genetic, metabolic or environmental protective factors may permit the 'selective survival' into old age of a subset of hypercholesterolemic individuals.

In the elderly, ascribing CHD as the cause of death may be confounded when several disease entities contribute to the final event. Finally, temporal changes occur in the lipoprotein profile and, in an elderly patient, a low level of LDL-C may reflect underlying disease or recent nutritional depletion and may not be a marker of habitual or life-long LDL concentration (Table I).

Even though the predictive value of LDL-C in determining CHD risk (relative risk) declines with age, the number of CHD events and CHD deaths increases dramatically. Hence the attributable risk of CHD due to elevated levels of LDL-C is much greater in individuals over the age of 55 than for

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Table I. Effects of age on the cholesterol/CHD relationship

Competing risk factors
Arterial-wall changes
Selective survival
Nonspecificity of CHD diagnosis
Low cholesterol as symptom of underlying disease
Temporal changes in lipid profile

Table II. Potential benefit of cholesterol reduction from 7.4 to 5.2 mmol/l

Age	Decrease in CHD risk %	Preventable CHD deaths M	F	CHD cases M	F
35–44	77.4	1.8	0.7	11.8	3.2
45–54	61.8	6.3	0.9	23.4	6.0
55–64	46.3	8.7	1.8	26.0	10.2
65–74	33.1	9.5	3.8	20.4	10.6
75–84	22.9	12.7	6.5	20.4	12.3

Gordon and Rifkind. Am J Card 1989; 83:48H

younger subjects; this enhanced attributable risk [4] also applies to individuals over 75 years (Table II).

Thus, treatment of hypercholesterolemia in the patient over 65 years may be justified to improve the quality of life and to make such interventions as bypass grafting, angioplasty and coronary-care-unit admission unnecessary. Since these interventions are more complicated and costly in elderly subjects, short-term cholesterol reduction may be more cost-effective in certain older as compared to younger individuals.

Decision to treat

Obviously not all elderly hypercholesterolemic patients are candidates for lipid-lowering therapy. The decision to treat should be based on individual quality of life and life expectancy as well as on the severity of the lipoprotein disorder, history of clinical CHD and the presence of other risk factors such as hypertension, cigarette smoking and diabetes mellitus that enhance the risk conferred by LDL-C. Elderly, non-institutionalized individuals without other life-limiting conditions and a good psychosocial and physical quality of life are candidates for lipid-lowering therapy if their estimated life expectancy is five to 10 years or greater, because over this period, one can anticipate a 40% reduction in CHD events including death [5]. More aggressive cholesterol reduction over a shorter time period ($2\frac{1}{2}$ y) has been shown to reduce clinical CHD events by 70% in patients with documented coronary vessel

Table III. Decision points for pharmacological treatment of hypercholesterolemic patients after dietary stabilization

LDL-C mmol/l	CHD risk factors[a]	Clinical CHD	Treatment	LDL-C treatment goal mmol/l
< 4.9	0	0	Diet	< 4.2
> 4.9	0	0	Medication	< 4.2
> 4.2	≥ 2	0	Medication	< 3.4
> 3.5	±	Present	Medication	< 2.5

[a] Other CHD risk factors including male sex, HDL < 0.9 mmol/l, diabetes mellitus, ≥ 10 cigarettes/day, hypertension, CHD in first degree family member before age of 60 y.

disease [6]. Other potential benefits include increased duration of graft survival after coronary-artery, bypass surgery [7].

Individuals of all age groups with LDL-C levels greater than 3.5 mmol/l (140 mg/dl) should adopt a program consistent with the principles of an AHA Step I diet. The elderly patient needs dietary advice although adherence may be difficult due to budget restrictions, difficulties with food preparation and engrained food habits. One should exclude secondary hyperlipidemias due to other drug therapy, preclinical hypothyroidism and renal disease. The decision to add pharmacological therapy to diet will depend on other risk factors or clinical CHD. We begin treatment at an LDL-C level of 4.9 mmol/l in the absence of other CHD risk factors and would begin pharmacotherapy at lower levels of LDL-C if the elderly patient has two or more other risk factors (LDL-C ≥ 4.2 mmol/l) or clinical CHD (LDL-C ≥ 3.5 mmol/l).

The goals of therapy are to achieve an LDL-C of 2.5 to 4.2 mmol/l dependent on other clinical factors (Table III) [8].

Choice of pharmacological agents

Elderly individuals respond well to all available hypolipidemic agents; with drugs such as HMG-CoA reductase inhibitors [9], niacin [10] and probucol [11], the cholesterol lowering efficacy of a given dose is superior in older than in younger individuals. Hence, usually we start treatment with the smallest effective dose and increase it as necessary. Generally we recommend a reductase inhibitor when LDL-C is elevated and triglycerides are < 4.0 mmol/l. Alternative agents include bile-acid sequestrants and niacin.

For the patient with more severe hypertriglyceridemia and/or a low level of HDL-C, the agent of choice is niacin, if it is tolerated. Acceptable alternatives are the fibric-acid derivatives (fenofibrate, gemfibrozil). With all of these agents, one should monitor transaminase and CPK levels every four months for the first year and, in the absence of symptoms, every 6 months thereafter (Table IV).

Controlled clinical trials of the effects of LDL-C lowering in the elderly

Table IV. Choice of hypolipidemic medication for the elderly patient

TC & LDL-C	TG	HDL-C	Drug of choice
Increased	< 4.0 mmol/l	> 0.8 mmol/l	HMG-CoA reductase inhibitor ± bile acid sequestrant
Normal or increased	> 4.0 mmol/l	< 1.0 mmol/l	Niacin or fenofibrate or gemfibrozil
Normal	Normal	< 0.8 mmol/l	Niacin

are now in progress. Present data offers a sound rationale for treating hyperlipidemia and other risk factors, such as hypertension and diabetes mellitus, in many patients over the age of 65 years.

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PART THREE

Parenchymal renal disease

CHAPTER 8

Glomerulonephritis in the elderly

DANIEL C. CATTRAN

Differences in certain immunological markers and their function in the elderly might be expected to translate into a change in the severity or type of glomerulonephritis ('the elderly' are those who have attained the age of 60 or more and have biopsy-proven glomerulonephritis). These abnormalities have been noted in both humoral and cell-mediated components of immunity. Alterations in T-cell function include a general reduction in T-helper cell and an increase in T-suppressor cell populations and an increase in anergy as demonstrated by a delayed hypersensitivity reaction to a number of different mitogens [1–3]. In humoral immunity, several workers have observed a decrease in soluble-substance elaboration such as migration-inhibition factor [4, 5]. In both the animal and human species, physical changes with age have been described and include alterations in both the thickness and composition of the glomerular basement membrane [6, 7].

Histologic types and incidence

The data in this review are based on the limited number of studies in the literature. Although few specifically discuss glomerulonephritis in the elderly, all agree that this is not a rare event and, in some types, the incidence is greater than in the younger adult [8]. In examining the prevalence of these varieties of glomerulonephritis in the elderly, we must consider the population base. In the United States in the early 1980s, the ratio of people 15–59 versus $\geqslant 60$ was approximately 4.5:1 [9]. Table I outlines the ratio and the absolute number of cases of the different types in the Toronto Glomerulonephritis Registry [10] and compares this data to the general population. This probably underestimates the numbers of elderly cases because nephrologists probably hesitate to perform a renal biopsy in this age group because of the risk of the procedure. Table II compares the major studies [11–15], which define the specific types that present with the nephrotic syndrome in the aged with the Toronto results. Recognizing that these studies span Europe, Japan and North America, it is surprising that there is a general

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Table I. Toronto glomerulonephritis registry data (1974–1990): Incidence and type (15–59 versus ≥ 60 years)

Type	Total Numbers	Ratio (15–59/≥ 60)
General Population		4.5:1
Vasculitis	110:80	1.37:1
Crescentic Glomerulonephritis	140:74	1.89:1
Membranous	343:129	2.6:1
IgA Nephropathy	508:41	12.2:1
Lupus nephritis	516:23	22.4:1

uniformity in the overall percentages of the different subgroups of primary glomerulonephritis. In all studies the most common type is membranous nephropathy followed by minimal-change disease and then focal sclerosing glomerulonephritis. Table III, which includes all presentations of glomerulonephritis in the elderly [11–14, 16], reveals that the acute nephritic onset is most commonly associated with crescentic and vasculitis type of pathology. When the latter group is included, this type of presentation makes up a significant proportion of many serious i.e. almost 30% in both Moorthy's [12] and the Toronto Registry reports. In studies that describe the crescentic variety in more detail, the pauci-immune and granular-immune-complex variants are more frequent and the anti-glomerular basement-membrane type is rare when compared with their frequency in the under 60 population [16, 17]. Prognosis and therapy in this group [12, 17] is further defined and discussed by Donadio elsewhere in this book.

Figure 1 shows by each decade of life the frequency of the different types of glomerulonephritis seen in our registry. Three of the more common primary types in the elderly are described below.

1. *Minimal change disease*

In primary minimal-change disease in the elderly, the remission rate after steroid therapy is equivalent to that in the younger adult [12–14]. Most authors report an 85–90% complete response although it may take 10–16 weeks of daily steroids as opposed to a mean of 4–6 weeks in childhood. Patients, who relapse, often will respond to a repeat course of prednisone. Approximately 70% of patients, who are either steroid-dependent or are frequent 'relapsers', will have complete remission after an 8-week course of a cytotoxic agent. In the aged population we should consider a cytotoxic drug as the first agent instead of high-dose daily prednisone, especially if they have a tendency to GI ulceration or fluid accumulation secondary to underlying cardiac disease. Although no one has compared these two thera-

Table II. Series in patient ⩾ 60 years of age: Incidence of histologic lesions associated with the nephrotic syndrome [% (number)]

Series	GN Registry United Kingdom	Moorthy United States	Zech France	Sato Japan	Bolton United States	Toronto GN Registry Canada	Totals
Histologic type							
Minimal Change Disease	15(35)	17(9)	30(19)	12(7)	25(13)	12(27)	16(110)
Focal Segmental Glomerulosclerosis	7(16)	30(16)	5(3)	–	19(10)	18(41)	12(86)
Membranous	48(116)	27(15)	49(31)	53(30)	40(21)	57(129)	49(342)
Membranoproliferative Glomeruonephrits	8(19)	4(2)	3(2)	12(7)	6(3)	12(27)	7(60)
Proliferative							
(i) Focal*	10(23)	13(7)	6(4)	–	6(3)	4(8)	7(45)
(ii) Diffuse	10(25)	9(5)	6(4)	21(12)	–	4(8)	8(54)
Total	(234)	(54)	(63)	(56)	(50)	(240)	(697)

* Igm, IgA, focal proliferative.

Table III. Elderly series: Incidence of histologic lesion associated with the acute nephritic syndrome

	Moorthy (U.K.)	Sato (Japan)	U.K. Reg	Kingswood (U.K.)	Toronto GN Reg (Canada)
Crescentic GN/Total Number	24/105	1/57	106/1386	9/82[+]	74/536
Vasculitis/Total Number	6/105	–	–	–	80/536
Percentage of series	23(29*)	2	7.6	11	14(29*)

* Including vasculitis.
[+] Subtypes

Anti GMB	12%
Granular Deposites	53%
Pauci Immune	35%

pies in the elderly with minimal-change disease, on the surface the risk-to-benefit ratio would favor a trial of the cytotoxic drug first.

2. *Focal segmental glomerulosclerosis*

Previously published studies show that this type has the greatest variance in terms of its recognition on biopsy as a case of the nephrotic syndrome in the elderly (Table II). However, the most recent surveys from the United Kingdom's Glomerulonephritis Registry [11] and our own Registry suggest that this type is responsible for between 7% and 18% of these cases. Only the smaller studies [13, 15] report the effects of therapy and these indicate that six treated patients showed no response. However, the drug type, dose and duration are not specified and these studies are too small to permit any firm conclusions. Our own data on the effects of treatment in adults [18] showed a complete remission in 15–30% of patients given a course of prednisone similar to that used in minimal-change disease.

3. *Membranous nephropathy*

The literature [12–14] on the outcome in 66 elderly patients with membranous nephropathy suggests that the prognosis is similar to younger adults. Complete remission was reported in 10–20%, persistent proteinuria in 30–50% and progressive renal failure in the remaining patients. Approximately 50% of these patients were treated with steroids and it was difficult to determine whether this therapy influenced the overall response rate. This lack of response is compatible with two recent controlled trials, which show no benefit even after up to 6 months of alternate-day therapy [19, 20]. In our own registry, of the 87 patients with membranous nephropathy over the

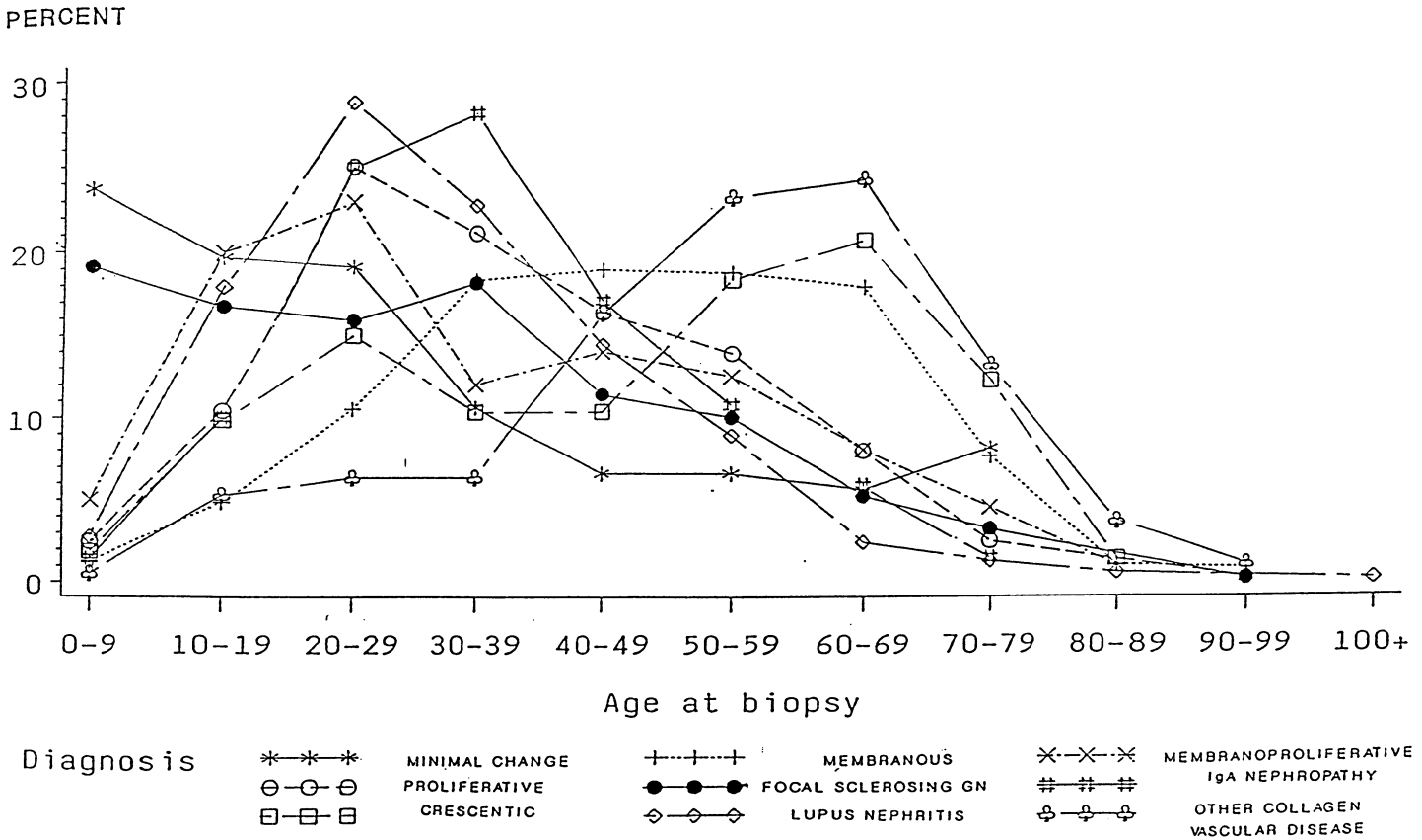

Fig. 1. Distribution of age and glomerular disease type at biopsy.

Table IV. Elderly series of secondary causes of the nephrotic syndrome. Number (% of total).

Series	Sato	United Kingdom Registry	Kingswood	Zech	Bolton
	26(31)	103(22)	21(42)	19(40)	15(24)
Differential					
Amyloid	9(35)	32(31)	11(52)	9(47)	9(60)
Diabetes Mellitus	12(46)	11(10)	–	–	4(27)
Malignancy	–	15(15)	3(14)	7(37)	2(13)
Others	5(19)	45(44)	7(33)	3(16)	–

age of 60, 50% have been treated with steroids. When compared with a similar number of untreated patients, we find that a similar percent have progressed or have had a complete remission. No data are available concerning the effect of treatment in this age group as compared with a more potent regimen such as that advocated by Ponticelli *et al.* [21]. We need a way to identify the patients most likely to progress before we can recommend any potentially toxic therapy in this aged population. A recent model for predicting outcome uses three parameters: Initial creatinine, severity and persistence of proteinuria, *plus* the change in creatinine over a fixed time period has demonstrated an improved sensitivity and specificity compared to earlier prognostic indices [22, 23]. This formula can also be used to identify the low-risk group i.e. approximately 60% of the membranous patients, and thus avoid potentially toxic therapy in this population.

Secondary causes of the nephrotic syndrome

Five reviews indicate the percentage and the specific agents responsible for the nephrotic syndrome in the elderly (Table IV). The prevalence of malignancy, like the prevalence of primary glomerulonephritis, should be compared to the same age group in the general public. Epidemiological data [24] estimates the number of new cases of cancer per year in this age group to be approximately 1660 per 100,000 people (1.66%). When this rate is compared to estimates of malignancy associated with renal disease [11, 13, 15, 25], the percentage varied between 4.7% and 11.8% of the total series of nephrotics, and from 13–37% of the specific secondary causes. In up to 80% of these cases, membranous nephropathy is the correlated histologic type. If one includes amyloid as a malignant process, this percentage is even higher (Table IV). Others have disputed these figures [26] based on local prevalence data, although no one denies the association between malignancy and the nephrotic syndrome in the elderly. Most of the related cancers are solid tumors of the gut, lung or genital urinary tract. A recent large series [11] has described other histologic types, including minimal-

change disease and focal sclerosing glomerulonephritis in association with malignancy in the elderly. A major reason to identify an identifiable cause for the nephrotic syndrome is that this group has an ominous prognosis. In one series, the mortality rate was as high as 80% at 2 years [27] and in another 67% at 2 years [28] when a secondary cause of nephrotic syndrome was discovered.

Patient evaluation

General aspects

Glomerulonephritis is not uncommon and the standard history, physical and laboratory examination of the elderly with renal disease, should place special emphasis on certain areas. The patient's medication list should be reviewed in detail. Consider the possibility of drug-induced renal disease secondary to such agents as gold or penicillamine therapy, and nonsteroidal anti-inflammatory agents in all elderly patients, who develop renal insufficiency and/or heavy proteinuria.

The cardiovascular system is examined with care because a presentation with congestive failure or left-ventricular dysfunction can obscure the fact that the fluid retention was secondary to the nephrotic syndrome or acute renal insufficiency. Failure to obtain and review the urinalysis and renal function tests in these patients at presentation can result in inappropriate therapy. Renal-function tests, which should be done with precision, include a urinalysis by an experienced physician, evaluation for paraproteins and an awareness that any estimate of renal function as measured by serum creatinine should be adjusted to the patient's age and sex [29].

In a search for underlying malignancy, consider whether the patient has membranous nephropathy or shows any hints of underlying cancer. Do a careful examination of the most common recognized primary sites for an occult malignancy and check major risk factors such as smoking or hydrocarbon exposure. Other tests that should be considered in these patients are the antineutrophilic cytoplasmic antibody test (ANCA), a simple test with good specificity and sensitivity for underlying vasculitis, a fasting and 2-hour PC blood glucose in regards to occult diabetes and, in any patients suspected of myeloma, a serum-protein electrophoresis.

General elements of management of the elderly patient management

Nutritional status should be assessed in these patients. We have not evaluated protein restriction in the elderly with renal disease, specifically the risk of precipitating significant malnutrition in the very elderly on markedly reduced dietary protein intake. It may be necessary to monitor urine urea with the

standard urine tests to guard against unexpected inadequate protein intake. Also dietary sodium restriction and diuretic therapy should be carefully monitored because some patients with renal insufficiency may have an obligatory sodium loss and volume depletion with pre-renal azotemia, which can aggravate and/or complicate the renal parenchymal disease component. Similarly, although we have effective lipid lowering agents i.e. competitive inhibitors of HMG-coA reductase, which are reasonably safe in the elderly [30, 31], these agents are expensive and we have no firm evidence that they will reduce the accelerated atherosclerosis seen in renal disease.

Antihypertensive drugs deserve special emphasis: these aim at a target diastolic pressure of $\leqslant 95$ mm Hg and a systolic of $\leqslant 160$ mm Hg. The newer agents such as the calcium-channel antagonists and/or the angiotensin-converting-enzyme inhibitors are better tolerated by the elderly and are more effective that some drugs. These newer agents are expensive and this factor may reduce compliance.

Summary

Glomerulonephritis in the elderly is not rare and a population-based comparison indicates that the vasculitis, crescentic glomerulonephritis and membranous nephropathy variants, are more frequent in the elderly than in younger adults. In contrast, other types of nephritis, such as IgA and lupus nephropathy, are rare in the elderly. The rest of the glomerular diseases seem to occur at approximately the same frequency as in the younger adults. For these reasons, and although there may be a slightly increased risk to biopsy in the elderly, because of the inaccuracies of clinical and laboratory tests alone to reach the correct pathologic diagnosis in either patients with a decrease in renal function or significant proteinuria, the decision to perform a renal biopsy should be based on the same considerations as in the younger patient.

All patients with minimal-change disease and most with focal sclerosing glomerulonephritis should be treated because they will respond like young adults. Cytotoxic agents should be used before high-dose, oral prednisone based on the patient's general condition. There is little evidence that steroids are effective in membranous nephropathy and, before embarking on any specific therapy, make an effort to identify high-risk patients using severity and persistence of proteinuria over time. IgA nephropathy is rare, the majority of these patients have a good long-term prognosis but the presence of hypertension, heavy proteinuria and/or renal insufficiency suggests a poor prognosis. In this group aggressive antihypertensive therapy is warranted and ACE inhibitors may help to preseve renal function in this high-risk group [32, 33].

The appearance of the nephrotic syndrome in the elderly should trigger a diligent search for a secondary causes. In most series, 40% have an underly-

ing disease and it is important to identify the specific type because it is closely tied to the prognosis.

In the management of all patients in this age group, the physician should review all of the patients' medications, be aware of the propensity of the elderly to volume depletion and do an ongoing evaluation of nutritional status.

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CHAPTER 9

Renal vasculitis in the elderly

JAMES V. DONADIO, JR.

The vasculitic syndromes are uncommon but, as an aggregate, each practicing physician during his or her career will see at least one patient with vasculitis. Herein, I discuss the classification of vasculitis, the clinical features of the more common forms that affect the kidney in older persons, and treatment and outcome.

Classification of vasculitis

In 1866, Kussmaul and Maier first recognized systemic necrotizing vasculitis [1]. Over the next 60 years, approximately 70 cases of polyarteritis were published with only about 10% reported as small-vessel disease. Beginning in 1925, the consistent use of the microscope by pathologists brought a dramatic increase in the number of cases reported; most of these were of the microscopic variety.

Case reports grew to clinicopathologic syndromes from which a variety of classifications were derived [2, 3]. Table I shows a classification of idiopathic vasculitic syndromes by Churg and Churg [3]. Most of these disorders were first described during this century. The polyarteritis nodosa (PAN) group and Wegener's granulomatosis, which commonly affect the kidney, occur frequently in older individuals. In the polyarteritis group, 'classic' PAN is defined as a focal, segmental, necrotizing vasculitis of small arteries, less commonly arterioles, and, rarely, venules. 'Microscopic' PAN is defined as focal and segmental, necrotizing glomerulonephritis. There is overlap between 'classic' and 'microscopic' PAN, but on renal-biopsy specimens, the technique by which PAN is defined in the kidney, the vast majority of cases (75%) are diagnosed as focal and segmental, necrotizing glomerulonephritis.

In a variety of secondary vasculitic disorders, the primary disease is known, especially for vasculitis associated with hepatitis B infection, ionizing radiation, and severe hypertension [3]. A systemic vasculitis has been reported in HIV infection, and other microbiologic agents and environmental factors have been implicated in vasculitis.

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Table I. Idiopathic vasculitis classified by clinicopathologic syndromes [3]

Polyarteritis nodosa
Wegener's granulomatosis
Allergic granulomatosis (Churg–Strauss)
Primary (granulomatous) vasculitis of CNS
Giant-cell (temporal) arteritis
Takayasu arteritis
Idiopathic granulomatous vasculitis
Small-vessel vasculitis
Henoch–Schönlein purpura
Behçet disease
Thromboangiitis obliterans

Another way to classify the primary vasculitic syndromes is by their association with antineutrophil cytoplasm antibodies (ANCA). These antibodies were first recognized in 1982 by Davies *et al.*, who described eight patients with focal, segmental glomerulonephritis and associated ANCA [4]. The Ad Hoc Nomenclature Committee of the Third International Workshop on ANCA [5] have proposed a classification of ANCA-associated vasculitic syndromes (Table II), which includes the more common vasculitides that involve the kidney in older individuals. There is an overlap in terminology as well as in clinical and pathologic features between classic PAN, the groups listed as microscopic PAN and necrotizing and crescentic 'pauci-immune' glomerulonephritis. In clinical practice, the latter diagnosis refers to that form of microscopic PAN with the most active and severe glomerular lesions. Hereafter, I shall refer to classic and microscopic PAN and necrotizing and crescentic pauci-immune glomerulonephritis as idiopathic renal vasculitis.

Antibodies to myeloperoxidase (aMPO) are found in all categories of idiopathic renal vasculitis. aMPO, a subset of ANCA, originally were identified by indirect immunofluorescence on substrates of ethanol-fixed human

Table II. Idiopathic systemic vasculitis classified by ANCA-association [5]

Wegener's syndrome
Wegener's granulomatosis (WG) – C-ANCA, 90% positive (+), active disease
Limited WG – C-ANCA, 50% +, active disease
Wegener's vasculitis – C-ANCA, ≃ WG
Small vessel vasculitis
Microscopic polyarteritis nodosa (PAN) – P-ANCA, C-ANCA, variably +,
Leukocytoclastic angiitis – P-ANCA, C-ANCA, variably +
Necrotizing and crescentic pauci-immune glomerulonephritis – P-ANCA, aMPO, 80% +, active disease
Churg–Strauss allergic angiitis – P-ANCA, variably +
Classic PAN – P-ANCA, variably +

neutrophils [6]. aMPO produce a characteristic pattern of perinuclear immunofluorescence on neutrophils referred to as the P-ANCA staining pattern [7] (Fig. 1). In a clinical study, Velosa *et al.* compared the indirect immunofluorescence method with an enzyme-linked immunoassay in the detection of aMPO in 112 patients with renal disease [8]. The enzyme immunoassay was more sensitive in detecting aMPO in patients with idiopathic renal vasculitis (76% vs. 48%) and was also more specific, yielding fewer false-positive results in other renal diseases (85% vs. 80%).

The other ANCA detected by indirect immunofluorescence is referred to as the cytoplasmic ANCA (C-ANCA) staining pattern [7] (Fig. 1). The important antigen that can be identified by solid-phase immunoassays consists of a 29-kD, neutral serine proteinase, designated proteinase 3 (PR3) [9]. C-ANCA shows a 90% positive reaction rate with active, generalized Wegener's granulomatosis or vasculitis, a 50% positivity with limited Wegener's granulomatosis, and the levels appear to rise and fall with activity and treatment of the disorders [10].

The pathogenic role of ANCA in producing or modulating endothelial injury in systemic vasculitis is under intense investigation [11]. ANCA *in vitro* activates neutrophils to produce reactive O_2 species, degranulation of the primary granules (the site of the important antigens), and damage to target cells, the antigens of which stimulate T lymphocytes from vasculitic patients. Furthermore, as a screening test for idiopathic renal vasculitis and Wegener's granulomatosis, ANCA appears to be especially useful in the active forms of the disease (Table II).

Clinical features

As a rule, idiopathic systemic vasculitis (used synonymously here with polyarteritis) is a multisystem illness with a spectrum of severity ranging from mild, limited disease to progressive, multisystem disease which may be fatal; because the early symptoms may be nonspecific – malaise, fever, myalgias, and weight loss. An accurate diagnosis may be delayed. When the diagnosis becomes evident, advanced renal disease may already be present thus precluding effective treatment.

There is hardly a typical clinical course for idiopathic systemic vasculitis because of the variable systemic involvement, especially among patients reported in unselected series. [12–16]. Table III shows the salient renal histologic and clinical findings in classic and microscopic PAN (idiopathic renal vasculitis). The vast majority of diagnoses are based on finding focal and segmental, necrotizing glomerulonephritis, often with associated cellular crescents. Most patients, at least 70%, are 50 years of age or older.

In an analysis of clinical laboratory and pathological variables in 170 patients with idiopathic renal vasculitis and glomerulonephritis studied at the Mayo Clinic [17], Wilkowski *et al.* defined a risk profile for a poor outcome

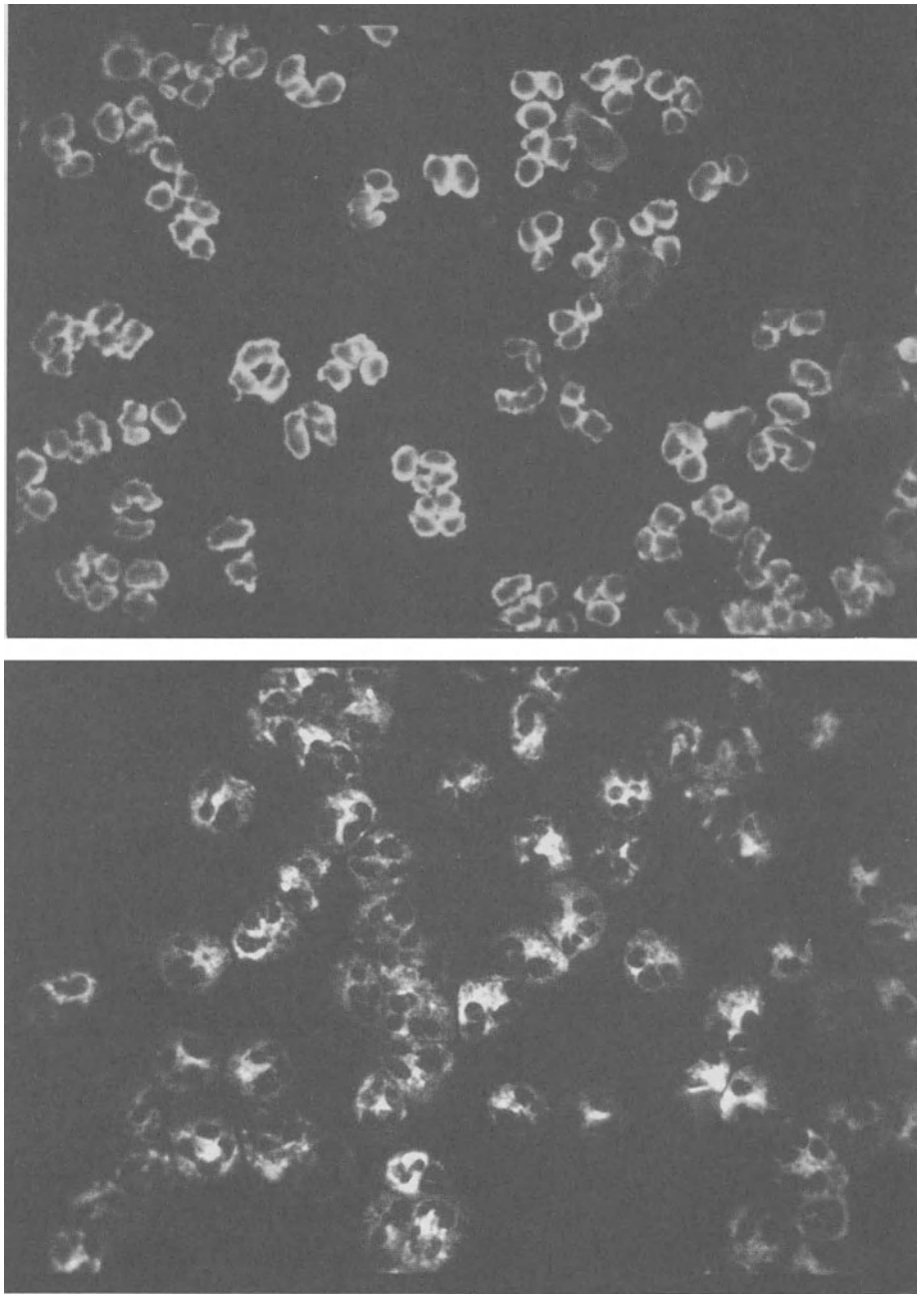

Fig. 1. Indirect immunofluorescence of human neutrophils fixed in ethanol and incubated with FITC-labeled anti-human immunoglobulin G. *Top:* the perinuclear (P-ANCA) pattern is associated with myeloperoxidase that has migrated to the nuclear membranes. *Bottom:* the cytoplasmic (C-ANCA) pattern is associated with a neutral serine proteinase, designated proteinase 3, that is located in the primary granules of the neutrophil.

Table III. Salient renal histologic and clinical findings in patients with idiopathic renal vasculitis

Histology
Classic PAN – arteritis, renal infarctions (uncommon)
Microscopic PAN – focal and segmental pauci-immune necrotizing glomerulonephritis (65–75%); glomerulonephritis + arteriolitis, arteritis (25–35%); cellular crescents common in all groups
Clinical findings
Classic – hypertension, hematuria, azotemia
Microscopic – microscopic hematuria, erythrocyte casts, proteinuria, azotemia, hypertension

(Table IV). Age 50 years and older was a significant risk factor for lower patient survival and for survival free of renal failure. The older patients did not have the other important risk factors associated with a worse prognosis such as disproportionate increases in hypertension, elevated serum-creatinine levels, leukocytosis, or tubular atrophy and interstitial fibrosis in renal biopsy specimens. Treatment with corticosteroids and immunosuppressive agents was approximately equal in younger and older persons. However, some studies have suggested that older persons do not tolerate these agents as well as do younger ones so that treatment is delayed or older patients are given smaller doses that may not be sufficient to control progressive renal disease.

There is a bimodal distribution for mortality in unselected series of patients with polyarteritis [13, 14]. 'Early' deaths, up to approximately 12 months, are related to active vasculitis that includes progressive renal failure, fatal pulmonary hemorrhage or intestinal perforation, while 'late' deaths beyond 12 months usually are related to cardiovascular events including strokes and myocardial infarctions, and cancer. The cardiovascular deaths may be a consequence of the vasculitic process and to prolonged use of corticosteroids, which leads to arteriosclerosis.

Wegener's granulomatosis is a granulomatous arteritis that involves a syndrome of upper airway, pulmonary and renal manifestations; often it begins in a more limited form involving the upper-respiratory tract consisting of necrotizing granulomatous lesions of the sinuses, orbit, pharynx and larynx and goes on to a more generalized vasculitis involving the upper respiratory tract, lungs, kidneys [18]. The median age for diagnosis of Wegener's granulomatosis is 50 years old. Renal manifestations are microscopic hematuria,

Table IV. Risks at diagnosis associated with an unfavorable outcome in patients with idiopathic renal vasculitis

Age >50 years old
Hypertension >150/90 mm Hg
Elevated serum creatinine level >4 mg/dl
Peripheral blood leukocytosis $>16 \times 10/mm^3$
Tubular atrophy, interstitial fibrosis in renal biopsy

Table V. Risks at diagnosis associated with an unfavorable outcome in patients with Wegener's granulomatosis

Age >60 years old
Proteinuria >2.5 g/24 hr
Elevated serum creatinine level >3 mg/dl
Cellular crescents in renal biopsy

Table VI. Summary of patient survival according to treatment in idiopathic systemic vasculitis (ISV) and Wegener's granulomatosis (WG)

	Patient survival	
Treatment	ISV 5-years	WG 1-year
Supportive	16	20
Corticosteroids	50	35
Steroids + immunosuppressives	50–60	80–95

proteinuria, and azotemia; the kidney lesions are similar to those observed in idiopathic systemic vasculitis and feature focal and segmental, necrotizing glomerulonephritis [19].

Table V shows a risk profile for clinical parameters at diagnosis associated with a poor outcome in Wegener's granulomatosis. Persons 60 years and older have a worse prognosis. It has been suggested that delays in diagnosis and an unwillingness to prescribe adequate corticosteroid and immunosuppressive therapy in older individuals, as in situations with idiopathic renal vasculitis, are responsible for the poor prognosis in older patients with this syndrome [20].

Treatment and outcome

Table VI shows an overview of treatment and patient survival for patients with idiopathic systemic vasculitis and Wegener's granulomatosis.

For idiopathic systemic vasculitis, the information is compiled from a variety of retrospective studies of unselected series of patients in which 63–100% had renal involvement [12–16]. Five-year patient survival improved from 16% in supportive-care groups (the precorticosteroid era), to 50% with the use of corticosteroids, to approximately 50–60% after therapy with combinations of steroids and immunosuppressive drugs, most frequently azathioprine and cyclophosphamide. Corticosteroids remain the mainstay of treatment for idiopathic systemic vasculitis. Clinicians have been frustrated by the lack of convincing evidence of superiority of the addition of immunosuppressive agents. Others remain convinced that cytotoxic drug therapy,

especially with cyclophosphamide, produces a favorable clinical response over and above that achieved with corticosteroids [21]. Unfortunately, there is only one randomized, controlled clinical trial, which involved 72 patients with idiopathic systemic vasculitis, about one-third of whom had Churg-Strauss allergic angiitis [22]. This study used a somewhat unusual treatment regimen in which every patient was given oral prednisone, 1 mg/kg/day for two months, plus plasmapheresis – 13 plasma exchanges for six months, and one-half of the patients were randomized to oral cyclophosphamide, 2 mg/kg/day for one year. Cumulative patient survival was approximately 65% after three years and did not differ between the two groups. Mortality was significantly higher in patients over 55 years old, and in both treatment groups serious treatment complications affected all age groups and caused 25% of the patients to withdraw from the study. In another prospective but nonrandomized study of 70 patients with systemic vasculitis, 37 of whom had Wegener's granulomatosis, Falk *et al.* compared the response to therapy in 59 of these patients who received one of three forms of therapy: 45 patients were treated with oral corticosteroids plus either intermittent intravenous cyclophosphamide (15 patients) or oral cyclophosphamide (30 patients), and 14 patients were treated with corticosteroids alone [23]. Patient survival and survival without renal failure were 75% at 24 months; no difference was seen among those treated with corticosteroid therapy alone versus the combinations of corticosteroids and cyclophosphamide; and no differences were seen in survival in patients with renal-limited disease and those with combined renal and pulmonary disease.

Turning to Wegener's granulomatosis, one-year patient survival improved from 20% in the supportive-care groups (presteroids), to 35% in corticosteroid-treated patients, to 80–95% in patients treated with steroids and cyclophosphamide combined (Table VI) [18, 24, 25]. Five-year survival data is not used in Wegener's granulomatosis because the mortality in the presteroid era was 100%.

Recently Hoffman *et al.* [25] reported a long-term study on the treatment of patients with Wegener's granulomatosis in which 133 patients received daily oral cyclophosphamide, 2 mg/kg, and prednisone, 1 mg/kg. Initial treatment with prednisone varied from 2–15 mg/kg, which gradually was tapered after four weeks and was changed to 60 mg on alternate days thereafter. Cyclophosphamide was continued for at least one year after the patient had a complete remission. Seventy-five percent of the patients achieved complete remission, and 50% of these were associated with one or more relapses. Thirteen percent of the patients died of Wegener's granulomatosis, treatment-related causes, or both. It is important to note that almost all these patients had serious morbidity from irreversible features of their disease (86%) that included chronic renal insufficiency (42%), hearing loss (35%), cosmetic and functional nasal deformities (28%), tracheal stenosis (13%), and visual loss (8%). In addition, there were major toxicities related to daily, long-term, oral cyclophosphamide including malignancy (acute myelogenous

leukemia, lymphomas and bladder cancers), hemorrhagic cystitis, bladder fibrosis, ovarian failure and infection. Hoffman did not examine age as a risk factor for a poor outcome.

Attempts to decrease the morbidity associated with long-term oral cyclophosphamide have included using intermittent high-dose (1 g/M^2) intravenous cyclophosphamide for six months. Hoffman *et al.* prospectively treated 14 patients with Wegener's granulomatosis; the study group was heterogeneous and included subjects with newly diagnosed disease, recurrent disease, and failure with low-dose oral cyclophosphamide [26]. There was a high initial response rate but, with pulse cyclophosphamide, only 21% of the patients experienced a sustained remission.

In another long-term study from the Mayo Clinic [24] of 151 patients with Wegener's granulomatosis, about one-third of whom had limited Wegener's confined to the upper respiratory tract (46 patients) or lungs (10 patients), opportunistic infections were responsible for 12/43 (30%) patient deaths. Individuals at highest risk were those with extensive, necrotizing skin lesions and ulcerations in the airway mucosa in whom prednisone and cyclophosphamide were started simultaneously. Undoubtedly, these ulcerative lesions serve as a preferred site for infectious agents, while at the same time defense mechanisms of the host are decreased. In these patients, we should consider beginning therapy with high-dose oral prednisone (60–80 mg/day) or intermittent 'pulse' intravenous methylprednisolone until the inflammatory lesions are controlled. Then cyclophosphamide (2 mg/kg/day orally) is added later, while the prednisone dose is carefully tapered. The duration of both prednisone and cyclophosphamide therapy should be judged by the clinical response and in many instances stopped after months rather than years of continuous administration. The issue of sustaining disease remission is unresolved, and we need further clinical trials to test the hypothesis of shortened immunosuppressive therapy in these patients.

Finally, in general, while the immunosuppressive effects of corticosteroids and immunosuppressive agents may have favorable effects on the overall activity of renal vasculitis and may induce remissions in most patients, in a major way their long-term effects on renal disease could be attributed to lower prednisone dosage, better control of hypertension and hyperlipidemia, and better general management and control of infections and metabolic complications of these diseases.

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CHAPTER 10

Maturity-onset diabetes and nephropathy

CATHARINE I. WHITESIDE

Kidney disease associated with diabetes mellitus is now the number one cause of end-stage renal failure (ESRF) in North America [1]. Non-insulin-dependent diabetes mellitus (NIDDM) patients over 60 years of age constitute the majority of those diabetics entering dialysis programs [2, 3]. Unlike insulin-dependent diabetes mellitus (IDDM), NIDDM shows more clear-cut, racial predispositions to progressive nephropathy [4]. This paper outlines the risk factors, current concepts about disease mechanisms, diagnosis and therapeutic strategies.

Disease mechanisms

It is unlikely that a single cellular mechanism accounts for the progressive mesangial matrix expansion, which typifies diabetic glomerulosclerosis in NIDDM patients. Since macrovascular disease is coincident with the glomerulopathy, arteriolar sclerosis of medium-sized arteries and preglomerular arterioles may contribute also to declining renal function. There is increasing evidence that glomerulosclerosis and arteriolar sclerosis may reflect the same disease process.

1. *Advanced glycosylation end products in diabetic glomerulosclerosis*

In the presence of glucose, extracellular proteins undergo nonenzymatic glycosylation. Over time, glucose irreversibly complexes to protein creating an advanced glycosylation end product (AGE) [5]. Normally an AGE-receptor-mediated, macrophage scavenging system prevents the accumulation of AGEs [6]. However, in diabetes, AGE formation exceeds the rate of degradation. Its accumulation in extracellular matrix, e.g., glomerular basement membrane and mesangial matrix, initiates mechanisms that lead to vascular smooth-muscle and mesangial-cell growth and matrix accumulation [7]. AGEs activate endothelial cells, enhancing their pro-coagulating proper-

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ties, e.g., decreased thrombomodulin synthesis [8]. Platelet-derived growth factor (PDGF), arising from activated endothelial cells and/or aggregated platelets, is a potent agent stimulating mesangial-cell mitogenesis and matrix-protein synthesis [9]. AGEs are chemotactic for circulating monocytes/macrophages. AGE-macrophage receptor interaction stimulates these cells to release tumor-necrosis factor and interleukin-1 [10]. Local glomerular release of these cytokines may stimulate mesangial-cell matrix production [11]. Finally, AGEs trap low-density lipoproteins (LDL) in the extracellular matrix. Similar to the evolution of atheroma in peripheral vessels, accumulation of LDL in the mesangial matrix may promote progressive sclerosis of the glomerulus [12].

Recent data in the streptozotocin rat model indicates that aminoguanidine, which prevents AGE formation, retards the appearance of increased albuminuria and glomerular mesangial expansion [13]. The efficacy of this drug in the prevention and treatment of human diabetic nephropathy is being investigated.

2. *Systemic and intraglomerular hypertension*

A raised, hydrostatic-pressure gradient across any vascular wall is potentially damaging. Endothelial cells exposed to shear stress are activated in response to stretch [14]. Growth factors, such as PDGF, are released by endothelial cells which, in turn, stimulate smooth-muscle-cell proliferation [15]. In the streptozotocin-treated rat, renal micropuncture studies show that the diabetic state causes decreased afferent arteriolar resistance, which allows higher hydrostatic pressure to be transmitted into the glomerulus [16]. All experimental manoeuvres that lower intraglomerular pressure in this model, e.g., low-protein diet, prevent progressive glomerulosclerosis [17, 18]. In contrast, the non-hypertensive, Zucker-rat model of obesity, NIDDM and hyperlipidemia does not display raised intraglomerular pressure, but does show progressive mesangial expansion [19]. Currently, in human glomerulopathy associated with NIDDM, we do not know whether intraglomerular pressure is raised. However, the presence of systemic hypertension in NIDDM is a definite risk factor for progressive diabetic nephropathy. Early treatment of systemic hypertension in NIDDM may prevent progression toward end-stage renal failure, but it is unclear whether this is a specific effect on glomerular or preglomerular vessels or both. The concurrence of hypertension and nephropathy in NIDDM patients may reflect their susceptibility to vascular disease at the cellular level.

3. *Polyol pathway and kidney function*

Hyperglycemia leads to increased synthesis of sorbitol *via* the aldose-reductase pathway in many cell types. Some workers have linked sorbitol accumulation to abnormalities in peripheral nerves of diabetic rats [21] and humans [22], particularly myoinositol and phosphatidylinositol metabolism and, in turn, in decreased Na^+-K^+-ATPase-dependent nerve conduction. Aldose-reductase inhibitors [23] and/or myoinositol feeding [24] prevent these abnormalities. Recently, it has been recognized that, in diabetes, there is a reduction of the cellular NAD^+/NADH ratio through the enhanced oxidation of sorbitol to fructose. This condition favors increased *de novo* synthesis of diacylglycerol (DAG) associated with activation of protein kinase C (PKC) [25]. PKC is a pivotal enzyme in growth hormone and vasoactive, peptide transmembrane signalling, leading to early, immediate, gene activation [26]. Extracellular matrix-protein synthesis by mesangial cells, enhanced by increased glucose, is controlled by this pathway [27]. Ayo and Kreisberg have demonstrated increased DAG-dependent PKC activation in rat mesangial cells exposed to a high glucose milieu [28]. Despite the conceptual link between increased cellular sorbitol and mesangial expansion, no experimental data support the use of aldose reductase inhibition in preventing glomerular structural changes in the streptozotocin rat model or in diabetic humans. The potential role of aldose-reductase inhibition in the treatment and prevention of human diabetic nephropathy is under clinical investigation.

Diagnosis of diabetic nephropathy in NIDDM

In IDDM, persistent microalbuminuria $> 20\ \mu g/min$ or > 20 mg/day is a sensitive marker for early progressive diabetic nephropathy [29]. In NIDDM, Mogensen [30] and others [31] have shown that elevated microalbuminuria (20–200 mg/day) predicts clinical nephropathy and increased risk of mortality due to cardiovascular disease. However, in NIDDM, the confounding factors of age, coincidental hypertension and/or hyperlipidemia, which independently may alter glomerular filtration, make increased microalbuminuria less specific than in IDDM. Therefore, in NIDDM patients, in the absence of an active urinary sediment or evidence of other primary glomerular disease, persistent proteinuria > 0.5 g/day is due most likely to diabetes. According to experts reviewing the indications for renal biopsy in diabetes, we should consider a closed renal biopsy in a patient with NIDDM, who develops clinical renal disease in the absence of proliferative retinopathy, regardless of the duration of the diabetes. Furthermore, a renal biopsy should be considered if the decline of glomerular filtration or worsening of proteinuria is too rapid to be due to diabetes, e.g., sudden onset of nephrotic syndrome or evidence of acute renal failure of unknown origin. Also, a renal biopsy

should be done for definitive diagnosis if clinical or laboratory findings, e.g., active urinary sediment indicate another primary or secondary disease [32].

Risk of developing nephropathy in NIDDM

In NIDDM, the late age of onset of nephropathy, compared to IDDM, confounds cross-sectional or prevalence data on proteinuria. Two studies have addressed the cross-sectional incidence of proteinuria in different populations in the U.S.A.

In Rochester, Minnesota, Ballard *et al.* [33] established the prevalence of persistent proteinuria over the past twenty years, as 8.2% at the time of diagnosis of NIDDM in a predominantly non-Hispanic white population. Of those without proteinuria at diagnosis, the cumulative incidence of proteinuria over 20 years was 25%. Risk factors for the development of proteinuria included: older age; higher initial blood glucose; male gender; macrovascular disease; diabetic retinopathy. No relation was seen between the onset of proteinuria and the presence of hypertension at the time of diagnosis of NIDDM.

Among the Pima Indians [20], newly diagnosed NIDDM patients also have an 8% prevalence of persistent proteinuria. However, in this group, hypertension at the time of diagnosis correlates with the presence of increased albuminuria. After 20 years of NIDDM, those patients without proteinuria initially have a cumulative 50% risk for the development of proteinuria.

There is evidence that NIDDM shows a familial clustering of nephropathy. Seaquist *et al.* [34] found that siblings of NIDDM patients with nephropathy have a significantly higher frequency of nephropathy than siblings of NIDDM patients without nephropathy. Two generations of Pima Indians have shown a familial clustering of diabetic nephropathy, i.e., the existence of proteinuria and/or end-stage renal failure in a parent is strongly associated with the risk of nephropathy in the offspring.

We now recognize the importance of a family history of hypertension in predicting the risk of progressive nephropathy in IDDM patients [35], but the exact relationship between familial (essential) hypertension and nephropathy in the general NIDDM population remains to be elucidated. We require more detailed studies to elucidate the relative importance of racial background, family history and other risk factors in the predisposition to nephropathy in NIDDM.

Risk of developing end-stage renal failure (ESRF) in NIDDM

ESRF due to NIDDM accounts for the majority of diabetic patients on dialysis in North America. However, the incidence of ESRF in NIDDM is more variable than in IDDM. In two prospective population-based studies

of ESRF, the incidence of ESRF in NIDDM patients was seven times higher in the Pima Indians (940/100,000 person – years) [34], than in the predominantly non-Hispanic, Caucasian population in Rochester, Minnesota (133/100,000 person – years) [33]. ESRF registries give some information about racial predisposition. In Michigan, the annual incidence of ESRF in blacks is 6.2/100,000 population, compared to 1.4/100,000 among whites [36]. In Texas, ESRF associated with NIDDM is four times higher in blacks and six times higher in Mexican-Americans than in non-Hispanic whites [37]. These figures are not controlled for the higher prevalence of NIDDM in blacks, 1.5 times, and Mexican Americans, 2–3 times, compared to non-Hispanic whites. When the data are corrected, the disproportionately higher frequency of ESRF persists in blacks and Mexican-Americans, compared to non-Hispanic whites. Canadian Indians also have a higher risk of ESRF, which is 2.5–4 times higher than the national rate, mainly due to diabetes [39].

Not all IDDM patients, who develop proteinuria, will reach ESRF. In Rochester, Minnesota, the cumulative incidence of ESRF in NIDDM patients was 11%, 10 years after the diagnosis of persistent proteinuria. Risk factors for the development of ESRF at the time of diagnosis of NIDDM included: persistent proteinuria (> 0.5 g/day); gender (2.8-fold excess in males); higher fasting-blood glucose; macrovascular disease; diabetic retinopathy; smoking; initial insulin therapy [33].

In the Pima Indians, after age and sex adjustment, the incidence of ESRF is approximately 20 times that of the general U.S.A. population. In this group with NIDDM, along with duration of diabetes, risk factors for ESRF included the presence of hypertension (systolic $\geqslant 160$ or diastolic $\geqslant 95$ mm Hg), which was associated with a 3.8-fold increased risk of nephropathy [39].

Identification of risk factors contributing to progression of diabetic nephropathy is important in planning appropriate treatment in this population.

Treatment of nephropathy in NIDDM

The presence of persistent proteinuria in NIDDM is an important predictor of ischemic heart and macrovascular disease [40]. The treatment of nephropathy focuses on management of NIDDM, i.e., normalization of body mass, normalization of blood glucose, and aggressive management of cardiovascular risk factors, including hyperlipidemia and hypertension. The benefit of a low-protein diet in preventing progression of diabetic nephropathy due to NIDDM is not known. It is reasonable to assume that once proteinuria > 0.5 g/day appears coincident with reduced glomerular filtration rate, an NIDDM patient already has significantly reduced glomerular filtration surface area (remnant kidney). In this context, a high-protein diet may contribute to raised intraglomerular pressure and hyperfiltration as observed in animal

models of the remnant kidney [41]. A moderate protein restriction of 0.9 g of protein/kg of body weight/day will avoid exposure to high-protein and prevent negative protein balance.

Glucose control

In the U.S.A., the University Group Diabetes Program Study revealed that NIDDM patients randomized to insulin treatment have a reduced risk of developing renal insufficiency, compared to placebo controls. This study suggests that better glycemic control may delay or prevent renal failure [42]. Since most of the renal-cellular abnormalities described to date relate directly to hyperglycemia, and since normalization of glycemia in NIDDM usually is achieved without major risk to the patient, strict blood glucose control is recommended.

Hypertension control

The treatment of hypertension in NIDDM patients is complicated by the presence of macrovascular disease. Lowering the blood pressure too quickly in the presence of macrovascular and preglomerular microvascular disease may result in hypoperfusion of organs, including the kidney. Evidence on history and/or physical examination of macrovascular disease (including coronary artery disease) must be reviewed before treatment of elevated blood pressure. The blood pressure should be lowered slowly and carefully while monitoring for reduced perfusion states, e.g., rising serum creatinine. One should avoid angiotensin-converting-enzyme (ACE) inhibitors in the presence of macrovascular disease. In the presence of bilateral artery or intrarenal arteriolar stenosis, glomerular-filtration rate is maintained by angiotensin-II-dependent, efferent-arteriolar constriction. Under these circumstances, inhibition of angiotensin II may cause acute renal failure. Furthermore, in advanced nephropathy, hyperkalemia is exacerbated by ACE inhibition. Calcium-channel blockers are advantageous because they do not adversely modify serum lipids [43] and have few side effects (e.g., fatigue). However, the various calcium channel blockers may have different hemodynamic effects on patients with diabetic nephropathy. In a three-month study of IDDM patients with advanced proteinuria and compromised renal function, Demarie and Bakris [44] showed that nifedipine increased proteinuria and decreased creatinine clearance, whereas diltiazem had no deleterious effects on either proteinuria or creatinine clearance. In this double-blind crossover study, both calcium-channel blockers had equal blood-pressure-lowering effects. When an ACE inhibitor is compared to a calcium-channel blocker, diltiazem *versus* lisinopril [45], nicardipine *versus* enalapril [46], in NIDDM patients with macroscopic and elevated microscopic albuminuria respectively, there were no differences in blood pressure lowering or adverse

side effects. More long-term and larger trials are required to determine whether the natural history of progressive nephropathy is altered more favorably by ACE inhibitors or by calcium-channel blockers. Diuretics and beta blockers should be considered second-line drugs because of their potentially adverse effects on serum lipids.

Institution of any antihypertensive treatment in patients with NIDDM and nephropathy requires close monitoring of renal function, including serum potassium, creatinine, creatinine clearance and urine-protein-excretion rates. The target blood pressure, aiming toward 140/90 mm Hg, should be achieved without compromising organ perfusion.

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PART FOUR

Water and electrolyte problems in the elderly

CHAPTER 11

Clinical approach to volume overload: predicting the vulnerable patient

KENNETH M. DAVIS, LORETTA C. FISH, DARIUSH ELAHI and KENNETH L. MINAKER

Introduction

Five general principles underlie the successful management of clinical disorders of volume and composition of extracellular fluid [1].

First, the symptoms of disordered regulation of volume and composition of extracellular fluid are not attributable to the renal, endocrine or cardiac systems. The clinician needs to be aware of the increased frequency of severe clinical disorders of this type in the elderly, and have a low threshold to obtain measures of BUN, creatinine, and electrolytes in all sick patients. Clinical estimates of central volume remain important features of the clinical examination. However, assessment of volume change is notoriously imprecise in the elderly owing to laxity of skin and hypotension under basal conditions (up to 30% of all elderly persons).

The second principle is that older patients delay seeking medical assistance because of altered cognition, decreased level of consciousness, impaired mobility, reclusiveness, and/or depression. This delay results in more advanced clinical deterioration in which generally subtle early findings will be lacking. When the patient shows the early signs of severe deterioration, initial management should be accompanied by aggressive pursuit of existing records, looking for accounts of similar episodes and response to previous treatment. These are the most helpful guides for ongoing care. Even when such records are available, family members often can provide substantial additional information to clarify the time course of the development of symptoms and patterns of changes in function and behavior. This is particularly helpful if someone has witnessed seizures or falls, if fluid intake behavior has changed, or if patterns of medication intake have been recorded.

The third principle is to consider the influence of medications in elderly patients, e.g. diuretics are the most common drugs to cause hospital admission in elderly patients. Often other medications taken concurrently worsen the clinical state e.g., sedatives taken when the patient is hyponatremic can produce mild confusion. Clinically, the elderly should avoid drugs that inhibit

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the thirst mechanism and the synthesis and release of AVP, including most of the sedatives and major tranquilizers, and drugs that inhibit the renal tubular action of AVP, especially lithium and demeclocycline. Also the use of osmotic diuretics, enteral feeding containing high protein and glucose, and bowel cathartics should be carefully monitored. Therefore the evaluation of every older person must include a careful review of all medications being taken, with appropriate adjustment of dosages made.

The fourth concern for elderly persons with disorders of regulation of volume and composition of extracellular fluid is their often-narrowed homeostatic physiologic reserve. It is almost unique to the elderly that therapy for dehydration without careful monitoring can lead to significant volume overload. Similarly, administration of fluid or osmotic loads, such as during intravenous pyelography, may produce a rapid fluid overload and cardiovascular decompensation in previously apparently stable older persons. Because patients show great variation in reserve function, therapy must include frequent careful monitoring for adverse side-effects. If possible, one should undertake full characterization of organ reserve, by determining baseline creatinine clearance and renal sodium conservation in an elderly patient with modest elevation of creatinine, once stabilized during a hospital admission. Until we have appropriate biomarkers of reserve capacity, this type of testing is justified.

The final principle is to be aware of the ever-present potential for a previously subclinical cascade of multiple pathologies to declare themselves during therapy. The development of focal neurologic signs or delirium after an episode of dehydration is more likely in the elderly because of compromised baseline cerebral blood flow or cognitive function. Similarly seizures may appear during hypernatremia (and its correction), or ischemic limbs during volume depletion.

Acute congestive heart failure (CHF), one of the most common and dramatic manifestations of extracellular volume overload, usually requires emergency admission to an acute care hospital. Recent studies [2, 3] have demonstrated that angiotensin-converting enzyme inhibitors reduce morbidity and mortality in patients with symptomatic cardiac dysfunction. While the treatment of CHF has improved in the last decade, little emphasis has been placed on the prediction and prevention of this major geriatric illness.

The aim of this study was to develop a model to predict risk for the development of acute pulmonary edema by incorporating bedside clinical examination measures, detailed review for previous history of CHF, and plasma venous ANP levels. ANP levels are increased in diseases associated with cardiac dysfunction and disorders that expand intravascular volume [4–10]. We hypothesized that ANP levels may be clinically useful in the prediction of CHF. Gottlieb *et al.* [11] have shown that atrial natriuretic peptide (ANP) levels have prognostic significance in younger patients with severe cardiomyopathy. Subjects with ANP levels over 385 pM had a significantly lower survival rate. Our study employed techniques adaptable to the clinical

care of the elderly in community or institutionalized settings, where many vulnerable elderly reside.

Methods

Study design

Three hundred and thirty-one, clinically stable, elderly residents of a 725-bed lifecare facility (the Hebrew Rehabilitation Center for Aged) underwent baseline physical examination, electrocardiogram and blood sampling for determination of venous plasma ANP levels. Each subject had a detailed retrospective chart review for CHF in the previous year. This elderly cohort was followed prospectively for one year from study entry date until they developed one of three mutually exclusive outcomes: CHF, death without CHF, or survival for one year without CHF ('No CHF'). CHF was defined as the presence of clinical signs and symptoms of acute cardiogenic pulmonary edema (dyspnea, pulmonary rales, elevated jugular venous pressure) with chest X-ray confirmation within 24 hours of new or increased pulmonary vascular congestion. Chest X-ray criteria for CHF included the presence of new or worsened, upper-lobe venous redistribution and/or interstitial or alveolar pulmonary edema. Clinical episodes of CHF were determined from review of physicians' notes from the lifecare facility, the Hebrew Rehabilitation Center for Aged (HRCA), and from the emergency room records of Boston's Beth Israel Hospital.

Subjects

Three hundred and thirty-one elderly lifecare-facility residents were enrolled (23% male, 77% female, mean age: 88 ± 0.4 (SE) range: 70–102 years). All subjects underwent medical chart review, interview of their primary care-givers, and detailed physical exam to verify their medical stability at study entry. Subjects were entered after verification that they were free of acute illness for the preceding two months. Subjects with adventitious lung sounds (primarily those with chronic obstructive or restrictive lung disease) were included in the study only after undergoing chest X-rays to confirm the absence of radiographically evident pulmonary edema.

The 331 elderly subjects had a number of stable chronic illnesses, varied medication usage, and a broad range of physical and cognitive function. Twenty-one died in the first 6 months of follow-up without CHF and were excluded, leaving 310 subjects for subsequent prospective analysis. Of the 310 subjects remaining in the study, 272 had detailed, one-year, daily medical records from the lifecare facility for retrospective review. All subjects (or their proxy) gave informed consent for the study. Protocols were approved

by the Committee on Clinical Investigation, New Procedures, and New Forms of Therapy at the Beth Israel Hospital and the Clinical Investigations Committee at the Hebrew Rehabilitation Center for Aged.

Physical examination and blood measures

All eligible subjects underwent detailed physical examination to confirm the absence of acute illness or symptomatic extremes of volume status. Physical examination measures included orthostatic blood pressure and pulse determinations, standardized assessment of jugular venous pressure employing the Modified Method of Lewis [12], cardiac exam for the presence of a third heart sound, lung auscultation, quantitation of the level of pitting edema of the lower extremity (above or below the lateral malleolus, mid-shin or knee), EKG determination of cardiac rhythm, and assessment by chart review and physical exam for the presence of an artificial cardiac pacemaker.

Subjects found to be free of acute illness underwent (within 48 hours of the physical exam) fasting, venous blood sampling between the hours of 6 and 8 a.m. All subjects were supine at least 15 minutes before blood draw.

Statistical analyses

The values for clinical variables are expressed as mean ± standard error of the mean (SE), unless otherwise stated. For statistical tests requiring that the dependent variable (ANP) be normally distributed (*t*-test, ANOVA), the natural log (Ln) of ANP was used to provide a more normal distribution of ANP values. For comparison between two group means, Student's *t*-test for independent samples was used. Sensitivity, specificity, positive predictive value, negative predictive value and relative risk (using person-time data) were calculated in standard fashion [13]. To test for differences among proportions, chi-squared contingency table analysis with Yates' correction was used. All p values are two-tailed. Data were analyzed using the SPSS-X statistical package [14] on a Digital VAX computer. Multiple logistic regression was performed using the SAS statistical package [15] in a backward elimination fashion, a significance level of $p < 0.05$ was required for inclusion into the final regression model.

Results

Fasting, supine plasma venous ANP levels of the 331 subjects entered at baseline ranged from 15–1622 pM, mean 244 ± 15 (SE). Two hundred and seventy-two subjects had one-year, retrospective, daily histories available from the lifecare-center medical records. Of these 272 subjects, 32 (12%)

experienced at least one episode of chest X-ray-confirmed CHF in the year before study entry. The mean ANP level of these 32 subjects with history of CHF was 407 ± 63 pM, their mean age was 90.6 ± 0.9 years. The 240 that did not have a history of CHF in the year before study entry had mean ANP levels of 222 ± 16 pM and mean age of 88.0 ± 0.4 years ($p < 0.005$ for differences in ANP values between those with a prior history of CHF and those without).

Outcomes during prospective one-year follow-up

After excluding from analysis the 21 subjects who died without CHF before 6 months of follow-up, 310 subjects remained for analysis.

Congestive heart failure

During one-year prospective follow-up, 46 of the 310 subjects (15%) had at least one episode of CHF. The mean ANP level of these 46 subjects at study entry was 493 ± 55 (SE) pM, mean age was 91 ± 0.8 (SE) years. Seventeen of the 46 (37%) had their index CHF episode documented in the hospital emergency room, and the remainder had clinical and chest X-ray confirmation of CHF at the lifecare facility.

No CHF group

There were 264 subjects who did not develop CHF during one-year prospective follow-up. Their mean ANP levels at entry into the study were 207 ± 15 pM and their mean age was 88 ± 0.4 years ($p < 0.001$ for differences in ANP values between the 46 developing CHF and the 264 that did not). Of these 264 subjects, 16 subjects died after six months of follow-up and had no CHF.

Deaths

Thirty-seven subjects died without CHF during the one-year follow-up period. Of these 37 subjects, 21 who died within the first 6 months of follow-up without CHF, were excluded from analysis. Their mean ANP level at study entry was 163 ± 31 pM, and their mean age was 88 ± 1.8 years. Sixteen subjects died after 6 months of follow-up without CHF and were included in the 'No CHF' group. Their mean ANP level at study entry was 321 ± 86 pM, and their mean age was 88 ± 2 years.

The 37 subjects, who died without CHF, were classified as cardiac or non-cardiac deaths. Eight subjects had documented acute cardiac events (including myocardial infarction, prolonged angina, cardiac arrhythmias, and aortic dissection) within one month of their demise and were classified as

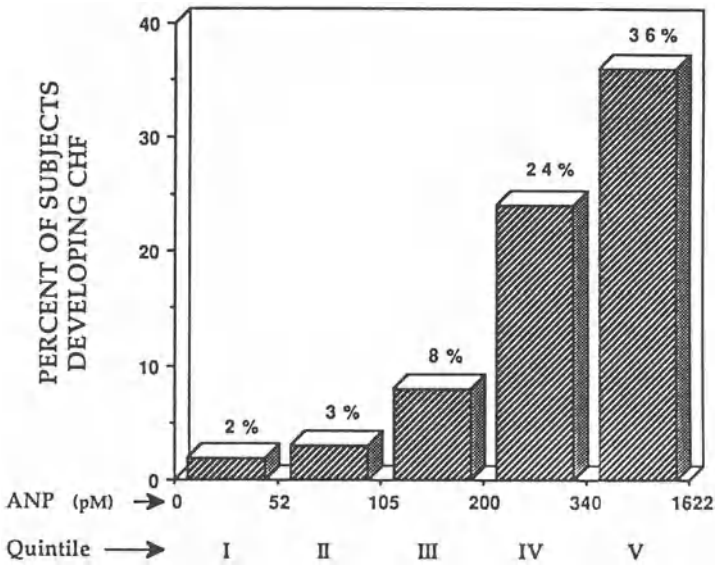

Fig. 1. Percentage of subjects developing CHF during prospective follow-up by study-entry ANP levels. The 310 subjects are divided into quintiles by ANP levels with 60 to 64 subjects in each quintile ($p < 0.001$ for differences in percentage developing CHF among the quintiles by Chi-squared contingency analysis).

cardiac death. The mean study entry ANP level of these 8 subjects was 450 ± 162 (SE) pM, and their mean age was 89 ± 5 (SE) years. Twenty-nine subjects were classified as non-cardiac deaths; their mean study entry ANP level was 172 ± 26 pM, and their mean age was 88 ± 2 years ($p = 0.13$ for differences in ANP levels between cardiac and non-cardiac death groups).

CHF risk stratification by ANP levels

To determine the association between ANP levels and CHF risk, the 310 subjects were divided into quintiles according to their baseline ANP levels with approximately 62 subjects in each group. The number of subjects developing CHF during the one-year prospective follow-up increased significantly with increasing study-entry ANP levels. (See Fig. 1.)

Predictive model for CHF

To establish a predictive model for the development of CHF in the frail elderly, we considered clinical variables related to CHF that could be readily assessed in the nursing home: age (greater or less than the mean of 88 years),

level of care in the nursing home (light or heavy nursing care), ANP value (greater or less than 200 pM), history of CHF in the previous year (yes or no), electrocardiogram findings, (sinus rhythm or other), artificial cardiac pacemaker (yes or no), mean arterial pressure (greater or less than 110 mm Hg), central venous pressure estimated by jugular venous distention (greater or less than 10 cm water), third heart sound (yes or no), and pedal edema above the lateral malleolus (yes or no). These 10 dichotomized variables were entered into a multiple logistic regression with the presence or absence of CHF during prospective follow-up as the dependent variable. Only two variables remained in the model independently predicting CHF at the $p < 0.05$ level: ANP with adjusted odds ratio of 7.9 (95% confidence interval 3.2 to 19.2), and history of CHF in the previous year with adjusted odds ratio of 7.0 (95% confidence interval of 2.9 to 17).

Sensitivity, specificity and relative risk of ANP and history of CHF

To examine the sensitivity and specificity of various cut-off values of baseline ANP levels to predict CHF, a receiver operating characteristic (ROC) curve was constructed with true positive rate (sensitivity) on the ordinate and false positive rate (1 − specificity) on the abscissa. The tangent to the ROC curve defines the ANP value with the combination of highest true positive rate and lowest false positive rate (highest sensitivity and specificity) in predicting CHF. The tangent of the ROC curve is near 200 pM. About 40% of the elderly cohort had ANP levels greater than 200 pM.

Using an ANP value of 200 pM as a cut-off (greater than 200 as a positive test predicting CHF), ANP has a sensitivity of 85% and specificity of 66%. History of CHF in the previous year has a sensitivity of 38%, specificity of 94%, positive predictive value of 53% and negative predictive value of 88% for predicting CHF. ANP has a greater sensitivity (more often positive in those developing CHF) and previous history of CHF has a greater specificity (more often negative in those that did not develop CHF).

The crude relative risk of developing CHF for subjects with an ANP level greater than 200 pM was 8.9 (95% confidence interval 3.9 to 20.5). The crude relative risk of CHF for subjects with a history of CHF in the previous year was 5.9 (95% confidence interval 2.9 to 12.0).

Development of risk groups for CHF

Two hundred and seventy-two of the 310 subjects had both ANP levels and complete daily medical records available for the previous year. Sixteen percent of these 272 subjects developed CHF during prospective follow-up (see

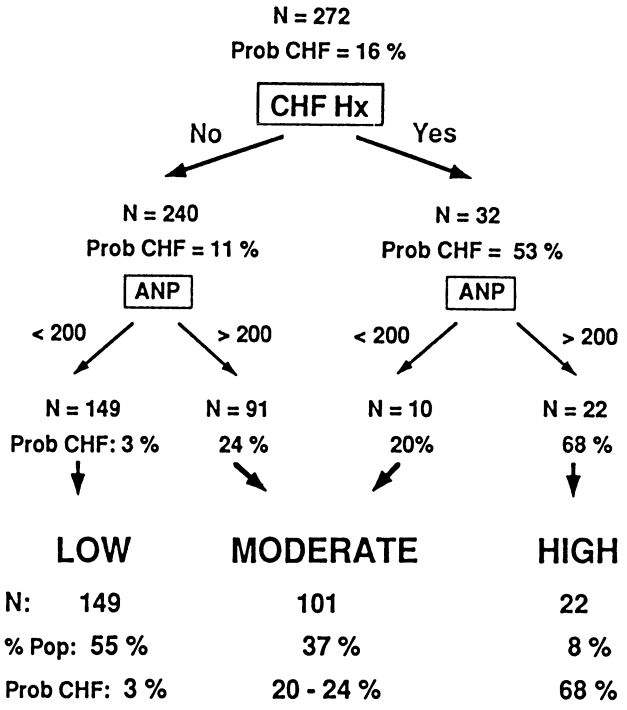

Fig. 2. The development of risk groups for CHF by first dividing the cohort by history of CHF in the previous year (CHF Hx) and then subdividing these groups by ANP levels.

Fig. 2). The 272 subjects were first divided by history of CHF in the previous year and then subdivided by ANP levels. As shown in Fig. 3, by this simple schema, the cohort can be classified into three risk groups: 149 subjects (55% of the cohort) had a low CHF risk of 3%, 101 subjects (37% of the cohort) had a moderate CHF risk of 20 to 24%, and 22 subjects (8% of the cohort) had a high CHF risk of 68%.

Discussion

This study demonstrates that a careful history and a venous blood test (ANP level) can identify elderly patients vulnerable to acute volume overload, manifested as CHF. The ability to better define risk groups for CHF may lead to more-efficient, cost-effective strategies for the prevention and early treatment of this highly morbid condition.

There is a tremendous need for the development of interventional strategies for the prevention and early treatment of the common illnesses affecting the elderly, especially those illnesses necessitating admission to an acute-

Table I. Outcomes during one-year prospective follow-up

Outcome	*N*	ANP (pM)	Age
CHF	46	493 ± 53 (SE) *	91 ± 0.8 (SE) *
No CHF	264	207 ± 15	88 ± 0.4
Deaths	37	231 ± 55	88 ± 1.5
<6 mths†	21	163 ± 31	88 ± 1.8
>6 mths††	16	321 ± 86	88 ± 2
Cardiac	8	450 ± 162	89 ± 5
Non-Cardiac	29	172 ± 26	88 ± 2

† Excluded from analysis.
†† Included in 'No CHF' groups.
* Two-tailed $p < 0.001$ between groups.

care hospital. Addressing the health-care needs of this expanding population will consume increasing amounts of health-care dollars over the next several decades. Recent studies in patients with symptomatic cardiac dysfunction have shown significant decreases in mortality and morbidity with the use of angiotensin-converting-enzyme inhibitors [2, 3]. These study findings further emphasize the need to identify patients at risk for morbid cardiac events.

The ANP frequency distribution in this clinically stable elderly population demonstrates a wide range of ANP levels, from 9–1622 pM. Twenty-five percent of the elderly cohort had ANP levels greater than 300 pM, a level associated with acute cardiac decompensation in previous studies involving younger subjects [4–10]. Fifteen percent of the elderly cohort developed at least one episode of CHF during the one-year-prospective follow-up. The subjects' likelihood of developing CHF during prospective follow-up increased dramatically with increasing study entry ANP levels. In the highest ANP quintile, 36% of the group developed CHF during the prospective follow-up.

Table II. Predictive model for CHF: logistic regression

Variables entered:		
Age	Artificial pacemaker	
Level of care	Mean arterial pressure	
ANP value	Jugular venous pressure	
History of CHF	Third heart sound	
EKG (sinus vs. other)	Pedal edema	
Variables emerged ($p < 0.05$):		
	Adj. Odds Ratio	95% C.I.
ANP value	7.9	3.2–19.2
History of CHF	7.0	2.9–17.0

In establishing a clinical predictive model, we chose 10 variables that are clinically related to CHF: advanced age, greater intensity of nursing care, history of CHF, other than sinus mechanism on EKG (primarily chronic atrial fibrillation), elevated blood pressure, jugular venous distention, third heart sound, pedal edema, presence of an artificial cardiac pacemaker and higher ANP levels. Presence of pulmonary rales was not considered since subjects with extensive rales on exam were considered clinically unstable and were not included in the study. The presence of a cardiac murmur was not considered since over 50% of this population has cardiac murmurs [16]. Only two of these 10 variables emerge independently predicting CHF: ANP values >200 pM and history of CHF.

To establish risk groups for CHF, we used the 272 subjects who had both ANP levels and one-year, detailed retrospective history available. These 272 subjects had been in the lifecare facility for at least one year before study entry. The remaining 38 of the 310 total subjects in the prospective follow-up had been in the lifecare facility for less than one year. Since we required detailed one-year medical records before study entry (reflecting daily medical assessment), these 38 were not included in this risk stratification. The biggest numerical impact of substratifying by ANP levels is to target those 91 of 272 subjects (33% of the population) who previously were in the low-risk group and are now at moderate risk.

What pathophysiologic mechanisms explain the high predictive value of ANP in this population? Previous studies have shown that ANP levels reflect cardiac-filling pressures [17–19] and are increased in diseases associated with chronic and acute cardiac dysfunction [4–10]. Higher ANP levels in these subjects most likely reflect a greater cardiovascular illness burden, and therefore serve as a marker for those subjects with chronically elevated cardiac-filling pressures associated with subclinical cardiac dysfunction. Subjects with higher ANP levels may have more limiting cardiac dysfunction and are more likely to have symptomatic CHF. Recently, studies have confirmed that diastolic dysfunction (manifested by ventricular stiffness and impaired ventricular relaxation) may be more important than systolic dysfunction in the pathogenesis of CHF in the elderly [20–22]. Elderly subjects with diastolic dysfunction often are 'preload sensitive', manifesting greater changes in cardiac-filling pressures with relatively small changes in vascular volume. In those elderly with normal systolic function, elevated ANP levels may be a marker for significant diastolic dysfunction with subclinical volume overload.

With the development of this simple clinical algorithm to target those elderly at risk for CHF, the challenge now is to study specific preventive interventions. Those at risk for CHF may benefit from more rigorous assessment and treatment. Future studies will determine if strategies that decrease central blood volume, as reflected by lower ANP levels, result in a reduction of CHF risk.

In summary, 15% of an elderly institutionalized population developed chest X-ray-confirmed CHF in one year of follow-up. Those developing CHF

had significantly higher baseline ANP levels compared to subjects who did not have CHF. The risk for developing CHF rose progressively with increasing study-entry ANP levels. Institutionalized elderly subjects can be stratified into low, moderate, or high CHF risk groups by the determination of two variables: history of previous CHF and venous plasma ANP levels. Targeting elderly subjects at risk for CHF may permit the development of efficient interventional strategies, which may decrease the incidence of this common, highly morbid and often fatal condition [23].

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PART FIVE

Urinary tract infection

CHAPTER 12

Urinary infection in the elderly

LINDSAY E. NICOLLE

Urinary infection is common in the elderly. The prevalence of bacteriuria in women living in the community is 5–10% at 65 years [1] and increases to about 15% by age 80 [2]. For men, the prevalence is only 1–2% at 65 but increases to 5–10% at age 80 [3, 4]. The prevalence is much higher in the functionally and physically disabled elderly, who are permanent residents of long-term care institutions. In studies of different populations worldwide, this prevalence has been from 17–55% for women and 17–50% for men [5]. Generally, bacteriuria in the institutionalized elderly remains higher for women than for men, but the female/male ratio is substantially lower than in younger populations. The small subset of the institutionalized elderly with urinary incontinence managed by long term indwelling catheters are always bacteriuric [6]. This review will discuss only the non-catherized elderly unless specific reference is made to the catheterized elderly.

The incidence of urinary infection is also high. In an elderly geriatric population Boscia *et al.* reported that 6% of men and 18% of women and bacteriuria at initial screening [5]. Over the next 12 months, with screening repeated at six-monthly intervals, the cumulative prevalence was 30% for women and 10% for men. In a Greek population, Kasviki-Charvati *et al.* found an initial prevalence of bacteriuria of 19% and 27% for men and women respectively; a further 11% and 23% of subjects who had negative urine cultures at entry, had a positive culture at 12 months [7]. A Canadian group of elderly institutionalized men had an incidence of new infections of 45/100 patient years [8]. Ten percent of previously nonbacteriuric subjects acquired bacteriuria in any three-month period.

Causes of bacteriuria

The factors responsible for this exceedingly high prevalence and incidence of bacteriuria have not been clearly defined. Table I summarized some factors which likely contribute to bacteriuria. For men, the major contributors are prostatic hypertrophy with obstruction and prostatic infection. The elderly

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Table I. Selected factors contributing to the high prevalence of bacteriuria in the elderly

	Women	Men	Both
1. Infection at 'protected sites'		Prostate	Renal
2. Associated diseases	Diabetes		Neurogenic bladder – Alzheimer's disease – Cerebrovascular accident
3. Genitourinary abnormalities	Cystocele Uterine prolapse	Prostatic hypertrophy	Bladder diverticulae
4. Aging – associated	Estrogen deficiency	Decreased prostatic bacteridical activity	

are more likely to have had previous genitourinary intervention, including catheterization. In men this may lead to prostatic infection which, once established, cannot be eradicated and may serve as a recurrent source for bladder bacteriuria [8]. Men who void with the aid of an external collecting device are also at increased risk of bacteriuria [9]. For women, local factors such as cystoceles likely contribute to impaired voiding and the high prevalence of bacteriuria. Specific aging-associated factors such as mucosal changes associated with a decline in estrogen in women, may contribute to bacteriuria but these remain poorly studied [10]. In over one-half of women with bacteriuria, the site of bacteriuria is localized to the kidney [11]. Generally renal infection is more difficult to eradicate with antimicrobial therapy, so renal localization may promote persistence in women. In older men, a decline in the bactericidal activity of prostatic secretions may contribute to bacteriuria [12]. No one has shown that immunologic changes associated with aging have not been shown to be associated with an increased occurrence of bacteriuria.

The major factors contributing to bacteriuria, especially for the institutionalized elderly, are the associated diseases and functional impairment [13]. Studies in the institutionalized elderly, have clearly documented that those with bacteriuria have a higher prevalence of functional impairment. Many have a neurogenic bladder secondary to previous cerebrovascular accidents, Alzheimer's disease or other neurologic diseases, which impairs complete bladder emptying. The single most important host defense in preventing bacteriuria is voiding and impaired voiding is a powerful promoter of bacteriuria. Diabetic women, but not men, have an increased prevalence of bacteriuria compared to non-diabetic women at all ages [14].

Table II. Microbiology of bacteriuria in the elderly

	Non-institutionalized		Institutionalized	
	Women	Men	Women	Men
Escherichia coli	+++	++	+++	++
Proteus mirabilis	+	++	++	+++
Klebsiella pneumoniae	+		+	++
Citrobacter freundii			+	+
Enterobacter cloacae			+	+
Providencia stuartii			+++	+++
Morganella morganii			+	+
Pseudomonas aeruginosa			++	++
Other gram negative			+	+
Acinetobacter spp.			+	+
Enterococcus faecalis	+	++	+	++
Group B streptococcus	+	+	++	++
Coagulase negative streptococci		+	+	++

+++ Very common.
++ Common.
+ Occasional.

Microbiology

Urinary infection, or bacteriuria, follows ascension into the bladder of organisms colonizing the periurethral area, with subsequent persistence in the bladder and, in many cases, ascension to the kidneys. The gut and vagina are the usual reservoirs for bacteria. The institutionalized elderly men with incontinence managed by external drainage devices may have these devices contaminated by cross-contamination within the institution, serving as a reservoir for bacteriuria. The microbiology of bacteriuria in the elderly is summarised in Table II.

In women in the community the most common infecting organism is *Escherichia coli*, isolated from 60–80% of all episodes of bacteriuria [2]. While it is the single most common organism, its relative frequency is lower than that identified in urinary infection in younger females. For men in the community, *Proteus mirabilis* and *E. coli* occur with approximately equivalent frequency. While *P. mirabilis* is a common uropathogen in the elderly, there is little data concerning morbidity from struvite-stone disease in this population. Stone disease appears to be exceedingly low given the extraordinarily high prevalence and, in some individuals, persistence of *P. mirabilis* infection [8, 15]. Gram-positive organisms including *Enterococcus faecalis* and coagulase-negative staphylococci are also isolated frequently. Group B streptococci are also identified, perhaps more frequently in diabetics.

The institutionalized elderly frequently harbor gram-negative organisms of increasing antimicrobial resistance [8, 16, 17]. These include *Klebsiella pneumoniae*, Serratia spp., Enterobacter spp., *P. mirabilis*, *Morganella mor-*

ganii, *Providencia stuartii* and other Providencia spp., and *Pseudomonas aeroginosa*. Infection with more than one organism occurs in 10–33% of subjects. The increased prevalence of these organisms in the institutionalized population likely reflects the high frequency of exposure to antimicrobial therapy, and opportunities for transmission of such organisms through environmental reservoirs or on the hands of staff working with residents, a high proportion of whom are incontinent.

Host/organism interactions

For many elderly subjects, bacteriuria is persistent or recurrent, with infection present for months or years [8, 15]. While most bacteriuria in the elderly is asymptomatic, pyuria is virtually universal. Over 90% of men or women with asymptomatic bacteriuria will have pyuria [11, 17]. The pyuria may persist at high levels for months to years [18]. One determinant of the degree of pyuria appears to be the level of infection. Elderly women with asymptomatic bacteriuria and renal infection have a higher degree of pyuria than those with a bladder localization [11]. To date, no one has shown that the presence or absence of pyuria or the quantitative level of pyuria, have any clinical significance. An assessment of the significance of pyuria, at least among the institutionalized elderly, is difficult because a high proportion of non-bacteriuric subjects also have pyuria [18].

Elderly individuals with invasive urinary-tract infection have an antibody response to antigenic components of their infecting organisms, including lipopolysaccharide and outer-membrane proteins [19, 20]. There is a systemic (serum) antibody response, and a local antibody response measured as urine antibody. For elderly subjects with persistent asymptomatic bacteriuria, the serum antibody response is more variable. Most subjects will have normal serum antibody, although there are exceptions. Approximately 1/3 to 1/2 have an elevated local urine antibody when compared to nonbacteriuric elderly individuals [21]. Subjects with elevated urine antibody may also have an elevated quantitative urinary leukocyte count, suggesting a greater immune/inflammatory response. Normal or elevated urine antibody tends to persist over time in a given bacteriuric subject. The clinical significance, if any, of this differential antibody response has not been determined.

In the elderly, organism-associated virulence factors in invasive infection are similar to those in younger populations. In particular, the P pilus of *E. coli* appears to be important in those with a clinical syndrome consistent with pyelonephritis [22], and increased production of urease is identified in *P. mirabilis* isolated from bacteremic strains relative to nonbacteremic strains [23]. Organisms isolated from subjects with asymptomatic bacteriuria have a decreased phenotypic expression of potential virulence factors, similar to observations in asymptomatic bacteriuria in younger populations [24].

Morbidity and mortality

Most elderly subjects with bacteriuria have no symptoms. While there is a high prevalence of chronic genitourinary complaints, especially in the institutionalized population, such chronic symptoms are similar in individuals whether or not they are bacteriuric [4, 25]. An acute exacerbation in a subject with previous stable symptoms, however such as deterioration in continence status, may be associated with bacteriuria. In elderly institutionalized subjects, difficulties in communication may make it difficult to determine whether or not they have symptoms.

When symptomatic infection occurs in the elderly, it is usually associated with irritative lower-tract symptoms or signs, similar to younger populations. Other manifestations that may be seen more frequently in the elderly include deterioration in continence, and, in men, epididymo-ochitis or, for those with external drainage devices, urethritis. There is no evidence that non-specific symptoms such as pain or 'general decline' with no localization to the urinary tract are, in the absence of fever, associated with bacteriuria [26].

The incidence of symptomatic infection is exceedingly low relative to the high prevalence of bacteriuria [8, 15]. There are, however, limited studies which characterize the occurrence of symptomatic infection in elderly populations, particularly the noninstitutionalized elderly. For the institutionalized, two prospective studies which identified symptomatic infection and suggested that the rates of symptomatic infection are 0.11 to 0.15 per 100 bacteriuric years. In another study, Boscia *et al.* [27] reported that 10 (16%) of 61 elderly women in a geriatric apartment with asymptomatic bacteriuria, became symptomatic during a 6-month period.

However, urinary-tract infection is the most common cause of bacteremic infection in both the institutionalized and noninstitutionalized elderly [28, 29]. Symptomatic urinary-tract infection is reported to be a frequent cause of transfer of elderly individuals from chronic care to acute-care institutions [30, 31].

The association between asymptomatic bacteriuria and survival in elderly populations is controversial. Initial studies from Finland [32] and Greece [33] suggested that the presence of asymptomatic bacteriuria was associated with poor survival for both men and women. However, studies enrolling subjects in Sweden [34], Finland [35] and Canada [13] have not confirmed these initial reports. In addition, autopsy studies of elderly nursing-home patients did not suggest that urinary infection is a frequent cause of mortality [36, 37]. Currently, it is felt that asymptomatic bacteriuria does not contribute directly to increased mortality in the elderly.

Management of bacteriuria

Asymptomatic bacteriuria in the elderly does not require antimicrobial therapy. In fact, antimicrobial therapy might be considered to be contraindicated

in this situation [8, 16]. Prospective comparative studies of therapy *vs* no therapy in the institutionalized population suggest that antimicrobial therapy is associated with increased cost, increased side effects and increased emergence of resistant organisms. In addition, reinfection and relapse of infection are so frequent in this population that antimicrobial therapy does not have a substantial long-term impact. The prevalence of bacteriuria is only moderately and transiently decreased [38, 39]. Few studies have examined the relative risks or benefits of treatment of asymptomatic bacteriuria in non-institutionalized populations. One study suggests antimicrobial treatment of noninstitutionalized women may lead to prolonged sterile urine in as many as 50% of subjects [27]. It is doubtful whether the benefits of such an approach outweigh the excessive costs associated with screening and treating all elderly individuals. Further studies in the noninstitutionalized population are, however, needed.

Asymptomatic bacteriuria should be treated in the elderly individual about to undergo an invasive intervention of the urinary tract. The high prevalence of sepsis and bacteremia following trauma to the mucosal surface can be prevented with appropriate antimicrobial therapy.

Symptomatic infection should be treated. The antimicrobials appropriate for symptomatic infection appear to be similar to those in younger populations [40]. Duration of therapy has not been well studied for elderly populations. Specific issues relating to the treatment of urinary infection are dealt with in the following chapter.

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CHAPTER 13

Urinary-tract infection in the elderly: evaluation and treatment

LINDSAY E. NICOLLE

The goals of investigation and therapy of urinary infection in the elderly individual must be clear prior to the institution of management. Short-term goals are to ameliorate symptoms and prevent complications including sepsis and death, or other potential manifestations such as impaired diabetic control. In addition, one should identify underlying abnormalities that could impair renal function or lead to a poor outcome. Long-term goals are to prevent such complications as renal failure or the formation of infection stones with their sequelae. The extent to which urinary infection may contribute to these complications determines the need and urgency of evaluation and treatment. We have little evidence that urinary infection by itself contributes substantially to long-term complications. Thus, the major goals of evaluation and therapy of urinary infection in the elderly is to prevent such short-term complications.

Asymptomatic bacteriuria

Asymptomatic bacteriuria in the elderly does not warrant treatment [1, 2]. Prospective comparative randomized trials of therapy with no therapy for bacteriuria in the institutionalized elderly with follow-up for one and two years, did not show any measurable benefit from antimicrobial therapy. In particular, there was no difference in symptomatic episodes attributable to urinary infection between treated and untreated populations. Subjects who received antimicrobial therapy for asymptomatic bacteriuria, however, had an increased number of adverse drug effects, and an increase in resistant organisms. Recurrence due to both reinfection and relapse was common in a relatively short time and extended periods free of bacteriuria were uncommon following antimicrobial therapy. Because asymptomatic bacteriuria does not require treatment, screening programs to identify bacteriuria in the elderly are not appropriate.

There are few studies of treatment of asymptomatic bacteriuria in the noninstitutionalized elderly. One study suggested that treatment of asympto-

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matic bacteriuria with a short course of antibiotics in elderly ambulant women decreased the incidence of symptomatic infection in the subsequent 6 months [5]. It did not, however, characterize morbidity attributable to symptomatic infection, and did provide a cost/benefit assessment. With the high prevalence of bacteriuria in the elderly, screening and subsequent treatment for all appears inappropriate. In addition, studies in children suggest that treatment of asymptomatic bacteriuria increases the risk of symptomatic infection in those treated [4, 5]. Presumably treatment eradicates an avirulent organism associated with asymptomatic bacteriuria and it is replaced by a more virulent organism, in a subject with a high propensity for infection. While similar observations have not been made in elderly populations, this is a theoretical argument against treatment of asymptomatic bacteriuria.

There is an indication for screening for asymptomatic bacteriuria and treatment for elderly subjects who are to undergo invasive genitourinary procedures. Sepsis frequently follows manipulation of the genitourinary mucosa in a subject with infected urine. Such post-intervention sepsis can be reduced by treatment before the traumatic procedure [6].

Symptomatic infection

Symptomatic infection in the elderly should be treated with antimicrobials. Symptoms in some elderly may be difficult to detect, particularly in the most functionally disabled, institutionalized subset. Frequently they have chronic genitourinary symptoms and may be unable to communicate any alteration in symptoms to caregivers [7, 8]. In situations where the contribution of urinary infection to putative symptoms is unclear, the subject should be observed for variation in symptoms or be given a trial of antimicrobials. If the latter course is chosen, one should identify the specific symptoms targeted for improvement before therapy. If these symptoms do not resolve within a couple of days with an antimicrobial effective for the identified organisms, one should not continue such therapy.

Antimicrobial therapy

There are multiple variations in pharmacokinetic parameters of antimicrobials in elderly compared to younger individuals [9]. These variations reflect many factors, including declining hepatic and renal function, alterations in bowel motility, associated diseases and medications. While alterations in absorption, clearance, volume of distribution and other parameters have been demonstrated many times in the elderly, none of them has been shown to occur with such consistency or magnitude to justify a systematic change in dose or agent simply on the basis of age. The guidelines for selection of antimicrobial therapy for urinary infection in the elderly is similar to that for

Table I. Selected oral antimicrobials for urinary infection in elderly populations

Antimicrobial	Dose
Amoxicillin	500 mg t.i.d.
Amoxicillin/clavulinic acid	500 mg t.i.d.
Cephelexin	500 mg q.i.d.
Ciprofloxacin	250–500 mg b.i.d.
Lomefloxacin	400 mg o.d.
*Nitrofurantoin	50 mg q.i.d.
*Nitrofurantoin macrocrystals	100 mg q.i.d.
Norfloxacin	400 mg b.i.d.
Ofloxacin	400 mg b.i.d.
*Trimethoprim	100 mg b.i.d.
*Trimethoprim/sulfamethoxazole	160/800 mg b.i.d.

* Suggested first-line agents.

Table II. Suggested parenteral antimicrobials for urinary infection in the elderly

Antimicrobial	Dose*
*Ampicillin	1 g q6L
Cefazolin	1 g q8L
Ceftriaxone	1 g q12–24L
Cefotaxime	1 g q6–8L
Ceftazidime	1 g q8L
Ciprofloxacin	200 mg q12L
*Gentamicin	$1\frac{1}{2}$ mg/kg q8h
Imipenem	500 mg q6h
Tobramycin	$1\frac{1}{2}$ mg/kg q8L
Trimethoprim/sulfamethoxazole	150/800 mg b.i.d.
Ticarallin/clavulanate	50 mg/kg q4–6L

* Appropriate adjustments should be made for subjects with impaired hepatic or renal function.

a younger population. That is, the antimicrobial is chosen on the basis of patient tolerance, known or presumed infecting organism and susceptibilities, physician experience, and cost. Tables I and II list appropriate oral and parenteral therapy. In most instances one selects an agent with which there is prior experience in the elderly, giving consideration to cost, patient-specific variables including tolerance, hypersensitivity, and renal and hepatic function must be considered in selecting the appropriate antimicrobial.

Duration of therapy

The optimal duration of antimicrobial therapy for treatment of urinary infection in elderly subjects is not well studied. Therapy of any duration in elderly women has a lower cure rate compared with younger women [10–12]. The reasons for this are not determined. Shorter courses of therapy, in particular,

are substantially less effective in older women [10, 13]. Single-dose therapy is not appropriate in elderly women. The specific age beyond which short-term therapy should not be considered effective is not known. One suggestion is that single-dose therapy should not be used in postmenopausal women. Three-days therapy is not as effective in elderly women as in young women but this duration will be effective for over one-half of women with an acute uncomplicated urinary tract infection, and may be an appropriate initial therapy [3]. Alternatively, all elderly women could be treated initially with 7 days of antimicrobials if they present with a clinical syndrome consistent with acute uncomplicated urinary infection.

Subjects who present with the clinical syndrome of pyelonephritis or other evidence of invasive infection or with complicated urinary infection, whether male or female, should receive two weeks of therapy. If symptomatic relapse occurs, men should be retreated with 6 or 12 weeks of therapy [14, 15].

Evaluation

Indications for urine culture

For elderly women living in the community who have not had recent antimicrobial therapy, the most common infecting organism isolated in acute uncomplicated urinary infection will be *E. coli* [16]. In this situation it may be appropriate to treat women with symptoms with empiric antimicrobial therapy without obtaining a culture. Such cultures should be obtained if the patient does not respond to therapy, or if they have recently had antimicrobials. For all elderly subjects with acute pyelonephritis or evidence of invasive infection, a urine specimen should be obtained before treatment. This allows the physician to select an antimicrobial specific for the etiologic agent and its susceptibility for infections that have the potential for high morbidity. Similarly, elderly subjects in nursing homes are likely to harbor more resistant organisms. In this instance, one should obtain a urine culture before treatment.

Follow-up urine cultures are seldom needed for subjects with symptomatic infection who have been treated and have no recurrence of symptoms following therapy. The goal of therapy, after all, is to ameliorate symptoms, not to sterilize the urine. In a small subset of such individuals, one may have residual concern about the potential long term effects of asymptomatic bacteriuria and, in these, it may be appropriate to obtain a culture. Because there is no clear indications for the treatment of asymptomatic bacteriuria in the elderly, there are no clear indications for followup culture in a patient who is asymptomatic following therapy.

Other investigations

With the high prevalence and incidence of bacteriuria in the elderly, it is clear that not all individuals with urinary infection require investigation. There are, however, no studies which identify which group of individuals might benefit from further investigations. Certainly, any male with urinary-tract infection needs assessment for prostatic hypertrophy. Other elderly subjects who may need investigation are those with recurrent or prolonged hematuria, with recurrent invasive infection, and with renal failure. These suggestions are based on the author's experience and have not been validated in clinical studies; such studies are needed to determine appropriate methods of evaluation in the large bacteriuric elderly population.

Summary and conclusions

Few studies have addressed the evaluation and treatment of urinary infection in the elderly. Such subjects with asymptomatic bacteriuria should not be treated with antimicrobials unless they are to undergo invasive genitourinary procedures. Symptomatic infection should be treated. Principles governing the selection of an antimicrobial agent for therapy do not differ for elderly subjects and age does not modify such selection. The appropriate duration of therapy in elderly subjects is not well studied. For elderly women shorter courses are significantly less effective for acute uncomplicated urinary infection than in younger women. Seven days of therapy may be the appropriate initial duration. For infections in men, and for invasive infections in women, initial therapy should be given for two weeks. In men, relapsing symptomatic infection may need to be retreated with 6 or 12 weeks of therapy.

Pretherapy urine cultures should be obtained in women with recent antimicrobial therapy or evidence of invasive infection, in all men with urinary infection, and in institutionalized subjects. Generally follow-up urine cultures are needed only if symptomatic infection recurs. Indications for further evaluative procedures and the impact of such evaluation on patient outcome have not been clearly defined for the elderly.

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CHAPTER 14

Urinary-tract infection in the elderly, epidemiology and pathogenesis

ANDREW W. BRUCE and GREGOR REID

Epidemiology

In both women and men, the incidence of urinary-tract infection increases steadily in the elderly, particularly in those over 65 years of age. They need more diagnostic investigations, increased antibiotic use, and have more morbidity. These factors mean increasing health costs, providing difficult decisions for health administrators and physicians involved in the care of the elderly. The sex ratio of urinary tract infections changes dramatically with age. In young adults, females outnumber men in a ratio of 20 to 1; in the older age group, this ratio drops to 2 to 1 at age 65 years or older [1]. Boscia and Kaye [2] have demonstrated differences in the prevalence of bacteriuria in both women and men, and have shown the marked impact of domicile. Table I shows the prevalence of bacteriuria in women and men able to live at home, compared to those restricted to a nursing home or hospital environment. Clearly, the impact of general health, mobility and those illnesses causing urinary and fecal incontinence become dominant in institutionalized settings.

Pathogenesis of bacteriuria

Hormonal and, to a lesser degree, immunological factors associated with the aging process *per se*, have a major influence on the etiology of bacteriuria. Important changes occur in the vagina *viz* reduction in estrogen levels, rise in pH, change in the normal flora and others. In the male, enlargement of the prostate gland, primarily under hormonal influence, is associated with aging. Both sexes have an increase in urological and gynecological surgical procedures, with indwelling catheters and urethral manipulation. Residual urine plays an important role in both sexes, more so in the male, due to prostatic obstruction. Bacterial adherence and cell receptivity to bacteria change in the elderly, and there is a decline in cellular defences against infection.

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Table I. Prevelance of bacteriuria in subjects over 65 years*

Setting	% Bacteriuria	
	Women	Men
Living at home	17–33	6–13
Nursing home	23–27	17–26
Hospital	32–50	30–34

* Boscia and Kaye [2], with permission.

Although *Escherchia coli* still is the most common infecting organism in the elderly, other pathogens, such as *Proteus*, *Serratia*, *Klebsiella*, *Pseudomonas* and *Enterococci* are found frequently [3, 4]. In our laboratory, we studied the virulence properties of bacteria in both postmenopausal and premenopausal women [5], and found no significant difference between strains isolated from the two groups. These included the production of adhesins [5] hemolysins [2], and urease, and the fermentation of sucrose, salicin and dulsitol. On the other hand, there were significantly different adherence values for three strains adherent to the cells of elderly and premenopausal women (Table II). The highest adherence values of uropathogenic bacteria were to the cells of the elderly women.

In women, the infecting organisms originate in the rectum, and then in a sequential manner adhere to the perineum, the introitus, the vagina, the urethra and the bladder, thence causing cystitis and possibly pyelonephritis. Colonization of the introitus is essential to the development of urinary-tract infection and it has been shown that women with a history of recurrent infection have a higher colonization rate than those without any previous infection [6]. The same study also showed an increase in adherence of pathogenic organisms in the elderly, in both the infected and control groups. Fifty-three per cent of those with a previous history of urinary-tract infection had pathogens on the introitus, compared to 20% of those without a previous history. In the elderly infected patients, this percentage increased to 65%.

Table II. Mean adherence values (±S.D.)

Bacterial strain	Cells from elderly women	Cells from premen. women
E. coli (MR)	108.13 = 17.74	71.17 ± 2.24
Proteus (MR)	68.63 ± 3.47	14.83 ± 3.18
E. coli (MS)	16.21 ± 0.471	9.43 ± 1.36

Kruskall–Wallis test
$p < 0.001$
[1 strain (*E. coli* M.S.) $p < 0.1$]

The role of normal vaginal flora

We have studied the importance of maintaining a bacteriological niche in the vagina, capable of protecting the patient from infection. Marrie [7] has shown that lactobacilli dominate the urogenital population of pre-menopausal women whereas, in the elderly, bacteroides and anaerobic organisms are the most prevelant. In *in vitro* studies [8] we showed that lactobacilli adhere effectively to squamous and transitional uroepithelial cells harvested from premenopausal women. In addition, we demonstrated that these organisms can interfere with the adherence of pathogenic organisms *in vitro* and that different strains of lactobacilli vary in their capability to block pathogens [9]. In animal experiments (both chronic and acute UTI models), we have shown that we can prevent bacterial infection by pretreating these animals with lactobacilli instilled into the vagina and bladder [10, 11].

Also we have completed some human studies. After careful examination of 100 strains of lactobacilli, we selected two strains: *Lactobacillus casei GR-1* capable of inhibiting *E. coli* growth and interfering with uropathogenic colonization and *Lactobacillus fermentum B-54* capable of inhibiting gram-positive pathogens. These strains have been prepared in suppository form. A study, involves, in the first instance, 10 women treated over a period of one year with weekly intravaginal installations of suppositories. There was a net reduction in infection rate of approximately 78%. A second study showed a similar reduction in infection rate using the same mode of therapy [12, 13]. We believe that lactobacilli in the vagina form a major defence against the infection of premenopausal women, but also may have a role in postmenopausal women, particularly in those receiving estrogens.

Finally, antibiotics have a marked impact on the vaginal flora [14]. In this study, which used broad-spectrum antibiotics to eliminate urinary-tract infection, a period of six weeks was needed before the normal vaginal flora recovered, suggesting that these patients need supplementary lactobacilli after antibiotic therapy.

The impact of biofilm formation on urinary catheters and on infection in the elderly

The concept of biofilm formation was developed primarily by Costerton and his group [15]. They showed that microbial biofilms often develop when foreign bodies are introduced into the body and almost always when the device is open to the outside. Infections are common with device use and, in many different clinical situations, may persist. Biofilm formation confers on the bacteria the ability to resist antibodies, phagocystosis and antibiotics [16]. These same authors also have shown that the standard minimum inhibitory concentration (MIC) for antibiotics is applicable to planktonic but not to sessile organisms. The results did not establish whether a certain agent

can eradicate the bacteria within the biofilm, as was demonstrated clearly by Olson *et al.* using a rabbit model [17]. Scanning-electron microscopy showed that increasing doses of antibiotics applied to the mucosa of these infected rabbits results in clearing of the organisms. However, with the same level of antibiotic therapy, one could not eradicate the bacteria from the catheter biofilm, indicating the source of continuing infection. Clearly, severe illness associated with mucosal and tissue infection can be corrected by appropriate antibiotic therapy but, as stated, the infection is likely to recur due to the persistence of bacteria on the catheter surface. Recently, in spinal-cord-injury patients, Reid *et al.* [18] showed that, even with antibiotic therapy, bacteria may exist in biofilms on bladder-mucosal cells. They studied 12 patients with spinal-cord injuries on intermittent catheterization and showed that 73% of the patients with infected urines had *in vivo* mucosal biofilms, and that 16% of those patients with sterile urines also had biofilm formation. This situation may call for a higher dosage of antibiotic or an antibiotic with more effective biofilm penetration, assuming that therapy is given at all.

The choice of antibiotics for biofilm therapy

A recent study in our laboratory showed that Ciprofloxacin has a greater ability to eradicate well-established biofilms with *Pseudomonas aeruginosa* than does Tobramycin [19]. Under experimental conditions, using a modified Robins device to clear the biofilm, it needed 10 times the normal MIC of Ciprofloxacin compared to 100 times the MIC when Tobramycin was used. It is important to appreciate that higher concentrations of antibiotics are required to eliminate sessile bacteria, thus we have adopted the term 'biofilm elimination concentration' to indicate this value.

In summary, changes in bacterial receptivity, urogenital flora, and the increasing incidence of biofilm-type infections have added to the clinician's problems in dealing with urinary-tract infections in the elderly.

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PART SIX

Hypertension

CHAPTER 15

Hypertension in the elderly: pathophysiology of aging of the cardiovascular system

HARALAMBOS GAVRAS and IRENE GAVRAS

Aging is characterized by anatomical, humoral, biochemical and functional alterations, whose rate of progression may vary, as indicated by the individual variability between biological and chronological age. Moreover, the rate of aging of different systems or functions may vary within the same individual. Nevertheless, both longitudinal cohort studies and cross-sectional population surveys have attempted to define normal standards for specific age groups. Knowledge of these standards for various cardiovascular parameters is a necessary requirement for appropriate decision-making during the diagnosis and management of hypertension and cardiovascular diseases, as well as metabolic and other systemic disorders. This review highlights a number of pathophysiologic changes that occur as part of the normal aging process and are relevant to the treatment of hypertension.

Anatomic and hemodynamic alterations

As a result of the gradual loss of elasticity of the collagen throughout the body, various organ tissues become increasingly sclerotic, particularly the blood vessels and the heart valves, leaflets and chordae. In the aorta and major elastic and muscular arteries, elastin is replaced by lipid infiltration and 'fatty streaks', which precede the formation of atheromatous and calcium-containing deposits. This atherosclerotic process, which leads to distension, elongation with tortuosity and segmental obstruction of the large arteries, reaches its maximum rate of progression in the decade between 50 and 60 [1]. The smaller arteries and arterioles, especially those of the kidney, develop thickening of the vascular wall due to hyaline degeneration, similar to that caused by severe hypertension leading to nephrosclerosis in the young [2]. The resulting increase in the wall-to-lumen ratio causes the increased systemic vascular resistance characteristic of aging. The rigid wall of the aorta and large arteries cannot distend and absorb the impact of left ventricular systole, hence the systolic blood pressure rises with age; it is also less capable of recoil during diastole to maintain pressure in the distant parts of the arterial

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Table I. Anatomic and hemodynamic alterations of the cardiovascular system with age

Collagen degeneration		
loss of elastin		
fatty streaks		
athermomata		
calcification		
Wide pulse pressure:	↑ systolic	↓ diastolic
Loss of body water		
Decreased myocardial contractility		
Decreased heart rate		↓ ejection fraction
Increased left-ventricular stiffness		↓ cardiac output
Electromechanical dissociation		↓ maximal work capacity
Increased afterload		
Decrease in number and sensitivity of adrenergic receptors		

tree, thus producing the wide pulse pressure characteristic of arteriosclerosis. These changes explain the fact that normally systolic arterial pressure continues to increase gradually, with a sharper rise after age 60, whereas diastolic pressure levels off at that point and tends to decrease thereafter – a phenomenon that leads to predominance of isolated systolic hypertension in later years. Also the increased rigidity of the arterial wall may contribute to the diminished responsiveness of aortic and carotid baroreceptors.

Normative aging changes in heart function include a tendency to diminished myocardial contractility with prolonged duration of contraction, longer time to peak tension and longer relaxation time. As a result, the stroke volume and ejection fractions tend to diminish and, along with a decreased heart rate, contribute to diminished cardiac output even at rest. However, these changes are far more important in limiting maximal work capacity, because they impair the cardiovascular response to stimuli [3–5]. Also the decline in maximal work capacity is due partly to noncardiovascular factors, such as musculoskeletal limitations and diminished lung capacity. Nevertheless, a decreased ability to respond to inotropic stimuli reduces exercise tolerance and, in part, can be attributed to depletion of the catecholamine content of myocardial tissue with age, decreased concentration and sensitivity of adrenergic receptors and impaired calcium influx into myocytes [5–9], leading to a relative electromechanical dissociation i.e. mechanical refractoriness in the absence of electrical refractoriness. Table I summarizes the anatomic and hemodynamic alterations of the cardiovascular system with age [10].

Humoral alterations

Normally total body water decreases with aging so that, by age 75, it is 18% less than at age 30; this is accompanied by a 40% shrinkage of extracellular

fluid volume and 8% reduction of plasma volume [11]. Along with the diminished lean body mass and partial replacement of muscle tissue with fat, these changes are relevant to the altered volume of distribution of lipophilic *versus* hydrophilic drugs in older patients.

Certain vasoactive systems, such as the renin-angiotensin-aldosterone system and the sympathoadrenomedullary system also are altered with aging. Levels of plasma-renin activity, angiotensin II and aldosterone decrease rapidly during early childhood to reach the usual adult levels by adolescence. Thereafter they decline slowly, with renin decreasing more than aldosterone, and tend to respond sluggishly to the stimuli of salt deprivation, diuretic treatment or reduction of effective blood volume [12–14].

On the contrary, plasma norepinephrine levels increase with age, so that at 70 they are twice as high on average as at 20 – mean levels are 400 pg/ml *vs* 200 pg/ml at ages 70 *vs* 20, respectively [15–18]. However, they do not indicate an overactive sympathetic system, as might be inferred by the fact that they represent a spillover from sympathetic nerve endings; on the contrary, they reflect the diminished numbers and sensitivity of adrenergic receptors in various tissues [8, 9, 17, 18] and the reduced catecholamine clearance from the circulation.

Also the baroreflex function becomes sluggish with age, partly because of intrinsic alteration of the baroreceptors and partly because of loss of aortic-wall distensibility. Thus, both the bradycardia and peripheral vasodilation in response to increased central pressure and the tachycardia and vasoconstriction in response to hypotension are attenuated [13]. This may be further aggravated by accompanying sinus-node dysfunction and diminished cardiac and vascular adrenoceptor sensitivity to catecholamines.

This 'normal' degree of autonomic insufficiency, i.e. diminished responses of pressor hormones and baroreflexes, as well as the anatomic (arterial-wall rigidity) and humoral (relative hypovolemia) changes of normal aging, render the elderly particularly prone to orthostatic hypotension, even without the added insult of treatment with diuretics or a sympathoplegic agent.

Regional blood flows and vital organ functions

The 'normal' decreases of blood volume and cardiac output, and the tendency to increased vascular resistance diminish regional blood flows in most tissues.

Between ages 20 and 80, there is a 50% decline in renal blood flow – from an average of 600 ml/min to 300 ml/min, and in glomerular filtration rate from 120 to 65 ml/min [19]. In elderly normotensives, interstitial fibrosis and fibrotic changes in the glomeruli, as well as hyaline degeneration of arterioles lead to benign nephrosclerotic changes similar to those encountered in young hypertensives. By the eighth decade, the number of functioning nephrons decreases by 50% leading to thinning and atrophy of the renal cortex. Also there is some loss of concentrating and excretory tubular capac-

ity. The slight increase in normal levels of BUN and serum creatinine reflect a much greater decrease in creatinine clearance, because these parameters are also affected by a slower rate of metabolism. These considerations are particularly important as they influence the kinetics of drugs.

Autoregulation of regional blood flows is also affected by aging because the vital organs maintain their autoregulatory capacity within a narrower range of arterial blood pressure. Cerebral blood flow decreases slightly with age, from an average of 61 ml/100 g/min at age 20 to 58 ml/100 g/min at age 70. More importantly, if mean perfusion pressure falls below 70 mm Hg, there may be symptoms of hypoperfusion and brain hypoxia [20]. Likewise, brain tolerance to shifts of acid-base or electrolyte and metabolic balances, which is normally narrow, becomes even narrower with aging. As small changes in these factors may cause temporary but reversible derangement in the sensorium, it is important to avoid mistaking them for expressions of organic brain syndrome or irreversible senile dementia.

In conclusion, knowledge of normative aging is important in evaluating cardiovascular disease, and in the choice and monitoring of therapeutic interventions directed at elderly hypertensive patients.

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CHAPTER 16

Pathophysiology of hypertension in the elderly

R.I. OGILVIE

Introduction

Although systolic hypertension is the most common form of hypertension in the elderly, the underlying mechanisms often are similar to those found for diastolic hypertension in younger individuals, an interaction of heredity and personal environmental factors (Table I). It has been estimated that at least one-third of elderly patients with isolated systolic hypertension have a previous history of diastolic hypertension or combined systolic and diastolic hypertension. When diastolic hypertension is found in the elderly, calculated total peripheral resistance is increased as it is in the younger population. Why some individuals convert from diastolic hypertension to isolated systolic hypertension is unknown. However, patients with isolated systolic hypertension also have reduced calculated total peripheral resistance in spite of a normal diastolic pressure [1]. It has been suggested that arteriolar resistance is actually increased because the diastolic pressure should fall as systolic pressure rises [2, 3].

Systolic hypertension in younger individuals almost always is associated with an increased cardiac output. Hormonal excess with thyrotoxicosis or with pheochromocytoma must be considered. Coarctation of the aorta is a rare cause. Young patients with diabetes mellitus also may develop systolic hypertension presumably due to altered large-blood-vessel compliance.

Arterial mechanics

Pulse pressure, the difference between systolic and diastolic pressure, is increased by increased stiffness (reduced compliance) of the arterial vascular bed, increased stroke volume and by an increased ejection rate of the left ventricle. All three mechanisms may be operative in elderly patients with systolic hypertension. Increased stiffness of the aorta and other large arteries is the cardinal pathophysiological finding in elderly patients with systolic hypertension [2]. Frequently, this is caused by sclerosis associated with age

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Table I. Factors, conditions and mechanisms involved in the development and outcome of hypertension in the elderly

Factors	Conditions
Obesity	Genetic background
Physical inactivity	Insulin resistance
Excess sodium ingestion	Sodium sensitivity
Reduced calcium ingestion	Increased sympathetic activity
Smoking	Occult thyrotoxicosis
Excess alcohol ingestion	Diabetes mellitus
NSAID use	Atherosclerosis
	Renal artery stenosis
Mechanisms	**Outcome**
Increased peripheral resistance	Stroke
Reduced aortic compliance	Myocardial infarction
Increased stroke volume	Congestive failure
Increased ejection velocity	Arrhythmia
Altered endothelial function	Aortic aneurysm
Left ventricular hypertrophy	Renal failure
Antihypertensive drug effects	Death

but obviously it can be accelerated in patients with abnormal lipid profiles, atherosclerosis or diabetes mellitus. The reduced compliance of large arteries fails to buffer the pressure head developed by the heart ejecting the stroke volume with each heart beat, leading to an increased pulse pressure. The increased blood pressure contributes to large-artery rigidity by stretching the walls and altering the histologic organization. Aging and blood pressure elevation alter the collagen-to-elastin ratio by increasing collagen content. Any factor that increases cardiac output or stroke volume can aggravate this and further increase systolic pressure. Hormonal excess such as occult thyrotoxicosis is a rare cause but probably should be ruled out by appropriate tests of thyroid function. Since renal function is gradually reduced with age, dietary sodium excess may increase circulating volume and therefore cardiac output, again increasing systolic pressure. Elderly hypertensives commonly have low plasma-renin activity [1] and salt sensitivity with marked increases in blood pressure may be more common in the elderly perhaps because of the age-related reduction in renal function. Suboptimal intake of calcium and perhaps magnesium and potassium may be involved [4]. Older individuals have higher circulating concentrations of plasma norepinephrine and a greater increase in plasma norepinephrine with any activity even with the assumption of the upright position or performing the hand-grip exercise [5]. This can increase the velocity and frequency of cardiac ejection as well as directly reduce large-artery compliance, markedly increasing systolic pressure. A great deal of the variability in systolic pressure observed in the elderly is probably due to this alteration in catecholamine release. The elderly have a reduced beta-adrenoceptor responsiveness, which could augment al-

pha-adrenergic increases in vascular tone [6]. Surprisingly, a low sodium diet can correct this defect [7]. The baroreflex response is depressed in the elderly further reducing buffering capacity to changes in blood pressure.

Obese individuals can have increased circulating plasma volumes and cardiac output, larger changes in plasma norepinephrine with activity, left-ventricular hypertrophy, altered plasma-lipid profiles and/or diabetes mellitus with increased atherosclerotic changes, all of which can increase the velocity of systolic ejection, stroke volume, and reduce large-vessel compliance. Physical inactivity can increase systolic pressure by leading to obesity but also by increasing plasma catecholamines with mild physical activity because of an inadequate cardiac response. Insulin resistance is common in obese individuals as well as in those with hypertension [8]. This can be associated with augmented sympathetic activity and increased sodium retention. Physical exercise can increase insulin sensitivity and augment sodium excretion as well as reduce blood pressure. Smokers and imbibers of alcohol can have augmented plasma-catecholamine concentrations and responses as well as changes in renal function.

An increasingly common cause for an increase in systolic pressure in the elderly is the use of non-steroidal anti-inflammatory drugs (NSAIDS). The already reduced renal function of the older individual is further compromised by NSAID use causing sodium and water retention, increased circulating volume and stroke volume/cardiac output, producing a higher pulse pressure when large artery compliance is reduced.

Renovascular hypertension

Since a large proportion of the elderly have generalized atherosclerosis, renovascular hypertension secondary to renal artery stenosis is relatively common [9]. Individuals with intermittent claudication appear to have a high incidence of renal-artery stenosis [10]. Atherosclerotic disease may cause unilateral or bilateral, renal-artery narrowing or occlusion. Either systolic, diastolic, or combined systolic-and-diastolic hypertension can ensue. The hypertension can appear abruptly *de novo* or worsen gradually or abruptly. Unfortunately, there are no clinical or laboratory clues to identify which individuals with renal-artery stenosis will progress to complete occlusion.

There is increasing interest in the local control of vascular-wall tension via endothelium-mediated mechanisms [11]. Factors that modify the endothelium such as the presence of atherosclerotic plaques, and shear stress of blood-flow dynamics may have important consequences in the development and maintenance of hypertensive states in the elderly. Drug therapy that provides endothelial protection and improves vascular-tone control may be an important consideration in the future.

Drug effects on systolic pressure

We are acquiring more knowledge of the effect of antihypertensive drugs on systolic pressure [12–14]. Low-dose diuretics may modify sodium balance returning the circulating volumes to normal if it has been raised and modifying sympathetic responses to activity. Nitrates, calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors can increase large-vessel-wall compliance and pressure-buffering capacity, thus more effectively dissipating the energy created during stroke-volume ejection by the heart. Nitrates and ACE inhibitors also may reduce preload by increasing total vascular compliance and venous capacitance thus reducing venous return. The timing of pressure waves reflected centrally from the peripheral vessels following each heart beat may be altered by nitrate therapy. Beta blockers and some calcium antagonists may reduce the velocity of systolic ejection by their negative inotropic effect. However, beta blockers without intrinsic sympathomimetic activity (ISA) may reduce large-vessel compliance and reduce the heart rate considerably, leading to a larger stroke volume being ejected into a stiff conduit. As a result, systolic pressure can be increased rather than reduced. Beta blockers with ISA may increase large-vessel compliance and maintain resting heart rates, thus improving systolic pressure. Hydralazine and other direct-acting arteriolar vasodilators such as minoxidil can increase the velocity of systolic ejection by reducing downstream arteriolar resistance and increasing sympathetic activity *via* the baroreflex response. Consequently, systolic pressure is often increased during their use. In addition, salt-and-water retention often follows with increased circulating volume aggravating the situation.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is a prevalent finding in the elderly and systolic hypertension is a commonly associated finding. Both conditions independently predict an adverse outcome [15–18]. There is a direct relationship between pulse-wave velocity and left-ventricular mass but it is not clear as yet whether one precedes the other. Clearly, an increased left-ventricular afterload can promote LVH. However, an early finding of LVH is increased systolic function with augmented velocity of systolic ejection. As a consequence, LVH may aggravate systolic hypertension [19]. The adverse consequences of LVH on cardiovascular morbidity and mortality are becoming increasingly evident. Impaired coronary reserve with a higher incidence of angina, myocardial infarction, arrhythmia and sudden death are end points that should be avoided. Impaired left-ventricular diastolic function, early as well as late in the development of LVH, can severely limit exercise tolerance. Impaired left-ventricular systolic function with congestive heart failure is all too often the ultimate outcome of LVH.

There are no clinical trials to demonstrate that reversal of LVH alters outcome in terms of cardiovascular morbidity or mortality in any age group. However, we have increasing knowledge about the effects of various drug groups on reversing LVH [20]. As outlined in a recent meta-analysis of 109 treatment studies [21], monotherapy with ACE inhibitors, calcium antagonists, beta blockers, methyldopa, alpha blockers or diuretics (thiazide, chlorthalidone, indapamide) can reduce echocardiographically calculated LV mass. ACE inhibitors have the most pronounced effect on LV mass and LV wall thickness. Beta blockers or calcium antagonists decrease LV mass and wall thickness slightly less than ACE inhibitors. The effect of diuretics on calculated LV mass is considered to be due primarily to a reduction in LV internal diameter because LV-wall thickness was little altered. It is uncertain if drug therapy of hypertension in the elderly should be selected based on a drug's capacity to reverse LVH. Recent major trials of hypertension treatment in the elderly [22–24] have shown considerable benefit treatment with low-dose thiazide-diuretic therapy in reducing cardiovascular end-points. As pointed out before, diuretics have little or no effect on LV-wall thickness. In one major trial, beta blockers failed to prevent stroke or coronary end points. Additional trials are required to determine whether drug groups, such as the calcium antagonists or ACE inhibitors, have similar or augmented benefits when compared to low-dose diuretic therapy. Since calcium antagonists and ACE inhibitors may improve large-vessel-wall compliance and reverse LVH, there is a theoretical basis to initiate such trials in comparison with low-dose diuretic therapy or combination therapy.

Conclusion

The pathophysiological mechanisms underlying hypertension in the elderly are characterized by factors and conditions that alter large-vessel-wall compliance, circulating volume and left-ventricular function (Table I). General health measures and non-pharmacological treatment approaches are excellent preventive as well as treatment modalities. Increased knowledge of the effects of drugs on these mechanisms, combined with trial evidence of efficacy without adverse effects, should have a major impact on the health of this increasingly large sector of the population.

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CHAPTER 17

Treatment of hypertension in the elderly

RAY W. GIFFORD, JR. and RAYMOND A. BORAZANIAN

By virtue of sheer numbers, hypertension in the elderly is a major public health problem: prevalence of hypertension is high in this age group, and the elderly segment of the American population is growing rapidly. The confirmed benefit of treatment of hypertension in the elderly, both isolated systolic and diastolic, makes it even more important now than ever to identify and treat such patients.

Definitions and prevalence

Hypertension in the elderly can be divided into diastolic ($\geq$ 90 mm Hg) and isolated systolic ($\geq$ 160 mmHg systolic; $<$ 90 mm Hg diastolic). Diastolic hypertension form peaks during the sixth decade, while the prevalence of isolated systolic hypertension increases with age [1]. Different cutoff criteria have been used in different surveys: data from the National Health and Nutritional Examination Survey (NHANES II) indicate that 64% of elderly people (age 65–74 years) have systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg or are taking antihypertensive medication [2]. In the Framingham cohort, about 40% of men and 50% of women age 65 or older have blood pressure $>$ 160 mm Hg systolic and/or $>$ 95 mm Hg diastolic or are taking antihypertensive medication; more than one-half of these elderly hypertensives have isolated systolic hypertension (defined as systolic blood pressure $\geq$ 160 mm Hg with diastolic pressure $\leq$ 95 mm Hg), less than one-third have combined systolic and diastolic hypertension, and the remainder have diastolic hypertension [2]. Among subjects age 60–69 who were screened for the Hypertension Detection and Follow-up Program (HDFP), 50.8% had systolic blood pressure $\geq$ 140 mm Hg, 19.9% had systolic blood pressure $\geq$ 160 mm Hg, 27.3% had diastolic blood pressure $\geq$ 90 mm Hg, and 14.8% were taking antihypertensive medications and had diastolic blood pressure $<$ 90 mm Hg [3].

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Risks associated with high blood pressure in the elderly

Diastolic elevation of blood pressure represents essential or primary hypertension in the majority of cases, just as it does in younger persons; only a few of these have secondary hypertension, usually atherosclerotic renovascular disease. Diastolic hypertension proportionally increases the relative risk of cardiovascular morbidity in older men, however, this trend is blunted in older women [1]. Systolic hypertension, reflecting loss of elasticity of the aorta and its large branches [4], may be even more important than diastolic hypertension as a prognostic index for cardiovascular disease [1, 5, 6].

Across all age groups, compared to normotensives, people with hypertension >160/95 have two to three times greater risk for cardiovascular events and deaths due to cardiovascular disease. At any blood pressure level, the risk is two to three times higher in older persons than in younger ones, and nearly always higher in men than in women [1].

Benefits of treatment

Diastolic hypertension

Four well-controlled trials have shown that treatment reduces morbidity and mortality for elderly patients (≥ 60 years of age) who have diastolic hypertension.

In the HDFP, patients 60–69 years of age with diastolic blood pressures of 90 mm Hg or more experienced a 16.4% reduction in five-year mortality when the stepped care (SC) group was compared to the referred care (RC) group [7]. The incidence of strokes was reduced 45.5% in this age group [8, 9].

In the Australian Trial, after five years of treatment, the 293 patients 60–69 years of age at entry with diastolic blood pressures of 95–109 mm Hg who received active treatment had a 39% lower incidence of trial end points (death or a specified cardiovascular event) than the 289 patients of the same age who received placebo ($p < 0.025$) [10].

The European Working Party on High Blood Pressure in the Elderly (EWPHE) trial showed a 38% reduction in cardiovascular mortality in the actively treated group compared to a placebo control group ($p = 0.023$); deaths from myocardial infarction were reduced by 60% ($p = 0.043$). These patients were all over 60 years of age when the trial was started and the average age was 72 years [11, 12]. The investigators calculated that treating 1000 hypertensive patients over 60 years of age for one year would prevent 11 fatal cardiac events, six fatal and 11 non-fatal strokes, and eight cases of severe congestive heart failure [13].

In the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension), 1627 patients aged 74–84 years with diastolic hypertension were as-

signed randomly to placebo or active treatment with either a diuretic or one of three beta blockers, and were followed for a mean of 25 months. Compared with placebo, active treatment significantly reduced the number of primary endpoints by 38% ($p = 0.0031$) and stroke morbidity and mortality by 45% ($p = 0.0081$). Total mortality was reduced by 43% ($p = 0.0079$). This study showed that the benefits of treatment were discernible up to age 84 years, and that treating 14 elderly patients for five years could be expected to prevent one stroke and one death [14].

Systolic hypertension

The Systolic Hypertension in the Elderly Program (SHEP) was a double-blind, placebo-controlled trial involving 4736 participants aged 60 years or older with systolic blood pressure ≥ 160 mm Hg and diastolic blood pressure < 90 mm Hg, who were randomly assigned to placebo or low-dose chlorthalidone treatment. Atenolol was added to the chlorthalidone if a goal systolic blood pressure of < 160 mm Hg and a reduction of at least 20 mm Hg was not achieved. The average follow-up period was 4.5 years. The five-year incidence of total stroke was reduced by 36% and the incidence of fatal and nonfatal coronary events was reduced by 27% in the treated group. This was the first study to demonstrate the benefit of treating isolated systolic hypertension [15].

The Medical Research Council recently published the results of a study in which 4396 patients aged 65–74 with systolic pressures of 160–209 and diastolic pressures < 115 mm Hg were randomized to receive either atenolol 50 mg daily, hydrochlorothiazide 25 mg or 50 mg plus amiloride 2.5 mg or 5 mg daily, or placebo in a single-blind fashion. The mean blood pressure at randomization was 183/91 in men and 186/90 in women. After a mean follow-up period of 5.8 years, the diuretic group had a 31% lower incidence of strokes ($p = 0.04$), a 44% lower incidence of coronary events ($p = 0.0005$), and a 35% lower incidence of all cardiovascular events ($p = 0.0005$) compared to the placebo group. The beta-blocker group experienced no significant reductions in these end points. However, overall there was no significant difference in mortality between the treated and placebo groups, with an apparent excess of cancer deaths among men in the atenolol group [16].

Beard *et al.* [17] have reviewed the major trials of treating hypertension in the elderly (Tables I and II).

The J-curve

Concern has been raised that lowering diastolic blood pressure below 85 mm Hg may increase the risk of mortality, a phenomenon called the 'J-curve' [18]. A putative explanation for this is that oxygen consumption of

Table I. Entry criteria, blood pressure at entry, goal pressure, and achieved pressures (mm Hg) in seven trials of treating hypertension in the elderly

	HDFP [9] (pts 60–69 at baseline)	Australian [10] (pts 60–69 at baseline)	EWPHE [11, 12]	Coope and Warrender [21]	SHEP [15]	STOP-hypertension [14]	MRC [16]
No. of patients	2376	582	840	884	4736	1627	4396
Age range (years)	60–69	60–69	60–97	60–79	60–	70–84	65–74
Blood pressure entry criteria							
Systolic		<200	160–239	170–280	160–219	180–230 or <180	160–209
Diastolic	≥90	95–109	90–119	105–120	<90	90–120 or 105–120	<115
Mean blood pressure at entry	170/101	165/101	182/101	197/99	170/77	195/102	185/91
Blood pressure goal:							
Systolic				<170	<160/ and >10 ↓	<160	≤160 or ≤150*
Diastolic	≤90/ and >20 ↓	<90, then <80	<90	<105		<95	
Treatment:							
Initial	Chlorthalidone	Chlorothiazide	HCTZ + triamterene	Atenolol	Chlorthalidone	(1) HCTZ + amiloride (2) Or atenolol or metoprolol or pindolol	(1) HCTZ + amiloride (2) Or atenolol
Add on	Reserpine or methyldopa Hydralazine Guanethidine	Various	Methyldopa	Bendrofluazide Methyldopa	Atenolol	(1) Atenolol or metoprolol or pindolol (2) HCTZ + amiloride	(1) Atenolol (2) Or HCTZ
Blood pressure obtained:							
Treatment group	/81	143/87	149/85	162/77	143/68	167/87	152/79
Placebo group	/86**	155/94	172/94	180/88***	155/72	186/96	167/85

* If systolic blood pressure was <180 mm Hg the goal was ≤150 mm Hg; if the systolic blood pressure was ≥180 mm Hg the goal was ≤160 mm Hg.

** This trial compared a stepped care regimen to referred care at usual sources in the community.

*** This was an open-label trial that compared a treated group to an untreated group of controls.

Adapted from Beard [17], with permission of the author and the publisher. HDFP data from Borhani [9].

Table II. Percentage change in event rates in seven trials

	HDFP [9]	Australian [10]	EWPHE [11, 12]	Coope and Warrender [21]	SHEP [15]	STOP-hypertension [14]	MRC [16]
Non-fatal events							
Stroke	−41	−36	−35	−27	−37*	−38*	−30
Myocardial infarction	−37	+20	NR	+10	−33*	−16	NR
All cardiac	NR	−8	−9	−26	−40*	NR	−13
All cardiovascular	NR	−17	−36*	−26	−36*	NR	−25*
Fatal events							
Stroke	−48	0	−32	−70*	−29*	−73*	−12
Cardiac	−22	−75**	−38*	0	−20**	−25**	−22**
All cardiovascular	−22	−62	−27	−22	−20	NR	−9
All non-cardiovascular	NR	+19	+21	NR	+5	NR	+5
Total deaths	−16	−26	−9	−3	−13	−43*	−3
All events							
Stroke	−45*	−33	−36*	−42*	−36*	−47*	−25*
Cardiac	−14*	−18	−20	−15	−27*	−13***	−19**
All cardiovascular	NR	−26	−34*	−23*	−32*	−40*	−17*

* $p < 0.05$.

** Ischemic heart disease.

*** Myocardial infarction.

Adapted from Beard [17], with permission of the author and the publisher.

the myocardium is more dependent on systolic pressure than on diastolic, whereas coronary flow is dependent on diastolic blood pressure. A disparity, therefore, between oxygen demand and supply might occur if the diastolic pressure is lowered excessively without lowering the systolic pressure, especially in people with overt or subtle ischemic heart disease.

An observation study of people over the age of 84 in Finland found J-curve relationships between both systolic and diastolic blood pressure and mortality [19]. In an analysis of the EWPHE trial, treated and placebo groups were divided into tertiles of systolic and diastolic blood pressure. Total mortality in the placebo group rose with increasing systolic pressure whereas it had a U-shaped relation with diastolic pressure. In the group given active treatment, total mortality showed a U-shaped relation with systolic pressure and an inverse relation with diastolic pressure. In both groups cardiovascular and non-cardiovascular mortality followed the same trends as total mortality. However, the patients who had the lowest systolic and diastolic blood pressures also had the most pronounced decreases in body weight and hemoglobin concentration, suggesting that they were ill; the investigators suggested that the increased mortality was not explained by a drug-induced, exaggerated reduction in blood pressure [20].

In an unblinded trial reported by Coope and Warrender, 884 patients aged 60–79 years used atenolol and/or bendrofluazide as active treatment and were followed for a mean of 4.4 years. Fatal strokes were reduced by 70% ($p < 0.025$) and all strokes were reduced by 42% ($p < 0.03$) in treated patients compared to untreated controls [21]. However, in this study, the incidence of myocardial infarction and total mortality was unaffected by treatment. There were J-curve relationships between diastolic blood pressure and myocardial infarctions and all deaths, both in the treated and in the control group. The authors concluded that it was unlikely that antihypertensive treatment caused this phenomenon [22].

No J-curve relationship has been reported in the SHEP trial, even though the average blood pressure on treatment at five years was 143/68 mm Hg [15].

The J-curve has been a retrospective observation in non-randomized clinical trials or randomized trials that were not designed to test this hypothesis. A prospective, controlled, randomized trial is needed to settle this issue.

Adverse drug reactions

It is a popular notion that elderly patients do not tolerate antihypertensive drugs well. Indeed, in a series of 315 consecutive elderly patients (mean age 76.6 years) admitted to an acute care hospital, Col and colleagues reported that 89 (28.2%) of the admissions were drug-related, 36 (11.4%) due to noncompliance, and 53 (16.8%) due to adverse drug reactions [23]. However, a different picture emerges from the data from the large clinical trials.

Table III. Adverse drug reactions according to age in the Hypertension Detection and Follow-up Program (HDFP) [24]

Age group (years, at baseline)	5-year incidence of adverse drug reactions (%)
30–39	34.1
40–49	36.8
50–59	38.0
60–69	29.8

In the HDFP, the five-year incidence of adverse drug reactions, severe enough to require some alteration in drug or dosage, was lowest in the 60–69-year-old group, the oldest group at the time of entry (Table III) [24]. Elderly patients also tolerated antihypertensive drugs well in the Australian [10] and EWPHE (13) trials.

A recent Veterans Administration trial compared the effects of hydrochlorothiazide in a low dose (25 mg daily or twice daily) with a higher dose (50 mg daily or twice daily) in 690 men older than age 60 with diastolic blood pressure 90–114 mm Hg and systolic blood pressure < 240 mm Hg. After 10 weeks of treatment, 50.4% of those assigned to the low dose and 58.5% of those assigned to receive the higher dose had achieved a goal diastolic blood pressure of < 90 mm Hg and at least 5 mm Hg below baseline DBP, with SBP < 160 mm Hg. The blood pressure declined by an average of 18.3/9.5 mm Hg with the low dose and 20.4/9.6 mm Hg with the higher dose. The difference in pressure response was not significant. Although the lower dose was associated with fewer biochemical changes, no differences were observed in subjective side effects between the two groups. Nonresponders were assigned randomly to receive hydralazine, methyldopa, metoprolol or reserpine in addition to the hydrochlorothiazide, in a double-blind fashion. Overall, there were no significant efficacy differences among the step-2 regimens. Patients receiving methyldopa experienced significant increases from baseline in postural dizziness, fatigue or tiredness, sexual dysfunction, dryness of the mouth and drug intolerance. The overall incidence of adverse effects was significantly greater with methyldopa and hydralazine than with reserpine or metoprolol [25].

These same patients underwent behavioral assessment at baseline, at the end of titration, and at the end of six months of maintenance therapy; a separate group of placebo-treated patients also received the same tests. In these studies neither blood-pressure reduction *per se* nor the use of any of the medication regimens produced substantive adverse cognitive or behavioral consequences [26].

In a short-term study of 242 women 65 years of age and older with diastolic blood pressure 95–114 mm Hg at entry, diltiazem lowered systolic and diastolic blood pressure slightly more than atenolol or enalapril did. After 16 weeks of therapy, patients on atenolol tended to have somewhat worse scores

on quality-of-life assessments than those receiving the other drugs, but none of the differences was significant [27].

In the Systolic Hypertension in the Elderly (SHEP) feasibility trial, in patients over the age of 60 with isolated systolic hypertension, the 443 patients who received chlorthalidone, and the 108 patients, who received placebo, underwent a battery of behavioral assessments at baseline and one year. The investigators concluded that active treatment did not have any significant impact on cognitive function or level of depression compared to placebo [28]. Similarly, a VA trial observed no deterioration in cognitive behavioral function in 51 elderly hypertensive men with isolated systolic hypertension, who were treated for 24 weeks with hydrochlorothiazide [29].

Metabolic side effects

Diuretics do all the wrong things to patients' laboratory values: they raise total cholesterol, LDL cholesterol, triglycerides, serum uric acid, and fasting blood glucose, and they lower serum potassium and magnesium. These changes tend to be dose-related, and abnormal values for cholesterol and glucose tend to regress to the mean over time [30]. Beta blockers also increase fasting blood glucose, and the agents without intrinsic sympathomimetic activity decrease serum HDL and raise triglyceride levels. Proponents of the newer classes of agents infer that diuretics and beta blockers are dangerous and should be avoided. Nevertheless, diuretics and beta blockers are the only classes of antihypertensive agents that, in controlled clinical trials, have been proved to prevent strokes and coronary events and prolong life. It is interesting to speculate that calcium blockers and ACE inhibitors may be even more effective because they do not cause metabolic side effects. However, until controlled clinical trials are carried out to test this hypothesis, we will never know.

Adherence to therapy

In the Hypertension Detection and Follow-up Program, at the end of five years, the cohort that was 60–69 years old at baseline had an average diastolic pressure of 81 mm Hg, 80% of them were on treatment, and 75% had achieved goal diastolic blood pressure. This was as good as or better than the record achieved by younger patients (Table IV) [7].

Recommendations for treatment

The objective of therapy is to reduce the risk associated with hypertension. In treating diastolic hypertension, the goal should be to reduce the diastolic

Table IV. Adherence according to age in the Hypertension Detection and Follow-up Program (HDFP) [7]

Evidence of adherence (5 years)	Age groups (years at baseline)		
	30–49	50–59	60–69
On treatment (%)	75	80	80
At goal blood pressure (%)	59	67	75
Average diastolic blood pressure (mm Hg)	86	84	81

pressure to below 90 mm Hg [31] and preferably 85 mm Hg. In treating isolated systolic hypertension, the goal of therapy should be to reduce the systolic pressure to less than 160 mm Hg and by at least 20 mm Hg [15]. Both nonpharmacologic and pharmacologic measures are employed.

If the patient is obese, weight reduction alone may reduce blood pressure. However, we must exercise caution in prescribing a calorie-restricted diet in the elderly, because many older patients subsist on marginal diets. If a reducing diet is attempted, proper counseling is needed to assure nutritional adequacy.

Ethanol intake should be limited to no more than 1 oz/day – the amount contained in 2 oz whisky, 8 oz wine, or 24 oz beer.

Cigarette smoking should be forbidden, because it is an independent risk factor for coronary artery disease and stroke, and it causes cancer and pulmonary disease.

Reducing sodium intake to 70–100 m Eq/day (1.5–2.5 g sodium or 4–6 g salt) will reduce blood pressure in some patients, but there is no way prospectively to identify those patients who will benefit. In any event, a moderate restriction of sodium produces no adverse effects. Since most dietary sodium comes from prepared foods, merely refraining from adding salt at the table is not enough to control hypertension. Nutritional counseling is needed to help the patient identify sources of sodium and understand sodium labeling of processed foods to reduce sodium intake and to maintain adequate overall nutrition.

If a trial of nonpharmacologic therapy proves unsuccessful, the clinician should proceed cautiously with pharmacologic therapy, bearing the following in mind:

Older patients are susceptible particularly to orthostatic hypotension. Therefore, blood pressure readings should be taken in the standing and seated positions at every visit. If there is a large orthostatic drop, the standing blood pressure should be used to guide dosing.

Older patients often are sensitive to antihypertensive drugs because they tend to have impaired baroreceptor reflexes, low plasma volume, and low cardiac outputs. Drug metabolism may also be impaired. Consequently, treatment should be started with one-half the usual adult dose and increases in dosage are made at intervals of no less than three weeks.

Table V. Diuretics in geriatric hypertension – clinical trials in patients older than 60 years

Trial	No. pts on active Rx	Duration	Diuretic dose (mg/day)*
Australian [10]	293	4.06 yrs	CTZ 500–1000
EWPHE [11, 12]	416	4.6 yrs	HCTZ 25–50 TRIAM 50–100
SHEP feasibility [28]	443	1 yr	CHLOR 25–50
SHEP [15]	2365	4.5 yrs	CHLOR 12.5–25
HDFP [7, 8, 9]	1204	6.0 yrs	CHLOR 25–100
VA [25]	644	6 mo	HCTZ 25–100
MRC [16]	1081	3.6 yrs	HCTZ 25–50, AMILOR 2.5–5
Total	6446		

* CTZ = chlorothiazide; HCTZ = hydrochlorothiazide; CHLOR = chlorthalidone; TRIAM = triamterene; AMLIOR = amiloride.

Frequently older patients take a variety of medications for conditions other than hypertension, thereby increasing the risk of drug interaction.

Because older patients may absorb some drugs more slowly than younger patients, ultimately they may require larger doses.

Older patients are more likely than younger to have multiple illnesses other than hypertension, such as diabetes mellitus, chronic obstructive pulmonary disease, heart block, sick sinus syndrome, gout, peripheral occlusive arterial disease, and asthma, which might have an influence on drug selection.

The possibility of pseudohypertension exists, particularly if the patient develops symptoms of hypotension while systolic blood pressure remains high. A helpful clue in this situation is the presence of Osler's sign.

The drug of choice for most elderly patients is a thiazide-type diuretic, simply because all the clinical trials used diuretic-based stepped care (Table V). The initial dose should be 12.5 mg of hydrochlorothiazide, chlorthalidone, or its equivalent in other diuretics, and the dose can be increased to 25 mg in about four weeks, if the desired blood pressure response is not achieved. If necessary, additional agents, including methyldopa, clonidine, calcium antagonists, or angiotensin-converting enzyme inhibitors can be added to control the hypertension.

Bühler and colleagues have advocated basing treatment choices on plasma-renin levels: patients with low levels (most elderly patients) would receive calcium antagonists or diuretics, while patients with high levels would receive angiotensin-converting enzyme inhibitors or beta blockers [32]. The Trial of Antihypertensive Interventions and Management (TAIM) bolsters this view by demonstrating that patients with high renin values had a greater reduction in diastolic blood pressure in response to atenolol than did patients with low values, while patients with low values had a better response to chlorthalidone than patients with high values did. Placebo-treated high-renin patients, who

followed a weight loss diet or a low sodium/high potassium diet had a greater decrease in diastolic blood pressure than low-renin patients did [33].

These studies support our clinical observations that elderly hypertensive patients respond better to diuretics or calcium antagonists than they do to beta blockers or angiotensin-converting-enzyme inhibitors. However, many elderly patients do respond well to the latter agents, which have proved safe and effective in treating hypertension in short-term clinical trials.

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PART SEVEN

Acute renal failure

CHAPTER 18

Risk factors for acute renal failure in the elderly

C. KJELLSTRAND

Causes of acute renal failure

The most common cause of acute renal failure is acute tubular necrosis but the events that precede this catastrophe have changed considerably over the last 40 years. In the 1950s and the 1960s most severe acute renal failure that required dialysis developed after trauma and surgery; now most such cases are secondary to iatrogenic toxins. Table I shows the causes of acute renal failure in 139 patients seen at Hennepin County Medical Center in Minneapolis and University Hospital in Edmonton, Alberta. In most of these episodes, renal failure was secondary to administered drugs, commonly antibiotics, followed by ACE inhibitors (Table II).

The degree of renal damage ranges from a slight increase in serum creatinine to full-blown acute renal failure requiring dialysis. There seems to be little difference in survival of young or old patient after such dialysis perhaps because in the elderly, acute renal failure develops after smaller insults. However, any increase in the serum creatinine level produces a direct increase in the death rate of hospitalized patients (Fig. 1). The direct relationship between mortality and rise in creatinineis is evident.

The renal insult has to be repetitive

A single renal insult rarely results in acute renal failure; in almost all instances, the kidney has sustained multiple insults. In 1978, Schwartz found that the incidence of acute renal failure after X-ray contrast injection correlated directly with the number of risk factors in the patients. While four patients without risk factors had only one episode of acute renal failure, six patients with four risk factors had four episodes [1]. Rasmussen *et al.* [2] reported similar findings and our studies of patients with acute renal failure show that virtually all had multiple drug insults or dehydration. Nowadays, acute renal failure is most often acute tubular necrosis and usually follows repetitive iatrogenic renal trauma. Figure 2 shows a patient who was dehy-

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Table I. Etiology of acute renal failure in 139 patients

Drug toxicity	44
Dehydration	31
Cardiac	15
Infection	13
Surgery	12
Immunological	3
Other	21

Table II. Drugs that were the primary cause of acute renal failure in 44 patients and contributed to such failure in 22 other cases

Drug	Primary cause	Contributory	Sum
Antibiotics	26	6	32
ACE-inhibitors	8	3	11
Diuretics	2	7	9
NSAIDs	5	1	6
Contrast	3	3	6
Other		2	2

drated by almost 10% of total body weight or almost one-half of his extracellular fluid volume, and then was assaulted repeatedly by intravascular and oral nephrotoxic contrast media.

In an experimental model of acute renal failure in rats, Zager showed the same results [3]: Clamping of rat's aorta for a short time produces a 25% decrease in glomerular filtration rate (GFR). If the rats are treated beforehand for 2 days with gentamicin, GFR falls 50% and if the rats are treated for 8 days, the GFR will fall 90%, showing the combined ill effects of ischemia and a renal toxin.

Is acute renal failure more common in the elderly?

In one study of 437 patients with acute renal failure, Pascual *et al.* found that 35% were over age 70, while during the period of the study, only 10% of patients admitted to that hospital were over 70 years [4]. Thus, among the older patients, acute renal failure was three times more common: one-half of the patients over 70 years of age had prerenal failure compared to only 32% younger patients. On the contrary, Schwartz did not find that age was an important risk factor for acute renal failure after contrast media [1]. In our own consultation study, we found that the patients, who had acute renal failure secondary to dehydration, were the oldest, 62 years of age versus 61 years in those who had drug intoxication. Those with other causes of acute renal failure were the youngest, the average age being 58. The

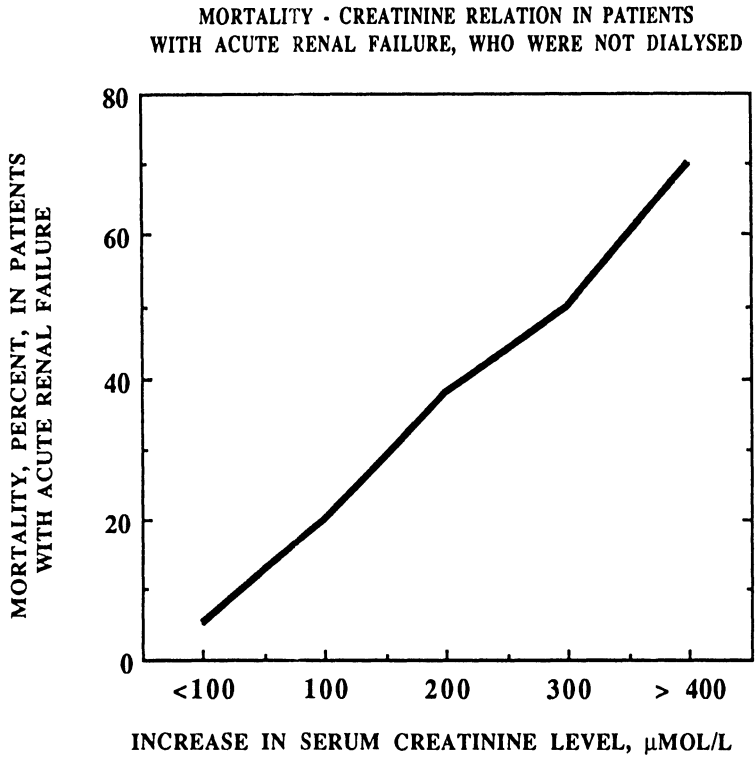

Fig. 1. The correlation between mortality and the increase in serum creatinine in hospitalized patients. If the increase in serum creatinine is < 100 μmol/l the mortality rate of acute renal failure patients is only 5%. It rises to 70% if the increase in creatinine exceeds 400 μmol/l.

patients in all these groups were older than others for whom renal consultation was sought, the latter being 42 years old ($p = 0.003$). Our consultation study also found more underlying chronic renal failure in those over 65 years of age; in these patients the incidence of chronic underlying renal failure was 22% compared to 10% in those younger than 65 years ($p = 0.07$). When dividing the patients into iatrogenic-induced renal failure versus other causes, those who had iatrogenic disease were older, 62 years versus 50 years in the US study [5], and 60 years versus 48 years in the Canadian study. In the European Infection Prevention Study of cancer patients, age and previous creatinine elevation also were the best predictors of renal toxicity following aminoglycosides [6]. Many studies have shown that diabetes mellitus is a major risk factor for contrast-induced acute renal failure [7].

It is clear that risk factors for acute renal failure are old age, dehydration, and repeated insults; underlying chronic renal failure and diabetes mellitus enhance this risk. Other risk factors of varying degrees of importance are: dosage of drug; liver failure; vascular disease; hypoalbuminemia; proteinuria and hypertension.

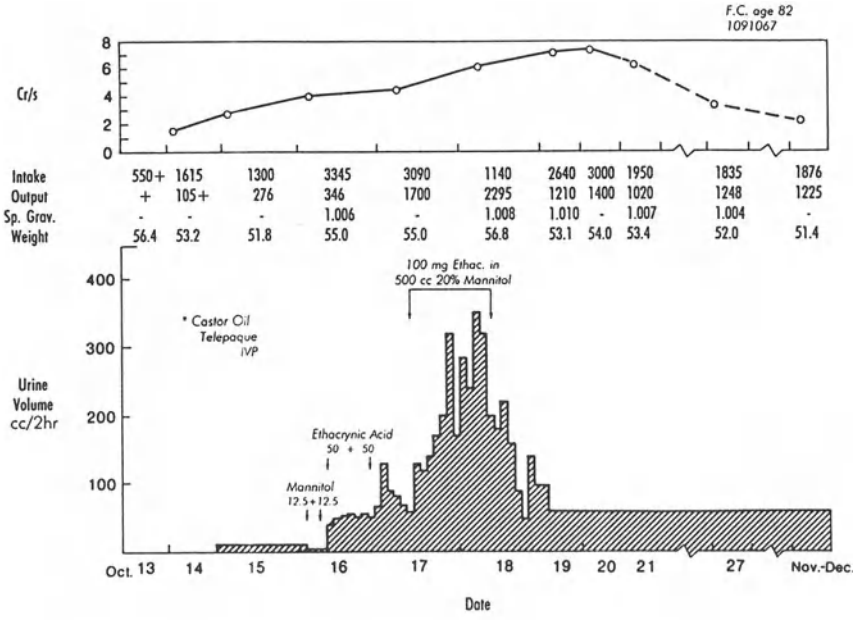

Fig. 2. An 82-year-old man was admitted with abdominal pain. He was denied oral fluid and was purged three times over a 48-hr period for X-ray studies. During this time he lost 5 kg, 10% of the total body weight, or almost one-half of his extracellular volume. Then the administration of both Telepaque and IV X-ray contrast precipitated serious acute renal failure and his creatinine rose to 8 mg/dl. This fate threatens many elderly patients who admitted are acute-care hospital under time constraints such as DRG.

Special causes of acute renal failure

An analysis of the causes of acute renal failure in 80 patients seen in consultation at the University of Alberta Hospital showed patients over 60 years of age have more underlying heart disease and surgery as the cause of their acute renal failure while in the younger patients, crush and trauma were more often the contributing factors. We also sought to determine whether older patients were particularly susceptible to any specific nephrotoxic therapeutic agent. Drugs that are involved both in primary and secondary renal insult are described in Table III. It is obvious that the major difference in drug susceptibility between the old and the young patients is nephrotoxicity from ACE inhibitors. We have reviewed 12 such patients from the US renal consult study [5] and from a similar ongoing Canadian study (M. Boiskin *et al.*, submitted for publication). Of these 12 who had severe renal failure after ACE inhibition, all but one were older than 65; the mean age was 76 ± 7 years. Seven had underlying chronic renal failure, 10 chronic heart disease, 7 hypertension, 4 were dehydrated, 2 had diabetes mellitus, none

Table III. Drugs that caused or contributed to acute renal failure in 80 patients seen in consultation. ACE-inhibitors are significantly more common in the elderly ($p = 0.03$)

Drugs	Age <60 years	>60 years	Totals
Antibiotics	15	10	25
ACE-inhibitors	0	5	5
NSAIDs	3	0	3
Others	6	6	12
Sum	24	21	45

had polycystic kidney disease and only 1 had renal-artery stenosis. Of these 12 cases, 5 sustained irreversible kidney damage and their creatinine level remained elevated (> 30 μmol) after withdrawal of the offending ACE inhibitor.

Iatrogenic renal damage seems to be particularly common in elderly patients with acute renal failure. Figure 3 includes all patients seen in the Canadian study and those who had an iatrogenic cause of their renal failure. Figure 4 shows a regression analysis of the percentage of patients who had

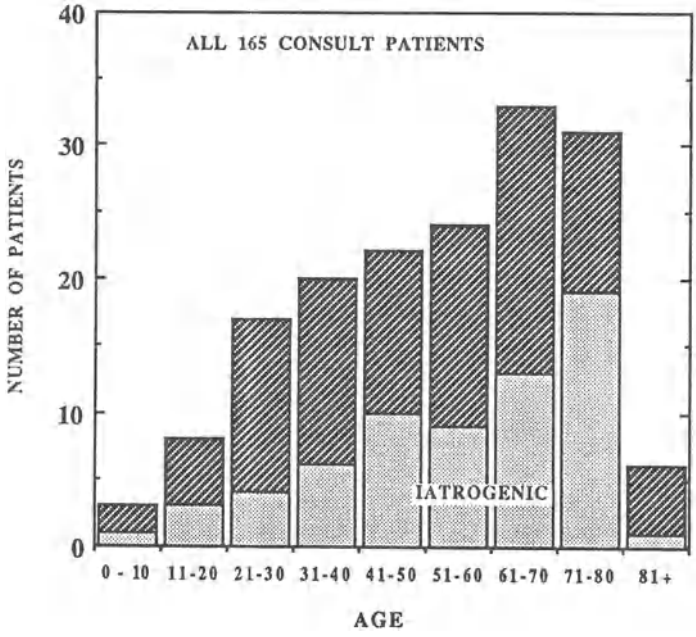

Fig. 3. The age distribution of all 165 new consults seen in 1991 at the University of Alberta and those in whom an iatrogenic drug caused renal failure. Both the incidence of renal failure and the fraction in whom failure is due to an iatrogenic cause increases with age.

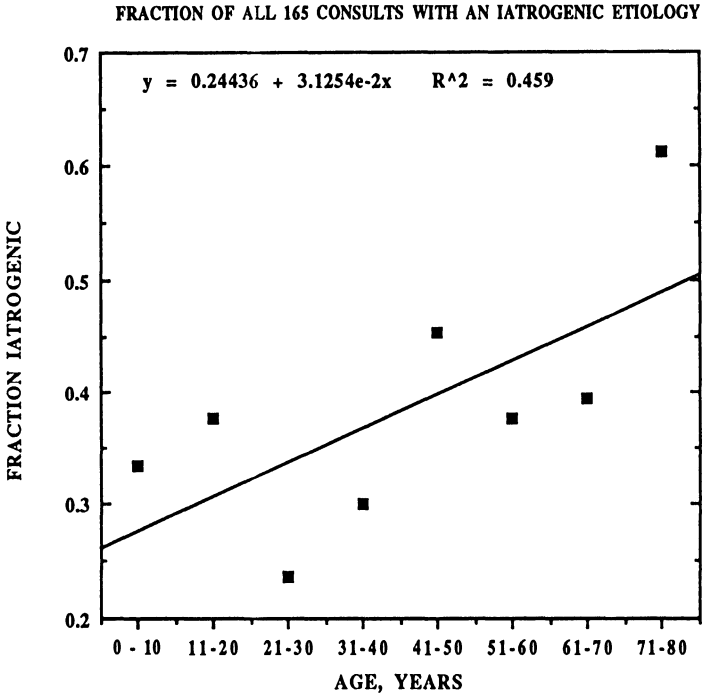

Fig. 4. Linear regression analysis of iatrogenic renal failure and age shows a good correlation ($R = 0.7$, $p = 0.065$).

iatrogenic renal failure versus age. It is clear that physicians and hospitals are very important risk factors for disease in the old.

Why are old patients so susceptible?

Concerning special risk factors (Table IV), there are two principal reasons for the special susceptibility of older patients to acute renal failure. The first is physiologic. Older patients develop acute renal failure easily because they have a decreased sensation of thirst, and a decreased total body water [8, 9]; therefore, when ill, they dehydrate faster and rehydrate more slowly. Finally, as the kidney ages it atrophies, an event that leads to disturbed water preservation. Between the ages of 30 and 90 years, the weight and volume of the kidney decreases by 30%, and the number of glomeruli decrease by 50%, while in the glomeruli, mesangial expansion takes place at the expense of capillary volume. In individual glomeruli, mesangial volume will increase 50% with a corresponding decrease in capillary surface. Both the volume and the length of tubules decrease, there is hyalinosis and stiffness in the blood vessels and the glomerular filtration rate will decrease 1 ml/min/year after age 40 [10].

Table IV. Special risks in the old. Special risks for acute renal failure include

I. Dehydration	
(i)	Decreased total body water
(ii)	Decreased thirst
(iii)	Frequent use of diuretics for hypertension, chronic heart failure, and chronic renal failure
II. Pharmacological	
(i)	Poor knowledge of pharmacology
(ii)	Increased susceptibility
(iii)	Presence of multiple risk factors, non-steroidals, diuretics, diabetes, chronic renal failure, dehydration

Secondly, with aging, a whole series of factors leads to decreased metabolism of many drugs. Decreased hepatic metabolism and decreased hepatic blood flow decrease the breakdown or detoxification of many drugs and, as mentioned above, the renal excretion of several drugs will decrease. Also there are changes in absorption and distribution [11] and, as a consequence, older patients are particularly susceptible to a larger dosage of drugs. Thus with flurazepam at a dose less than 15 mg, patients older than 70 have twice as many side effects as those below age 40 but these are increased eight times at a higher dose of 30 mg [12]. Studies to establish safe dosage of drugs are often done in young patients and then thoughtlessly applied to the elderly. Clarfield, reviewing 1943 articles published between 1980 and 1982 in JAMA, New England Journal of Medicine, British Medical Journal and Annals of Internal Medicine, found that two-thirds were not relevant to older patients, in spite of generous interpretation of relevance. In this study, an article was deemed to be relevant if the mean patient age was over 60 or the mean age ± 2 standard deviation included 70 years, or if the range included even one patient age 70 or 20% over 60 years of age [13].

Of risk factors in the elderly, some are unique – the anatomic changes, physiological changes, the decreased thirst and smaller total body water. The other risk factors such as dehydration, excessive drug doses and underlying diseases, although they are not unique are much more common and explain their greatly increased risk of acute renal failure.

What can be done to decrease acute renal failure in the old?

Many of these hazards could be avoided by simple knowledge and common sense. First, in the old, one should avoid nephrotoxic drugs especially if they also have diabetes mellitus and/or chronic renal failure. However, drugs such as aminoglycosides in sepsis are useful. One way then to decrease the incidence of acute renal failure is at least to avoid repeated insults within a short time, as illustrated in Figure 2.

We should treat dehydration quickly with fluids. Older patients must be weighed as soon as they come to the hospital and the weight followed daily because this is the only accurate means of following changes in total body water. Nephrotoxic drugs should be avoided or replaced with non-nephrotoxic drugs, if possible. If this is not possible, renal toxic assaults should be widely spaced. The acronym WASH (Weigh-Avoid-Space-Hydrate) summarizes the management of these patients.

Finally, we need to strengthen the education of physicians with respect to the dangers of acute renal failure and to correct use of therapeutic agents both in undergraduate and postgraduate training. We believe simple education and thoughtfulness will decrease the high incidence of acute renal failure in these elderly patients.

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CHAPTER 19

Recognition and prevention of drug-induced acute renal failure

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Iatrogenic causes of acute renal failure may be more poorly tolerated by elderly individuals than by their younger counterparts [1]. The aging kidney may have pathologic changes, such as those produced by chronic hypertension or diabetes mellitus, which place it at increased risk of renal damage [2]. Abnormalities that also place the aging kidney at risk include atherosclerosis, congestive heart failure and dehydration [3]. In addition, a variety of diagnostic, and therapeutic agents commonly used in older patients are associated with the development of acute renal insufficiency [4–6].

Recently, Davidman *et al.* noted that aminoglycosides were responsible for renal insufficiency in a significant number of patients with acute renal failure [7]. It has been suggested that estimation of creatinine clearance by a formula, such as that described by Cockcroft and Gault [8], can be used to adjust dosages of therapeutic agents in older patients. It is noteworthy that Davidman's patients received appropriate dosage of aminoglycosides and the drug blood levels, which were monitored, were not in the toxic range. This suggests that, in the development of nephrotoxic acute renal failure, intrarenal levels of nephrotoxic drugs and, perhaps, urine flow rates, may be more important than blood levels.

Older patients are at particular risk with respect to drug-induced, acute renal failure [7, 9]. Therefore, it is important to recognize and prevent this type of renal failure in the older patient. This paper will discuss (1) drug-induced acute interstitial nephritis, (2) renal, fluid and electrolyte disorders secondary to nonsteroidal anti-inflammatory drugs, and (3) alterations in renal function secondary to the use of converting-enzyme inhibitors.

Drug-induced acute interstitial nephritis

Currently, in developed nations, drugs are a common cause of acute interstitial nephritis (AIN). This reaction is immune-mediated and the development of AIN is associated with fever, skin rash and eosinophiluria [3]. Hematuria, both microscopic and macroscopic, and eosinophilia also may be present.

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Table I. Drugs associated with acute interstitial nephritis in the elderly

Antibiotics	Diuretics
cephalosporins	furosemide
ciprofloxacin	thiazides
penicillin & derivatives	triamterene
sulfonamides	
others	Miscellaneous
	allopurinol
Nonsteroidal Anti-inflammatory Drugs	captopril
ibuprofen	carbamazepine
indomethacin	cimetidine
naproxen	
others	

Unfortunately, since these clinical features are apparent in only one-third of AIN, recognition and diagnosis of this condition often is delayed.

Recently, the use of Hansel's stain on urine sediment has enhanced our ability to detect urinary eosinophils and, when AIN is suspected, it is recommended instead of standard Wright's stain [10, 11]. Hansel's stain (methylene blue and eosin-y in methanol) allows for more precise identification of bilobed eosinophils, because it produces bright-red cytoplasmic granules in them. The presence of urinary eosinophils is not pathognomonic for AIN, however, since cholesterol embolization to the kidney also can produce this finding [12]. Gallium-67 nuclear scanning also may assist in the diagnosis of AIN, by revealing increased activity over the kidneys [13].

Therapeutic agents associated with the development of AIN include the penicillins, and first, second, and third-generation cephalosporins, as well as ciprofloxacin, erythromycin, rifampin, sulfonamides, and vancomycin. In addition, one must check for nonsteroidal anti-inflammatory drugs, diuretics and unrelated chemical agents such as captopril, phenytoin, carbamazepine, allopurinol, cimetidine, and cyclosporine (Table I).

If one suspects AIN in an elderly patient, he must conduct a careful review of present and recently discontinued medications including both prescription and non-prescription drugs. When possible, causative agents are identified, the drug(s) is withdrawn and usually the course of AIN is limited once the culprit drug is discontinued. However, in patients of an advanced age, it is not uncommon to see a protracted period of oliguric renal failure requiring dialysis.

A definitive diagnosis of AIN requires renal biopsy, which demonstrates a cellular interstitial infiltrate, which spares the glomeruli; there are no significant fibrotic changes [14]. The use of steroids in AIN is controversial, but a short therapeutic trial of these agents may be considered in patients whose renal failure appears to be protracted [15].

Nonsteroidal anti-inflammatory drug-associated renal insufficiency

Nonsteroidal anti-inflammatory drugs (NSAIDs) are in wide use among older individuals, especially those with rheumatic disorders [16], in part because of the availability of NSAIDs in lower-dose, non-prescription formulation. NSAIDs are believed to decrease prostaglandin synthesis by inhibiting the enzyme, cyclo oxygenase [3]. Prostaglandins may play an important physiologic role in maintaining renal blood flow and glomerular filtration in conditions associated with decreased renal perfusion [17], e.g. in congestive heart failure and dehydration from various causes. Thus in the elderly NSAIDs may induce renal insufficiency when renal blood flow and glomerular filtration have been maintained by prostaglandin effects. Indeed, Sandler *et al.* have reported renal insufficiency associated with NSAIDs in older individuals [16]. However, in the healthy elderly, this risk may be minimal or absent when prostaglandins do not maintain renal function [18]. When administering NSAIDs to an elderly patient, one should conduct a careful evaluation and follow-up.

NSAID use also has been associated with the development of AIN and nephrotic-range proteinuria [19]. Typically, in this form of AIN, one does not see manifestations of an allergic reaction such as fever, rash, and eosinophilia [3]. It has been postulated that modification of the lipoxygenase pathway, resulting in altered T-lymphocyte activation and lymphokine production, directly promotes cellular infiltration in NSAID-associated AIN [20]. The nephrotic-range proteinuria in AIN secondary to NSAIDs may reflect altered renal tubular function, and changes in the glomerular basement membrane [19].

In addition to alterations in renal blood flow and glomerular filtration rate, NSAIDs also produce significant changes in body sodium, potassium and water regulation. Prostaglandin inhibition is associated with antinatriuresis, in part, secondary to decreased aldosterone production, and, also, as the result of intrarenal vascular events [3]. Prostaglandins stimulate increases in plasma-renin activity (PRA), and prostaglandin inhibition can be associated with significant decreases in PRA and plasma aldosterone levels (hyporeninemic hypoaldosteronism) with resultant significant hyperkalemia [21, 22]. Since renal potassium excretion also may be limited by other drugs used in the elderly, such as converting enzyme inhibitors, and potassium-sparing diuretics, this effect of NSAIDs may be particularly significant [23].

Prostaglandins also antagonize the effect of antidiuretic hormone (ADH) and facilitate water diuresis [24]. NSAID therapy has been associated with water retention syndromes and hyponatremia [25]. Since stimulated ADH levels already may be elevated in older patients [26, 27], serious hyponatremia may develop. Again, since the elderly frequently are given other agents, such as loop diuretics, which also can produce hyponatremia, the additive effects of these drugs and NSAIDs may produce life-threatening decreases

Table II. Renal complications of NSAID* therapy

Azotemia, secondary to increased vasoconstriction
Azotemia, secondary to acute interstitial nephritis
Nephrotic-range proteinuria
Hyperkalemia
Hyponatremia

*NSAID = nonsteroidal anti-inflammatory drug.

in serum sodium levels. The renal complications of NSAID therapy are shown in Table II.

Renal insufficiency in association with converting enzyme inhibitors (CEIs)

Drugs that inhibit the action of angiotensin-converting enzyme are used widely for hypertensive disorders and cardiovascular insufficiency [28, 29]. These agents suppress the formation of angiotensin II, which is a potent vasoconstrictor and a stimulus for aldosterone secretion. Angiotensin II constricts a variety of vessels, including the postglomerular efferent arteriole, an action that is beneficial when a reduction in glomerular filtration pressure is desirable in such disorders as diabetes mellitus and nephrotic proteinuria [30]. Among the agents with an inhibitory action on the converting enzyme, seven are approved by the US Food and Drug Administration for the treatment of hypertension (Table III).

Converting-enzyme inhibition produces a variety of untoward effects, which include angioneurotic edema, taste disorders, interstitial nephritis, hyperkalemia, cough and excessive hypotension (Table IV). In addition, azotemia has been noted in patients with bilateral renal artery stenosis or those with unilateral renal artery stenosis and a single kidney [6]. The mechanism behind the development of azotemia in patients on CEI therapy relates to a decrease in the compensatory efferent arteriolar tone, which maintains glomerular filtration pressure in patients with decreased renal perfusion due to obstructive large artery disease.

In addition, circumstances associated with decreased renal perfusion, such as dehydration, also may require an increase in efferent arteriolar constriction to maintain adequate glomerular function. When this efferent arteriolar response is suppressed by a CEI-induced decrease in angiotensin II, the result is decreased glomerular filtration and significant azotemia. Warner and associates found that when a CEI was added to a regime that already included furosemide, there was an increase in blood-urea nitrogen and creatinine levels [31]. Following this development, furosemide dosage was reduced by 50% and the azotemia reversed to baseline levels.

Recently, Toto *et al.* added further insight into the development of azotemia in association with CEI therapy [32]. They described patients who de-

Table III. Converting enzyme inhibitors for hypertension*

Drug	Daily dosage	Dosage for renal impairment
Benazepril–Lotensin (Ciba)	Initial: 10 mg Usual: 20–40 mg qd or bid Maximum: 80 mg	Serum creatinine > 3 mg/dl: 5–40 mg
Captopril–Capoten (Squibb)	Initial: 25 mg bid or tid Usual: 25–150 mg bid or tid Maximum: 450 mg	Decreased
Enalapril–Vasotec (Merck)	Initial: 5 mg Usual: 10–40 mg qd or divided Maximum: 40 mg	Serum creatinine > 3 mg/dl: 2.5–40 mg
Fosinopril–Monopril (Mead Johnson)	Initial: 10 mg Usual: 20–40 mg qd or bid Maximum: 80 mg	No change
Lisinopril–Prinivil (Merck) Zestril (Stuart)	Initial: 10 mg Usual: 20–40 mg qd Maximum: 80 mg	Serum creatinine > 3 mg/dl: 5–40 mg
Quinapril–Accupril (Parke–Davis)	Initial: 10 mg Usual: 20–40 mg qd or divided Maximum: 80 mg	Decreased
Ramipril–Altace (Hoechst)	Initial: 2.5 mg Usual: 5–10 mg qd or bid Maximum: 20 mg	Serum creatinine > 2.5 mg/dl: 1.25–5 mg

*Modified from The Medical Letter ®34:27, 1992 and reprinted by special permission of the publisher.

veloped azotemia while receiving CEIs and diuretics for the management of hypertension. A companion group treated for hypertension with non-CEI type drugs, had similar decreases in mean arterial pressure without accompanying azotemia. These authors suggest that a decrease in mean arterial pressure, in association with failure to compensate for an increase in efferent arteriolar tone, explains the development of azotemia in the patients receiving CEIs. Further, they conclude that this type of azotemia, resulting from alterations in systemic blood pressure and/or volume status in patients receiv-

Table IV. Renal complications of CEI* therapy

Hyperkalemia
Nephrotic-range proteinuria with glomerulopathy
Azotemia, with large-vessel, renal-artery stenosis
Azotemia, with decreased intrarenal perfusion pressure

*CEI = converting enzyme inhibitor.

ing CEI therapy, may be much more common than that described in patients with large vessel disease.

Hyperkalemia also develops in association with CEI therapy, secondary to decreased aldosterone secretion, which results from decreased angiotensin II production following an inhibition of converting enzyme [33]. In patients with mild to moderate renal insufficiency, a pre-existing limitation of potassium excretion might provoke serious hyperkalemia following the institution of therapy with CEIs. This problem may be aggravated by other drugs used in elderly patients to treat cardiovascular disease or musculoskeletal disorders. Beta-blocking agents, which decrease renin secretion, may be associated with the development of hyperkalemia, which may then worsen when CEI therapy is added. By limiting the renin-stimulating effects of prostaglandins, nonsteroidal anti-inflammatory drugs can precipitate hyporeninemic hypoaldosteronism, and concomitant hyperkalemia.

In addition, the use of potassium-sparing diuretics in elderly patients to prevent hypokalemia also can hasten the development of hyperkalemia in those on CEI therapy. Indeed, since elderly patients often are on multiple therapies, which may include potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs and beta-blocking agents, they are under high risk of an increase in serum potassium, even without the addition of CEIs. Therefore, when one uses CEIs in older patients who are on any or all of these agents or who may tend toward potassium retention by virtue of age-induced, low-plasma-renin activity and low aldosterone levels, he should monitor serum potassium levels frequently. In addition, it has been reported that diabetes mellitus and chronic interstitial nephritis are associated with hyporeninemic hypoaldosteronism and may further complicate the use of the medications cited [22]. The use of multiple medications in the elderly, the possibility of drug-drug interactions, and drug-disease interactions make elderly patients particularly susceptible to untoward effects from pharmacologic therapies.

In summary, the prevention of drug-induced, acute renal failure in the elderly requires a thorough knowledge of age-related physiologic changes, drug effects and interactions, and careful evaluation of risk: benefit ratios of all medications and/or procedures being considered.

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CHAPTER 20

Contrast-induced renal failure in the elderly

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In view of the preponderance of elderly patients requiring invasive, diagnostic and therapeutic radiographic studies, it has become increasingly apparent that contrast-induced nephropathy is an important cause of morbidity in this population. While it is unlikely that all cases of acute renal failure due to contrast can be avoided, recognition of risk factors and the use of appropriate prophylactic regimes may help to minimize the incidence of contrast-induced nephropathy. A prospective study by Hou *et al.* in 1983 [1] found that the third leading cause of hospital-acquired renal failure was radiocontrast agents and accounted for 12% of all episodes of acute renal failure. A review by Barrett and Parfry [2] grouped all previous studies with reference to potential risk factors. Despite obvious differences in study design and in the definition of acute renal failure, an aggregate incidence can be defined. Among patients with previously normal renal function, the overall aggregate incidence of contrast-associated nephropathy appears to be approximately 7% with a range of 0–29%. In contrast, patients with pre-existing impairment of renal function experienced an incidence of contrast-associated nephropathy of approximately 22% with a range of 0–60%. Finally, diabetic patients with existing renal insufficiency were at a particularly high risk of developing this entity with an aggregate experience of 60% and a range of 8.8–92%. Thus, while radiocontrast agents are relatively safe in patients with normal renal function, patients with underlying renal dysfunction may be at a measurably higher risk for developing contrast-associated nephropathy.

An elderly patient, who may have a mild-to-moderate reduction in renal function, must be considered as having a high-risk for developing acute renal failure following contrast agents. At least three studies appear to support the concern that age alone is a risk factor for the development of contrast-associated nephropathy. In a study by Gomes *et al.* [3] of 364 patients undergoing major arteriography, 26 or 7% had acute renal dysfunction, defined as a 50% rise in creatinine. Five of these patients required dialysis. When evaluated using logistic regression analysis, age was an independent risk factor even in the presence of apparently normal renal function. The mean age of patients developing acute renal failure was 71.5 years compared

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Table I. General guidelines for prevention of contrast-associated nephropathy in the elderly

1. Use non-contrast studies when possible
2. Perform contrast studies for specific indications
3. Use lowest possible dose of contrast
4. Monitor serum creatinine daily for 2–3 days
5. Avoid repeat studies
6. Maintain adequate hydration

to 61 years in those that did not. Similarly, Cochran *et al.* [4] demonstrated in 266 patients undergoing renal arteriography that age was an independent risk factor for acute renal failure following a contrast study. Forty-five of 266 patients (17%) had a least a 20% increase in serum creatinine; 6 patients developed oliguric or anuric renal failure. One of these patients required permanent dialysis. Once again, age was an independent risk factor: patients over the age of 55 were 1.9 times more likely to develop contrast-associated nephropathy. More recently, in 183 patients 70 years of age or older who were undergoing cardiac catheterization, Rich and Crecelius [5] prospectively evaluated the incidence and risk factors associated with the development of acute renal failure. The clinical course revealed that, of the 183 patients, 21 (12%) had a rise in creatinine greater than 44 micromoles/liter (0.5 mg%). Five patients had persistent renal dysfunction, but none required dialysis. Two deaths were related to cardiac disorders. Independent predictors of nephrotoxicity included a contrast volume greater than 200 milliliters, serum albumin of less than 35 grams/liter, the presence of diabetes mellitus, a serum sodium of less than 135 millimoles/liter, a serum creatinine greater than 133 micromoles/liter or a New York Heart Association Class 3 or 4. Thus, an interaction between age and pre-existing renal dysfunction seems to place the older patient at a higher risk for renal failure following contrast administration. While short-term or even chronic dialysis is not required for all cases of contrast-associated nephropathy, one should anticipate the need for dialysis in the elderly patient especially in the setting of pre-existing renal dysfunction.

General guidelines may reduce the incidence of contrast-associated nephropathy in the elderly population (Table I). These include: use of non-contrasts studies whenever possible, performing contrast studies for specific indications only, using the lowest possible dose of contrast material, monitoring serum creatinine daily for 2–3 days after the study, avoiding repeat studies, and maintaining adequate hydration. In a prospective study, Eisenberg [6] prevented acute renal failure by adequate hydration with 550 milliliters of normal saline per hour during angiography. While dehydration should be avoided during contrast studies, it is important also to correct volume-overload states particularly in view of the extrarenal effects of these agents (Table II). Congestive heart failure may be caused by contrast-induced expansion of the plasma volume, a decrease in systemic vascular resistance,

Table II. Extrarenal effects of contrast agents

Cardiovascular
– Expand plasma volume
– Decrease SVR and BP
– Negative ionotropy
– Increase LVEDP
Pulmonary
– Noncardiac pulmonary edema
– Depressed FEV and FVC
Hematologic
– Decreased red-cell deformability
– Increased red-cell clumping
– Increased blood viscosity

Table III. Renal effects of contrast agents: tubular

1. Altered sodium transport: naturesis associated reduction in renal blood flow
2. Enzymuria: LDH, SGOT, CPK excretion increased
3. Vacuolization of proximal tubular cells
4. Precipitation of Tamm – Horsfall mucoproteins
5. Increased excretion of uric acid and oxalate

Table IV. Renal effects of contrast agents: ischemia

1. Reduction in RBF and GFR by 30% to 50%
2. Transient initial vasodilation
3. Prolonged vasoconstriction due to:
– Na^+ depletion
– PRA/A II mediated
– Adenosine/Ca^{++} mediated
4. Shunting of blood from cortex to medulla
5. Leftward shift in O_2–Hb dissociation curve

negative inotropy and an increase in left ventricular end-diastolic pressure. In addition, an alteration of respiratory physiology can produce noncardiac pulmonary edema and a depression of both the FEV and the FVC. Hematologic effects of contrast agents include a decrease in red-cell deformability, an increase in red-cell clumping and a decrease in blood viscosity.

Despite our recognition of the risk inherent in the use of contrast agents, specific strategies employed to prevent renal failure have thus far been met with varying success. This is likely because of the diverse mechanisms by which contrast agents cause renal dysfunction. The renal effect of contrast agents may be classified as tubular (Table III) and vascular leading to ischemia (Table IV). A prominent tubular effect of contrast agents is altered sodium transport; the resulting natriuresis is associated with a reduction

Table V. Specific maneuvers in the prevention of contrast-associated nephropathy in the elderly

1. Hydration (avoid overhydration)
2. Discontinuation of nonsteroidal agents
3. Rule out multiple myeloma
4. Mannitol and Lasix
5. Calcium-channel blockers
6. Nonionic, low-osmolality contrast agents
7. Atrial natriuretic factor (ANF)

in renal blood flow and glomerular filtration rate. Other effects following administration of contrast agents are enzymuria leading to an increased excretion of LDH, SGOT and CPK, vacuolization of proximal tubular cells, precipitation of Tamm–Horsfall mucoproteins, and an increased excretion of uric acid and oxalate. In addition to these tubular effects, contrast agents can cause renal ischemia with a 30–50% reduction of renal blood flow and glomerular filtration rate. While there is a transient initial vasodilitation, animal models have demonstrated a subsequent prolonged vasoconstriction. The observed renal-vascular response to contrast agents has been attributed to sodium depletion with activation of the renin-angiotensin system [7], intrarenal adenosine generation with stimulation of calcium-dependent vasoconstriction [8] and an alteration in prostaglandins [9]. There is also evidence of shunting of blood from the cortex to the medulla and a leftward shift in the oxyhemoglobin curve. There may be profound tissue hypoxia in the medullary area. Brezis *et al.* [10] have shown that oxygen tension falls precipitously as one moves from the cortex to the medulla, even under normal tissue oxygenation. Any significant reduction in renal blood flow, as is seen following contrast administration, can led to profound ischemia of the medulla with subsequent tubular necrosis. An experimental model demonstrating necrosis of the thick ascending limb of the loop of Henle has been developed by Heyman and his associates [11].

In view of the apparent importance of maintaining renal blood flow and avoiding vasoconstriction, specific maneuvers have been proposed to minimize renal ischemic damage during contrast administration. These maneuvers (Table V) include hydration, discontinuation of non-steroidal agents, the use of mannitol and furosemide, calcium-channel-blocker administration, the preferential use of non-ionic low-osmolality contrast agents and the as-yet-experimental use of atrial-natriuretic factor. In several studies, mannitol and furosemide effectively reduced the incidence of contrast-associated nephropathy. Porush *et al.* [12] noted that, despite hydration with 1500 ml of one-half normal saline over a 12–16 hour period, 70% of the patients with baseline renal insufficiency (average creatinine of 3.8 mg%) sustained acute renal failure with at least a 25% rise in creatinine. Mannitol, given as 250 ml of 20% mannitol 60 minutes after the contrast infusion, reduced the incidence of renal failure with only 22% of the patients experiencing a rise in creatinine.

Table VI. Radiocontrast agents

Generic name	Brand name	Osmolality (mOsm/l)
Ionic		
sodium diatrizoate	Hypaque Sodium	1470
meglumine iothalamate	Conray 60	1400
meglumine-sodium diatrizoate	Renografin 76	1690
Ionic dimer		
ioxaglate	Hexabrix 320	600
Nonionic monomers		
iohexol	Omnipaque 350	862
iopamidol	Isovue 370	796
Nonionic dimer		
iotrol		390

Finally, hydration coupled with administration of furosemide (dose of 4000 mg divided by the creatinine clearance in ml/min) at a rate of 100 mg over 5 minutes was accompanied by an 18% incidence of acute renal failure. In an animal model of contrast-associated nephropathy, Heyman *et al.* [13] evaluated the use of furosemide and saline. They found that 28% of control rats treated with normal saline alone had necrosis of the medullary, thick ascending limb of the loop of Henle but this was seen in only 1–2% of rats treated with furosemide alone or in conjunction with normal saline. Administration of calcium-channel blockers also reduces contrast-associated nephropathy. Deray *et al.* [8] studied the effects of such blockers on the vasoconstriction induced by contrast agents in dogs. While contrast administration produced a 50% fall in renal blood flow, pretreatment with diltiazem or verapamil markedly blunted this reduction.

The standard contrast agents are 2,4,6-tri-iodinated benzoic acid derivatives with an ionic content ranging from 26–37% and an osmolality of 664–1780 milliosmoles (Table VI). Agents in this class include sodium diatrizoate (Hypaque Sodium), meglumine isothalimate (Conray-60), and meglumine-sodium diatrizoate (Renographin-76). To reduce the osmolality of these agents while maintaining the iodine content, newer agents have been developed [2]. Ioxaglate is an ionic dimer with 6 iodine atoms attached to each osmotically active particle and an osmolality of 600 compared to 1690 of meglumine-sodium diatrizoae. Iohexol, iopamadol and metrizamide are new nonionic monomers, which have eliminated the sodium and meglumine ions, but maintain 3 iodine atoms per molecules. Despite some controversy over their relativley nephrotoxicity, recent studies suggest that, in high-risk patients, the non-ionic low-osmolality agents are associated with less acute renal failure. Using a linear regression analysis, Campbell *et al.* [14] noted that a reduction of contrast-associated, renal injury was apparent with the low-osmolality agents, Hexabrix 320 (ioxaglate) and Isovue 370 (iopamidol),

compared to Omnapaque 350 (iohexol) especially in the presence of baseline renal insufficiency. At the 1991 meetings of the American Society of Nephrology, Rudnick and his associates [15] described a study of the incidence of nephrotoxicity following cardiac angiography through a randomized, double-blind, multicenter trial of ionic and nonionic contrast medium. Their results from 1194 patients demonstrated that non-ionic contrast agents have a lower risk of causing renal dysfunction when compared to an ionic contrast agent. The overall relative risk of nephrotoxicity from meglumine diatrizoate was approximately double that of iohexol and the major difference was seen in high-risk patients. Also reported at this meeting was data suggesting that activation of endothelin by ionic contrast agents was a mediator of acute renal failure [16]. Finally, atrial natriuretic factor may be important in preventing contrast-associated nephropathy. Recently Margulies *et al.* [17] studied atrial natriuretic factor during the induction of radiocontrast nephropathy in a dog model. The protective action of atrial natriuretic factor appears to be related to an increase in glomerular filtration rate minimizing the contrast-induced renal impairment.

Based on the available data, one can recommend the following measures to minimize the risk of contrast-associated nephropathy in an elderly patient: (1) avoid contrast agents, if possible, in the elderly patient with multiple-risk factors, particularly if the patient has renal insufficiency; (2) multiple studies should be avoided; (3) one should evaluate for the presence of multiple myeloma before any contrast study because in this setting renal insufficiency is a particular risk and generally leads to irreversible renal failure; (4) in view of experimental data that nonsteroidal anti-inflammatory agents reduce renal flow and the fact that they are used in animal models to induce contrast-associated nephropathy, these agents should be strictly avoided in the elderly patient; and (5) one should maintain adequate hydration in this patient population. Newer data suggest the use of non-ionic low-osmolality contrast agents in the elderly patient with renal insufficiency. It is also advisable to use the lowest possible dose of contrast agents. In a study of 115 patients over a 10-year period, Cigarroa [18] showed that a contrast-material dosing formula reduced the incidence of renal insufficiency. The formula used to calculate the dose is as follows: 5 ml of contrast per kg of body weight divided by the serum creatinine (in mg/dl). The maximum dose never exceeded 300 ml of contrast. The use of mannitol-furosemide combination recommended by Berkseth and Kjellstrand [19] or a modification with furosemide alone appear to offer some benefit in reducing contrast-induced nephropathy in the high-risk patient. If used, the doses are as follows: 500 ml of a 20% mannitol with the addition of 100 mg of furosemide per mg% of serum creatinine or 500 ml of normal saline with 100 mg of furosemide per mg% of serum creatinine. Both infusions are given at the rate of approximately 20 ml per hour to maintain an output of 200–300 ml per hour. It is crucial that the urine output be matched ml for ml with solutions such as 5% dextrose in 0.45% saline with potassium. The rate of

urine output can be excessive and patients easily can get dehydrated turning what should be a protective maneuver into one that could create more renal insufficiency. Finally, newer data suggest that calcium-channel blockers may minimize the vasoconstriction induced by contrast agents. The appropriate route of administration is under investigation with direct intrarenal infusion of calcium channel blockers being compared to oral agents. This exciting new development may prove valuable in reducing the incidence of contrast-induced nephropathy.

Clearly the elderly patient can benefit greatly from the many advances made in invasive diagnostic and therapeutic radiology. Unfortunately, these same patients are at a high risk for experiencing untoward events during these procedures. Furthermore, renal failure following contrast administration may be associated with a greater morbidity in the elderly patient making prevention particularly important. With the current availability of specific preventive measures, we hope that contrast-induced renal failure can be avoided in the elderly patient.

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PART EIGHT

The elderly patient on dialysis

CHAPTER 21

Selection of dialysis mode in the elderly with end-stage renal disease

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The proportion of elderly patients in the population receiving chronic dialysis for end-stage renal disease (ESRD) has increased rapidly, in the United States and world-wide. Only 7% of chronic dialysis patients in the United States in 1967 were 55 years of age or older [1]. However, by 1986, this number had increased to 48%, and data from the USRDS indicate that, between 1987 and 1989, the median age of new ESRD patients was 60 years (Table I) [2]. Table I shows the prevalence and distribution (by treatment modality and age) of dialysis patients in the U.S at the end of 1989 [2]. Fifty-eight percent of the 122,257 patients were on center hemodialysis, 1.6% were on home hemodialysis, and 9% were receiving continuous peritoneal dialysis (CPD). Nearly 49% of the total dialysis population was $\geqslant 60$ years of age, and the proportion of such elderly patients on CPD was 40%, an increase from 33% in 1988. Thus, while the proportion of elderly patients on CPD is rising, peritoneal dialysis still appears to be underused in this population.

This distribution of patients on chronic dialysis probably is related to a variety of factors. The 'aging' of the dialysis population has been accompanied by an increase in the number of diabetic and non-diabetic patients, who have significant comorbid diseases at the initiation of replacement therapy for ESRD [3]. Accordingly, patients entering chronic dialysis today are not only older but also sicker than their predecessors. This should not be surprising since, in general, the health problems of elderly patients differ importantly from those of their younger counterparts, and the incidence of chronic illness increases with advancing age. Thus, 78% of individuals older than 65 years have a chronic illness, and 30% have 3 or more chronic diseases [4].

Given the high prevalence of diabetes mellitus and symptomatic cardiovascular disease in elderly dialysis patients, peritoneal dialysis appears to be the ideal therapy in many such individuals, because of its relatively minimal hemodynamic stress, the efficacy of intraperitoneal insulin therapy, and obviation of the need for vascular access. In spite of these important advantages, peritoneal dialysis is not used universally in the elderly, and in them treat-

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Table I. Living ESRD patients on 12/31/89 by treatment of modality by patient age*

	Hemodialysis		Peritoneal dialysis		Dialysis, modality unknown	All patients chronic dialysis
	Center	Home	CPD	IPD		
Age ≤ 60	44,217	1,730	8,789	1,303	5,617	62,607
Age > 60	50,448	951	5,956	684	2,562	59,650
(% of Total)	(53%)	(36%)	(40%)	(34%)	(31%)	(49%)
Total	94,665	2,681	14,745	1,987	8,179	122,257

*From USRDS 1991 Annual Data Report, page C5 [2].

ment failure may be more frequent than in younger patients. Interestingly, the proportion of elderly patients on home hemodialysis (36%) or IPD (34%) (Table I) is comparable to that on CPD, suggesting perhaps that elderly patients are more commonly placed on center hemodialysis for reasons related to home dialysis in general, rather than to the specific modality. Elderly patients are more likely to live alone and more likely to have intellectual [5–7] and functional impairment [6]. Such conditions not only may hinder the performance of home dialysis, but may also increase mortality [8]. There is a paucity of data regarding the selection of an appropriate dialysis modality, but it is likely that, along with physician and nursing bias [9], some of the aforementioned problems in the ESRD population influence both the choice of dialysis modality and the outcome of dialysis. The following discussion, based in part on our own experience at the University of Alabama at Birmingham (UAB), summarizes the medical and psychosocial factors that influence our selection of peritoneal dialysis for the elderly patient.

The evaluation and selection of a dialysis modality in elderly ESRD patients

Earlier, we discussed the process by which an interdisciplinary assessment team evaluates patients for dialysis modality selection at UAB [10]; we emphasize issues that are important to the elderly dialysis population, and encourage patients and families to be active participants. Our goal, of course, is rational interventions that are beneficial, cost-effective and that protect the independence of the elderly [5].

The assessment, which includes individual meetings between the patient (and family) and home training nurse, social worker and dietitian, provides specific information about available types of chronic dialysis, evaluates the ability of patient and potential home partner to grasp new concepts and to perform simple tasks (a 'hands on' approach is vital to establish whether the elderly patient who desires to stay at home can perform independently or may need some assistance), and exposes them to other patients and families, either in training or after they are established on home dialysis. We discuss levels of independence, the potential benefits of home *versus* center dialysis,

Table II. Contraindications to peritoneal dialysis

Abnormal peritoneal transfer surface area
Morbid obesity
Diverticulitis
Hernias
Recurrent pancreatitis
Abdominal aortic aneurysm
Chronic ostomies
Inability to perform self-dialysis

insurance coverage, and (for those in the 60 to 65 age range) early retirement *versus* continuing to work.

The choice of home *versus* center dialysis is influenced by patient and physician bias, the availability and convenience of center dialysis to the patient, and multiple social and financial issues. Elderly patients tend to outlive their spouses and/or close relatives other than children, and frequently the existing social support system is lacking in such situations. On the one hand, elderly patients often are concerned that they are burdens to their families; their preference to maintain independent households and to use peer groups for support, and their ability to rely on past experiences, may allow them to meet the demands of complex medical treatment better than any other group [7]. On the other hand, elderly patients on any form of chronic dialysis, let alone home dialysis, need an adequate social support system, of which the family unit is probably the crucial component. This is often the pivotal factor, which determines the long-term stay of the patient in the community *versus* institutionalization. Certainly, without strong family support, impairment of mental function and physical disability will increase the likelihood of institutionalization, and diminish the potential for successful home dialysis.

While with good reason, nephrologists may fear the aftermath of vascular-access placement in patients with severe peripheral vascular disease, the hemodynamic consequences of hemodialysis in patients with advanced cardiac disease, or the placement of a peritoneal access in the morbidly obese patient, there are relatively few absolute contraindications to either hemodialysis or peritoneal dialysis. Table II lists some of the usual reasons to avoid peritoneal dialysis in the adult of any age; for the most part, these are relative contraindications. For example, pre-existing hernias may be repaired, and recurrence minimized by performing continuous cycler peritoneal dialysis (CCPD) rather than continuous ambulatory peritoneal dialysis (CAPD). Similarly, the availability of a suitable partner allows CCPD in the patient incapable of self dialysis. On the other hand, peritoneal transfer surface area must be sufficient to support adequate dialysis. When this area is at the lower limits of normal, CCPD (with an increased number of nocturnal exchanges)

Table III. Medical and psychosocial advantages of peritoneal dialysis

Less hemodynamic stress than hemodialysis
No need for vascular access
Efficacy of intraperitoneal insulin therapy
Psychosocial
– increased mobility
– increased sense of control over illness
– better psychological adaptation
– can be done without a partner

may be somewhat better than CAPD, but neither technique will be adequate when peritoneal transfer surface area is clearly below normal.

Some nephrologists regard chronic peritoneal dialysis as the treatment of choice, while others use it only when hemodialysis is judged to be contraindicated or impossible. However, data from the EDTA Registry [11] and the last report of the National CAPD Registry [12] suggest that patients who undergo CPD as initial therapy of ESRD, whether because it was their first choice or because it was the only available option, remain on CPD longer than patients initially managed by chronic hemodialysis. The reasons for the differing technique survivals are unclear, but may relate in part to the greater residual renal function in the former patients at the onset of CPD. To be sure, the dropout rate from chronic peritoneal dialysis exceeds that from chronic hemodialysis, and the debate continues as to which modality provides the most adequate treatment. Nonetheless, the number of patients managed successfully for five years or more by some form of continuous peritoneal dialysis (CPD) is growing, and, apart from the issue of adequacy, CPD may offer some advantages over chronic hemodialysis (Table III).

In certain circumstances, such as advanced cardiomyopathy, low cardiac output, hypotension, and in patients with hemodynamic instability due to ischemic heart disease or autonomic dysfunction, the lesser hemodynamic stress of peritoneal dialysis may make it preferable to hemodialysis. In particular, there appears to be considerable enthusiasm for CPD in insulin-dependent diabetics, in whom intraperitoneal insulin administration (during peritoneal dialysis) gives more dependable blood sugar control, as compared to subcutaneous insulin therapy in similar patients undergoing chronic hemodialysis. In Europe, from the beginning of the EDTA Registry until 1985, nearly twice as many patients with ESRD due to diabetes were treated with CAPD than with hemodialysis [11].

Continuous peritoneal dialysis is used increasingly in the elderly, both in the U.S. (Table I) [2] and in Europe [11]. Apart from mortality, which is higher in the elderly for all dialysis modalities, older patients appear to fare just as well, or better, on CPD than do their younger counterparts. For example, the incidence of peritonitis, exit-site or tunnel infections or catheter failure is similar in patients $\geqslant 60$, as compared with patients 15 to 59 years

of age [12]. Likewise, the incidence of most complications leading to abandonment of CAPD is no different in patients > 65, than in those < 65 years of age [11]. Finally, patients > 65 years of age who undergo CPD as initial therapy of ESRD, whether as first choice or as only available option, have longer technique survival than do patients > 65 years of age under similar circumstances [11].

Major health problems of the elderly on continuous peritoneal dialysis at UAB

The outcome of peritoneal dialysis in the elderly may be affected by major health problems such as inability to perform self dialysis due to inadequate social support, physical debilitation, dementia, or major depression; nutritional disorders; and infection. Sixty-four patients began CPD in our unit between 1985 and 1989 (Table IV). Fifty-four patients were under age 60 and 10 patients were age 60 or older. Although the mean duration of CPD was greater in patients over age 60, the difference was largely due to the withdrawal of 13 patients in the younger group after renal transplantation. Survival and the frequency of withdrawal to hemodialysis were similar in the two groups. There were no significant differences between the two groups with respect to cause of ESRD; importantly, the incidence of diabetes mellitus was similar in the two groups (50% in patients ≥ 60 and 35% in patients ≤ 60). Both coronary-artery disease (60% *versus* 13%, $p < 0.05$) and atrial fibrillation (30% *versus* 2%, $p < 0.01$) were more frequent in patients $\geq$ age 60. The groups were similar in most other respects, including the frequency of congestive heart failure, atherosclerotic peripheral vascular disease, cerebrovascular accidents, gastrointestinal bleeding and infections other than peritonitis. Only one individual (age < 60 years) had lower GI bleeding associated with colonic diverticuli, and in no instance was it necessary to stop CPD as the result of diverticular disease. Finally, the frequency of hernias, catheter leaks, and/or wound infections was similar in patients above and below the age of 60.

Depression and dementia

The prevalence of major depression in the elderly is 4 to 5% [5], but we saw significant depression in only one patient in each of our patient groups, and it led to termination of CPD in one patient under age 60. It is our impression that the frequency of depression in elderly dialysis patients in our facility is relatively low. Although there are no objective data, one reason may be that our evaluation process facilitates more rapid resolution of the grief stage by providing adequate communication and support. Dementia, the leading cause of institutionalization in the elderly, is found in more than one-half of nursing

Table IV. Patients beginning CPD at UAB 1985–1989

Group	Number	Age at onset PD[a]	Months on PD	Alive (%)	Dead (%)	Withdrawn alive			Peritonitis	Exit-site	Tunnel/ infection	Catheters
						Hemo (%)	Transplant (%)	Other (%)				
Age ≤ 60	54	39.8	13.2	47	7	8	13	1	1.4	1.1	0.3	3.0
		11.6	11.5	(87)	(13)	(14.8)	(24.1)	(1.9)	1.6	1.9	0.5	1.4
Age ≥ 60	10	67.1	21.8	7	3	4	0	0	2.8	1.1	0.4	1.6
		6.0	10.9	(70)	(30)	(40)			2.2	1.3	0.7	0.5
p		< 0.0005	< 0.025	< 0.5		>0.10	> 0.20		< 0.05	> 0.4	> 0.375	> 0.4

[a]Mean ± SD.

home residents [6]. Dementia and/or organic brain syndrome, which occurred more often in our patients ≥ 60 (40%) than in those ≤ 60 (2%)($p < 0.001$), was the primary reason for stopping CPD in one of our elderly patients.

Nutritional abnormalities

Malnutrition is common in the elderly for such reasons as low income, lack of understanding of basic nutritional requirements, social isolation, physical disability, impaired intellectual function, as well as malabsorption and drug effects (including alcohol) [13]. Furthermore, we have few data that delineate the specific nutritional requirements of the elderly [13, 14]. Continuous peritoneal dialysis is associated with increased maintenance requirements for protein, due to loss of protein and amino acids in drainage fluid. Protein losses may reach 20 to 140 g/week, and 8.4 to 23.8 g of free amino acids/week [15]; the magnitude of these losses increase in the presence of peritonitis. Continuous peritoneal dialysis, particularly CAPD, imposes other nutritional stresses, including diminished oral intake as the result of peritoneal glucose absorption and abdominal fullness. Thus, total energy intake may be deficient in spite of peritoneal glucose absorption. Inadequate dialysis, often resulting from failure to increase the intensity of dialysis as residual renal function declines after the first few months, may contribute further to anorexia and protein-calorie malnutrition. For all of these reasons, protein-calorie malnutrition probably is more frequent in patients on CPD, compared with hemodialysis, and may be even more likely to occur in the elderly.

Malnutrition was more common in elderly patients (20%) than in the younger (2%) ($p \leq 0.05$), and, with depression, was the reason for stopping CPD in one elderly patient. Inadequate dialysis led to a change in dialysis modality in only one of our patients age < 60. On the other hand, when dietary energy intake is not impaired, the increased carbohydrate load due to peritoneal glucose absorption may contribute to hyperlipidemia although we do not know the extent to which hyperlipidemia enhances clinically significant atherogenesis in this age group.

Infection

The elderly are at increased risk from infection for such reasons as immunodeficiency, which results both from aging of the immune system and malnutrition. However, the role of immunodeficiency in the development of peritonitis in these patients is unclear. Peritonitis and/or catheter infections are the most common complications of peritoneal dialysis, but also are the leading causes of morbidity and technique failure. Limited data from the National CAPD Registry [12] suggest that age ≥ 60 years increases the risk

of peritonitis in patients on CAPD. In our patients, the incidence of peritonitis (Table IV) was higher in patients ≥ 60 years old than in younger patients ($p < 0.05$) and it was the chief reason for stopping CPD more often in elderly patients (30%) than in those ≤ 60 years old (6%) ($p < 0.02$). On the other hand, the incidence of tunnel and exit-site infections was similar in the two groups.

The presence of dementia, depression or severe motor impairment eliminates self-dialysis as a therapeutic option, but it does not necessarily preclude successful CPD. Twenty-seven per cent (16/59) of patients undergoing CPD in our home program are ≥ 60 years of age. Diabetics comprise 25% (4/16) of patients age ≥ 60, while 30% (13 of 43) of patients age < 60 are diabetic. Interestingly, of those patients in whom a home partner is required, 4 of the 5 patients age < 60 are diabetic, while only 2 of the 5 patients age ≥ 60 are diabetic. Thus, CPD may be successful in patients who are incapable of self dialysis, as long as the patient lives at home and if a partner is available to assume the responsibility of performing CPD. Admittedly such patients usually do not realize several advantages of home CPD, i.e., increased mobility and increased self-control of illness. Clearly, CPD is not an attractive choice for institutionalized patients for many reasons, including the increased risk of infection and inadequate nutrition, and reduced quality of life.

Summary

The evaluation of elderly patients for chronic dialysis, and the selection of a dialysis modality, should emphasize those medical and psychosocial problems, which affect both the individual patient, and the elderly patient, in general. Aged individuals and their families should have an opportunity to discuss such issues as quality of life, known medical risks, expected longevity, and the demands of medical management. This encourages patients to verbalize fears and concerns related to their illness, thereby fostering a sense of security, and trust of the health-care system. Ideally, the process is sensitive enough to identify the specific needs of both patient and family, and to recognize the importance of imparting a sense of control to aging individuals who face a chronic illness. Technologically, continuous peritoneal dialysis is a simpler form of chronic dialysis than is home hemodialysis, and requires a relatively short training period. Patients managed with home dialysis, especially CAPD, show better psychological adaptation than those receiving other forms of dialysis [16]. This may result, in part, from the increased sense of control which home care fosters in the elderly. Furthermore, CPD has certain medical advantages in selected patients. On the other hand, such benefits must be weighed against the potential medical liabilities of CPD in the elderly. In general, we encourage home CPD for elderly patients with no absolute medical contraindication, and in whom we can demonstrate

adequate cognitive skills, emotional control, independent living skills and/or adequate family support.

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CHAPTER 22

Hemodialysis of the elderly

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Since the inception of Medicare funding in 1972 (Public Law 92.603) and the Medicare mandate against age discrimination for ESRD treatment, there has been a marked increase in the number of elderly patients receiving ESRD treatment in the U.S. [1]. Based on the U.S. Renal Data System [2], the proportion of patients on renal replacement therapy (RRT) who are 65 years old and over has increased from 16.5% to 26.2% during the decade between 1977 and 1987. If this trend continues, the fraction of ESRD patients older than 65 will approach 40% by the year 2000, yet this age group will constitute only about 13% of the U.S. population. Because elderly people with ESRD are unlikely to have a suitable living-related donor and because cadaveric organs are given preferentially to younger recipients, hemodialysis will remain the principal form of RRT for the elderly, particularly since chronic peritoneal dialysis is underused in this age group [3].

Overall mortality in the ESRD population is higher relative to the general population. Mortality is even higher in the elderly dialysis patient and increases with advancing age [30, 31]. However, it is most disturbing that the 5-year survival of middle-aged and elderly dialysis patients is worse in the United States than in Europe or Japan [32].

According to the USRDS [33] 1991 Annual Data Report, the projected expected remaining life time for prevalent dialyzed ESRD patients, based on death rates observed between 1986 and 1989, is approximately one-fourth to one-sixth that of the general population through age 50, while the ratio is often close to one-third for older patients; that is, even though the mortality rate for dialysis patients increases with advancing age, the risk of death for dialysis patients relative to the general population decreases with age [31–33]. Preliminary analysis indicates improved survival on dialysis for all age groups in the 1988 incident cohort [33], but we will need follow-up reports to determine whether this trend will be sustained. This paper will review the potential causes of increased or excessive morbidity and mortality in the dialysis patient, with particular attention to the adequacy of dialysis.

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Table I. Management of dialysis-induced hypotension

- Frequent assessment of dry weight
- Avoid excessive interdialytic weight gain (restrict to 3% of body weight)
- Avoid antihypertensive drugs before dialysis
- Reduce, as much as possible, intake of narcotic analgesics and sedative hypnotics
- No food on, and just before dialysis
- If low, increase hematocrit to 30%
  Erythropoietin
- Evaluate for silent pericardial effusion
- Use dialysate sodium of 140 mEq/L
- Switch to bicarbonate dialysis (especially with high Q_B)
- Administer prophylactic oxygen, especially in elderly patients with cardiac or respiratory disease and a predialysis $PaO_2 < 80$ mm Hg
- Switch to biocompatible membrane
- In selected patients, use a cool dialysate (34°C)
- Use dialysis machines with UF controls
- Use sequential UF – dialysis; occasionally necessary when high UF rates are required
- Ameliorate risk factors for LVH (Anemia, hyperparathyroidism, aluminum overload)
- Improve nutritional status and hypoalbuminemia

Adequacy of dialysis

Several recent studies have documented the relationship between the dose of dialysis and mortality [4–7]. Although generally data on dialysis dose is not available for different age groups, several factors favor the delivery of lower doses of dialysis to the elderly. Perhaps most important is that generally elderly patients have decreased protein intake and therefore have low urea concentrations (see below). Despite several studies, which pointed out the poor correlation between predialysis urea level and adequacy of dialysis [8], many nephrologists continue to prescribe lower doses of dialysis to patients with low, predialysis-urea levels [9, 13]. Thus, older patients with low urea and low creatinine concentrations from decreased muscle mass are likely to receive less dialysis. Also elderly patients experience more intradialysis complications than do younger patients. Hypotension and other adverse symptoms such as nausea and vomiting are more common in the elderly than in younger patients, and often the treatment of hypotension is associated with temporary cessation or early termination of hemodialysis. These hypotensive episodes are more likely in the elderly because of their limited cardiac reserve, their pre-existing coronary heart disease and their need for multiple medications – nitrates or antihypertensive medications, which predispose them to hypotension.

Even when one does kinetic modeling to assess adequacy of dialysis, the dose prescribed often is equivalent to a Kt/V of less than 1.0. Such a target is based on Gotch and Sargent's retrospective analysis of dialysis adequacy, based on the results of the National Cooperative Dialysis Study (NCDS) [10]. However, the NCDS study population did not include diabetic patients

Table II. Causes of malnutrition in elderly dialysis patients

1. Anorexia, nausea, vomiting (underdialysis with low Kt/V)
2. Endocrine abnormalities
   (A) Decreased biologic activity of anabolic hormones
   Somatomedin C (IGF-1)
   (B) Increased concentration of catabolic hormones
   Glucagon, PTH
3. Hemodialysis-related catabolism
4. Gastroparesis
5. Postdialysis weakness and decreased motivation to eat
6. Dyspepsia due to phosphate binders or aluminum supplements
7. Intercurrent illnesses
8. Metabolic acidosis
9. Deranged metabolism of amino acids
10. Others: low income, depression, ill-fitting dentures, malabsorption, social isolation

and the mean age was considerably younger than that of the current U.S. dialysis population. Thus, the standard of adequacy set by the NCDS may not be applicable to the current U.S. population, particularly the elderly.

Finally, increasing evidence suggests large differences between the prescribed dose of dialysis and the delivered dose [11], which arise from the inappropriate application of an *in-vitro* dialyzer clearance (K) to an *in-vivo* situation, errors in the estimation of the volume of distribution (V) and attempts to greatly shorten dialysis time (t). Because of these errors, we deliver only a fraction (approximately 0.65 to 0.75) of the dose of prescribed dialysis. Although we have no data to suggest that the elderly experience a greater decrease in the dose of delivered dialysis through these mechanisms, such a reduction is likely to effect the elderly to a greater extent, because the major manifestations of underdialysis are similar to the manifestations of aging, namely an increased incidence of cardiovascular disease, infections and malnutrition.

Nutritional considerations in elderly dialysis patients

In 1983 Acchiardo *et al.* [12] and in 1990 Lowrie and Lew reported the negative effect of malnutrition on morbidity and mortality in hemodialysis patients [13]. While it is estimated that approximately 10% of hemodialysis patients have moderate to severe malnutrition, the incidence of malnutrition is even higher in the elderly – up to 20% [14] – for a variety of reasons including low income, lack of understanding of basic nutritional requirements, social isolation, malabsorption, ill-fitting dentures, depression, and drug effects, including alcohol. Table II shows the effect of several other factors producing negative nitrogen balance and muscle wasting.

Table III. Clinical and biochemical markers of malnutrition in elderly dialysis patients

- Non-fluid weight loss
- Decreased PCR ($\leq$ 0.8–1 g/kg/day)
- Decreased IGF-1 (somatomedin-C)
- Decreased serum albumin ($\leq$ 3.5 g/dl)
- Decreased transferrin saturation
- Low BUN ($<$ 50–60 mg%)

Markers of malnutrition are summarized in Table III. Non-fluid weight loss remains the best predictor of insidious malnutrition. The protein catabolic rate (PCR) probably is the best gauge of daily protein intake. Serum albumin and transferrin saturation are satisfactory markers of the visceral protein compartments. As an independent risk factor, a low serum albumin may be the most potent laboratory predictor of mortality [13]. In a patient with no significant residual renal function ($<$ 3 ml/minute) and a KT/V that does not indicate excess dialysis, a low BUN also indicates low protein intake. One should consider aggressive nutritional support in any dialysis patient with weight loss associated with a serum albumin, $<$ 3–3.5 dl, a PCR, $<$ 0.8 g/kg/day, or a BUN $<$ 50–60 mg% (Table III). This may be accomplished by more rigorous dietary therapy, improvement in the dose of dialysis as estimated by *Kt/V* [15] and concomitant treatment of depression, nausea or vomiting; one can improve food intake on dialysis days by avoiding postdialysis hypotension and fatigue.

Although the impact of reversal of malnutrition on reduction in morbidity and mortality among hemodialysis patients has not been established, attempts at improving the nutritional status have been undertaken. One strategy, intradialytic parenteral nutrition (IDPN), uses a formulation that contains 500 ml of 50% dextrose, 500 ml of 8.5% amino acids, and 200 ml of 20% lipids, infused over three to four hours during hemodialysis. The beneficial effect of IDPN may not be apparent before three months. As Wilmore and colleagues [16] have shown, the beneficial effects of hyperalimentation are enhanced by the concomitant administration of recombinant human growth hormone. Even though immunoreactive GH levels usually are elevated in chronic renal failure, the levels of insulin-like growth factor-1 (IGF1), also known as somatomedin-C (one of the mediators of GH action), are decreased in malnourished hemodialysis patients. As a biochemical marker of malnutrition, IGF-1 may be reduced even before one can demonstrate any anthropometric changes [17].

Hypotension in the elderly dialysis patient

The most frequent complication in elderly hemodialysis patients [18–20] is intradialytic hypotension, which occurs in 20–30% of treatments. Its frequency increases with age and, in elderly dialysis patients, is a particularly

debilitating morbid event. In the elderly, this hypotension can be sudden and profound and associated with loss of consciousness and often it happens without any prodromal signs, such as sweating, tachycardia, or apprehension [18, 21, 22]. It can occur with minimal extracellular fluid volume loss [18] and may be more difficult to reverse than the hypotension seen in younger hemodialysis patients. In the elderly, the sequelae of dialysis-associated hypotension may be grave and include seizures, cerebral infarction, myocardial ischemia, aspiration pneumonia, and vascular access closure.

Dialysis-associated hypotension is a complex phenomenon and its etiology is multifactorial [22, 23]. Here we review only those factors pertinent to old age.

The major cause of dialysis-induced hypotension is removal of fluid from the intravascular space that is more rapid than plasma refilling rate, coupled with an inability to increase peripheral vascular resistance. The factors that can impair a normal response to volume removal such as autonomic dysfunction and a low cardiac reserve are more prominent in elderly dialysis patients [24–26]. Autonomic dysfunction is more apparent in the elderly diabetic. Postprandial hypotension also is more common in the elderly [27, 28] and in patients with severe autonomic nervous system dysfunction; in such patients postprandial hypotension may be due to an ability to increase cardiac output under the obligatory increase in splanchnic blood flow and in the presence of reduced, total-peripheral-vascular resistance.

The limited cardiac reserve in elderly patients is related to such changes as LVH, dilated cardiomyopathy (predominantly a systolic dysfunction with ejection fraction less than 55%), hypertrophic cardiomyopathy with supersystolic function ($EF > 70\%$) and ischemic cardiomyopathy. The 'safety margin' by which blood pressure can decline during ultrafiltration dialysis is reduced further because elderly patients have a lower average predialysis blood pressure. Elderly patients also may have impaired cardiopulmonary/pressor receptor reflex function [29] especially in the presence of coexisting diabetes, LVH, severe CHF, or with certain drugs such as clonidine, propranolol or diltiazem.

Finally, osmotic equilibration between intracellular and extracellular fluid compartments may occur more slowly in the elderly than the removal of osmotically active solutes from the ECF during dialysis, leading to impaired refilling of the intravascular space. Table I shows the interventions available to reduce the frequency of this complication. Most important of these is frequent assessment of dry weight, especially when the nutritional condition is unstable, and the avoidance of excess interdialytic weight gains.

Survival and quality of life

The fundamental outcomes of any form of renal replacement are patient survival and an acceptable quality of life. Literature from selected centers

Table IV. Survival during maintenance hemodialysis in elderly patients in select centers

Author	Age (yr)		Number of patients	Survival (%)					
	Mean	Range		1 yr	2 yr	3 yr	5 yr	6 yr	7 yr
Westlie [34]	75	70–87	157	78	47		22		
Chester [35]	75	70–85	45		42				
Husebye [36]	75 ± 3.5	71–84	239						17
Schaeffer [37]	> 75		242				50		
Park [38]	> 60		22	75		52			
Port [39]		60–95	1831	65	46	35	20		
Tapson [40]	64.5 ± 4	60–76					53		
Wall [41]	69.5	65–74	28	77	68	46			
Rotellar [42]	74	65–85		70	50	31	15		
Loew [43]		60–70					45		
		70–80					25		
Benevent [44]	72	65–79	31	82	55	45			

(Table IV) and international registries shows that, despite complex comorbid medical and psychosocial conditions, the elderly patient with ESRD [34, 52] can expect acceptable levels of survival and quality of life on hemodialysis.

In a study of 157 patients with a mean age 75 years (range 70–87) who started dialysis between 1966 and 1983, Westlie and colleagues [34], found a one-, three-, and five-year survival of 78%, 47%, and 22% respectively. At initiation of dialysis, 17.2% had diabetes, 35% ASHD, 10% CVA, 18.5% COPD, and 22% had peripheral vascular disease. More than 90% of patients lived at home, were active and had a high degree of social wellbeing and enjoyment of life. These authors concluded that the elderly are 'excellent dialysis candidates'.

Chester *et al.* [35] reported a 2-year survival of 42% in a group of 45 patients (mean age 75), compared to 58% in control patients with average age of 42 years. Nine of these elderly patients were over 80 and had a 2-year survival of 41%. Elderly patients had a significantly lower mean predialysis blood pressure (142/73 ± 3/1 mm Hg) than the controls. These elderly also seemed to adjust better to chronic disease than did young patients with lower interdialytic weight gains and lower serum phosphate levels, probably reflecting better patient compliance with diet and medications.

Of 239 patients over the age of 70 years followed at the Regional Kidney Disease Program at Hennepin County Medical Center in Minneapolis, the seven-year cumulative survival was 17%. In this program, the most common cause of death was withdrawal from dialysis accounting for 40% [36].

Port *et al.* [39] found a one-year survival rate for the 60 to 95-year-olds of 65% and 46% at two years. In a United Kingdom study in which patients may have been selected more rigorously, the five-year survival rate for those over 60 years of age was 53%, compared to 68% for those under 60 years [40]. A French study found an 80% survival at six years in a small group of

patients over 60 years of age on home dialysis [52]. In another French study [44], 31 patients (mean age 72 years) had a one and three-year survival rate of 82% and 45% respectively.

Ghantous *et al.* [49] showed that about one-half of patients age 50–80 years could manage on home hemodialysis, attesting to the ability of elderly people to adapt to a complicated regimen. Similarly, in a group of 154 patients over 50, Walker *et al.* [50] showed that home hemodialysis was feasible for many elderly patients (82 patients were on self-dialysis). In addition, self-dialysis patients survived longer than those who required in-center dialysis and, for the first three years, was as long as that of the self-dialysis patients under age 60.

In the Batelle study [51] of 859 dialysis and transplant patients, 70% of the elderly (comprising 16% of the dialysis patients) fell in the top four categories of overall functional status using the Karnofsky index.

In the aggregate, therefore, prolonged survival is feasible for elderly hemodialysis patients. Quoting British renal consultants, Rodney Deitch [53] said in 1984 that 'if a 60-year-old person is successfully treated for renal failure, he had every chance of living healthily into the 80s'.

Conclusions

Virtually all reports of hemodialysis in the elderly with ESRD have been encouraging, with a 5-year survival of 20–40%. Elderly patients should not be denied this life-sustaining treatment if there is hope for an enjoyable span of life.

Improved survival of the elderly on hemodialysis may be possible with delivery of 'optimal' dialysis, prevention of malnutrition, use of biocompatible membranes and erythropoietin. As well, in this age population we need a better understanding and treatment of the various factors that lead to LVH [54] and ischemic heart disease.

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CHAPTER 23

Creative strategies for chronic peritoneal dialysis in the elderly

ALLEN R. NISSENSON

The general population in the United States is aging progressively. In 1987, 12% of the population was age 65 or older and this is projected to increase to over 21% by early in the next century. This trend is also reflected in the ESRD population. In 1987 only 47% of patients were 65 or older, and this is expected to reach over 60% by the end of this decade. Recent data from the United States Renal Data System (USRDS) confirms these trends [1]. The overall incidence of ESRD in the U.S. in 1978 was 68 per million population and this had risen to 166 per million population by 1989. The corresponding figures for the 65–74 and 75+ age groups are 191 and 88 (1978) and 590 and 502 (1989) respectively (Table I). When expressed as the annualized change in incidence over time, from 1984–86 to 1987–89, the 75+ group increased the most dramatically, 13.0% per year, closely followed by the 65–74 year old group at 8.7% per year.

Additional USRDS studies have examined the expected life span of patients with ESRD and compared it to the general population and to patients with prostate, colon and lung cancer. A 40-year-old person starting dialysis has one-fourth the expected remaining lifetime as that of an age-matched control. A 59-year-old starting dialysis has the expected life span (4.2 years) equal to that of a 59-year-old with colon cancer, one-fourth that of a 59-year-old with prostate cancer. As anticipated, the life expectancy of older ESRD patients is even less; those over 85 years old at onset of renal failure are likely to live an average of 1.4 years, similar to the general population of this age.

Morbidity also is greater in elderly compared to younger ESRD patients. The USRDS data set examined one measure of morbidity, namely hospitalizations; the number of days spent in hospital per year increases progressively with increasing patient age, reaching a median of 15.0 in those 65 and older. When compared to other Medicare patients without ESRD (1984–1986 data), those with ESRD spent four times as many days in hospital annually. Clearly, both morbidity and mortality are significant in this aged population.

Both hemodialysis (HD) and chronic peritoneal dialysis (CPD) have been used in elderly ESRD patients [2, 3]. Although, in general, CPD is the most

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Table I. ESRD incidence per million population for elderly patients in the United States

	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
65–74 years old	191	220	242	251	287	369	372	421	451	495	521	590
75+ years old	88	123	133	136	171	255	265	307	349	388	428	502

rapidly growing ESRD therapy worldwide, it is underused in the elderly in many parts of the world, including the United States [3]. This is particularly ironic considering what physicians state they feel is the best ESRD modality for elderly patients. In a recent study, Mattern *et al.* found that physicians in Southern California, North Carolina, and Australia and New Zealand believed that CPD was the preferred mode of dialysis for elderly ESRD patients [4]. However, in these areas, particularly the former, physicians used in-center HD in the vast majority of patients in this group, illustrating that in the aged patient, non-medical factors are important determinants of the mode of ESRD treatment.

A number of medical and psychosocial factors favor CPD as a mode of ESRD treatment for the elderly [5–7]. CPD avoids vascular access and its complications, a major source of morbidity and mortality in this group. Similarly, hemodynamic instability, common with HD in the elderly, is avoided. In addition, intra- and interdialysis arrhythmias, at times life-threatening, are rare with CPD when compared to HD [8, 9]. For those patients who are malnourished, CPD provides a source of calorie nutrition through the dialysate. Both cognitive function and brain electrophysiology are maintained better on CPD than on HD, although the elderly do worse on these measures than younger patients on either modality [10–12]. Finally, in addition to improving the overall quality of life, CPD can promote independence, self care and a sense of self worth [13].

The major impediments to the greater use of CPD in the elderly are psychosocial. Physicians might overcome psychosocial barriers to the use of CPD in medically suitable elderly patients by three specific creative approaches. These include CPD in nursing homes, the use of home peritoneal dialysis helpers or aides, and the development of adult daycare centers for CPD patients.

Nursing homes

In the United States, 5% of the general population over the age of 65 live in nursing homes. In a 1987 survey, 5.6% of U.S. ESRD patients in this age group lived in nursing homes [14]. Historically, nursing-home patients with ESRD have been treated with in-center HD although this may not be the best treatment, as outlined above. In addition, transportation to and from dialysis by ambulance usually is necessary, at high cost. Recently, Anderson

et al. described their experience with CPD in the nursing-home setting [15]. Forty-four ESRD patients were placed on CAPD and cared for in a single 50-bed nursing unit in a nursing home. A trained CPD nurse evaluated patients 5 days per week, performed morning and noon exchanges and maintained dialysis records. In addition, nursing-home staff were trained to perform afternoon, evening and weekend exchanges. The peritonitis rate was 1.3 episodes per patient-year, and hospitalizations averaged 18.5 days per patient-year. Patient survival (after admission to the nursing home) was 53% and 29% at 6 and 12 months, respectively. Predictors of poor survival included low Activities-of-Daily-Living score and no prior outpatient dialysis. Of note, 12 patients were discharged home, some on CPD. This study illustrates that CPD can be performed successfully in a nursing home. A recent Toronto study described a small hemodialysis facility in a chronic-care facility [16], which permitted intermittent HD without the expense or inconvenience of transporting patients to an outside facility. Of 35 patients treated in the facility, nine were discharged, although seven were not elderly, but rather rehabilitation patients. Therefore, one can deliver excellent ESRD care in the setting of a chronic care facility.

Home-assisted peritoneal dialysis

For those patients unable to perform their own CAPD exchanges or to set up a CCPD cycler, the use of home aides might make this possible. These individuals could provide assistance for some or all dialysis needs at home, e.g. for those on CCPD, they could make one visit per day to set up a cycler. The patient could connect and disconnect from the machine on their own. Such a program would use technicians rather than nurses, and thus be very cost effective. Recently Biemond *et al.* described a variation of this approach for CAPD patients [17]. Hospital staff trained community nurses to help patients perform CAPD at home. To date four patients have been enrolled in the study and are doing well. We await the medical, psychosocial and financial outcomes of this approach because this might permit greater use of CPD in medically appropriate patients.

Adult daycare centers

Such centers would provide additional support services to elderly patients and encourage them to use CPD when it would be medically advantageous but other limitations had precluded this. A model for such a program exists in California for the elderly in general and for those with Alzheimer's disease in particular. Frail elderly adults qualify for participation in the Adult Day Health Care Program (ADHC) if they:

(1) Have a medical condition requiring treatment or rehabilitation services prescribed by a physician.
(2) Have physical/mental impairments that constitute a handicap to activities of daily living but are not so serious as to require 24-hour institutional care.
(3) Have reasonable expectation that preventive service will maintain or improve the present level of functioning.
(4) Have a high potential for further deterioration and probable institutionalization if ADHC were not available.

Clearly, elderly ESRD patients fit this description!

Benefits of ADHD programs recognized to date include a reduction in depression, increase in self esteem and dignity, stabilization of medical conditions, improvement in communication skills, enhancement of sleep, relief of loneliness and boredom, increase in contentment, opportunity to meet new friends, chance to engage in activities (music, exercise, arts and crafts), and availability of door-to-door transportation and health maintenance programs.

To be certified in California, an ADHC requires the services of a physician (personal or staff), nurses, social workers, physical therapists, occupational therapists, speech therapists, psychiatrists and psychosocial workers, pharmacists, nutritionists, recreational and social therapists, and transportation coordinators.

Types of providers include city or county governments, visiting nurses associations, nutrition service companies, rehabilitation hospitals, acute-care hospitals, prepaid health plans, community service organizations, community health clinics, senior citizen organizations or dialysis facilities. Sites have included homes, churches, hospitals, office buildings, clinics, community centers, and schools.

In the elderly, ADHC may be a feasible adjunct to CPD that improves socialization, rehabilitation and quality of life. Many questions need exploration, however, including the cost of such programs. They are certainly worthy of further, in-depth consideration.

In summary, outcome of CPD in the elderly is excellent, both medically and psychosocially. The judicious use of CPD in nursing homes, the use of home helpers, and the development of ADHCs may enable physicians to offer CPD to more elderly patients who would benefit from this form of ESRD treatment.

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CHAPTER 24

Hemodialysis in a chronic care facility

JANET M. ROSCOE

The number of elderly patients entering ESRF programs continues to increase in most countries offering dialysis therapy. In Toronto, Ontario, the Toronto Region Dialysis Programs have kept statistics from 1981 to the present. During that time the percentage of patients over age 65 at entry into treatment has increased from 18% to 38% in 1991 (Fig. 1). This last total represented 117 patients age 65–74 and 54 patients over the age of 75. In Toronto the number of elderly patients maintained on chronic dialysis, has risen from 349 in 1989 to 459 in 1991.

This general increase in number of elderly ESRF patients has been accompanied by an increase in the number of dialysis patients who can no longer maintain themselves at home due to degenerative disease processes such as atherosclerotic heart disease (ASHD) with stroke or amputation. Earlier chronic-care institutions and nursing homes in the Toronto area had refused to accept patients requiring dialysis because they perceived that these patients would be more complicated to care for and require extra ancillary support such as dietary staff. In addition these institutions were penalized financially because these patients spent days away for dialysis for which the institutions were not paid. There was no mechanism to reimburse the institutions for transport costs. As a result these patients previously required care in acute hospital beds or were counselled to discontinue dialysis therapy. Often a discontinuation decision was unacceptable to the family and patient, who felt pressured to come to a rapid decision on an emotionally sensitive issue.

A survey of dialysis centres in Toronto in 1989 revealed that 36 patients were being cared for in an acute-care institution at a time when there was a shortage of acute-care beds. In 1990, The Wellesley Hospital and The Riverdale Hospital obtained funding from the Ministry of Health for a pilot project to establish a hemodialysis facility in a chronic hospital to care for patients needing dialysis.

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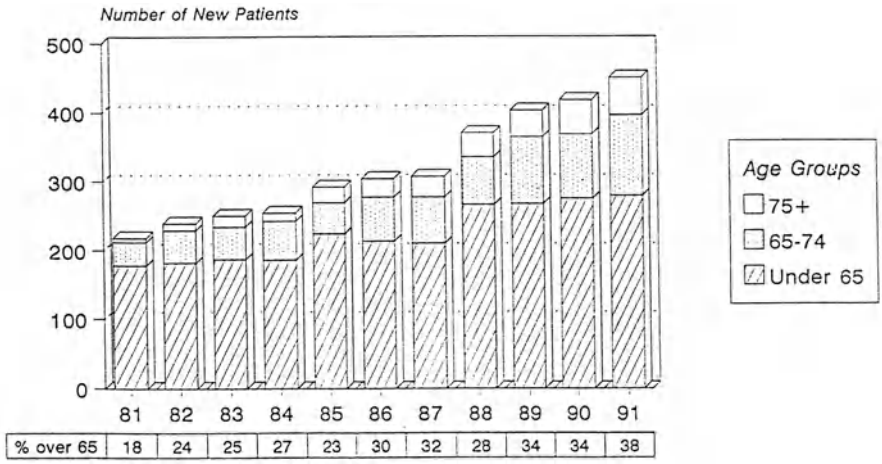

Fig. 1. Increase in elderly patients entering Toronto region dialysis programs 1981–1991.

The concept

The Riverdale Hospital is a large chronic-care institution located 10 minutes drive from the Wellesley Hospital, an acute-care hospital with an established nephrology program caring for 65 hemodialysis, 90 home dialysis and 12 centre peritoneal dialysis patients. We chose hemodialysis as the mode of therapy because the cost per patient with full-care treatment was cheaper than that for peritoneal dialysis, if specific dialysis nurses were to be supplied for each. Originally funding was provided for chronic care only, however some patients were admitted to receive other rehabilitation programs within the hospital.

The unit had four stations operating two shifts per day and had a capacity of 16 patients. Hemodialysis nursing and technical staff rotated from the Wellesley Hospital, under the supervision of Wellesley hemodialysis-unit nursing administration. Medical care on dialysis was provided by nephrologists from the Wellesley Hospital. Medical care on the floor at the chronic hospital was provided by the staff physician (a general practitioner) at the Riverdale hospital and by the floor nurses. No new ancillary staff were hired. We provided appropriate educational sessions and maintained close communication between both groups. We held administrative meetings with members of both hospital staffs at monthly intervals.

Admission to the facility was open to the entire Toronto community, and applications for chronic care were reviewed by the dialysis staff. Two members of the planning committee were from other institutions, to allow input from other dialysis units.

Table I. Causes of death

Cause	Chronic	Palliation	Rehab
Sepsis	1	8	1
Malignancy	1	0	0
Sudden/cardiac	2	0	0

Results of first year

Thirty-five patients were admitted in the first year of operation. Ten were admitted for rehabilitation and 25 for chronic care. All received comprehensive medical care and we made considerable efforts to normalize blood parameters with nutritional support, calcium supplementation and erythropoietin. However, despite all efforts, a group of patients were so significantly impaired and had such a decreased quality of life that aggressive therapy was not warranted. We removed aggressive support and/or dialysis only after full consultation with patient and family. After retrospective classification of the chronic patients, 16 were assigned to a chronic classification and 9 were assigned to palliative care. Of the 35 patients, 13 died. Eight of these 13 patients, were in the palliative-care group and four were from the chronic-care group. Only one rehabilitation patient died, from complications of aspiration pneumonia – the result of a severe CVA. Overwhelmingly, the most frequent cause of death was sepsis (Table I), frequently of vascular graft material either in the dialysis access or in grafts to the lower extremity. One patient died of malignancy and two previously stable patients died suddenly. At the time of attempted resuscitation, one of these patients had hyperkalemia.

Ten patients were discharged. Eight of these were rehabilitation patients and one had been admitted for chronic care. One additional patient, who was returned to his referring hospital as a failed admission, had been transferred from CAPD to hemodialysis and refused to allow us to replace his (temporary) vascular access when it became occluded. Four other patients were upgraded from chronic care to the nursing-home level after a period of rehabilitation.

Partly due to short followup, length of stay of all groups was similar and averaged 4.1 months (chronic), 3.9 (palliation), and 3.7 (rehabilitation). As can be seen, most of those on rehabilitation and palliation had either died or been discharged in an average of 4 months. Twelve original patients were still in residence after 12 months of operation, 10 from the chronic group and one each of the rehabilitation and the palliation group. Subsequently the rehabilitation patient was discharged and the palliation patient has since died.

Table II. Albumin as risk for death, Sept. 1990–1991 followed to 1992

Category	Serum albumin
Alive	33.7 ± 5
Dead	29.5 ± 7*

* $p < 0.05$ Dead vs alive.

Table IIIa. Serum phosphorus

Category	Adm. phosp. mmol/l	Final phosp.
Chronic	1.44 ± 0.45	1.73 ± 0.62
Palliative	0.89 ± 0.45*	1.41 ± 0.59
Rehab.	1.35 ± 0.48	1.51 ± 0.80

* $p < 0.05$ vs Chronic and rehab.

Table IIIb. P(adm) as risk for death, Sept. 1990–1991 followed to 1992

Category	Serum P (adm)
Alive	1.40 ± 0.45
Dead	1.15 ± 0.53 (NS)

Parameters associated with outcome

Low-serum albumin is a marker of adverse outcome. We evaluated biochemical parameters in these patients to assess whether some of them were associated with adverse outcome in this population. Both chronic and palliative groups had a low serum albumin on admission – 29.8 g/L palliation and 30.9 g/L chronic; albumin was normal in the rehab group (34.5 g/L). The serum albumin was significantly lower in the palliation group *versus* the rehab group but all other comparisons did not show significant differences. In addition the mean serum albumin of patients admitted between Sept 1990 and Sept 1991, who died during followup to March 1992, was significantly lower than those followed during the same period but who lived (Table II).

Admission serum phosphorus was significantly lower in those classified as palliation than in those categorized as rehabilitation or chronic care (Table III). No differences in parameters of calcium metabolism, such as serum calcium or alkaline phosphatase were seen in the three groups. All patients with low serum phosphorus were brought to normal levels with oral phosphate Sandoz but this did not affect the adverse outcome in the palliation group. The mean serum phosphorus of those who died during followup also was lower than those who lived but this difference did not reach statistical significance.

All patients were treated with erythropoietin (EPO) as necessary to

Table IV. Vascular access (admission), first twelve months

Thirty-five patients admitted	
AV Fistula	2
AV Graft	17
Vascath	11
Permcath	3
Cardiomed	2
Total	35

achieve a goal hemoglobin of 100 g/L or greater. Admission levels were lowest in the rehabilitation group, possibly reflecting a more acute illness, but rose significantly from 80 to 98 during followup. In the chronic group mean hemoglobin was 90 on admission and 89 g/L at end of followup and for the palliation group was 83 on admission and 92 g/L on followup. These two groups did respond to erythropoietin but did not achieve the goal hemoglobin as did the rehabilitation patients. Response to EPO did not seem to differ between the chronic and palliation groups.

Vascular access

Maintenance of vascular access is difficult in the elderly who have a high incidence of ASHD. We predicted that such access would be a problem in this group and believed that hemodialysis would be precluded in some patients. Table IV shows the status of vascular access on admission: 19 patients had permanent vascular access – 2 fistula (lower arm) and 17 grafts. Sixteen had either subclavian or internal jugular lines. During the first year, we placed 40 new vascular accesses of which 15 were permanent and 25 temporary. During the year, 14 of 32 grafts were lost due to infection or occlusion. Twenty-one of 41 temporary accesses were lost. Serum albumin below 32 was associated with significantly more access infection (12 of 18, 9 lost) *versus* serum albumin above 32 (5 of 17, 2 lost).

Only 3 patients were transferred from hemodialysis to peritoneal dialysis. One patient, who refused further hemodialysis after occlusion of temporary access inserted to facilitate transfer to Riverdale, was returned to his home hospital. One, who was returned to CAPD after successful stroke rehabilitation and discharge, and one patient had difficulty with vascular access and we could not establish acute temporary access when her permanent access clotted. This patient was placed on peritoneal dialysis for three weeks until we could provide replacement vascular access.

Transfers to acute-care facilities

Transfers back to acute-care facilities were another problem we predicted. The acute backup was provided by the Wellesley Hospital and not by the original hospital. There were 65 transfers between institutions in the first year of operation. Of these transfers, 26 were for replacement of central vascular access and 28 were for difficulties with peripheral access. Many of these transfers were for outpatient or short-stay procedures; only 11 were for such medical indications as sepsis.

Conclusions

The experience of the first year suggests the following conclusions: End-stage renal failure patients have excellent rehabilitation potential and can be expected to complete appropriate rehabilitation programs. In addition, some of those categorized initially as chronic may improve to less-severe disability categories or even to discharge. Some patients will have a quality of life that is so poor that aggressive therapy is unwarranted. Usually these patients do not survive and some chose to discontinue aggressive care in this supportive environment. We provide compassionate palliative care to this patient group in this setting without undue and unnecessary prolongation of life. Such care calls for increased social work and rehabilitation support to facilitate rehab, maximize discharge potential and to support patients, and the families of those receiving palliative care.

Evidence of malnutrition, such as low serum albumin and phosphorus, was associated with poor level of function and death. We encountered frequent difficulties with vascular access but rarely did this result in failure of hemodialysis.

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CHAPTER 25

Peritoneal dialysis in the nursing-home patient

CHARLES R. SCHLEIFER

As nephrologists, we find ourselves in the forefront of geriatric care. In 1984, 25% of the ESRD population of the U.S. was 65 and older. By 1990, approximately 40% of the ESRD patients were 65 and older, and by the year 2000 it is projected that 60% will be in the geriatric group. Frequently, in our hospital consultations, we see the very old patients and are called upon to make life-and-death decisions after other treatment modalities have been exhausted. It, therefore, behooves us to be aware of the problems of the aged, including their long-term care.

An overview of geriatrics and ESRD

The U.S. population is aging and organized medicine has begun to recognize the need for training in geriatrics within the realm of internal medicine [1]. Figure 1 shows the projected U.S. population from 1980 to 2030. Almost 13% of the population in 1990 (27 million) are 65 and older. Projections for future population growth reveal that by the year 2030, there will be 64 million people age 65 and older, more than double the present number and represents 21% of the projected U.S. population. By the year 2030, there will be 10 million people in the US age 85 and older.

In 1989 the incidence of ESRD in the group 65 and older averaged 600 per million population [2]. If we assume the same incidence (probably an underestimate), there will be approximately 22,000 new ESRD patients 65 and older in the year 2000, and approximately 40,000 new ESRD patients in the year 2030.

The dialysis population has grown approximately 10% per year from 1985 to 1990 [2]. At this rate, this population will grow from approximately 130,000 in 1990 to over 300,000 by the year 2000. If the projections concerning the aging ESRD population are accurate, 60% of the dialysis population (180,000 patients) will be 65 or older by the end of this century.

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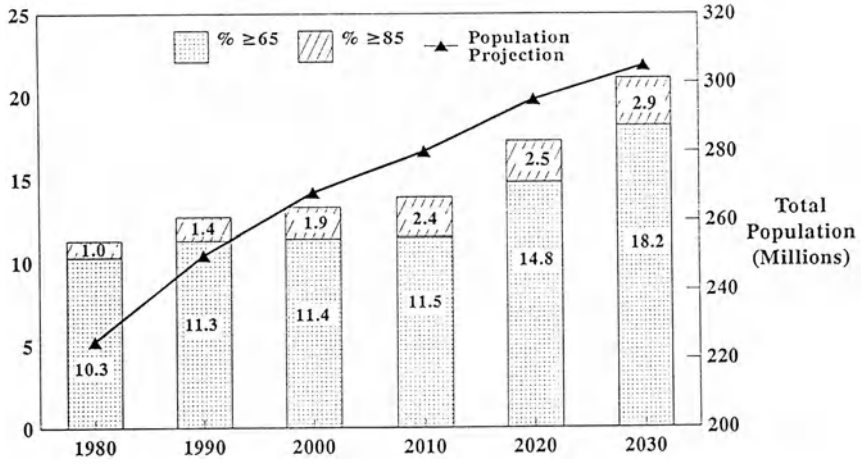

Fig. 1.

Table I. Treatment modality in geriatric patients (1989)*

	Total number	% of total
In-center hemodialysis	38,000	82.0
Home hemodialysis	650	1.4
CAPD/CCPD	4100	9.2
Other, peritoneal	2200	4.8
Unknown	–	2.6

* USRDS 1991 Annual Data Report – based on HCFA Treatment Modality, ≥ 65 age group, 1989.

Treatment of ESRD in the geriatric patient

Let us now review the treatment of ESRD in the geriatric patient. For this discussion I will define 'geriatric' as age 65 and above. This is, of course, an arbitrary chronologic definition and should not imply a physiologic condition. Of the 116,000 dialysis patients on the HCFA rolls in 1989, 46,000 were in the geriatric group. The breakdown of treatment modality is shown in Table I.

The overwhelming majority of elderly patients are being treated by in-center hemodialysis, which is surprising in view of the results of a survey of clinical practices in geriatric patients by Gentile *et al.* [3]. In this select group of 11 dialysis centers, 35% of their patients received peritoneal dialysis, three times the national figure. Control of cardiovascular instability was cited as one of the major benefits of peritoneal dialysis in the elderly, yet nationwide only about 10% of the elderly are receiving peritoneal dialysis [2]. There

seems to be a discrepancy between mode of treatment chosen and medical opinions about what therapy is better for the elderly.

The success of dialysis therapy in the geriatric patient is no longer in question. Studies in hemodialysis patients [4–6] well into their 80s have shown that age alone was not a major risk factor for death. The presence of atherosclerosis, dialysis 'in-center', hypertension and low BUN were found to be associated with poor survival. In these patients, measurements of life satisfaction and enjoyment in coming to the dialysis center were above average. Survival in some of these populations was as high as 50% at four years. However, a high drop-out rate was found in a group of patients whose mean age was 75 years [7]. The percent death due to withdrawal of dialysis was as high as 43% between 1981–1985. Residence in a nursing home was the major risk factor for termination of dialysis. According to the USRD [2] only 8.5% of all ESRD deaths from 1987–1989 was due to withdrawal from dialysis. In the geriatric group, withdrawal of dialysis accounted for 11.4% of deaths.

The elderly patient on CAPD/CCPD

An increasing number of elderly are being treated with peritoneal dialysis. The National CAPD Registry has data on 26,554 patients from 1981 to 1988 [8]. Patients age 60 and older comprised 33% of the CAPD patients and almost 30% of the CCPD patients. Whites had a 50% higher representation on both modalities compared to blacks. Relative risk of death was higher in the group 60 years and over. CAPD patients over the age of 70 had 27% dropout rate. A report from the United Kingdom in 1984 found survival on CAPD of 72% and 61% at one and two years. These authors concluded that there was "... no medical grounds for denying CAPD to most elderly patients with renal failure ..." [9]. Kaye also reported a favorable outcome with a group of elderly CAPD patients [10]. CAPD was the major modality in a group of 62 patients with a mean age of 67.8 years [11]. Almost half the patients lived in total independence. The long-term outlook of these dialysis patients was better than that of age-matched patients with certain cancers or cirrhosis of the liver.

CAPD, the preferred treatment for the elderly [12], has changed the practice of nephrology in the United Kingdom. There were no differences in actuarial survival for elderly patients on CAPD and hemodialysis [13, 14]. A Canadian report on CAPD in the elderly demonstrates no difference in patient survival up to 5 years between hemodialysis and CAPD [15]. In 1987 the Italian Multicenter Study on CAPD showed that 41.5% of new CAPD patients were age 65 or older. The four-year survival of 30.8% in the 65 or older group and the 30-month survival of 44.2% for the 75 or older group justified open acceptance of the elderly for CAPD [16].

Diaz-Buxo *et al.* [17] studied 527 patients undergoing hemodialysis and CCPD between 1986–1988 and found that their elderly CCPD patients exhib-

ited a higher level of physical activity, had a lower rate of hospitalization, required less medical 'consults' and were on less medication than the in-center hemodialysis patients. CCPD has become their preferred modality for nursing-home patients.

Long-term care and the nursing home industry

Historically long-term care was the responsibility of the family, fraternal organizations or religious groups, but now it has become an endeavor of government and private business. Nursing homes are the most costly part of long-term care, which includes home care, adult day care, public housing and boarding homes, etc. [18]. There are over 19,000 nursing homes in the U.S. with between 1.5 to 2.0 million beds [19]. Approximately 5% of persons 65 and older reside in nursing homes; of the 85 and older group, 20% reside in nursing homes. The typical nursing home patient is an 86-year-old woman who was admitted after a hip fracture and was unable to carry out the usual activities of daily living (ADL). The average length of stay is 2.9 years. Of those persons 65 and older who entered a nursing home in 1990, 21% remained in the nursing home for more than five years. By the year 2000, there is projected to be 2.5 million nursing home residents, and by the year 2030, the projection is for 4.5 million residents. The nursing home industry is in a period of growth and expansion.

What factors determine survival in a nursing home? In an early study of nursing-home residents in New York City, Goldfarb describe four characteristics associated with the highest one-year mortality [20]. The coexistence of two or more of the following factors: organic brain syndrome, failure on mental status examination, dependency of activities of daily living, and incontinence could predict death within one year with 95% accuracy. Lichtenstein *et al.* studied Tennessee Medicaid Data [21]. The 12-month death rate was 30 to 50%. The most important factor for survival was the ability of the nursing-home resident to be independent in bathing and dressing. Ambulation and bladder and bowel control were less important. Of interest for the ESRD patients was the study of Husebye and Kjellstrand [7], which showed that residing in a nursing home was the major risk factor for termination of dialysis. A more recent study from Greece followed a group of independent, continent, non-diabetic patients over an 11-year period from 1978 to 1988 [22]. Death risk was determined using the Cox proportional hazard model. Results show that even mildly impaired mobility in previously independent people was the highest predictor of death. Smoking, EKG abnormalities and male gender were also strong predictors. Therefore, the major thread that runs through all these studies is that patient independence, ambulation and the ability to carry out ADLs are associated with better survival in a nursing home.

Peritoneal dialysis and nursing homes

Few published studies have described the acceptance of dialysis patients by nursing homes. There is even less published data on CAPD/CCPD in nursing homes. The American Association of Homes for the Aged was unable to supply data for this report. The State of Pennsylvania Department of Health was unable to provide data on dialysis and nursing homes in their recent long-term care questionnaire of nursing homes.

Anderson *et al.* [23] described CAPD in a nursing home that was a teaching institution owned by John's Hopkins University Hospital. Compared to the usual prevalence rate of 6% among elderly in nursing homes, their rate of ESRD patients was 2%. They followed 44 nursing-home residents between 1986–1989. Peritonitis rates were 1.3 episode/patient/year. Hospital days averaged 18.5 days/patient/year. Their one-year survival, however, was only 29% from entry into the facility. Patients with the poorest outcome had ADL scores below 8 and no prior outpatient dialysis history. Of the 10 patients discharged from the facility, four had been admitted for rehabilitation services only. The ADL scores of those patients discharged were significantly higher than those remaining.

Anderson *et al.* [24] studied nursing-home admissions of patients in ESRD Network #5 (Maryland, Washington, D.C., Virginia and West Virginia). The patients were older (66 y vs 57.2 yr.), disproportionately female, white and diabetic compared to the overall prevalence in Network #5. The mean admission ADL score was 8.1 ± 5.2. Patients were treated by hemodialysis in 85% and PD in 15% of cases. Survival was not good. Mean survival was 125 ± 114 days. In a Cox analysis, mortality was significantly worse for patients > 75 years with ADL scores ≤ 8, and for those patients treated on peritoneal dialysis rather than hemodialysis.

In a 1989 study of nursing homes' acceptance of dialysis in the five-county area around Philadelphia, PA [25], I found that almost one-half (48%) of the respondents accepted ESRD patients. Of those facilities that accepted dialysis patients, 81% of the patients were on hemodialysis and 19% were on CAPD. The two major reasons cited for rejecting ESRD patients were lack of trained nurses and transportation problems.

In a 1989 nationwide study of 80 dialysis units [25], I found that 93% of the 238 responders had placed hemodialysis and/or peritoneal dialysis patients in nursing homes. Hemodialysis was the modality in 91% and 9% were treated by peritoneal dialysis. Over 80% of the peritoneal dialysis performed in nursing homes was CAPD, automated peritoneal dialysis (APD) accounted for 11%, and 9% of the patients had been on both modalities.

Recently we surveyed the social workers in the 102 dialysis facilities in ESRD Network #4 (Pennsylvania, Delaware). Of the 73 responders, 10 were deleted because of lack of nursing-home acceptance. Therefore, 63 units placed 845 patients over a 5-year period from 1985 to 1990. In Network #4, 291 different nursing homes accepted ESRD patients.

Table II. Network #4 Dialysis Unit Survey. Reasons nursing homes do not accept ESRD patients

Lack of trained nurses	44%
Financial concerns	40%
Transportation problems	33%
Administrative objection	23%
Lack of physician coverage	15%
Fear of infection	3%

The survey showed that 93% of the nursing-home patients were on hemodialysis and 7% were on peritoneal dialysis. Of those on peritoneal dialysis, 77% were on CAPD and 23% were on APD (both methods were used in about 5% of patients at some time). The nursing home staff did PD procedures in about 50% of cases; by the patient in 20%; by the family in 10%; and by the dialysis unit staff in 15%. In one response, a home dialysis company contracted to do cycler dialysis. In this survey the longest nursing home survival was 44 ± 33 months, compared to the shortest survival of 9 ± 29 months. There was no difference in the average age of the long-time and short-time survivors, (74 ± 11 years *versus* 74 ± 8 years respectively). Although we never ascertained how often a nursing home turned down the social worker, we found that 22% of the time, placement was never refused. However, Table II shows the reasons cited for refusal in the survey.

Compared to our previous survey [25] transportation problems are less important probably because this deals with a smaller geographic area. Financial concerns are more common, which may reflect the recent economic climate. Difficulties with nursing in PD was not as common in the Network 4 survey, possibly because of better training and teaching of peritoneal dialysis to nurses and nursing students.

The future of nursing home dialysis

At the current acceptance rate of U.S. geriatric patients for dialysis, by the year 2000, 180,000 patients age 65 and above will be on this treatment. If only 5% of these patients lived in a nursing home, this would be approximately 9000 people. If our current trends continue, 90% of this group will be treated by hemodialysis and 10% by peritoneal dialysis. Although CAPD will predominate, cycler use will increase as it has in the general ESRD population. If funding for transportation continues to be restricted, more nursing home patients will be treated by PD. As the nursing home-industry continues to grow, there will be more competition for patients and more nursing homes will open their doors to the ESRD patients. Hospitals will be under greater pressure to discharge patients earlier. Changes in nursing-home reimbursement will pay more for the sicker patient. Medicare will

have to extend its coverage for peritoneal dialysis as an admission criterion. Hospitals will open their own nursing homes on campus (bed-shifting) to accommodate the increased number of elderly.

Conclusion

The United States is an aging country. We spend one-third of our health-care dollars on the aged. In an editorial in the *New England Journal of Medicine* [26], Lonergan and Krevans reviewed the findings of the Institute for Medicine of the National Academy of Science. Research is needed on the degenerative disease in the aging. Clinical research is needed on disability and rehabilitation. We need social and behavioral studies and studies of delivery of health services and biomedical ethics.

As physicians, we must be advocates for our patients. As nephrologists, we must not abandon our responsibility for long-term care after we have treated the acutely uremic patient. We must choose modalities that atre appropriate, not expedient or financially rewarding. It has been shown that dialysis succeeds in the elderly. As this century ends, we must become geriatric nephrologists. As it was said a long time ago: "Honor your father and your mother so that *your* days may be long upon the land . . ."

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CHAPTER 26

Aluminum intoxication in the elderly dialysis patient

ELLEN D. BURGESS

Aluminum toxicity is manifested by neurological impairment, bone disease and anemia. Neurological involvement includes speech disturbances, myoclonus, personality changes, loss of muscular and motor co-ordination, convulsions and eventual coma [1]. The bone disease is characterized by bone pain, spontaneous fractures, hypercalcemia, resistance to vitamin D therapy. Recently an adynamic or aplastic form of bone disease has been attributed to aluminum toxicity [2]. The anemia, which may be an early feature, is a reversible, non-iron-deficient, microcytic hypochromic form [3]. Initially, we thought the most important source of aluminum was from contamination of the dialysate. Since that cause has been addressed by reverse osmosis and deionization of the water used in dialysis, medication has become the most important source of aluminum for the patient with chronic renal failure. Treatment is based upon limitation of exposure to aluminum and chelation with deferoxamine [4, 5].

Several toxicokinetic factors of aluminum may be altered in chronic renal failure and may increase the risk of aluminum toxicity [6, 7]. We absorb only a small proportion of ingested aluminum (2–7%); most of it is retained in the gut lining, and is not absorbed systemically. There are two methods of absorption – an active carrier-mediated process and a passive absorption. The solubility of aluminum may be augmented by coadministration of weak acids, most importantly, citric acid and ascorbic acid [8]. Enhanced solubility permits increased passive absorption of aluminum.

Ingestion of aluminum-containing phosphate binders with orange juice or citrate will increase absorption significantly [9]. The citrate may be given in medications such as effervescent tablets or Shohl's solution. Animal and human studies suggest that gastrointestinal absorption of aluminum is increased in uremia [10, 11], which may be related to secondary hyperparathyroidism. The protein binding of aluminum to albumin and transferrin may be decreased in uremia, leaving an increased free or unbound fraction to equilibrate with tissue [7]. Although aluminum is present in bile [12], the major route of elimination is renal excretion, which obviously is decreased

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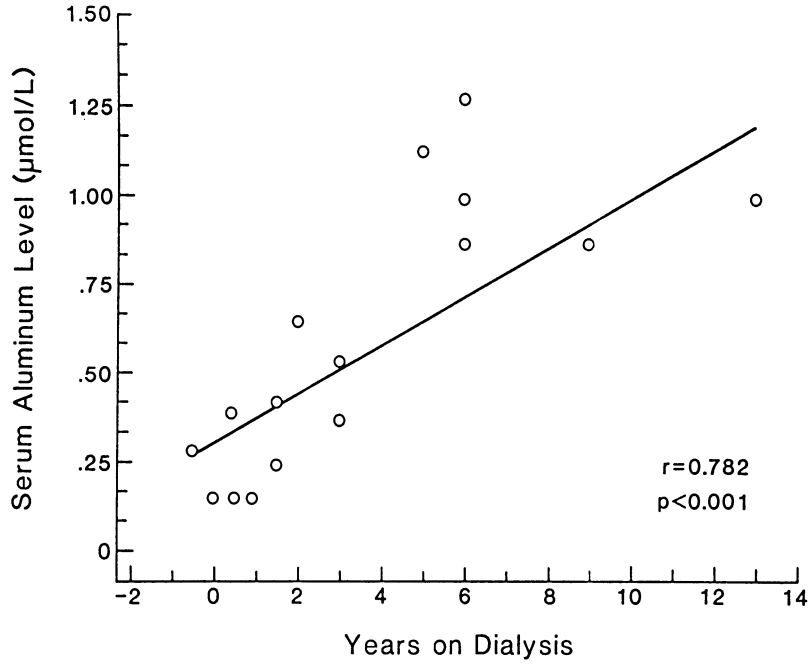

Fig. 1. The serum aluminum levels are related directly to the duration of dialysis ($n = 16$, 1 pre-dialysis, 7 CAPD, 8 hemodialysis patients) $r = 0.782$, $p < 0.001$).

in patients with chronic renal failure. Therefore several factors increase the risk of aluminum in patients with chronic renal failure.

Patients with low bone turnover appear to be at increased risk of aluminum bone disease [2]. The rate of aluminum accumulation on bone surfaces is increased in those with insulin-dependent diabetes on hemodialysis, which may reflect low bone turnover rates commonly seen in these patients [13]. Accumulation of bone aluminum and symptoms of bone pain and fractures begin as early as two years after starting dialysis.

The cumulative dose of aluminum to which a patient is exposed is an important risk factor for the development of aluminum bone disease. In a small group of elderly dialysis patients (mean age 68.5 ± 6.1 years of age) on dialysis for a mean of 3.6 ± 3.7 years (range −0.5 to 13 years), serum aluminum concentrations were related directly to the length of time on dialysis ($r = 0.782$, $p < 0.001$) (Fig. 1). Not all patients had received aluminum-containing phosphate binders (four received no binders or calcium supplements, seven received Riopan – 1 or 2 tablets three times daily with meals, three received Oscal 500 mg 1 or 2 tablets three times daily at meals, and five received Tums 1–3 tablets three times daily at meals).

Aluminum accumulation and toxicity has been reported in both predialysis and dialysis patients. Medications, chiefly the aluminum-containing phosphate binders, are the major source in these patients [14, 15]. However,

many medications may contain aluminum as a buffer – buffered acetylsalicylic acid or as a salt – sucralfate. Although many have recognized the risk of aluminum hydroxide as a phosphate binder, sucralfate has been proposed as an alternative binder on the assumption that aluminum absorption is minimal. However, aluminum absorption from sucralfate is the same as from conventional aluminum-containing phosphate binders [16, 17]. Several workers have reported aluminum toxicity from sucralfate [18, 19].

An illustrative case [20] is that of a 67-year-old woman who developed renal failure and began dialysis in 1985. From November 1985 to March 1986 she was given aluminum hydroxide 15 ml TID as a phosphate binder. Magaldrate was substituted in April 1986. In September 1986, during investigation for epigastric pain, she was found to have significant esophagitis and a duodenal ulcer and the gastroenterologist placed her on sucralfate 1 g QID in addition to the magaldrate. On a return visit to the nephrologist's office in March 1987, the sucralfate was stopped. At that time she complained of myalgias, bone pain in her shoulders and back and was noted to have postural hypotension (120/70 to 106/50) with no compensatory increase in heart rate. Before sucralfate, her hemoglobin had been 104 g/l and now was 88 g/l despite resolution of the gastrointestinal symptoms.

Serum A1 levels done by the flameless atomic absorption technique before sucralfate therapy had been 1556 nmol/L (Sept 29), rising to 1955 nmol/l and 2919 nmol/l 14 and 24 days after therapy respectively. The serum A1 level was 4434 nmol/l in Feb 1987, and deferoxamine therapy was given from March 1987 to July 1987. This lowered the serum A1 levels to 3355 nmol/l in April and 1916 nmol/l in July 1987 (Fig. 2).

She continued to have episodes of confusion and weakness particularly after dialysis, and was institutionalized permanently.

To assess the absorption and excretion of aluminum, we studied 13 patients with normal and abnormal renal function [21, 22]. All had two baseline determinations of serum and urine aluminum. Thereafter, they received sucralfate 1 g QID for 21 days. Serum and urine collected on Days 2, (3), 8, 15, 22, (23, 24), 29 and 36 timed from the beginning of the drug administration. (On the days indicated in parentheses only serum was obtained).

Aluminum analyses are sensitive to external contamination. Thus, powder-free, polyvinyl gloves were worn throughout the collection and analytical procedures. Blood samples were collected in 7 ml TMF Vacutainer tubes (Becton Dickinson Dark Blue No. 6526). Samples were assayed by graphite-furnace, atomic-absorption spectrophotometry. Serum and urine creatinine concentrations were measured using standard methods.

Renal clearance (ml/s) was calculated using the formula:

$$U*V/P$$

where U = urinary concentration of substance; P = plasma concentration of substance; V = flow rate of urine.

Fractional excretion of aluminum was calculated as:

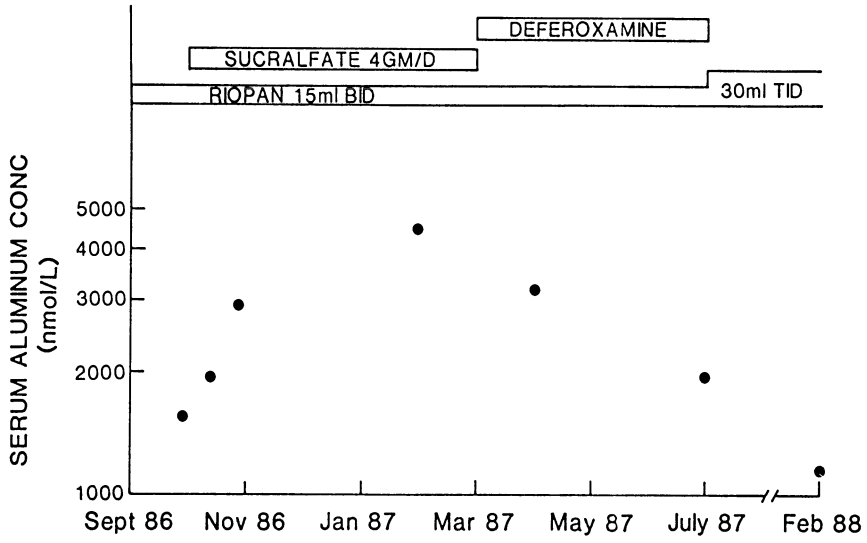

Fig. 2. Time course of a hemodialysis patient, who developed aluminum toxicity while on sulcralfate and antacids.

clearance of aluminum/clearance of creatinine.

Pharmacokinetic parameters were determined using model-independent methods. Area-under-the-curve (AUC) was calculated according to the trapezoidal rule. Half-life was calculated from a semi-logarithmic plot of the beta-phase, serum-concentration, time plot.

Repeated measures within the group were compared using one-way analysis of variance. Measures at two time points only were compared using Student's *t*-test for unequal variance. Measures between two groups were composed using unpaired Student's *t*-test. Linear correlation was done using the least-squares method. All calculations were done using Medical Research-Time Oriented Database (MR–TOD), Retriever Systems, Seattle, Wash.

In this study the six subjects with chronic renal insufficiency (CRF) (3M: 3F) had creatinine clearances ranging from 0.2 to 0.9 ml/s (mean ± SD 0.40 ± 0.25 ml/s or 24 ± 15 ml/min). Seven subjects had normal renal function (creatinine clearance 2.52 ± 0.46 ml/s, or 151 ml/min).

Serum-aluminum levels at baseline did not differ between groups (CRF 0.11 ± 0.12 vs normals 0.12 ± 0.12 μmol/l) but the serum aluminum level at the end of the steady state (Day 22) was higher in CRF (0.83 ± 0.48 μmol/l) than in normals (0.24 ± 0.17 μmol/l) ($p = 0.025$). In the CRF, the serum levels remained above normal (<0.37 μmol/l) until after Day 24.

Urinary content of aluminum did not differ between groups at baseline (CRF 0.62 ± 0.26 vs Normal 0.42 ± 0.22 μmol/D) or at the end of steady state (5.11 ± 2.57 vs 6.81 ± 3.54 μmol/D).

Renal clearance of aluminum calculated on Day 22 was significantly lower

in CRF than in normals (0.09 ± 0.06 vs $0.30 \equiv 0.08$ ml/s)($p < 0.001$). There was a direct correlation between creatinine clearance and renal aluminum clearance (0.829, $p = 0.002$, $n = 11$). The fractional excretion of aluminum, calculated on Day 22, tended to be higher in CRF than in normal (23.12 ± 11.60 vs $11.87 \pm 4.22\%$, $p = 0.062$), suggesting an augmented renal excretion in CRF despite the reduced creatinine clearance.

The elimination-rate constant (k_{el}) could not be calculated in two CRF subjects: in one, the serum aluminum levels fell to undetectable levels by Day 23, and in another there was no decline in serum aluminum levels after Day 24. The elimination half-life was 13.1 ± 3.1 days in the four remaining patients. The k_{el} could not be calculated in normal subjects because serum aluminum concentrations fell promptly to undetectable levels.

Since coadministration of nonsteroidal, anti-inflammatory drugs (NSAIDs) and sucralfate is not uncommon, we studied absorption of aluminum in patients with and without NSAIDs using the same protocol as described above. In the non-NSAID group, the serum aluminum level increased from 0.09 ± 0.11 to 0.82 ± 0.45 nmol/l ($p = 0.003$), and from 0.15 ± 0.04 to 0.87 ± 0.58 in the NSAID group (baseline compared to Day 22). Fractional excretion (FE) Al (%) was higher during therapy than during recovery, 14.5 ± 5.6 vs 6.7 ± 4.8, suggesting renal tubular secretion in addition to filtration. Based upon measures at steady state (Day 22), there was no difference in renal aluminum clearance, urine aluminum excretion, or fractioal excretion of aluminum across groups. However, there was a significant difference in elimination half-life: no-NSAID 12.0 ± 3.2 vs NSAID 6.4 ± 2.2 days, $p = 0.031$. We have no explanation for this apparent difference in half-life but it may be related to differences in protein binding.

These studies support the assumption that aluminum is absorbed from aluminum-containing medications. In instances of acute loading, the serum level appears to correlate with tissue levels of aluminum, but with chronic exposure, the serum level grossly underestimates the tissue burden [23, 24]. Studies on renal excretion suggest that glomerular filtration of free serum aluminum may not be the only renal route of elimination. Monteagudo *et al.* have suggested a distal renal tubular handling of aluminum [25], and the studies demonstrating a change in fractional excretion of aluminum in chronic renal failure compared with normal renal function [26], and others demonstrating a direct correlation between serum level of aluminum and renal excretion suggest a more complex renal handling of the cation.

Aluminum toxicity is a devasting complication of chronic renal failure. Although initially the predominant source of the aluminum had been water contamination, it is now medications. Aluminum hydroxide usually is not used as a phosphate binder, but other antacids are. Although they may have a low dose of aluminum per tablet, the cumulative dose over time poses a significant risk for aluminum bone disease. Renal failure alters the toxicokinetics of aluminum in several ways, and hence augment aluminum accumulation. Adequate studies have not yet been done to answer several questions

concerning aluminum toxicity in the elderly predialysis and dialysis patients, including the effect of aluminum-containing medication in the ever-increasing predialysis period, and the effect on aging bones of aluminum accumulation and aluminum bone disease.

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CHAPTER 27

Angioaccess for hemodialysis in patients 65 years and older

BRUCE G. SOMMER, ANNE-MARIE MILES, NABIL SUMRANI, ELI A. FRIEDMAN and JOON H. HONG

With acceptance of older patients with end-stage renal disease (ESRD) for maintenance dialysis therapy, vascular access has become a critical link in successful renal replacement. Yet, in all age groups, complications associated with the creation and prolonged use of vascular access have contributed to the increased morbidity and cost of end-stage renal disease therapy [1]. We wondered if certain problems affected only the more elderly population who needed angioaccess for maintenance hemodialysis. Many have thought that the natural aging of the cardiovascular and epidermal systems plays a significant role in the development of complications following vascular access procedures in older uremic patients [2–4]. However, this assumption is not yet supported by the few surgical reviews that concentrate on the mobidity associated with vascular access in older patients [5, 6].

Methods

We reviewed the hospital charts and operative reports at a large urban municipal hospital of all patients undergoing vascular access procedures between January 1, 1987 and December 31, 1991. During this time 468 patients had primary circulatory access for chronic hemodialysis. Of these, 88 were 65 years of age or older and are the basis for this retrospective analysis. The Kings County Hospital Center (KCHC) is a teaching hospital associated with the State University of New York Health Science Center at Brooklyn. Each procedure was performed by a senior surgical resident under a direct supervision of an attending surgeon. We chose the non-dominant arm as the angioaccess site unless an autogenous arteriovenous (AV) fistula could be constructed in the dominant arm or unless the non-dominant arm had been exhausted of angioaccess sites. All bridge-graft fistulas were created primarily in the upper arm using reinforced, expanded polytetrafluoroethylene (PTFE) because previously forearm graft placement in older patients resulted in only short-lived angioaccess. The operation was performed with a regional anesthetic block (1% Lidocaine) and monitored anesthesia care.

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Many of the patients receive chronic dialysis in the hospital center, however, some elect to be dialyzed at satellite centers within the metropolitan area, which are more convenient. The follow-up of four patients after establishment of primary vascular access at KCHC was thought to be incomplete and hence they were excluded.

In general patients admitted to the KCHC for the creation of primary vascular access tend to be economically depressed but have free and immediate access to health care for all complications related to vascular access. All these complications have been included. We considered all patients, who died with a functioning vascular access, to be withdrawn from the study and not to have nonfunctional angioaccess. Each angioaccess was deemed patent until the patient needed a new site for vascular access.

For national reference the Medical Products Division of W.L. Gore and Associates, Inc. has supplied data from their registry of patients, who have had bridge-graft access established with expanded reinforced PTFE grafts. This data is scrupulously maintained with the help of 17 vascular-access surgeons. Where applicable, we performed statistical analysis of group and patient variance using chi-square analysis and the Fisher exact test. Angioaccess patency was calculated by life-table analysis [7].

Results

During the 60 months studied, 468 primary vascular access procedures were performed, 88 (18.8%) in patients 65 years and over (Fig. 1). More primary angioaccess procedures were done in elderly females than elderly males (Table I). Fifteen (17%) of the 88 patients expired during the initial hospitalization from complications unrelated to the vascular access procedure or to maintenance hemodialysis. Of the older patients, 45% had diabetes as a primary cause for their end-stage renal disease. Unlike patients under 65 years of age, no patient in this age group had either AIDS/HIV or drug-related nephropathy as a cause for renal failure (Fig. 2).

Figure 3 shows the location and type of vascular access. Most of these patients (87.5%) had primary vascular access using an expanded PTFE graft in the upper arm in a loop configuration. No PTFE grafts were done in a straight configuration due to the surgeons' preference and need with the loop configuration for only one major incision. A few PTFE grafts (6.8%) were placed in the forearm. We used all of these forearm grafts for dialysis, however, five of them thrombosed within six months and required revision or a new graft in the upper arm to resume dialysis. On the other hand, over two-thirds of the primary upper-arm grafts continued to work for at least nine months. The rate of early failure between the upper arm and forearm PTFE grafts was statistically significant ($p < 0.05$). Graft revisions to restore angioaccess patency included simple thrombectomy when no venous outflow tract obstruction could be identified or, more commonly, a thrombectomy

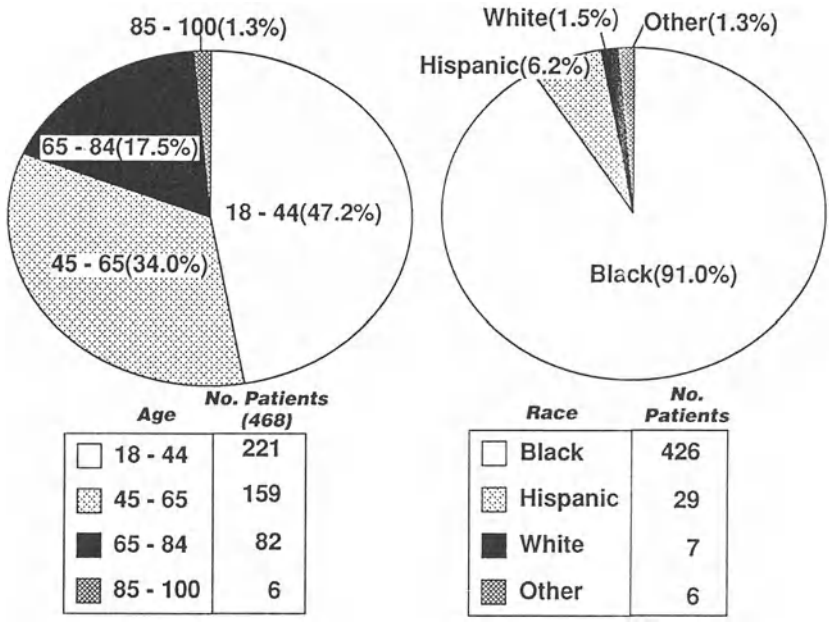

Fig. 1. Age group and race analysis of all patients having primary vascular access created at Kings County Hospital Center between 1987 and 1991. Patients 65 years of age or over constitute nearly one-fifth of the population.

with insertion of an interposition, jump graft, past the point of venous outflow tract obstruction.

Five patients had a peripheral subcutaneous autologous AV fistula between the cephalic vein and the radial artery at the wrist. Four of the AV fistulas were used for chronic maintenance hemodialysis. In all instances, both with

Table I. Demographics of patients 65 years and over having vascular access placement

	Number	Percent
Male	38	43
Female	50	57
Black	82	93
Hispanic	4	5
White	2	2
Total	88	
Expired during initial admission	15	17

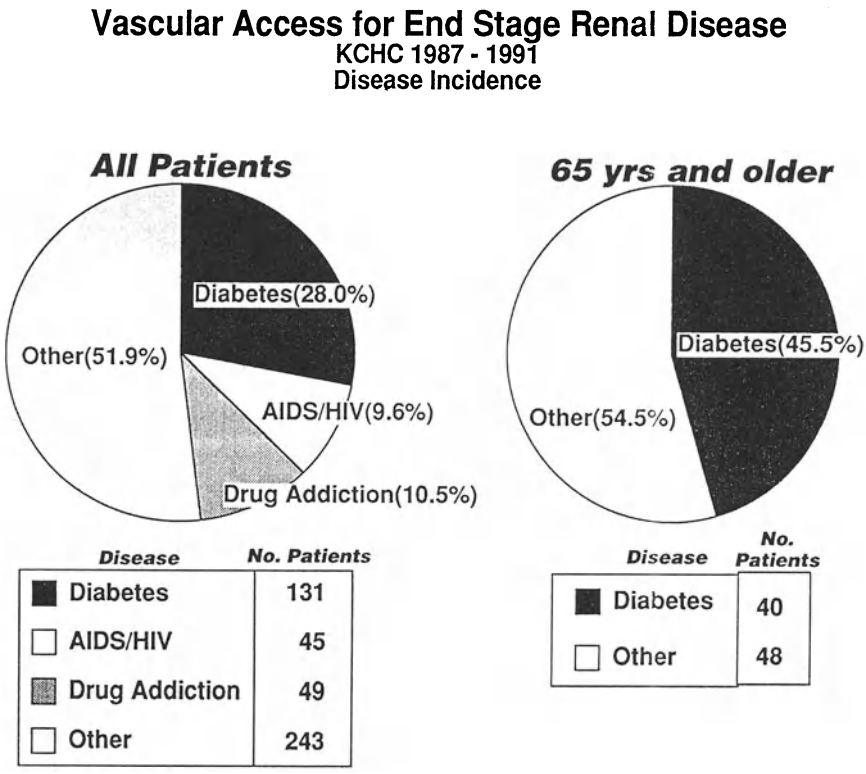

Fig. 2. Contrasting disease incidence for patients requiring vascular access procedures at Kings County Hospital Center. Note that 30.5% of the diabetics were 65 years of age or older.

placement of autologous AV fistulas and loop, PTFE-bridged graft fistulas, the vein distal to the venous anastomosis was ligated to prevent complications associated with venous hypertension.

Four patients developed wound infections at the site of PTFE graft placement. One required removal of the graft and the others were treated with local care and systemic antibiotic therapy. Three patients developed infections due to dialysis-needle puncture wounds and required total or partial removal of the PTFE bridge-graft fistula. Three with upper-arm grafts developed 'steal syndrome' of the lower arm and hand. All these patients were diabetics who smoked cigarettes and had other evidence of peripheral vascular disease. The ischemic symptoms responded to narrowing of the arterial inflow tract or graft ligation in one instance.

Most patients presented at the hospital with fuminant end-stage renal disease requiring immediate hemodialysis. In circumstances where immediate dialysis access was needed, temporary angioaccess was provided with a femoral or internal jugular catheter for at least two weeks before use of the bridge graft or autogenous AV fistula.

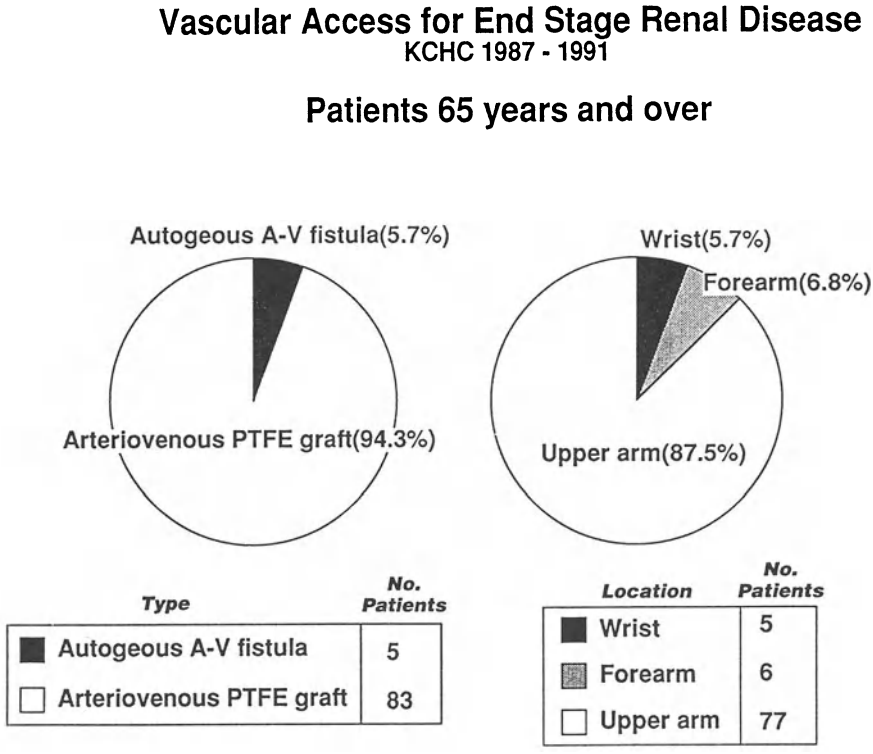

Fig. 3. Location and type of vascular access placed during the initial creation of the angioaccess in 88 patients with end-stage renal disease.

Although only a few autologous AV fistulas were created, complications resulting from the fistula included only one incidence of steal syndrome, which was treated by ligating the distal radial artery.

Discussion

The placement of vascular access in older patients with end-stage renal disease can be technically demanding and must be tailored to the individual patient. The peripheral subcutaneous autologous arteriovenous fistula, developed by Appell and described by Brescia and Cimino in 1966, remains the preferred procedure for hemodialysis due to both excellence in primary patency and to a low incidence of complications [8, 9]. It should not be surprising that it was not possible to create an autogenous AV fistula in most of our patients. This was attributed to the high incidence of peripheral vascular disease in older patients and lack of sufficient arterial inflow but most commonly was due to the destruction of a suitable outflow tract by

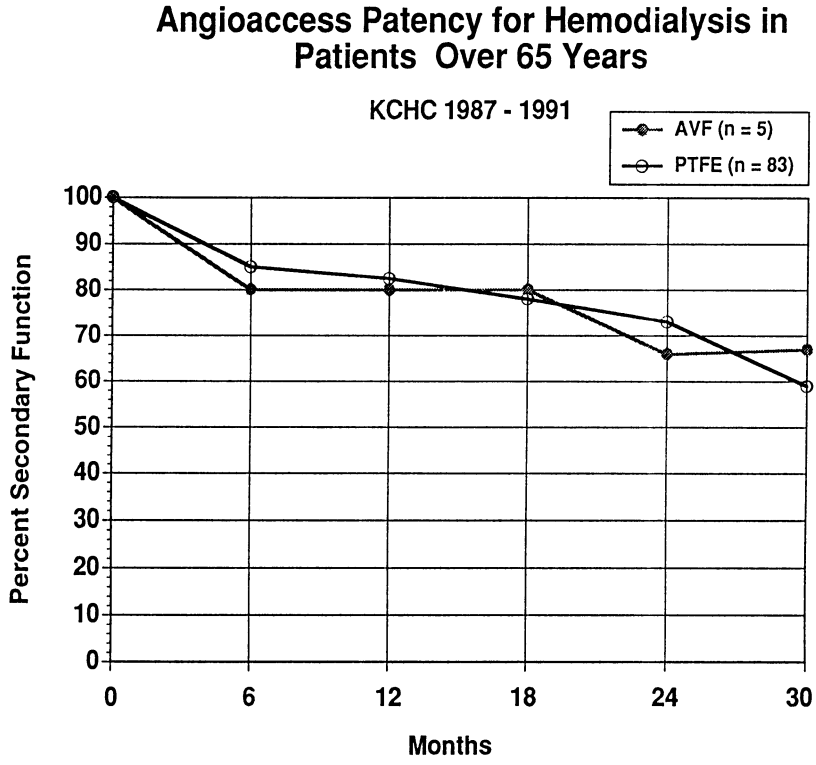

Fig. 4. Cumulative probability of secondary patency for vascular access placed in patients 65 years of age or older.

health-care personnel. Careful planning for the creation of AV access in uremic patients demands the preservation of a suitable superficial vein, specifically the cephalic vein, in the non-dominant arm. Unfortunately this vein is often cannulated at the wrist for intravenous access or at the antecubital fossa by the phlebotomist, making it useless for dialysis access. Each patient with developing end-stage renal disease must be told and shown which vein is inviolable and must be saved for the creation of a peripheral subcutaneous AV fistula.

Even when we could construct an autogenous AV fistula, the cephalic vein in the elderly patients tends to be thinner and requires more time to 'arterialize' before it can be regularly cannulated for scheduled dialysis. Routinely we ligate the vein distal to the vascular access to prevent venous hypertension [10], a complication that in older patients can lead to serious digital ulceration and even digital necrosis. We have not applied this technique to the distal artery in AV-fistula construction because the distal artery may account for up to one-third of the blood volume passing through the fistula [11, 12]. Generally the 'steal syndrome' can be managed easily by

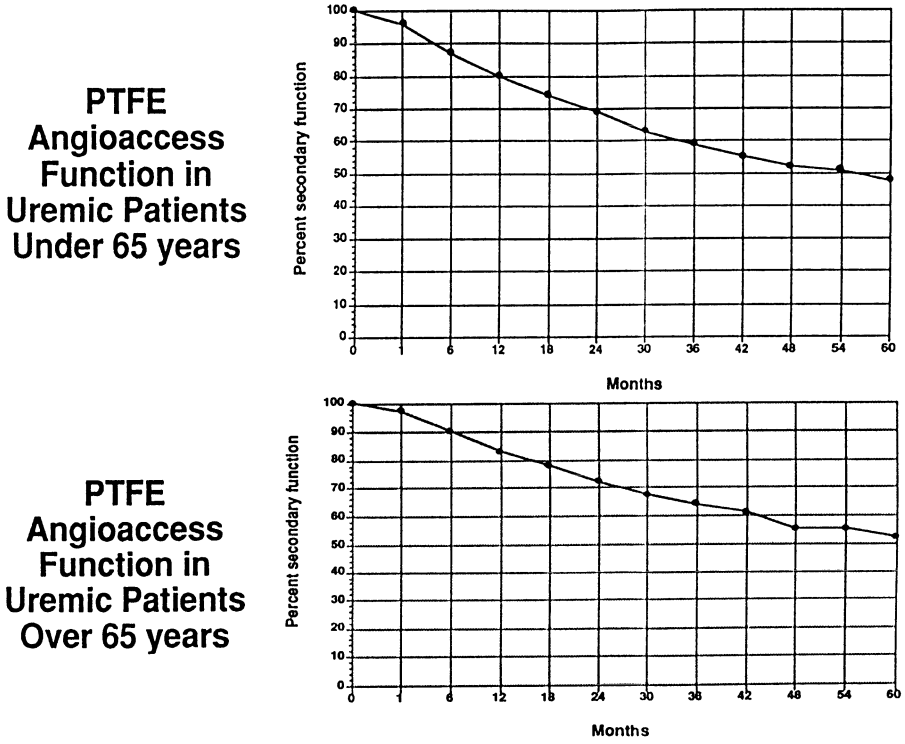

Fig. 5. Cumulative probability of secondary patency of PTFE bridge graft fistula according to age (from W.L. Gore and Associates, Inc. Vascular Registry) 10,019 patients over 65 years and 16,059 under 65 years old have been entered into the data base.

ligation of the artery immediately distal to the fistula or by venous-outflow banding [13].

For patients in whom we cannot create an autologous fistula, the preferred alternative method is a conduit made from reinforced expanded polytetrafluoroethylene (PTFE). The PTFE graft material comes in a variety of lengths and diameters and its ease of handling has increased with the addition of tapered and stepped grafts. The conduit lends itself to thrombectomy and revisions to maintain patency [14]. Infections associated with the PTFE graft generally can be managed without it being entirely removed [15]. However, use of PTFE for bridged graft fistulas demands an aggressive surgical approach to maintain patency by interposition grafting, patch angioplasty and thrombectomy [1, 16]. Most late graft thrombosis is due to a poorly understood mechanism that causes intimal hypertrophy and leads to venous outflow-tract obstruction [17]. The numerous revisions needed to maintain PTFE bridge-graft patency and the other complications unique to the graft material, however, leads to a complication rate 4 to 5 times that seen with autologous AV fistulas [18]. Routinely one should achieve a secondary patency rate with

PTFE grafts of 70% at two years in older patients; this does not differ from their younger counterparts (Figs. 4, 5).

Since we have used routinely the tapered 4.5 mm × 6.5 mm PTFE conduits for bridge-graft fistula construction in the upper arm, we have not seen a significant case of arterial steal syndrome in this elderly population, which did not improve with time. The upper-arm access produced less venous thromboses than grafts placed in the lower arm. The use of more proximal vein sites in older patients does not preserve sites for future access as would be recommended for younger patients; however, in most instances, a high-flow, functional PTFE bridge-graft fistula tended to serve the older patient well until they died from causes unrelated to the access.

Routinely vascular access can be created in elderly patients for successful maintenance hemodialysis, with results comparable to younger patients.

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CHAPTER 28

Outcomes of CAPD versus hemodialysis in the elderly

WENDY E. BLOEMBERGEN, CHRISTOPHER B. NELSON and FRIEDRICH K. PORT

Over the past decade, the incidence of treated end-stage renal disease (ESRD) has increased rapidly in the U.S. [1] and in many other countries [2–6]. This rise has been greatest among the elderly (Figs. 1 and 2), who now have the highest incidence of ESRD. In the U.S., the median age of the overall ESRD population has increased from 55 years in 1980 to 61 years in 1990.

Although renal transplantation is performed in some elderly patients [7], when ESRD develops they (and the nephrologist) usually are faced with a choice between hemodialysis (HD) or peritoneal dialysis (CAPD/CCPD). The best choice of dialytic modality for this age group has not been established probably because few studies have attempted to answer this question. Therefore the choice is usually made on the basis of which modality best fits the patients' social needs, unless there is a clear medical contraindication.

In the U.S. 9% of elderly ESRD patients were being treated with peritoneal dialysis on December 31, 1989 [1] the same percentage as for the U.S. ESRD population of all ages combined (Fig. 3). In contrast in Canada approximately 30–35% of new elderly ESRD patients are started on CAPD/CCPD [2] and in Australia 36% of elderly ESRD patients were on CAPD in 1990 [5]. Despite these differences, most countries use HD more often than CAPD/CCPD. If the current practice reflects the physician's belief regarding outcomes of the various modalities, it seems that many consider that peritoneal dialysis is less efficacious than hemodialysis.

This paper reviews available data on outcomes of CAPD/CCPD as compared to HD in the elderly ESRD population. Important outcomes to consider when comparing these modalities include mortality, causes of death, morbidity, technique survival, and quality of life. Quality-of-life comparisons will not be discussed in this paper.

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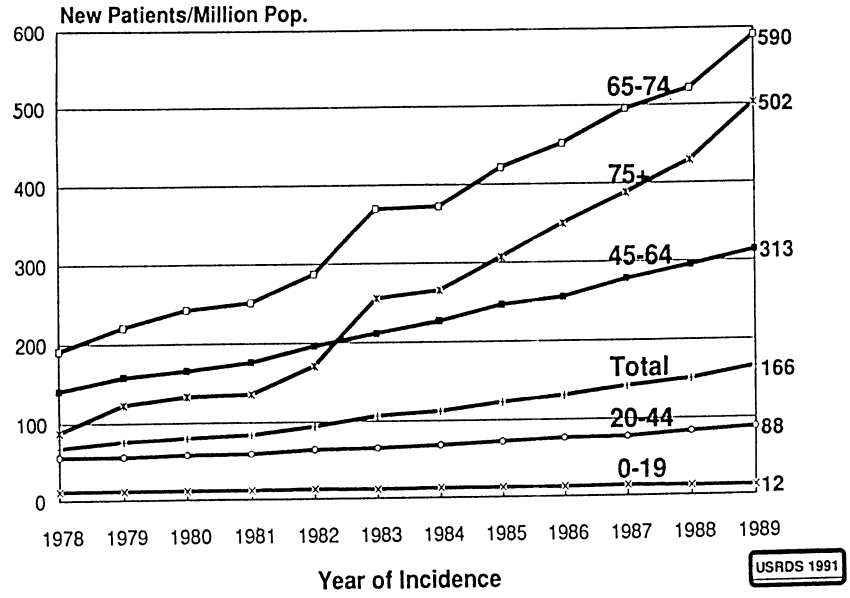

Fig. 1. Incidence of treated U.S. ESRD by age group per million population of the same age, 1978–1989, unadjusted, Medicare patients only. Reproduced from the 1991 USRDS Annual Data Report [1].

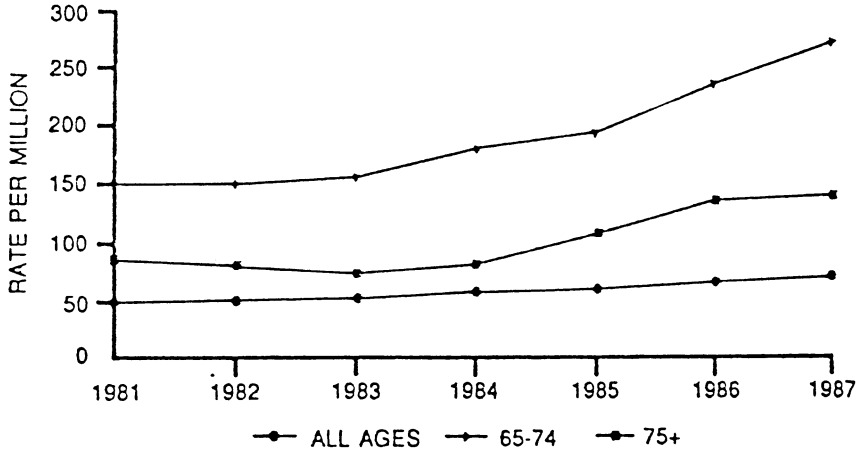

Fig. 2. Incidence of treated Canadian ESRD for all ages, age 65–74 and 75+, per million population of the same age, unadjusted, Canadian Registry, 1981–87. Reproduced from Posen *et al.* [6].

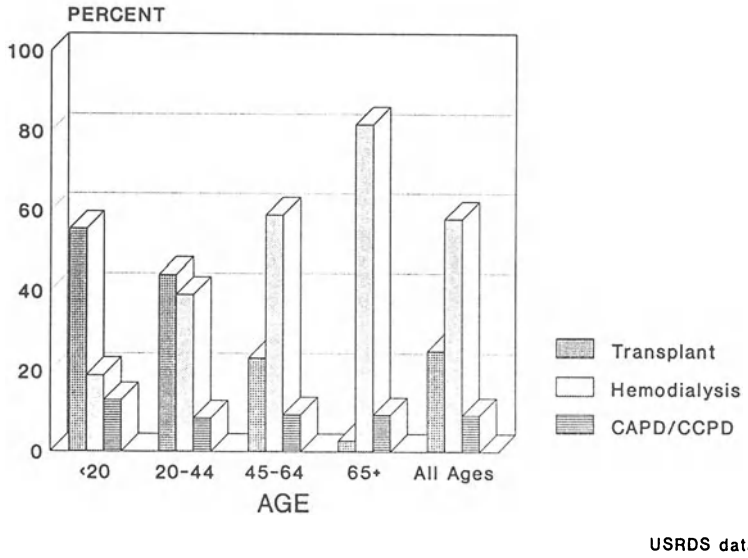

Fig. 3. Percent distribution of treatment modalities by age for prevalent patients on December 31, 1989, Medicare patients only. (USRDS data) [1].

Potential advantages and disadvantages of dialytic modalities

Peritoneal dialysis

Theoretical advantages to CAPD/CCPD in the elderly include: (1) rapid fluid and electrolyte shifts are avoided by continuous therapy; (2) being home-based, it avoids frequent trips to a treatment facility; (3) it appears to maintain better residual renal function [8]; (4) generally patients on peritoneal dialysis have less severe anemia, although this may be less important with the availability of erythropoietin. However, this mode also has disadvantages: (1) peritonitis and catheter-related infections are relatively common complications; (2) malnutrition may develop due to protein and amino-acid loss through the peritoneum [9], and/or peritoneal glucose absorption leading to suppression of appetite [10]; (3) peritoneal clearance may decrease over time [11, 12], however, some studies [10, 13] have not confirmed this. As the elderly population usually is retired or works only part-time, the time needed for CAPD is usually not an issue.

Hemodialysis

HD suits patients who are dependent or who lack social supports that enable self-care. A study has shown that the elderly enjoy going to their dialysis

unit because of the social interaction with personnel and fellow patients [14]. Disadvantages of HD in the elderly include the higher risk of hypotension or disequilibrium due to rapid fluid and electrolyte shifts, the necessity of anticoagulation and its attendant risk of bleeding, vascular-access thrombosis and infection.

Comparing peritoneal dialysis and hemodialysis: some considerations

Due to patient selection, those treated with CAPD/CCPD likely differ from those treated with HD in terms of demographics, comorbid conditions, and social circumstances. These factors may impact on outcome, independent of dialytic modality. Randomization of new patients into CAPD/CCPD or HD would virtually ensure that both groups would be similar with regard to baseline variables but, practically and ethically, it is difficult to perform such a study. As an alternative, one can make statistical adjustments for pretreatment differences in baseline variables using techniques such as the Cox proportional hazards regression model [15].

Sample size considerations are important. Failure to detect a difference between two interventions may be due to inadequate power of the study unless sample-size calculations indicated otherwise. Often studies that aim to detect a small, yet-important difference in mortality need large sample sizes [16].

An analytic consideration unique to CAPD/CCPD *versus* HD comparisons is the issue of how to deal with patients who switch to alternate forms of dialysis, receive a transplant or are lost to follow-up. In general two methods are used: an 'intent to treat' analysis which ignores changes in dialytic therapy and continues follow-up until death or end of study or a 'treatment history' analysis which censors survival times when the patient changes therapy. In both, survival time is censored when a patient receives a transplant.

Mortality

Although a number of comparisons have been made of mortality between HD and CAPD for the ESRD population as a whole, few specific studies have addressed the elderly subgroup. This subgroup is different in a number of ways, for example, there are more comorbid conditions, transplantation is used less frequently and overall survival is shorter. Consequently one may observe different outcomes with these dialysis modalities in the older compared to the younger ESRD population.

Two small studies by Walls *et al.* [17] and Benevent *et al.* [18] compared mortality between CAPD and HD in the elderly. Both obtained data on comorbid conditions which were more common in patients treated with

CAPD. Despite negative selection for CAPD, overall mortality appeared comparable. One cannot draw definitive conclusions from these studies because of the small sample size and lack of statistical adjustment for comorbid conditions.

Maiorca and coworkers [19] compared outcomes of 480 patients on CAPD and 373 patients on HD (all ages) in six Italian centers. Using a Cox proportional-hazards-regression analysis, they adjusted for differences in demographics and comorbid conditions between the two groups. They concluded that, overall, there was no difference in mortality between the two groups, however among older patients mortality was higher for those treated with HD. In this study the proportion of patients treated with CAPD was substantially higher than in Italy as a whole or in the U.S., which raises questions concerning the general application of these results. In addition, the CAPD/CCPD population in the U.S. is significantly younger than those on HD [1], whereas, in Maiorca *et al.* it was six years older on average.

At the Michigan Kidney Registry, Nelson *et al.* [20] compared mortality between HD and CAPD in the elderly ESRD population. This Registry contains demographic and treatment data collected prospectively for over 20 years on all ESRD patients treated or living in the state of Michigan. Identification of treated ESRD patients and data collection is more than 99% complete and 97% accurate [21]. This study included 3431 patients over the age of 60, who began therapy for ESRD between January 1, 1980, and August 31, 1989, and who used either incenter HD or home CAPD on day 120 of ESRD. Using the Cox proportional hazards regression model, the authors compared mortality between CAPD and HD while adjusting for age, race, sex, mode of therapy, and year of ESRD initiation. They performed both 'intent-to-treat' and 'treatment-history' analysis and they found no significant difference in mortality between the two modalities although in the subgroup with diabetic ESRD there appeared to be a trend favoring HD. The relative risk of mortality of CAPD compared to HD was 1.19 (i.e. 19% higher) approaching statistical significance ($p < 0.08$). *The 'intent-to-treat' and 'treatment-history' analyses gave comparable results.*

Held et al. [22] presented results from the USRDS Case Mix Severity Study at the XII Annual Conference on Peritoneal Dialysis. In this study, 759 CAPD/CCPD and 3399 HD patients (all ages) were selected randomly from 291 units in the U.S. Extensive baseline data on comorbid conditions collected by a retrospective chart review was supplemented with follow-up data from the USRDS database. Modality was classified on day 30 of therapy. Both 'intent-to-treat' and 'treatment-history' analyses were performed. For all ages, after controlling for age and diabetes, HD patients were more likely to have had a cerebrovascular accident, an amputation due to peripheral vascular disease (PVD), and be incapable of independent ambulation. In the elderly, however, the only significant difference between the CAPD/CCPD and HD patients was that the latter were more likely to be incapable of independent ambulation (Fig. 4).

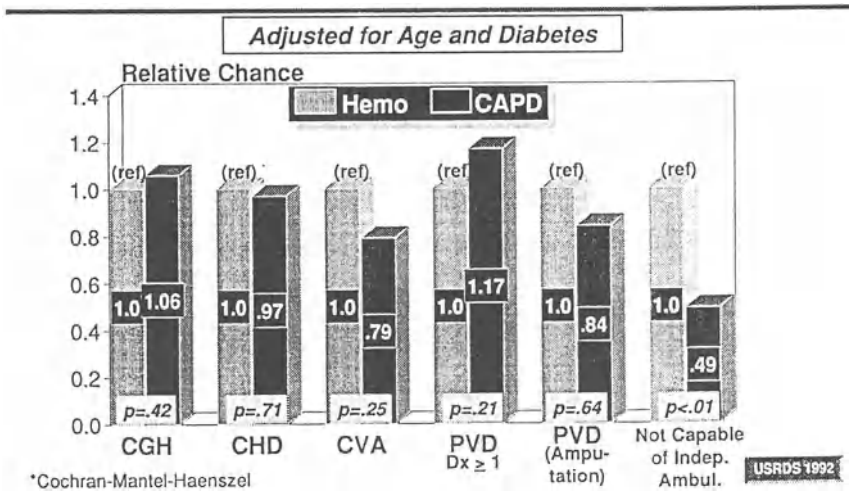

Fig. 4. Relative chance of CAPD for selected conditions by modality, age 65 and over, USRDS Case Mix Study [22]. Selected conditions include congestive heart failure (CHF), coronary artery disease (CAD), cerebrovascular accident (CVA), inability to ambulate independently, peripheral vascular disease (PVD), and its subcategory, amputation due to PVD.

The Cox proportional-hazards regression model was used to compare mortality between CAPD/CCPD and HD after adjusting for comorbid conditions and differences in demographics between the two groups. In all ages, again, Held *et al.* found no difference in mortality between CAPD/CCPD and HD among nondiabetic patients. However, in the CAPD/CCPD group, diabetics had a significantly greater mortality; their relative risk of mortality was 1.25 compared to HD ($p < 0.04$). Thus CAPD/CCPD had a 25% higher relative risk compared to HD. Subsequent analysis provided evidence that the higher mortality risk among diabetic CAPD patients may be accentuated among elderly diabetic CAPD patients.

Causes of death

To compare causes of death between ESRD patients treated with CAPD/CCPD versus HD, we analyzed data obtained from the USRDS 1991 Annual Report which included all patient deaths for 1987–89. The USRDS collects demographic and clinical information on patients who survive at least 90 days on renal replacement therapy and qualify for Medicare (approximately 93% of the total U.S. ESRD population). For each death, the USRDS obtains the primary cause of death from the HCFA Death Notification Form which lists 22 causes; for the purpose of this analysis, these have been collapsed into seven causes. Each death is ascribed to the modality the

Table I. Death rates for causes of death for CAPD/CCPD compared to hemodialysis (HD) in diabetics and nondiabetics, USRDS data [1]

	Relative death risk (HD = 1.00)	
Cause of death	Diabetic	Nondiabetic
Myocardial infarction	1.69**	1.32**
Other cardiac	1.56**	1.11
Cerebrovascular	1.58*	1.27
Infection	1.58**	1.42**
Malignancy	0.89	0.76
Withdrawal	1.33	1.12
Other/unknown	1.53**	1.16**

*$p < 0.01$.
**$p < 0.001$.

patient was using on January 1 of the year in which the patient died. Because multiple comparisons are being made, a conservative approach would consider significant only those relative risks associated with a p value of < 0.01.

The death rates for each cause of death and the per cent distribution of causes of death were compared between elderly patients (> 65 years) treated with CAPD/CCPD and HD (Tables I and II). Because these results are not adjusted for demographics and comorbid conditions, differences found may be due either to selection factors or to some factor associated with the dialysis itself. Therefore, this analysis should be seen only as descriptive. For both diabetics and nondiabetics, the risk of dying of all causes except malignancy was greater for CAPD/CCPD that for HD (RR > 1), although not all causes were significant. This reflects overall higher mortality with CAPD/CCPD. Comparing the percentage distributions of cause of death among patients who died reveals that only nondiabetics in the CAPD group have a higher percentage of deaths due to infection compared to the HD group. In part fatal peritonitis may be responsible, if this is a true finding. In addition, in

Table II. Comparison of percentage distribution of causes of death between CAPD/CCPD versus hemodialysis (HD) in diabetics and nondiabetics, USRDS data [1]

	Percent of deaths (odds ratio)	
Cause of death	Diabetic	Nondiabetic
Myocardial infarction	1.11	1.13
Other cardiac	1.02	0.91
Cerebrovascular	1.02	1.07
Infection	1.02	1.23*
Malignancy	0.58	0.64*
Withdrawal	0.85	0.94
Other/unknown	0.99	1.01

*$p < 0.01$.

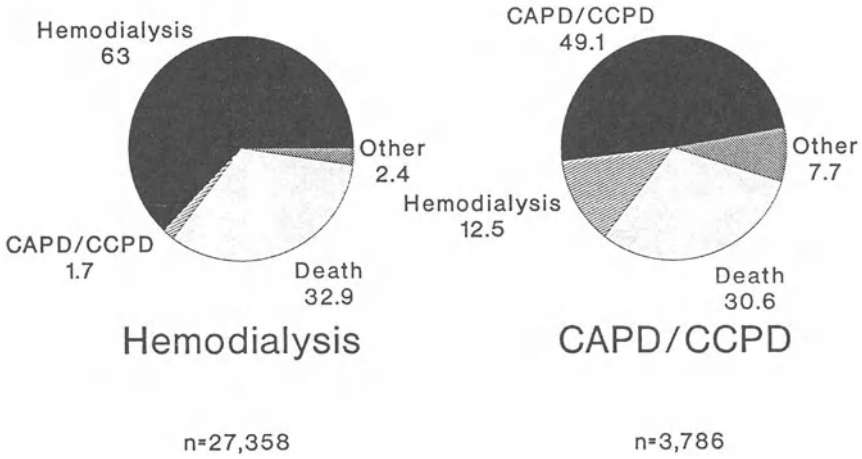

Fig. 5. Patterns of first modality switch in elderly patients followed for one year. Starting modality is classified as hemodialysis or CAPD on day 90, 1986–1988. USRDS data.

the hemodialysis group, nondiabetics have a higher percentage of deaths due to malignancy which may be related to longer exposure to dialysis and to dialysis-related agents [23].

Morbidity

Few studies have compared measures of morbidity between CAPD and HD in the elderly ESRD population. O'Brien *et al.* [24] compared number of hospital days and access-related morbidity in 30 CAPD/CCPD and 31 HD treated elderly. Although comorbid conditions were more common in the CAPD/CCPD patients, there was no difference in number of days hospitalized between the groups, and there was more access-related morbidity in the HD treated group. In a similar study of the elderly in France, Benevent *et al.* compared 39 CAPD and 31 HD patients. Again, there were more comorbid conditions in the CAPD groups, however, the number of days hospitalized was greater in the HD group.

Technique failure

We analyzed data obtained from the USRDS to determine the percentage of elderly switching modalities (Fig. 5). Among elderly ESRD patients (age > 65 years) who started on HD (defined by treatment on day 90 of ESRD, $n = 27{,}358$), 1.7% switched to CAPD/CCPD within the subsequent 12 months. The corresponding number for patients who started on

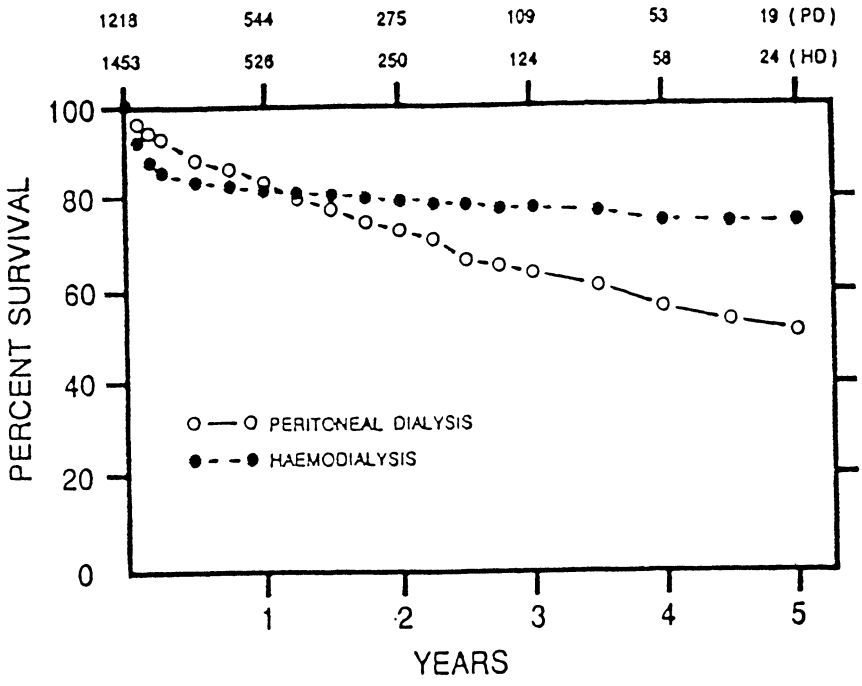

Fig. 6. Technique survival of patients treated with CAPD or hemodialysis, 1981–1987, Canadian Registry. Reproduced from Posen *et al.* [6].

CAPD/CCPD (n = 3786) and switched to HD at one year, was 12.5%. The fraction of HD patients, who remained on HD at one year, was 63% and that of CAPD/CCPD patients remaining on PD was 49%. The remainder of the patients died, were transplanted, or switched to another modality. This analysis does not include modality switches before 90 days of therapy, a time when such switches are frequent [25].

Using data from the Canadian Registry, Posen *et al.* (Fig. 6) [6] compared technique survival from day 1 of therapy and showed that, with HD, there is a rapid decline in technique survival within the first 6 months which then begins to level off; in the CAPD group there is a more gradual, but continuing decline. At approximately one year, where the curves intersect, technique survival was approximately 80%.

Summary

Elderly ESRD patients and their nephrologists usually must choose between HD or CAPD/CCPD for renal replacement. Overall, in terms of outcome, there is little evidence to suggest that one modality clearly is superior for the elderly ESRD population. At least in the long term, technique survival

appears to be higher in HD-treated patients. Studies evaluating morbidity suggest the it may be lower in CAPD-treated patient. Studies of mortality give rise to conflicting conclusions. Two epidemiologic studies in the U.S. suggest that HD may be associated with less mortality in the elderly diabetic. All of the available studies comparing morbidity and mortality are limited by small sample size or the possibility of selection due to variables, which were not measured and thus not controlled for.

We need larger and prospective studies, which will consider and control for differences in selection and confounding variables to confirm the possibility that HD improves outcome in diabetics, and to determine if modality choice truly makes no difference in outcome in nondiabetics.

Acnowledgements

Randall Webb and Marc Turenne of the USRDS Coordinating Center assisted in the analyses presented in Figs. 4 and 5.

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CHAPTER 29

Quality of life for elderly dialysis patients: effects of race and mode of dialysis

NANCY G. KUTNER, BROOKE FIELDING and DONNA BROGAN

In the United States and many other countries, the number of elderly ESRD patients treated by dialysis continues to increase. Many of these receive treatment for a relatively short time before they die. Our own analysis of factors related to survival on dialysis of 1354 black and 965 white patients, who began treatment during 1982–1986 at age 60 or older, showed median survival times of only 2.7 years for black patients and 1.7 years for white patients [1]. Data reported by Neu and Kjellstrand [2] and by Eggers [3] indicate that elderly patients are significantly more likely to withdraw from dialysis than are younger patients, raising questions about the value that elderly persons attribute to life on dialysis. As Marai *et al.* have noted, "with the shorter life expectancy in the elderly, particularly in the group over 65 the 'quality of life' provided by dialysis is particularly relevant..." [4]. We investigated the quality of life of elderly dialysis patients, using responses from a large probability sample of older patients living in the southeastern United States, and will discuss the relation of demographic variables, health status, and dialysis treatment modality to patients' quality of life responses.

Conclusions about older dialysis patients' quality of life vary depending on the particular comparison group that is used. When younger dialysis patients are used, it has been found that older patients are rated as more functionally impaired but older patients themselves report more positive psychological affect and overall satisfaction with life [5]. When the comparison group is older persons who do not have ESRD and are not on chronic dialysis, older persons on dialysis report not only significantly greater functional impairment but also significantly more emotional distress, more negative psychological affect, and lower life satisfaction levels [6]. In addition, we have found an interesting interaction between patients' race and their receipt of dialysis therapy, i.e. older white patients associate dialysis with lowered life quality to a significantly greater degree than do older black patients [6]. Generally these findings are consistent with other data suggesting that blacks 'do better' on dialysis relative to whites [7], and that there are

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unmeasured severity (or frailty) differences between white and black dialysis patients of all ages [3].

Mode of dialysis is an important potential contributor to quality-of-life differences among patients (e.g., Refs. 8–10). In the United States, most dialysis patients, especially older patients, are treated by hemodialysis (HD) in a medical facility. In contrast, in Canada, older patients are frequently placed on peritoneal dialysis (PD), especially continuous ambulatory peritoneal dialysis (CAPD) [11]. All treatments for ESRD have advantages and disadvantages, and medical, psychological, and/or social factors may rule out a specific therapy for a particular patient. However, age *per se* need not be a barrier to any mode of dialysis. Walker *et al.* reported that survival rates of older patients on intermittent peritoneal dialysis (IPD) appear comparable to those on hemodialysis, with 'reasonable physical rehabilitation' [12]. Kaye *et al.* compared patients using CAPD, who were aged 65+, with those using CAPD who were younger than 65, and found no differences in complication rates or reasons for terminating CAPD. These investigators concluded that elderly patients adapted well to CAPD both medically and psychosocially. No difference was seen between older and younger patients' adjustment to the stresses of CAPD except that older patients relied more heavily for support on other family members and on the dialysis training staff [13, 14]. After an analysis of elderly patient outcomes in two large chronic peritoneal dialysis programs, Nissenson *et al.* [15] concluded that, although there was increased mortality among elderly patients, there were small differences between elderly and younger patients with respect to outcomes, such as hospital days and catheter problems. This suggests that chronic peritoneal dialysis is an acceptable form of renal replacement therapy in the elderly. Avram *et al.* found no significant differences in the Karnofsky scores assigned to patients ages 70+, patients ages 60–69, and patients under age 60 treated by chronic HD, and an analysis conducted with a subset of HD patients suggested that increasing age was correlated with better compliance. They concluded that most of their HD patients led active, involved lives, and that "age *per se* is not a contraindication to . . . adaptation on CAPD, hemodialysis, or any other form of life maintenance therapy for the geriatric patient with renal failure . . ." [16].

There has been little investigation of older dialysis patients' quality of life in relation to the mode of dialysis. To our knowledge, no studies have compared the quality of life of older black patients and older white patients in relation to dialysis modality. Our previous work suggests differences in the quality of life reported by older blacks and older whites receiving chronic dialysis treatment in the southern United States [6]. Quality of life is the product of many influences in the individual's personal and social environment. In the analysis reported here, our strategy is to determine whether quality of life is associated with type of dialysis after adjusting for demographic and health-status variables and their interactions.

Methods

Sample

In 1988 we conducted interviews with 349 persons aged 60 or older living in Georgia and receiving chronic dialysis. These individuals were identified in a stratified random sample, drawn from the ESRD Network 20 census, constituting approximately 25% of all patients aged 60 and older living in Georgia. The sample was stratified by race and sex so that blacks and whites, and women and men, would have approximately equal representation. Details of the sampling procedure were reported in Kutner *et al.*, 1991 [6]. The interview focused on self-reported quality of life; interviews also were conducted with a control group of 354 older persons living in Georgia, who were not receiving chronic dialysis.

Most of the patients interviewed (308, 88%) were receiving HD in an outpatient treatment center. Only 3 patients in the sample were on home hemodialysis. Patients treated by chronic PD included 30 on CAPD and 3 on CCPD; in addition, 5 were on in-center PD. For the purposes of this analysis, we consider all patients on HD as one category and all patients on PD as one category. Thus, our total N for HD patients was 311, and our total N for PD patients was 38.

The mean age of interviewed patients was 69 years, with a range of 60 to 88 years. At the time of interview the median total number of months on dialysis was 31.0, with a range of 6 months to 16 years.

Table I compares demographic and health status characteristics of our sample of older patients, who were on HD and PD. In comparison to older patients on HD, older patients on PD were significantly more likely to be white. Their average number of months on their current mode of dialysis and their average total months on dialysis were significantly less than HD patients' months on their current mode and total months on dialysis, respectively.

Measures

Dialysis-related problems and hospitalization

Our interviews included questions about problems that patients might have experienced specific to HD: whether they had any problems with their access getting infected, their access not clotting the way it should, or difficulty in needling the access. We included questions about problems patients might have experienced specific to PD: peritonitis during the past 6 months, experiencing a dizzy feeling when draining out the dialysis fluid, exit-site infections, and/or lower back pain since beginning PD treatment. Both HD and PD

Table I. Sociodemographic and health status characteristics of older dialysis patients interviewed in Georgia, by dialysis treatment modality

	Hemodialysis ($n = 311$)	Peritoneal dialysis ($n = 38$)	p
Sociodemographics			
% Black	59	37	0.01[a]
% Male	50	50	0.96
Age (mean yr)	68.7	69.8	0.28
Education (mean yr)	8.0	8.9	0.18
Health status variables			
% with cardiovascular problems[c]	46	42	0.67
% primary diagnosis of diabetes	26	26	0.96
Months on current modality (median)	30	22.5	0.02[b]
Total months on dialysis (median)	32	23	0.02[b]

[a] p-value is from a chi-square test.
[b] p-value is from a Wilcoxon 2-sample test.
[c] Cardiovascular problems = one or more of the following during past 6 months: heart attack or heart trouble, hardening of the arteries, circulation trouble, and/or stroke.

patients were asked whether they had experienced poor appetite during the past 6 months and the number of nights, if any, that they had been hospitalized during the past 6 months.

Quality of life measures

There is general agreement with Spitzer [17] that quality-of-life measurement should include assessment of physical function, social function, emotional and/or mental status, burden of symptoms, and perceived well-being. These quality-of-life domains may all be incorporated in a single instrument, e.g. Ware's MOS Short-Form Health Survey [18], or the researcher may select separate instruments to measure these different domains. We elected to use the latter strategy because our study was concerned with exploring quality of life in some detail, and because we were interested in the degree of consistency in response patterns across varying quality-of-life measures within a particular domain. The measures that we used are widely accepted in the literature on quality of life among older persons.

We included both generic and disease-related quality-of-life measures in our research. Generic measures were necessary in order to make comparisons with a non-ESRD control group, which was our first research goal [6]. Measures that are more disease-related have the advantage of allowing the investigator to explore quality-of-life outcomes more closely related to the underlying disease or its treatment. These are areas likely to be of particular

clinical interest, for example, what are the levels of fatigue reported by different categories of patients? Again, one comprehensive disease-specific instrument may be used, and disease-specific measures have been developed for many conditions, e.g. cardiovascular disease, cancer, arthritis, and chronic lung disease. Examples in ESRD include the Kidney Disease Questionnaire [19] and the Hemodialysis Quality-of-Life (HQL) questionnaire [20]. Rather than selecting one ESRD disease-specific instrument, we elected to continue using disease-related measures that we have incorporated in prior studies of ESRD patients' quality of life [9, 21–23].

Table II describes our quality of life measures and their instrumentation.

Data analysis

For this analysis, we consider all patients on HD as one category and all patients on PD as one category. The number of HD patients who were dialyzing at home was extremely small [3], and the majority of PD patients (33 of 38) were not receiving treatment in-center. These differences certainly should be kept in mind. Our sample sizes do not permit an analysis which considers separately home and in-center treatment.

Problems specific to patients on HD and PD are reported using descriptive statistics (percentage of patients reporting the problem). For variables that could be compared across modalities, i.e. percentage of patients reporting poor appetite and percentage reporting hospitalization during the past 6 months, a chi-square test was used.

Each quality-of-life measure was analyzed as a separate dependent variable, using regression analysis. The GLM procedure in SAS version 6 [32] was used to fit a regression model for each dependent measure with the following independent variables: age, years of education, race, sex, the interaction of race with sex, cardiovascular problems (yes/no), diabetes primary diagnosis (yes/no), dialysis treatment modality (HD vs. PD), and the interaction of dialysis modality with race. For a given dependent measure, *F*-tests of the importance of each independent variable were carried out conditional on all other independent variables in the model. Then the predicted values from the regression analysis for each quality-of-life measure were used to calculate adjusted means within each of the four dialysis modalities by race groups.

Results

Table III shows dialysis-related problems reported by older HD patients and older PD patients. PD patients more often said that they experienced problems specific to PD treatment, e.g. exit-site infection, than HD patients said that they experienced problems specific to HD treatment, e.g. vascular access infection. However, poor appetite and hospitalization during the past 6

Table II. Quality of life measures and instruments

	Instruments
Generic measures	
Functional status	Index summarizing whether R spends most/all of day in bed/chair and R's degree of difficulty bathing independently, climbing a few flights of stairs, walking several blocks, and performing heavy work around the house, each measured on a 5-point scale from 1 (cannot do) to 5 (no difficulty). Responses form Gutman-type scale summarizing functional impairment at 4 levels (1 = most severe, 2 = moderately severe, 3 = least severe, 4 = no impairment).[a]
Freedom from health limitations on daily activity	"How much is what you do every day limited in any way by your health or by health-related problems?" Measured on 5-point scale from 1 (a great deal) to 5 (not at all)[a]
Self-rated health status	10-rung ladder graded from 1 (low) to 10 (high). Rs asked to visualize top of ladder as the best their health could be and the bottom as the worst their health could be.[b]
Leisure activity score	Number of activities R reports doing for entertainment or interest during past week, excluding routine household tasks.[c]
Psychological affect balance score	Bradburn's Affect Balance scale, which ranges from −5, negative mood predominant, to +5, positive mood predominant.[d]
Depressive symptomatology	Center for Epidemiologic Studies Depression (CES-D) Scale; score range 0–60.[e]
Overall dissatisfaction with life	5-point scale from 1 (completely satisfied) to 5 (not at all satisfied).[f]
Dissatisfaction with present financial situation	5-point scale from 1 (completely satisfied) to 5 (not at all satisfied).[g]
Disease-related measures	
Subjective fatigue rating	Score ranging from 0 (total fatigue) to 300 (no fatigue), based on summed values for three 100-point visual analog scales representing usual fatigue upon arising, at midday, and upon retiring.[h]
Dissatisfaction with dialysis treatment modality	5-point scale from 1 (completely satisfied) to 5 (not at all satisfied)
Intrusiveness rating	"I still do everything I want to do". Measured on a 4-point scale from 1 (strongly agree) to 4 (strongly disagree).[j]
Lack of control over own future health	"How much control do you think you have over your future health?" Measured on a 4-point scale from 1 (a great deal of control) to 4 (none at all).[a]

[a] House [24].
[b] Garrity *et al.* [25]; Cantril [26].
[c] Kane [27].
[d] Bradburn [28].
[e] Radloff [29].
[f] Campbell *et al.* [30].
[g] Kutner *et al.* [6].
[h] Cardenas and Kutner [22].
[i] Kutner *et al.* [9].
[j] Devins *et al.* [31].

Table III. Dialysis-related problems reported by older patients interviewed in Georgia, by dialysis treatment modality

	Hemodialysis (n = 311)	Peritoneal dialysis (n = 38)	p[a]
Hemodialysis problems			
% access infections	12		
% difficulty sticking access	23		
% access clotting problems	26		
Peritoneal dialysis problems			
% peritonitis in past 6 mo		45	
% exit site infections		45	
% lower back pain		42	
% dizziness when draining fluid		32	
Poor appetite, %	41	50	0.29
Nights hospitalized in past 6 mo (% 1+)	50	53	0.72

[a] p-value is from a chi-square test.

months were not significantly different for PD and HD patients. In addition, blacks and whites on PD and HD did not differ significantly in the modality-specific problems they reported, nor was there a significant interaction between dialysis modality and race with respect to poor appetite or reported hospitalization.

Table IV, which shows the results of the regression analysis, gives p-values for F-tests of each independent variable and the multiple R^2 for each model. Several independent variables other than race and treatment modality were significantly related to specific, dependent, quality-of-life measures, as follows:

- As patients' age increased, scores indicating depressive symptoms were more likely to be reported.
- The higher patients' educational status, the more positive was their reported quality of life with respect to functional status, freedom from health limitations, self-rated health status, leisure activity score, psychological affect balance score, depressive symptoms, dissatisfaction with financial situation, subjective fatigue, and perceived control over own future health.
- Older black dialysis patients reported significantly higher self-rated health status, less depressive symptomatology, less dissatisfaction with life, and less subjective fatigue; however, older black patients appeared to be significantly more dissatisfied with their present financial situation.
- Older male dialysis patients reported significantly more leisure activities and less subjective fatigue than did older female dialysis patients.
- Among older white dialysis patients, men were more likely to report perceived control over own health; among older black dialysis patients, women were more likely to report perceived control over own health.

Table IV. *p*-Values of independent variables for generic and disease-specific quality of life indicators ($n = 343$ respondents)[a]

	Independent variables[b]									
Dependent variables	Age	Education	Race	Sex	Race by sex interaction	Cardiovascular problems	Diabetes primary diagnosis	Dialysis modality	Modality by race interaction	Multiple R^2
Generic indicators										
Functional status	0.10	0.003[d]	0.93	0.87	0.94	0.0001[i]	0.60	0.74	0.047[k]	0.12
Freedom from health limitations	0.79	0.002[d]	0.13	0.73	0.25	0.005[i]	0.007[i]	0.69	0.13	0.11
Self-rated health status	0.73	0.001[d]	0.003[e]	0.66	0.28	0.0001[i]	0.70	0.13	0.75	0.14
Leisure activity score	0.09	0.003[d]	0.82	0.04[g]	0.24	0.10	0.41	0.38	0.49	0.07
Psychological affect balance	0.52	0.003[d]	0.13	0.10	0.37	0.001[i]	0.34	0.58	0.74	0.07
Depressive symptomatology	0.02[c]	0.002[d]	0.02[e]	0.18	0.13	0.005[i]	0.42	0.08	0.99	0.10
Dissatisfaction with life	0.99	0.15	0.002[e]	0.42	0.82	0.01[i]	0.34	0.21	0.83	0.09
Dissatisfaction with financial situation	0.31	0.002[d]	0.0008[f]	0.16	0.69	0.0008[i]	0.54	0.13	0.01[k]	0.13
Disease-related indicators										
Subjective fatigue rating	0.19	0.0007[d]	0.001[e]	0.001[g]	0.42	0.10	0.97	0.38	0.62	0.16
Dissatisfaction with dialysis modality	0.06	0.91	0.83	0.29	0.58	0.04[i]	0.54	0.16	0.77	0.04
Intrusiveness	0.45	0.41	0.12	0.79	0.28	0.10	0.78	0.80	0.11	0.08
Lack of control over own health	0.07	0.01[d]	0.15	0.75	0.006[h]	0.03[i]	0.02[j]	0.21	0.08	0.14

[a] Number of observations per dependent variable varies slightly due to missing information.
[b] All *p*-values for a given independent variable are controlled for all other independent variables in the model.
[c] As age increases, quality of life decreases.
[d] As educational level increases, quality of life increases.
[e] Black patients have increased quality of life.
[f] Black patients have decreased quality of life.
[g] Male patients have increased quality of life.
[h] Among white patients, men less likely to report lack of control; among black patients, women less likely to report lack of control.
[i] Patients with cardiovascular problems have decreased quality of life.
[j] Patients with diabetes primary diagnosis have decreased quality of life.
[k] Among blacks, HD patients report higher quality of life; among whites, PD patients report higher quality of life.

- Among older patients who reported cardiovascular problems, quality of life was significantly lower with respect to functional status, freedom from health limitations, self-rated health status, psychological affect balance, depressive symptoms, dissatisfaction with life, dissatisfaction with financial situation, dissatisfaction with dialysis modality, and perceived control over own health.
- Among older patients whose primary diagnosis was diabetes, quality of life was significantly lower with respect to freedom from health limitations and perceived control over own health.

As a main effect, dialysis modality was not significant for any of the 12 quality-of-life indicators. However, for two quality-of-life indicators, a statistically significant interaction effect of race and dialysis modality was observed (Table IV), indicating that white patients reported higher quality of life on peritoneal dialysis (PD) while black patients reported a higher quality of life on hemodialysis (HD). These two variables were functional status and degree of dissatisfaction with current financial situation. With regard to functional status, our previous work indicated significantly impaired functional status among older dialysis patients, both blacks and whites, as compared to older community-dwelling persons who were not ESRD patients. This analysis indicates that older white patients on PD, as compared to older white patients on HD, have better average functional status, while the reverse is true for black patients; older black patients on HD, as compared to older black patients on PD, report better average functional status.

In our earlier study in which we compared older dialysis patients' quality-of-life responses with responses given by age-matched peers living in the community who were not on dialysis, dissatisfaction with current financial situation was not significantly different for the two samples. In each sample, older blacks were significantly more dissatisfied with their financial situation than were older whites. In the current analysis that focuses only on older dialysis patients, the strong race effect exists, with black patients more dissatisfied with their financial situation than white patients. However, among white patients, those on HD report more financial dissatisfaction, while among black patients, those on PD report more financial dissatisfaction.

No *statistically significant* interaction between older dialysis patients' race and their dialysis treatment modality was found for the remaining quality-of-life variables, once adjustments were made for all independent variables in the model. In order to examine more closely the importance of race and dialysis treatment modality for specific dependent quality-of-life measures, predicted values from the regression analysis were used to calculate adjusted means within each of the four dialysis modality by race groups. Tables V and VI present the results of this analysis. All means are adjusted for race, gender, race/gender interaction, age, education, cardiovascular problems (yes/no), primary diagnosis of diabetes (yes/no), dialysis modality, and race/dialysis modality interaction, i.e. all of the independent variables in Table IV.

Table V. Adjusted means and standard deviations for generic quality-of-life indicators, by patients' race and dialysis modality*

	Whites				Blacks			
	PD	*n*	HD	*n*	PD	*n*	HD	*n*
Functional status[a]	2.21	24	1.74	122	1.69	13	2.00	168
	(0.41)		(0.32)		(0.34)		(0.31)	
Freedom from health limitations[a]	2.25	24	1.96	125	2.00	13	2.48	182
	(0.48)		(0.33)		(0.35)		(0.37)	
Self-rated health status[a]	5.77	24	4.90	124	6.38	13	6.03	176
	(0.82)		(0.68)		(0.67)		(0.63)	
Leisure activity score[a]	2.04	24	1.63	125	1.77	13	1.73	181
	(0.38)		(0.40)		(0.31)		(0.30)	
Psychological affect balance score[a]	0.96	24	0.47	122	0.92	13	0.96	181
	(0.75)		(0.53)		(0.52)		(0.57)	
Depressive symptomatology[b]	14.71	24	19.40	124	13.54	13	15.95	180
	(3.95)		(3.57)		(2.52)		(2.96)	
Dissatisfaction with life[b]	2.56	23	2.81	125	2.00	13	2.26	182
	(0.26)		(0.18)		(0.21)		(0.19)	
Dissatisfaction with financial situation[b]	2.39	23	2.70	121	4.08	13	3.10	180
	(0.42)		(0.35)		(0.29)		(0.32)	

* Sample sizes vary slightly across analyses due to nonresponse for selected items. Standard deviations are in parentheses.

[a] Higher score indicates better quality of life.

[b] Lower score indicates better quality of life.

Note: In our previous analysis, older dialysis patients differed significantly from an older control group on all of the above variables except dissatisfaction with financial situation; in addition, the dialysis effect was significantly stronger for white patients than for black patients [6].

Table VI. Adjusted means and standard deviations for disease-related quality-of-life indicators, by patients' race and dialysis modality*

	Whites				Blacks			
	PD	*n*	HD	*n*	PD	*n*	HD	*n*
Subjective fatigue rating[a]	152.64	22	134.50	122	179.46	13	175.99	178
	(20.11)		(18.37)		(22.32)		(20.50)	
Dissatisfaction with dialysis treatment modality[b]	1.67	24	1.93	123	1.62	13	1.81	180
	(0.13)		(0.16)		(0.15)		(0.14)	
Intrusiveness rating[b]	2.83	24	3.14	123	2.92	13	2.53	180
	(0.14)		(0.12)		(0.11)		(0.14)	
Lack of control over own future health[b]	1.88	24	2.31	123	2.00	13	1.92	180
	(0.24)		(0.26)		(0.23)		(0.22)	

* Sample sizes vary slightly across analyses due to nonresponse for selected items. Standard deviations are in parentheses.

[a] Higher score indicates better quality of life.

[b] Lower score indicates better quality of life.

Tables V and VI show *trends* indicating an interaction effect between race and dialysis modality for several variables: freedom from health limitations, self-rated health status, leisure activity score, psychological affect balance score, depressive symptoms, subjective fatigue rating, intrusiveness rating, and control over own future health. Three categories of interaction effect are evident in Tables V and VI.

(1) Older white patients appear to have better quality of life on PD, while older black patients appear to have better quality of life on HD. The data for the variables *freedom from health limitations* and *intrusiveness rating* illustrate this pattern, as did the two variables discussed above, *functional status* and *dissatisfaction with current financial situation*.
(2) Older white patients appear to have better quality of life on PD, but dialysis modality does not seem to be related to quality-of-life differences for older black patients. The data for the variables *leisure activity score*, *psychological affect balance score*, *subjective fatigue rating*, and *perceived control over own future health* illustrate this pattern.
(3) Both older white patients and older black patients appear to have better quality-of-life on PD, but the difference between quality-of-life responses for patients on PD and patients on HD is larger among older whites than among older blacks. The data for the variables *self-rated health status* and *depressive symptomatology* illustrate this pattern.

Responses for the two variables *dissatisfaction with life and dissatisfaction with treatment modality* did not demonstrate any of these patterns.

Our analysis suggests, therefore, that being on PD rather than on HD may have quality-of-life advantages for older white patients, but that this is not necessarily true for older black patients. The number of patients on PD relative to HD in our sample was small and, as Table IV indicates, the total amount of variation in the dependent variables explained by the model was relatively small. However, we believe that our analysis suggests hypotheses that could be investigated in a more balanced sample of PD and HD patients.

Discussion

The responses we obtained from a probability sample of older dialysis patients living in the southern United States suggest that PD may have quality-of-life advantages for older white patients but not necessarily for older black patients. Our data also suggest that these findings are not a function of older whites' experiencing significantly fewer dialysis-related problems as compared to blacks on PD or of older blacks' experiencing significantly fewer dialysis-related problems on HD as compared to whites. However, dialysis-related problems were more likely to be reported by PD patients than by HD patients, and it is possible that older blacks on PD cope with such problems less successfully. Kaye *et al.* [13, 14] noted that older CAPD patients; in comparison to younger CAPD patients, relied more heavily for

support on other family members and on the dialysis treatment staff. Responses from patients in our study indicated that older white patients on PD received support from significantly more sources than did older black patients, both black patients on PD and black patients on HD. Thus, the greater social support reported by older white patients on PD may have contributed to the differences we observed. In addition, although the differences were small, among patients on CAPD or CCPD, older white patients (70%) were more likely than older black patients (60%) to say that they were completely satisfied with the nursing support that they received from their backup dialysis facility; when asked about the social work support they received from their dialysis facility, the respective responses from the two groups were 57% as compared to 40% who said they were completely satisfied. Most patients were generally satisfied with the nursing support and the social support available to them, but these data *suggest* that older whites were more comfortable than were older blacks with the backup support they perceived as available to them.

The percentage of older patients in our stratified random sample who were on PD was small (10.9%), and only two of the race/modality interaction effects that we report were statistically significant. In addition, other independent variables contributed significantly to variation in the dependent quality-of-life measures we examined. However, race/modality interaction effects on older dialysis patients' quality of life, and the potential role of social support differences in contributing to these effects, suggest avenues of study that are relevant to questions recently posed by Nissenson [33]: what is the quality of life of elderly CPD patients? Can it be further enhanced?

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CHAPTER 30

Rehabilitation of elderly patients on hemodialysis

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Hemodialysis is the most broadly applied form of renal replacement therapy. For a growing number of older patients with end-stage renal disease (ESRD), hemodialysis is the only practical option in dialytic therapy because most cannot learn to perform ambulatory peritoneal dialysis (CAPD), and many are too old for kidney transplantation. Recent demographic data reveal that those over 65 are the fastest growing segment of the population; a reality that is reflected in the dialysis population. It has been projected that, by the year 2010, patients 65 and over will represent about 60% of the total hemodialysis population [1]. Current studies assessing the efficacy of maintenance hemodialysis emphasize survival, adequacy of dialysis, and other technical indices, while giving less attention to morbidity, quality of life, and functional status, although less pragmatic and admittedly difficult to quantify.

Few studies have assessed rehabilitation in elderly dialysis patients [2–4], and previous studies in dialysis patients have not compared the patients' premorbid state to that at the time of survey [2–9]. Other reports have focused on employment and vocational rehabilitation [7]. Elderly patients are much more likely to be retired than are young patients, and, even when they desire employment, face disincentives within the reimbursement system that could lead to loss of benefits. To overcome these limitations, we broadened our definition of rehabilitation, measuring both vocational and functional status. To gain a true perspective of the impact of ESRD, we compared each patient's present level of function, medical and social variables, and employment status to his/her level two years before initiation of hemodialysis. We also assessed the influence, if any, of recombinant human erythropoietin, as well as comorbid conditions, on current level of functioning. Finally, we compared rehabilitation in patients over age 65 to the degree of rehabilitation in a randomly selected control group of dialysis patients under age 65.

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Methods and patients

Subjects

We interviewed all patients aged 65 and over in seven outpatient hemodialysis units in Brooklyn, who have been receiving maintenance hemodialysis for at least six months. A total of 103 patients were interviewed. In addition to comparing each patient's functional status to his/her level two years before starting hemodialysis, we also compared the elderly cohort to 20 randomly selected control patients under the age of 65, receiving maintenance hemodialysis at the same facilities. Twenty of the patients, aged 65 and over, were interviewed again by a different interviewer to validate the reproductibility of the scoring system. The survey was carried out by two physicians and four nurses. All interviews were conducted on site.

Karnofsky activity scale

The Karnofsky activity scale [10] was modified to have 14 levels of activity ranging from < 30 (Hospitalized, progressive fatal process) to > 96 (Normal function, no disability) as shown in Table I. The well-recognized limitations in the clinical application of the Karnofsky scale [11], led to our modified scoring system, that narrows the range at each level of diminish observer variation. A score of 76 and above meant the subject was independent and participated in activities outside of hemodialysis and its attendant effects.

Social and medical status variables

Data collected from each subject included: (a) age, (b) gender, (c) etiology of ESRD, (d) number of years on hemodialysis, (e) highest educational level acheived, (f) marital status, (g) number of people in household, (h) number of prescription and over the counter medications, (i) employment, (j) income source/public assistance (k) type of health insurance, (I) contribution to housework: part/full or none, (m) satisfaction with sexual activity, (n) statement of the most positive aspect of hemodialysis, (o) statement of the most negative aspect of dialysis, (p) subjective perception of a positive effect of recombinant erythropoietin therapy. For questions f to k, patients were asked to recall their circumstances two years before starting hemodialysis.

Comorbidity index

To ascertain a numerical comorbidity index, the presence and severity of signs, symptoms, and medical conditions in eight major organ systems were

Table I. Functional status

		Subjects ($n = 103$)		Controls ($n = 20$)	
		Now	Before	Now	Before
1. Karnofsky scale					
Activity	*Score*				
Normal function, no disability	96–100				
Minor signs and symptoms, full activity	91–95				
Usual activities with effort	81–94				
Independent, most out of home activities	76–80	33	81	15	18
Independent, limited to home	70–75				
Needs assistance with errands	65–69				
Needs assistance with meal preparation	60–64				
Needs assistance with bathing/dressing	55–59	39	16	3	2
Home attendant, not totally disabled	50–54				
Disabled, living at home	45–49				
Nursing home for chronic care	40–44	31	6	2	–
Hospitalized, fair condition	35–39				
Hospitalized, poor condition	30–34				
Hospitalized, progressive fatal process	< 30	–	–	–	–
Mean Karnofsky score		66	85	80	95
2. Contribution to housework					
Part		47	54	6	5
Full		31	39	12	13
None		25	10	1	1
3. Use of wheelchair		**14***	**1**	–	–

*Due to weakness (9), CVA (3) and arthritis (2).

noted from 0 to 3. Zero = no symptoms, three = severe symptom or condition in that organ system. A notation was made if a wheelchair was used.

Laboratory data

From patient records, we obtained the most recent predialysis laboratory data including: Serum creatinine, blood urea nitrogen, total serum protein, serum albumin, and hematocrit.

Statistics

For statistical analyses, we used Student's *t* test and chi-square analysis.

Table II. Demographic profiles and comorbidity index

	Subjects ($n = 103$)	Controls ($n = 20$)
Mean age, years (range)	74.5 (65–90)	44.6 (29–63)
Gender, M/W	53/50	9/11
Diabetics	34	9
Nondiabetics	69	11
Mean duration on HD, years (range)	3.8 (0.5–11)	4.06 (0.5–15)
Black	59	13
White	39	7
Hispanic	5	–
Level of education		
Below High School	34	2
High school	60	14
College	9	4
Mean co-morbidity index	7.8 ± 2.93	4 ± 2.17 ($p < 0.00001$)

Results

General

Of the 103 patients aged 65 and older, 53 were men and 50 women. Their mean age was 74.5 years (range 65–90) as shown in Table II. Of the group, 33% had diabetes mellitus, 57% were black, 38% were white, and 2% were hispanic. The mean duration of maintenance hemodialysis was 3.8 years (range 0.11). Few in the group (9%) had a college-level education; 58% had a high-school education, and 36% had less than a high-school education. Nearly all (97%) of the patients lived at home, while 3% lived in a chronic-care facility. Patients stated that current living arrangements are the same as they were two years before starting hemodialysis, but significantly more patients (25%) now have a home attendant, compared with 5% before starting dialysis. Of those living at home, 36% live alone and 38% live with their families.

Functional status

Mean level of function according to the modified Karnofsky scale was 66 ± 12.3 (range 44–92), compared with patients' recollection of a mean score of 84 ± 14.3 (range 44–100), two years before initiation of hemodialysis (Table I). Seventy patients, (68%) reported severe debility, stating that they did not leave their place of residence for any activity other than reporting to the dialysis facility. The reason proffered for a lack of outside activity was weakness. By contrast, 80 patients (78%) participated in outside activities two years before starting hemodialysis. Scoring on the modified Karnofsky

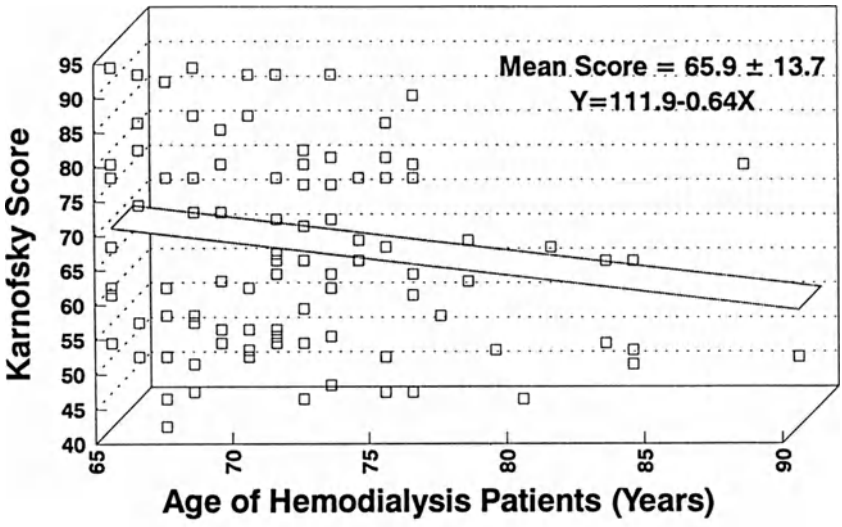

Fig. 1. Elderly hemodialysis patients. 103 Brooklyn outpatients.

scale correlated with age, as shown in Fig. 1. Fully 9% of elderly hemodialysis patients were wheelchair dependent because of weakness in 9, prior stroke in 3, and debilitating arthritis in two patients. Only one patient gave a history of wheelchair use two years before hemodialysis. Ability to contribute to housework decreased from 95% two years before dialytic therapy to 76% now (Table I).

As expected current employment was low at 4%, since most subjects were past retirement age (Table III), while 25% were employed two years before starting hemodialysis. The control group also had decline in employment rate from 95% before starting hemodialysis to 25% at present.

There was suprisingly little change in satisfaction with sexual activity, which declined from 65 patients (63%) expressing satisfaction, to 55 patients

Table III. Employment status

	Now			2 yrs prior to HD		
	Employed	Unemployed	Retired	Employed	Unemployed	Retired
Subject (n = 103)	4	6	93	28	7	68
Controls (n = 20)	5	13	2	19	1	–

Table IV. Laboratory data

	Subjects ($n = 103$)	Controls ($n = 20$)
Serum creatinine (mg/dL)	11.9 ± 3.67	13.7 ± 3.83 ($p = 0.004$)
Blood urea nitrogen (mg/dL)	79 ± 21.1	81.4 ± 20.6 (NS)
Hematocrit (%)	28.3 ± 4.61	26 ± 4.12 (NS)
Serum albumin (g/dL)	3.8 ± 0.36	4 ± 0.29 (NS)
Total serum protein (g/dL)	6.8 ± 0.57	6.7 ± 0.48 (NS)

(53%) at present. Decline in sexual satisfaction was more pronounced in the control group; only 35% said they are satisfied currently, compared to 55% stating satisfaction two years before hemodialysis.

Medical and social variables

The mean comorbidity index of the elderly dialysis patients was 7.8 ± 2.93 of a possible 24, compared to 4.0 ± 2.17 ($p < 0.0001$) for the control group (Table II). This is most likely due to the higher prevalence of chronic diseases in the elderly. Mean values for hematocrit, total serum protein, serum albumin, blood urea nitrogen, and serum creatinine concentration are given in Table IV. The only significant difference in laboratory values was that controls had a higher serum creatinine ($p = 0.004$).

Table V gives a summary of what elderly patients considered the most positive and negative aspects of hemodialysis. Of 87 (84%) under treatment on recombinant human erythropoietin (Table VI), 12 (14%) stated that they did not know or were not aware of receiving the drug. By comparison, all knew what normal saline was and were aware of its use in treating dialysis-related hypotension. A positive effect of erythropoietin was noted by 35 (40%) of elderly patients, which was substantially less than the 16 (80%) patients in the younger control group.

Elderly dialysis subjects were receiving a mean of 8.6 ± 3.12 medications, while the mean recalled for two years before dialysis was less than one medication; the control group was receiving a mean of 6.7 ± 2.87 (NS) medications.

Regarding insurance coverage, 12% of elderly patients had Medicaid only, 23% Medicare only, 28% both Medicare and Medicaid, 25% Medicare and private insurance, and 4% had all three. Only 2 (1.9%) subjects had no insurance coverage; they were illegal aliens not eligible for Medicaid or Medicare.

Table V. Feelings about hemodialysis

	'Most positive aspect of hemodialysis?' Subjects ($n = 103$)	Controls ($n = 20$)
1. 'Keeps me alive'	32	3
2. 'I feel better'	49	16
3. 'None'	22	1
Significance $p < 0.0158$		
	'Most negative aspect of hemodialysis?'	
1. 'Lasts too long'	20	1
2. 'Drop in BP and weakness'	17	1
3. 'Needle stick'	7	4
4. 'Confines me'	7	–
5. 'It is three times a week'	6	–
6. 'Everything'	5	4
7. 'Cramps'	5	–
8. 'Dietary and fluid restriction'	2	4
10. 'I urinate less'	1	–
11. 'Access clotting'	1	–
12. 'I gained weight'	1	1
13. 'I am on it till death'	1	–
14. 'None'	30	5

Table VI. EPO in patients on hemodialysis

	Subjects ($n = 103$)	Controls ($n = 20$)
On EPO	87 (84%)	20 (100%)
Subjective Benefit	35 (40%)	16 (80%)
No effect	40 (46%)	2 (10%)
Don't Know	12 (14%)	2 (10%)
Significance	$p < 0.003$	

Diabetics vs nondiabetics

Diabetics and nondiabetics did not differ with regards to age or laboratory indices. However, the co-morbidity index was 8.4 ± 2.68 in diabetics and 5.83 ± 3.15 ($p < 0.0001$) in nondiabetics (Table VII). There was also a difference in the functional status as measured by the modified Karnofsky scale; nondiabetics scored higher (mean 68 ± 13.6) than diabetics (60.9 ± 12.3) ($p < 0.001$. Confidence limits; upper = 12.58, lower = 1.62), Fig. 2. Only 28 (40%) of nondiabetics required assistance for everyday activity, as compared with 25 (74%) of the diabetics ($p < 0.0033$). While this difference is a holdover from an equivalent difference in scoring predialysis, the decline in function in nondiabetics was steeper. Only 7 (10%) nondiabetics required

Table VII. Diabetics vs nondiabetics

	Diabetics ($n = 34$)	Nondiabetics ($n = 69$)
A. Karnofsky score		
> 70 Do not require assistance		
2 yrs prior to HD	26 (76%)	62 (90%)
Current	9 (26%)	41 (60%)
< 70 Requires assistance		
2 yrs prior to HD	8 (24%)	7 (10%)
Current	25 (74%)	28 (40%)
B. Mean Karnofsky score		
2 yrs prior to HD	83.6 ± 14.4	86 ± 15.7 (NS)
Current	60.9 ± 12.3	68 ± 13.6*
Percent change	24.4%	20.9%
C. Race		
Black	26	33
White	8	31
D. Mean Age, years	70 ± 4.03	72.7 ± 5.54 (NS)
(range)	(65–83)	(65–90)
E. Mean comorbidity index	8.4 ± 2.68	5.83 ± 3.15**
F. Laboratory data		
Serum creatinine (mg/dL)	11.3 ± 3.68	12 ± 3.71 (NS)
Blood urea nitrogen (mg/dL)	85 ± 21.7	73.3 ± 20.12 (NS)
Total serum protein (g/dL)	6.8 ± 0.55	6.7 ± 0.54 (NS)
Serum albumin (g/dL)	3.8 ± 0.32	4.1 ± 0.33 (NS)
Hematocrit (%)	27.1 ± 4.3	28.6 ± 4.42 (NS)

* $p < 0.001$.
** $p < 0.0001$.

assistance for everyday activity before dialysis, against 8 (24%) of the diabetics ($p < 0.001$).

Effect of race

There were more blacks than whites in the survey (Table II), primarily because of the inner city location of the hemodialysis units we surveyed, and the disproportionately larger number of blacks on hemodialysis. There were no significant differences with regard to age, or years on hemodialysis, but there was a significant difference in the frequency of diabetes mellitus. More blacks than whites carried this diagnosis.

Etiology of ESRD

Etiology of ESRD in these elderly patients can be found in Fig. 3.

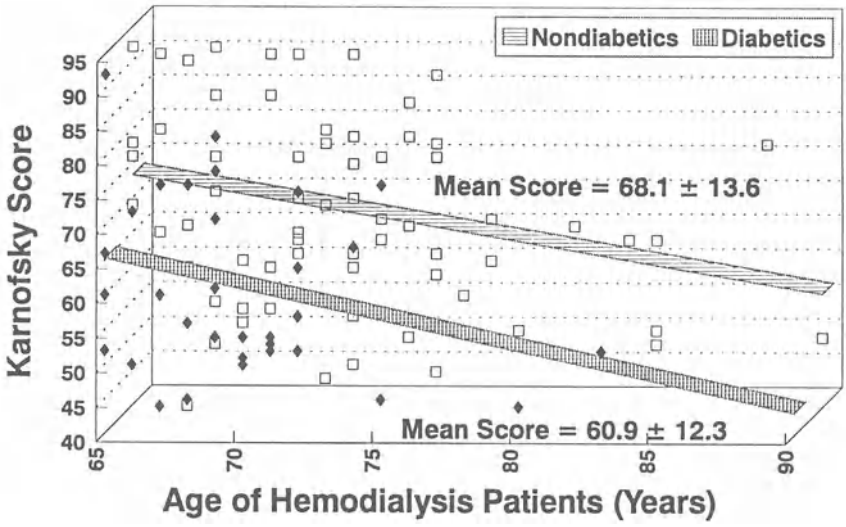

Fig. 2. Elderly hemodialysis patients. Diabetics (n = 34) vs. nondiabetics (n = 69).

Discussion

One of the major goals of any renal replacement therapy is the complete or partial return of patients to their premorbid level of function rather than just survival. Health-care providers in general have focused heavily on survival statistics and have used them, often exclusively to judge the success or failure of their endeavors. While prolonging survival is indeed a worthy objective, we should devise indices that monitor ongoing functional status, giving them as much weight as we do survival statistics. Futhermore, ongoing monitoring of functional status is not only prudent and appropriate, but can be a tool to guide corrective interventions, because in some poor functional status by Karnofsky scale may predict earlier death [12]. Our results show that the objective of functional or vocational rehabilitation has not been met in this group of elderly hemodialysis patients. Only about 32% are independent and participate in any outside activity other than coming for hemodialysis, as compared to over 78% who had broader activities and interests two years before hemodialysis (Table I). About 9% of patients needed a wheelchair to get around in the absence of any obvious organic disease, their only complaint being weakness; this is against $< 1\%$ before dialysis. About 75% of the patients now participate partially or fully in housework vs $> 90\%$ two

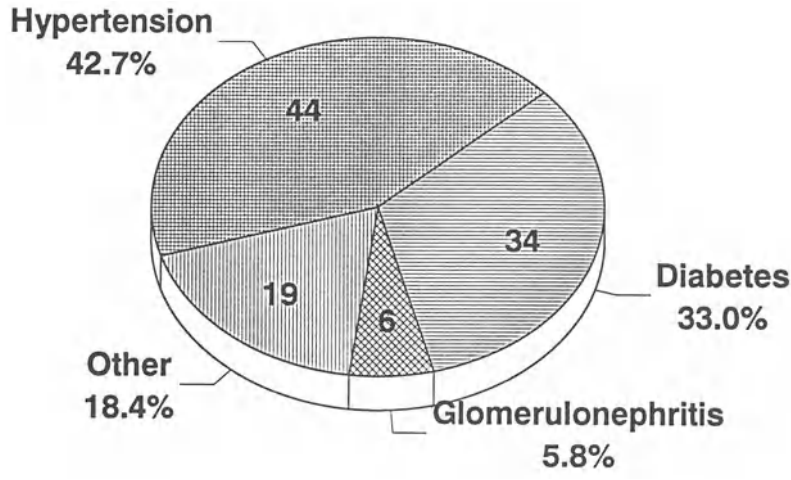

Fig. 3. ESRD Etiology. Elderly hemodialysis patients (n = 103).

years before hemodialysis; this too was attributed to weakness. We also noted a decline in the score obtained by modified Karnofsky with advancing age (Fig. 1). This is likely part of the physiologic process of aging, as well as of decreasing muscle mass represented here by declining predialysis creatinine with age (Fig. 4). However it is not easily explained why the serum albumin should decrease with advancing age (Fig. 5). There are no control studies in the literature. Perhaps this decline may be related to suboptimal nutritional status with aging. Fifty-one of these patients had been on dialysis for more than 2 years, and 23 on renal replacement therapy for 5 to 11 years. Clearly advancing age, ESRD and hemodialysis all must be considered to play some role in their current circumstances. Assessment of vocational rehabilitation in the elderly is difficult, since most are retired, and even those who wish to work risk losing their benefits if income exceeds a set limit. Less than 4% of the subjects are currently employed, although 27% were working two years before starting hemodialysis. The change in employment status is more dramatic in the control group; only 25% are working despite their mean age of 44.6 years (range 29–63), while 95% were employed two years before starting dialysis. Our results show a worse outcome in the elderly than some previous studies [3, 4, 7, 9] but are comparable to results of studies from the seventies [8, 13], and one from the last decade [5]. This poor functional status is more striking considering the significant improvements in

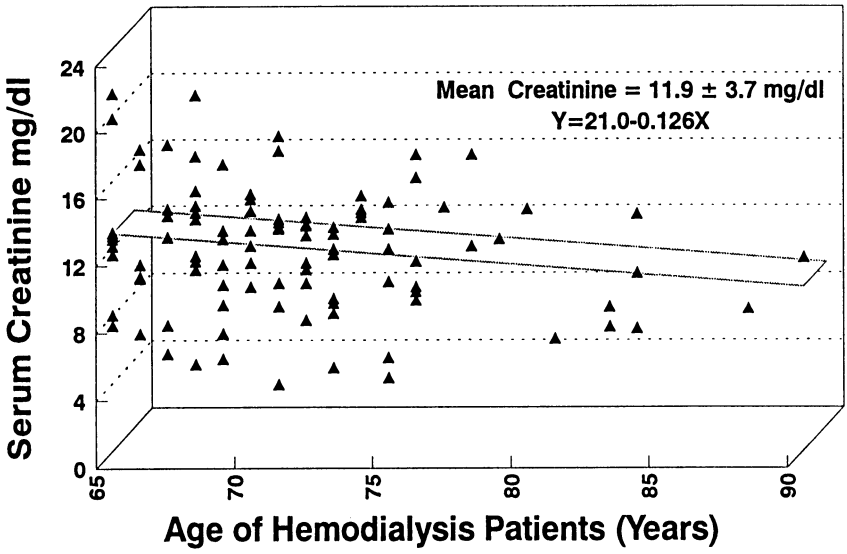

Fig. 4. Elderly hemodialysis patients. Serum creatinine mg/dl (n = 103).

hemodialysis, including more efficient dialyzers and the use of erythropoietin (rHuEpo) [14]. The emergence of rHuEpo raised expectations of improvement in functional rehabilitation of hemodialysis patients. Although the many problems faced by our patient population (poor, inner city, less educated, substantial percentage with diabetes) would suggest a poor clinical outcome, this is unlikely because in many ways these patients represent the dialysis population in the United States. Our study may be a harbinger of the future, because it is clear that the demographics of the hemodialysis population are changing, with disproportionately more black patients, an increase in their average age, and more are urban dwellers.

Elderly patients, in general, have more conditions and, not surprisingly, their average comorbidity index was 7.8 ± 2.93 compared to 4 ± 2.17 ($p < 0.00001$) in the control group. Multiple comorbid problems usually correlate with difficulties in sexual activity [15], only 53% of our patients expressed satisfaction with their current sexual activity as against 63% two years before dialysis. Satisfaction with sex correlated negatively with the Karnofsky score, but more men were satisfied with sexual function than women, consistent with findings in healthy elderly people [16]. Although sexual dysfunction usually is more common in older people [17], there was a surprising change in the younger control group: only 35% said they were

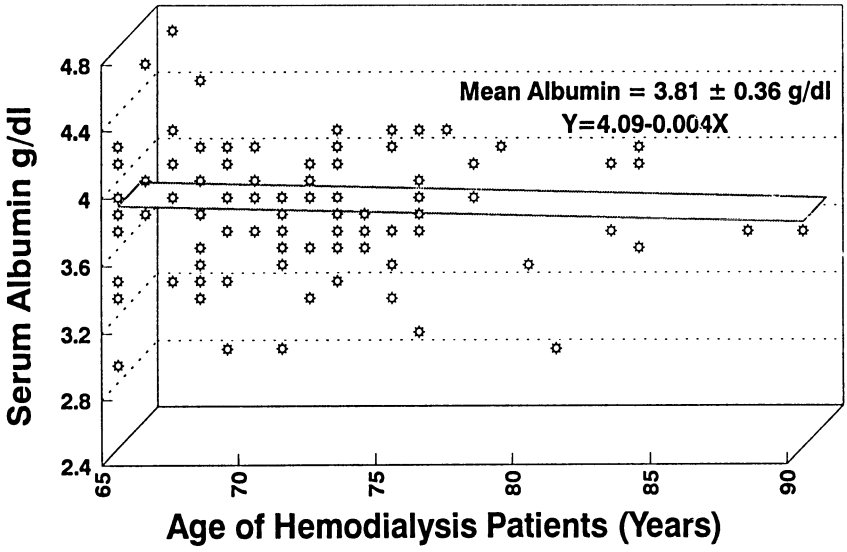

Fig. 5. Elderly hemodialysis patients. Serum albumin.

satisfied, while 55% were content two years before starting hemodialysis. This, however, may be a reflection of expectation.

The family unit is strained by chronic illness, but there was no increase in separations or divorces after starting hemodialysis. This, perhaps, mirrors the stability and codependence more commonly seen in elderly married couples.

On average the subjects were on 8.6 medications, comparable to the number reported by others [3]; the control group was on slightly fewer drugs, an average of 6.7. This difference is understandable, since healthy elderly people use an average of 3.2 medications [18]. However, both groups were on an average of < 1 medication two years before hemodialysis. This rather low number in the premorbid situation may suggest undertreatment of conditions present before treatment for ESRD, and may reflect the dirth of general medical care among this population.

One of the major events in hemodialysis in the last decade was the introduction of recombinant human erythropoietin (rHuEpo) [14]. In addition to the primary increase in hematocrit, secondary benefits include increased appetite, increased exercise tolerance, and improved general feeling of wellbeing [19]. Eighty four percent of the subjects and all the control patients were on erythropoietin. Of those getting rHuEpo, 40% of the older

patients and 80% of the control group reported a positive effect from the EPO; 40% of the patients said there was no noticeable effect, while 14% of them did not know about EPO, even though they were receiving it. The latter group was mostly comprised of those with very low Karnofsky scores and high comorbidity indices; we suspect they were too debilitated to assimilate any sort of patient education.

When asked what they felt to be the most positive aspect of dialysis, over 50% said either 'it keeps me alive', or had nothing pleasant to say about hemodialysis. This suggests a more dismal outlook in this group of patients than had been reported in the past. Other investigators have shown that a significant number of elderly dialysis patients wish for alternate therapy, most often kidney transplantation [3], even when they knew that their chances for such treatment were slim. About 48% of patients responded that they 'feel better'. When asked about the most negative aspect of dialysis, there was a wide range of response. Most disturbing was the significant number, just under 20%, who felt that dialysis treatments were too long. The range of hemodialysis time for our subjects was 3.5–4 hours. The danger here is that they may play into the hands of practitioners who will acquiesce to their demands by shortening dialysis time, but whose motivations are based on a desire for profit, with disastrous results for the patients.

One of the most obvious differences between any two groups is the presence of diabetes mellitus. Diabetics with ESRD do poorly on hemodialysis [20], and generally have greater comorbidity [6]. However, the difference in levels of function between elderly diabetics and nondiabetics was not as exaggerated as in younger populations [6]; perhaps because the elderly have other significant medical problems [21] that presumably elevated their comorbidity indices even in the absence of diabetes mellitus. Once again their expectations of function may play a role, but the rate of decline in function from predialysis to the present was similar, suggesting that diabetics merely transfer their poorer functional status from the pre- to the hemodialysis state.

In conclusion, we have shown that the functional and vocational rehabilitation of elderly hemodialysis patients is poor; most show a substantial decline from their level of function two years before starting hemodialysis. Those with diabetes scored lower than nondiabetics on the modified Karnofsky scale, but both groups showed a similar degree of decline in functional status from their recalled predialysis score.

In its present form renal replacement by hemodialysis does not return elderly patients to their predialysis level of function. The majority spend most of their time indoors due to poor health, and the psychological consequences of such prolonged inactivity are well documented. In our view, goals for the elderly hemodialysis patient should be adequate functional rehabilitation, not just survival. This will require reliable and reproducible indices to monitor their functional status, allowing us to seek measures to

improve the quality of their lives. This survey casts some light on the natural history of this population with current interventions and, as such, may give us insight into a more productive approach to our greying dialysis population.

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CHAPTER 31

Geriatric rehabilitation in the elderly with end-stage renal disease

GARY NAGLIE

The population of the United States and Canada is aging [1, 2]. Projections suggest that the number of persons over the age of 65 will increase dramatically in the next 50 years, during which the 85+ age group will expand to the greatest extent [1, 2]. In conjunction with this aging, the dialysis population also is growing progressively older [3]. The most rapidly growing segment of this population is those over 75 years of age [3]. Medicare data in the United States demonstrate that, between 1978 and 1987, increases in newly treated renal failure patients aged 65–74 years and 75+ years were 192% and 461%, respectively, compared to an increase of 81% for patients less than 65 years of age [3].

In the United States, about 5% of the elderly (65+ years) reside in institutions, while in Canada about 8.5% of the elderly do so [1, 2]. Institutionalization rates increase dramatically with increasing age [1]. With aging and the high costs of institutional care, great efforts must be taken to maximize the function of disabled elderly so as to keep them in the community. In recent years, geriatrics has emerged as a recognized subspecialty and geriatric rehabilitation has become a distinct type of practice [4–7]. This paper reviews the principles of geriatric rehabilitation and describe how geriatric rehabilitation can be applied to disabled elderly patients with ESRD.

Definition of geriatric rehabilitation

The hallmark of geriatric care is comprehensive assessment and treatment of frail elderly persons at high risk for institutionalization. A National Institutes of Health Consensus statement defined comprehensive geriatric assessment as "a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan developed to focus interventions on the person's problems" [8]. Typically, this includes an in-depth assessment with respect to several domains: (i) physical health; (ii) mental

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health (cognition and affect); (iii) social and economic status; (iv) functional status (activities of daily living – bathing, dressing, toileting, transferring, mobility, continence and feeding; and instrumental activities of daily living – e.g., meal preparation, grocery shopping, housework, use of transportation, medication management, financial management and use of telephone); and, (v) environmental characteristics (evaluation of patient's home environment) [8]. Rehabilitation has been defined as the process of assisting disabled patients in restoring lost physical, psychological, or social skills necessary for functional independence and independent living [4, 9]. The several components of rehabilitation include: (i) diagnosing and stabilizing the underlying problem(s); (ii) preventing secondary complications and secondary disability (including that from disuse); (iii) restoring as much lost functional ability as possible; (iv) promoting adaptation of the person to the environment; (v) adapting the environment to the person; and, (vi) promoting family adaptation [9].

Geriatric rehabilitation represents a merging of the principles of comprehensive geriatric assessment and those of rehabilitation. The goal of comprehensive geriatric rehabilitation is to restore frail elderly persons to their maximal level of physical, mental and social function, and it goes beyond traditional rehabilitation in terms of the population it serves. Often we offer geriatric rehabilitation to those who are rejected by traditional rehabilitation programs because they do not have a specific diagnosis (e.g., stroke, hip fracture, amputation), they have multiple medical and/or psychosocial problems, they have cognitive impairment or are at high risk for long-term institutional care. Such rehabilitation can be provided in various settings including acute hospitals, rehabilitation hospitals and chronic hospitals [4, 9].

Appropriate patient selection is an important ingredient to the success of such programs [8, 10]. Some preliminary targeting criteria have been established for those patients most likely to benefit from geriatric rehabilitation [8, 10]. A major criterion for inclusion in an inpatient geriatric rehabilitation program is an identifiable medical, functional or psychosocial defect leading to impaired independent living, as demonstrated by suboptimal activities of daily living or instrumental activities of daily living [10]. Exclusion criteria may include persons who are fully independent, those who have achieved their maximum rehabilitation potential and those with severe dementia or terminal diseases, who are unlikely to benefit [8, 10].

Special features

Physiologic changes commonly seen in the elderly and age-associated diseases must be considered when tailoring rehabilitation programs to the elderly. Physiologic changes that may impact on geriatric rehabilitation include (i) visual changes including presbyopia (decreased ability to focus on near objects), diminished color discrimination and sensitivity to glare [11]; (ii) audi-

tory changes including high frequency hearing loss, diminished speech discrimination and abnormal loudness perception [12]; (iii) decreased skeletal muscle mass and decreased muscle strength (can be increased with exercise) [13]; and, (iv) decreased aerobic capacity and physical performance (can be increased with exercise) [14].

Older persons are much more likely to have multiple diseases [15] and many of these may have a bearing on geriatric rehabilitation e.g.: (i) cataracts, glaucoma, diabetic retinopathy and macular degeneration leading to visual disability; (ii) symptomatic coronary artery resulting in diminished exercise tolerance; (iii) diabetes mellitus, which can lead to numerous complications – heart disease, peripheral vascular disease, stroke, peripheral neuropathy and diabetic retinopathy, that can impede rehabilitation; (iv) dementia and depression, which may reduce compliance with a program; and, (v) osteoarthritis, which can limit mobility and function.

The elderly tend to be particularly susceptible to the deconditioning effects of bedrest [16]. Bedrest and immobility can lead to decreased cardiac output, decreased aerobic capacity, orthostatic intolerance, relative hypoxemia, atelectasis, muscle atrophy and loss of strength, bone loss, joint contractures, sensory deprivation, impaired ambulation and impaired endurance [16]. Physiologic changes seen in the elderly resemble those related to bedrest, and there is some evidence that these changes may be additive [16]. The implications of bedrest highlight the importance of programs that encourage the early mobilization of all bed-bound patients.

Social and economic status may affect planning for the elderly individual. Social isolation is common due to the death of spouse and friends and diminished vocational and social activities [17]. Social work intervention may be necessary to help establish alternate supports. When social supports exist, caregiver burden should be assessed because this can be an important predictor of institutional placement [18]. If caregiver burden is high, we should seek alternate supports and consider respite services. Finally, in many elderly, a limited income [17] may impair ability to pay for support services or assistive devices.

The interdisciplinary approach

As described above, rehabilitation in the elderly often is complicated by multiple concomitant disorders and by functional, psychological and social problems. Therefore, geriatric rehabilitation usually requires an interdisciplinary team approach [19]. Such a team has representatives from several disciplines, who work interdependently in the same setting and interact formally, e.g., case conferences, and informally, e.g., notations in the chart in planning and implementing patient care [19]. Usually interdisciplinary teams meet periodically to discuss the patient, to establish goals and to monitor progress. Usually the plan for the patient includes: (i) prompt treat-

ment of treatable aspects of the underlying problems(s); (ii) early ambulation and use of all bodily functions possible; (iii) early return to a normal social and physical environment; (iv) use of assistive devices as deemed necessary; and, (v) follow-up and reassessment to monitor compliance with the plan and to allow for modifications to the plan as needed [20].

Various disciplines may contribute to the geriatric rehabilitation team, e.g., geriatric medicine, nursing, physiotherapy, occupational therapy, and social work [4, 19]. Other disciplines may include speech therapy, nutrition, pharmacy, podiatry, chaplaincy, recreational therapy, geriatric psychiatry, clinical psychology, physiatry, audiology, ophthalmology, urology and dentistry [4, 19]. While each team member has a specific expertise, the specific activities and contributions of each team member may vary with different patients, and each must be flexible [4, 19].

Effectiveness

Two randomized trials, one based in a Veterans Administration hospital [21] and the other in a community rehabilitation hospital [22], have corroborated the positive findings of uncontrolled studies concerning the effectiveness of geriatric rehabilitation programs [23, 24]. The populations in both studies included patients with a variety of medical and/or surgical diagnoses who were at high risk for nursing-home placement. Both studies evaluated comprehensive geriatric assessment linked with active treatment and rehabilitation and in both trials, the control group received 'usual care' from the attending physician.

Both trials [21, 22] demonstrated that patients, who received comprehensive geriatric assessment and rehabilitation, had improved survival, improved functional status and reduced nursing home placement at one year follow-up. The Veterans Administration study also revealed that the treatment group had an improved morale, a decreased rate of rehospitalization, a reduced number of prescribed medications and lower overall one-year costs [21].

Geriatric rehabilitation for elderly patients with ESRD

That elderly ESRD patients are more disabled than young ESRD patients was demonstrated by a study of 84 elderly hemodialysis patients (mean age 68.6 years; range 60–88 years) in St. Louis [25]. The average number of specified major medical problems in addition to ESRD was 2.6; 89% had cardiovascular disease and 38% had diabetes mellitus; 38% had significantly decreased vision and 10% had significant hearing loss. Concerning functional capacity, 48% needed varying degrees of assistance with activities of daily living and 38% needed ongoing care and assistance, including 11% who

required nursing home care. Concerning mental status, 24% had mild to severe cognitive impairment. Based on the Beck Depression inventory, 38% of the patients were mildly depressed, 23% were moderately depressed and 11% were severely depressed. Many of the patients had limited social supports; 18% lived alone.

The St. Louis Study [25] suggests that many elderly dialysis patients have multiple medical, functional, cognitive and social problems, which would make them good candidates for geriatric rehabilitation. A computerized search of the MEDLINE database did not find any specific references to rehabilitation of patients with ESRD. This being so, the rest of this paper is based on anecdotal observations of the Conjoint Geriatric Program at The Toronto Hospital, a tertiary care, university-affiliated acute hospital, and Queen Elizabeth Hospital, a university-affiliated chronic hospital. Its core services include a community outreach team, a day hospital, outpatient clinics, an acute hospital geriatric unit, an acute hospital consultation team and a chronic hospital geriatric rehabilitation unit. The last two participate in the care of many elderly patients with ESRD who were at risk for long-term institutionalization. Most of these patients return to live in the community with various support services.

Case review

The geriatric rehabilitation unit at the Queen Elizabeth Hospital has been able to discharge about 80% of patients to their homes (unpublished data). The following case review is representative of elderly patients with ESRD admitted to the unit. This 75-year-old widow on the nephrology service at The Toronto Hospital was seen in consultation. She had been in hospital for about one year after she developed ESRD secondary to bilateral renal-artery stenosis. In the past she had coronary-artery disease, hypertension, congestive heart failure, atrial fibrillation, hypothyroidism and a small stroke. Before her admission, she was living alone in a house and was completely independent. She had two daughters, each of whom had their own families, which limited the time they could spend with her. During her hospitalization, the daughters sold her house.

Her prolonged acute hospitalization was made necessary by numerous complications related to her ESRD. Initially she was treated with continuous peritoneal dialysis, but she suffered recurrent peritonitis and was switched to hemodialysis *via* a subclavian catheter. Her course was complicated by several bouts of septicemia secondary to the subclavian catheter, a subclavian-artery thrombosis (after which a subclavian catheter was inserted on the opposite side), a right-leg deep-venous thrombosis, pulmonary edema, intermittent confusion, *Clostridium difficile* colitis and a seizure.

During the prolonged hospitalization, severe deconditioning and weakness led to functional difficulties that prevented her from returning to independent

living in the community. She required assistance with bathing, walking and transferring bed-to-chair and on-and-off the toilet. She was independent in feeding, dressing and grooming, but carried out these activities slowly due to poor endurance. She was fully continent of urine and stool. She had no significant cognitive deficits, but intermittently was confused just before dialysis.

The team considered her to be a good candidate for geriatric rehabilitation and transferred her to the Queen Elizabeth Hospital. The goal of the admission was to restore her functional independence to enable her to return to independent community living. During her stay, the interdisciplinary team – a geriatrician, a primary-care nurse, a physiotherapist, an occupational therapist, a social worker and a dietician, met weekly to establish and update the care plan and to monitor her progress. She continued on hemodialysis at the acute hospital three times a week.

The social worker arranged transportation to the dialysis treatments and a change in the times for dialysis to facilitate transportation and to minimize disruption to the rehabilitation program. The social worker also provided counselling to the patient and her family, helped her find an appropriate apartment and helped her to hire a housekeeper once she returned home. After nutritional assessment, the dietician prescribed a low-protein, low-potassium, fluid-restricted, no-added-salt diet. Appropriate nutritional supplements were added to increase her calorie intake. The dietician also educated the patient and the homemaker regarding the patient's dietary needs.

The geriatrician monitored the patient's cardiovascular, fluid and mental status, and reviewed and modified her drug regimen. He noted that she tended to fluid overload, with weakness and confusion before her Tuesday dialysis, which corresponded to the longest interval between dialysis sessions. By experimenting, this physician found that by administering 60 grams of oral sorbitol on Monday mornings, he could minimize her symptoms while she waited for the next dialysis. Also, during her admission, he arranged for a blood transfusion for symptomatic anemia.

The physiotherapist assessed her musculoskeletal system, her balance and gait, and her ability to carry out transfers. She prescribed lower-extremity-strengthening exercises and a wheeled walker and gradually increased her walking distance and slowly reintroduced stair climbing. The occupational therapist assessed her capacity for self-care and homemaking abilities (including bathtub and kitchen activities) and visited the home to assess that environment. This therapist taught her energy minimization techniques and prescribed a raised toilet seat, toilet frame, bath-transfer seat, bath grab-bars and a hand-held shower. She also trained her to use a motorized scooter for longer trips outside the home. The primary care nurse monitored the patient's skin, fluid and mental status and assisted with the exercise and walking program.

This patient was discharged to a one-bedroom apartment 111 days after admission to the rehabilitation unit. Home-support services included a house-

keeper hired to provide daily homemaking assistance, a visiting nurse to monitor medication compliance and train the housekeeper to assist the patient with bathing, and a community occupational therapist to monitor the home modifications and to assist the patient in the use of the motorized scooter. A follow-up home visit four months after discharge found that the patient was coping well.

Tailoring geriatric rehabilitation to ESRD patients

Such rehabilitation must be tailored to the characteristics and needs of these elderly patients. The team requires special education about ESRD, including common symptoms and complications of chronic renal failure and dialysis-related complications [26]. Because of the specialized needs of ESRD patients, the team needs good communication with the nephrologists so as to help with problems as they arise. The timing of hemodialysis is negotiated between the rehabilitation team and dialysis unit to minimize any symptoms which might interfere with rehabilitation and to facilitate, for example, the scheduling of dialysis treatments on the weekend or at night when there is no active rehabilitation. When setting up a rehabilitation schedule for patients on dialysis, particularly hemodialysis, the staff must consider fluctuations in symptoms and functional status. Those on hemodialysis may experience uremic symptoms or fluid overload before dialysis that can impair their ability to participate in rehabilitation. After dialysis, these patients may experience dizziness, fatigue and/or hypotension which may also interfere.

Because most ESRD patients are on several medications, one must provide close observation of medication compliance and side effect. Doses of renally excreted medications must be adjusted appropriately. ESRD patients require close monitoring of blood pressure, cardiovascular symptoms and fluid status. Depression, confusion and malnutrition are common in elderly ESRD patients [22, 26, 27]. These conditions must be investigated and treated appropriately to achieve maximal benefits from rehabilitation. The anemia associated with ESRD may produce more symptoms in the elderly who tend to have diminished cardiac reserve. They may need erythropoietin or blood transfusions to allow them to participate maximally in rehabilitation.

Summary and conclusions

ESRD patients over 75 years of age represent the most rapidly growing segment of the dialysis population. Many of these elderly have functional, social, cognitive and affective defects in addition to multiple medical conditions. These frail elderly ESRD patients are at risk of long-term institutionalization, which often can be averted with geriatric rehabilitation. Such rehabilitation is based on comprehensive geriatric assessment linked with active

rehabilitation by an interdisciplinary team working towards the goal of restoring elderly patients to their maximal physical, mental, and social function. Future research should evaluate the effectiveness of geriatric rehabilitation for frail elderly ESRD patients.

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CHAPTER 32

Surrogates of nutritional status as prognostic indicators for elderly hemodialysis patients

WILLIAM F. OWEN

In an unprecedented fashion, the patient with end-stage renal disease (ESRD) is subjected to analysis of laboratory variables on a frequent and routine basis. The nephrologist has to evaluate this large data base to determine if the dialysis and ancillary therapies are adequate for the individual patient and appropriate for any emerging problems. Although we have known for over two decades that patients with ESRD on maintenance hemodialysis are at a significantly greater risk of protein-calorie malnutrition [1–6], this major clinical problem is still neglected. However, as will be discussed at length, the use of selected common laboratory variables can provide an accurate and clinically relevant assessment of a patient's nutritional health.

The current neglect of malnutrition in patients with ESRD is reflected in the infrequent appearance of 'malnutrition' as a concurrent diagnosis for hemodialysis patients in the greater Boston area and among other large hemodialysis practices within the United States (Lazarus JM, personal communication). Of the hemodialysis patients discharged from a Boston hospital during 1991, fewer than 10% carried a concurrent diagnosis of malnutrition. Except for one retrospective case-mix study, the 1991 United States Renal Data Survey did not recognise or discuss malnutrition (Port F, personal communication). However, as will be discussed later, clinically significant malnutrition is not uncommon among hemodialysis patients.

The infrequency of the diagnosis of malnutrition in these patients arises from a multiplicity of factors. Typically, the hospital does not have careful records of a patient's premorbid weight and, therefore, objective documentation of critical weight losses is not possible. Dietary histories are notoriously inaccurate, laborious to collect, and tedious to quantitate. Because of increases in adiposity and body water, the physical exam of many hemodialysis patients does not detect the stigmata of protein-calorie malnutrition that are so observed readily in patients without ESRD. Anthropometrics depend upon the investigator and are extremely time-consuming. Although complimentary physical-based techniques, which permit the assessment of lean body mass, such as dual emission X-ray absorptiometry, bioelectrical impedance, and nuclear magnetic resonance imaging are extremely sensitive, they are

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not routinely available. Lastly, laboratory measurements such as plasma aminoacid profiles and the serum prealbumin and transferrin concentration are not performed routinely. The serum albumin concentration is influenced by the individual's volume status and liver function and, because of its long turnover, may not seem to be sufficiently dynamic. Therefore, nephrologists do not routinely perform nutritional assessments on patients with ESRD because they are not easy to do!

A nihilistic view of malnutrition among patients with ESRD is that these patients do well despite an inactive pursuit of its presence – therefore, why be concerned about it? However, we should be concerned about every patient's nutritional status regardless of their renal function. The critical role of adequate nutrition in patients on hemodialysis was emphasized by the National Cooperative Dialysis Study (NCDS) [7–9]. Although the clearance of the dialyzers and the patients' dialysis times were the variables that were manipulated during the study, the patients' protein catabolic rate (PCR), a surrogate of dietary protein intake at steady state, was a major predictor of an adverse patient outcome. Patients with a low PCR (less than 0.8 g/kg/day) did poorly, irrespective of the quantity of their dialysis. Also, Arcchiardo *et al.* reported that, of the small number of hemodialysis patients they evaluated, the subjects with the lowest mortality were those with the highest BUN [11]. Presumably such individuals had greater PCRs and were better nourished than their counterparts with lower BUNs. As a consequence of these two studies, the PCR has become the principal measure of nutritional adequacy for hemodialysis patients.

However, problems may arise when PCR is used to assess the nutritional state of hemodialysis patients. Because many patients being dialyzed in the United States are too old and ill to have qualified for the National Cooperative Study which was conducted in the 1970s, the PCR recommended may be inadequate for patients in this decade. Further, the PCR, which is a measure of dietary/protein intake only if the patient is in a metabolic steady state, is derived from the patient's urea generation rate and the volume of distribution for urea. Accurate extrapolation of all of these variables in turn depends upon precise measurements of the dialyzer urea clearance, dialysis time, and blood and dialysate flows [10]. Therefore, this almost incestuous relationship between the PCR and the time-dependent fractional clearance of urea (KT/V) renders the PCR error prone.

Pursuant to defining a simple and widely applicable means of evaluating the nutritional status of hemodialysis patients, a logistic regression model was established to evaluate the death risk contributed by demographic variables and by selected common laboratory variables. The initial patient data base was 22,550 hemodialysis patients who were served during 1989 by the large dialysis provider, National Medical Care (NMC). To be included in the study, the patient must have been treated by thrice-weekly hemodialysis and must have either died or completed the year on dialysis. Patients who survived the year, regardless of their general health, were defined as suc-

Table I. Influence of case mix and laboratory variables on death risk

Predictors	Regression coefficient	*SE*	χ^2	*p*
Case mix				
Age	0.032	0.002	281	*
Sex (female)	−0.411	0.051	65	*
Race (non-white)	0.066	0.052	2	0.204
Diabetes	0.180	0.052	12	*
Laboratory tests				
Albumin	−1.545	0.082	359	*
Creatinine	−0.0880	0.008	94	*
Cholesterol	−0.002	0.001	19	*
BUN	0.005	0.002	9	*

* $p < 0.005$.

cesses, whereas those who died, irrespective of the cause of death, were defined as failures. Lowrie and Lew have previously described logistic regression models and the validation of their use [12]. In brief, they performed a base analysis using a forward, stepwise, logistic regression to evaluate case-mix variables. Then laboratory values were added to the logistic model. Crude risk ratios were estimated, whereas risk ratio adjusted for case mix were estimated by a logistic model that included a series of binaries, which divided the variable of interest into groups.

The median age of the final patient sample of 13,535 was 61.0 years (58.6 ± 14.9; mean ± SD); 50.4% of the patients were women, and 53.3% were non-white [12]. Thirty-two percent of the patients were diabetic. At the time of evaluation the median duration of dialysis was 39.9 months (54.9 ± 44.9) [13]. The risk of death analysis is illustrated in Table I. The chi-square statistic in this analysis, which quantitates the relative importance of each variable to the model, was greatest for age. Females suffered less risk than males (exhibiting a relative risk of approximately 0.66), whereas race was not a predictor of an increased mortality when laboratory variables were included in the analysis. Lastly, diabetics suffered a greater death risk than non-diabetics (relative risk of approximately 1.12).

Serum albumin was the most significant laboratory variable, followed by the serum creatinine concentration. Surprisingly, higher creatinine concentrations were associated with a lower death risk (negative regression coefficient). Likewise, the cholesterol and BUN were highly significant predictors of an increased death risk.

An analysis of the relative death risk over a range of serum albumin concentrations yielded a 'J'-shaped curve. Using a reference concentration range of 4.0–4.5 g/dl (value of 1.0), the death risk increased to 1.5 for values between 3.5–4.0 g/dl, 3.0 for values between 3.0–3.5 g/dl, 7.5 for values between 2.5–3.0 g/dl, and 16.2 for values less than 2.5 g/dl (case mix and

laboratory adjusted). Therefore, a serum albumin concentration that is considered within the range of normal by many laboratories (3.5–4.0 g/dl) is associated with a significantly increased death risk for hemodialysis patients.

Similarly, the relative risk of death is greater with a reduced serum creatinine concentration, such that a plot of a range of creatinine vs. death risk value also yields a J-shaped curve. Using a reference range of 12.5–15.0 mg/dl, the death risk increased to 1.25 for values between 10.0–12.5 mg/dl, 1.4 for values between 7.5–10 mg/dl, 2.25 for values between 5–7.5 mg/dl, and 4.75 for values less than 5.0 mg/dl.

The serum albumin and the serum creatinine concentrations were highly correlated ($r = 0.411$, $p < 0.0001$) in a curvilinear fashion, which suggests a common clinical attribute. We postulate that the serum albumin, which is a measure of visceral protein mass, and the serum creatinine concentration, which is a measure of somatic protein mass, are powerful shared predictors of death risks for hemodialysis patients; both depend upon the patient's nutrition. Although it may be argued that these surrogates of nutrition are reduced by life-threatening comorbid conditions such as diabetes, and that hypoalbuminemia and a low serum creatinine simply indicate one of these comorbid illnesses, our model states just the opposite. Improved nutrition with a comorbid illness reduces the death risk!

The relationship between the relative death risk and the BUN and cholesterol is more complicated. When death risk was adjusted for case-mix differences, both a reduced BUN (less than 50 mg/dl) and an increased BUN (greater than 110 mg/dl) were significant death-risk predictors. However, when the BUN was adjusted for laboratory variables, the influence of a low albumin was so great that the BUN became insignificant. It is tempting to speculate that the increased death risk observed with an elevated BUN is a consequence of inadequate dialysis. Therefore, unlike the serum creatinine an elevated BUN increases the death risk because of the greater influence of uremia on the BUN vs the influence of nutrition on creatinine. A similar pattern was observed for the cholesterol. Studies are underway to determine whether dialysis adequacy or nutrition has the greater influence on death-risk among hemodialysis patients.

In summary, the serum albumin concentration is a powerful and simple predictor of death probability for hemodialysis patients. Further, this analysis has allowed us to identify threshold albumin values which place patients at an increased risk. We have observed that virtually 50% of the patients studied have serum albumin studied outside the 'safe' levels and therefore are at a significantly increased risk. Modern patient management should include a reinterpretation of the laboratory data base with the realization that neither a low creatinine nor a low BUN are indicators of good dialysis. Measures that encourage patients to eat more may greatly improve the lot of those on maintenance hemodialysis.

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CHAPTER 33

Nutrition in the elderly CAPD patient

BARBARA E. WENDLAND

Elderly individuals are at risk of malnutrition due to the aging process. Concurrent disease further impacts on the ability of the body to absorb and use nutrients. Chronic renal insufficiency, with its frequent protein-energy malnutrition, can severely compromise nutritional balance.

Within the Toronto region, the number of elderly patients undergoing dialysis has increased progressively; about 45% receive continuous ambulatory peritoneal dialysis (CAPD). These patients are at risk of significant nutritional problems because of age and renal insufficiency but also because of subclinical malnutrition, when they are maintained on CAPD [1, 2].

Malnutrition

With aging, the body's homeostatic balance shifts producing disease, alterations in nutritional status and changes in medication requirements. The malnutrition is due to such factors as decreased intake, an increase in losses and changes in the metabolism of nutrients [3] (Fig. 1). Risk factors for malnutrition include social and economic circumstances, psychiatric disorders, cultural practices and inadequate knowledge/education.

Table I lists factors to be considered when evaluating malnutrition in patients on dialysis. Biochemical abnormalities such as hyperglycemia, hyperphosphatemia, potassium imbalance and acidosis are common in those on the peritoneal techniques. Metabolic acidosis can cause tissue catabolism. Correction of acidosis using dietary bicarbonate improves nitrogen balance in humans [4], and reverses muscle protein degradation in animal models [5].

Some patients with uremia have changes in taste acuity, nausea and vomiting, as well as anorexia. Sometimes peritoneal dialysis itself will achieve inadequate clearance of toxic factors, thereby compromising the patient's ability to consume an adequate diet. Hyperglycemia, abdominal distention and pain with dwell-and-drain procedures also can interfere with nutrition.

This population may have concurrent medical problems involving the

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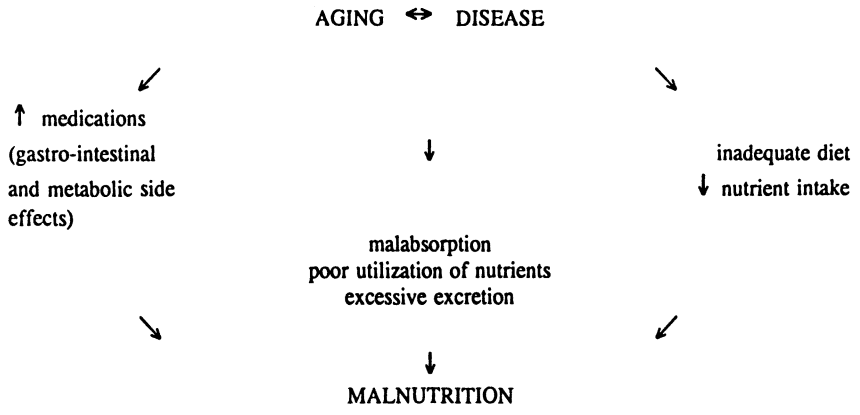

Fig. 1. Aging and malnutrition.

Table I. Factors that increase the risk of malnutrition with dialysis

Biochemical abnormalities
Uremic factors that prevent adequate consumption and absorption of nutrients
Peritoneal dialysis
Concurrent medical problems
Medications

gastrointestinal tract, as well as diabetes, carcinoma, and cardiovascular insufficiency. Intercurrent illness usually produces changes in eating patterns, often with accompanying anorexia. In addition, many medications have gastrointestinal and/or metabolic side-effects, further compromising nutritional balance.

Continuous Ambulatory Peritoneal Dialysis (CAPD)

Protein-energy malnutrition affects about 41% of the CAPD population [6]. Earlier studies reported an incidence ranging from 42 to 56% [7, 8].

The continuous dialysis procedure offered by CAPD offers some nutritional advantages (Table II). The improved control of metabolic acidosis and the avoidance of intradialytic catabolism maintain greater nutritional stability. Also dextrose absorption from each dialysis exchange provides a continuous source of energy which is beneficial in some individuals.

Some major nutritional problems are associated with CAPD (Table III). Of particular significance are the daily losses of protein and amino acids with the exchange procedures and peritonitis, which causes an additional loss of protein. The inflammatory response to bacterial infections in peritonitis may

Table II. Nutritional advantages with CAPD

Stable metabolite levels due to continuous dialysis
Prevention of hyperkalemia and other electrolyte disorders
Improved control of metabolic acidosis
Effective removal of middle molecules
Continuous energy supply
Intradialytic catabolism (such as in HD) is avoided

From Ref. [2], with permission.

Table III. Nutritional problems with CAPD

High incidence of peritonitis
Loss of protein (5–15 g/d) and amino acids (2–4 g/d)
Anorexia due to glucose absorption, abdominal filling, insufficient dialysis
Hyperglycemia and hyperinsulinemia
Hyperlipidemia and dyslipoproteinemia
Obesity

From Ref. [2], with permission.

impose a strong catabolic stimulus and enhance protein loss, contributing to a negative nitrogen balance [2].

Recently, Bergstrom illustrated the changes in appetite experienced before and after the commencement of CAPD therapy (Fig. 2). Initially there is a decrease in appetite as glomerular filtration rate (GFR) decreases. With the initiation of CAPD, appetite begins to increase, despite a progressive fall in

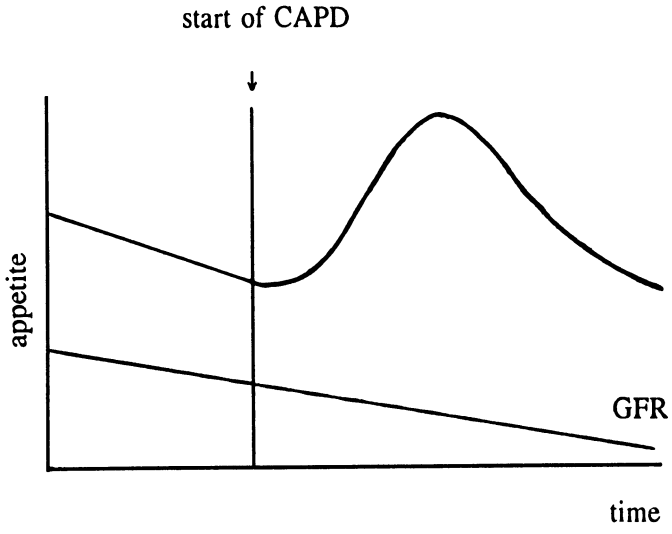

Fig. 2. Charge in appetite before and after CAPD.

GFR; however, over time appetite again begins to decrease in conjunction with GFR, despite the continuation of dialysis.

A multicenter international study using the subjective nutritional assessment [1] found that varying degrees of malnutrition existed within the CAPD population. Of 224 patients, about 8% were severely malnourished, while about 33% were mildly affected and 59% were judged to be normal. In this population, marginal deficits may be quite significant.

Health-care professionals are not always aware of the contribution of nutrition to the maintenance of health throughout the life cycle. Sub-clinical or marginal deficits may go unnoticed and undocumented [9].

Nutritional assessment

One diagnoses, characterizes and quantitates malnutrition through nutritional assessment [10–12]. Similar to clinical diagnosis [12] the overall evaluation requires a systematic approach: the patient's history, physical examination, the evaluation of anthropometric measures, nutrient intake and significant laboratory parameters. Rarely is any one piece of information conclusive. The diagnosis of malnutrition is made not by a fixed formula but from a synthesis of information gathered during the assessment [11, 12].

Medical history

In reviewing the medical history, it is important to discuss changes in body weight, pre-uremic weight and overall appetite status. Careful questioning about gastrointestinal symptoms, intercurrent illness, functional capacity, as well as medications is necessary in a comprehensive review for risk factors for malnutrition.

Physical examination

Interpretation of physical examination data is dependent upon the training, skill and experience of the clinician [11]. Subtle forms of malnutrition can occur. It is particularly important to evaluate patients for muscle wasting and loss of subcutaneous fat, as well as the presence of edema.

In a study done by Cohn *et al.* [13] it was found that in the elderly, although usual body weight may remain stable, typical changes in body composition occur with age. There is a trend towards an increase in body fat stores along with a decrease in muscle mass, with the aging process in men. Munro has further discussed this phenomena [14].

Table IV. Nutritional assessment in dialysis patients – laboratory parameters

Biochemical parameters
Serum urea and creatinine
Serum sodium, potassium, bicarbonate, calcium, phosphorus
Serum total protein, albumin, transferrin
Blood glucose
Serum triglyceride, cholesterol
Hemoglobin, hematocrit, ferritin
Urine and dialysate outflow volumes (per 24 hr)
Urine and dialysate protein losses
Total (renal and dialysate) creatinine and urea clearance and calculation of urea nitrogen appearance

Adapted from Ref. [2], with permission.

Anthropometric measures

In the dialysis patient it is important to monitor body weight (post-drain), height-to-weight ratio, as well as percent relative and desirable body weight. Body water may fluctuate in circumferential measures and skinfold thickness might be used in some situations. However, the usefulness of these measurements in accurately assessing nutritional status remains questionable.

Evaluation of nutrient intake

Assessment of nutrient intake can be accomplished by the active involvement of a professional dietitian. Nutritional interviews, evaluation of intake, monitoring response to therapeutic intervention, and education are the primary activities of this health professional.

Dietary protein intake can also be estimated by calculating urinary plus dialysate urea nitrogen appearance rate. Protein loss into the dialysate and glucose absorption with each peritoneal exchange must be considered when evaluating total nutrient intake [2].

Biochemical parameters

A number of biochemical parameters can be used to evaluate nutritional status as well as dialysis adequacy. Table IV indicates the most significant laboratory studies.

Data published in the 1970s popularized the use of albumin and transferrin as major indicators of protein malnutrition in individual patients [15]. A low serum albumin level is commonly found in patients with protein-energy

malnutrition, as a result it has gained widespread acceptance as s measure of nutritional status [16].

Data published by Shizgal and co-workers suggested that albumin is a poor parameter for evaluating an individual patient's nutritional state; however, it is a valid marker of nutritional status of large populations for epidemioligcal studies [16].

Studies suggest that there is a significant association of reduced serum albumin concentration with increasing age [17, 18]. In the CAPD population, serum albumin in elderly patients was found to be significantly lower than levels in younger patients, and to remain lower over time [18].

In a study of albumin synthesis in CAPD patients, Kaysen *et al.* found that albumin homeostasis was maintained through a decrease in catabolism concurrent with an increase in synthesis of this protein. All major albumin pools were also maintained despite massive albumin loss with dialysis [19].

Hypoalbuminemia is common in hospitalized patients as a result of alterations in anabolism and catabolism, loss of albumin, or its redistribution between various body compartments [20]. There is a marked correlation between depressed albumin levels and the incidence of morbidity [21] and mortality [20]. Low serum albumin is common in patients with infection [21] and also is associated with delayed wound healing [20].

Within the CAPD population, survival was longer in patients with an initial serum albumin above the median, compared to those initially below [18]. Initial serum albumin is also believed to be a more significant predictor of success and failure on CAPD than is age, diabetic status, sex or urea clearance (KT/V) [18].

In CAPD patients, the appearance of signs and symptoms related to inadequate dialysis or malnutrition often is insidious. Over the short term, laboratory measures used to assess changes in uremia control during dialysis are difficult to interpret accurately [2]. As a result, we are challenged to determine cause and effect relationships regarding the control of uremia through adequate dialysis and prevention of malnutrition [2].

Single measurements of serum urea and creatinine are not useful in determining dialysis requirement or the need for modifications in protein intake. Serial analyses are needed to detect trends in these variables and allow for corrections in the dialysis prescription to enable optimal clearance of toxic metabolites. Also, serial measurements of creatinine and urea levels may provide valuable information regarding nutritional status, particularly if corrected with data on urea and creatinine clearance over 24 hours [2].

Urea kinetic modelling has been widely used to assess treatment adequacy in the hemodialysis population for a number of years. By the standards of urea kinetics, many CAPD patients would be described as underdialyzed [22]. However, at present, studies have not shown a significant difference between morbidity and mortality between CAPD and hemodialysis patients [22].

In a recent study published by Blake *et al.* it was suggested that urea

kinetics in CAPD patients had limited relevance in assessing the adequacy of dialysis in this population [22]. It was felt that the present model is predictive of some biochemical outcomes but not clinical outcomes. Of particular interest is the discrepancy between actual and recommended protein intake in the CAPD population. Under stable conditions, protein catabolic rate should be equivalent to dietary protein intake. These data suggest that under stable conditions, the requirements for dietary protein is about 0.9–1.0 g/kg/day in CAPD patients (not the ≥ 1.2 g/kg/day advocated for the past several years) [2].

Nutritional intervention

Protein-energy malnutrition and wasting are common in patients on maintenance dialysis. The major causes are inadequate intake and the impaired metabolism of protein and energy in uremia [2].

The ongoing nutritional management of these patients requires interval assessment of their nutritional status. Recommended daily nutrient intakes are presented in Table V.

When working with the elderly dialysis patient, it is important to maintain a humane approach to care. The ideal model would be of a multidisciplinary team, providing individualized care, with realistic goals which are aimed at integrating the physiological needs of the patient.

Table V. Recommended nutritional intakes in patients undergoing CAPD

Dietary energy intake	$\geq$ 30 kcal/kg/d
Total energy intake	$\geq$ 35 kcal/kg/d
Dietary protein intake	$\geq$ 1.2 g/Kg/d
Water and sodium chloride	As tolerated by fluid balance
Potassium	60–80 mmol/d
Magnesium	200–300 mg/d
Calcium	1.0–1.4 g/d
Phosphate	0.7–1.2 g/d
Supplemental vitamins:	
Ascorbic acid	100–200 mg/d
Vitamin B_1	10–40 mg/d
Vitamin B_6	5–15 mg/d
Folic Acid	0.5–1.0 mg/d
Vitamins B_{12}, A, E & K	None
Trace elements	Not established

From Ref. [2], with permission.

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CHAPTER 34

'You can't teach an old dog new tricks'

LINDA CALLAGHAN, MAGGIE CHU, ALICE CUMINGS, ROSE FARATRO, BONNIE HOUGHTON, KIMMY LAU and BETTY KELMAN

This well-worn cliché heard frequently from persons entering the Home Dialysis Unit at The Toronto Hospital offers an opportunity to explore the feelings and beliefs of both nurses and patients about the learning experiences of the elderly in the home-dialysis setting. Six nurses and one staff educator co-operated to present aspects of learning in the elderly. The group reflected on the shared experience of learning relationships in light of recommended principles for effective learning. A literature review suggests that barriers to learning are potentially overwhelming in persons facing normal aging processes combined with the changes associated with renal failure. Yet, despite all the perceived barriers, effective learning frequently does occur.

The concept of intuitive learning validates our feelings about the nature of the learning relationships in the Home Dialysis Unit. Denis and Richter define intuitive learning as a process that results in the acquisition of "knowledge, skills, habits or actions without recourse to objectives, goals or consciously planned steps" [1]. Following their recommendations regarding intuitive learning, we elected to "reflect upon and draw new insight from (their) own experience." Each learning encounter represented a new experience for teacher and learner in the Home Dialysis Unit. As a result, all participants were learners and created an environment for behavioral change and individual development.

The group expanded the sharing to include individuals who had completed home dialysis training. We drew up interview questions and videotaped seven people in conversation with nurse-interviewers. Two and one-half hours of interviews were edited to a half-hour presentation for discussion purposes. The final videotape included interviews with four women and two men. Three of them had a short period of home dialysis while the remaining three had been on self-care CAPD for several years. William 74, and Emily, 75, had been on home CAPD for one year each. Charlotte, who was 85, had been trained for home CAPD but, after six months at home, had returned to hospital intermittent peritoneal dialysis (IPD) for medical reasons. She lived at home independently and commuted to hospital twice weekly for her treatment. At 77 Elaine had been on home CAPD for 14 years. Recently

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she had transferred from System III 'spike' set (Baxter) to the Ultraviolet Flash (R) (Baxter) system and needed a retraining course. Finally, Andrew and Maude worked as a team. Originally they started with the Oreopoulos–Zellerman (O–Z) set seven years ago and had just transferred to the Ultraset®. Gradually Andrew, 82, had assumed greater responsibility for his wife, who was 81. The experience of home training varied for these individuals. Some had memories of the initial training period while others could reflect on both the initial and follow-up sessions in the Home Dialysis Unit. However all believed that learning did not stop with training but was a continuing process for those adapting to life with renal failure.

Adult learning principles

The discussion focussed the participants' attention on the patients' and family members' perceptions of issues relevant to the theoretical principles. In their text, 'Adult Learning Principles and Their Application to Program Planning' Brundage and MacKeracher [2] spelled out 36 adult learning principles. Of these, 12 related to motivation, health, self-image and organizational strategies and these were chosen for a panel discussion prior to showing of the videotape.

Adult learning assumes that adults enter programs voluntarily out of need or desire. Thus, the voluntary learner is motivated to learn. Those who are compelled into learning program by others may feel anxious and threatened by the experience and these feelings may impair the learning process. People entering dialysis are not voluntary learners. For many, the learning is imposed suddenly at a time of increased stress and physical debilitation. Another principle explains in part why so many people are able to learn despite anxiety and other normal stress reactions. Adults focus on learning material that is immediately relevant to personal problems, concerns or tasks. Brundage and MacKeracher [2] suggest that life crisis constitutes a strong motivator for learning. Both William and Charlotte were able to identify the motivating factor in succinct and graphic comparisons. William said: "I have a very forthright daughter. She said it's either this or a pine box. It's a crude way of putting it but true." Charlotte asked, "What else can you do with me? Throw me out in the garbage!"

Counterproductive to learning in home dialysis settings is the principle that "adults learn best when they are in good health, are well rested, and not experiencing stress." When individuals in renal failure enter dialysis, they may be stabilized but still have uremic symptoms, such as fatigue, decreased concentration, forgetfulness and slower response times. Brundage and MacKeracher [2] suggest that individuals over the age of 50 may show a slight decline in "overall mental ability", not because of changes in verbal ability but because of alterations in non-verbal ability. Thus, learning that

requires physical flexibility, speed and mental recall may be impaired by the changes associated with aging [3, 4].

Despite health status and aging, our patients agreed that it was possible to learn about renal failure and dialysis. William noted that, although he had been depressed by his unexpected loss of renal function and the need to adjust to this loss, the skills had been easy to acquire. Charlotte was not intimidated by the technique even though her cardiac and nutritional deficits prevented her from continuing with CAPD. Emily had learned the skills but initially needed a visiting nurse's help with bag medication. She had hand tremors but, after a few months, Emily was able to continue independently. With increased strength and confidence, her ability to perform CAPD improved over time. Andrew and Maude noted that their initial training had been difficult due to Maude's poor health, but with acceptance that Andrew would be the primary partner, the learning progressed. Andrew found it difficult to learn the selected CAPD system so on the second day the nurse transferred Maude to an alternate system. The staff nurse must carry out an ongoing evaluation of the individual's capabilities to adjust the approach and system to the individual's actual performance. Elaine noted that her 14 years of CAPD did make easier transition from one CAPD system to another, also she expressed nervousness and anxiety about new episodes of learning. All of the patients believed that they could learn dialysis but overwhelmingly, wanted to discuss coping with home dialysis following discharge from the training unit. William said that, only after six months, was he able to accept CAPD into his life. Perhaps acceptance of the treatment may reach only a stage of tolerance.

These people were able to use established patterns to cope with the learning experience; according to Brundage and MacKeracher [2] past experience may prove to be either a help or a hindrance. If one has been successful in the past and values the experience, entry into new experiences may be less threatening. For example, on the first day of training Emily described herself as "too stupid to learn" whereas William felt that his lifelong commitment to education provided a foundation for learning. Many people do not appreciate that learning is not always a formal or institutional experience but is lifelong. Thus, the 'housewife' who arrives stating that "I am too stupid to learn, I never even finished high school" may not realize that the knowledge and skills acquired in the running of a household and raising a family may help her to learn CAPD. Frequently North American society equates intelligence and abilities with certificates and diplomas but equally life experiences allow for individual growth and development. Charlotte who had worked a farm, raised 18 children, cared for a husband injured in the war, and learned basic nursing skills on moving to the city, had no illusions about her ability to learn. She "was willing to try anything" and felt herself able to rise to the new demands because "there's not one of us can't learn if we just put our minds to it."

Because living had a purpose, these individuals were inspired to cope with

new learning needs but this is not always the case. For example one man, who had difficulties during training but had learned the skills and been discharged home, returned to hospital. He was transferred to hemodialysis. At 67, this man was the youngest to be interviewed and, in spite of strong home supports, had not been able to continue home CAPD. His ambivalence towards treatment made training and interviewing difficult. On the surface, he seemed to want to please caregivers by participating in training but his subsequent actions contradicted his stated willingness. Thus not all older individuals will cope with learning.

In selecting patients for home CAPD, one cannot easily predict outcomes. Thus, we avoid labeling individuals as 'learners' or 'non-learners' but instead, respect their differences and explore with the individual patients, their abilities and strengths for home dialysis. As Charlotte would say, "nothing tried, nothing gained." Emily who believed she could not learn, did learn. Emily's family had been told death was imminent. After transferring from a suburban to a teaching hospital, Emily was stabilized and entered into the home training program. A year after this brush with death, Emily was coping well with home CAPD. At one point, however, she said, "You know Rose, I get so tired. You know yesterday, I had my hair done, went out to lunch, went grocery shopping with my son and then had my grand-children in to visit. And I was so tired at the end of the day." Emily's sense of humor, her fighting spirit and enjoyment of life prevailed even though she said she was too stupid to learn.

This paper attempted to highlight that learning may be described as the intuitive process. We may sense, feel and reflect what is hard to capture by scientific enquiry; however, we can learn much by this exploration into experience.

Brundage and MacKeracher recommend that sensory capabilities such as vision and hearing be in the best condition possible because "without good sensory capabilities, the learner will take in reduced or inaccurate information" [2]. While Andrew and Maude used posters in large print that had been produced by hand as guidelines, Charlotte found her eyesight was not sufficient to read written materials. Familiar with government manuals, William found the patient manual a useful adjunct to learning. While printed materials should be varied according to individual preference, good lighting is essential if all individuals are to complete bag exchanges safely. Hearing is often reduced in the older individual, which made the nurses more conscious when giving instructions while wearing a mask. Many older people compensate by relying on lip reading. Thus, a wide variety of sensory formats help the elderly to overcome individual losses in sight and hearing.

Adult learners learn best when they know what is expected and when they can practice in a non threatening environment with feedback and reinforcement [2, 5]. Both William and Elaine stressed the need to work in a quiet setting both during training and on a continuing basis. William said he was easily distracted when someone interrupted the teaching nurse during a

training session. He said background noise and activity should be kept to a minimum because such distractions result in mistakes. One of the nurses found that older individuals have greater difficulty when they were asked to work on a model and then transfer the skills to real life. Thus, they need an opportunity to practise in a controlled setting with realistic options to learn.

Did these people feel they had been treated differently because of their age? The consistent answer was 'no'. They felt age was not a major factor and further they did not view themselves as old or elderly. Each individual saw 'self' as a unique personality in whom life experience and belief structures were of greater importance than number of years lived. Respect of the individual is a fundamental principle of adult learning. To truly see the spirit of the individual and respect that unique human quality is crucial to any learning relationship.

Summary

Learning takes place at all levels because anyone who is participating fully in life has the option of learning. It is difficult to capture what learning is but if we consider learning in part as a change in behavior, this paper attempted to provide insight into the experience of learning home dialysis. In writing this paper the greatest benefit for us was the opportunity to stop, think, talk and reflect upon the experiences of those with whom we have shared a learning relationship. We will continue this exploration and discussion but doubt that we need to focus on the elderly as a specific group because much of this applies to all adult learners in the dialysis community. The question remains, 'Can you teach an old dog new tricks?' Our experience says yes, if one takes into account all of the variables that affect life as perceived by the learner. Sometimes, even taking that approach, the answer may be no. Each learning relationship is a unique opportunity to discover whether learning is possible. In any event, age is not the only factor.

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CHAPTER 35

Challenges in the training of elderly CAPD patients

BETTY KELMAN

In this paper, challenge refers to 'something that requires a special effort and a dedication of spirit'. In this instance, the nurses in our dialysis units are dedicated to assist the elderly in acquiring the life skills needed to support life on CAPD despite doubts within the community about the social usefulness of such a treatment for the elderly. Recently, Daniel Callahan [1] has written about the necessity of setting limits to medical care. He asks society to accept the concept of life span as a natural event with a natural ending at the right and appropriate time. Further he suggests that, given this acceptance, interventions like dialysis would not greatly increase the life expectancy of the elderly patient and thus, in the future, should not be applied in this population.

Educators in dialysis are challenged to determine whether CAPD is a desirable option for the elderly, who develop end-stage-renal disease. Callahan urges us not to be afraid to face our mortality and stresses that society and particularly, leaders of health care must change their attitudes and approaches to chronic illness in the elderly in order to accept the inevitable.

In the current situation, we still view the elderly as a group who may benefit from the treatment of renal failure. Many of our patients reflect a strong desire to live and frequently this is the prime motivating force for entering home dialysis. In commenting on the alternatives to life on CAPD, a patient used such strong images as the pine box and the garbage heap about his other options. Other reasons to live such as caring families and goals not yet realized were also cited as factors influencing the decision to continue living.

The individual entering home dialysis has many complex problems: the normal aging process is complicated by renal failure which may create barriers to learning. Not all people experience the same changes; thus before the training period, each will need individual assessment of needs and capabilities.

In examining potential barriers to learning, a survey of nurses in the Toronto area, who were working in dialysis asked them to define such terms as 'elderly' and 'old'. It asked them to identify challenges in preparing the

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elderly for self-care during dialysis. The nurses also were asked to comment on four specific case histories and the decisions made with respect to dialysis (*vide infra*)

In the survey, 50% of the questionnaires were returned. There were 32 female and 2 male nurses. The mean age was 41 ± 8 with a range of 25 to 62 years. These nurses had a mean experience of 17 ± 7 years. Most considered themselves knowledgeable and skilled in teaching and in the care of the elderly. Those who did not feel knowledgeable and skilled were closer in age to the elderly; perhaps the closer we get to senior status, the less we feel we know.

In defining the elderly or old, many nurses noted the difficulty in defining status in terms of chronological age. While some defined 'elderly' as those over the age of 65, others felt that individuals over the age of 75 were old. While 53% of the nurses believed that age should not be a factor in selecting patients for home dialysis, the remainder believed age was important. A few set limits for home dialysis at the age of 75 to 80 while others emphasized the need for individual assessment. Even those who accepted limits for home dialysis waivered when it came to deciding treatment suitability in the case histories.

Of these nurses 88% felt that older learners were different from younger learners. In describing the differences, I will examine a few specific barriers and will make recommendations for minimizing their effect on learning.

Barriers to learning

With aging, vision declines; few people have normal vision by the seventh decade, Developing skills required for CAPD-bag exchanges may be impeded by decreased visual acuity and adaptability to light changes, loss of color discrimination to blue, green and violet and increased sensitivity to glare [2–4]. The learner may be helped by incandescent lights rather than fluorescent lighting because the latter creates greater glare. Generally, older people need three times as much light as younger people. Devices such as the Baxter-UV Flash and Abbott SCD may reduce the risk for patients who cannot see well enough to make bag or transfer set connections. Special posters and flipcards are produced for the individual who cannot read the standard type found in many manuals and printing resources.

Occasionally, patients lack numeracy skills and thus cannot distinguish differences in bag strengths. In the past, different colored labels were affixed to the bags to make a 1.5% look different from a 4.25%. The colors should be easy to discriminate such as reds, yellow and oranges rather than from the blue end of the spectrum.

It is estimated that 23% of those between the ages of 65 and 74 and 40% over the age of 75 have hearing loss [4]. People may not be able to distinguish sounds or speech patterns especially high pitched tones, which may include

consonants like 't', 'd', 's', 'f', and 'g' [2]. Accelerated speech patterns may also be difficult. In one series, altering the speed from 170–125 words per minute did improve comprehension. Also some older people may speak softly because conduction blockages make their own voices seem louder to them than to other people.

When speaking, it is important to face individuals to allow them to pick up speech clues through lip reading, facial expressions and gestures. In addition, avoiding loudness, speaking slowly and placing exaggerated stress on consonants may also be helpful The elderly also have trouble when increased background noise interferes with their concentration on the information conveyed; thus, it may prove beneficial to reduce distractions.

Musculoskeletal changes impair psychomotor skills because movements are slower and responses more sluggish, related to prolonged contraction and latency periods. Type I muscles responsible for endurance do not tend to atrophy with age, whereas Type II muscles responsible for high speed performance may be affected. Exercise can help retard the loss of muscle strength [4]. When assessing individuals for the best CAPD system, consider loss of dexterity and flexibility combined with fatigue. Involuntary tremors may be related to drug effects or impairments; however, the tremors may have no known cause [4]. Frequently, nurses who teach patients come up with custom-fit arrangements for their learners. A nurse in our unit, concerned about a patient's agility and strength in pulling tags off a transfer set, bent a coat hanger to create a good gripper for the patient who then used the hook portion and gross motor movement to remove the tag.

Some cognitive abilities such as verbal comprehension and numerical skills improve with age but memory and problem-solving may decline [5]. Problem-solving may reflect a haphazard order rather than a systematic, concentrated approach with the result that the older persons may doubt their ability to solve problems related to equipment errors. In the elderly, short-term memory may be intact although, when remembering items, older people may forget more items learned at the beginning and middle of a sequence than younger people, while having similar recall for the last learned items. Since information retrieval may be difficult, cues for retrieval and organizational assists may be useful. Many of our posters are organized by number so people remember the number of steps to complete.

It is important to clearly state and direct learning sessions with objectives known in advance. Setting the pace, teaching only meaningful information and avoiding irrelevant information may also help the older learner to focus [3]. Concentrate on the essentials. The patient does not need to understand how diffusion and osmosis work in order to remember that 'the strong bags take off more water'. Use appropriate language and decide on a mutually agreeable vocabulary. Most important of all is an objective assessment of individual strengths and weaknesses.

Learning objectives may be categorized as cognitive or knowing, psychomotor or doing, and affective or valuing. In teaching CAPD, emphasis is

placed on the first two categories but the individual must also appreciate the worth of what is being learned in order to succeed; however, feelings of self-worth are important in coping with learning that requires mistakes in order to gain competence. Older people often view mistakes as threatening their perceptions of self-worth and do not recognize that making errors is a normal step on the road to wisdom. The older person must sometimes learn to accept the value of experimentation in learning. Rather than take risks, many older people prefer a cautious approach to minimize errors because they may not trust their own response time or judgment.

The older learner may not accept body changes associated with aging which may lower his sense of dignity and result in loss of control. Respecting and valuing individual personality differences is vital in establishing a trusting relationship to achieve the growth and development required to cope with life on dialysis.

Survey response to case histories

In the survey, four case histories were presented for discussion:

1) Emily is 85 years old. She is a widow who had raised 18 children. She maintains an active interest in the family, enjoys knitting for the grandchildren and caring for her cat and two birds. With her pets, she lives alone in a two-bedroom apartment. A son lives in the same building. Emily is noted to have a slight tremor in her hands during the interview. She has angina and a history of two past heart attacks.

When Emily presented at 85 years old for dialysis, my first reaction, before meeting Emily, was that home CAPD was a ridiculous notion and that we should consider no treatment. Meeting her, I learned that she has raised 18 children, worked a farm while caring for a husband invalided from the war; despite hand tremors she had just knitted 12 sweater sets for grandchildren. She explained that her hands always shook whenever doctors came near her. Emily believed she was important to her family and was ready to accept the challenge of home dialysis. Of the nurses, 91% agreed that Emily should have the opportunity because she was active and was enjoying life. Those who felt she should not do home CAPD did so because she had pets in her home.

2) Sarah is 71 years old. She has been healthy all of her life but, on a recent admission for investigation of anemia, was found to be in renal failure. Sarah was a public school teacher for 40 years and still maintains an active correspondence with many former students. Sarah never married but lives in her own home and cares for her 91-year-old mother.

Sarah was not a problem to anyone. All of the nurses considered her to be a good candidate because she had a valuable caregiver role. Also her professional background suggested she might do well. Of course, we still do not know what kind of teacher or learner she was in the past. Many nurses

did wonder whether Sarah could continue caring for her mother as well do home CAPD.

3) James is 67 years old. He is deaf and visually impaired. James dropped out of school in Grade I. He is unable to read or comprehend numbers. James has an unstable cardiac history with hypertension and angina of several years duration. He lives with his wife. A married daughter lives close by. She works part-time and cares for two children.

James was a problem. Of the nurses, 36% felt that he was not a good candidate for home dialysis given his hearing and visual impairment and lack of literacy skills. Others were also concerned about his cardiac history. Another 32% agreed to home CAPD if the wife or daughter performed the treatment. Working with someone from the blind-deaf division of the Canadian National Institute for the Blind, James learned CAPD with an assist device. He did receive home help from a visiting nurse who did blood pressure, weights and bag selection.

4) Albert, 68, lives with his wife, Maude, in a self-contained unit in a senior citizens' complex. Light housekeeping is provided and some basic nursing assistance such as help with bathing is available. Meals are provided in a central dining room. For several years, Albert has cared for his wife, who has Parkinson's disease. Without Albert, Maude could not function in activities of daily living such as dressing and remembering to take medications. Recently, Albert has been told he has end-stage renal disease.

Sixteen per cent of the nurses did not feel that Albert could cope with home CAPD because of burdens and lack of storage space. Those who felt Albert could learn emphasized his need to maintain his caregiver role and suggested that he would be highly motivated to learn. Three months spent negotiating with the senior citizens' complex to ensure that the hospital administration would be accountable for Albert's management and support, but Albert elected to withdraw from dialysis. During his hospital stay while negotiations continued, Albert had become increasingly withdrawn and depressed. In addition, medical complications contributed to his decision to withdraw from therapy and die.

Summary

Nurses face difficulties in dialysis because the people they deal with are people not statistics, not data, but real people with hopes and wishes, fears and concerns and yet unfulfilled dreams. In making decisions about dialysis for the elderly, we must be aware of our own values and beliefs about the role of the older person in our society. Stereotyping may influence outcomes and produce a type of prejudicial behavior known as 'ageism'. If it undervalues the elderly person's status and rights, our decision-making may create a new class of victims. Who is to say that Emily's knitting sweater sets is less important than the writings of Bertrand Russell, who continued his intellec-

tual achievements well into his 'senior' years? We are challenged to determine not if the elderly can learn, but whether we accept Callahan's vision of a natural end in preference to treatment of chronic disease. Perhaps the acceptance of life and death would create a new period of enlightenment or perhaps it would mark a return to the Dark Ages when much knowledge and skill was lost. The answers will never be straightforward as long as we accept life's challenges to find meaning and value in our lives.

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PART NINE

Renal transplantation

CHAPTER 36

Host resistance and immune system

MARC E. WEKSLER, ARIE BEN-YEHUDA and
ELISABETH DUGAN

Elderly humans are more susceptible and more vulnerable to many infections than younger adults. For this reason, the elderly may be considered an 'immunocompromised host', due to the effect of age itself on the immune system and also to diseases that accompany aging which themselves compromise immune function. It has been shown that antibody response of elderly subjects to influenza immunization are inversely correlated with the severity of their associated illness [1]. Thus, immune senescence contributes to the diseases of aging which in turn, further compromise immune competence.

The age-associated decline in the immune responses to influenza vaccine reflects the generalized decline in the immune response to 'foreign' antigens. This phenomenon has been termed age-associated immune deficiency, however, there is no evidence that the total activity of the immune system declines with age [2]. Total antibody production is unchanged with age despite the decreased response to 'foreign' antigens, which is explained by the increased production of monoclonal immunoglobulins and antibodies to 'self' antigens. Similarly, the production of certain cytokines, e.g. IL-2, declines with age, while the production of other cytokines, e.g. IL-4, increases with age [3]. For these reasons, it is best to view immune senescence as a state of immune dysregulation rather than a state of immune deficiency.

The T lymphocyte

The T-lymphocyte population undergoes major alterations with age. Thymic involution leads to the appearance of antiself reactive T cells and T cells that do not express self-MHC, thus restricting antigen recognition. The increase in suppressor activity with age may be a compensatory mechanism to maintain tolerance. Independently, many T cells are impaired in their capacity to leave G0 or G1 phases – a defect in proliferative capacity that leads to a decreased helper activity, delayed type hypersensitivity and cytotoxicity. These defects affect approximately 50% of T cells from the elderly; the other T cells function normally.

D.G. Oreopoulos, M.F. Michelis and S. Herschorn (eds), Nephrology and Urology in the Aged Patient, 331–335.

Concerning the clinical consequences of a decline in cell-mediated immunity, a recent study [4] showed that anergic, delayed-hypersensitivity skin tests were associated with an increased risk of mortality and that anergy may be a good indicator of not only all-cause mortality but also perhaps of cancer mortality in healthy elderly individuals [6].

The diminution in cell-mediated immunity may contribute to the reactivation of viral, fungal and mycobacterial diseases. After age 45, the incidence of varicella zoster increases markedly. Between 75 and 85 years, the incidence of zoster increases five-fold despite well-maintained humoral immunity to the varicella virus [5]. The reactivation of primary tuberculosis in the elderly also appears to be related to diminished cell-mediated immunity. As a consequence, old dormant granulomata disseminate mycobacteria leading to pneumonia or miliary tuberculosis. Skin tests show that, while 30% of tuberculosis patients over 55 years of age are unresponsive to PPD, only 10% of patients with culture-proved tuberculosis under the age of 55 do not respond to PPD [6].

Persons over 65 years of age have a 5-fold excess death rate from influenza compared to young adults [7]. This excess death rate can be attributed to several factors, one of which is the decline in cell-mediated immunity. Because of this increased morbidity and mortality, it is recommended that vaccination against influenza be routine in persons over 65 [8]. However, 35% of the elderly over 65 do not respond because of a failure of T lymphocytes to provide adequate help to B cells to form protective antibodies; for this reason, novel strategies such as reimmunization or new vaccination are necessary to increase protection in the elderly [7].

The B lymphocyte

Recent controlled studies indicate that the aged retain unimpaired the potential function of the B cell. However, the frequencies of precursor cells to self and foreign antigens change, the repertoire of Vh usage changes, and the balance of B cells subsets are altered with age [9]. To a considerable extent, these changes are a consequence of thymic involution and alterations in T-cell repertoire and function.

Antigen presenting cells (APCs), natural killer cells and granulocytes

We can define no striking changes in APCs with age and, in general, their function is preserved. Similarly, in the elderly, natural killer-cell subsets and activity were found to be normal and their activity showed no change from that in young adults with respect to the binding of target cells and their lysis [10]. Studies of neutrophil function in the elderly have yielded conflicting results. Some investigators found phagocytosis and intracellular killing to be

reduced but others found these to be normal. In a recent report, which documented normal adherence of granulocytes to endothelium [11], migration, phagocytosis and granular secretion all were indistinguishable in old and young donors. However, *in vivo* chemotaxis of neutrophils to skin abrasion was reduced in old subjects [12]. Another group reported that senescence was not associated with deficiencies in the response of neutrophils *in vitro* to chemoattractants like streptococcus pneumonia [13]. So far, the information regarding changes in neutrophil function in the elderly is still inconclusive.

Organ-specific host resistance

In addition to the immune system, some organs have their own defense mechanisms, which protect the individual, in a non-specific fashion, from invasion and proliferation of pathogens like bacteria.

The urinary tract

Advanced age is one of the predisposing factors (reviewed in [14]) for urinary infections, probably secondary to other diseases and the loss of some host resistance factors. The decline in renal function that accompanies advanced age leads to a diminished ability to acidify the urine, maintain its high osmolality and excrete a high urea and organic-acids load. In the urine of the elderly, the level of Tamm Horsfall protein is decreased which facilitates bacterial adherence and colonization in the bladder.

While some local defense mechanisms that prevent infection are defective in the aged, other resistance factors, like the immune system, function well enough to compensate and clear most of the urinary tract pathogens.

The respiratory tract

There is no evidence of a reduction, in the aged, of mucosal immunity, which is responsible for specific IgA secretion into the lumen of airways or reduced function of alveolar macrophages. With age, the increased frequency of reduced levels of consciousness, dysphagia and malfunction of the lower esophageal sphincter may lead to aspiration of gastric contents. The cough reflex diminishes and the response to aspiration predisposes to pneumonia. As with urinary tract infection, the risk of acquiring pneumonia increases with poor living conditions and associated diseases. Thus, community-residing elderly are at less risk to pneumonia than those in nursing home. The major risk factors for pneumonia are those associated with blunted host defenses, neurologic diseases, renal diseases, deteriorating health, altered

level of consciousness, disorientation, aspiration, difficulty with oropharyngeal secretions or presence of nasogastric tube, which lead to aspiration pneumonia [15].

The gastrointestinal tract

The gastrointestinal tract maintains host resistance to a variety of pathogens mainly by gastric-acid secretion and by the gut-associated lymphoid tissue. As has been documented repeatedly, gastric acidity declines with age, secondary to gastric mucosal atrophy. The use of antacids like H_2-blockers accentuates this problem. These and perhaps other declines in host defenses which accompany age explain the 2–3-fold excess risk of the aged to develop such infections as shigellosis and salmonellosis.

The skin

The skin is a major barrier to pathogen invasion. With age, the skin undergoes extrinsic and intrinsic changes which produce functional alterations. Skin changes increase the tendency to soft-tissue infection and epidermal and dermal viral and fungal infections. Thus the skin can become a source and a focus of infection rather than a mechanism for protection.

Summary

The aging human is at increased risk for infection because of alterations in T-lymphocyte function coupled with diminished host resistance due to altered skin function and secondary to conditions such as diabetes, cerebrovascular disease, decreased functional and mental states and iatrogenic intervention.

Acknowledgements

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CHAPTER 37

Complications and preparation of the elderly recipient for transplantation

MARIANA S. MARKELL

The number of elderly patients being treated for endstage renal disease (ESRD) in the United States has risen progressively over the past 10 years. According to the 1991 US Renal Data Systems annual report, 78,478 patients over the age of 55 were receiving ESRD treatment at the end of 1989; 45,790 of these patients were over the age of 65 [1]. Renal transplantation has become the replacement therapy of choice for the majority of patients with ESRD [2]. An increasing number of older patients are asking for the transplant workup and an increasing number of elderly patients are receiving kidney transplants (Fig. 1). Despite this, the rate of transplantation among the elderly remains much lower than for the younger population, even for those at the lower end of the age range. Only 20.7% (3167) ESRD patients between the ages of 55–59 had functioning kidney transplants at the end of 1989, compared with 40% (5708) of all patients between the ages of 40 and 44 years and 46.5% (4265) of all patients between the ages of 30 and 34 [1]. For patients over the age of 60, the rate drops even lower; only 5.7% (984) of patients between the ages of 65 and 69 had a kidney transplant as their ESRD therapy.

The cause of the discrepancy in transplant rate is not obvious from gross data analysis but probably is the result of a combination of factors, including concomitant illnesses in the patients rendering them unsuitable for transplantation, nephrologist bias, resulting in under-referral of older patients, and undereducation of patients themselves, resulting in refusal of transplantation as an option due to fear of poor outcome or complications after transplant. In addition, insufficient preparation of the elderly ESRD patient before referral for evaluation for placement on the cadaveric transplant waiting list may result in delays due to completion of the required workup and finally, bias on the part of the transplant center may keep patients from the list because of poorly defined 'medical contraindications'.

It is to be hoped that as the number of studies addressing transplant complications and outcome in older, renal-transplant recipients increase, decisions regarding appropriate recipient selection in the older person will become easier. This paper addresses the issues of optimal preparation of the

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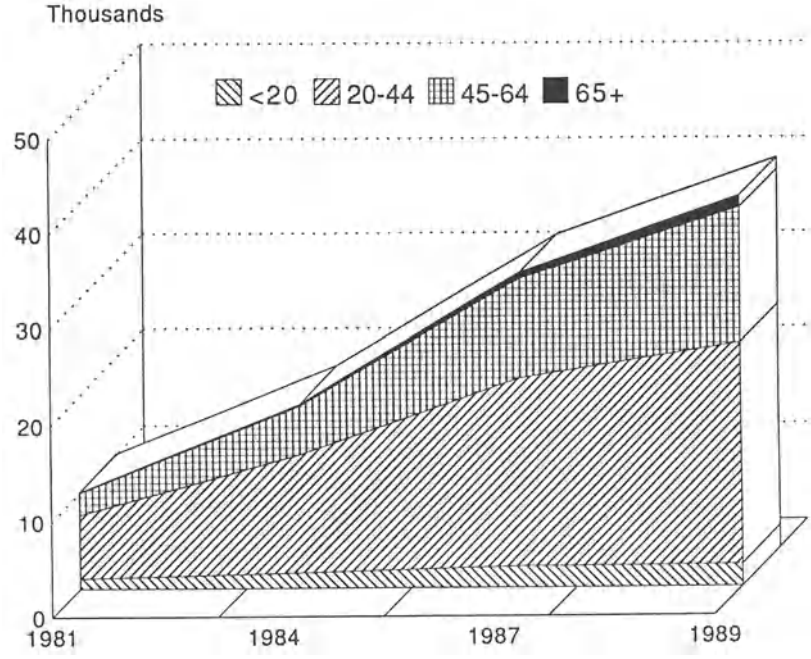

Fig. 1. Number of ESRD patients with functioning transplant by age and year of report, data taken from USRDS report [1].

older, renal-transplant candidate at our center and complications that have been encountered in kidney-transplant recipients older than 55 years of age.

Patient selection and immunosuppression

Pretransplant referral

Data were collected retrospectively from all 219 patients referred for pre-transplant evaluation to SUNY Health Science Center at Brooklyn for the calendar year 1991. We stratified groups according to age greater or less than 55 and calculated rates of acceptance for placement on the cadaveric transplant waiting list. For patients who were not accepted, reason for refusal was recorded.

Complications following transplantation

Data were collected retrospectively through chart review for all 161 patients transplanted at our center over the age of 55 years. Patients were divided into

a 'conventional' immunosuppression group (1974–1983) and a 'cyclosporine treatment' group (1984–present) for analysis of graft and patient survival and complication rate. Patients in the precyclosporine group received azathioprine (2–3 mg/kg to start) and tapering doses of prednisone (2 mg/kg/day immediately postoperatively to 0.25 mg/kg/day by 3 months). Patients transplanted using cyclosporine immunosuppression received one of two protocols. From 1984–1988, initial cyclosporine dose was 12–15 mg/kg/day tapered to achieve blood levels of 100–200 ng/ml by HPLC, and prednisone was administered in a tapered fashion as well (1 mg/kg/day tapered to 0.25 mg/kg/day as above). After 1988, patients with initial delayed function received ALG (Minnesota) or ATGAM (Upjohn) at 15 mg/kg/day or monoclonal antibody OKT3 (Ortho pharmaceuticals) at 5–10 mg/day, in addition to azathioprine 1 mg/kg/day and prednisone 1 mg/kg/day, tapered as above, with introduction of cyclosporine at 8 mg/kg/day when the serum creatinine dropped by 50% without dialysis. Further details of our immunosuppression regimens have been published elsewhere [3, 4].

Statistical analysis: 2-tailed Student's *t*-test and chi-square analysis were used where appropriate. *p*-Values of < 0.05 were considered significant.

Results

Preparation of the elderly transplant recipient

We have routine requirements which must be fulfilled before a patient is accepted onto the cadaveric transplant waiting list; however, our center, like others [5], requires older patients and those in other special circumstances to undergo further workup (Table I). Because of the high prevalence of cardiovascular disease in them, all patients over the age of 60 years (or 30 years, if they have diabetes) undergo cardiology clearance, including stress testing (thallium or persantine), echocardiography if there is indication of myocardial dysfunction or murmur, and if these tests are abnormal, cardiac catheterization. In patients with diabetes, it has been demonstrated that pretransplant cardiovascular surgery reduces mortality and morbidity in the peri- and post-transplant period [6].

If the patient is anuric or in a male patient who complains of obstructive voiding symptoms a voiding cystourethrogram and urologic consultation is performed. For patients with a history of cerebrovascular accident or transient ischemic attack, we recommend neurologic clearance and carotid Doppler studies.

Of the 219 patients referred to our center between January and December of 1991, 24% (53) were over the age of 55 years. For the total population, 61% (134) were placed on the cadaveric transplant waiting list. There was no significant difference in the acceptance rate between those over and under 55 years of age, with rates of 58% (31) and 62% (103) respectively. Of the

Table I. Suggested pretransplant workup; specific considerations for elderly patients are highlighted

All patients
Medical Summary, including family history
Social Work Summary: citizenship status, *support systems*, financial status, psychosocial evaluation, *patient's expectations of transplant, if blind or handicapped: who will assist with medications*
Recent chest X-ray (within 6 months) and PPD status
Current laboratory values and hepatitis serologies
HIV and cytomegalovirus testing
Recent electrocardiogram (within 6 months)
Recent Pap smear and *mammography*, if performed
Recent dental exam
Special considerations:
History of cancer: cancer free for 5 years or more
History of stroke or transient ischemic attack: neurologic evaluation including Doppler studies of carotid arteries
History of cardiac disease, diabetes (age > 30 years) or *all patient over age 60 years: cardiologic evaluation including echocardiogram if heart murmur, stress test (thallium or persantine), cardiac catheterization if indicated.*
Anuria or *male patient with obstructive symptoms: voiding cystourethrogram and urologic evaluation*
History of peripheral vascular disease or claudication: Doppler-flow studies of lower extremities

63 patients younger than 55 years who were not listed, reasons for exclusion included: 19% (12) who received living, related kidneys and 13% (8) who were HIV+. The majority, 57% (36), required further workup, including cardiac, neurologic or urologic clearance (Table II).

None of those older than 55 received living-related transplants or were HIV+, however one patient died during the workup and 94% (15) required

Table II. Patients not accepted for the cadaveric transplant waiting list, Jan–Dec. 1991. Total $n = 219$. Numbers in parentheses are percentage of reference population

Age < 55 years:	166 (75.5)
Total listed:	134 (61)
Reasons for not listing:	
Received living, related transplant	12 (19)
HIV positive	8 (13)
Medical contraindications	4 (6)
Required further workup	36 (57)
Age > 55 years:	53 (24.5)
Total listed:	31 (58.4)
Reasons for not listing:	
Patient death	1 (6)
Required further workup	15 (94)

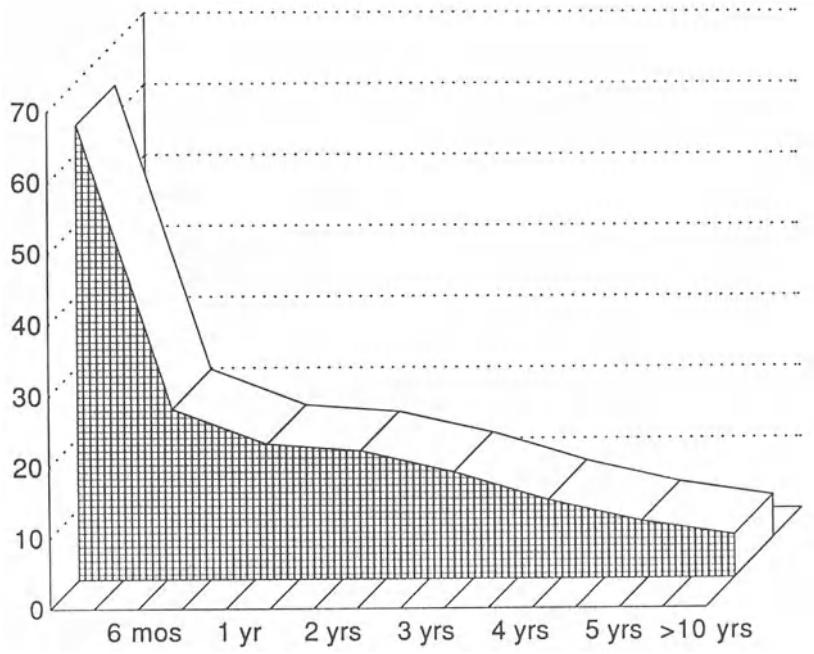

Fig. 2. Graft survival in patients older than 55 years of age transplanted at SUNY Health Science Center at Brooklyn from 1973–1984, before the routine use of cyclosporine. Numbers represent actual number of patients.

further evaluation by a cardiologist, urologist or neurologist. Obviously having the clearance data available before a patient is sent for pretransplant evaluation, greatly improved the chance of being accepted. In fact, all patients over the age of 55 years, who arrived with these data, were placed on the transplant list.

Complications in the elderly transplant recipient

Sixty-four patients older than 55 were transplanted before 1983, the average age was 57.5 ± 2.62 years (range 55–68). Only 9% (6) of these remain with functioning grafts, although the average duration of graft function was 26.2 ± 47.2 months. Fifty-six percent (36) of the patients suffered graft failure, the majority (61%, 22) in the first six months post-transplant due to rejection (Fig. 2). Death with a functioning graft accounted for 20% (7) of the overall graft losses of a total of 21 patient deaths. Causes of death and graft loss are listed in Table III. The predominant causes of death were infectious (sepsis) and cardiovascular regardless of age or renal replacement therapy chosen (Fig. 3); this was true for ESRD patients surveyed by the

Table III. Causes of death and graft loss in patients older than 55 years. Numbers in parentheses are percent of reference population

1974–1983:	Total patient number:	64
	Functioning grafts:	6 (9)
	Graft failure:	36 (56)
	Patient death:	21 (33)
	Lost to followup:	1 (3)
Causes of death:		
Total number:		21
Cancer:		1 (5)
Cardiovascular disease:		2 (10)
Sepsis (infection):		5 (24)
Unknown:		13 (62)
Causes of graft failure:		
Total number:		36
Immunologic (rejection)		22 (61)
Patient death*		7 (19)
Non-immunologic (infection)		3 (8)
Technical		3 (8)
Recurrence		1 (3)
Noncompliance		0
Unknown		3 (8)
1984–present:	Total patient number:	97
	Functioning grafts:	51 (53)
	Graft failure:	31 (32)
	Patient death:	12 (12)
	Lost to followup:	3 (3)
Causes of death:		
Total number:		12
Cancer:		2 (16)
Cardiovascular disease:		2 (16)
Sepsis (infection):		3 (25)
Unknown:		7 (54)
Causes of graft failure:		
Total number:		31
Immunologic (rejection)		14 (45)
Patient death*		8 (25)
Non-immunologic (infection)		2 (6)
Technical		2 (6)
Recurrence		0 (0)
Noncompliance		1 (3)
Unknown		4 (13)

* Death with functioning transplant.

USRDS [1]. Most of the deaths, 16 of 21 (76%) occurred during the first six months post-transplant. This may reflect the high-dose immunosuppression used both for maintenance immunosuppression and for treatment of rejection in the early post-transplant period before the introduction of cyclosporine.

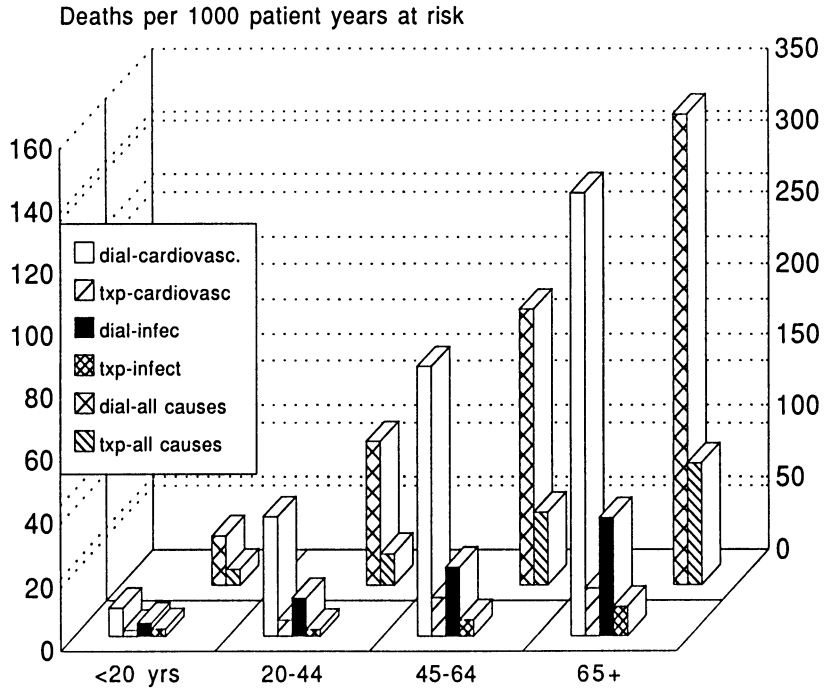

Fig. 3. Death rates for patients with ESRD comparing those on dialysis and those with functioning kidney transplant by age and cause of death. Total death rates are plotted on the rear graph. Data taken from USRDS report [1].

Of 3 patients with diabetes transplanted before the introduction of cyclosporine, all died within six months.

Following the introduction of cyclosporine, 97 patients older than 55 years transplanted from 1984–present had greatly improved overall patient and graft survival, despite being significantly older, 60.4 ± 4.06 years ($p < 0.001$) than the patients over the age of 55 years transplanted before 1984. Of the 97 patients transplanted since 1983, 53% (51) remain with graft function, although the mean length of graft survival, 29.7 ± 28.0 months is not significantly different from that of patients transplanted before the introduction of cyclosporine. This is because of the extremely long graft survival in patients from the azathioprine-prednisone era whose grafts retain function. Of the 31 (32%) patients whose grafts failed, 45% (14) lost their grafts due to rejection and 25% (8) due to patient death with a functioning graft (Table III). Similar to the findings in patients transplanted before the introduction, of cyclosporine graft loss in cyclosporine-treated patients occurred primarily during the first 6 months following transplantation; this happened in 80% (25) of all grafts lost during this period. Most of the patients (84%, 43) whose grafts are functioning have sustained such function for more than one year (Fig. 4).

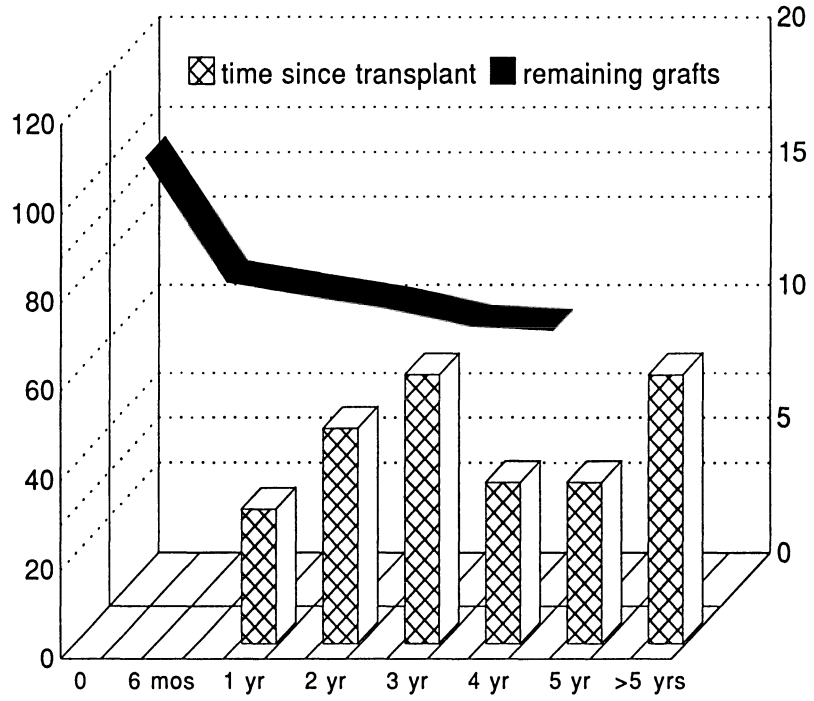

Fig. 4. Residual graft survival and length of time with functioning grafts (grafts still presently functioning) for patients older than 55 years of age transplanted at SUNY Health Science Center at Brooklyn, 1984–present, using cyclosporine. Numbers represent actual numbers of patients with functioning grafts at each time point.

Of the 12 (12%) patients who died, the major causes were cardiovascular and infectious (sepsis), while 16% (2) of the patients were lost to malignant disease (Table III). Sixty-six percent (8) of the deaths occurred within the first 6 months, again suggesting the contribution of high-dose immunosuppression, either for maintenance or treatment of rejection.

The most common complications in our older patients with functioning grafts are shown in Table IV. Ten percent (5) developed gout and 10% developed diabetes mellitus, similar to our background population [7]. Eight percent (4) developed cataracts and 12% (6) suffered cardiovascular complications (angina, myocardial infarction or stroke). The 15 patients with diabetes pretransplant, who received cyclosporine immunosuppression, show greatly improved results compared to the precyclosporine era. Fortysix percent (7) still have graft function, with a mean survival time of 4.6 ± 1.8 years. Although the 33% (5) mortality is higher than the overall population, this difference does not achieve significance because of the small number of patients.

Table IV. Severe complications encountered in cyclosporine-treated patients over the age of 55 years with presently functioning grafts

Cancer (breast and pancreatic)	2
Cardiovascular (myocardial infarction)	2
(angina, CABG)	2
Infectious (pneumonia, sepsis)	5
Gout	5
Neurologic (stroke)	1
(transient ischemic attack)	1
Diabetes	5
Bowel disease (perforation)	1
(small-bowel obstruction)	1
Pancreatitis	1
Cataracts	4
Hepatitis	1
GI disease (peptic ulcer)	3
(with GI bleed)	2
Polycythemia	1
Parathyroidectomy	1

Discussion

All patients who undergo kidney transplantation are at risk for the less common but devastating complications of surgery and immunosuppression, including cardiovascular disease, sepsis and malignancy, and the more common sequelae of the post-transplant period: rejection, hypertension, diabetes and minor infection. When dealing with the elderly patient, who by virtue of age is at increased risk for cardiovascular, malignant and infectious diseases, we must ask whether these complications occur with unacceptable frequency following transplantation, whether they occur at a greater rate than in elderly patients treated by other types of renal replacement and whether there are ways to screen out candidates with unacceptably high risk.

USRDS data on death rates in ESRD patients [1] suggest that, as might be expected, patients in the older age groups, 45–65 years and 65+ years, are at higher risk of death regardless of modality chosen for renal replacement (Fig. 3). Death rates for dialysis (hemo- and continuous ambulatory peritoneal dialysis, CAPD) patients, who have never been transplanted, are substantially higher than those for patients with functioning transplants at all age groups. When comparisons are made between transplanted patients and those who remain on dialysis, it must be borne in mind that, in the past when cadaveric kidneys were more readily available, the healthiest patients were referred for transplantation, selecting out a population of sicker patients to remain on hemodialysis or CAPD, thus inflating the death rate and complicating true comparisons between modalities. Now that waiting times for cadaveric kidneys have lengthened to years in the United States, it may

be possible to compare the health of ESRD patients waiting for kidneys with that of transplanted patients.

Smaller single-center studies examining patient and graft survival in the elderly renal transplant recipient suggest that both patient and graft survival have improved since the introduction of cyclosporine immunosuppression. An early study from Sweden, which involved 34 patients over the age of 60 treated with azathioprine and prednisone alone, compared with 34 patients under the age of 60 receiving the same immunosuppressive regimen, found a 59% patient survival in the older group compared with 79% in the younger group at 1 year. Graft survivals were not significantly different, 47% and 59% respectively, with younger patients suffering more rejection, a finding which has been corroborated subsequently [8]. Two other groups, however, did not find adverse survival in elderly patients treated in the precyclosporine era, and it is unclear whether patient selection or immunosuppression protocol accounts for this difference [9, 10]. In our series, patient survival was better in cyclosporine-treated patients, especially among those with diabetes. There was a major difference in death rates during the first six months following transplantation, suggesting that the higher-dose immunosuppression used before the introduction of cyclosporine may have been responsible, but also that even in the cyclosporine era, rejection or the use of high-dose immunosuppression still kills older patients.

Some centers have reported patient survival in older renal transplant recipients following the introduction of cyclosporine to be as high as 87–91% at 1 year and 65–85% at 3 years [11–13]. The highest survivals are reported by centers that carefully prescreen recipients [13], including extensive cardiovascular and urologic workup as we require of patients older than 60 years of age. As we have found, graft survival ranges from 66–81% at 1 year and remains relatively constant, with minimal attrition, at 3 years [12–15]. The most common complications in our patients whose transplants continue to function include cardiovascular diseases, diabetes and cataracts, all of which are more frequent in the elderly *per se*.

Although death rates are higher in the older transplanted person than in the younger, the rates are far lower than in patients maintained on hemodialysis. The actual results of transplantation in the elderly, as quoted above, do not suggest that transplantation entails undue risk, if patients are carefully screened and one avoids over-immunosuppression.

Finally, it should be noted that most studies to date have dealt with patients under the age of 75 years and it is unclear whether there is an age above which transplantation becomes unduly hazardous. Even if transplantation carries minimal risk for extremely old patients, cadaveric kidneys are a limited resource and living-related donation usually is not an option for an elderly patient. This raises the ethical question whether assignment of an organ to a younger persion is of more benefit because of a potentially longer lifespan. Undoubtedly this complex issue will haunt us as the population ages and such issues assume greater importance.

Summary

Renal transplants in the 'elderly' population have increased steadily over the past 10 years. Optimal pretransplant preparation of the elderly patient has not been defined. At our center, all patients over the age of 60 years require cardiovascular studies, including stress testing and coronary angiography if indicated. In addition, male patients with symptoms of obstruction and all anuric patients require urologic clearance. Despite more stringent requirements, there was no difference in the rate of acceptance onto the cadaveric waiting list for older *versus* younger patients; 58.4% (31 of 53) of those over the age of 55 years and 61% (134 of 166) of those under the age of 55 years were accepted for cadaveric transplant. In both age groups the most common reason for refusal to list was necessity for further cardiac, neurologic or urologic workup.

Results in the older patient undergoing renal transplant have improved since the introduction of cyclosporine. At our center, of 64 patients over the age of 55 years who were transplanted before 1984, only 9% [6] remain with graft function, with 56% [36] suffering graft failure and 33% [21] patients have died. For 97 patients transplanted after the introduction of cyclosporine in 1984, 53% [51] remain with graft function, 32% [31] have lost their grafts and 12% [12] have died. Most of the deaths occurred within the first 6 months following transplantation, regardless of immunosuppression used, suggesting that increased immunosuppression or treatment for rejection may have played a role in these deaths. Mortality was 100% for the 3 patients with diabetes transplanted before cyclosporine and fell to 33% [5] following its introduction. The most common complications in patients with persistent graft function include cardiovascular disease, cataracts, diabetes and gout, although the latter two problems do not occur with a frequency above that of our background population.

Transplantation in the elderly patient does not appear to impose excessive risk of death or complications if patients are carefully screened and cardiovascular interventions carried out before transplantation. High-dose immunosuppression for maintenance or for rejection therapy may increase risk of death and should be avoided. Complications which are common in ageing populations are common in post-transplant recipients and must be anticipated.

Acknowledgements

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CHAPTER 38

Renal transplantation in the elderly: the Toronto experience

EDWARD H. COLE

The results of renal transplantation have improved remarkably over the past 10 years; one-year graft survival is in the range of 80–85% and one-year patient survival is around 95% [1]. As a consequence, the number of patients with end-stage renal failure wanting a renal transplant has increased substantially, but unfortunately cadaveric organ donation is on a plateau. As a result, the list of patients waiting and the waiting time for cadaveric organs have increased substantially. The average waiting time for an adult kidney in the City of Toronto is now about 24 months [2]. As cadaveric kidneys become even more precious, many have expressed concern that the organs be reserved for those who can benefit most. After his recent review, Kjellstrand suggested that, more than any other variable, age influences the likelihood of being transplanted; older patients are far less likely to received a transplant in the United States and a number of other developed countries [3]. These considerations, and the patient's wish to understand therapeutic options, have lead many groups to examine the results of renal transplantation in older individuals. While, in general, such patients should receive therapy for end-stage renal failure, many fear that transplantation would be associated with a higher mortality. In fact, the reverse is true: in older patients in both the European and Canadian series, the death rate is substantially less for transplanted patients compared to those on dialysis [4, 5]. On the other hand, these statistics must be interpreted with caution because patients with serious extrarenal disease are less likely to be offered transplants, more likely to remain on dialysis, and more likely to die.

Recently, Hricik reviewed nine clinical trials conducted between 1980 and 1990, which compared renal transplantation in older and younger patients [6]. The older group in general, consisted of patients over 55 or 60 years of age, with a sample size of from 17–82 patients. One-year, patient survival in older patients varied from 59% – Ost *et al.* in 1980 to 91% – Pirsch *et al.* from 1989 [7, 8]. Shah *et al.* showed an 84% 5-year survival in patients aged 50–64 compared to an 85% 5-year survival in those aged 17–49 [9]. As well, most studies showed a similar graft survival, particularly after 1 year.

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Table I. Time to renal function

Age (yr)	Time to function (days)
< 30	6 ± 8.6
31–40	5.2 ± 6
41–55	5.0 ± 6.1
> 55	5.1 ± 6.9

This paper evaluates the University of Toronto experience from 1981–91 in cadaveric renal transplantation and compares older and younger patients.

Methods and results

Demographics

We reviewed 1022 adult, first, cadaveric renal transplants performed between 1981–1991 at the University of Toronto. Mean follow-up time was 45 ± 33 months (1–124). In this series, 159 patients were less than 30 years old, 249 aged 31–40, 377 aged 41–55, and 237 were older than 55 years. The average age of all was 44.6% ± 12.8 years.

Of the patients 64% (654) were male, 18.5% (189) were diabetic, 94% (927) were transfused. At the time of transplantation the panel reactive-antibody level was less than 50% in 94% (942) of patients. In general, this population was poorly matched, 57.6% (546) received 0 or 1 ABDR matches, 41.5% (395) received 2–4 antigen matches, and only 0.9% (9) received 5 or 6 antigen matches. The average cold ischemia time was 33.7 ± 10.3 hours. There was no difference in any of these factors between the different age groups.

Therapy

All patients were treated with steroids and 63% (644) received a prophylactic antilymphocyte preparation; cyclosporine therapy was begun when good renal function was established; 82 (8%) received cyclosporine from the time of transplantation; 262 patients (25.6%) received other therapy.

Renal function

Onset of graft function was defined by a fall in serum creatinine of at least 10% and the excretion of at least 1 litre of urine per day without dialysis (Table I). There was no significant difference in time to graft function for

Table II. Renal function versus age.

Age (yr)	Serum creatinine 1 yr (μmoles/l)	Serum creatinine 2 yr
< 30	163 ± 52 (1.85% MG%)	172 ± 72
31–40	165 ± 59	161 ± 57
41–55	164 ± 62	153 ± 61
> 55	144 ± 42* (1.64 MG%)	135 ± 38

* $p < 0.005$ *vs* ≤55.

recipients older than 55 years as compared to younger patients. Table II compares serum creatinine values at 1 and 2 years post-transplantation in recipients of different ages with functioning grafts. The mean serum creatinine at 1 year was significantly lower in patients older than 55 years as compared to the other groups. At two years, renal function appeared to be better in the older patients but, because of lower numbers in this group, the data was not significant.

Graft and patient survival

Figure 1 shows actuarial patient and graft survival for all patients. Patient survival was 92.4% at 1 year, 82% at five years and 65.8% at 10 years. Graft survival was 80.3% at 1 year, 65% at five years, and 43% at 10 years. Figure

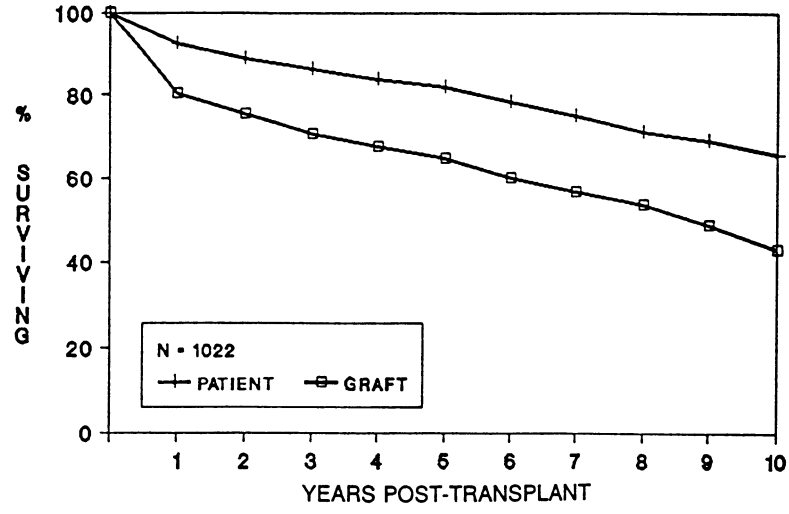

Fig. 1. Actuarial patient and graft survival. 1st transplants: Toronto 1981–91.

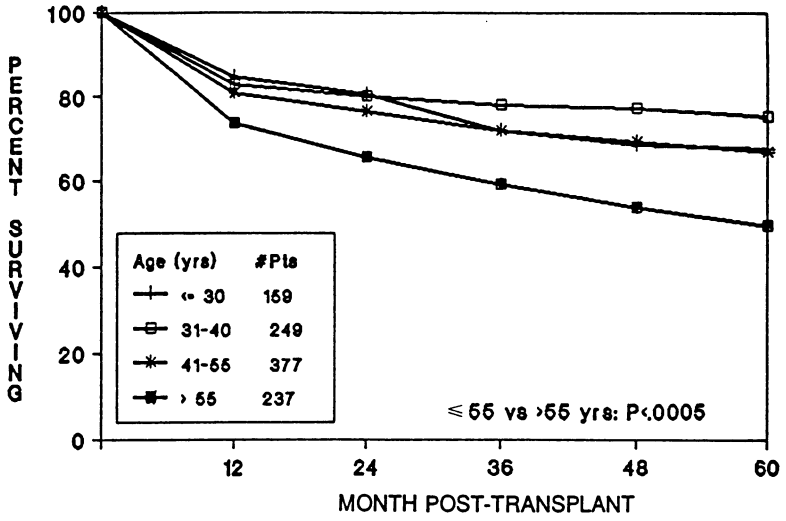

Fig. 2. Graft survival: adult 1st transplant 1981–91. Increasing recipient age.

2 analyzes graft survival *versus* age. Graft survival was significantly lower in patients older than 55 years; it was 74% vs 82% at 1 year and 50% vs 75% at 5 years ($p < 0.0005$).

Subsequently, we compared the major causes of graft failure in patients up to 55 years old and those over age 55. In both groups the incidence of graft loss due to rejection was similar, 16% (126 patients) in the younger and 17% (40 patients) in the older group. However, the incidence of death as a cause of graft loss was significantly different in the two groups; 9% (71 patients) in the younger *versus* 24% (56) in the older group ($p < 0.0005$). When actuarial graft survival was plotted excluding deaths with a functioning graft, the difference in graft survival was no longer significant up to 5 years (Fig. 3).

Figure 4 shows patient survival in the different age groups. Actuarial patient survival was significantly lower in patients over 55 years of age; 85% at 1 year and 65% at 5 years ($p < 0.0005$). The major causes of death were compared in those older and younger than 55 years. Infection caused death in 3.7% ($n = 43$) of younger patients and 13.5% ($n = 32$) in those older than 55 years ($p < 0.0005$). Cardiac disease accounted for most of the remaining deaths in both groups of patients; 5.5% (n = 43) of younger patients and 13.5% (n = 32) in patients greater than 55 years old ($p < 0.0005$).

In view of the high mortality in older patients and the increase in infection-related deaths, we analyze rejection episodes in older and younger patients. Of patients aged < 40 years ($n = 83$), 37% were free of rejection during the first year post-transplant, compared to 44% ($n = 115$) among those aged 41–55 and 48.5% ($n = 58$) in those older than 55. Freedom from rejection was significantly greater in patients 41 years or older than in those below 40 years

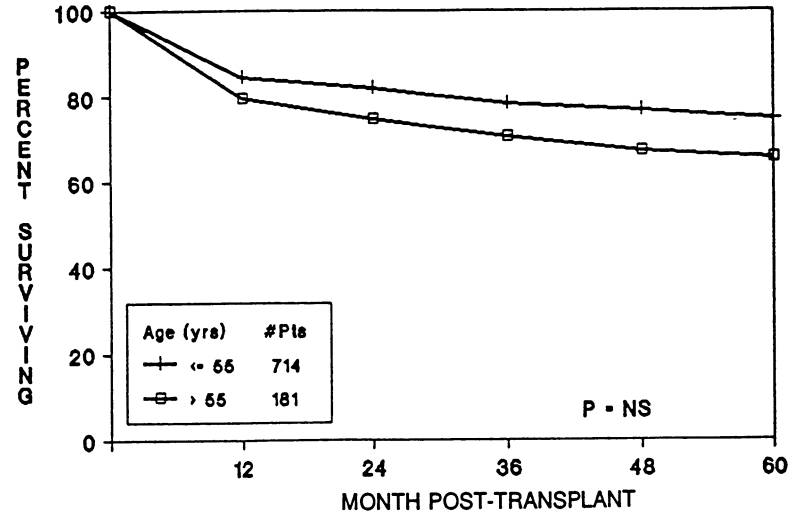

Fig. 3. Graft survival: adult 1st transplant 1981–91. Increasing recipient age excluding deaths with a functioning graft.

of age ($p < 0.0001$); also it was significantly less in those over 55 years than in all of the remaining patients ($p < 0.0005$). An important association was found between rejection and mortality in older patients. In 276 patients up to 55 years old with no rejections, the mortality was 15.9% ($n = 38$). The mortality was not significantly different in 484 patients up to 55 years old with 1 or more rejection episodes. In 107 patients older than 55 years with

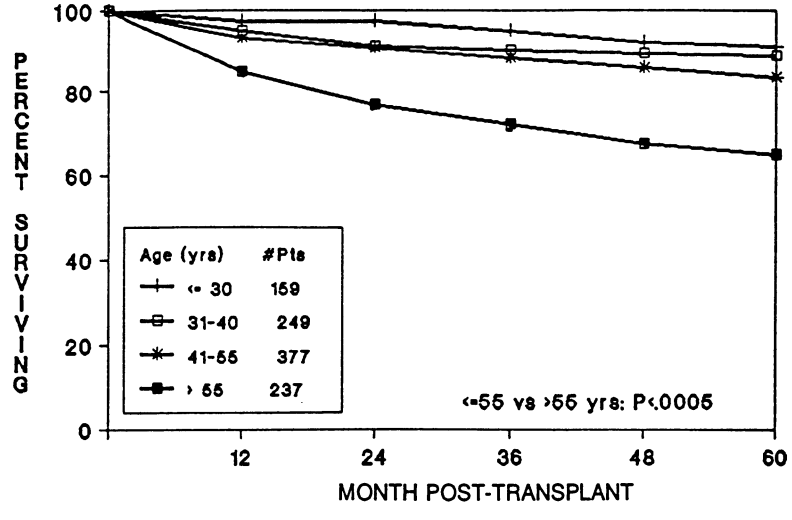

Fig. 4. Patient survival: adult 1st transplant 1981–91. Increasing recipient age.

no rejection episodes, 25% died ($n = 27$). However in 121 patients of this age group with one or more rejection episodes, the mortality was almost twice as high at 45% ($n = 54$) ($p < 0.005$).

Discussion

The data in this paper confirms the reduction in graft and patient survival in older persons. The definition of 'older patient' varies with different authors. We chose age 55 as the cut-off point because it permits comparison with most other data on the subject. Patients over 55 years were analyzed further to determine whether any significant differences could be found within that patient population. We found no difference in actuarial graft or patient survival or in frequency of rejection episodes in patients 56–60, compared to those 60–64 or 65–69 years of age (data not shown). The whole group contained only 14 patients aged 70 years or older – a number too small to allow comparisons with other groups, however, there was a suggestion that graft and patient survival were further reduced in this group (data not shown).

While our data indicate reduced patient and graft survival in this older group, it is noteworthy that about 50% of these patients have functioning grafts at 5 years – a result that is similar to that in other reports [6, 10]. Furthermore, studies comparing the death rate in patients over 55 with end-stage renal disease treated with dialysis or transplantation show that the death rate is significantly lower in the transplantation group, although there is surely bias in patient selection [4, 5]. Nevertheless, our data reinforce the view of other authors that transplantation is a useful mode of therapy for older patients with end-stage renal disease.

The central problem with transplantation in the older patients is the increased patient mortality because if we exclude patients dying with a functioning graft there is no longer any statistically significant difference in graft survival between younger and older patients. Most older patients died from either cardiac disease or infection, as noted by others [7–10]. Thus we might improve our results considerably by careful screening of older patients for cardiovascular disease before transplantation with appropriate treatment where possible, and by exclusion of patients with severe cardiac disease. It is difficult to know whether this group of patients would do better on dialysis but one should explain the risks and give them the option of staying on dialysis if treatment of cardiac disease is not possible.

The increase in death from infection and the association of rejection with a significant increase in mortality in older patients confirms that this group does not tolerate immunosuppression as well as younger individuals do. Our data indicates that, while the incidence of graft loss from rejection does not differ between younger and older patients, the incidence of rejection is significantly less in those over 55 years. It would seem appropriate to consider

reducing immunosuppression in older patients. This study did not find any specific increase in mortality with the use of antilymphocyte preparations in older patients, but clearly these agents do make a significant contribution to infectious deaths and hence should be used with caution.

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PART TEN

Urinary incontinence

CHAPTER 39

Epidemiology of urinary incontinence in the elderly

ANANIAS C. DIOKNO

Prevalence of urinary incontinence (UI) is an estimation of the extent to which a population is affected by UI at any given time. On the other hand, incidence of UI is an estimation of the probability of becoming incontinent of urine during a specified period. Most early estimates of the prevalence of UI were based on studies in Europe. Although there were several reports on the prevalence of UI, reports on the actual incidence of UI is scarce. Although a few studies have collected information at two points in time, incidence rates had not been established in the United States before the report by Herzog *et al.* on the 'incidence of UI in community dwelling population' in 1990 [1]. Similarly, American data based on the prevalence of UI have been scarce. The most definitive report was the 'Survey on the medical, epidemiologic and social aspects of aging' (MESA), conducted in Washtenaw County, Michigan, U.S.A. [2].

Review of existing prevalence data on urinary incontinence in the elderly suggests a rate ranging from 11% to as high as 34% [2–7]. The wide range of estimates can be ascribed to the differences in the definition of incontinence and the samples used in the survey. Another possible cause of the wide range is the method used in the survey.

Campbell reported the incidence of UI among persons 65 years old and older living in a community in New Zealand [4]. He estimated that approximately 10% of continent older adults developed incontinence over a 3-year period.

The remission rate – the situation where an incontinent respondent became continent over time has been reported. Thomas in 1980 and Yarnell and St Leger in 1979 reported a maximum rate of 33% [5, 6]. Unfortunately these studies did not clarify the reason for such remission, that is, whether it was spontaneous or the result of certain intervention.

MESA results on prevalence, incidence and remission rates of UI

In 1983, a large scale survey of persons 60 years and older living in a county of Michigan was undertaken. The project called MESA identified 13,912

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households through a probability sampling in Washtenaw County, Michigan. Trained interviewers sought out all respondents 60 years of age and older. All consenting seniors were interviewed. Second and third interviews were conducted one and two years after the initial or baseline interviews using identical, but fewer questions.

The baseline survey (1983–84) interviewed 66% (1956) of the 2968 eligible respondents. The second and third reinterviews resulted in a 69% and 72% response rates. These non-response rates were not unusual for surveys of older populations. Furthermore, further analysis of the effect of non-response on the estimates of incontinence suggests that the bias in prevalence and incidence estimates introduced by nonresponse was inconsequential and therefore did not justify the use of weights to adjust for nonresponse.

In the survey urinary incontinence was defined by a series of probing questions. 'In the past 12 months, on approximately how many days have you lost any urine, even a small amount, beyond your control?' Those who reported no urine loss were probed further by asking them to be certain that there have not been any days where he/she might have lost any amount of urine at all. Any respondent, who reported any uncontrolled urine loss within the 12 months before the interview, was considered incontinent. When the urine loss was less than 6 days, the respondent was classified as continent if the loss was due to unavoidable factors.

The type of incontinence was based on the response to specific questions that define the specific clinical type of UI. The questions were formulated to elicit involuntary loss of urine preceded by a severe urge to void or uncontrolled voiding with little or no warning as urge incontinence. Stress UI is referred to as involuntary loss of urine at times of increased physical activity such as lifting, coughing, laughing, etc. When the self-report is both 'urge' and 'stress', it is labelled mixed. When it does not fit either category, it is called 'other'.

The MESA prevalence of UI for females was 37.7% and for males was 18.9%. The 2:1 ratio of prevalence between genders is highly significant ($p < 0.001$).

The incidence rate between the baseline interview and the first reinterview is 22.4% for females and 9.0% for males whereas the incidence rates between the first and second reinterview were 20.2% for women and 10.6% for men. The differences in rates between genders remain highly significant ($p < 0.001$).

The remission rates (incontinence to continence) between the baseline and first reinterview were 11.2% for females and 26.7% for males whereas, between the first re-interview and second re-interview, the remission rates were 13.3% for women and 32.3% for men. Again, the sex differences are statistically significant ($p < 0.001$).

The prevalence based on the types of UI varies according to gender. Among women, 55.5% reported mixed urge and stress type, 26.7% with stress, 9.0% with urge and 8.8% with other. Among men, urge was the most

predominant at 34.9%, 28.9% reported mixed, 28.3% with other and 7.9% with stress.

The quality and frequency of involuntary urine loss were also were reported by the respondents. Among men, 10.6% reported urine loss in 300–365 days per year and 12.1% reported losing 1/4 cup or more urine per day. Among women, 16.1% reported urine loss 300–365 days whereas 15.8% reported losing 1/4 cup or more urine per day.

Further analysis of pattern changes showed that most continent women, who developed UI, developed a type of stress or mixed urge/stress variety. Among continent men, urge type is the most common type that will develop among previously continent men. Of those who are incontinent at baseline, women with stress UI remained the same or developed mixed urge/stress type whereas men with urge tend to stay with urge type or go into remission.

Continent respondents, who became incontinent, were most likely to develop a mild form for both men and women. Incontinent respondents tend to stay at their level with few advancing into the next level of severity. Most women with severe incontinence remained severely incontinent whereas, among men, the direction was less clear – some became moderate, some remission, etc.

In summary, urinary incontinence is a highly prevalent condition in America. The incidence and remission rates as well as the pattern changes have been established.

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CHAPTER 40

Surgical treatment of stress-urinary incontinence

SIDNEY B. RADOMSKI

Stress incontinence in women can be classified as Type 0, 1, 2 and 3 [1] (see Table I). Type 1 and 2, which show descensus of the bladder neck, i.e., inferior and posterior descent of the bladder neck with an increase in intra-abdominal pressure most commonly is due to relaxation of the pelvic ligaments and muscles following childbearing. Type 1 and 2 stress incontinence are the most common types in the geriatric population. Its surgical treatment is based on procedures that prevent bladder neck descensus. With Types 1 and 2 stress incontinence, two basic types of operations have been used successfully, namely the retropubic and the vaginal suspension procedures.

Retropubic suspensions (Marshall, Marchetti, Krantz (MMK) [2] and Burch [3])

MMK – Through an abdominal incision the operator enters the retropubic space and places sutures into the periurethral tissue and adjacent vaginal wall on both sides of the bladder neck. The sutures are secured to the periosteum of the symphysis pubis and the inferior portion of the rectus sheath and are then tightened while the vagina is lifted with two fingers so that the bladder neck is well supported.

The Burch is similar to the MMK procedure except that, in this procedure, sutures are placed only in the vaginal wall. Then the sutures are placed into Cooper's ligament along the pubic ramus and secured in a fashion similar to the MMK. The vaginal wall does not have to be approximated to Cooper's ligament.

The short-term success of these two procedures is good ($> 75\%$). Long-term results (> 5 years) may not be as good. Today, most authors believe that the Burch is the retropubic operation of choice for stress incontinence, chiefly because of its success rate and its low incidence of complications.

The most common complication with these two retropubic procedures is urinary retention. If retention develops, intermittent catheterization may be

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Table I. Classification of stress incontinence

Type 0	Patient complains of stress incontinence but not able to demonstrate on testing.
Type 1	Less than 2 cm of descent of bladder neck and urethra with stress.
Type 2	Greater than 2 cm of descent of bladder neck and urethra with stress.
Type 3	Minimal descent of bladder neck. Urethra does not coapt. Intrinsic urethral damage. (Drain pipe urethra.)

difficult for some geriatric patients and hence they may need a chronic indwelling Foley catheter.

Vaginal suspension procedures

Usually these procedures are performed *via* a vaginal approach and cystoceles and rectoceles can be corrected at the same time as the suspension. In general these procedures seem to produce less morbidity. The short term success rates are good (> 75%) but the longterm results (> 5 years) may go down to approximately 50%. Some of the current procedures are the modified Pereyra, Stamey, Raz, and Gittes.

The Kelly plication, which 'tightens' the anterior vaginal wall, is not recommended for stress incontinence because the long-term failure rate is as high as 52%. Here I describe only the Raz procedure.

Raz procedure [4]

The operator makes a vaginal incision in the anterior vaginal wall at the level of the bladder neck and the proximal urethra. The retropubic space is opened up on either side of the bladder neck *via* the vaginal incision. Sutures are placed helically through the anterior vaginal wall at the level of the bladder neck. A small suprapubic incision is made down to the rectus sheath. Taking care to avoid the bladder, a long needle is passed through the incision just inferior to the pubis to the vaginal opening; the sutures then are brought out through the suprapubic incision. Using a cystoscope the bladder is inspected for any sutures or injury. The sutures on either side then are tied suprapubically to raise the bladder neck to the correct position. If the patient has a cystocele or rectocele, it can be repaired at the same time. In general, these procedures produce less morbidity which is of particular benefit in the geriatric patient.

Because these procedures involve vaginal surgery, the vaginal mucosa must be healthy. This may require that the patient be placed on Premarin (vaginal cream or p.o.). This fact may be even more important to the geriatric female. Complications with these procedures are similar to those with the retropubic procedures, i.e., retention.

Type 3 stress incontinence

Normally the female urethra collapses on itself to produce mucosal coaptation. In Type 3 incontinence, there is minimal descensus but there is stress incontinence because the urethra does not collapse on itself. This 'drainpipe' urethra is caused by previous procedures for stress incontinence or by vaginal procedures that damage the periurethral tissues and urethral musculature. The urethra is scarred open and is incapable of mucosal coaptation. There is little urethral resistance and, with any increase in intra-abdominal pressure, these patients leak.

Because there is minimal descensus in Type 3 stress incontinence, procedures, that prevent descensus (i.e. MMK and Raz) are of no value and are doomed to fail. In general, these bladder neck suspensions do not compress the urethra. In contrast, rectus sheath sling procedures compress the urethra and induce mucosal coaptation. As a result the sling procedure is the recommended surgical option [5]. After operation this procedure has a higher incidence of retention, which may create a problem for elderly patients who may not be able to perform intermittent catheterization. This procedure is successful over the long term in over 80% of patients.

Fascial sling procedure

An abdominal incision is made down to the rectus fascia. A fascial strip of adequate width and length is freed up and the distal end is left attached. An inverted U-shaped vaginal incision is made. Through the vaginal incision the retropubic space is entered on either side of the bladder neck. The sheath is passed through both openings so that it sits under the bladder neck. The proximal end of the sheath is sutured to the opposite rectus sheath. Minimal tension on the rectus sheath provides coaptation. Then the vaginal and abdominal incisions are closed.

Intraurethral injectable bulking agents

Many years ago teflon was injected into the urethra to provide bulk and mechanical resistance but for many reasons it did not become popular. Teflon is difficult to inject, it forms granulomas and does migrate, although no harmful effects have ever been demonstrated. Gax-Collagen is bovine collagen that is treated with gluteraldehyde to make it resistant to breakdown by collagenase. This also makes the collagen significantly less antigenic. Furthermore, Gax-Collagen is easy to inject, it rarely forms granulomas and does not migrate or breakdown significantly. In studies in the U.S. and Canada, patients treated for stress incontinence with Gax-Collagen have done well, especially women. In women, $> 85\%$ have been cured or signifi-

cantly improved [6, 7]. Many of them have been followed for more than two years. Men have less success and cost effectiveness is poor. As a result, the mainstay of treatment for male stress incontinence is such techniques as the artificial urinary sphincter.

In over 200 patients no major side effects have occurred with intraurethral Gax-Collagen injections.

This simple procedure is well tolerated by women. Under local anaesthesia, a spinal needle is inserted into the urethra, and, with the help of cystoscopy, a bleb is raised with collagen so that the urethra appears to be obstructed.

In general 10–12 ml of collagen are deposited usually over two sessions. Usually patients leave the cystoscopy suite dry. Our data suggest that patients with minimal or mild descensus, i.e., Type 1 and 3, do best with collagen. Patients with no mucosal coaptation (Type 3 stress) should do well with collagen injections because it provides mechanical resistance. Furthermore, this is an excellent procedure for the geriatric patient because of the decreased morbidity and few complications. However, collagen is expensive and this may limit its use.

Geriatric male stress incontinence

This is much less common than the same symptom in women. Most commonly this is due to injury to the external sphincter during a transuretheral resection of the prostate for benign disease or after a radical prostatectomy for cancer.

Insertion of an artificial urinary sphincter is the most successful and cost-effective treatment [8]. The success rate is close to 90%. The revision rate is approximately 20% in five years. Collagen does not have the same success in elderly men probably because intraurethral scarring it difficult to raise a bleb. Often large amounts of collagen are required. As a result, this procedure often is far more expensive than an artificial sphincter.

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CHAPTER 41

Pharmacologic challenges to treatment for urinary incontinence

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Research in the 1970s promised a pharmacologic cure for urinary incontinence in the elderly. The bladder and urethra are an autonomic functional unit whose relaxation and contraction is controlled through alpha and beta adrenergic and muscarinic receptors. The smooth muscle of this functional unit is subject to local regulatory factors such as calcium, prostaglandins and hormones such as estrogen and vasointestinal peptides (VIP) [1]. Such discoveries opened the way for the use of pharmacologic agents in the management of urinary incontinence based on sound pharmacologic principles.

Drugs have been only partially successful in controlling symptoms related to urinary dysfunction. In the literature, there is a paucity of randomized controlled studies [2]. Most studies are limited by small sample size, and were conducted over short periods and were done in diverse elderly populations. Few studies meet the criteria of the randomized clinical trial (RCT) [3]. Moreover, these studies have raised many questions regarding the complex and multifactorial causes of incontinence in the elderly. Unlike incontinence in young adults, the elderly comprise a markedly heterogeneous group, both biologically and functionally [4], for example, the 'old–old' *versus* the 'young–old' and those who live in the community *versus* those in institutions. Furthermore, the phenomenon of functional incontinence largely designated for the institutionalized disabled elderly group has presented some challenges with respect to definition and treatment.

The available studies show significant variability in outcome measures and different definitions of 'cure'. Should one rely solely on subjective criteria for outcome or does one need more objective (measurable) criteria such as the 'pad weight' test or urodynamic studies? In the selection of candidates for pharmacologic treatment, should one treat the symptom complex or treat the urodynamic abnormality, i.e., should one treat detrusor instability or the symptom of urge incontinence? These questions are complex because we now know that urgency is not the equivalent of detrusor instability [5]; that stress symptoms are not always related to sphincter incompetence; that

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symptoms of urgency and uninhibited detrusor contractions may be associated with impaired emptying of the bladder [6, 7].

In analyzing outcome, statistical significance must relate to clinical benefit; there has to be an established overall efficacy balancing the benefit *versus* the side effect to the patient. Since urinary incontinence is a costly and annoying but non-life threatening symptom, the treatment must improve quality of life, and many of the pharmacologic agents have unpleasant side effects, e.g., dry mouth, dizziness, etc.

Pharmacologic treatment for urinary incontinence is not the panacea that it was thought to be. However, the past 20 years have clarified some of the complexities of this neuropharmacologic system and its relationship to other physical and psychological functions.

The bladder and urethra function as an autonomic unit with alpha and beta receptors, muscarinic receptors and smooth muscle responsive to local regulatory factors such as calcium fluxes, prostaglandins and estrogens. Through their connections with the central nervous system, the bladder and urethra have two basic functions: 'a storage function' which requires both smooth-muscle detrusor relaxation, and the competence of the sphincter at rest even in the presence of increased intra-abdominal pressure; an 'emptying function' requiring smooth-muscle contraction at maximal bladder capacity. In addition, there should be synergistic relaxation of the sphincter when the detrusor is contracting and there is no mechanical outlet obstruction [1].

The detrusor smooth muscle has a large number of muscarinic receptors, which when acted upon will promote bladder contraction. At the same time, stimulation of the beta receptors in the detrusor causes relaxation. Calcium and prostaglandins act directly upon the smooth muscle to enhance contractions. The urethra and trigonal areas have a large number of alpha receptors, which when stimulated will effect closure and tight apposition of the mucosal surfaces. Estrogen is necessary for maintenance of mucosal thickness, sensitivity and appropriate numbers of the alpha receptors, counteracting the loss of collagen content of urethral structures and improved muscle tone [8].

A common dysfunction of the lower genitourinary tract in the elderly is failure or impairment of the storage function with symptoms of urgency, frequency, nocturia and leakage with cough or increased intra-abdominal pressure. The mainstay of pharmacologic treatment to enhance bladder storage is to increase the bladder capacity, decrease uninhibited detrusor contractions while at the same time increasing the outlet resistance until voiding is desired.

One of the common difficulties encountered in choosing a specific pharmacologic agent is the identification of the part of the system that is 'faulty'. Urodynamic studies have not proved helpful because, as mentioned earlier, urge incontinence does not always indicate detrusor instability (uninhibited detrusor contractions) and, moreover, some patients with uninhibited contractions have impaired contractility with incomplete emptying [5–7]. Many incontinent elderly, particularly those in institutions, have functional inconti-

Table I. Drugs used to decrease bladder contractility and increase bladder capacity

Anticholinergic Agents	*Drugs with 'Direct' Effects*
Propantheline Bromide	Flavoxate
Emepronium Bromide	Calcium antagonists
Drugs with Mixed Actions	*Prostaglandin Synthetase Inhibitors*
Oxybutynin Chloride	Indomethacin
Dicyclomine	Flurbiprofen
Imipramine	
Terodiline	
Other	
Baclofen	
Desmopressin	
Bromocriptine	

nence for which we have no specific pharmacologic treatment. Incontinence in the institutionalized group is multifactorial; detrusor and sphincter dysfunction is just one component among many, mobility, cognition, environmental barriers, medication, etc. [9].

Table I gives a partial list of the types of pharmacologic agents that promote urinary storage. This paper will review the various agents within each group that are used most frequently and which are supported by at least two controlled clinical trials in the elderly.

Drugs for urge incontinence related to detrusor overactivity

Propantheline bromide

This agent has been used widely as a pure anticholinergic agent for blockade of the muscarinic receptor in the normal as well as the unstable bladder. This inexpensive drug has been reported to be effective in uncontrolled case studies. Sinc 1965, of five randomized controlled studies, only three have been done in the institutionalized elderly [10–14]. Of 259 patients in these studies, 82% were female. The average dose was 15–30 mg tid to qid; one of the studies administered 60 mg at bedtime.

In the nursing-home studies, the agent reduced incontinence frequency by 13% to 17% over placebo but one half of the subjects reported side effects and one fifth withdrew because of severe side effects [10, 11]. These side effects were those associated with anticholinergic agents such as dryness of mouth, nausea, constipation, tachycardia, drowsiness and confusion. The drug is contraindicated for patients with narrow-angle glaucoma and those with a history of ileus or urinary retention. Also propantheline bromide has low biological availability, which can vary markedly among individuals [15]. Therefore, it should be taken on an empty stomach. The starting dose is

7.5 mg tid and this is titrated upward until the desired effect is achieved or side effects ensue.

Oxybutynin chloride

This agent has a mixed mechanism of action; primarily anticholinergic activity and direct smooth-muscle relaxation properties as well. Also it may have a weak anesthetic effect on the trigone and urethra. Six randomized clinical trials involving 309 patients have reported on the efficacy of this agent [16–21]. Of the five studies in middle-aged adults living in the community, there was a decrease in incontinence frequency of 15% to 56% [16–20]. In two of the five studies, there was a subjective cure rate of 44% and 57%. The only study involving the institutionalized elderly showed no clinical or statistical benefit [21]. Another study of the institutionalized elderly, which did not meet the RCT criteria also was negative [22]. The side effects, such as dry mouth, blurred vision, constipation, dry skin and an increase in residual volume, related to its anticholinergic properties. The side effects increased with higher doses. Oxybutynin chloride in doses of 2.5 mg to 5 mg tid to qid is well tolerated; it is recommended for uninhibited bladder contractions and symptoms of urgency and frequency in patients who have complete bladder emptying (i.e., low residual volumes). It is contraindicated in those with narrow-angle glaucoma, ileus or urinary retention.

Dicyclomine hydrochloride

From broad clinical experience, this drug is known to have a mixed anticholinergic and direct smooth-muscle-relaxing activity. There have been few randomized control trials using this agent consisting of only 40 patients; the side-effect profile is similar to that seen with oxybutynin chloride [13, 23]. It can be prescribed in doses of 10–20 mg tid, and can be used as an alternative to oxybutynin chloride. In our experience, dicyclomine has weaker anticholinergic properties at the recommended doses than oxybutynin has.

Flavoxate

Flavoxate is a tertiary amine with minor anticholinergic properties but with mainly a smooth muscle relaxation effect. Flavoxate has been used widely in Europe for the treatment of detrusor hyper-reflexia. There are only four randomized clinical studies [18, 24–26]. While it has a favorable side-effect profile at doses at 100 mg to 200 mg qid, it has no significant benefit in decreasing urinary symptoms or incontinence. Therefore, it cannot be recommended as an effective agent.

Trycyclic antidepressants

These agents have a wide spectrum of autonomic activity affecting alpha and beta receptors, and they also have anticholinergic and serotoninergic properties. In addition, they act centrally in a poorly understood way to cause bladder relaxation [8]. In spite of the widespread use of these agents, only three controlled clinical trials have examined their efficacy of urinary incontinence [27–29]. Imipramine is the most commonly used tricyclic antidepressant, however, other antidepressants have been shown to be equally effective. Milner *et al.* showed that imipramine, desimipramine and nortriptyline produced statistically significant reductions in 'wet nights' in psychiatric inpatients. The average daily dose of these agents was 75 mg [27]. The side-effect profile for each of the agents was acceptable with a dose of 75 mg at bedtime.

Another randomized study evaluated doxepin in 19 women with a median age of 53 years in an outpatient setting. This drug produced a significant decrease in night-time micturition and night-time incontinence and patients preferred it over placebo [28]. Castleden *et al.* studied imipramine in 19 elderly, community-dwelling patients. The average age was 75 years. A dose ranging from 25–100 mg with an average dose of 54 mg produced a significant decrease in nocturnal incontinence [29]. Patients often complained of insomnia with imipramine. Because of side effects, which included fatigue, xerostomia, dizziness, blurred vision, nausea, insomnia and the increased association with falls resulting in hip fractures, in spite of their efficacy these agents should be used with caution in the elderly. Since the half life in the elderly can be twice as long as in a young adult, the starting dose should be low – 10 mg to 25 mg od and increased to tid. The total daily dose for any of these agents should not exceed 100 mg.

Other agents

Because of limited clinical experience with calcium channel blockers e.g., Nifedipine and Flunarizine [30] and prostaglandin inhibitors e.g., indomethacin and flurbiprophen, they are not recommended for routine use in urinary incontinence at the present time.

Terodiline

Terodiline has both anticholinergic and calcium-antagonist properties and was thought to be one of the more promising drugs for the treatment of motor urge incontinence or detrusor instability. To date, seven randomized clinical trials all conducted in community dwelling populations have involved 278 individuals [31–37]. The usual dose ranged between 25–75 mg daily in

Table II. Drugs that enhance sphincter competence

Alpha Adrenergic Agonist
Ephedrine
Phenylpropanolamine (PPA)
Tricyclic Antidepressants
Imipramine
Estrogens
Estriol
Estradiol

divided doses. In five of the seven clinical trials, Terodiline was superior to placebo and reduced incontinence frequency by 14–85% [31–35]. In two of these studies, 25% and 72% of the patients became continent. Clinically, the anticholinergic properties of terodiline seemed to dominate and therefore its side effect profile was similar to that of propantheline. However, because of its association with serious ventricular arrhythmias resulting in 'sudden death', this drug has been withdrawn from the European market and likely will not be introduced into North America.

Drugs for stress incontinence related to sphincter insufficiency (Table II)

Phenylpropanolamine (PPA)

This alpha adrenoreceptor agonist acts to increase urethral pressure. In the eight clinical trials in community-dwelling, middle-aged women with an average age of 55 years, PPA gave good results [38, 45]. In three of these eight trials, there was significant improvement in the degree of incontinence; in five studies, 9–14% of the patients became 'dry' or were cured [38–40]. Reported side effects were those of nausea, dry mouth, insomnia, rash and itching; no individuals experienced an increase in blood pressure. In a geriatric 'old–old' population, any alpha agonist drug should be used with caution; it should be avoided in individuals who have a history of hypertension, hyperthyroidism, cardiac arrhythmias and angina. The recommended daily dose is between 25 mg and 75 mg in sustained-release form administered orally twice daily.

Estrogen therapy

As is well known, the urethral mucosa in the postmenopausal female is sensitive to estrogen stimulation, which increases the thickness of the epithelium and thus enhances the effectiveness of the 'mucosal seal'. It also

increases the sensitivity of the alpha-adrenergic receptor as well as the number of adrenergic receptors. Also it is thought to increase smooth-muscle tone, counteracting the loss of urethral collagen. Only one study of 18 elderly women (average age of 79) was conducted in a nursing home [46]. Two studies, using estradiol 4 mg daily, showed that up to 14% of the patients became 'dry' and 29% experienced improved continence compared to placebo [44, 47]. Only one study failed to show a significant improvement in continence over placebo, but 60% had significant improvement in the symptom of urgency. Wilson in a study using estrone derivatives in 36 postmenopausal women with an average age of 57 years, showed subjective and objective improvements but the results were not statistically significantly better than placebo [48]. While it is still uncertain whether estrogens are beneficial in stress incontinence, they have been shown effective in the treatment of urgency.

The potential side effects of estrogen include palpitations, trembling, breast tenderness, leg pain, chest pain and vaginal bleeding. Such therapy is contraindicated for those with a history of breast carcinoma, thromboembolism, endometrial carcinoma, hypertension, and liver or cardiac disease. Because of the potential for development of endometrial hyperplasia or carcinoma, estrogens should be used cyclically in low dosage either vaginally or orally and with the addition of progesterone. The recommended dose is 0.3 mg–1.25 mg daily orally or as much as 2 g per day vaginally. Medroxyprogesterone 2.5–10 mg daily may be given continuously or intermittently.

Combined alpha-adrenergic agonist and estrogen supplementation

Because estrogens enhance the number and sensitivity of alpha-adrenergic receptors in the female urethra, the addition of an alpha agonist potentiates the alpha-adrenergic contractile responses and produces tighter closure. In four studies where estrogen and alpha adrenergic agonists were combined, they showed some additional benefit over adrenergic theory alone [44, 49–51]. Since the side effects of estrogens and alpha-adrenergic agonists are different, the combined side effects are only additive and not multiplied.

As stated before imipramine is a tricyclic antidepressant, which has been used in the treatment of stress incontinence because of its alpha adrenergic effect on the smooth muscle of the bladder base and proximal urethra. Long clinical experience and uncontrolled studies in stress incontinence show that it can be useful in this condition [52]. Care must be taken with respect to the side effect profile particularly postural hypotension, weakness, fatigue, confusion, and insomnia in elderly people. Therefore, low dosages of 10–25 mg od to tid are recommended.

Conclusion

The pharmacologic treatment of elderly people with urinary incontinence requires attention to certain basic principles. One should treat in accordance with sound physiological principles and have a clear endpoint in mind. Whichever drug is chosen, there should be no contraindication to its use, the dosage should be low and increased slowly to avoid undue side effects. Often, for the individual patient, one drug is more effective than another, e.g., oxybutynin vs. imipramine. The drug regimen is kept simple to ensure compliance and avoid confusing the patient. Because of the increased risk for the frail institutionalized elderly, one should select candidates according to their functional abilities and vulnerabilities. Regular follow-up of symptoms particularly urinary retention, weighing benefit *versus* side effect is mandatory. Too often we leave patients on anticholinergic treatment to endure the side effects without any clear evidence of improvement in the incontinence. If there is no benefit as perceived by the patient then the medication should be discontinued.

Pharmacologic therapy seldom achieves cures. On an empirical basis, combined modalities should be more successful. While there are few published studies, combined modalities, which do not have the potential for interacting side effects such as pelvic floor exercises *plus* estrogen therapy or scheduled toileting with an anticholinergic agent often are useful. Many questions need to be answered given our current understanding of the pharmacology of incontinence. Which patient is likely to benefit? Do you use urodynamic data, symptom data or functional indices for selection and outcome measurement?

In dealing with the frail elderly, particularly those in institutions, we need new validated research methods to facilitate further drug studies. The wave of the future in clinical trials for this population may be randomized trials in individual subjects [53]. The greatest challenge in this area is the pharmacology itself. We need to develop new drugs specific to bladder receptors that have few systemic side effects.

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CHAPTER 42

Behavioral program for urinary incontinence: indications, techniques and results

J. ANDREW FANTL

Behavioral aspects of urinary continence

Urinary incontinence is an acquired physiologic characteristic. At birth and during early childhood, involuntary detrusor contractions periodically empty the bladder. Such automatic detrusor activity is abolished when toilet training is completed. The bladder of the trained, continent individual fills to capacity with minimal intravesical pressure increments (accommodation) and without automatic contractility (detrusor stability). Cortical inhibition of sacral reflex activity is thought to be the responsible neurophysiologic mechanism for the acquired stability of the bladder. The striated muscle component of the urethral sphincteric mechanism is also subject to cortical modulation. It responds to both voluntary and reflex activity with contraction or relaxation. Reflex striated-muscle contractility occurs during bladder filling, proprioceptive stimulation and valsalva. On the other hand, relaxation can be demonstrated before and during micturition.

The ability to inhibit automatic detrusor contractility to contract or relax urethral striated musculature seems to follow the principles of operant learning. Such principles indicate that behaviors leading to favorable consequences (reward) will be maintained, whereas those inducing unfavorable results (punishment or lack of reward) will not. Continence is achieved when the individual is taught a specific social conduct. The effective learning of such behavior demands normal anatomy and function of the lower urinary tract and nervous systems. In addition, mental, functional and environmental requirements should be fulfilled. Cognitive status must permit awareness of the need to void, and mood should encourage motivation to be continent. Functional ability must permit toileting, and the environment must be adapted to the functional limitations. Urinary continence represents a sociophysiologic behavior, which is acquired through an operant-learning mechanism. It demands not only structural and functional adequacy of the bladder, urethra and nervous systems, but also suitable mental, functional and environmental status.

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Bladder training program

Rationale

Voluntary, repetitive efforts to suppress and induce bladder activity are expected to reinstate or improve cortical detrusor control. Following the principles of operant learning, it is expected that the reward of continence and/or decreased urgency will influence behavior. Reward also is reinforced with approval, praise and encouragement.

Patient selection

Patients admitted to the program undergo a full urogynecological evaluation. This includes an extensive history with emphasis on genitourinary symptoms. Physical examination includes a screening neurologic examination, which includes testing of the bulbocavernosus reflex. Should there be evidence of neuropathology, a full neurologic assessment is requested. Urinary-tract infection is ruled out through urine culture obtained by the 'clean catch' midstream technique.

Bladder training protocol

All patients receive a simple but full explanation of their problem. Tracings and figures are reviewed to clarify pathogenesis. The protocol demands weekly visits for 6 weeks. During each visit, compliance and progress are monitored. Positive behaviors are reinforced through praise and encouragement.

The patients are assigned a voiding schedule which is adjusted weekly. Voidings are scheduled only during the hours when the patient is awake. A voiding schedule is not followed during sleeping hours. Initially, usually the interval between voidings is 30 to 60 minutes, depending on the patient's symptoms. The interval is subsequently adjusted every week. Usually increases of 30 to 60 minutes in the voiding interval are expected. Instructions to the patient include the following:

Go to the bathroom and empty your bladder at the scheduled time.
Do so regardless of whether you feel the urge to void or not.
The amount of urine voided is irrelevant.
The important aspect is the voluntary mechanics of voiding.
Avoid going to the bathroom between scheduled times.
Make a special effort to suppress urgency.
Do not feel embarrassed if you leak.

The goal of the program is to increase the interval between voidings up to 3 or 4 hours and to restore continence. The treatment is a success if the

patient voids every 3 to 4 hours, is continent, and is free from sensory symptoms. Self-monitoring is used to assess compliance and to determine progress. Charting is done on preprinted cards. Appropriate behavior is reinforced at each weekly visit through praise, by approving the improvements obtained and by asserting a successful outcome.

We obtained favourable results with this program in the first 92 patients. It has been our continuous observation that anticholinergics do not produce statistical change in the outcome. We must admit, though, that on occasion the addition of an anticholinergic or musculotropic agent has aided individual patients. These drugs remain our first line of management in neuropathic conditions or in those transient cases of instability due to surgery or infection. Eventually further knowledge concerning the specific etiologies or conditions leading to detrusor instability will lead to specific therapies. To date, however, behavior modification represents a satisfactory approach to those patients whose incontinence results from an idiopathic etiology, because it is non-invasive, inexpensive, is free of side effects and can be performed on an outpatient basis.

CHAPTER 43

Behavioral programs for urinary incontinence: pelvic muscle exercise and prompted voiding

THELMA WELLS

Pelvic muscle exercise is known by many different names: Kegel exercise, post-partum exercise, pelvic floor exercise. The generic label, pelvic muscle exercise, is a clearer designation for this behavioral program. Basically, this exercise which evolved from midwifery practice, consists of a planned process of perivaginal muscle contraction and relaxation based on theories of muscle physiology and learning [1].

The urethra passes through a sling-like muscle structure formed by the levator ani pubococcygeus muscles, which extend from the posterior bone to the vagina. We believe that, by increasing muscle mass through exercise, maximal urethral pressure will increase. A structural result may be greater stabilization of the urethra. Further, contraction of the pubococcygeus muscles moves the vesical neck anteriorally against the precervical arc, exerting a closing force on the urethra [2].

Pelvic-muscle exercise requires an explicit program, which should start with perivaginal muscle-awareness techniques. One method is to attempt to stop the urine stream at the end of voiding. The sensation of closing and lifting with objective evidence of response helps women understand the muscle function involved. This urine stream stopping is not the actual exercise but is only an early-awareness cue to learning.

While the exercise can be taught in various protocols, no one format is superior. The basic technique we have used over the past 10 years is to have the woman practice while sitting on a firm chair with her feet flat on the floor, and legs slightly apart. She is asked to hold her hands on her abdomen to guard against the tendency to increase abdominal pressure. We believe chair firmness enhances proprioception and that conscious methods to relax abdominal and other muscles are essential. We use various muscle-contraction imagery but all describe pulling in or up with a contraction goal of 10 seconds, followed by an equal period of relaxation. One exercise is, thus, 20 seconds consisting of both the contracting and relaxation period. We teach the woman progressively from short, fast contractions ('flicks') to sustained or controlled contractions, aiming for 60–80 exercise units throughout the day in a routine that best suits the individual's lifestyle.

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In the literature contract time ranges from 2–30 seconds with 10 seconds a common norm. Frequency of exercise per day varies from as little as 15 units of contract/relax time to over 300. In our work with older incontinent women, we found 40 exercise units the absolute minimum and 80 units the best [3].

The distribution of exercise across the day ranges from 5 exercises every half hour to 100 units at one time. Since adherence to the protocol is critical, we have found most helpful a distributed, building-in-frequency pattern linked to the individual's typical behavior. Concerning duration of exercise, protocols vary from two weeks to six months with varying follow-up monitoring. It seems logical that duration of learning and intense practice will depend on adequate teaching and adherence to protocol. Little is known about the level of pelvic muscle exercise required to sustain pelvic muscle strength.

Other issues in pelvic-muscle exercise are active *versus* other teaching methods. Theoretically, resistive devices, as in vaginal sensors, cones, or fixed static probes, should enhance muscle education. Having a force to work against and increased sensory stimulation, the learner should increase muscle strength more quickly, however, there is no agreement concerning the efficacy of resistive devices. The term 'biofeedback' covers a variety of techniques that engage the subject in awareness and control of body functions. These should enhance learning. Once again the literature has no agreement or consistency concerning this question. We have found the following issues to be essential in pelvic muscle exercise. First, the teacher must observe the technique. Simply passing out a Xeroxed instruction sheet or providing 30 seconds of oral teaching will not do. Women have to distinguish and isolate a set of muscles they do not see and of which they are not conscious until trained. They may tend to push, in contrast to squeezing and pulling in and up. The pelvic examination is ideal time to do initial teaching and observe performance.

Second, record keeping, while a great aggravation to learners, seems to be essential to behavior change. We give the women daily diaries to record specific practice time, urine control patterns, and to make notes about behavior.

Third, learning must be monitored. It is critical to measure pelvic-muscle strength through subjective evaluation scales or vaginal sensors using pressure or EMG. It is astounding that in the reported research on pelvic muscle exercise, less than one-half of the studies measured the primary treatment outcome: pelvic-muscle strength. It makes little sense to examine urodynamics or wetting outcomes unless one knows that exercise has increased pelvic-muscle strength.

Lastly, written materials are helpful, they should be graphic and suggest imagery for the technique as well as ideas for putting the exercise into one's life pattern.

While research on pelvic-muscle exercise reports cure rates of 31–73% or success rates from 38–93%, it seems logical that pelvic muscle exercise is

not a cure-all [1, 4–6]. No one has yet validated the exact mechanism of pelvic muscle exercise on pelvic muscle strength and subsequently on urine control. The literature suggests that the exercise works best for women with milder degrees of stress leakage. Concerning variables that may affect outcomes, a Danish study found that while subjects more than 10% overweight had significantly higher stress grades before and after exercise compared to normal-weight subjects, it found no difference in cured or improved rates between the two groups [6]. In other words, overweight women could learn the exercise and benefit as well as normals. This study also found that women with a positive hormone status had a significantly better chance of cure.

In sum, pelvic muscle exercise is a safe and theoretically sound treatment. It has no known risks, and no complications. Pelvic muscle exercise does increase pelvic muscle strength and wetting in some women is decreased to such an extent that other treatments such as operation may not be needed. Pelvic muscle exercise is appropriate for all women with stress or mixed incontinence, especially those in the mild to moderate categories. However, such muscle training should be understood as a complex skill and the teacher must understand both muscle physiology and behavioral theories.

Behavioral programs for urine control in institutionalized incontinent individuals also include toileting techniques which are appropriate for individuals with functional urinary incontinence. They have episodic urine loss but normal detrusor and sphincter function. Usually their urine leakage is related to disturbances of mobility, communication, or memory. Generally behavioral toileting techniques include routine toileting – patients are toileted regardless of need every 2 hours; habit training – in which two-hourly checks are made to determine a pattern and toileting is fixed to that specific pattern; and contingency management in which explicit individualized rewards or withholding of such are linked to the habit pattern and consistently followed.

A newer technique, prompted voiding, builds on aspects of previous toileting techniques [7]. Prompted voiding is an aide or caregiver communication protocol linked to a toileting program. Patients are checked for incontinence hourly progressing to 3 hourly during the day, followed by a question about their perceptions: Are you wet or dry? This tuning-into-self technique challenges the subject to take responsibility. Immediate feedback is given with social approval and reinforcement (if correct) or else corrective information and encouragement. In either case the subject is prompted to toilet and given social reinforcement if willing to try.

A randomized clinical trial of prompted voiding in severely debilitated nursing-home patients reported a 50% reduction in frequency of incontinence during treatment [8]. Based on toileting ability, bladder-storage characteristics and mental responsiveness, an initial assessment period can identify patients most likely to succeed on the program. Key to the technique is staff compliance. With others, Schnelle has developed and tested a computerized assessment and management system to facilitate nursing-home use [9].

Prompted voiding is feasible in the typical nursing home. It is critical, however, to understand that the technnique is behavioral change for both the nursing-home care provider, usually an aide, and the patient. Both must appreciate the complexity of such multiple and interactive behavior changes in the context of nursing-home routines.

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PART ELEVEN

Bladder cancer

CHAPTER 44

Treatment of metastatic bladder cancer in the elderly

MALCOLM J. MOORE

Approximately 11,000 patients in North America die from bladder cancer each year. The median age of patients presenting with advanced bladder cancer is 65 and the peak incidence is between 60–75 years. Thus many patients who are considered for chemotherapy are elderly. There have been improvements in the systemic treatment of bladder cancer over the past decade, but the newer and more effective methods are associated with an increase in morbidity and mortality. These factors must be taken into account when deciding whether to proceed with aggressive combination chemotherapy in an elderly patient. This paper will provide an overview of chemotherapy of the bladder cancer and will conclude with comments on the application of this knowledge to the elderly.

Chemotherapy of metastatic bladder cancer

The past five years have seen an upsurge of interest in the use of more intensive treatments for metastatic disease stimulated in large part by the combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) developed at Memorial Sloan Kettering Cancer Centre [1]. Prior to the use of combination chemotherapy, a large number of Phase II studies of single agent therapy were done [2]. The assessment of the results of all these Phase II trials has been difficult because of the variability in eligibility and response criteria between different studies. The most active single agents are cisplatin and methotrexate while vinblastine and doxorubicin have more modest activity. Efoposide, vincristine, mitoxantrone and bleomycin have minimal activity against transitional-cell carcinoma.

Cisplatin is given at a dose of 60–100 mg/m^2, with intravenous hydration, every 3–4 weeks. Escalation of single doses beyond this level is limited by nephrotoxicity; cumulative neurotoxicity, ototoxicity and nephrotoxicity limits the number of cisplatin cycles. Cisplatin produces severe nausea and vomiting, which can now be controlled reasonably well with the new antiemetics including the 5-hydroxytryptamine blockers and steroids.

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While we can reduce the effects on the kidney by intravenous hydration and mannitol, we have no means to reduce the neurotoxicity and ototoxicity. Patients with renal dysfunction or pre-existing, high-frequency hearing loss will be more sensitive to the effects of cisplatin. This drug does present problems in patients with bladder cancer because many have compromised renal function on the basis of age, urinary obstruction and/or infection. In a number of phase II studies, the overall response rate in 320 patients treated with cisplatin was 30%.

The cisplatin analog, carboplatin, has a much lower incidence of adverse effects on the kidney, hearing, and peripheral nerves, which might make it a more suitable alternative in the elderly. However, the overall response rate in 80 patients was only 11% [3]. In addition, the dose-limiting toxicity of carboplatin is myelosuppression, which would render it a poor substitute for cisplatin in combination regimens that include other myelosuppressive drugs even if it did have equivalent activity.

Methotrexate, a folic-acid analog, can be given weekly as a single agent at doses of 30–40 mg/m^2, or less frequently at somewhat higher doses. Methotrexate is primarily excreted unchanged in the urine. Patients with compromised renal function have reduced methotrexate clearance and hence experience excess toxicity. The acute dose-limiting toxicity, myelosuppression and stomatitis, can be severe. The use of the reduced folate, leucovorin, will decrease toxicity but also may protect the tumor; this agent should be used routinely only in patients with renal dysfunction or third space accumulations of fluid. At the Memorial Sloan Kettering [4], responses were seen in 10/33 (30%) of patients treated with weekly methotrexate. There may be a dose-response relationship because responses were seen in 3/23 patients receiving 50 mg/m^2 and in 12/22 who received 100 mg/m^2 [5]. Higher doses of methotrexate ($>$ 100 mg/m^2) require the co-administration of leucovorin 24 hr later. It is not known whether high-dose methotrexate regimens plus leucovorin rescue will give better results than have been achieved with maximally tolerated doses of methotrexate without leucovorin.

Doxorubicin (Adriamycin) is given by bolus intravenous injection every 3–4 weeks at dosages ranging from 30–75 mg/m^2. As with methotrexate, the dose-limiting toxicity is myelosuppression and stomatitis. Cardiomyopathy is seen at cumulative doses greater than 500 mg/m^2 although this usually does not occur with the schedules used in bladder cancer. In early trials it was reported that this drug had significant activity against bladder cancer; 30/87 (35%) of patients achieved a response [6]. Recent experience suggests these trials may have overestimated its activity; and the drug had a more modest response rate of 18% in 223 patients.

Vinblastine, a derivative of the periwinkle plant, acts as an inhibitor of mitosis. It can be given weekly at doses of 0.1 to 0.15 mg/kg and is excreted in the bile. Its major toxicity, myelosuppression, is dose related. However, neuropathy is seen in some patients and constipation may occur. This drug

has not been widely studied; however responses were seen in 5/28 (18%) patients given weekly vinblastine as a single agent [7].

Frequently, patients with bladder tumors have impaired renal function, which may be due to age, coexistent disease, chronic infection or obstruction with dilatation of the upper tracts. Since renal dysfunction increases the toxicity from cisplatin and methotrexate, one should perform percutaneous drainage or stenting before chemotherapy in patients with upper-tract obstruction. Often cisplatin dosage is calculated based on glomerular filtration rate (GFR) to limit further deterioration of renal function by the drug. Because cisplatin is not cleared by the kidney, any reduction in dosage will also limit the tumor's exposure to the drug and thus reduce response. Methotrexate is excreted via the kidney and the clearance decreases proportionately to the fall in creatinine clearance. Maintenance of methotrexate dosage in the presence of renal dysfunction will lead to excessive toxicity. A study of chemotherapy in patients with ureteric obstruction found a higher incidence of serious hematologic toxicity and a lower response rate to systemic therapy if dilated upper tracts were not drained [11].

Combination chemotherapy

Generally the combination of two active agents has not produced dramatic improvements in antitumour efficacy e.g. the combinations of cisplatin with cyclophosphamide, doxorubicin or methotrexate all give response rates similar to cisplatin alone.

The highest response rates reported are with the use of more intensive regimens, which combine three or more active drugs at the maximally tolerated doses. These series report that a small group of patients achieved durable complete response and possibly are cured of their disease. All these regimens are associated with moderate to severe, normal tissue toxicity.

In a pilot study, the MD Anderson Cancer Centre combined cyclophosphamide, doxorubicin plus cisplatin (CISCA). In 97 patients, there was an overall response rate of 64%; 36% had a complete response [8]. Approximately one-half of these patients, who achieved a complete response, remained free of relapse after two years. The median survival was less than 10 months but 10% of patients were alive five years later.

The Northern California Oncology group treated 58 patients with metastatic disease with cisplatin, methotrexate, and vinblastine (CMV) [9]. The overall response rate was 56%; one-half of these were complete responses. However, only 4 patients remained in complete remission and the median survival was 8 months. The main side effects were nausea and vomiting, mucositis and granulocytopenia, with granulocytopenia being dose-limiting.

The most renowned combination for metastatic, transitional-cell carcinoma is that of methotrexate 30 mg/m^2 on days 1, 5 and 22; vinblastine

3 mg/m^2 day 2, 15 and 22; cisplatin 70 mg/m^2 on day 2 and doxorubicin 30 g/m^2 on day 2 (MVAC). In their most recent update on 133 patients, investigators from Memorial Sloan Kettering in New York [1], reported an overall response rate of 72%, with 36% of these patients achieving a complete response. Median survival was 13 months and 19% of patients remained alive at 4 years. The major complication of treatment is myelosuppression; 90% of patients had neutropenia and 25% had neutropenic sepsis. Mucositis was seen in one-half of the patients; other side effects were less frequent.

Other centres have reported less favorable outcomes with MVAC. In our initial experience, we achieved responses in 12/30 (40%) patients with measurable disease at the cost of quite severe toxicity [9]. Fifty-four percent required hospitalization for a toxic complication; most commonly this was sepsis. There was one drug-related death. Four patients achieved a complete response and two of these responses were maintained at three years.

Phase III trials in advanced bladder cancer

A prospective randomized study is needed to assess the relative merits of single agent versus combination therapy. While many Phase II studies have been done of single agents or of combination chemotherapy, only 6 randomized trials have been reported. Studies comparing cisplatin alone to cisplatin with cyclophosphamide; cisplatin, doxorubicin, and cyclophosphamide (two different studies); and cisplatin plus methotrexate did not show improvements in patient survival. A large multinational study compared cisplatin alone to MVAC in 246 patients with measurable metastatic bladder cancer [10]. The median age of these patients was 65; they ranged from 30 to 82 with 44% being older than 65. The overall response rate were 12% for cisplatin alone and 39% for MVAC ($p < 0.0001$); complete responses were seen in 3% of cisplatin and 13% of MVAC-treated patients. The median survival times were 8.2 months for cisplatin, and 12.5 months for MVAC ($p < 0.005$). The 2-year survival of MVAC-treated patients was increased twofold. Of patients treated with MVAC, 17% developed Grade 3 or 4 mucositis and 10% neutropenic fever; neither of these complications was observed with cisplatin. The 5 drug-related deaths were due mostly to sepsis; all occured in patients receiving MVAC. Only 24% of patients could tolerate this combination chemotherapy without dosage reductions or treatment delays.

This trial was the first to demonstrate the benefits of intensive treatment of bladder cancer rather than single agent therapy. It also provides a useful data base for understanding which patients are most likely to benefit from chemotherapy. A good performance status, the absence of weight loss, and metastases confined to nodal areas were associated with response and survival. Patient age did not influence response rate or survival; similar outcomes were seen in those < 65 and ≥ 65. The response rates in this trial demonstrate

the effect that the standardization of response criteria, patient selection and independent review of responses that are contained in phase III studies can have on results. The overall response rate to MVAC and the frequency of complete response rates were significantly less than those initially reported and the response to cisplatin, generally considered the most active single agent against TCC, was only 12%.

New approaches in systemic treatment

Transitional-cell carcinoma is a chemosensitive tumor and a dose–response relationship has been suggested by the MVAC versus cisplatin study. Further escalations in treatment are limited by normal tissue toxicity, particularly myelosuppression and mucositis. The hematopoietic growth factors – granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are being studied to determine whether they can protect against hematologic toxicity and thus allow escalation of dose.

We have treated 21 patients with advanced, transitional-cell carcinoma with a combination of standard MVAC plus GM-CSF [12]. In this population GM-CSF is associated with some toxicity. Several patients had a first-dose reaction of hypotension and hypoxemia and seven had to discontinue the drug because of side effects. There was evidence of protection against neutropenia in the first two courses, but this effect diminished with repeated treatment cycles so that most patients had severe neutropenia by their 3rd or 4th cycle. Our experience suggests that growth-factor support likely will permit only modest escalations in dose. Others also have tried to increase drug dose in the presence of growth factors but have encountered serious complications [13].

Regimens, such as MVAC, contain the most active of the currently available anticancer agents at a maximally tolerated dose. Therefore, it is unlikely that minor alternations in drugs or schedule will lead to major improvements in outcome. One study modified MVAC by substituting mitoxantrone and carboplatin for doxorubicin and cisplatin [14]. There was less subjective toxicity although myelosuppression remained a serious complication; responses were seen in 21/33 patients. Such approaches may reduce some of the toxicity associated with chemotherapy and allow us to treat patients in poorer general condition. Because the substituted drugs appear to have lower activity against these cancers, this gain might be achieved at the expense of a lesser effect against the cancer.

The testing of new cytotoxic and biologic agents for activity against transitional cell carcinoma should remain a high priority. When we incorporate new drugs into current programs, we should prefer those whose dose-limiting toxicity is not myelosuppression or mucositis. One new agent that shows promise is gallium nitrate, which is given by continuous infusion over 5–7

days. Patients refractory to standard chemotherapy have responded but ocular toxicity is a dose-limiting factor [15]. Other promising new drugs, such as taxol and the topoisomerase inhibitors, have yet to be tested.

While the aggressive chemotherapy improves the survival of patients with metastatic bladder cancer, any benefit is modest and the additional life can be measured in months. Patients, who achieve complete remission, may have a more sustained benefit; unfortunately, these are a minority. Complete remissions to chemotherapy and 2-year survival are most common in those with a small burden of disease. These patients have tumor cells that have a lower probability of resistance to therapy and they are better able to tolerate aggressive treatment. Chemotherapy may yield its greatest benefit when it is used as an adjunct to local therapy at a time when the systemic burden of disease is the smallest.

Adjuvant chemotherapy

Adjuvant chemotherapy indicates local treatment (in any sequence) for potentially curable disease. While superficial bladder tumor can be treated with transurethral resection and intravesical therapy, the outlook changes dramatically once the disease has invaded the muscle of the bladder wall. Overall the 5-year survival is only 50%; these patients die from metastatic disease within two years. Patients with larger primary tumor have a worse outlook. Because these patients die of metastatic disease, several studies have examined the value of chemotherapy before (neoadjuvant) or after (adjuvant) local therapy.

These studies examined the ability of chemotherapy to reduce treatment failures due to distant metastases, to improve local control and possibly to allow organ preservation. Chemotherapy can produce dramatic shrinkages of primary bladder tumors. In patients receiving neoadjuvant MVAC before surgery, 48% had complete regression of the tumor at cystoscopy although one-half of these had tumor in the cystectomy specimen [16]. In another study, 71 patients were treated with cyclophosphamide, doxorubicin, and cisplatin following cystectomy [17]. They received chemotherapy if they had pathological findings which predicted for a high probability of relapse. Treated patients had considerably better outcome than a group of high-risk patients who did not receive chemotherapy because of refusal, non-referral or medical contraindications. While it might be true that adjuvant chemotherapy improved the outcome of these patients, the result may also have been due to patient selection.

Five published trials randomized patients with muscle-invasive bladder cancer to local treatment alone, or local treatment with chemotherapy. None of these showed an improvement in survival, although one of these trials reported a significant increase in time to relapse. Four of these used chemotherapy regimens that would not be considered optimal by today's standards –

doxorubicin *plus* 5-fluorouracil, single-agent cisplatin (two studies) or methotrexate. The other was flawed by small patient numbers, a poorly defined protocol that was not well adhered to, and the performance of subgroup analysis with correction of *p*-values.

The true value of these approaches awaits the results of two large randomized studies. An American trial is comparing MVAC followed by cystectomy to cystectomy alone, and an international study is using CMV followed by local therapy compared to local therapy alone. Already, the international trial has accrued over 1000 patients and hence should have sufficient power to demonstrate any benefit, if it exists.

Treatment in the elderly

With advances in systemic treatment of bladder cancer over the past 10 years, intensive chemotherapy now can improve the survival of patients with metastatic disease. However this improvement is modest and almost all patients still die of their disease. When deciding whether to treat an elderly patient with MVAC or a similar regimen, one should weigh the potential benefits and probability of 'palliating' the disease against the toxicity and patient morbidity.

Fossa *et al.* [18] treated 27 elderly patients with cisplatin *plus* methotrexate and had a response rate of 48% with only modest toxicity. The MD Anderson Cancer Centre reviewed 36 patients between the ages of 76 and 84 who had received cisplatin-based combination therapy [19]. They demonstrated no difference in response rate or toxicity compared to that seen at the same centre with younger patients. In another study neoadjuvant therapy in selected patients aged 70–79 did not cause excessive morbidity [20].

Studies of chemotherapy in selected elderly patients has not demonstrated any evidence of a reduced likelihood of benefit or any excessive toxicity. The extent of disease, performance status and presence of co-existent illness are more important than patient age in determining outcome. Age-related declines in renal function may require reductions of methotrexate dose and measures to protect against further cisplatin nephrotoxicity. However elderly patients with good performance status, who have advanced bladder cancer should not be denied potentially beneficial therapy, solely on the basis of age.

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CHAPTER 45

Radiation in muscle-invasive bladder cancer

MARY K. GOSPODAROWICZ

Most patients with bladder cancer present with superficial disease, without evidence of invasion of the muscle wall. Only approximately 20% of patients have more advanced, muscle-invasive disease at diagnosis. This latter group presents a great challenge to physicians, because of the considerable mortality associated with such a presentation and the high risk of recurrence and metastases associated with advanced disease. Currently, almost 50% of patients with muscle-invasive bladder cancer die of their disease despite radical treatment.

Although the most common therapy in such patients is radical cystectomy, often the elderly are referred for consideration of radiation therapy (XRT) in preference to surgery. Coexistent medical illnesses, concern regarding the operative risks and preference for organ preservation lead physicians to consider alternatives to cystectomy. We have recognized that radiation is effective in the treatment of bladder cancer since the early 1900s, but to date have reached no consensus concerning its exact role in management [16]. With decreasing operative mortality and morbidity of cystectomy, the introduction of bladder substitution and continent urinary diversion, the relative role of surgery and radiation in treatment of bladder cancer will evolve further in the next decade [19]. In general, most patients are suitable for treatment with radiation, but usually the younger and fit patients are selected for cystectomy. Therefore, it must be understood that the outcome in patients, who are treated with XRT, because they are deemed not to be suitable for cystectomy, should not be compared to that of a healthier population undergoing primary cystectomy [5].

Muscle-invasive bladder cancer is a heterogenous disease and multiple factors affect its outcome, however the single most important factor affecting survival is the depth of bladder-wall invasion. Other important determinants of outcome include tumor size, presence of a palpable extravesical mass, presence of ureteric obstruction, elevated serum creatinine, solid tumor configuration, high tumor grade, vascular invasion and presence of metastases. Many of these factors are interrelated, for example, high histological grade

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is associated with advanced T category and obstructive uropathy occurs mostly in tumors with extravesical extension [3, 4, 8, 9].

The depth of bladder wall penetration is expressed by the T category in the TNM staging classification [8, 9, 13]. However, extension through the bladder wall may be manifested by a palpable extravesical mass and indeed in some studies this finding is of greater prognostic significance than the pathological definition of bladder-wall invasion [6, 9]. Although numerous clinical and pathologic prognostic factors have been described, there is a relative paucity of information regarding the more fundamental immunologic, biochemical and molecular markers that may have considerable prognostic importance in invasive bladder cancer [7]. Since depth of bladder-wall invasion is a crucial prognostic factor, all patients with disease limited to the bladder should have adequate documentation of muscle invasion. Clinical staging, although it is not interchangeable with pathological staging, is a powerful indicator of prognosis. It is our practice to assess each patient being considered for radical XRT with cystoscopy and bimanual examination under anesthesia (EUA) before treatment. Patients with evidence of muscle invasion and especially those with high-grade tumors also should be assessed before treatment with chest X-ray, bone scan and CT of abdomen and pelvis to exclude distant metastases.

Patients with localized disease are suitable for treatment with radiation if there are no contraindications to such treatment. Radiation with curative intent is not appropriate for those with inflammatory bowel disease, previous pelvic irradiation, extensive pelvic surgery or chronic pelvic infections. Radiation is delivered by external-beam therapy, usually on a high-energy linear accelerator. Therapy is given daily at a low dose per fraction (180–200 cGy) over 6 or 7 weeks. Patients are able to maintain a normal lifestyle and, time and distance permitting, to continue employment. Acute toxicity is minimal, especially in patients with satisfactory pretreatment bladder function, and includes mild diarrhea, frequency and dysuria. Response to radiation is assessed 4 to 12 weeks after completion of therapy. The goal of post-XRT assessment is to determine the presence of residual invasive disease. If residual disease is present and there is no evidence of metastases, a salvage cystectomy should be performed, even in patients with coexistent medical problems. Invariably untreated muscle-invasive bladder cancer leads to the patients' death, although sometimes survival may be prolonged with a more conservative approach. Late radiation complications include mild hematuria due to telangiectatic changes in bladder mucosa, minor and self-limited rectal bleeding due to the similar changes in rectal mucosa, and impotence. Severe late complications including hemorrhagic cystitis, bowel obstruction or fistula formation are rare if patients are carefully selected pretreatment and a low dose per fraction approach is used.

Most of the prognostic factors in muscle invasive bladder cancer influence the risk of metastases and therefore are associated with survival, but T category, size of extravesical mass, tumor size and configuration also affect

the probability of response to radiation. There is concern regarding the impact of coexistent carcinoma *in situ* (CIS) on the response to XRT and on sustained local control in patients treated with external-beam radiation. While some have suggested that the presence of CIS has no major impact on the success of radiation, others have found that CIS is rarely controlled by radiation alone and that its presence is associated with a high rate of new tumor occurrence after radical radiation (Wolf: CIS-70%, no CIS-0%) [17, 20, 23]. It is possible to treat patients with persistent CIS following XRT with intravesical BCG but no published reports have yet assessed the long-term efficacy of such treatment. Also, it should be noted that patients with history of bladder cancer are at a life-long risk of new tumor formation and require careful cystoscopic monitoring.

In spite of the extensive experience with radiotherapy in bladder cancer, well-conducted prospective trials are uncommon. It is widely accepted, especially by the radiation oncologists, that radical radiation is a useful approach in bladder cancer [15]. Longterm follow-up of patients treated with external-beam radiation suggests that a proportion (15–25%) can be cured and preserve normal bladder function [4, 9]. However, the results of radiation have been disappointing due both to poor local control and high distant relapse rates [4, 8, 9, 13]. A major clinical problem in patients treated with full-dose radiation is that some 50% of them will never achieve complete clearance of the tumor or will develop a local recurrence. Studies with murine tumor models have shown a significant activity with the combination of Cisplatin and radiation against transplantable transitional cell tumors, but until early 1980s we did not know whether the human bladder could tolerate the combination of chemotherapy and radiation without a significant increase in the late complications [14]. High complete response rates were reported in phase II clinical trials of concurrent Cisplatin and XRT and, in a prospective randomized study, patients treated with Cisplatin and radiation had a decreased rate of pelvic recurrence compared to those treated with radiation alone [1, 2]. Therefore, current policies of radiation alone should consider the addition of concurrent Cisplatin to optimize local control and bladder preservation. At the present time we do not know whether concurrent chemotherapy will avoid persistent carcinoma *in situ* following radiation.

A policy of radical radiation should always encompass salvage cystectomy in the event of local failure. Often patients are referred for radical radiotherapy because they are 'not fit for cystectomy', but fitness for a particular therapy reflects merely a degree of risk. If such patients fail radiation, the only option for cure is cystectomy despite the increased operative risk. In general, patients who are fit for radical radiation are fit for cystectomy, albeit at a greater risk. The advantage of radical radiation is that a proportion of patients will be cured while preserving normal bladder and sexual function. In most solid tumors, radiation achieves a local control rate inferior to that obtained by surgery, this is true also in bladder cancer. Thus, efforts to preserve bladder function often result in a local control rate lower than that

achieved by cystectomy and even if XRT achieved a 100% response rate, it cannot be expected to eliminate the risk of new tumor formation. Because total cystectomy removes the urinary bladder and has only limited ability to cure, radiation remains an important option in muscle-invasive bladder cancer. However, we have not answered the question whether XRT, with an option of cystectomy for salvage, would yield results comparable to those obtained by cystectomy.

In the last two decades preoperative XRT was investigated in an attempt to improve local control in the pelvis and thus improve survival in patients with locally advanced disease. Several retrospective studies indicate that preoperative XRT confers a survival advantage but, so far, this has not been confirmed in prospective randomized trials. Soon we should have the results of the prospective randomized trial conducted by the Southwestern Cooperative Oncology Group, in which patients with muscle invasive disease (T2–T4A) were randomized to treatment with cystectomy alone or to preoperative XRT, using 2000 cGy in 5 fractions over one week. However, if the above trial is negative, the question will remain unanswered concerning the value of higher-dose preoperative XRT (40–45 Gy in 4–5 weeks), especially in patients with extravesical tumor extension (T3b) [11, 13].

We now appreciate that, in unselected patients with muscle-invasive bladder cancer, approximately 50% will die of metastatic disease and therefore any treatment, with either XRT or surgery alone that is reported to be better than 50%, is more likely to be the result of selection rather than of treatment. Recognizing that distant failure is the major threat in patients with muscle-invasive bladder cancer, current clinical trials are being directed to the role of systemic chemotherapy in combination with surgery or radiation [12, 14]. The goal of treatment is to improve survival by eradicating micrometastases and, in case of XRT, improve local control without increasing complications, as would be expected if this was attempted by increasing the radiation dose alone. Current randomized trials include a study of neoadjuvant CMV (cisplatin, methotrexate, vinblastine) chemotherapy before either radical cystectomy or radical radiation for patients with operable, muscle-invasive disease [12]. It is important to maintain a high standard of radiotherapy, so that we can evaluate the incremental role of chemotherapy in clinical trials [19]. This approach is expected to improve the quality of life by allowing bladder preservation [14, 21]. However, we should exercise caution in the interpretation of preliminary information from nonrandomized trials of combined modalities [22]. Prevailing enthusiasm for trials involving combined modality therapy should not deter radiation oncologists from investigating factors that may predict radiation sensitivity as well as new fractionation schemes. We require prospective studies, preferably randomized and stratified for prognostic factors, to prevent selection bias and to avoid misleading comparisons of new data with historical experience.

Patients with locally advanced and inoperable bladder cancer have a poor prognosis and a median survival of 6 months. It is unlikely that treatment in

this group of patients will improve until a more effective chemotherapy will become available. Currently, there is no evidence that an aggressive approach will benefit patients with large fixed tumors (T4B) [10].

Summary

While radical cystectomy is the most common approach to muscle-invasive bladder cancer, radiation has been used alone as definitive therapy (radical XRT) or as an adjuvant before cystectomy (preoperative XRT). The major advantage of radical radiotherapy over cystectomy is that it offers an opportunity to preserve normal bladder and sexual function. Radical radiation results in local tumor control in approximately 50% of patients but further efforts are needed to improve results and reduce the number of patients requiring salvage surgery. The main goal of preoperative radiotherapy is to prevent local recurrence after cystectomy, but to date prospective clinical trials have not documented its benefits. To improve both local control and overall survival, combination chemotherapy *plus* radiotherapy programs, with possible bladder sparing, are being tested in prospective clinical trials in selected patients with muscle-invasive bladder cancer.

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PART TWELVE

Sexual dysfunction

CHAPTER 46

The diagnosis of impotence

ALVARO MORALES

The sexual needs of the elderly male differ in many ways from those of younger groups. However the physical causes of erectile dysfunction are the same and are exaggerated by the deterioration of the involved systems (vascular, neurological). Emotional causes, on the other hand, frequently are dissimilar. The methods to establish an etiological diagnosis in impotence is the same regardless of age; the indications for initiating the process and for conducting some of the tests, however, may be different in the elderly. The physician has the responsibility of determining the patient's needs, to inform him of the therapeutic options and advise him of the most appropriate ones.

This review of impotence in the elderly male will update available methods, leaving the individual physician to choose measures appropriate for the individual patient.

Despite the prevalence of impotence, many misunderstandings exist among health care workers as to the basic ways to manage erectile difficulties. The initial step in the management of impotence is to establish common ground for discussion, including a definition of impotence. We employ the following definition.

> The inability to develop and/or maintain an erection of sufficient quality for vaginal penetration, during any type of sexual activity, for a continuous period of no less than 3 months.

This definition provides a basis for understanding among members of the team concerning who should be investigated and treated. The choice of three months is not only arbitrary but empirical but it helps to eliminate the psychogenic (e.g. situational) impotence. On the other hand, it provides a firm background for establishing which individuals merit further assessment.

This synopsis will explain the why, when and how of the investigation for impotence in general and the elderly male in particular.

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Why?

Over the last decade techniques have been developed to determine, with an increasing degree of accuracy, the causes of impotence in most cases and new and effective treatments have been developed. Thus a condition, which was poorly understood and badly treated just a few years ago, now can be effectively managed. It must be emphasized that the fundamental step in successful treatment for an impotent man is the proper identification of the cause(s).

Frequently the older patient is embarrassed and apologetic because he has the added burden of believing he is either 'too old for these things' or the victim of an inexorable process. He requires assurance that his interest is legitimate and nothing to be ashamed of. Unfortunately, frequently his misconceptions are shared by his partner, peers and members of the medical profession.

When?

Most sexual dysfunction clinics and individual urologists are overwhelmed by the numbers of patients. Generally a couple coming to the first interview has waited for several weeks or months; hence the investigation should be initiated without further delay. However, many patients arrive at the clinic poorly informed and, in many instances, with unrealistic expectations. They must be informed of the need for patience, co-operation and determination. If they lack commitment they probably will not pursue the necessary investigations once they realize that there is no prescription for the "power pill about which I read in the paper".

How?

The initial interview should establish the presence of impotence but should bring to light other factors, i.e. premature ejaculation, severe marital disharmony. Early awareness of the patients or the couple's additional problems may re-direct the investigation in more fruitful ways.

Many different approaches have been taken to the investigation of erectile failure. The basic assessment, however, includes an interview with the patient and his partner, a physical examination and a metabolic and hormonal screening to establish the need for additional testing.

The patient goal-oriented approach popularized by Lue [1] includes a detailed history and physical examination and a thorough biochemical, metabolic and hormonal evaluation. If it uncovers no obvious correctable cause e.g. hypogonadism, the patient is offered simple medical treatment, e.g. yohimbine, or a comprehensive diagnostic evaluation that varies from center

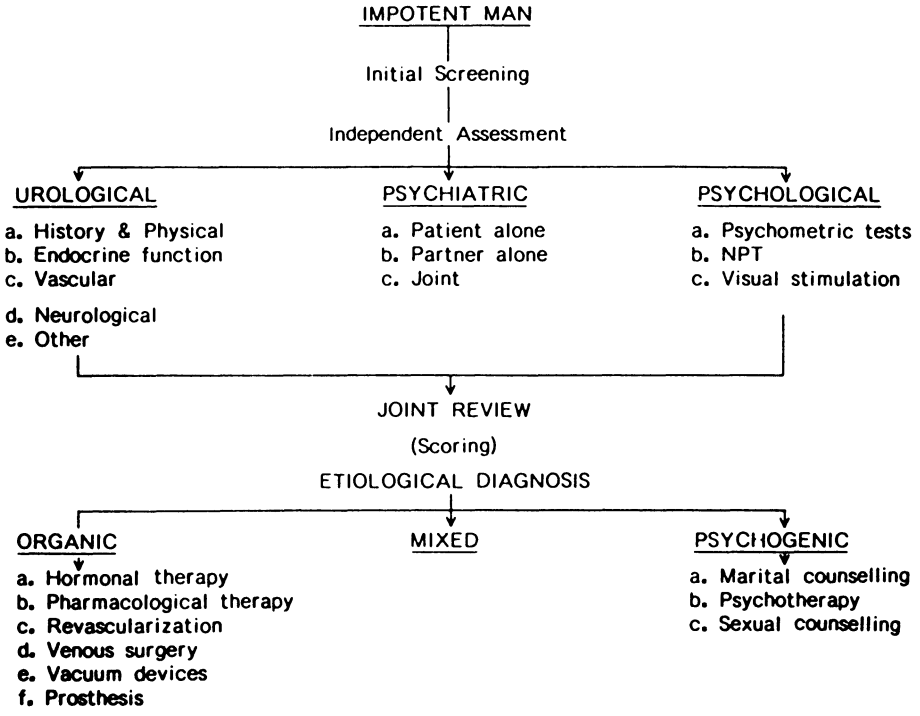

Fig. 1.

to center. At this point many patients particularly older ones decide 'to leave things as they are, it is not worth the hassle'. At this stage one might consider the intracavernosal administration of vasoactive drugs as a diagnostic procedure.

In our clinic, the diagnostic process follows an established program, leading to therapeutic recommendations. The flow diagram (Fig. 1) shows the various steps of the process at our institution. Because new techniques appear frequently, changes are introduced almost every year into the flow diagram. At a glance these diagrams provide a clear and simple guide to the various possibilities in investigation and treatment. Obviously, when a likely cause is found, further evaluation may be deemed unnecessary.

We recommend two basic assessments, one by the urologist and another by a psychiatrist or psychologist, with special interest and expertise in the area of sexual functioning.

Urological

Urologists are best qualified to conduct the initial assessment, which includes the history and a thorough physical examination. As with any specialized

investigation, a form listing specific areas of consequence must be completed. A systematic record of the data on every patient keeps the interviewer from neglecting areas of importance. A standardized record is particularly important in new programs or in centers in which a variety of individuals (i.e. trainees) conduct the initial interviews.

Each facility should develop a form that best fulfils its needs. Appendix 1 shows a simple form that has proved to be useful at our institution [2]. However, this or a similar form is no substitute for a proper history and physical examination; it is simply a guideline to remind the interviewer of areas of special interest or relevance. For example, the form does not include the data from a proper physical examination (i.e. blood pressure). Such information is omitted because it can be retrieved from the patient's chart. On the other hand, a practitioner may wish to develop a more elaborate form. Currently, a number of computer programs permit the storage of data which includes most of the important information in the area of sexual dysfunction. Nevertheless no form will satisfy the specific needs of all centres, particularly if they have undertaken some form of research or systematic accrual of data.

Appendix 1 is not meant to imply that all the information in this form in necessarily relevant. For instance we limit the initial hormonal screening to the determination of a serum testosterone because we do not have evidence that supports the need for an exhaustive hormonal and metabolic assessment early in the patient's evaluation.

After the history, the physical and the blood sample for hormonal and metabolical screening, further ancillary tests include: (1) assessment of the arterial supply to the penis by the penile-brachial index or more accurately and objectively by duplex ultrasonography [3], (2) neurological assessment by penile biothesiometry, (3). evaluation of venous competence by cavernosometry ± cavernosography, (4) dynamic arteriography. These tests should be available in any centre investigating impotence and should be used in the individual patient on a 'need-only' basis and in a progressive manner. For instance, if the individual exhibits excellent erections during visual sexual stimulation, other invasive tests are not required. There is no need to subject every patient to all of these tests. In progressive diagnostic evaluation, more complicated and invasive tests are conducted only if simpler, non-invasive methods do not establish the diagnosis.

Psychological

Most patients and couples seeking advice concerning sexual dysfunction do not require a psychiatric assessment. However, in our view, a psychological evaluation is mandatory. Usually the urologist lacks the expertise to determine whether subtle psychological factors may be operating in the couple's dysfunction and the team involved in the psychological assessment must rely

exclusively on its training and experience. That is to say, in sharp contrast to the urological assessment, the psychologist/psychiatrist has no biological markers to confirm his diagnosis. Psychological assessment involves more than a consultation with any psychologist or psychiatrist, the person conducting the evaluation must be qualified by training and experience to deal with sexual dysfunction. The opinion that 'no mental illness is present' is of little help in dealing with an impotent patient, at any rate, the urologist should be aware that much psychopathology may exist in this condition [4]. The psychologist has two instruments for the investigation of the impotent man (a) psychometric assessment and (b) recording nocturnal penile tumescence.

Psychometric assessment

Of a number of questionnaires now available, the most widely accepted are the Sexual Interaction Inventory (SII) which appears to be consistent in discriminating normal from sexually dysfunctional couples. The Derogatis Sexual Functioning Inventory (DSFI), a self report, also has been found to be consistent and reliable. Frequently the Minnesota Multiphasic Personality Inventory (MMPI) is used in an attempt to differentiate between organic and psychogenic impotence, but this test was not designed for this purpose and cannot make such a differentiation [5]. As mentioned the urologist can do a psychological assessment of the sexually dysfunctional patient (and couple) if he/she is aware of his/her shortcomings in this regard. A questionnaire similar to that shown in Appendix II has been used at our institution for several years.

Nocturnal penile tumescence (NPT)

Frequently, the urologist asks: Is NPT really necessary? The short answer is a qualified yes. Although NPT still has wide acceptance for medical and legal purposes, it has lost its pre-eminent place in diagnosis for the following reasons:

1. A better understanding of the physiological mechanisms of penile erection,
2. The development of techniques to pinpoint specific physiological disturbances,
3. Doubts about the reliability and specificity of NPT,
4. Fundamental questions on the as-yet-unproven similarities of the central mechanisms controlling sexual and nocturnal erection and,
5. The introduction of alternative techniques to measure responses to erotic stimuli.

The rationale for NPT monitoring is appealing: if erections occur during sleep, it is presumed that a man complaining of impotence would have a psychogenic dysfunction, while the opposite would be presumed if no erec-

tions occur. Unfortunately this is not always true, and recent investigations have demonstrated that NPT records must be interpreted with caution. A further complicating problem is the quality of the NPT records. The best and most reliable forms of NPT monitoring are polysomnographic recording including EEG (to ascertain sleep), oculogram (to measure rapid eye movement [REM] sleep), respiration (to rule out sleep apnoea), limb monitoring (to rule out myoclonus) and obviously, penile tumescence and rigidity. Unfortunately these procedures are costly and a great deal of expertise is needed to set up the procedures and interpret the results. Due to these drawbacks, less costly but also less reliable-methods have been developed to assess NPT. Of these, the only one with diagnostic value is the RigiScan (Dacomed Corporation, Minnetonka, Minnesota), which can measure penile tumescence and rigidity but does not record the important more central parameters.

The substantial appeal of NPT as an etiological indicator should not obscure the difficulties inherent in its use and interpretation. The measurement of penile erections during the sleep cycle has diagnostic value but the test should be regarded as only one element in the assessment of the dysfunctional couple. Under the best circumstances, the NPT record shows only erectile activity during sleep. We have no proof that sexual and sleep erections are controlled by the same central mechanisms. Nevertheless, the absence of biological markers for psychogenic dysfunction is being filled, albeit imperfectly, by the recording and analysis of NPT [6]. In an extensive study by Bock and Lewis at the Mayo Clinic, over 800 men underwent a comprehensive evaluation including polysomnographic recording. These investigators concluded that "sleep lab analysis is an essential part of the evaluation of erectile dysfunction, but is neither specific or sensitive enough to be employed (as) a single modality. NPT should be used in conjunction with other appropriate diagnostic studies to evaluate erectile dysfunction" [7]. I agree. However, one cannot ignore the difficulties faced by the urologist who practises outside a tertiary care institution and cannot refer his patients to a sleep laboratory.

Alternatives to NPT recording

Newer techniques, such as the intracavernous administration of erectogenic drugs and exposure to erotic material, have brought substantial changes to the diagnosis of erectile failure.

1. As part of the initial screening, the intracorporeal administration of vasoactive drugs may make unnecessarily more elaborate evaluation. It has been reported that a positive response to intracavernosal drugs conclusively rules out a vascular lesion – a major factor in impotence. We [9] and others [10] have suggested that this assumption may not be accurate, especially when the results are inconclusive or when clinical appraisal suggests that the findings may be spurious (i.e. false negative). Under these circumstances the

interpretation of findings is unreliable; the response to vasoactive drugs is notoriously inconsistent, particularly when the test is done in a clinic or laboratory setting. Progressively larger doses and several sessions may be necessary before one can conclude with confidence that the test result is a true negative. Once again, this is an important diagnostic manouver if it is incorporated into a comprehensive approach; in isolation, it is unreliable and misleading.

2. Erotic stimulation with the simultaneous recording of carefully measured penile responses is an option that has become available only recently. As with NPT, the assessment of erectile response to erotic material (Visual Sexual Stimulation [VSS]) has considerable intuitive appeal. VSS approaches the issue of erectile response through an assessment that endeavours to approximate the actual sexual situation. In the VSS procedure, the man is shown a segment or segments of erotic material and erectile response is measured using conventional measurement techniques typically a mercury-in-rubber strain gauge attached to a single or multichannel polygraph. Alternatively, one can employ the RigiScan or a similar device in the real time mode.

At present, although there is a good deal of interest in VSS as a diagnostic modality, we have scanty scientific evidence concerning its clinical usefulness and we have no data about whether NPT and VSS employ the same system pathways; they may be different. A recent evaluation [11] attempted to establish the role of VSS as a diagnostic procedure. In spite of this and some other promising results, questions about stimulus characteristics, metric properties, and interpretive strategies must be answered before its use can be recommended in the assessment of impotence.

Conclusion

The use of VSS as an alternative to NPT is attractive for a variety of reasons. It is less cumbersome to perform, it can be done in a relatively short time, it is significantly less costly and, probably, requires much less expertise for interpretation. The face-validity of VSS, which is due to the apparent congruence between the phenomenon being measured (erections in response to erotic material) and the criterion behaviour (erections in an erotic situation), may be the key factor in the validity accorded to VSS testing. This apparent congruency is dangerous if it encourages us to ignore the unknowns of the technique when we interpret its results. We should avoid the traps that made NPT recording a controversial issue in the diagnosis of impotence. Although VSS may be an alternative to NPT, we should not accept it into the diagnostic workup until we answer several fundamental questions. The most immediate task is the development of standards for stimulation, and thus avoid variations attributable to inconsistent assessment techniques, that is, inconsistency of results due to inconsistency of techniques.

As a technique NPT recording has been well researched in the last three decades and its limitations are generally known. On the other hand, VSS is a newcomer and a number of parameters remain to be assessed. At this point in our understanding, there is no alternative to the cumbersome procedure of evaluating both simultaneously and to establish the relative value of each in conjunction with other physiological measures. We will need a significant investment of effort to answer the remaining questions about VSS but the results will be worth such an effort.

Appendix I. Organic assessment of impotence

QUEEN'S UNIVERSITY - DEPARTMENT OF UROLOGY
Q SCALE (ORGANIC)

Name _____ C.C. No._____ Age ____y.o. Date seen_____

SECTION I. HISTORY

A. Age _____ B. Onset of Impotence:
0. Sudden
1. Gradual

C. Duration:
_____ months
_____ years

C. Sexual Erections:

a. Quality
0. Good quality
1. Poor quality
2. Absent

b. Frequency
0. Intermittent
1. Continous
2. Permanent

c. Percentage: Usual % of erection obtained ____% If it varies specify range: from ____% to ___%

Comments:
_____
_____

E. Early Morning Erections:

a. Quality
0. Good quality
1. Poor quality
2. Absent

b. Percentage: Usual % of erection obtained ____% If it varies specify range: from ___% to ___%

Comments:
_____
_____

F. Medications: List all current medications and dosages.
_____
_____
_____

G. Non-prescription drugs:
_____

H. Alcohol Consumption:
_____

I. Cigarette smoking:

a.Current smoker--▸ Quantity per day _____ Number of years _____

b.Ex-smoker --▸ Years since quitting _____ Quantity per day _____ Number of years ____

c.Non smoker ___ Does partner smoke? ____ Heavy ? ___ Light ? ____

J. Past Illness:

Likelihood of affecting erections: Specify:

0. None
1. Possible
2. Pobable
3. Definite

K. Current Illness:

Likelihood of affecting erections: Specify:

0. None
1. Possible
2. Probable
3. Definite

L. Previous Surgery:

Likelihood of affecting erections: Specify

0. None
1. Possible
2. Probable
3. Definite

M. Ejaculation:

0. Antegrade Comment
1. Premature
2. Retrograde
3. Absent

N. Libido:

0. Normal Comment
1. Increased
2. Decreased

O. Partners attitude to problem:

0. Concerned & supportive Comment
1. Indifferent
2. Angry & resentful

SECTION II. EXAMINATION

A. Gynecomastia: Explain as needed for each category

0. Absent
1. Present

B. Facial Hair:

0. Normal
1. Abnormal

C. Pubic Hair:

0. Android
1. Gynecoid

D. Femoral pulses:

0. Normal bilaterally
1. Normal unilaterally
2. Diminished bilaterally
3. Diminished unilaterally
4. Non-detectable bilaterally
5. Non-detectable unilaterally

E. Penis: Explain as needed for each categroy

0. Normal
1. Abnormal

F. Peyronie's plaque:
0. Present
1. Absent

G. Testicles:
a. Presence
0. Both present
1. One absent
2. Both absent

b. Location
0. Both descended
1. Unilateral cryptorchidism
2. Bilateral cryptorchidism

c. Size
0. Both normal
1. One abnormal
2. Both abnormal

d. Consistency
0. Normal
1. Abnormal

G. Scrotum and contents, excluding testicles:

0. Normal
1. Abnormal

H. Prostate:
0. Normal
1. Abnormal

I. Bulbo-cavernous reflex:

0. Present
1. Absent

J. Other potentially contributory physical findings:

SECTION III. CLINICAL TESTS

A. Testosterone

B. Prolactin

C. F.S.H.

D. L.H.

E. Alk. Phosph

F. F.B.S.

G. Thyroid function

H. Renal function

I. Hematology

J. Vascular Studies:

a. Brachial B.P.:

--> LEFT _____/_____ { } --> RIGHT _____/_____ { }

b. Penile Flow:

Dorsal: LEFT: strong / weak /absent RIGHT: strong / weak / absent

Cavernosal: LEFT: strong / weak / absent RIGHT: strong / weak / absent

c. Penile B.P.:

LEFT: _____ RIGHT: _____

d. P.B.I. Comments

LEFT (stethoscope) _____ (doppler) _____

RIGHT(stethoscope) _____ (doppler) _____

MEAN (stethoscope) _____ (doplIer) _____

e. DUPLEX US:

RIGHT cavernosal: Pre-GTN ml/s —▸ Post-GTN ml/s

LEFT cavernosal: Pre-GTN ml/s —▸ Post-GTN ml/s

K. Sleep Studies:

No. of nights: Sleep cycle: Avge. # of erections/night

Quality of best erection by CCT: Night #1_____% Night #2____% Night #3____%

Abnormal sleep cycles:

L. Visual Sexual Stimulation:

Response to VSS

Quality of erections: Segment #1_____% Segement #2_____% Segement #3_____% Segement #4_____%

Appendix II. Psychological assessment of sexual dysfunction

QUEEN'S UNIVERSITY - DEPARTMENT OF UROLOGY
Q SCALE (NON-ORGANIC)

NON-PHYSICAL ASSESSMENT FORM

Name:_____ C.C. No._____ Age:_____ Date Seen:_____

A. DEMOGRAPHICS:

Marital Status
0 - never married
2 - single
3 - currently married/common law
4 - separated
5 - widowed
0 - divorced

Number of previous marriages: _____

Number of previous common law relationships: _____

Current living arrangements:
0 - with spouse/partner only
1 - with spouse/partner & others (e.g. children, parents)
2 - with family (e.g. parents, sibs, grown children)
3 - with friend(s)
4 - with children only (under 19 years)
5 - alone
6 - other (specify) _____

B. EMPLOYMENT:

Patient is presently:
0 - employed
1 - unemployed
2 - retired (length of retirement) _____

Occupation
(if retired, occupation prior to retirement _____

Patient is experiencing financial difficulties: Yes [ ] No [ ]

C. HISTORY OF ERECTILE FAILURE:

Date of onset: Month:_____ Year: _____
Onset was: Rapid (<1 month) [ ]
Gradual [ ]

If rapid, circumstances at time of first appearance (list any events which may have been of significance) _____
_____
_____

D. SEXUAL ERECTIONS (In Past Three Months):

Quality:
0 - intermittent, good quality
1 - good quality, not maintained
2 - consistent, poor quality
3 - gradually worsening quality
4 - absent

Frequency of sexual erections: _____
Frequency of attempts at intercourse: _____
Are erections sufficient for vaginal penetration: Yes [ ] No [ ]
If yes, frequency: _____
Usual percentage of erections obtained: _____%
If it varies, specify range: from _____ to _____%
Comments: _____
_____
_____

EARLY MORNING ERECTIONS:

Quality:
0 - good quality
1 - poor quality
2 - absent

Usual percentage of erections obtained: _____%
If it varies, specify range: from _____ to _____%
Comments: _____
_____
_____

PSYCHOLOGICAL MARITAL ASSESSMENT:

1. History of Sexual Dysfunction: Yes [ ] No [ ]
   Type: _____
2. Number of previous psychiatric admissions: _____
3. Number of previous psychiatric disturbances that need intervention: _____
4. Current psychiatric disturbance: Yes [ ] No [ ]
   If yes, specify: _____
5. Previous substance abuse: Yes [ ] No [ ]
   Type: _____
6. Level of sexual desire
   (in comparison to period prior to erectile problem:
   Patient:
   -increased
   -normal
   -slightly decreased
   -severely decreased
   Partner: -increased
   -normal
   -slightly decreased
   -severely decreased

7. Level of concern/anxiety about erections (fearfulness in or out of sexual situation):

Patient: -no concern
-mild performance anxiety
-moderate performance anxiety
-severe performance anxiety
Partner: -no concern
-mild performance anxiety
-moderate performance anxiety
-severe performance anxiety

8. Impact of loss of intercourse on self esteem: (how is patient/partner different because of problem?):

Patient: -relieved
-no impact
-mild loss of self esteem
-moderate loss of self esteem
-severe loss of self esteem
Partner: -relieved
-no impact
-mild loss of self esteem
-moderate loss of self esteem
-severe loss of self esteem

9. Current psychological functioning (depression, other psychiatric disorders, substance abuse):

-excellent
-fair
-poor

10. Physical disorders or conditions:

_____
_____
_____

11. Partner's Health status:

-excellent
-mild health problems
(no more than slight functional impairment)
-moderate health problems
(some functional impairment)
-severe health problems
(marked functional impairment)

12. Current state of relationship:

-well adjusted
-mildly dysfunctional
-moderately dysfunctional
(constant arguments and lack of communication)
-severely dysfunctional
(considering separation)

13. Affection and attention: (in comparison with period prior to erectile problem)

_____
_____

14. Pleasure/satisfaction with affection/attention: (in comparison with period prior to erectile

Patient: -same
-less
-more than before
Partner: -same
-less
-more than before

15. Degree of pleasure with current sexual activity (in comparison with period prior to erectile problem):

Patient: -same
-less
-more than before
Partner: -same
-less
-more than before

16. Willingness to pursue treatment:

Patient: -refusal
-doubtful
-somewhat enthusiastic
-enthusiastic

Partner: -refusal
-doubtful
-somewhat enthusiastic
-enthusiastic

17. Appraisal of significance of non-physical factors:

From 1 (very unlikely significant) to 4 (very likely significant)

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CHAPTER 47

Pharmacological treatment of male sexual dysfunction

ALVARO MORALES

In the last decade interest in the physiology of the erectile process has been rekindled with the development of pharmacological approaches to the therapy of erectile failure. Improved understanding of the vascular and trabecular tissues of the penis permits the development of new and effective strategies to facilitate penile erections. Activity of the genital organs, of course, is only a portion of the human sexual response; however, once such a response occurs, we can measure, quantitate and promote a variety of compounds which can affect it.

Gross hormonal abnormalities interfering with a normal sexual response can be readily diagnosed and are treated with agents that are effective and, generally, do not require invasive procedures. When given systemically, non-hormonal pharmacological agents in clinical use are of limited effectiveness. Compounds injected into the corpora cavernosa are active but carry all the drawbacks of repeated needle punctures in a relatively small area. Some of these help to establish an etiological diagnosis and may provide important information in regard to prognosis; also they can be effective therapeutically.

Non-hormonal considerations

Patients with organic impotence rarely are candidates for hormonal manipulation and, as a general rule, such an approach should be limited to those with thoroughly documented deficiencies. Nevertheless, it has been demonstrated in an animal model that an appropriate androgenic milieu is essential for an adequate erectile reponse. Until this milieu is understood in humans, we should not contemplate indiscriminate hormonal (androgen supplementation or inhibitors of prolactin secretion) manipulation in the absence of a definite causal relationship. In many erectile dysfunctions, other organic factors, vascular or neurological, are the primary cause and they could benefit from treatment with non-hormonal agents. Furthermore, a significant group of men with a predominantly psychogenic impotence also could derive significant benefit from such therapy. The introduction of intracavernosal drugs

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brought a fundamental change in our approach to impotence; currently the injection of single or multiple agents is the first choice for many patients. We are making slower and much less dramatic progress in developing non-invasive, preferably oral, alternatives. However, basic research that is increasing our understanding of the physiology of libido and erection, is about to translate into significant therapeutic developments.

For instance, we have identified zones in the medial preoptic area (MPOA) of the diencephalon that are strongly associated with erectile function and sexual behaviour, and a peripheral neural network, which controls sexual reflex responses. Equally important, we have determined the fundamental role of adrenergic, dopaminergic and serotonergic activities in the regulation of erections in men as well. Mainstream vascular physiology has been extended to reveal the role of nitric oxide in cavernosal hemodynamics. These discoveries provide a basis for effective pharmacological therapy in erectile failure. For example, there is convincing evidence that alterations in catecholamine metabolism alter sexual behaviour, thus suggesting that both adrenergic and dopaminergic receptors participate in sex drive. They will be discussed as potentially therapeutic agents.

Pharmacological treatment of erectile dysfunction

A better understanding of the central and peripheral mechanisms of the human penile erection has lead to a proliferation of treatments. Much has been accomplished with the local (penile) treatment. Alteration of central mechanisms by systemic therapy has not been as successful although a few compounds are available with erectogenic activity.

Central pharmocology

Adrenoceptor antagonists

This class of drugs is based on the fact that commonly arterial constriction is adrenergically mediated, therefore, adrenoceptor blockers should promote vasodilatation. As seen below, this effect of adrenoceptor antagonists may only be part of their activity in erectile function since they may also affect central mechanisms. Of the large number of drugs in this group, the most commonly used are phentolamine and yohimbine. Phentolamine is employed alone or in combination with papaverine for intracorporeal administration. Preliminary evidence, based on a small study, indicates that oral phentolamine exhibits erectogenic activity [1]; but we need additional studies of its effectiveness with this route of administration.

On the other hand, yohimbine has received much attention as an oral treatment for impotence. This indole alkaloid is an alpha-2 adrenoceptor

Table I. Drugs used in the treatment of impotence[1]

1. *Neuropharmacotherapy*
   a. Dopaminergic Agonists
      L-dopa
      amphetamine
      deprenyl
      apomorphine
      pergolide
      quinelorane
      methylenedioxy-propyl-noraporphine
      fenfluramine
   b. Adrenoceptor Antagonists
      yohimbine
      phentolamine
   c. Serotonergic Agonists
      trazodone
      methysergide
   d. Opiate Antagonists
      naltrexone
      naloxone
   e. Oxytonergic Agonists
      oxytocin

2. *Hormonal*
   a. Hypogonadism
      testosterone
   b. Hyperprolactenemia
      bromocryptine

3. *Vascular*
   nitric oxide derivatives
   pentoxyfillene
   minoxidil

[1]Proof of their activity is properly documented in a few while in others is still controversial and in some purely anecdotal.

antagonist with profound central and peripheral effects in animals and humans. It has been widely touted as an aphrodisiac for over a century but it has not been properly investigated until recently. Although early reports claimed that yohimbine was effective, recent studies suggest that, under the best circumstances, yohimbine is of limited effectiveness [2]. However, the drug is well tolerated and it can be recommended as the first line of treatment. It is possible that larger amounts, i.e. 30 mg daily in divided doses may be more effective. Recently, it has been reported that an empirical combination of yohimbine and the serotonergic agonist, trazodone, is more effective than yohimbine alone. Early experience with this approach at our center supports this concept but a larger study is needed to determine the synergistic value of these two drugs.

Although the mechanism of action of yohimbine on sexual functioning is

unknown, recent evidence indicates that its effects are primarily central. In rats administration of clonidine into the MPOA achieved complete inhibition of sexual performance–mounting, intromission and ejaculation. Sexual functioning was restored by the administration of yohimbine systemically or directly into the MPOA. These studies suggest that alpha-2 adrenoceptors are important in the control of male sexual behavior and that alterations of adrenergic mechanisms in the MPOA may underlie many kinds of sexual dysfunctions. It is conceivable that this particular portion of the diencephalon integrates a number of neurotransmitter interactions, which are important in the regulation of penile erection.

Dopamine receptor agonists

We know some of the details of the central neurotransmitter systems that contribute to the control of sexual behavior. In addition to norepinephrine, dopamine, which is also widely distributed in brain tissues, is a facilitator of male copulatory performance in animals, while the administration of dopamine-blocking agents inhibits their copulatory behavior. The dopamine agonist, apomorphine, induces bouts of yawning and penile erections both in animals [3] and humans [4], an effect that gave rise to animal models for the investigation of potency. Clinical studies indicate that apomorphine may have a role to play in the treatment of erectile dysfunction in men. Montreal researchers have shown that apomorphine, when administered subcutaneously, induces erections in normal subjects and in impotent men. Trials are in progress to determine the effectiveness of apomorphine and other dopaminergic agonists, i.e. bromocryptine in impotence from various causes. Also sublingual apomorphine may be effective in the treatment of Parkinson's disease, which suggests that this drug may be administered orally for erectile dysfunction. A trial of sublingual apomorphine is in progress at our institution.

Serotonergic receptors

Serotonin-related compounds have a recognized major involvement in the erectile process. Study of serotonergic agents appears to be more complex than adrenergics or dopaminergics because they seem to have central inhibitory effect on sex drive but a peripheral erectogenic effect may act by the enhancement of serotonergic activity. In normal and impotent males treated with trazodone however, an alternative mechanism may be its alpha-adrenoceptor blocking properties and its interference with the sympathetic control of penile detumescence. We need to understand much more about serotonergic receptors and the drugs affecting them in the context of sexual function. At this juncture they seem to play an important role in the erectile process and

their pharmacological manipulation may become significant in the treatment of disturbances in sexual function.

Of other receptors believed to be involved in the human penile response, opiate antagonists, such as naloxone, may enhance sexual performance and induce erections. A more fruitful approach may be the addition of a psychopharmacological agent such as yohimbine and a neuropharmacological agent such as naloxone. Although this concept is attractive, the categorization of drugs as neuro- or psychopharmacological agents is artificial, probably inappropriate and certainly confusing. Regardless of nomenclature, we lack reliable information about any synergistic effect of these various classes of compounds. In any case the use of two agents may be necessary because we must have an adequate hormonal environment for any appropriate response to a neuropharmacological agent.

Peripheral pharmacology

Oral and transcutaneous drugs may have profound effects in the penis, for example nitric oxide (NO) mediates the relaxation of cavernosal smooth muscle as it does in other vascular beds. Organic nitrates and nitrites are well-recognized vasodilators through their relaxant effect on vascular smooth muscle. Among the best known of these compounds is nitroglycerine, which is absorbed readily after topical administration. To investigate this in patients with impotence, we evaluated the effect of 2% nitroglycerin paste in a placebo-controlled, double-blind study. After application of nitroglycerin paste or a placebo ointment base, penile tumescence was recorded while subjects viewed an erotic video. Relative to the placebo, a significantly larger number of patients demonstrated an increase in penile circumference after nitroglycerin. In an additional study, we showed that the topical application of nitroglycerin to the penile shaft is followed by a significant dilatation of the cavernosal arteries and a concomitant increase in blood flow. Although others have confirmed these observations, nitroglycerin and related compounds have not been investigated outside the laboratory. Their effectiveness in the treatment of impotence remains speculative but we would anticipate that their main role would be in those patients with an underlying vascular defect. Nevertheless, new avenues for therapeutic research have opened with the proven role of nitric oxide (NO) or endothelium-derived relaxing factor (EDRF) as a powerful vasodilator with a putative role in cavernosal physiology. Recent work suggests that EDRF and nitric oxide are identical, thus, the 'trickle-down' from mainstream vascular physiology and pharmacology [5] may open new possibilities to manipulate the penile vascular bed with NO-derived, or other simple nitrogen-based compounds. In an Italian study, the topical application of minoxidil (best known for its capacity to reverse alopecia androgenetica) was more effective than nitroglycerine in enhancing penile tumescence in impotent men [6]. Needless to say, an erection requires

more than simple vasodilatation. If a deficiency in arterial response is the main or a significant contributor, the impotence could be treated with a simple local measure thus avoiding the side effects of systemic therapy.

Conclusions

Any effective pharmacological agent requires, at least, some preservation of the erectile mechanisms in the penis. For instance, it would be absurd to anticipate any response from a penis with severely occluded cavernosal arteries. On the other hand, until recently, undue emphasis has been placed on pharmacological events at the target-organ (penis) level leading to a neglect of higher mechanisms. This imbalance is understandable given the relative accessibility of the penis for animal and clinical investigations. However, a more comprehensive and integrated approach is mandatory in the search for successful strategies in male sexual dysfunction.

We have come full circle since the 1960s when multiple ingredients were combined in a single tablet for the treatment of impotence with, reportedly, good results. In three decades our understanding of the mechanisms of sexual functioning has increased considerably and the diagnostic process is also much more sophisticated. However we should consider again a multipronged approach to the treatment of impotence.

We do not yet have a non-invasive pharmacological cure for erectile failure in part because of the enormous complexity of mechanisms involved in an erection, for example, the regulation of substantia-nigra, dopamine-cell firing by adrenergic neurotransmitters or the effect of adrenergic antagonists on the hydroxytryptamine receptor-mediated inhibition in the same area of the brain. Findings such as these suggest a scenario in which all neurotransmitters influence sexual behaviour in a close but interdependent fashion. Certainly, a multiplicity of central and peripheral neurotransmitter systems are involved in the sexual human response; therefore, it is likely that a combination of agents, or a highly specific diagnostic process with a specifically defined therapeutic target, will be needed for successful treatment. We have listed a variety of compounds that have been reported to exert a positive effect in the erectile mechanisms. Combined treatment seems appropriate until we understand the contributions of each of the various central and peripheral systems.

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CHAPTER 48

Non-prosthetic treatment of male sexual dysfunction

IRWIN GOLDSTEIN

Impotence

Introduction

Impotence is the consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse. The degree of erectile dysfunction may range from a partial decrease in penile rigidity to complete erectile failure. This definition is restricted to the erectile capability of the penis and is differentiated from problems of libido, ejaculation or orgasm.

In many individuals, impotence, a common, benign disorder, has a profound impact on well being. Recently, the field of erectile dysfunction has undergone significant change. There is now an improved understanding of the physiological mechanisms of penile erection and how these may be altered to cause impotence. New diagnostic tests enable the recognition of specific causes of erectile dysfunction. Treatments such as intracavernosal self-injection of vasoactive agents, vascular reconstructive surgery and vacuum erection devices have been added to the previous options of hormonal therapy, psychologic counselling and penile implants.

Nomenclature

Potency

The ability to achieve an erection of sufficient rigidity to achieve penetration and of sufficient duration to maintain penetration until ejaculation.

Normal Erections

Normal erections, after appropriate stimulation, achieves intracavernosal pressures approximating the mean systemic arterial blood pressure. The

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cavernosal arterial inflow hemodynamics and veno-occlusive hemodynamics are normal.

Erectile insufficiency

Changes in rigidity or sustaining capability compared to normal that are consistent among morning, masturbation and coital erection for a period of one year.

Erectile failure

Inability to achieve any erection of adequate rigidity or sustaining capability, consistent among morning, masturbation and coital erection for a period of one year.

Impotence treatment

Oral non-hormonal medical therapies

The most widely used oral medication has been yohimbine hydrochloride, an alpha-2 adrenergic blocking agent. Yohimbine has long been considered an aphrodisiac and 25 years ago its positive effect on erectile dysfunction was first described. In a prospective, double-blind, placebo controlled study in patients with predominantly organic disease, yohimbine did not produce a statistically significant greater response over placebo control although 21% of patients did receive a complete response when given yohimbine. A similar study in patients with psychogenic impotence demonstrated that yohimbine provided a statistically significantly greater response (31%) than the placebo (5.3%).

Neuropharmacologic therapy of erectile dysfunction has been based largely on dopaminergic and serotonergic agonists. The positive erectile effects of dopaminergic agonists was first noted in patients treated with L-Dopa. In addition, it has been shown that subcutaneously administered apomorphine, a dopaminergic agonist, enhances erectile response in man and this has been corroborated in laboratory investigations in rats and monkeys. In a recent study a dopaminergic compound that mimics the action of apomorphine and lengthens the duration of clinical response (methylenedioxy-*n*-propylnorapophrine) was found to induce penile erections when given orally to rats.

Trazadone, a drug used for depression, has been associated with priapism. Metachlorophenylpiperazine (MCPP), a serotonergic agonist and metabolite of trazadone, induces erections in rats and monkeys (Szele *et al.*, 1988). A recent case report showed the beneficial qualities of trazadone in the treatment of organic erectile dysfunction. Six potent subjects, when treated with oral trazadone, trimiprimine (a tricyclic antidepressant) and placebo, had a

statistically significant increase in nocturnal erectile activity with trazadone, as compared to the other two agents. *In vitro* studies suggest that blockade of sympathetic-mediated detumescence prolongs erectile activity. This requires further clinical trials in impotent patients.

Nitroglycerin, a smooth muscle relaxant, has been used widely in paste form for transcutaneous delivery in the treatment of angina. It has also been used in a similar manner, for the treatment of impotence. Thirty patients, received one centimeter of nitroglycerin paste or placebo paste on the penis and then were offered visual sexual stimulation. The group receiving nitroglycerin paste developed erections of better quality than those receiving placebo paste. This limited study was performed in a clinical laboratory but further clinical testing appear warranted.

Hormonal therapy

Hormonal therapies for impotence should be reserved for those with hypogonadal disorder or hyperprolactinemia. Patients with hypogonadal disorders (hypogonadotropic hypogonadism or hypergonadotropic hypogonadism) receive testosterone to maintain normal serum levels and thereby restore potency and libido. Because of the relatively unpredictable serum levels with oral administration, intramuscular testosterone enanthate is given in doses of 200–300 mg every two to three weeks. The amount and frequency of administration varies with the individual and can be titrated. One should not treat with testosterone solely on the basis of a single low serum testosterone level. It should be remembered that in patients who do not suffer from hypogonadal disorders, testosterone may induce a marked increased in libido without a positive effect on erectile capabilities. Oral preparations may also damage the liver and may produce abnormalities of serum lipid levels. Lastly, many impotent patients are older men who may have adenocarcinoma of the prostate. In these individuals testosterone may increase the rate of growth of the prostatic adenocarcinoma. Two cases have been reported who developed clinical adenocarcinomas of the prostate after normal prostatic rectal examination prior to testosterone therapy. Thus, before beginning testosterone replacement in men over the age of 50, one should measure serum PSA levels and possibly do transrectal ultrasound studies. Obviously indiscriminate use of testosterone in impotent men should be avoided.

The treatment of hyperprolactinemia is: (1) cessation of medication causing hyperprolactinemia (e.g. estrogens, alpha methyldopa, etc.), (2) administration of bromocryptine, or (3) surgical ablation or extirpation of a pituitary prolactin secreting tumor. Treatment with exogenous testosterone to restore the diminished levels of serum testosterone usually seen with this disorder does not appear to reverse the erectile dysfunction.

Vacuum constrictor devices

Of a variety of external penile appliances, the majority have three common components: a vacuum chamber, a vacuum pump that creates negative pressure within the chamber, and a constrictor or tension band that is applied to the base of the penis after erection is achieved. While standing the patient places his penis within a suitably sized chamber, which is attached to a pump that can create a negative pressure within the chamber. Before pump activation, one ensures a correct airtight fit of the chamber. When the vacuum pump is activated, the negative pressure created within the chamber draws blood into the penis and produces an erection-like state, after five to seven minutes. When he achieves adequate tumescence and rigidity, the patient transfers a constrictor band from the base of the chamber to the base of the penis thereby 'trapping' blood within the penis.

A vacuum-induced erection is significantly different than one physiologically induced. The latter is achieved by the initial relaxation of the corporeal smooth musculature, which allows blood to fill the lacunar spaces. In a vacuum-induced erection, corporal smooth-muscle relaxation does not occur initially and blood is simply trapped in both the intra- and extracorporeal compartments of the penis. Distal to the constricting band at the base of the penis, there is venous stasis and decreased arterial inflow, which may result in penile distension, edema and cyanosis if the device is used for too long. In most cases, manufacturers recommend that the vacuum-induced erection be maintained for less than 30 minutes. Secondly, physiologically induced erection will cause rigidity along the entire length of the corpora in contradistinction to a vacuum-induced erection which causes rigidity only distal to the constricting band; the penis is allowed to pivot at its base.

In monkeys, the increase in cross-sectional corporal area secondary to vacuum-induced erections was only 50% of that induced by intracavernosal papaverine. This difference may be secondary to the continued smooth muscle contraction of the corpora limiting corporal expansion. In humans, vacuum constrictive devices may induce a penile diameter equal to or greater than that attained during a physiologically induced erection, presumably secondary to blood trapped in extra-corporeal tissues. In addition cavernosography before and after application of a vacuum constrictor device demonstrated the disappearance of previously opacified glans penis, corpus spongiosum and dorsal vein. Venous drainage from the corpora proximal to the constrictor device was not altered.

Theoretically vacuum-constrictor devices (VCD) should create penile regidity sufficient for vaginal penetration in almost all impotent men. However, patients with significant intracorporeal scarring such as those with severe Peyronie's disease, post priapism or previously infected penile implants may not be able to develop adequate rigidity. Men who have a penile prosthesis removed still may be treated with a vacuum-constrictor device. Theoretically, these devices may induce a more physiologic erection when used in conjunc-

tion with intracavernosal vasoactive agents capable of relaxing corporal smooth musculature. Patients, who do not obtain sufficient penile rigidity from intracavernosal pharmacotherapy alone, could be candidates for a VCD while continuing self-injection.

To date the complications from these devices, which have been minor and self-limited, include difficulty with ejaculation, penile pain, ecchymoses, hematomas and petechiae. Patients taking aspirin or coumadin are more likely to develop vascular complications. Many of these devices have a valve, which limits the vacuum pressure (less than 250 mm Hg), and this may decrease the complication rate.

Patient acceptance of and satisfaction with VCD devices has been reported to be 68–83%. The reasons given for discontinuing this treatment include premature loss of penile tumescence and rigidity, penile pain, pain during ejaculation, and inconvenience.

Vacuum-constrictive devices are a viable option for patients with erectile dysfunction because they have no significant complications and have a high degree of acceptance.

Self-injection therapy

One of the most important advances in the treatment of impotence over the past decade has been self-administered intracavernosal injection of vasoactive agents. Erection is initiated *via* a neurotransmitter-induced relaxation of the corporal smooth musculature. Vasoactive agents administered by intracavernosal injection directly relax the corporal smooth musculature or block adrenergic tone.

The pioneering work in this area involved the use of papaverine hydrochloride, a direct smooth-muscle relaxant, or phenoxybenzamine or phentolamine mesylate, both alpha blocking agents. As the use of these agents became more clinically widespread, several issues became apparent. Intracavernosal injection of phentolamine alone was not as effective as papaverine. In addition, papaverine alone was not as effective as the combination of papaverine and phentolamine injected together. Recently, the synthetic prostanoid, prostaglandin E_1, a direct smooth-muscle relaxant, has restored potency when injected intracavernosally. A variety of solutions containing these agents now are being used in clinical practice: papaverine alone, papaverine and phentolamine, prostaglandin E_1 alone, phentolamine and prostaglandin E_1 or a mixture of all three. Papaverine hydrochloride and prostaglandin E_1 act by direct smooth-muscle relaxation. Therefore, when injected intracavernosally, they will maximize arterial inflow and corporal venoocclusion by relaxation of both arterial and trabecular smooth musculature respectively. Phentolamine, on the other hand, blocks adrenergically induced muscle tone and given alone does not initiate erections.

Intracavernosal injections work best in men with a normal arterial inflow

and a normal corporal veno-occlusion mechanism, and in those with purely neurogenic impotence or with psychogenic impotence. Men with arterial insufficiency may also respond by virtue of the long-acting, smooth-muscle relaxation these injections provide. Men with significant corporal venoocclusive dysfunction will be the least likely to respond. In general we offer intracavernosal pharmacotherapy to most of our patients with organic dysfunction. Those with poor manual dexterity, poor visual acuity, morbid obesity or those in whom a transient hypotensive episode may have a deleterious effect (e.g. unstable cardiovascular disease and transient ischemic attacks) should be carefully assessed before they are offered this option. We have treated successfully some men who concomitantly are taking aspirin or coumadin. Men who have significant psychiatric disease or potential for misuse or abuse of this therapy should be excluded from treatment. Once offered intracavernosal pharmacotherapy, the patient should be informed of its risks and complications (see below). Also he should be told that this therapy will not improve orgasm or ejaculation and is given solely to restore erectile capabilities. The goal is to create a rigid enough erection to permit vaginal penetration lasting between 30 minutes and one hour.

Before entering a pharmacologic erection program, men should first read and sign a detailed informed consent that sets out the known complications of this treatment and discusses the long-term side effects. The initial dosage determination phase identifies the lowest dose that will achieve an appropriate erectile response. Initially patients are injected with low doses that are increased incrementally. In patients with purely neurogenic impotence one starts with an extremely low dose because they are most likely to respond. Usually patients with vascular disease will begin the dosage determination phase with a higher dose and subsequently need higher increments in dose. Use of an insulin syringe with a 27–30 gauge needle minimizes pain and bleeding. These patients are taught to compress the site of injection for three minutes after injection.

After the appropriate dose is determined the patient is instructed in proper injection techniques and followed by nurse- or physician-monitored self-injection-program. Commonly, when the patient gets home to a more sexually stimulating environment, the dosage determined in the office can be decreased. Patients are told not to inject more frequently than once per day.

Reports have been published of approximately 4000 men treated worldwide with papaverine alone or in combination with phentolamine. Side effects include hematomas, burning pain after injection, urethral damage, cavernositis or local infections, fibrotic changes of the corpora cavernosa, curvature, and prolonged erections or priapism. Cavernositis or infection due to injections has been extremely rare. Burning pain at the time of injection is most common with prostaglandin E_1 and this complaint is less prominent when prostaglandin E_1 is mixed with other agents. Hematomas were noted in a small percentage of patients undergoing autoinjection therapy and usually resolved within a few days without any permanent sequelae.

The most important complications are prolonged erections and localized fibrotic changes in the corpora cavernosum. Prolonged erections, usually seen during the dosage determination phase, have been reported in 2.3–15% of those treated. These men must be cautioned to call their physician if an erection persists for four hours or longer. Most of these prolonged erections will detumesce on their own, however, some will require an intracavernosal injection of an alpha-agonist such as epinephrine, phenylephrine, and metaraminol. We use an initial intracavernosal injection of 200 μg of phenylephrine, which may be repeated as necessary until detumescence. If treated by this protocol, one should not see any permanent sequelae from this side effect.

The most distressing side effect of intracavernosal pharmacologic therapy, formation of painless fibrotic nodules within the corpora cavernosa that may lead to penile curvature, has been reported in 1.5–60% of men treated for one year. In one series, the development of fibrotic nodules was related to the frequency of injection and the duration of treatment. Fibrosis does not seem to be related to the pH of the injected solution. Corporal fibrosis and prolonged erections are less common when one injects prostaglandin E_1 alone. We believe that cavernosal fibrotic nodules are secondary to trauma and bleeding within the corpus, hence we stress compression over the injection site for three minutes and when possible, attempt to decrease the volume of fluid injected. We like most patients to inject less than 0.5 ml and in those injecting 1 ml or more of the papaverine and phentolamine mixture, we can decrease this volume by the addition of prostaglandin E_1. Almost invariably diffuse fibrosis of the corpora following intracorporal injections is associated with markedly prolonged erections. A case of diffuse fibrosis following a test does of intracavernosal papaverine leading to a prolonged erection of longer than 36 hours has been reported in which the patient was still able to be successfully treated intracavernosally with a combination of papaverine and phentolamine. We do not know how much corporal scarring and fibrosis is needed to block the positive results of intracavernosal pharmacotherapy.

We have had good results in a small group of psychogenically impotent patients treated with intracavernosal injections in conjunction with sex therapy. These men must understand the undesired side effects of injection especially fibrotic nodules within the corpora.

Systemic side effects of intracavernosal injections include vasovagal episodes and syncope, probably related to hypotension. These side effects are infrequent and are seen usually during the dosage determination phase. Men with significant corporal veno-occlusive dysfunction will exhibit an increased systemic absorption of intracavernosal agents and therefore be more susceptible to this side effect. Intracavernosal pharmacotherapy with papaverine has been associated with hepatotoxicity. During a mean follow up of 26 months, we found three men (1.5%) with abnormal liver function tests in the first 201 patients that we treated. Others have seen no changes in liver function while one series reported that 40% of men had at least one chemical liver-function abnormality after this therapy.

Clearly cavernosal injection of vasoactive agents is one of the urologist's most effective means of treating the man with erectile dysfunction. In our institution initially we use a mixture of papaverine, phentolamine and prostaglandin E_1 in most of these men. Two possible alterations in drug delivery deserve investigation. Firstly, a prosthetic implant consisting of a subcutaneous pump/reservoir mechanism connected to a tube going directly into the corpora cavernosa that could deliver a predetermined dose without repetitive injections. Secondly, delivery of drugs into the corpora without injection by transcutaneous means or by iontophoresis. However, one might envision an iontophoretic system which can deliver drugs transcutaneously into the corporal tissue.

Priapism

Evaluation and management

Priapism, a prolonged penile erection not associated with sexual stimulation, requires urgent evaluation because it may develop into a closed compartment syndrome with compression of the cavernosal arteries and resultant corporal ischemia. Fibrosis of the corpora cavernosa secondary to ischemic necrosis may lead to permanent impotence.

There are two forms. Veno-occlusive priapism, the most common form, results from persistent obstruction of lacunar-space, venous outflow. This form is accompanied by corporal pain and tenderness. The lack of outflow, once the corporal bodies have been fully expanded, impedes blood inflow, which leads to ischemia and pain. Obstruction of lacunar space outflow may be secondary to the extravascular compression of subtunical venules by persistent corporal smooth muscle relaxation. This can occur following the administration of intracavernosal vasoactive agents, oral psychotropic agents such as trazodone, or due to persistent neurogenic stimulation, e.g. cerebral aneurysm, herniated lumbar disc. More rarely, obstruction of lacunar space outflow is secondary to intravascular obstruction of the draining veins, due to hematologic disorders (e.g. sickle-cell hemoglobinopathies, leukemia, multiple myeloma, primary thrombocythemia), intravascular fat emboli (e.g. hyperalimentation with 20% Intralipid), and metastatic neoplasms to the penis. Most cases, particularly those not treated promptly, will progress from extravascular obstruction of venous drainage to an intravascular component due to the pooling and clotting of blood in the corpora. In many cases of veno-occlusive priapism, the cause is unknown and hence these are classified as 'idiopathic' priapism. Recurrent post-ischemic priapism, a recently described form of recurrent veno-occlusive priapism, results from ischemia to the neurologic and/or endothelial mediated mechanisms which regulate flaccidity and detumescence.

The second form of priapism is rare. This develops after trauma to the

perineum or the penis. This form of priapism may be called arterial priapism and is a high-flow, non-ischemic event. Painless, pulsatile corpora are characteristic of arterial priapism. Following the injury, a lacerated cavernosal artery 'bleeds' directly into the lacunar spaces, bypassing the high resistance to flow offered by the helicine arteries. This form is not associated with a closed corporal compartment syndrome because lacunar space venous outflow persists.

Management

Initially all cases of priapism should be considered as a potential arterial vascular emergency. The first step in veno-occlusive priapism is to establish the status of flow in the cavernosal artery either by Doppler ultrasound or by blood-gas analysis of the corporal aspirate. Blood-gas determinations demonstrating hypoxemia and acidosis are pathognomonic of veno-occlusive priapism. In the absence of cavernosal artery inflow, there is a medical emergency due to an acute arterial vascular insufficiency. In such cases, fibrosis of the corpora cavernosa secondary to ischemic necrosis may lead to permanent impotence. Initial management is aimed at re-establishing arterial inflow, either by corporal aspiration and/or corporal irrigation with heparinized saline. If these fail, one should attempt corporal administration of adrenergic agonists based upon the recent appreciation that contraction of corporal smooth muscle results in detumescence of the erect penis. If such non-surgical maneuvers fail and cavernosal artery inflow remains poor, one should perform surgical shunting precedure, such as shunting the corpora to the glans or corpus spongiosum.

In priapism with a history of trauma, documented cavernosal artery flow and bright red corporal aspirates, one should suspect arterial priapism. If the pariapism persists despite intracavernosal injection of adrenergic agonist, one should do a selective internal pudendal arteriogram to visualize the site of arterial trauma. Treatment consists of embolization of the affected artery with sterile autologous clot.

CHAPTER 49

Prosthetic treatment of male sexual dysfunction

DROGO K. MONTAGUE

Patient selection

The ideal candidate for a penile prosthesis is the man with organic impotence that is either not treatable by other means or the man rejects other forms of treatment. Penile prostheses should not be implanted in men with situational, reversible, or temporary forms of erectile dysfunction. Men with psychogenic erectile dysfunction should only be considered for penile prosthesis implantation if they have failed sex therapy and are recommended for a prosthesis by their therapist, or if the therapist believes that sex therapy is not feasible for this individual or couple.

Patient and partner education

Operation and anesthesia

While some penile implantations have been done under local anesthesia, I prefer to use general, spinal or epidural anesthesia. The need for an anesthetic and the type of anesthetic should be discussed with the patient. The operation is described in general. I discuss the incision (penoscrotal) and tell the patient that, in most cases, prosthesis implantation does not require any tissue removal. Usually blood loss is minimal and to date we have never given a blood transfusion.

Postoperative course

The length of hospital stay usually is 1 or 2 nights. Patients are made aware that postoperative pain is significant and on the average, lasts 4 to 6 weeks although this is quite variable. Patients should restrict strenuous physical activity for at least 4 weeks and usually coitus is not advisable for at least 4 weeks.

D.G. Oreopoulos, M.F. Michelis and S. Herschorn (eds), Nephrology and Urology in the Aged Patient, 439–447.

Table I. Non-hydraulic penile prostheses

Prosthesis type	Prosthesis name
Semirigid rod	Small-Carrion
Malleable	AMS Malleable 600 Jonas Silicon-Silver Mentor Malleable
Positionable	DuraPhase
Mechanically activated	OmniPhase

Short-term complications

The short-term complications are chiefly infection and erosion and the patient is told that usually infection or erosion require device removal. I discuss the less common, short-term complications such as suboptimal sizing or device positioning as well as device malfunction immediately after the procedure.

Penile-prosthesis expectations

The patient is made aware that ordinarily implantation of a penile prosthesis does not affect libido, orgasm, ejaculation or genital sensation. He must understand that the erection produced by a prosthesis always differs from a normal erection and that as well the flaccid penis will have a different appearance to some degree. Of course, this departure from normal is variable, and depends both on the type of prosthesis and on differences in individual anatomy.

Long-term complications

Infection and erosion are discussed as possible long-term complications; I emphasize that these complications may lead to prosthesis removal. Concerning mechanical complications, the patient needs to know that any type of penile prosthesis can fail mechanically and that usually the correction of device failure requires reoperation.

Types of prostheses

The variety of penile prostheses currently available may be divided into two general categories: non-hydraulic (Table I) and hydraulic (Table II). I believe that potential prosthesis recipients should be offered a choice of devices.

Table II. Hydraulic penile prostheses

Prosthesis type	Prosthesis name
One piece	AMS Dynaflex
Two piece	Mentor GFS
Three piece	AMS 700CX AMS Ultrex Mentor Inflatable

Device selection

Patient wishes

The patient and whenever possible the partner are given explanations on the points mentioned above. The prostheses offered by the implanting surgeon should also be discussed and contrasted. I believe that there is no single prosthesis that is best for every patient and that the patient's own wishes should also count in the decision.

If the patient wants a simple device, which has the lowest possibility of subsequent mechanical failure, and is willing to accept the limitations inherent in a non-hydraulic prosthesis, I implant a malleable or a positionable prosthesis. If, on the other hand, the patient wants the most natural flaccidity or the most natural erection possible with today's devices, he should choose a three-piece inflatable. Other devices, such as one and two-piece inflatables, are a compromise between non-hydraulic and three-piece inflatable devices.

Patient capabilities

When considering hydraulic penile prostheses, one should consider factors such as patient motivation, intelligence, manual dexterity, and strength in order to avoid implantation of a device that the patient will be unable to cycle.

Cost

Sometimes cost is an important factor in decision making; and this, of course, depends on the patient's insurance coverage or on his own financial resources. In general, the cost of a prosthesis is proportional to its design complexity, and usually the surgical implantation fee depends on device complexity as well.

Anatomic considerations

Abnormalities of the corporeal tunica albuginea, such as fibrotic plaques or weakened areas, may complicate prosthesis implantation; fibrosis of the intracorporeal tissue also may create difficulties. Usually, almost any type of prosthesis can be implanted using techniques such as plaque incision or excision and corporal augmentation procedures made possible by Dacron or Gortex patching. However, under these circumstances, non-hydraulic prostheses frequently can be implanted with little or no extracorporal surgery. This lessens the potential morbidity of the procedure.

Abnormalities of the scrotum may influence the surgeon's decisions with prostheses that have scrotal components. Likewise, lower abdominal abnormalities may influence decisions about devices that have abdominal reservoirs.

Special considerations

Spinal-cord injury patients are at a high risk for infection and erosion. In these patients erosion occurs in part because of infection; however, lack of sensation and relative thinness of the tunica albuginea also contribute to erosion. Hydraulic prostheses in spinal cord injury patients clearly offer a reduced risk of erosion.

Often hydraulic prostheses are considered advantageous in patients, such as those with a history of bladder tumor, who require periodic lower tract endoscopic procedures.

The ideal penile prosthesis

The ideal prosthesis when palpated should make the penis feel normal. Hydraulic or fluid-filled devices do this; rod prostheses do not. Hydraulic prostheses have a further advantage in that the incidence of erosion is lower. Another characteristic of the ideal prosthesis is relative freedom from mechanical failure. Finally, and perhaps most importantly, the ideal prosthesis should produce a penis that when both flaccid and erect comes as close as possible to the natural flaccidity and erection. To do this the volume of fluid that must be transferred into and out of the cylinders is large enough to require an abdominal fluid reservoir.

The AMS Ultrex prosthesis

The AMS Ultrex Penile Prosthesis comes closest to meeting these criteria. The principal difference between the AMS Ultrex and its predecessor, the

AMS 700CX prosthesis, is the cylinders; the pump, tubing, and connectors are the same for both. The reservoir design is the same; a 65 ml reservoir for the AMS 700CX and a choice of the 65 or a 100 ml reservoir for the AMS Ultrex prosthesis.

The *CX cylinder* is triple-ply, with the inner and outer layers made of silicone; the middle layer, woven fabric, controls cylinder girth expansion. The CX cylinder has a resting diameter of 12 mm and an 18 mm diameter when inflated. Length expansion does not occur with the CX cylinders. To date no aneurysms have been reported with the CX cylinder, and the incidence of leaks is quite low. The CX cylinder comes in lengths of 12, 15, 18, and 21 cm. Length adjustment between sizes is made by adding of 1, 2, or 3 cm rear-tip extenders (RTEs).

The *Ultrex cylinder* is similar to the CX except that the middle layer controls both girth and length expansion. Like the CX cylinder, the Ultrex has a resting diameter of 12 mm and an inflated diameter of 18 mm, and it comes in the same lengths. The CX cylinder is capable of 20% length expansion; thus an 18 cm cylinder expansion to 21.6 cm. It is important to note that, as the CX cylinder is inflated, the girth expands first and then the length. The amount of length expansion in each patient depends on the elasticity of each recipient's tissues.

The implant procedure

Position and incision

The patient is placed in the supine position; we use the surgical isolation bubble system (SIBS). A high, transverse 3 cm upper scrotal incision is made, and Dartos and Buck's fasciae also are opened transversely. Exposure of the urethra and both corpora cavernosa is maintained with the Scott ring retractor.

Corporeal preparation

Longitudinal corporotomies (2 cm) are made on each side. Dilatation is started with an 8 mm Hegar dilator and proceeding to 14 mm distally and to 16 mm proximally. If difficulty is encountered in dilating, long Metzenbaum scissors are carefully inserted and spread as they are withdrawn. With a sizing instrument, we determine the total corporal length from each end of the corporotomy. The corporotomy is not included in the measurement because the sizing is done on the surface of the corpora and the actual internal corporeal length is shorter. To select the proper length for the Ultrex cylinder, we subtract 1 cm from the total external corporal measurement. This selects a cylinder that is somewhat shorter than the corpus cavernosum,

which fits well inside the corpus, and produces no bulging or buckling, which might promote cylinder wear. Since the Ultrex cylinder can lengthen, there will be no SST deformity.

Prosthesis preparation

Cylinders of the correct length are filled with normal saline (because silicone is semipermeable, isotonic fluid must be used). The cylinders are filled but not distended. The pump is filled by cycling it while the tubes are held under the surface of normal saline. The reservoir is filled with normal saline to displace the air, and then the saline is withdrawn since the reservoir will be implanted empty.

Cylinder implantation

The cylinders are implanted distally with the aid of the Furlow cylinder inserter. If we need any rear-tip extenders, they are now applied. For the cylinder tubing, the stab incision is located approximately one-half of the distance between the corporotomy and the bony attachment of the crus. This tubing is brought from the inside to the outside of the corpus cavernosum through this incision, and the proximal portion of the cylinder is inserted manually into the crus. Cylinder fit is checked and the corporotomies are closed with running horizontal mattress sutures of 2–0 PDS.

Pump implantation

A small incision is made through Dartos fascia in the septum of the scrotum. We introduce a long clamp through this incision and spread it to create a Dartos pouch for the pump. The pump is placed in this pouch so that the single tube going to the reservoir is located anteriorly. A right-angled clamp is used to bring the pump tubing, which goes to each cylinder, out through the fascia that forms the back wall of the pouch. Likewise the pump tubing which goes to the reservoir, is brought through the back wall of the pouch.

Pump-cylinder connections

The protective covering on the outside of the cylinder tubing is removed. Then the pump and cylinder tubing are irrigated with antibiotic solution to wash off any blood and with clean scissors, the tubing is cut to appropriate lengths making clean, right-angled cuts. Each cylinder is connected to one of the cylinder tubes from the pump using straight connectors from the Quick

Connect System. Care is taken to ensure that each tubing end is inserted completely into the connector up to the central stop. After the connector rings are seated with the closure tool, the completed connection is inspected to ascertain that both rings have been evenly and completely forced into each end of the connector. The Quick Connectors should be used only for initial implants or for revision when a connection is being made between two new components. If during a revision one makes a connection to a component that was implanted previously, the tie-on plastic connectors must be used. The Quick Connectors are not secure when they are used to connect tubing that has a lipid coating.

Reservoir implantation

An 18-F Foley catheter is inserted and the bladder is completely emptied. The surgeon introduces his index finger through the incision and then places it in the external inguinal ring. Then he uses long Metzenbaum scissors to perforate the transversalis fascia in the floor of the ring. The scissors are placed medial to the finger and thus protect the cord structures, which are lateral to the finger. The scissors are spread and then withdrawn, as the surgeon introduces his finger into the retropubic space, from which he should be able to feel the back of the symphysis pubis and the empty bladder. With the inguinal reservoir introducer, he then places the empty reservoir into the retropubic space. The reservoir is filled with either 65 ml or 100 ml of normal saline. Saline is allowed to return to the glass syringe until the pressure in the reservoir is zero. Generally I leave 50 to 55 ml in a 65 ml reservoir and 85 to 90 ml in a 100 ml reservoir. A connection between the pump and the reservoir is made with a straight Quick Connector.

Hydraulic dilatation and intraoperative testing

The prosthesis is fully inflated and deflated three times to stretch the corpora and to see that the prosthesis is functioning correctly. Running 3-0 Dexon is used to close the Dartos fascia over the pump. A second 3-0 Dexon suture is used to close transversely the dartos fascia under the incision. The skin is closed with a running subcuticular 4-0 Vicryl suture. The prosthesis is left fully deflated; to avoid chordee, the penis is kept up on the lower abdomen for the first four postoperative weeks.

Preventing autoinflation

To date we have not been able to incorporate a mechanism in the prosthesis to prevent autoinflation. Therefore, if the reservoir pressure is sufficiently

high, fluid will flow through the pump and into the cylinders until cylinder pressure equals reservoir pressure. This results in partial erection and a phenomenon known as autoinflation.

The 65 ml and 100 ml reservoirs are designed to hold these volumes of fluid under zero pressure. However, this determination is made when the reservoirs are filled outside the body. In the body, as the reservoir expands with fluid, it pushes against body tissue and the zero pressure state is reached sooner.

Two things must be done to avoid or minimize autoinflation. After the empty reservoir is implanted, it should be filled with 65 or 100 ml of normal saline, after which fluid is allowed to escape from the reservoir tubing until the pressure is zero. The second measure is to be sure that the cylinders are left deflated while healing takes place. Usually we do not inflate the device for at least 4 and sometimes 8 weeks after the operation. The body reacts to silicone by forming a fibrous pseudocapsule around it. The energy generated by pumping will stretch the capsule that forms around the cylinders. On the other hand, deflation of the prosthesis takes place passively and, if the cylinders are left inflated while healing is taking place, the capsule that forms around the partially empty reservoir will prevent deflation at zero reservoir pressures.

Postoperative care

The Foley catheter is removed on the first postoperative day, and the patient is discharged on the second. He is allowed to shower on the third. One month after surgery an attempt is made to inflate and deflate the prosthesis. If tenderness around the pump is still present, instruction on device inflation and deflation is delayed until 2 months after surgery. It is important to keep the cylinders fully deflated while healing is taking place, and the penis should be kept up on the lower abdomen. Once the patient learns how to cycle the prosthesis, he is instructed to inflate and deflate it fully twice daily for 4 weeks. Coitus can be attempted whenever the patient is pain free. The patient and his partner are instructed to use a water-soluble lubricant and plenty of foreplay before vaginal intromission.

Results

We have implanted the AMS 700CX prosthesis in 116 men. Follow-up is from 3 months to 68 months (mean 41 months). Four surgical complications resulted in device removal. One patient developed a periprosthetic infection and the prosthesis was removed at 7 months. Two patients, who had a previous penile prosthesis, developed urethral cylinder erosion and one patient had reservoir erosion into the bladder; these patients had their devices

Table III. Pubis to midglans increase

cm Increase	No. of patients
1	14
2	29
3	5
4	2

removed. There were two mechanical failures, a tubing leak and a cylinder leak. The tubing leaked at 7 weeks, and undoubtedly this complication was due to tubing damage during closure. The only cylinder leak occurred at 4 years and 2 months. This experience compares favorably with other reports concerning this prosthesis [1, 2].

We have implanted the AMS Ultrex prosthesis in 78 men. Follow-up is from 2 to 26 months (mean 10 months). One device was removed at 3 weeks because of infection, and there was one mechanical failure, a reservoir leak. At the conclusion of each implant procedure, the pubis-to-midglans distance was measured with the cylinders deflated and then fully inflated. Table III shows the increase in the pubis to midglans distance from the flaccid to the erect state in the first 50 patients.

As Table III shows, there is a variable increase in penile length from one patient to another, which is due primarily to differences in tissue elasticity. This intraoperative increase in penile length was measured again postoperatively at last follow-up in 46 of the 50 patients. There was no change in 28 men; in 6 there was 1 cm less increase and in 12 there was 1 cm greater increase.

Experience with the Ultrex prosthesis is still somewhat limited. However, some observations and projections can be made. Because of similarity in design, the mechanical reliability of this device probably will be similar to that of the AMS 700CX prosthesis. Because the Ultrex cylinders can lengthen, corporeal measurement and cylinder selection are no longer as critical as they once were. Indeed, implanters are being advised to implant a cylinder that is about 1 cm less that the total corporeal length. Also the patient can be told that his penis may lengthen with erection; at present the Ultrex device is the only prosthesis that offers this advantage.

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PART THIRTEEN

Prostatic diseases

CHAPTER 50

Prostate cancer: defining the challenges

E. DAVID CRAWFORD

When the American Cancer Society released its statistics on new cases in 1989, prostate cancer became the most common cancer in men. It is projected that in 1992 132,000 new cases of prostate cancer will be diagnosed in the United States and nearly 34,000 deaths will be attributable to the disease. During the past 12 years, there has been a 50% increase in the number of new cases diagnosed and a 40% rise in the death rate from this neoplasm.

A number of significant challenges relative to prostate cancer need to be addressed. Because of the rising incidence, with concomitant increase in mortality, strategies need to be developed to deal with this epidemic.

If one considers that at the present time approximately 35 million Americans are over the age of 65 and that in the next 20 years that number will double, the challenge becomes magnified. Prostatic carcinoma is associated with aging and with the 'graying' of the population and the number of new cases and deaths will continue to escalate.

To respond to statistics, we can consider several interventions:

1. Preventing development of the disease.
2. Implementation of widespread screening – hopefully leading to earlier diagnosis and cure.
3. Development of a treatment to arrest the disease once it has reached a metastatic phenotype.

Regarding prevention, a number of proposed clinical trials are in the design phase which are aimed at chemohormonal prevention. These agents presumably would prevent either development and/or progression. Initially, clinical trials should target high-risk populations including those with a family pedigree of the disease, ethnic groups at high risk (blacks), and men found to have premalignant lesions. If effective and tolerable interventions are defined, we could undertake a large-scale trial in populations at intermediate risk.

Another area in need of focused clinical research is the optimal management for localized cancer. We are challenged to identify those men with an overt localized lesion, who would benefit from curative therapy with either

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radiation or radical prostatectomy, and those who would be better served by observation or hormonal therapy.

Since most patients now diagnosed present with locally advanced or metastatic disease, hormonal manipulation is the cornerstone of therapy. We need to define the value of early hormonal therapy in the asymptomatic patient with locally advanced (stages C, D_0 and D_1) and advanced (D_2) disease.

A final challenge is prostatic cancer research support. In 1991, only $9 million was allocated by the National Institute of Health for prostate *disease* research. This number is projected to increase to $26 million in 1992 but this financial allocation does not adequately support progress in understanding and treating this disease.

This paper will highlight three important areas in prostate cancer: screening, surgical management of the localized lesion and hormone therapy for advanced disease. In all three, there is controversy and we lack definitive answers.

Screening

The recent interest in early diagnosis of prostatic carcinoma through screening efforts is based on the rising incidence, development of more effective, less morbid treatment for the local lesion and public attention to the disease. In 1989 we surveyed 1072 men, asking them a number of question. Only 1/3 of men over the age of 40 in the survey had had a recommended physical exam within the last year. Appallingly, of those that did, only one-half had had a digital rectal exam (DRE) as part of this annual physical examination. These men were asked about topics discussed with their physicians and prostate cancer ranked number 10, after such disease processes as hypertension, high cholesterol, colon polyps and diabetes. We determined that public awareness of prostate cancer was low and coined the term 'the ignored male disease.'

The Prostate Cancer Education Council consists of physicians and healthcare workers around the United States. The goals of the council were to:

1. Educate the public about prostate cancer,
2. Encourage screening, and
3. Investigate new modalities for earlier diagnosis.

The third week of September 1989 was designated Prostate Cancer Awareness Week. Initially, 15 sites around the United States were targeted to participate in this screening event. The response was overwhelming and 91 sites screened 15,000 men. Unfortunately, only 10,000 case report forms were printed and returned. The screening produced a number of demographic facts. The mean age of men who filled out a questionnaire and had a DRE was 62.4 years. Fewer than 20% of men stated that they had a digital rectal exam within the last year. Approximately 75% of those participating in the screening were Caucasian and 9% African-American. During the 1989

screening, prostatic specific antigen (PSA) pilot studies were done in 3000 men at several institutions. 16.9% of men who had a digital rectal exam were found to be abnormal. 12% had an abnormal PSA by the Hybritech method. Prostate biopsies and follow-up were only reported from 20 institutions (300 men). Therefore the results may not reflect the total number of men screened. However, it was interesting that the combination of PSA and digital rectal examination yielded a higher positive biopsy rate, 62%, than either digital rectal examination or PSA alone. Also, in men who had an abnormal digital rectal exam and normal PSA, the positive biopsy rate was only 8%. We concluded from Prostate Cancer Awareness Week 1989 that the public was receptive to the educational efforts and that physicians were willing to participate in the screening. Also, important information was generated regarding PSA and DRE.

Predicted on the results from 1989, we were encouraged to perform PSAs in the 1990 screening. Over 150,000 men at 900 sites received information, filled out the questionnaire and had screening for prostate cancer. 40,000 PSAs were done in tandem with digital rectal examination. The demographic data were similar to that from the previous year, but it became apparent that we were attracting fewer minority groups and also tended to attract those with a higher educational level. The abnormal digital rectal exam rate decreased to 12.9% and abnormal PSAs were 18%. The increase in abnormal PSA values may reflect the utilization of several different assays in the 1990 screening, leading to a higher false positive rate (sensitivity increased but specificity decreased). We confirmed the findings of the previous year relative to positive biopsies, namely that the combination of digital rectal exam and PSA was superior to any one method alone. During this year, we received follow-up biopsy reports on over 5000 patients.

As a part of Prostate Cancer Awareness Week, several ancillary studies were performed with PSA. It had been thought that a digital rectal examination would produce a spurious elevation of the PSA, if it was measured immediately afterward. To address this issue, approximately, 2,700 men participating in Prostate Cancer Awareness Week 1990 underwent PSA blood levels before and immediately after DRE. No rise was noted using the Hybritech assay. The only exception was in patients with a baseline PSA level above 20, a group who would undergo further evaluation independent of the projected rise, because their baseline was above 4 ng/ml. Because of the alleged higher sensitivity of the Yang assay, we sampled frozen serum from the previously described cohort. No significant rise in PSA was noted after a screening digital rectal examination.

Prostate Cancer Awareness Week 1991 continued to embrace the same goals. In this national event over 400,000 men were screened at approximately 900 centers. At present time data analysis is incomplete but the preliminary review confirms the data from previous years. Over the past three years approximately 1500 patients have undergone accurate staging procedures. Interestingly, just 5% who participated were metastatic (stage

D_2) and most cancers were localized within the gland. This finding contradicts many earlier studies in which screening events tended to pick up more advanced cases.

Our target population for 1992 is 500,000 men. With the demographic data, we hope to generate a patient profile that more precisely defines risk factors and reduces the false-positive biopsy rate.

While this and other screening events have been successful, they do not address the value of screening. Controversy exists relative to its screening value based on a number of facts. Those who argue against screening assert that such testing may discover insignificant cancers. Autopsy studies have revealed that nearly 30% of men over the age of 50 will have microscopic cancer yet few of these develop clinically overt cancer. Analysis of our current techniques suggest that none of these tests (DRE, PSA, and transrectal ultrasound) predictably detect these microscopic cancers. In fact, most cancers detected by an abnormal digital rectal exam turn out to be pathologic stage C after a radical prostatectomy. In an autopsy series where PSA was compared to volume of prostatic cancers, no patient with a PSA above 4 had an insignificant cancer. In our experience 70% of cancers detected by transrectal ultrasound alone turned out to be pathologic stage C on final examination of the extirpated gland.

Those who do not support the concept of screening assert that patients participating in these events often are older and will die with, rather than of, prostate cancer. The Prostate Cancer Awareness Week reveals that the mean age was 62.4 and that few men were over the age of 75. A counter proposal says that screening should be used selectively in men, who are at high risk of developing the disease between the ages of 50–70. An additional caveat is that screening should be done only in men with a 10-year life expectancy.

No large clinical study has been done to prove the benefit of screening, nor one that refutes its value. Therefore, the practicing physician must base his judgement on existing facts. I believe that, until a large randomized trial is completed, screening should be used selectively in men who have at least a 10-year life expectancy and are between the ages of 50 and 70. Men with risk factors such as family history and black race should be considered for earlier screening. The results of Prostate Cancer Awareness Week definitively establish the value of the combination of digital rectal exam and PSA, over either one alone.

Management of localized prostate cancer

Radical prostatectomy remains the mainstay of treatment for localized lesions. In several large series, men with cancer confined to the prostate and treated by a radical prostatectomy have a survival that matches the normal expected survival for their age group. Recent advances in the surgical tech-

nique have reduced the morbidity and mortality while improving the quality of life. Routinely sexual potency is maintained in 70% of men who are potent before the procedure. Total urinary incontinence is a rare event. In our series of over 500 radical prostatectomies, the total incontinence rate is less than 1%. 5–8% of people will experience stress urinary incontinence. The mortality rate in our series is one patient in 500.

We should employ radical prostatectomy in men who have at least a ten-year life expectancy because subtle differences in survival rate between radical prostatectomy and radiation take at least 10 years to materialize. Also, recent evidence suggests that well-differentiated small nodules of the prostate can be followed without any treatment for 10 years and most of these patients are expected to survive.

Controversy rages over the optimal treatment because there are no accepted large randomized trials. Also the natural history of these localized lesions is slow progression and, in older age groups, there are other competing causes for death. In addition, with the evolution in existing technology, refinements in radical prostatectomy have decreased the morbidity and mortality and new methods of delivery of radiation have increased local tumor response and ameliorated many of the complications.

In 1988 the Southwest Oncology Group began a randomized trial of radical prostatectomy vs. external beam radiation for localized prostate cancer. Quality of life parameters were included in this clinical trial. Unfortunately, poor accrual necessitated closing this study. Therefore, definitive answers are not at hand and both the clinician and patient must make a decision based on existing facts, which seem to favor radical prostatectomy because of an improved overall survival rate.

Hormonal therapy

In 1941, Huggins and Hodges ushered in the era of hormonal manipulation when they demonstrated the beneficial effect of estrogens or bilateral orchiectomy on the disease. Pharmacologic agents that can interrupt the hypothalamic-pituitary-testicular axis eliminate, reduce or block the action of testosterone and can suppress prostate cancer cell growth. The major circulating androgenic hormone, testosterone, is generated and controlled by complex interactions between the hypothalamus, pituitary, testis, and adrenal glands. Two releasing factors, luteinizing hormone-releasing hormone (LHRH) and corticotropin-releasing factor (CRF), produced by the hypothalamus, act on the pituitary, which responds by releasing luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH) to the testes and adrenal cortices. LH stimulates the production by the testes, of approximately 95% of circulating androgens while the remainder is generated by the adrenal cortices in response to ACTH in the form of the adrenal precursors, androstenedione and

dihydroepiandrostene. These precursors are converted to testosterone and its active metabolite, dihydrotestosterone.

Orchiectomy

Bilateral orchiectomy has been 'the gold standard' to which other forms of therapy are compared. Surgical castration is performed under local, regional, or general anesthesia. Complications are minimal, and side effects include impotence and hot flashes. Patient acceptance has been excellent although, in a recent survey, of patients offered a choice between orchiectomy and LHRH analogues, more than 70% chose the latter as a primary treatment.

Estrogens

Estrogens suppress LHRH secretion and reduce circulating testosterone to castrate levels. Diethylstilbestrol (DES) is the most commonly administered form of estrogen and several different dosage regimens have been employed in clinical trials. A 1 mg dose appears to produce a response equivalent to those associated with 5 mg daily, without the increased cardiovascular deaths observed with the higher dose. However, patients treated with this lower dose appear to have incomplete suppression of serum testosterone. A daily 3 mg dose of DES produces approximately the same cardiovascular risk as 1 mg but gives more reliable suppression of serum testosterone. Side effects of DES therapy include feminizing effects, cardiovascular events, gastrointestinal complications and peripheral edema. Cost of estrogen therapy is minimal; however, complications, primarily morbid and/or fatal cardiovascular events, dramatically escalate the cost profile. Parenteral administration may avoid some of the cardiovascular and gastrointestinal side effects associated with the oral route. A recent clinical trial randomized between orchiectomy and estrogens for D_2 prostate cancer found a serious cardiovascular event that necessitated hospitalization within a mean of five months of initiation of estrogens in 25% of patients, whereas none was observed with orchiectomy. I believe that estrogens should be relegated to the historical archives in view of this serious side effect and the availability of therapeutically equivalent options for the management of D_2 prostate cancer.

LHRH analogues

LHRH analogues suppress the pituitary release of LH. Substitutions at the sixth, ninth, and alteration of the tenth positions of the decapeptide produce a synthetic analogue with approximately 90 to 100 times the potency of natural LHRH. LHRH is released in a pulsatile fashion from the hypothala-

mus, triggering the release of LH and follicle-stimulating hormone (FSH). In turn, LH promotes testosterone production from the Leydig cells of the testis.

A paradoxical desensitization of the pituitary occurs with chronic administration of LHRH agonists, resulting in a decrease in testosterone production to castrate levels. Leuprolide (Lupron, depot Lupron) and goserelin (Zoladex) are the only LHRH analogues approved for use in the United States. Several large multicenter studies have demonstrated the effectiveness of these agents as first-line therapy for advanced prostate cancer. LHRH agonists are well tolerated and obviate the need for surgical castration, a procedure many men are reluctant to consider initially. However, therapeutically, LHRH analogues do not appear to be superior to orchiectomy or estrogens.

In the United States, in a prospective trial, which compared leuprolide to 3 mg DES in D_2 prostate cancer, 98 patients were randomized to receive leuprolide 1 mg subcutaneously daily, and 101 were assigned to receive DES 3 mg orally each day. Of the evaluable patients, 86% receiving leuprolide had a favorable objective response, compared to 85% of evaluable patients receiving DES. There was no significant difference with regard to resolution of bone pain, improvement in performance status, or median time to progression. The median survival had not been reached at the time of publication, but recent follow-up showed no difference. Estrogen-treated patients had a significantly higher incidence of peripheral edema, nausea, vomiting and gynecomastia but there was no statistically significant difference in the incidence of venous thrombosis, phlebitis, and pulmonary embolism. Leuprolide was associated with a higher incidence of hot flashes.

Initially LHRH agonists may produce a phenomenon known as tumor flare; this phenomenon is the result of the initial stimulatory phase in which there is a transitory rise in LH and subsequently in testosterone. The rise in serum testosterone peaks within 72 hours and reaches castrate levels after several weeks. The effect can be ameliorated with simultaneous administration of an antiandrogen. Flare is characterized by an increase in pain and/or increased symptoms of outlet obstruction. Of particular clinical concern is the risk of spinal cord compression and azotemia. There is no evidence that flare, however, reduces survival.

Antiandrogens

Antiandrogens, a unique group of drugs, are used to treat metastatic prostate cancer. Nonsteroidal agents exert their benefit by blocking the cellular metabolism of androgens at the target organ and by inhibiting nuclear uptake of DHT without reducing serum testosterone levels. Therefore, they have the potential to inhibit both gonadal- and adrenal-produced testosterone.

Flutamide (Eulexin), a synthetic nonsteroidal antiandrogen approved for use in the United States, is metabolized to an active pharmacologic agent,

hydroxyflutamide, during first passage through the liver. Its side effects, which are minimal, are limited to mild diarrhea, gynecomastia, and reversible hepatic toxicity. Nilutamide (Anandron), a nonsteroidal antiandrogen, does not have to be converted into an active metabolite. Clinical trials have demonstrated its efficacy; side effects include visual disturbances, alcohol intolerance and, in several reports, acute interstitial pneumonitis, which regresses upon withdrawal of the drug. Casodex, a new potent antiandrogen, can be administered once a day but a recent trial shows that, when used alone to treat metastatic prostate cancer, it is inferior to either orchiectomy or a depot LHRH agonist.

The synthetic steroidal antiandrogens, including megestrol acetate (Megace) and cyproterone acetate, interrupt the hypothalamic-pituitary-testicular axis at many points. In addition to interfering with binding of androgens to receptors, they suppress LH release. An unexplained rise in serum testosterone associated with these steroidal agents can be circumvented with 0.1 mg of DES once daily.

Glucocorticoids inhibit ACTH production and, in high doses, may produce undesirable side effects. Aminoglutethimide inhibits conversion of cholesterol to pregnenolone, thereby inhibiting adrenal steroid-hormone production. Glucocorticoids and occasionally mineralocorticoids are given as replacement therapy to prevent the ACTH over-ride of the blockade. The antifungal agent, ketoconazole, blocks adrenal and testicular androgen synthesis and can produce a rapid lowering of serum testosterone; however, its use has been limited by gastrointestinal intolerance.

Regardless of the therapy employed, median times of progression of advanced prostate cancer range from 12–18 months and median survival ranges from 18 to 28 months. In the past, the choice of therapy has been tempered by clinical bias, cost and option selection based on performance status, potency, and side-effects profile.

Combined androgen blockade

Here 'combined' suppression refers to the effects of both adrenal and testicular androgens. Although this concept is not new, the emergence of new drugs has rekindled interest. Protagonists of combined adrenal blockade emphasize that approximately 30% of patients with advanced prostate cancer who relapse with disease progression after traditional endocrine therapy do respond to surgical and medical adrenalectomy. Additionally, it is recognized that the administration of testosterone can cause disease exacerbation in patients thought to be refractory to hormones. Supporters of total adrenal blockade argue that these findings signify continued hormonal responsiveness and conclude that low levels of adrenal androgens contribute to the growth of prostate tumors.

Two models of hormone resistance attempt to explain clinical relapse in

patients treated only with monotherapy on the cellular level. The first theory asserts that prostate cancer cells are variably sensitive to androgens and that relapse following initial treatment is the result of inadequate suppression of androgens; i.e., the adrenal component. In accordance with this theory, combined androgen blockade would produce a more profound reduction in hormonal clones and prolong time to progression and thus increase survival. The second model proposes that, with respect to their requirement for androgens, cells are heterogeneous and that relapse is due to the development of resistant clones. In this scenario, combined androgen blockade would have little or no effect.

Animal studies support both theories. The principal model, the androgen-sensitive, Shionogi-mouse, mammary cancer, has been used both to support and to refute the value of combined androgen blockade. In several studies, preincubation of the androgen-sensitive, Shionogi-mouse, mammary-cancer cells for 15 days in the absence of androgen induces complete resistance of growth to the effect of androgens. However, cellular androgen sensitivity could be maintained by incubation with flutamide in the absence of androgens. This study implies that the administration of antiandrogens might avoid or at least delay the development of androgen resistance, thus improving the chance of success.

Ellis and Isaacs compared the effects of partial *versus* complete androgen ablation in rats with the Dunning 3327II (a well-differentiated tumor) and 3327R (a poorly differentiated tumor). Using control groups, tumor-bearing rats were treated by orchiectomy alone or by orchiectomy and cyproterone acetate and a progestational antiandrogen. No difference in tumors growth or animal survival was seen in the two groups.

Theoretical arguments aside, the clinical trial is the definitive laboratory. Investigators have designed studies to evaluate the clinical response and survival of patients with stage D_2 prostate cancer which compare combined therapy with monotherapy as the control. The most strident advocate of combined therapy is Dr. Fernand Labrie; unfortunately, his studies were not randomized and were from a single institution. Several studies with combined androgen blockade have produced mixed results. One of the larger studies by Beland in Canada, which compared orchiectomy and Anandron to orchiectomy and a placebo, registered 211 patients. His results suggested a statistically significant difference in progression-free survival and survival that favored combined androgen blockade. However, combination therapy was significantly more toxic than monotherapy.

The largest study of advance prostate cancer, which was begun in 1984 by the National Cancer Institute, was designed to evaluate the possible benefit of combined androgen therapy. This placebo-controlled, double-blinded, prospective, and randomized study entered 617 patients, 603 were deemed evaluable. All eligible patients had untreated, histologically confirmed D_2 prostate cancer with bone or measurable soft-tissue metastases.

Both regimens were well tolerated although the combined therapy arm

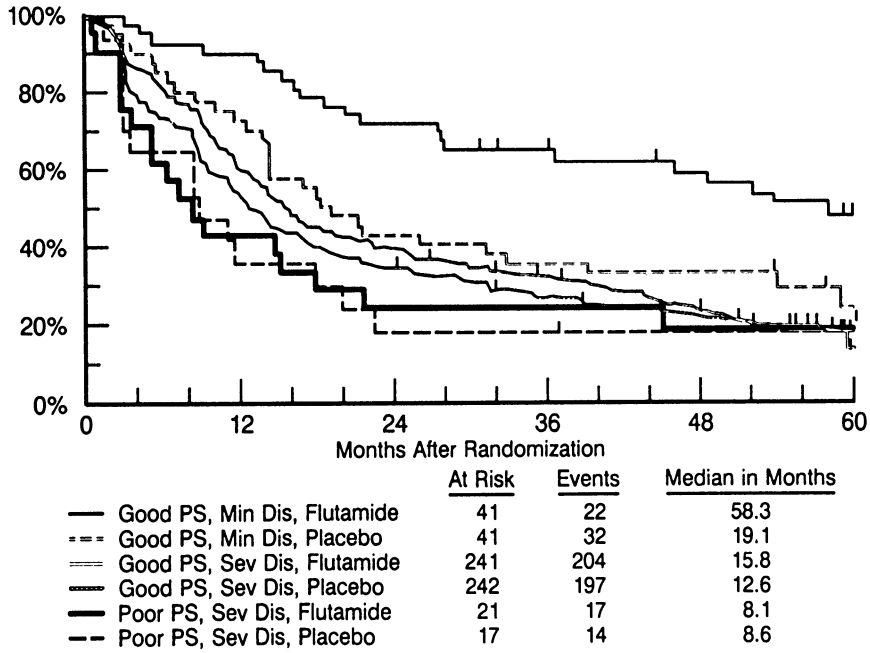

Fig. 1. National Cancer Institute Intergroup Protocol 0036. Progression-free survival calssified by stratification and randomized 'treatment. September 1991.

had a significantly increase incidence of diarrhea (13.5% *versus* 5%). Analysis of variables for flare revealed that the combination reduced the flare phenomenon. The time to progression increased from 13.9 months to 16.5 months and there was a statistically significant difference in survival rate – 35.6 months with combined compared to 28.3 months with monotherapy. Most patients have benefited from this therapy; however, those with minimal disease and a good performance status enjoyed even longer progression-free and overall survival rates (Figs. 1 and 2). Recently, a large (EORTC) trial showed that an LHRH agent and flutamide gave a survival advantage over bilateral orchiectomy.

From the existing data we can reach the following conclusions:

1. If the LHRH analogue, leuprolide, is chosen to treat D_2 prostate cancer, the addition of the antiandrogen flutamide offers a survival advantage over leuprolide alone.
2. In a subset of patients with minimal metastatic disease, combination hormonal therapy appears to confer a marked benefit.
3. Not all patients showed improved survival with combined therapy, particularly those with severe disease and poor performance status.
4. The survival benefit noted in patients with minimal disease challenges us to evaluate this therapy at an earlier stage of this disease.

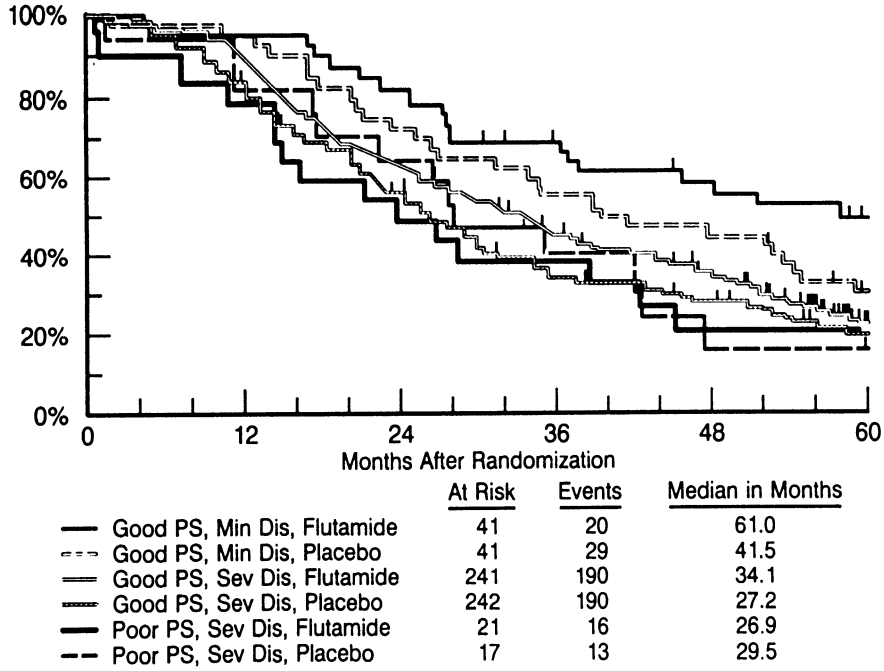

Fig. 2. National Cancer Institute Intergroup Protocol 0036. Survival calssified by stratification and randomized 'treatment. September 1991.

5. Combined androgen blockade with bilateral orchiectomy and an antiandrogen gives a better result than bilateral orchiectomy alone.

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CHAPTER 51

Early detection of prostate cancer

LAURENCE KLOTZ

There is great interest in the new diagnostic assays, transrectal ultrasound (TRUS) and prostate specific antigen (PSA) to detect prostate cancer at an early, curable stage. However, screening for prostate cancer faces many problems. This paper addresses the potential benefits and the risk of screening and suggests some clinical implications.

About 30% of men over 50 undergoing autopsy have histologic prostate cancer – a rate that is three times higher than the prevalence of clinical prostate cancer, and 15 times higher than the likelihood of death from prostate cancer. Therefore, a screening program must provide a means to identify most (or all) of the patients with clinically significant prostate cancer and to exclude most (or all) with insignificant disease. Otherwise, there is a risk of substantial overtreatment with its attendant morbidity and cost, without having an impact on mortality.

One major distinction between clinically significant tumors and the latent lesions identified on autopsy studies relates to tumor volume. In McNeal's autopsy study, 80% of the incidental tumors were less than 1 cm^3 [1]. In a subsequent study of 68 prostates removed at cystectomy for bladder cancer, incidental prostate cancer was present in 38%. Of these, 75% were less than 1 mm^3. Before cystectomy the patients had a normal prostate by digital rectal exam (DRE). McNeal has shown that biologically active tumors (those with the tendency to invade locally and/or metastasize) are almost always larger than 1 cm^3. Clearly, efforts directed at diagnosing patients with tumors in the 1 cm^3 range will be more likely to identify biologically significant disease.

Epidemiologists have proposed criteria for evaluation of early detection programs. Table I shows one such set (1a) and illustrates that this is a multifaceted task.

How well do DRE, TRUS, and PSA assays satisfy these criteria? Clearly DRE and TRUS improve early detection when used as part of a screening program. Frequently tumors detected by either screening modality are localized clinically – about 75% of those detected by DRE and 90% of those detected by TRUS. This compares favorably to the proportion of patients

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Table I. Criteria for an early detection program [1a]

1. Efficacy: Do controlled trials show that the program reduces morbidity or mortality? If not:
   a. Is there a test that permits early detection?
   b. Is the current treatment more efficacious at an earlier stage?
   c. Is the treatment agreed upon for all cases, especially those which are borderline?
   d. Is the sensitivity and specificity of the detection method known? Are the false-negative and false-positive rates known for the disease prevalence in the population?
   e. Are the adverse effects of the detection maneuvre known? What are they?
   f. Are the negative effects of the program outweighed by the benefits?
2. Effectiveness and availability
   a. Are there sufficient diagnostic and treatment facilities (of adequate quality) to manage the anticipate workload?
   b. Will physicians (and other providers) comply with the recommended testing, treatment, and follow-up protocol?
   c. Will patients comply with the testing, treatment, and follow-up protocol?
3. Efficiency
   a. What is the cost-effectiveness of the proposed program?
   b. How does the cost-effectiveness of the program compare to the cost-effectiveness of other health-care programs, which are competing for existing resources?

whose tumors are discovered following development of symptoms; in these, only 40% have clinically localized disease.

Studies have been done on screening with DRE, TRUS, and PSA, which examine their sensitivity but none has considered survival or mortality.

Digital rectal exam (DRE)

In eight studies of DRE screening, which included 13,000 patients, the results were abnormal in 3.2% to 10% (mean 6.5%). Prostate cancer was detected in 0.2% to 7.5% (mean 1.25%) and the positive predictive value varied from 5% to 34% (mean 25%). The wide range in positive tests is a function of the DREs variability in the accuracy of the examination (a function of the skill and commitment of the practitioner), the population being screened, and variation in biopsy strategies e.g., single versus multiple, random versus systematic, etc.

The DRE data illustrate one of the major problems in interpreting all screening results: there is no gold standard of diagnosis. In general, the biopsy is accepted as determining disease status. However, generally patients whose screening tests are negative are not biopsied; accordingly, we do not know the true denominator of disease incidence, i.e., sensitivity of the test. In addition, a needle biopsy may be misleading: some patients with negative biopsies harbor occult microfoci, which were missed; others with a positive

biopsy may have minimal disease, which was clinically insignificant. Studies of serial screening may provide some answers.

Transrectal ultrasound (TRUS)

High-resolution (6–7.5 MHz) transrectal ultrasound produces images of the peripheral and transitional zone of the prostate, the seminal vesicles and the urethra. Both sagittal and transverse scans, necessary for proper evaluation, have now been combined in one probe.

Because prostate cancer has no pathognomonic echo pattern, test specificity is poor. Most tumors (70%) are hypoechoic and, because it is recognized that peripheral hypoechoic lesions often are malignant, these lesions are biopsied, thus improving the technique's specificity. The limit of resolution is 4 mm to 5 mm. Most palpable tumors can be seen on ultrasound. Specific capsule echo patterns can be identified. Extension outside the capsule into fascia and fat can be seen as a bulging, thickening irregularity or asymmetry of the capsule. An echo-poor pattern is thought to be due to replacement of echogenic glandular epithelium by homogeneous (therefore, less echogenic) tumor.

It is difficult to do a sonographic assessment of the seminal vesicles because normal seminal vesicle and prostate cancer both are hypoechoic compared with normal prostatic tissue. Ultrasound changes in the seminal vesicles involved with tumor have not been established. One's level of suspicion should increase with abnormal internal echoes, anterior displacement or disparities in size and shape.

Spring-loaded automated biopsy devices have enhanced the value of TRUS as a diagnostic tool. Accurate sonographically guided biopsies of the suspicious areas and random biopsies can be obtained on an outpatient basis with minimal discomfort and morbidity.

Sensitivity

TRUS is more sensitive in detecting prostate cancer. A summary of eight screening studies, which included 3500 patients, found abnormal results that varied from 7.1% to 43% (mean of 25.8%). The percentage of patients with prostate cancer varied from 1.7% to 18% with a mean of 7.3%. This wide range reflects variability in operator skill and differences in biopsy strategy. Essentially, the more biopsies performed, the higher the incidence of prostate cancer detected, due to the high prevalence of histologic prostate cancer.

In four studies that compared screening by DRE and TRUS, TRUS detected twice as many prostate cancers as DRE. Lee [2] found cancer in 2.6% by TRUS and 1.3% by DRE. Cooner [3] biopsied 40% of 167 screened

patients and found cancer in 14.5%. Ragde [4] biopsied 18% of 1051 patients and found cancer in 4.7%.

At present, ultrasound suffers from the same pitfalls as DRE; it is operator dependent and subject to significant interobserver variability. It is valuable because it directs biopsies to suspicious areas including the seminal vesicles and the apex of the prostate, rather than because it defines tumor extent. At present it does not seem to have a role as a primary screening modality in asymptomatic patients.

Prostate-specific-antigen assays (PSA)

The discovery of PSA as a tumor marker for prostate cancer was a landmark in urology. PSA has potential in such areas as screening, staging, monitoring, and evaluating responses to treatment. Its role in these areas is the subject of much debate and research, but clearly PSA is the best serum marker for prostate cancer.

PSA is cleared from the serum by first-order elimination kinetics with a half-life of about three days. Therefore, two to three weeks must pass before PSA returns to normal after manipulation of the prostate. Certain maneuvers – e.g. transrectal biopsy – may produce transient prostatitis and even more prolonged PSA elevation. There is no significant diurnal variation of PSA. Stamey reported a mean 18% reduction in serum PSA following hospitalization, which may reflect a decrease in ejaculation frequency or the effect of recumbency The effect of DRE on PSA has been reported as substantial (increased 2 or more times for up to two weeks) to negligible.

We have performed PSA before and after DRE on 24 patients with localized prostate cancer. Mean PSA before and after DRE was 11.79 and 12.17 ng/ml (Hybritech). The mean difference was 0.38. Standard deviation was 0.73. This data indicates that, while DRE does increase PSA, this increase is slight and generally not clinically significant. It is likely that even in a screening intervention, a DRE before PSA will produce only a mild increase in false positive rate.

Cystoscopy and prostate biopsy may produce a marked increase in PSA levels in most patients. Transurethral resection of the prostate (TURP) produces a transient rise in PSA followed by a long-term decrease. Using TURP data, Stamey calculated that the PSA rose 0.5 ± 0.4 ng/ml/g of benign prostatic tissue (BPH tissue assay); for prostate cancer, the increase was 10 times higher (Stamey *et al.*: J Urol 141; 1070, 1989).

Assays available

There are five assays for PSA: the Tandem R (Hybritech), the Tandem E, the PROS-check (Yang), IMx PSA (Abbott), and the IRMA-count (Diagnostic Products Corp.).

The Tandem R, a solid-phase sandwich assay, uses two monoclonals and an immunoradiometric technique. The normal range is 0 ng/ml to 4 ng/ml. With this assay, 3% of normal men over 40 have a PSA greater than 4, and 8% of men with BPH have a value between 4 and 10. The Tandem R assay is the most widely used in Canada; hereafter, the reference values given will be to this assay.

The Tandem E assay uses an enzyme-linked, monoclonal rather than a radioactive-labelled antibody. It is slightly less sensitive than the Tandem R assay but otherwise is equivalent.

The PROS-check assay, a polyclonal radioimmunoassay, has an upper limit of normal of 2.5. However, results from PROS-check (Yang) at values greater than 10 are 1.6 times higher than those from the Tandem R assay. Note that the normal upper limit value of the Yang assay is lower than the normal value of the Tandem R assay.

The IMx PSA assay is a new, ultrasensitive, microparticle enzyme immunoassay (MEIA). This assay has a lower limit of detection of 0.01 ng/ml, 20 times lower than the Tandem assay.

The IRMA-count assay, which is widely used in Europe, resembles the Tandem R assay in that it is an immunometric radioimmunoassay.

Sensitivity and specificity

How well do the PSA assays detect early prostate cancer? Their sensitivity and specificity depends on the upper limit chosen and the population selected. Eight studies recently published use a range of cutoffs and assays. In the three largest, the sensitivity with an upper limit of 10 ng/ml (Hybritech) was 35% [5, 5a, 6]. In the first three studies mentioned, using an upper limit of 4 ng/ml, the sensitivity increased to 70%. However, as the sensitivity improves and the upper limit is lowered, the specificity decreases. Overall, 10 to 20% of screened men will have a PSA greater than 4 ng/ml. Thus a substantial proportion of screened men are identified as abnormal and would undergo further tests, including in many cases a prostate biopsy. Their quality of life will be reduced by the attendant anxiety about the positive test, even in the absence of a positive diagnosis. About 2% of screened males will have PSA greater than 10 ng/ml, but two-thirds of prostate cancer would be missed at this level.

A study by Catalona [7] screened 1653 men with PSA assays alone; later it was expanded to include 10,212 men [8]. PSA levels were 4.0 ng/ml or less in 90%, 4.1 ng/ml to 10 ng/ml in 8%, and greater than 19 ng/ml in 2%. Of patients with a PSA between 4 and 10, 26% had prostate cancer; 73% of these had pathologic organ-confirmed disease. Importantly, only 7% of the prostate cancer patients with a normal DRE and elevated PSA had pathological stage A-1 disease. The remainder (95%) had 'clinically significant' disease, i.e., pathologic A_2/B/C lesions.

In a second phase of this study [8], 4749 patients were screened with PSA

assays and DRE. The two tests together detected 27% more cancers than would have been detected by PSA assays alone, and 34% more than by DRE alone. Cancers in patients with an elevated PSA and normal DRE were confirmed on pathological examination in 77%, compared with 54% when PSA and DRE were abnormal.

This data and other evidence indicate that PSA is the best single test for the early detection of prostate cancer. In addition, the combination of DRE and PSA assays detects clinically important cancers, which would be missed by either method alone.

Bias in screening studies

To date, none of the screening studies has been controlled. The interpretation is subject to leadtime bias, lengthtime bias, and the presence of clinically insignificant tumors. These three pitfalls make uncontrolled screening look far better than it actually is.

Leadtime bias refers to the time between detection of a tumor by screening and its recognition in the absence of screening. Stage for stage, the screened patient will appear to live longer with his disease than the patient whose tumor is identified after symptoms develop. Thus survival in the screened group is improved regardless of whether the technique has any impact on the disease.

Lengthtime bias refers to the tendency for screening studies to identify patients whose disease has a longer natural history. A patient with a virulent, rapidly progressive tumor is less likely to be identified by screening than one whose disease is slowly progressive. Thus screening will identify a subset of patients who are likely to have a better survival than the overall group.

Stage migration due to more accurate staging methods (such as TRUS and PSA) also may produce spurious improvements in stage specific mortality. In some studies a patient with a clinical B2 lesion whose TRUS demonstrates seminal-vesicle involvement becomes a stage C; subsequent analysis will show improved outcome both in stage B2 (the worst B2s are excluded) and in stage C (favorable Cs, formerly B2s, are included).

Screening studies from other tumor sites throw some light on the likely benefits of prostate cancer screening. Randomized trials have shown that screening with mammography produced a 25% reduction in breast cancer mortality in certain age groups [9].

Assuming a best-case scenario of 25% improvement in mortality, these are the implications of screening: In Canada, there were 3000 prostate cancer deaths in 1990; a 25% reduction would prevent 750 cancer deaths.

In six studies in the last 15 years, the surgical mortality following radical prostatectomy averaged 1%. Canada has about 2.5 million men between the ages of 50 and 70. With a detection rate of 5%, this would mean the initial screening would find prostate cancer in 75,000 patients. If 50% of these

elected radical prostatectomy, one would expect 375 deaths from surgery, substantially negating the benefits of screening. Other issues, including quality-of-life effects of impotence, incontinence, and urethral strictures, have an additional impact. Of course, screening might reduce the mortality rate by more than 25%, increasing the benefits of screening.

The discounting effect makes a late cancer death preferable to an early surgical mortality even if calculations show an overall benefit in terms of life-years saved.

Conclusion

Evaluation of an early-detection program (Table I), makes it apparent that several criteria have not yet been met for prostate cancer. Screening with PSA in conjunction with DRE permits earlier detection of prostate cancer. In most cases, cancers detected are clinically significant (by virtue of cancer volume) and on pathological exam are more likely to be confined to the organ than those detected by DRE alone.

However, a number of important uncertainties remain. Substantial data suggests that earlier treatment is beneficial although this has not been proved. The mode of treatment is not agreed upon in all cases. There exists no formal decision analysis assessing benefit versus harm and any such analysis is weakened by the vagaries of available data. The negative effects of screening may outweigh the benefits. We have no measure of cost effectiveness either in absolute or relative terms, i.e., cost per quality-adjusted year of life relative to other healthcare programs.

The solution to these problems is to test the utility of screening in a randomized trial. The National Institutes of Health has proposed a study that would compare two cohorts of 50,000 men each, with chest X-ray, colonoscopy, DRE and PSA assays with selective TRUS in one group, and no tests in the other. A parallel arm would include screening for ovarian cancer in women. The primary endpoint would be disease-specific and all-cause mortality. Funding for this study has been approved.

In the meantime what should be our practice? The PSA assay is the best single test for the early detection of prostate cancer. The cost of the assay is low. Hence, it seems logical to screen men between the ages of 50 and 70 with an annual PSA assay. DRE should be continued because it is complementary to PSA assays and has other functions, e.g., screening for rectal cancer. Patients with a family history of prostate cancer, i.e., a first-degree relative who died of prostate cancer, should be screened with DRE and PSA assay starting at age 40.

Although this recommendation has been adopted by the Canadian Urology Association's Task Force on Prostate Cancer Screening, it is based on flawed and incomplete evidence. Our knowledge has substantial gaps and emerging data may alter the picture. The weight of uncertainty led the

Canadian Task Force on the Periodic Health Exam (PHE) to recommend against PSA screening and to state that "there is poor evidence to support the inclusion or exclusion of DRE in the periodic health exam" [8].

At present there is no role for primary TRUS screening; the yield in patients with a normal DRE and PSA is extremely low.

A reliable method for assessing the progression capability, i.e., growth rate and metastatic potential of a detected tumor would make screening far more appealing and this may come as a consequence of research in genetic markers of tumor biology, particularly flow cytometry and oncogene expression. Such a tool would permit stratification of patients into high- and low-risk groups.

In addition, we may reduce the morbidity and mortality of treatment and acquire definitive data on the results of radical therapy. These developments would improve the likelihood that screening will reduce disease-specific mortality from prostate cancer at an acceptable human and financial cost.

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CHAPTER 52

Prostatic-specific antigen in the diagnosis, staging and management of adenocarcinoma of the prostate

A.W. BRUCE, A. TOI and M. BULBUL

Tumor markers may be tumor-specific or tumor-associated. Both acid phosphatase (AcP) and prostatic-specific antigen (PSA) are tumor-associated antigens, i.e. they are specific for prostatic epithelial cells but not for prostatic cancer cells. Acid phosphatase has been used for the past 50 years in diagnosis, in staging and in monitoring response to therapy of adenocarcinoma of the prostate. This enzyme may be measured enzymatically or by immunological testing, however, both methods lack adequate specificity and sensitivity. Prostatic specific antigen was discovered in seminal fluid by Hara *et al.* [1] in 1971. In 1978, Wang *et al.* [2] isolated an identical antigen from prostatic tissue and showed that it reacted only with prostatic-tissue cells, both benign and malignant. Both acid phosphatase and prostatic-specific antigen are glycoproteins, AcP has a molecular weight of 100,000 daltons compared to 34,000 for PSA.

PSA has replaced acid phosphatase as the tumor marker of choice for investigation of adenocarcinoma of the prostate, although many clinicians use acid phosphatase, measured enzymatically – an elevated value indicates a poor prognosis and is a contraindication to radical prostatectomy. PSA, a serine protease produced by the epithelial cells lining the acini and ducts of the prostate gland, is involved in the liquefaction of seminal fluid. This enzyme has a half life of 2.2–3.2 days [3, 4] without a diurnal or circadian pattern. Stamey has shown that PSA values are low when one examines blood from an ambulatory patient, compared to those in a hospital setting.

Currently three main assay kits are available for PSA measurement.

1. a solid-phase, 2–site immunoradiometric assay using 2 murine monoclonal antibodies (Hybritech Incorporated, San Diego, CA).
2. a polyclonal, double-antibody radioimmunoassay (Yang Laboratories, Bellevue, Washington) and
3. a monoclonal immunometric assay using two monoclonal antibodies (Diagnostic Products Corporation, Los Angeles, CA).

D.G. Oreopoulos, M.F. Michelis and S. Herschorn (eds), Nephrology and Urology in the Aged Patient, 473–480.

Table I. Per cent of biopsies yielding prostate cancer at different PSA levels

PSA values**	T.G.H. series	Cooner *et al.*
	(357)*	(263)*
< 4.0 μg/ml	19%	20.2%
4.0–10.0 μg/ml	46%	35.0%
> 10.0 μg/ml	71%	58.0%

* Number of patients.
** Monoclonal PSA, μg/ml.

Diagnosis of early carcinoma of the prostate

Many investigators have studied the respective values of digital rectal examination (DRE), PSA measurement and transrectal ultrasonography (TRUS) in the diagnosis and staging of prostate adenocarcinoma. In 1181 consecutive TRUS examinations done over a one-year period in our institution (Toronto General Hospital), two physicians did careful DRE's and measured PSA values before any patient manipulation. From this group of patients, we examined 439 biopsies using one or more of the following indications: a suspicious finding on DRE (hardness or a nodule), an abnormal TRUS examination (a hypoechoic area), or a PSA serum level above 10 μg/ml. These patients were selected and do not represent the wide range of men examined under screening programs. In this study the positive biopsy rate (45%) corresponds well with other reports. When each test was examined in isolation, an elevated PSA value produced a greater yield of positive diagnoses than either TRUS or DRE, (63%, 53% and 48%, respectively). This study also showed a marked rise in the yield of positive biopsies as the PSA values increased and this corresponds closely with the results of Cooner *et al.* [5] (Table I). In his studies, Cooner does not include patients with abnormal digital rectal examinations, normal TRUS findings and positive pathology. Furthermore a study of the two series using all these evaluations showed a marked increase in the positivity rate; in our patients who had abnormal DREs, positive TRUS examinations and PSA values greater than 10 μg/ml., 90% had adenocarcinoma of the prostate; in Cooner's series, 72.2% had positive biopsies when they had positive TRUS findings and similarly elevated serum PSA levels. Of 123 patients who had abnormal DRE's but normal TRUS findings, an additional 4.9% of patients had biopsies positive for cancer.

Using logisitic regression and relative risk analysis, we examined the data from the TGH patients (Table II) and clearly demonstrated the relative risk of an abnormal DRE finding, an abnormal TRUS and an elevated PSA. A patient with all these abnormal findings has a 50 times greater chance of having a prostatic cancer compared to one who has all these values within the normal range. It should be noted that, with an abnormal DRE and TRUS but with a normal PSA, the risk factor is only five-fold greater.

Table II. Relative risk of CaP (360 Patients)*

		PSA value – μg/ml (D.P.C.)		
		< 4.0	4.0–10.0	> 10.0
D.R.E.	–ve	1.0	3.10	9.47
TRUS	–ve			
D.R.E.	+ve	1.84	5.70	17.62
TRUS	–ve			
D.R.E.	–ve	2.93	9.08	20.08
TRUS	+ve			
D.R.E.	+ve	5.40	16.71	51.70
TRUS	+ve			

* Logistic regression and relative-risk analysis.

These studies demonstrate clearly the relative values of the different modalities and emphasise that PSA elevation is the most significant.

Patient investigation using DRE, TRUS and PSA

The relative values of these examinations have been established in men presenting with urologic symptoms and/or with abnormal physical, ultrasound or PSA findings. The annual rectal examination is well accepted and the addition of PSA appears to be of even greater value, particularly in patients with early prostatic symptoms. When should a TRUS be ordered and when is a prostate biopsy indicated? Stamey has shown that the doubling time for untreated localized (stages A and B) adenocarcinoma of the prostate is 4 or more years and that 86% of patients in this category will have a rising PSA [6]. From his studies and from those of Cooner's, he concludes that patients with a normal DRE and a PSA in the 4 to 10 μg/ml. range should be followed clinically, but that similar patients with a rising PSA should have a TRUS with biopsy. We have offered physicians a practical guide for investigating selected patients requiring a prostatic workup. Table III lists the different categories of patients and the recommended evaluations. In patients with a normal DRE and a serum PSA in the 4–10 μg range, there are three possible investigative routes: (1) Watch clinically for a rising PSA value, (2) proceed to TRUS examination with biopsy only if a hypoechoic area is seen, or (3) use PSA density. We favor the last approach. It is essential to make patients aware of the high incidence of carcinoma of the prostate and the relative values of the different studies.

Table III. Patient management depending on digital rectal examination findings and PSA* levels

DRE abnormal	PSA > 4	TRUS and biopsy (selected or systematic)**
	PSA < 4	TRUS. Biopsy only if TRUS abnormal or DRE convincingly abnormal.
DRE normal	PSA > 10	TRUS and biopsy (selected or systematic)**
	PSA 4–10	(i) follow PSA for rise at six monthly intervals (ii) TRUS. Biopsy only if TRUS abnormal. If no biopsy then follow as above or (iii) use PSA density as guide for biopsy.
	PSA < 4	Regular clinical follow up as appropriate.

* Monoclonal PSA ng/ml.

** Selective means biopsy directed at ultrasonographic abnormality, systematic means samples taken from the upper, mid and lower portions of right and left lobes for a total of six samples.

Table IV. Per cent distribution of PSA in 'screening' *versus* urologically referred patients in men 50 years or older

Patients	Prostate Specific Antigen (ng/ml) $0 \leqq 4$	4.1–10	> 10	Positive DRE
Urological [1] ($n = 2648$)	65%	20%	15%	33%
'Screening' [2] ($n = 2659$)	85–90%	8–12%	< 3%	17%

[1] Cooner, 1991.

[2] Stanford series, (478); Brawer (1240); Boxer (700); Hudson (241).

From Stamey (1992) with permission.

Problem areas in diagnosis of carcinoma of the prostate

Three areas require further study:

i. the relationship between the pathological findings and the volume of prostatic carcinoma in different populations e.g. screened *versus* selected patient groups,
ii. the volume of prostatic carcinoma in relationship to the volume of BPH in any one gland, and
iii. the significance of a prostatic cancer diagnosed primarily by an abnormal PSA finding.

Table IV, from Stamey's presentation in 1992, compares two large groups of patients from five different reports [6]. In the urologically referred group, a high proportion have an abnormal PSA while, in the asymptomatic screened group, a high percent have normal PSA values.

Several investigators are working to develop a method of relating prostatic volume to PSA values so as to develop a PSA-density value. This would allow us to establish a relationship between PSA level and size of the prostate. A moderately high PSA may be consistent with a large prostate but with a

small prostate the same value should arouse suspicion of cancer. Thus prostate volumes, as calculated from TRUS measurements, may allow us to interpret PSA in a more sensitive and sophisticated way. Also, such a figure will have a better positive prognostic calculation.

Finally, at this time we do not know if prostatic cancer diagnosed by isolated PSA elevation behaves differently from that diagnosed by rectal or TRUS examinations. Currently studies and preliminary reports suggest that there is no clear difference between the two groups of patients. These three modalities have markedly improved the detection of early prostatic cancer and every physician should use these studies in a careful manner. None of the tests used singly can match the results obtained when all three studies are used and clearly one must apply them appropriately.

Staging of adenocarcinoma of the prostate

Unfortunately, the addition to DRE PSA values and TRUS examinations has not produced a significant improvement in staging accuracy, and we still cannot differentiate localized, organ-confined disease from cancer involving the prostatic capsule and the seminal vesicles.

Most investigators have found a steadily rising PSA value with increasing clinical stage [7, 8], and Stamey has shown that increasing serum values correspond with increasing volumes of disease (Fig. 1). Although PSA levels differentiate various clinical stages in large populations, in individual patients it does not differentiate intracapsular from extracapsular disease.

Many investigators have correlated preoperative PSA values with pathological stage in patients undergoing radical prostatectomy. As with clinical staging, when one examines the final pathological stage of those groups, there is marked overlap in PSA values, as illustrated by Partin *et al.* [9]. In a small sample of 44 patients undergoing radical prostatectomy, we found that only 26% of those with pathological intracapsular disease had normal PSA values, while, of those with extracapsular spread, 43% had serum values of less than 10 μg/ml. Clearly, the high incidence of false-positive and false-negative PSA findings makes this test unsuitable for the selection of patients potentially curable by radical prostatectomy. Although rising PSA values are associated with increasing stage and volume of disease in large populations, this does not apply to the individual male with potentially curable localized disease.

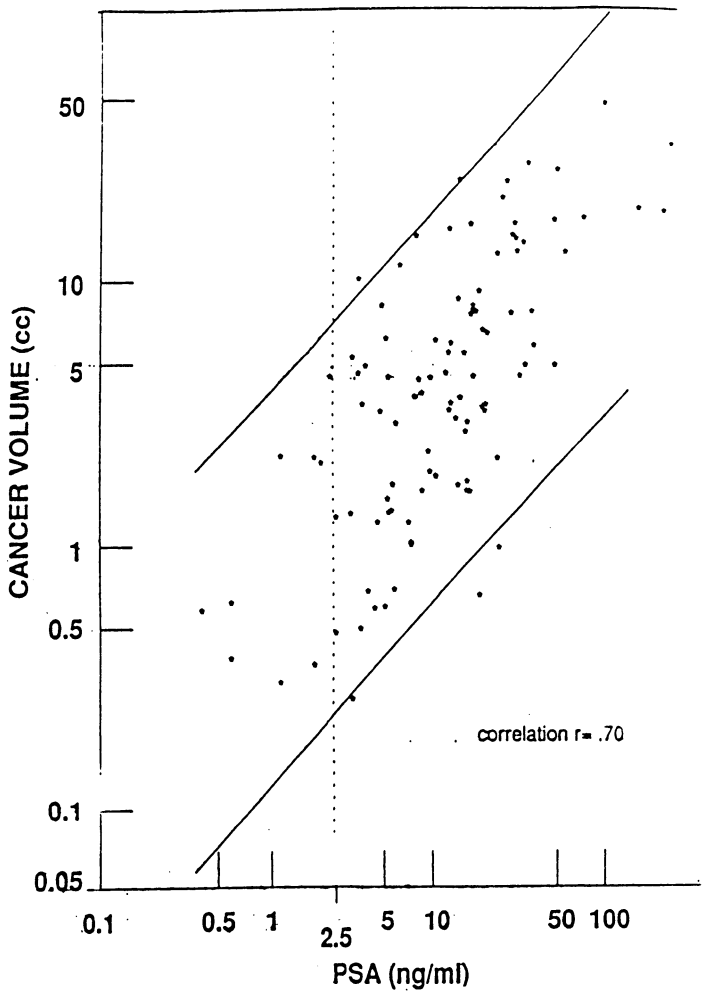

Fig. 1. Cancer volume vs. PSA. From Stamey (1992) with permission.

Management of adenocarcinoma of the prostate

Monitoring advanced disease

Killian *et al.* [10], who compared PSA and other tumor markers including acid phosphatase and alkaline phosphatase, found that PSA was more sensitive than the others in detecting progression and regression of disease. In addition, Ercole, Lange *et al.* [11] showed that, with active clinical D2 disease, PSA values were elevated in 98% of patients, compared with only 77% using prostatic acid phosphatase, measured immunologically. Many

other studies have demonstrated the superior efficacy of PSA and virtually all centres use this marker to demonstrate and monitor prostatic cancer. However, Lange has cautioned that this tumor marker may be normal in 2% of untreated D2 disease and as high as 5% in patients with D3 disease (hormonally resistant prostate cancer).

PSA following radical prostatectomy

PSA measurements are carried out routinely following radical prostatectomy. In a series of 174 such operations, Hudson *et al.* [8] have shown that, with organ-confined disease, 89% had normal values (less than 0.6 μg/ml), those with pC_1 and pC_2 disease were normal in 87% but when there was seminal vesicular involvement only 34% had normal PSA levels following surgery. Lightner *et al.* [12] advocate biopsy of the anastomotic site in patients who do not achieve normal PSA levels after radical surgery. These authors showed that, in 57 such patients, 42% had residual detectable disease, amenable to adjunctive therapy.

In summary, PSA has a high sensitivity and low specificity when used in studying patients with adenocarcinoma of the prostate. This marker plays a major role in the diagnosis of this cancer, in monitoring disease progression and regression, and in following patients after radical prostatectomy.

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CHAPTER 53

Transrectal prostate ultrasound: strengths and limitations

A. TOI

Introduction

Transrectal ultrasound (TRUS) has been used for over 25 years but, since 1985, it has shown explosive growth following the work of individuals like Lee of Ann Arbor USA, who initially defined the most reliable criteria for sonographic diagnosis of malignancy [1], McNeil of San Diego, who has redefined the anatomy and Lindgren of Sweden, who developed the first spring loaded, automated biopsy needle driver.

The 'new anatomy'

McNeil described 5 major division(s) of the prostate, each of which has a different susceptibility for disease [2]:

1. Peripheral zone (PZ), which surrounds the posterior and lateral aspects, is the site of about 70% of malignancies as well as inflammation and atrophy.
2. Central zone (CZ), which contains the ejaculatory ducts, is a wedge at the base of the gland between the transitional zone and peripheral zone. It is relatively immune from disease but about 5% of cancers originate here.
3. Transition zone (TZ), which is central in the gland on either side of the internal urethral sphincter, is the site of benign prostatic hypertrophy and about 20% of malignancies.
4. Internal urethral sphincter, a large muscle ring surrounding the proximal urethra at the base of the prostate, has a echopoor acoustic texture, which can mimic malignancy to the uninitiated.
5. Anterior fibromuscular zone covers the anterior aspect of the gland and is relatively immune to disease.

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Appearance of malignancy at ultrasound

In 1985 Lee suggested that prostate cancer is seen as an echopoor nodule in the peripheral zone and is not echogenic as previously thought [1, 3]. More recent experience has shown that this is not always the case and that lesion echogenicity varies with the pattern of growth, which may be nodular (40%), nodular and infiltrative (30%) or infiltrative (30%). It is the nodular component that alters the sonic texture of prostate and so renders the tumors visible as an echopoor nodule. About 70% of tumors have a nodular component and hence are visible [4, 5]. The remaining 30% infiltrate the prostate and do not stand out against the background tissue texture. It is common to find one lesion in the prostate by TRUS only to find additional lesions in the final prostatectomy specimen [6, 7]. Similarly, very small lesions with well-differentiated histology (Gleason 2–3) will not be seen. Tumors that have an isoechoic infiltrating pattern can be detected through secondary ultrasound signs such as disruption of internal echo architecture and asymmetry of the gland. In men with palpable nodules, systematic TRUS-guided biopsy of normal-appearing prostate has yielded cancer in the 'normal' appearing portions in 21% of instances, and in 7% only the 'normal' appearing part was shown to be malignant at biopsy [7, 8].

Transition-zone cancers pose a special problem because benign hypertrophy renders the TZ very heterogeneous and, if cancers are to be detected, the examiner must be sensitive to subtle contour alterations in areas of capsular weakness.

Cancer detection by ultrasound imaging is limited because other pathologic processes such as inflammation, BPH, prostatic intraepithelial neoplasia (PIN), atrophy and even normal area of the gland also can be echopoor and can be differentiated from cancer only by biopsy. In our experience and that of others, about 50% of biopsies of echopoor nodules show cancer and the remainder are benign [9, 10].

Prostate biopsy

The accuracy, ease and safety of TRUS-guided biopsy show a tremendous advantage compared to all other modes of biopsy. Staging biopsy consists of deliberate biopsy of tissues outside the prostate adjacent to a visible tumor nodule. This is to show if there is tumor extension outside the prostate which may be seen under the microscope but may not be visible at ultrasound. Studies comparing finger-guided biopsy to TRUS-guided biopsy consistently show about a 40% higher yield of cancer in the TRUS group. TRUS biopsies take 5 minutes to perform in the outpatient department without analgesia and using antibiotic cover. In over 2000 biopsies, we have always obtained excellent tissue and have a complication rate of under 1% consisting mainly of minor febrile episodes treated with antibiotics. The precision of biopsy

guidance has allowed sophistication of the technique to include systematic sampling biopsies and staging biopsies of the seminal vesicles [7].

In addition TRUS guidance allows easy and accurate needle guidance into other structures such as utricular cysts and seminal vesicles [11] and guide therapy with radioactive seeds.

Cancer staging

TRUS has been only moderately helpful in staging. In clinical stage-A disease, TRUS is useful to look for residual cancer following discovery of positive 'chips' at TURP. In 19 men at our hospital with clinically impalpable Stage-A disease, TRUS showed a nodule in 12 (63%) and at biopsy cancer was found in the nodule in 7 (37%). An additional 4 cancers were found at systematic TRUS-guided biopsy about the transurethral prostatectomy (TURP). In all, using TRUS and biopsy, we demonstrated residual cancer in 58% of men with clinically non-apparent, stage-A disease.

In clinical stage-B disease, TRUS has slightly improved the accuracy of staging over clinical examination but understaging is reported in 40–60% and overstaging in 10–20%. Seminal-vesicle involvement is especially difficult to detect [12, 13]. It is difficult to detect microscopic extension beyond the capsule and in the perineurial spaces. Pontes *et al.* [13] have suggested strategic staging biopsy to overcome this limitation.

Follow-up of treated cancer

Following successful chemo- or radiotherapy, the prostate becomes smaller and the lesion less evident. With recurrence, the lesion again becomes more evident. We have found that follow-up is not as easy to perform as has been suggested. PSA seems to be a sensitive and objective index of disease activity. If nodules do recur after radiotherapy, they can be easily biopsied. Also after radical prostatectomy, TRUS can be used to search for, and biopsy pelvic recurrence.

Benign prostatic hypertrophy

TRUS has limited value in BPH. The appearance of the prostate and the degree of enlargement of the transitional zone do not correlate with obstructive symptoms. TRUS does allow examination and biopsy of glands that have enlarged beyond the range of the palpating finger. Also it allows precise volume estimates, which are useful in monitoring chemical 'prostatectomy'. It is also useful to guide hyperthermic and laser treatment of BPH and in

the pretreatment evaluation to look for unsuspected cancer, which otherwise might have been detected at TURP.

Pretreatment examination of the kidneys using conventional abdominal ultrasound is done for hydronephrosis and unsuspected cancer. The bladder can be examined is done for trabeculation and post-void residual with TRUS. Postoperatively the surgical defect generally is smaller than expected from the surgery and the appearance of the surgical resection does not reflect the postoperative function changes.

Infertility

Most men with azospermia have normal prostates and seminal ducts. Occasionally we find obstructions and congenital absences. With unilateral disease, we scan the ipsilateral kidney for disorders. TRUS allows seminal vesicle aspiration, contrast injection, and drainage of obstructing utricular cysts [11].

Screening

Screening has goals different from those in case finding. In screening, the goal is not detection of prostate cancer but rather an improvement of population health – i.e. does the suggested screening and subsequent management maneuvre result in a healthier population? In published series, ultrasound detects more cancer than digital rectal examination (DRE). Lee reported a cancer detection rate of 2.8% [15]. TRUS detected tumors in 2.6% of men and of these 77% were under 1.5 cm diameter (considered likely curable). DRE alone found 1.3% of which 41% were under 1.5 cm. Of those undergoing surgery, only 17% were pathologically upstaged to more extensive tumors extending outside the prostate. These findings contrast with screening studies using only DRE where cancer detection ranges from 1.8–2.2%. In these DRE series, initially 68–80% were considered curable only to be 'upstaged' at pathology in 50–60%. It is generally accepted that TRUS can find more cancer and at an earlier stage but we have not established whether this will result in better outcomes.

Currently an increasing number of men are being screened for cancer using a combination of DRE and PSA as suggested by Catalona and Labrie [18, 19]. We find that TRUS is most helpful in the further evaluation of those with palpable nodules or elevated prostate-specific antigen (PSA].

Summary

TRUS can be recommended for prostate cancer diagnosis and biopsy; for prostate-volume determination which allows rational interpretation of PSA; and for guiding prostate manipulations such as hyperthermia.

It is moderately useful in cancer staging and in infertility evaluation.

It is not especially helpful in evaluating clinical significance of BPH.

Whether to use TRUS for cancer screening is controversial. Currently TRUS is probably best employed as the diagnostic test when other screening tests such as DRE and PSA are abnormal.

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CHAPTER 54

Transurethral prostatectomy

WINSTON K. MEBUST

Transurethral prostatectomy is the treatment of choice for bladder-outlet obstruction, secondary to benign prostatic hypertrophy. Today, approximately 90% of patients with an obstructing prostate will have a TURP. Over 400,000 are done each year at a cost of approximately 3 to 4 billion. It is the second most common operation in the Medicare age group, second only to cataract surgery. Any alternatives, either medical or surgical, will have to be compared to TURP.

In the United States and throughout the world, TURP is the most common operation for BPH. It was not accepted by urologists until the 1960s. Its evolution began in the early 1800s when physicians blindly inserted a cutting blade into the bladder-neck to incise the prostatic tissue but was abandoned because of significant bleeding and morbidity.

According to Nesbit [8], three inventions were responsible for the renewed interest in TURP. First, Edison's development of the incandescent lamp in 1879 permitted good visualization of the prostate thus improving the precision of transurethral surgery. DeForest's invention of the vacuum tube provided a sustained high-frequency current that could cut tissue. Subsequently, Young developed the fenestrated transurethral tube, which would carry the electrosurgical equipment needed for the resection. In the 1930s, McCarthy put these various modalities together in the modern resectoscope.

Initially the procedure was associated with significant morbidity and mortality. However, as surgeons gained experience and the equipment improved, the mortality rate was reduced from 2.5%, as reported by Holtgrewe and Valk [3] in 1961, to less than 0.2% in 1989, as reported by Mebust *et al.* [5]. The morbidity remained the same (18%) as in 1961 [3], 1974 [6] and 1989 [5]. However, the morbidity in the last study did not significantly prolong hospital stay, and the criteria for morbidity was 'any happening other than an uneventful course, be it minor or major'.

Urologists consider, as absolute, many indications for intervention in patients with obstructing benign prostatic hypertrophy. They include refractory urinary retention, recurrent urinary-tract infections, recurrent bleeding, bladder calculi and renal insufficiency, secondary to an obstructing prostate.

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Table I. Indications for prostatectomy and combination of operative indications

	No.	(%)
Indications for prostatectomy		
Symptoms of prostatism	3522	(90.7)
Significant residual urine	1336	(34.4)
Urinary retention, acute	1053	(27.1)
Recurrent urinary infection	479	(12.3)
Hematuria	465	(12.0)
Altered urodynamic function	385	(9.9)
Renal insufficiency	176	(4.5)
Bladder stones	116	(3.0)
Combination of Operative Indications		
Symptoms of prostatism only	1145	(29.5)
Prostatism, residual urine	577	(14.9)
Prostatism, acute retention	372	(9.6)
Prostatism, acute retention and residual urine	217	(5.6)

However, symptoms of prostatism are the most common reason for seeking medical attention for an obstructing prostate. Arbitrarily these have been divided into obstructive symptoms, such as a weak stream, hesitancy, having to forcefully push to void, etc. and bladder irritation, including urinary frequency, urgency and nocturia. This complex of symptoms, obstructive and irritative, has been termed 'prostatism'. In the Mebust [5] study, 90% of patients, who underwent surgery, had symptoms of prostatism. However, 70% had more than one indication, such as urinary retention, residual urine, recurrent infection, etc. (Table I).

Table II lists the preoperative evaluation, including laboratory and X-ray tests. Intravenous pyelogram was done in 58% of patients. Recently, a panel established by the Agency for Health Care Policy and Research (AHCPR) developed guidelines for the diagnosis and management of benign prostatic hypertrophy. They believed that upper-tract imaging should be reserved for those who have a history of hematuria, recurrent infections, stone disease, azotemia or prior urologic surgery. It should not be done routinely. Also in Table II, from the Mebust study, are the indications for upper tract imaging. As one can see in most of the patients upper-tract imaging was a routine, so restricting the indications for upper tract imaging to those suggested by the AHCPR panel could reduce costs significantly.

Also, office cystoscopy is not used routinely to evaluate a patient with straightforward symptoms of prostatism. All patients have cystoscopy immediately before undergoing TUR-P. Office cystoscopy should be reserved for those in whom the diagnosis is unclear or the surgeon needs to know something about the anatomy of the patient's prostate and to advise concerning the appropriate procedure, medical or surgical for him (Table II). While residual urine is common in prostatism, there is no consensus concerning the level of residual urine beyond which bladder damage will be irreparable.

Table II. Preoperative evaluation (Laboratory and X-ray tests)

CBC	97%
UA	92%
Bleeding studies	68%
Chemistry profile	90%
Chest X-ray	85%
EKG	91%
Imaging studies	
IVP	58%
Renal sonogram	6%
KUB	7%
Prostate sonogram	0.7%
IVP indications	
Total patients with IVP – 2246	
History of hematuria – 311	14%
History of stones – 77	3.4%
History of infection – 285	13%
Therefore, the majority of intravenous pyelograms were done routinely.	
Additional preoperative evaluation	
Office cystoscopy	25%
Urodynamic studies	13%
Urine culture & sensitivity	60%
positive	11%
negative	49%

Nevertheless, for many years urologists have used residual urine to follow their patients and determine if they are developing bladder decompensation.

In the Mebust [5] study, 77% of patients had previous medical problems – chiefly pulmonary and gastrointestinal disease and myocardial infarction. However, typically TUR-P did not exacerbate the underlying condition. About 11% had pre-existing infection and another 60% were given prophylactic antibiotics. A total of 10% were known to have prostate cancer and in another 10% cancer was discovered.

The average weight of the resected prostate was 22 grams and the average resection time was 57 minutes. However, there was no correlation between the amount of prostate resected and the degree of obstructive or irritative symptoms. The average age was 69. In 1961, in a study of 2015 men, Holtgrewe and Valk [3] also noted that the average tissue resected was 22 grams and the average age, was 69 years, which suggests that the indications for surgical intervention in symptomatic BPH has not changed significantly over the last 30 years.

In the Mebust [5] study, 7% of patients had intraoperative complications, the most common being bleeding (2.5%) (Table III). In those patients, bleeding was defined as 'the need for transfusion' but of those requiring transfusions, 80% required two units of blood or less. The second most

Table III. Complications

Intraoperative complications	
Overall rate	6.9%
Bleeding	2.5%
TUR syndrome	2%
Arrhythmias	1.1%
Extravasation	0.9%
Postoperative complications	
Overall rate	18%
Most common	
Failure to void	6.5%
Bleeding	3.9%
Clot retention	3.4%
Urinary infection	2.3%

Table IV. Mortality

Year			Cause	Rate
1989	Mebust *et al.*	5/9	Sepsis	0.2%
1974	Melchior *et al.*	15/30	MI	1.3%
1961	Holtgrewe *et al.*	18/51	MI	2.4%

common complication was dilutional hyponatremia – the TUR syndrome. Most of these patients were managed with diuretics during the operation and occasionally with hypertonic saline after the operation.

Eighteen percent had postoperative complications (Table III) but, as noted previously, these did not prolong hospital stay significantly. The most common was failure to void (6.5%) secondary to a hypotonic bladder. Bleeding occurred in 3.9% but again, most of these patients required two or less units of blood.

In his series, the mortality rate was 0.2% (Table IV); the most common cause was sepsis in patients with multisystem disease, who were extremely debilitated. This contrasts with the mortality rate noted by Holtgrewe [3] (2.4% in 1961) and Melchion [6] (1.3% in 1974); in these studies the most common cause of death was myocardial infarction.

Concerning risk factors for the operation, intraoperative bleeding was significantly increased in patients who required a resection time over 90 minutes and when the glands were heavier than 45 grams. Patients presenting with acute retention more commonly failed to void postoperatively than those who did not present with acute retention. Those with decreased renal function, i.e. a serum creatinine greater than 1.5 mg% or who were over age 80 also had a higher morbidity rate. In the Mebust study the mortality rate was so low that these risk factors had no apparent influence on mortality (Table V) [5].

Table V. Risk factors identified

Black population
Acute urinary retention
Gland over 45 grams
Prolonged resection time over 90 minutes
Decreased renal function
Age over 80

The nature and consequence of the morbidities associated wiht TUR-P have changed. As noted in the 1989 study, morbidity was defined as 'anything other than a perfect postoperative course' [5]. However, in the current study, as compared to the 1961 study, pyelonephritis was not a problem and typically morbidity did not seem to prolong hospital stay. The patients remained catheterized for a shorter period and were discharged earlier in the Mebust study.

Following hospitalization, we noted other complications with transurethral prostatectomy. Approximately 0.5% of patients had incontinence which can be secondary to bladder hyperreflexia, injury to the external sphincter mechanism or combination of the two. While postoperative incontinence is quite rare, it is a risk of the surgical procedure.

Sexual dysfunction may follow transurethral resection. However, we understand little about its etiology or its prevention. To a certain extent impotence is a subjective complaint on the patient's part. Approximately 50% of men undergoing transurethral resection may have retrograde ejaculation and may confuse this with impotence. In the literature, the incidence of postoperative sexual dysfunction ranges from 4% to 40%. However, in the Mebust [5] study, in 1000 cases with adequate data, approximately 13% experienced postoperative sexual dysfunction. The risk of such dysfunction probably is somewhere between 5% to 10%.

The longterm outcome of TURP is unknown, chiefly because patients have not been followed systematically for long periods. In a small series, Ball [1] found that such patients maintained a good urinary flow rate for at least five years. In another study, Meyhoff [7] noted that irritative bladder symptoms became apparent after five years and about 7% of patients required repeat transurethral resection. In a series followed for three years, Bruskewitz *et al.* [2] reported a re-operation rate of approximately 12%, but many were secondary to vesical-neck contracture and only a small percentage secondary to prostatic regrowth. In 1989, Roos, Wennberg and others [4, 9, 10] reported outcome based on insurance claims data, which suggested that, as compared to open prostatectomy, TURP was associated with a higher late mortality rate and a higher re-operation rate. The 90-day mortality rate reported by them was 2.5%. The re-operation rate was as high as 2.5% per year, a rate that is significantly higher than that associated with open prostatectomy. These findings were totally unexpected. Previously reported

re-operations rates and mortality figures were based on 30-day postoperative data.

There is no intrinsic reason why minimally invasive procedures, such as TUR-P, should have a higher mortality rate than an open procedure. Many urologists have concluded that the observed difference must be related to patient-selection criteria because it is logical to assume that patients with compromised health would be offered the less invasive procedure (TURP).

To answer this question, it will be necessary to carry out a prolonged randomized study comparing TURP to other methods of therapy. The American Urological Association is initiating a national prospective study to compare open prostatectomy with TURP and to investigate some of the emerging alternatives, such as balloon dilatation, alpha blockers, etc.

We cannot determine the cause of the higher re-operation rate following TURP from the insurance claims data. Obviously, as reported by Bruskewitz [2], patients may have vesical-neck contractures, a scarring procedure that can occur following surgery. Urethral strictures may require repeat operation. Finally, the initial operation may have been inadequate. Again to determine the probable incidence of re-operation following TURP, we need a national co-operative prospective study.

In summary, transurethral prostatectomy is 'the gold standard' against which other modes of therapy must be compared. The AHCPR BPH Panel noted that, when comparing TURP to other modalities, the former resulted in a significant reduction in symptoms, a reduction that was significantly greater than that achieved by other modalities of therapy. Concerning objective measures such as maximum flow rates, TURP compared to other modalities produced greater improvement.

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CHAPTER 55

Benign prostatic hyperplasia: pathogenesis and the role of medical management

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Etiology of BPH – the role of sex steroids

Two factors, critical for the development of benign prostatic hyperplasia (BPH), are androgen production by the testes and aging. A classic study by White in 1895 showed that removal of the testes by castration resulted in rapid atrophy of the prostate in 87% of 111 men, with 58% experiencing relief of symptoms of outflow-tract obstruction [1]. Also, Cabot in 1896, demonstrated substantial improvement of obstructive symptoms following castration in 84% of 61 men with presumed BPH; approximately 45% were relieved of urinary retention [2]. It has been known for years that men with gonadotrophin deficiency and men castrated before puberty do not develop BPH [3]. Also, only two cases of BPH have been reported in men castrated before the age of 40 [4, 5]. Thus, these clinical observations strongly suggest that androgen production by the testes plays a major role in the development of BPH in man.

Two major androgens are present in the male: testosterone, a major secretory product of the testes, and dihydrotestosterone, a product mainly of the peripheral conversion of testosterone.

Until the 1960s, testosterone was believed to be the only physiologically important male hormone. However, it was known that, in bioassay systems, 5α-dihydrotestosterone, a metabolite of testosterone, is at least twice as potent as testosterone. Later, a series of studies in rat, rabbit, and human fetuses measured dihydrotestosterone formation in the anlage of the internal and external genitalia at the time of differentiation, between the 8th and 14th weeks of gestation [6, 7]. These studies found that 5α-reductase activity and consequently dihydrotestosterone formation was extremely high in the area of the urogenital sinus, which gives rise to the prostate; the urogenital swellings, which become the scrotum; and the urogenital tubercule, which becomes the phallus. In distinction, at the time of sexual differentation 5α-reductase enzyme activity was not present in the Wolffian ductal anlage, which gives rise to the vas deferens, epididymides and seminal vesicles. Thus, it was postulated that testosterone and dihydrotestosterone have distinct

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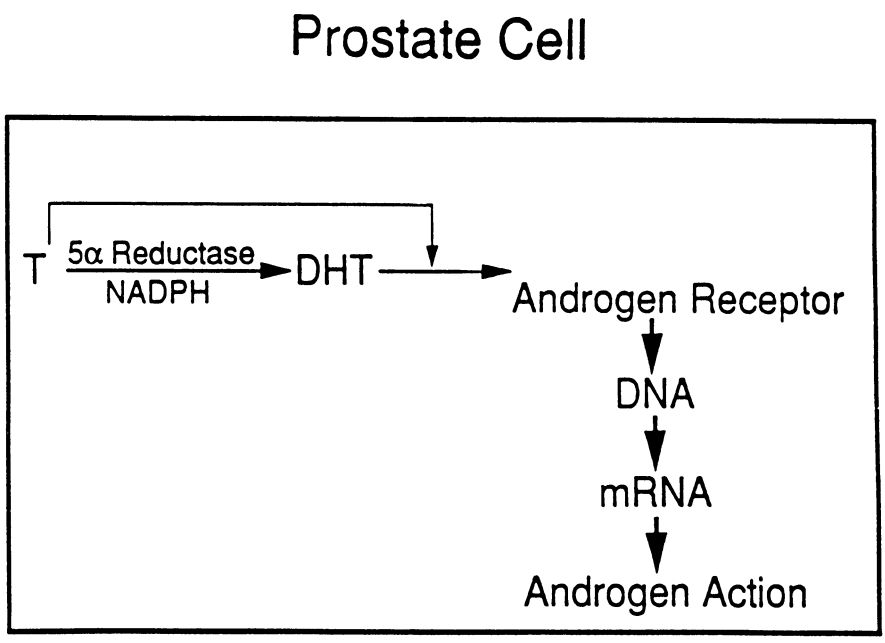

Fig. 1. Intracellular testosterone (T) is reduced by the enzyme 5α-reductase to dihyrotestosterone (DHT). DHT binds to the androgen receptor. The resulting androgen-receptor complex binds to DNA initiating mRNA synthesis and further translation into protein, resulting in different androgenic effects depending upon the tissue involved.

roles in male sexual differentiation. Dihydrotestosterone mediates prostate and external-genital development, and testosterone mediates differentiation of the epididymides, vas deferens and seminal vesicles.

In the prostate, testosterone passively diffuses into the cell where it is reduced by the microsomal enzyme 5α-reductase to dihydrotestosterone. In the adult male, dihydrotestosterone (DHT), as 90% of total prostatic androgen, is the major intracellular androgenic metabolite within the prostate [8]. Testosterone (T) and DHT bind to the same high-affinity-androgen receptor protein. The prostate androgen receptor, however, has five times greater affinity for DHT than T, and a decreased dissociation constant for the receptor as compared to T [8–10]. DHT receptor complex binds to specific DNA sites in the nucleus, which results in increased transcription and, ultimately, stimulation of protein synthesis (Fig. 1).

Two related human DNAs have been isolated that encode two 5α-reductase isozymes which differ in biochemical, pharmacological, and genetic properties. The two enzymes share a sequence identity of 50% [11]. The type 1 isoenzyme is encoded on chromosome 5 and has a basic pH optimum. It is expressed at low levels in male sexual tissues such as prostate, and is relatively insensitive to the 4-azasteroid 5α-reductase inhibitor, finasteride [Proscar, 17β-(*N*-tert-butyl)carbamoyl-4-aza-5α-androst-1-en-3-one] [11–14].

The type 2 isoenzyme is encoded on chromosome 2. It has an acidic pH optimum, is expressed at high levels in the prostate, and is sensitive to finasteride inhibition [11, 14]. The type 1 gene has been excluded as the disease locus in male pseudohermaphrodites with inherited 5α-reductase deficiency [14].

As will be discussed later in this paper, strong clinical evidence for the role of DHT in prostate differentiation and growth is derived from studies of male pseudohermaphrodites with inherited 5α-reductase-deficiency type 2 and decreased dihydrotestosterone production. Despite the fact that their testosterone levels are normal to elevated, affected subjects have nonpalpable or barely palpable prostates on rectal exam or transrectal sonography [15, 16].

Animal studies

Experimental studies in the beagle provide support for the role of DHT in the pathogenesis of BPH. In early experiments, castrated dogs treated with DHT developed histologic evidence of BPH, but the prostatic weights were not equal to those in dogs with spontaneous BPH [17]. Subsequent studies, however, with higher doses of DHT or with androstanediol, which is metabolized to DHT in the prostate, produced both histologic and gross evidence of BPH in the beagle [18–20].

In spontaneous canine BPH, initially workers found an increase in prostatic DHT concentration [21]. However, subsequent studies found no difference in DHT content between dogs with normal prostates and those with spontaneous BPH [22]. Also it was interesting that the DHT content in the prostate decreased in beagles after age 4 years, while the incidence of BPH continued to increase [22]. These findings suggest that, in the beagle, the disease once initiated continued despite lower DHT levels. A possible reason for this continued growth is the increased androgen receptors in the prostate reported in beagles with this condition [23], which could result in increased sensitivity to DHT. Another theoretical possibility is that other regulatory factors triggered by DHT contribute to the evolution of BPH in the dog.

Studies in humans

Recent data suggests that the DHT content in human BPH tissue is identical to normal tissue [24], although previous studies reported it to be higher [25]. 5α-Reductase activity is present in both epithelial and stromal tissue [26], although there is a significantly increased V_{max} and K_m value in stromal 5α-reductase compared to epithelial 5α-reductase, suggesting that the various histologic areas of the prostate and elsewhere throughout the body may contain multiple 5α-reductase isoenzymes [26].

Also androgen receptors are present both in epithelial and in stromal cells of the prostate, although initial data was contradictory concerning the presence of androgen receptors in the stroma [27–29]. It has been postulated that the maintenance of androgen receptors in the aging prostate permits androgen-dependent prostate growth in the presence of normal levels of prostatic DHT [30].

In humans, there may be a possible role for estrogen/androgen synergism in the development of BPH. In advanced age, total plasma-testosterone levels decline while estrogen levels remain the same, thereby altering the estrogen (E) to testosterone (T) ratio [31, 32]. However, since the T/E2 ratio changes in later years, it is unlikely to play a role in the initiation of BPH, but may contribute to its perpetuation [30]. However, a recent study demonstrated a correlation between the higher free plasma T and estrogen levels and larger BPH prostates when corrected for age. Confusing the issue, however, is data demonstrating that estrogen receptor levels are significantly lower in BPH than in the normal prostate [33]. When administered to humans or dogs, estrogen alone does not produce the same histology as is seen in normally occurring BPH. Significant squamous metaplasia occurs in the urethra and ducts of the prostate, which is not found in spontaneously occurring BPH [19].

A possible factor underlying the development of BPH is stromal-epithelial interactions. McNeal [34] suggests that BPH results from a 'reawakening' of the embryonic interactions between the stromal and epithelial cells, as has been shown elegantly by Cunha *et al.* [35]. As in the developing embryo, it can be postulated that the stromal cells of the BPH prostate have retained the ability to induce the growth and development of epithelial cells. Thus, under the influence of dihydrotestosterone, probably through the androgen-mediated release of growth factors, BPH develops [36].

Medical therapy of BPH

Urinary outflow obstruction in BPH consists of both static and dynamic components [37]. The static component is due to mechanical obstruction of the urethra by the hyperplastic prostate tissue, which produces urethral narrowing and obstruction of urine flow. The dynamic component is said to be secondary to increased prostatic α-1 adrenergic muscle tone. While there are few α-1 adrenergic receptors in the bladder, they are abundant in the prostatic capsule, prostate adenomatous tissue and the bladder neck [38, 39].

Medical therapy for BPH, therefore, is directed towards: (1) Relieving the static component induced by the physical enlargement of the prostate, and (2) relaxing the increase in prostatic muscle tone and bladder neck, which is under the control of α-1 adrenergic sympathetic nervous system.

The remainder of this paper will discuss the treatment of the static component of BPH with a selective 5α-reductase inhibitor.

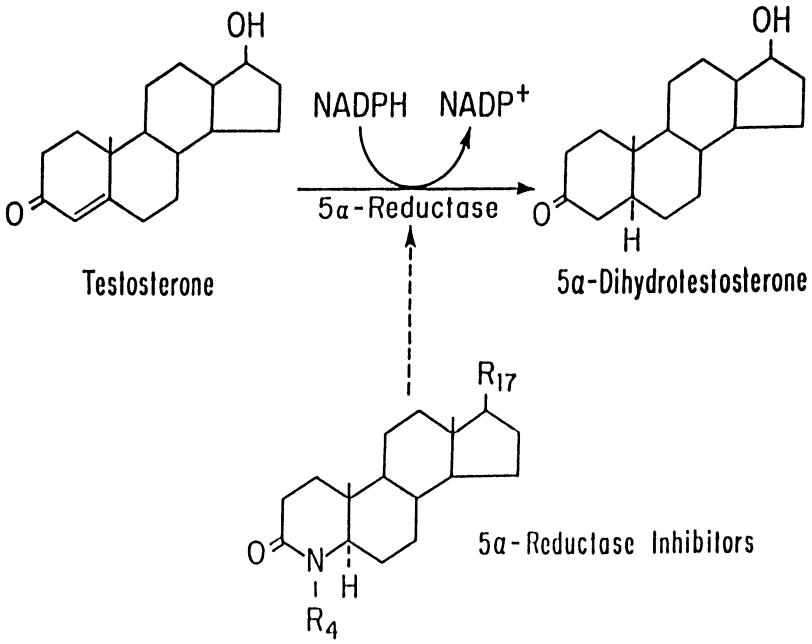

Fig. 2. 5α-Reductase inhibitors competitively inhibit the enzyme 5α-reductase preventing the conversion of T to DHT.

5α-Reductase inhibition therapy

A unique and novel approach to treatment of BPH developed partly as a consequence of studying subjects with hereditary 5α-reductase deficiency. This human model of 5α-reductase deficiency highlighted the importance of DHT in the growth and development of the prostate. The enzyme defect is inherited as an autosomal recessive trait. Affected males are born with severe ambiguity of the external genitalia and most have pseudovaginal perineoscrotal hypospadias. The patients virilize at puberty, but they have decreased facial and body hair and no gynecomastia. They do not develop baldness. It is of particular importance that the prostate is not palpable on rectal exam. Transrectal sonography reveals a small rudimentary prostate [40]. Patients state that they have a normal libido, suggesting that DHT deficiency has a major impact on prostate growth and development without significant effect on libido [15, 41–44]. Also, male-pattern baldness, acne and hirsutism in women may be dependent on a critical level of DHT.

Clinical trials are in progress with the 5α-reductase inhibitor, finasteride, a drug belonging to a class of azasteroid compounds that has been demonstrated to be potent competitive inhibitor of the enzyme 5α-reductase and consequently of dihydrotestosterone production (Fig. 2). The effectiveness of azasteroid 5α-reductase inhibitors first was demonstrated with the parent

compound 4M. Significant inhibition of the conversion of testosterone to dihydrotestosterone was demonstrated in acute studies with rat prostate and liver to dihydrotestosterone [45–47]. 4MA was also found to inhibit 5α-reductase activity and DHT formation in fibroblasts cultured from human foreskin [47]. Inhibition of prostate growth and regression of prostate size was demonstrated in long-term studies with 4MA in rats [45] and dogs [48–50].

Also other azasteroid 5α-reductase inhibitors were demonstrated to inhibit the formation of DHT in the developing male rat fetus, resulting in genital ambiguity and impairment of prostate differentiation [51]. Although male rats treated *in utero* had some prostatic differentiation [51], the number of developing prostatic buds was decreased significantly [52].

While 4MA was shown to have moderate affinity for the androgen receptor, other analogs, such as finasteride (MK906, Proscar) are pure 5α-reductase inhibitors that have virtually no affinity for the androgen receptor [53]. Finasteride possesses no androgenic, estrogenic, or progestational properties.

Finasteride was demonstrated to decrease plasma DHT levels in humans by approximately 45% at a dose as low as 0.2 mg/day for 3 or 6 months [54]. Although not statistically significant when compared to post-treatment placebo control levels, mean plasma testosterone levels tend to rise with increasing doses of finasteride [54]. The lack of a clinically significant change in circulating testosterone correlates with the lack of a clinically significant change in baseline LH levels in finasteride-treated subjects over 3 to 6 months. Thus, it is likely that finasteride does not cross the blood-brain barrier to a significant degree to inhibit 5α-reductase activity and decrease dihydrotestosterone formation, thereby preventing a compensatory rise in serum LH. This finding differs from that observed in the inherited condition where LH levels are elevated substantially [55].

The urinary 5β/5α C19 and C21-steroid metabolites are elevated in finasteride-treated subjects: a pattern similar to the inherited disease. There is a dose-related increase in the 5β/5α ratios of the urinary metabolites – etiocholanolone (5β)/androsterone (5α) – and the 5β/5α ratios of cortisol and corticosterone. With the greater doses of finasteride, the 5β/5α metabolite ratios are much higher than those found in subjects with the inherited condition [55].

Skin and other peripheral tissues have only 5α-reductase activity. In the liver, however, both 5α- and 5β-reductases are present. Urinary 5β/5α metabolite ratios, therefore, are an expression of both peripheral and hepatic metabolism. Thus, it can be concluded that the decrease in 5α-reductase activity secondary to the 5α-reductase inhibitor, finasteride, appears to be global affecting both C19 and C21 5α-reduction, and involving both hepatic and peripheral metabolism. The biochemical profile of finasteride, therefore, mimics that of the inherited disease.

Following one week of 50–100 mg/day of finasteride administered to men with BPH before TURP, prostate-tissue DHT concentration declined to

almost one-tenth of that found in subjects receiving placebo. Tissue levels of DHT were similar to levels found in prostate tissue following castration or LHRH administration [56].

Results of a one-year, open, extension study following a double-blind, placebo-controlled, 3 month, phase II study demonstrated an approximate 30% decrease in prostate volume as compared to original baseline volumes. This change was associated with a ≥ 3 ml/sec increase in maximum urinary flow in almost 70% of the subjects whose baseline flow rates were less than 15 ml/sec. Overall, the maximum urinary flow increased an average of 4.0 ml/sec by month 12. Finasteride demonstrated an excellent safety profile. Seven patients reported serious adverse experiences, but none were considered drug related [57].

Stoner has reported more recent Phase-III results from two, parallel randomized, double-blind placebo-controlled studies of 12 month duration [58]. A total of 1645 men with BPH were enrolled in two multicenter studies (North America and Europe). In this enormous study, almost one-half of the patients on finasteride had at least a 20% decrease in prostate volume as measured by magnetic resonance imaging or transrectal ultrasound, as compared to an approximate 3% decrease in prostate volume in patients receiving placebo. About one-third of treated patients had a 3 ml/sec or more increase in the maximum urinary flow rate at the end of treatment.

A smaller study of longer duration suggests that decrease in prostate size persists [59]. Seventeen patients completing 24 months of finasteride (5 mg/day) in an open study after a 6-month, double-blind, placebo-controlled study had a mean percent decrease in prostate size of approximately 30% [59]. Of 5 patients completing 30 months of treatment, the mean percent decrease in prostate size was 34% [59].

The incidence of impotence was low and no significant side effects were evident.

Summary

As the proportion of men in our society over 65 years of age continues to increase, so does the number of them with symptomatic benign prostatic hyperplasia. At present, the treatment of BPH is surgical resection of the prostate, yet interest in developing a medical therapy is exceedingly high.

As has been discussed, DHT plays an important role in the development of the prostate. Also, DHT appears to have a significant role in the development of BPH. Thus, the investigation of 5α-reductase inhibitors in the treatment of BPH has a rational basis. The first 5α-reductase inhibitor to be used in clinical trials, finasteride, decreased circulating and prostatic DHT levels. Further, clinical trials have demonstrated significant shrinkage of the prostate and an associated increase in urinary flow rates, without significant side-

effects. Therefore, finasteride, and 5α-reductase inhibitors in general, will likely prove to be effective therapy for BPH.

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CHAPTER 56

Alpha blockade in the therapy of benign prostatic hyperplasia

HERBERT LEPOR

Rationale for the use of alpha antagonists in BPH

Recently Shapiro *et al.* developed a technique for quantifying the cellular elements of the prostate that applies double immunoenzymatic staining and color-assisted, computer-image analysis [1]. The epithelium and smooth muscle were labeled with rabbit antidesmin and a mouse antihuman prostatic acid phosphatase (PSAP), respectively. Originally the area densities of the organ's cellular elements were determined from eight transrectal, guided biopsy specimens obtained from males with clinical BPH. The area densities of smooth muscle, connective tissue, epithelium, and glandular lumen were $22 \pm 4\%$, $54 \pm 4\%$, $16 \pm 6\%$, and $9 \pm 1\%$, respectively. Overall, the ratio of stroma:epithelium was 4.8. Shapiro *et al* found that mouse antiactin is a more sensitive label for prostate smooth muscle than rabbit antidesmin [2]. Double immunoenzymatic staining was done on 19 transrectal biopsy specimens from males with clinical BPH, using both mouse antiactin/rabbit anithuman PSAPP and rabbit antidesmin/mouse antihuman PSAPP. The area densities of smooth muscle, connective tissue, epithelium, and glandular lumen in the antiactin/antihuman, PSAP-stained tissues were $39 \pm 3\%$, $38 \pm 3\%$, $12 \pm 1\%$, and $11 \pm 1\%$ respectively. These morphometric studies demonstrated that BPH primarily is smooth-muscle and connective-tissue hyperplasia.

Raz *et al.* [3] were the first to study the physiology and pharmacology of prostate smooth muscle. Their isometric tension studies demonstrated that the rat prostate contracts in the presence of norepinephrine, an adrenergic agonist. Subsequently Caine and associates demonstrated that the human prostate adenoma and capsule also contract in the presence of norepinephrine [4]. Caine recognized the therapeutic implications of pharmacologically altering the tension of prostate smooth muscle in males with symptomatic BPH [5]. *In vitro*, isometric tension studies showed that the contractile properties of human prostate adenomas are mediated primarily by alpha$_1$ adrenoceptors [6–8]. Radioligand, receptor-binding studies have shown that the human prostate contains a relative abundance of alpha$_1$ adrenoceptors [9, 10]. Based

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Table I. Alpha Blockers evaluated for therapy of BPH

Nonselective alpha blockers
Phenoxybenzamine
Selective Alpha$_1$ blockers
Prazosin
Alfuzosin
YM617
Indoramin
Selective long-acting alpha$_1$ blockers
Terazosin
Cardura

upon these physiological and pharmacological observations, it was postulated that alpha$_1$ adrenergic blockers should decrease the resistance along the prostatic urethra by relaxing the organ's smooth muscle component. Presumably selective alpha$_1$ blockade is effective in BPH because it relaxes prostatic smooth muscle. Therefore it follows that the magnitude of the clinical response to selective alpha$_1$ blockade in BPH would be directly related to the proportion of the hyperplasia that is smooth muscle. Recently Shapiro *et al.* [11] examined the relationship between the percentage area density of prostate smooth muscle in the adenoma and the clinical response to terazosin, a selective alpha$_1$ blocker and observed a direct relationship between the increase in urinary flow rate and the percent area density of smooth muscle. The direct relationship between smooth-muscle content and clinical response strongly supports the hypotheses that the development of bladder-outlet obstruction is mediated by prostate smooth-muscle relaxation.

Alpha blockage in BPH: Summary of the literature

In 1976 Caine reported that phenoxybenzamine, a nonselective alpha$_1$ blocker, was effective in the treatment of BPH [5]. Over the past 15 years, alpha blockade in the treatment of BPH has been evaluated in at least 30 clinical trials [5, 12–37]. Most of these studies were deficient in design: sample sizes were small, treatment periods were short, and criteria for enrollment and assessment of efficacy were not well defined. Twenty-seven of the 30 clinical trials confirmed Cain's observation that alpha blockers were effective in the treatment of BPH.

The alpha blockers administered in the BPH studies can be subgrouped according to receptor subtype selectivity and duration of half-life (Table I). Phenoxybenzamine antagonizes alpha$_1$ and alpha$_2$ adrenoceptors whereas prazosin, alfuzosin, YM617, indoramin, and terazosin are selective alpha$_1$ antagonists. Selective alpha$_1$ antagonists have a lower incidence and severity of adverse events than do the non-selective alpha blockers. Terazosin, the

Table II. Outcome of alpha blockers in BPH

Alpha Blockers	# Subjects Evaluated	% Subjects Improved	%ΔSymptom Score
Nonselective	333	75%	–
Selective alpha$_1$	863	82%	–
Selective long-acting alpha$_1$	399	93%	–49%

only long-acting formulation that has been studied in BPH, has a longer half-life, which allows for a once-a-day dose and probably improves compliance. The most common adverse events associated with selective alpha$_1$ blockers include dizziness, light headedness, and asthenia. A once-a-day formulation taken at bedtime reduces the incidence and severity of these symptoms. Cardura, another long-acting selective alpha$_1$ blocker, is being investigated for its value in BPH, but here there are no published data concerning its safety or effectiveness. There is as yet no agreed definition of effectiveness as it relates to BPH therapy. Since there exist no universal guidelines for reporting such effectiveness, studies in the literature have used highly variable measures to ascertain outcomes following alpha blockade. Most of the reported clinical trials exclude subjects with absolute indications for intervention such as urinary retention, urinary-tract infection, and renal insufficiency. Therefore, clinical studies have used relief of symptoms as their primary outcome measure. Nine clinical trials used symptom improvement that was ascertained using a quantitative symptom index. Ten clinical trials evaluated the subjects' self-assessment of improvement. Although objective symptom indices were established in the 1970s, these instruments were used to ascertain clinical response only sporadically in BPH clinical trials. Now symptom indices are used routinely to assess symptom improvement. All of the reported clinical trials evaluating terazosin used the Boyarsky symptom index. Overall, the mean improvement in the total symptom score was 49%. Historically, subjective improvement often was graded by the patient's self assessment. Subjects rated the level of improvement (marked, moderate, or slight) or simply indicated whether or not they had improved. A limitation of many of these subjective self-assessments is that 'slight' improvement may not represent a clinically significant outcome. The percentage of subjects, who had any degree of symptom improvement following administration of a non-selective, selective alpha$_1$ or selective long acting alpha$_1$ blocker was 75%, 82%, and 93%, respectively. The available clinical data indicates that the relief of symptoms is similar in the three groups of alpha blockers (Table II).

Uroflowmetry has been used to assess the effectiveness of BPH therapy. Although this procedure may reflect the degree of obstruction along the prostatic urethra, the outcome measure is of limited clinical significance. The change in maximum urinary flow rate (φ_{max}) was reported in 24 of the alpha

Table III. Outcome of alpha blockers in BPH

Alpha blockers	# Subjects Evaluated	$\%\Delta Q_{max}$
Nonselective	333	+41%
Selective alpha$_1$	863	+47%
Selective long-acting alpha$_1$	399	+44%

blocker studies. The mean improvement in φ_{max} following a non-selective, selective alpha$_1$ and selective long acting alpha$_1$ blockers was 41%, 47%, and 44%, respectively. The clinical data suggests that the improvement in urinary flow rate is similar for the three groups of alpha blockers (Table III). The next section will present detailed review of representative randomized, placebo controlled studies to illustrate the safety and efficacy of alpha blockers in the therapy of BPH.

Randomized placebo-controlled studies

Phenoxybenzamine

Caine *et al.* described a placebo-controlled, double-blind study of phenoxybenzamine in benign prostatic obstruction. Fifty patients with BPH received 10 mg of phenoxybenzamine or placebo twice a day. The clinical trial lasted only 14 days, and 49 patients completed the trial. The assessment of efficacy was based on improvement in urinary flow rates. In the phenoxybenamine and placebo groups, maximum urinary flow improved 82% and 30%, respectively. There was a significantly greater improvement in daytime and nighttime urinary frequency among the phenoxybenzamine-treated patients. The drug's primary limitation was the incidence and severity of adverse reactions. Eleven patients reported tiredness, dizziness, impaired ejaculation, nasal stuffiness, or difficulty with visual accommodation. A single adverse reaction was observed in the placebo group. Caine's study demonstrated the therapeutic advantage of phenoxybenzamine over placebo. However this study did not establish specific entry parameters, was of short duration, and the assessment of symptomatic outcome was qualitative.

Prazosin

Kirby *et al.* [24] described a randomized, placebo-controlled study to evaluate prazosin in the treatment of prostatic obstruction. Eight men with BPH between the ages of 50 and 80 years received 2 mg of prazosin or placebo twice a day. Only 55 patients completed the one month clinical trial. Assess-

ment of efficacy was based on improvement in urinary flow rates, frequency of micturition, and postvoid residual volume. The peak urinary flow rate improved 59% and 6% in the prazosin and placebo-treated groups, respectively. There was a statistically significant improvement in residual urine and voiding frequency in the prazosin-treated group. This group had no adverse reactions whereas one subject receiving placebo complained of dizziness and diarrhea. Neither group reported orthostatic hypotension and erectile or ejaculatory dysfunction. Kirby's study gave an unequivocal demonstration of therapeutic advantage of prazosin over placebo. The pitfalls of the study were the large drop-out rate (32%), its short follow-up, and the lack of specific entry criteria.

Terazosin

Recently Lepor *et al.* reported a multicenter, Phase III, double-blind, parallel group, randomized placebo-controlled study of once-a-day terazosin to patients with symptomatic BPH [38]. Three hundred and fourteen patients entered the double-blind treatment with placebo, 2, 5, or 10 mg terazosin once daily. All terazosin groups had statistically significant ($p < 0.05$) decreases from baseline obstructive, irritative, and total symptom scores. The 10 mg groups also had significantly greater decreases in irritative and total scores. The 5 and 10 mg groups had a significantly greater decrease in obstructive scores relative to the placebo group. The level of improvements in the symptom scores was dose-related. The percentage of patients with a more than 30% improvement in the total symptom scores for the placebo, 2, 5, and 10 mg treatment groups was 38%, 54%, 63%, and 70%, respectively. Significantly more patients in the 5 and 10 mg groups experienced a greater than 30% improvement in total symptom score than the placebo group.

All treatment groups had statistically significant improvement from baseline in the peak and mean urinary flow rates. The 10 mg group had a significantly larger increase from baseline in peak and mean urinary flow rates. The 5 mg group also had a significantly larger increase in mean urinary flow rate than the placebo group. The change in urinary flow rate was also dose-related. The percentages of patients with a greater than 30% increase in peak urinary flow rate in the placebo, 2, 5, and 10 mg treatment groups were 25%, 36%, 35% and 58%, respectively. In the 10 mg terazosin group, a significantly greater proportion of patients had a greater than 30% improvement in peak urinary flow rate.

Overall, in the four treatment groups the adverse events were minor and reversible. Although the terazosin groups had a higher incidence of asthenia, flu syndrome, and dizziness, the differences from placebo were not statistically significant using Fisher's exact test. A significantly greater incidence of postural hypotension was seen in the 5 mg terazosin group than the placebo group. One patient in the 5 mg treatment group developed syncope.

In the 10 mg group, the incidence of syncope was one out of 79 (1.3%), and in all terazosin treated patients it was less than 0.5%.

To identify clinical or urodynamic factors that would predict a favorable outcome to terazosin therapy, we examined the relationships between percentage change in total symptom score and peak urinary flow rate with baseline age, prostate size, peak urinary flow rate, mean urinary flow rate, post void residual, and total symptom score. There was no significant association between treatment effect and baseline factors using an analysis of covariance model with terms for baseline factor, treatment groups and their interaction.

Combined pharmacotherapy

Bladder outlet obstruction secondary to BPH is related to dynamic and static factors; the former reflect prostatic smooth-muscle tension and the latter are related to the enlarged prostatic adenoma encroaching upon the bladder outlet. The two different pharmacologic strategies for the treatment of BPH are based upon the present concept of outlet obstruction in BPH. Selective alpha$_1$ blockers are used to relax the prostatic smooth muscle whereas androgen suppression reduces prostate volume. Because the presumed action of alpha blockade and androgen suppression are unrelated, it is reasonable to assume that the clinical response following co-administration of these drugs is at least additive. Combination pharmacotherapy for BPH represents an attractive approach for the treatment of BPH.

Lepor and Machi [37] described an open-label, pilot study to compare selective alpha$_1$ blockade vs. the combination of selective alpha$_1$ blockade and androgen suppression. Twenty-nine males received terazosin alone for one month and the combination of 5 mg of terazosin and 250 mg of flutamide 3 times daily for the subsequent 5 months. The indices of efficacy included change in Boyarsky symptom scores, uroflowmetry, and the subjects self-assessment of symptom improvement. These indices were evaluated at 1 month (terazosin alone) and at 6 months or at the time of (early) withdrawal from the study (combination therapy). Terazosin alone was associated with statistically significant improvements in total Boyarsky symptom scores ($\downarrow$ 56%) and maximum urinary flow rate ($\uparrow$ 38%). Combination therapy produced a further reduction of 8% in total symptom scores. Twenty-five percent of subjects exhibited moderate symptom improvement following the addition of the antiandrogen. The differences in outcome between terazosin alone vs. combination therapy were not statistically significant. The failure to demonstrate a statistically significance is related to the small sample size. Most subjects in the pilot combination study developed severe adverse events to flutamide, which resulted in either dose reduction or premature withdrawal from the study. The mean reduction of prostate volume in the 24 evaluable

patients receiving combination therapy was 25% indicating that androgen suppression was adequate.

The optimal study design for evaluating drug therapy for BPH is a randomized, placebo-controlled study. I have organized a multicenter randomized, placebo-controlled study to compare four treatment groups – placebo, selective alpha$_1$ blockade, androgen suppression, and the combination of selective alpha$_1$ blockade and androgen suppression. Terazosin was selected as the alpha$_1$ blocker because dose ranging studies have demonstrated the optimal dose. Finasteride was selected for androgen suppression because this drug has a favorable toxicity profile. Thirty VA Medical Centers will enroll 1200 subjects into this study between 5/1/92 and 4/1/93 and it is anticipated that the active treatment phase of the study will be completed by 4/30/94. This study, which will be shared by Abbott Laboratories, Merck Sharp and Dome, and the Department of Veterans Affairs, will compare selective alpha$_1$ blockade and androgen suppression in a similar cohort of subjects using standard outcome measures. The relative efficacy of combination therapy will be compared to the individual monotherapies. Because it is conducted under the auspices of Veterans Affairs, this study will be free of the inherent bias associated with industry-supported research.

Conclusions

There is a definite physiologic and pharmacologic rationale for alpha blockade in the treatment of BPH. Clinical studies have confirmed Caine's initial observation that alpha blockade represents effective therapy for BPH. Randomized, placebo-controlled studies have demonstrated that the incidence and severity of adverse events associated with selective alpha$_1$ blockers are typically minor and reversible. Likely, the long-acting selective alpha$_1$ blockers such as terazosin and cardura will emerge as the preferred alpha blockers since a once-a-day regimen is likely to improve patient compliance and improve patient tolerance. The lightheadedness, dizziness, and tiredness associated with selective alpha$_1$ blockade is reduced if the drug is administered at bedtime.

The encouraging clinical database for selective alpha$_1$ blockers must be interpreted cautiously. The safety of alpha$_1$ blockers assumes that the dose is judiciously titrated and that consideration is given to potential interactions with other cardiovascular medications. The long-term effectiveness and compliance of alpha$_1$ blockade remains to be established. Symptom improvement following terazosin persisted for over 24 months. Abbott Laboratories is sponsoring long-term, open-label follow-up studies. Approximately 300 patients are to be enrolled. Over 150 patients followed for a minimum of 18 months maintained their improvement in symptoms.

We have yet to define the optimal candidate for selective alpha$_1$ blockade. But he appears to be an individual with troublesome urinary symptoms that

impair his quality of life. Candidates for selective alpha$_1$ blockade must be counseled that the drug's long-term effectiveness is unknown, and that this option requires a life-time commitment to medical therapy. The male with hypertension and symptomatic BPH is an optimal candidate for selective alpha$_1$ blockade because this single drug likely will control both the symptomatic BPH and hypertension. It is unreasonable to insist that alpha blockers be offered before prostatectomy since many subjects may be averse to long-term medical management or prefer definitive intervention.

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CHAPTER 57

Flutamide in BPH

NELSON N. STONE

Benign prostatic hypertrophy (BPH) is an age-related phenomenon in which hormonal regulation appears to play a significant role. While the precise influence of either androgens or estrogens remains to be determined, there is ample evidence to support pharmacologic manipulation of these hormones in the treatment of BPH.

Hormonal regulation of BPH can be manipulated by one of several approaches:

(1) decrease of available dihydrostestosterone (DHT) by blocking the conversion of testosterone (T) to DHT by a 5a reductase inhibitor
(2) prevent the binding of either T or DHT to the receptor by an antiandrogen or
(3) prevent the action of estrogens by an antiestrogen or the synthesis of estrogens by an aromatase inhibitor.

This paper will discuss the use in BPH of flutamide, an antiandrogen.

Flutamide

Flutamide (*a*, *a*, *a*-trifluoro 2–methyl-4[1]–nitro-*m*-propionotoluidine) is a nonsteroidal antiandrogen that is metabolized into a hydroxylated derivative, which competes competitively with either T or DHT for cytosol androgen receptor sites [1]. (Figs. 1, 2). With oral dosing, flutamide is rapidly absorbed and excreted mainly through the kidneys [2].

Studies of androgen deprivation with flutamide in the rat and dog support its use in treating both BPH and prostate cancer [3]. When given in a range of 5–50 mg/kg to dogs for six weeks, it has a significant effect decreasing both prostate volume and epithelial-cell height [4]. Further reduction in prostate volume and epithelial-cell height occurred for up to one year suggesting that prostate-gland involution is a lengthy process. The favorable results in animal studies lead to the design of human clinical trials.

The minimal toxicity with flutamide in animal studies implied that it might be a safe and acceptable compound in man. While it is known that castration

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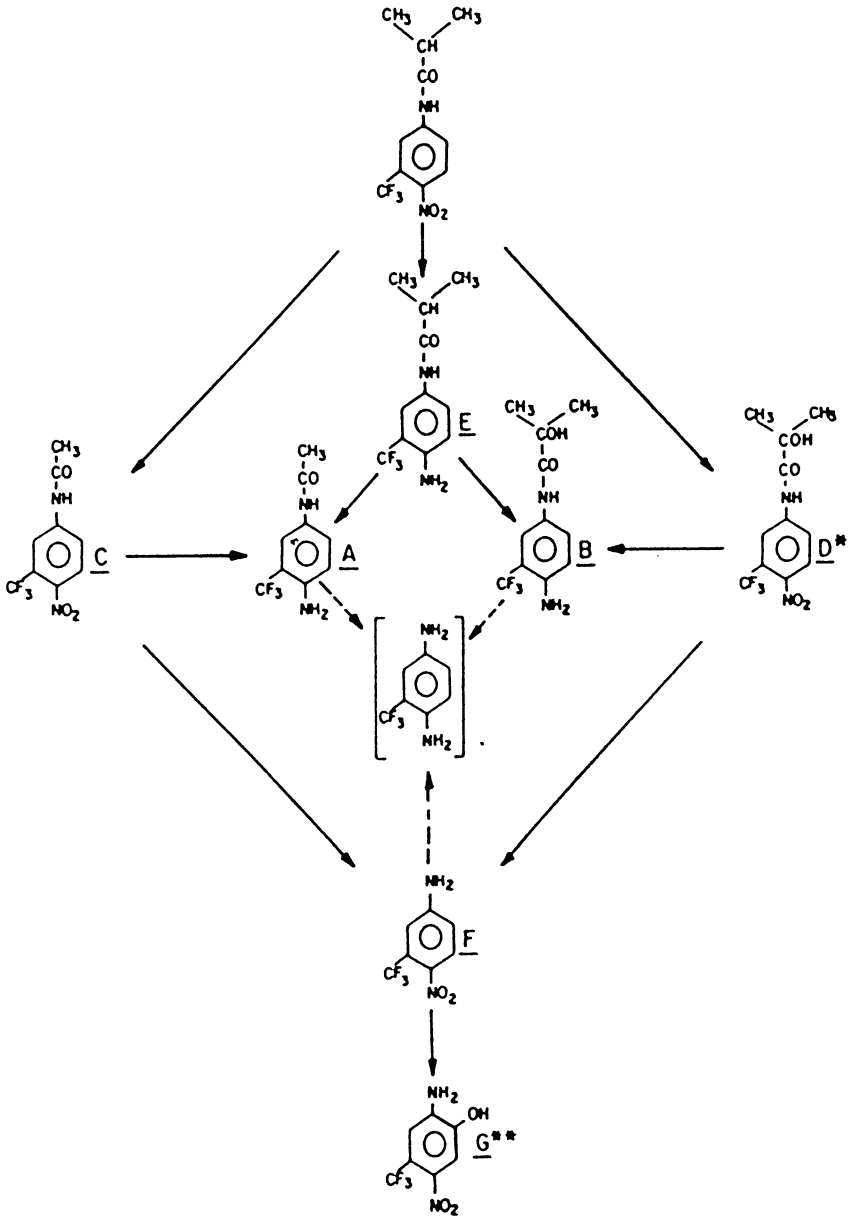

Fig. 1. Metabolism of flutamide. (From JCE&M 1975; 41:376.)

produces impotence and decreased libido, the animal studies using flutamide to achieve androgen deprivation showed no such side effects [5]. Thus, flutamide's antiandrogen activity could be used without sacrificing potency – clearly a major advantage in treating men with BPH.

Few clinical studies have been done on the use of flutamide for prostatic

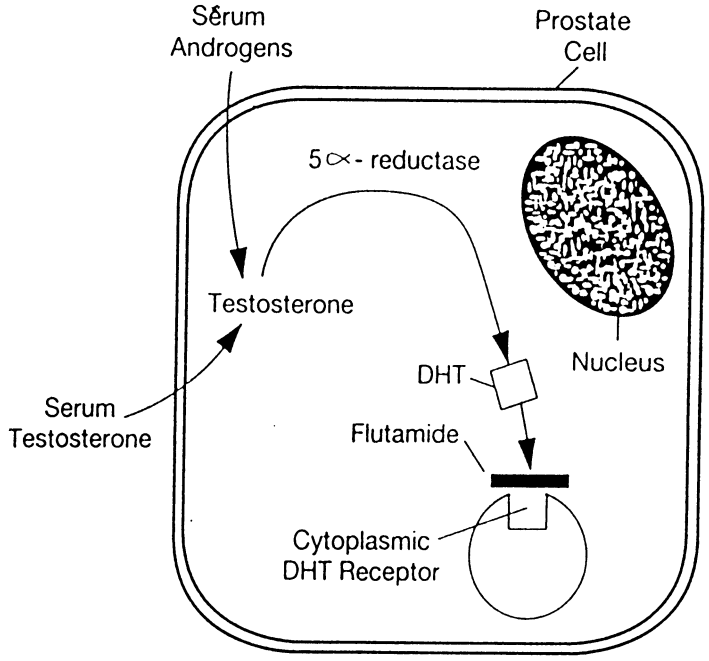

Fig. 2. Method of action of antiandrogen flutamide. (From Urology 1989; 34:65.)

diseases. More data is available in flutamide monotherapy for prostate cancer than for BPH and thus a brief review of flutamide in prostate cancer is worthwhile.

Studies of flutamide monotherapy have been done in patients with newly diagnosed, stage-D2 prostate cancer in the hope of achieving androgen deprivation without impotence. Sogani studied 80 men with advanced prostate cancer and found a 70% response rate with preservation of potency in most of these patients [6]. However, the side effects including gynecomastia were significant. The greatest concern with this method of androgen ablation was generated in a study of 11 patients in whom serum testosterone rose with continued administration of flutamide. Thus the fear of tumor escape greatly reduced the use of flutamide in this stage of the disease [7].

Flutamide binds and blocks the androgen receptor in the gonadotroph cells leading to an increase in LH levels in the face of high testosterone concentrations [3, 4, 8]. Higher LH levels result from both an increase in LH synthesis and release [9, 10]. Because flutamide is a competitive inhibitor, the rising T level potentially compromises the androgen blockade and, theoretically, might permit disease progression. However, long-term flutamide monotherapy in patients with prostate cancer does not appear to produce chronically elevated, serum-testosterone levels [11]. Nevertheless, because of these initial concerns, flutamide monotherapy for prostate cancer has not been actively pursued in the United States.

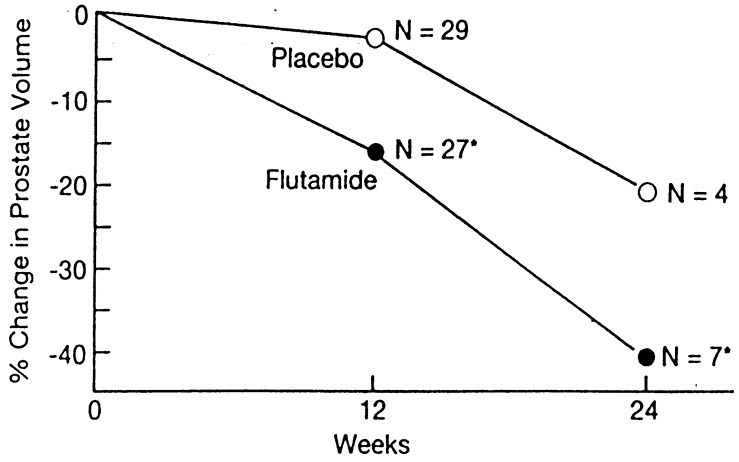

Fig. 3. Median percent change in prostate volume at twelve and twenty-four weeks ($p < 0.01$). (From Urology 1989; 34:66.)

Caine first introduced the concept of using flutamide for patients with BPH. In a double-blind trial, 30 patients were given 300 mg of flutamide or placebo for 12 weeks [12]. Significant improvements in maximum and average uroflow rates were noted in the flutamide group. They reported no reduction in prostate-gland size, but, because they measured the size of the prostate gland by digital rectal exam and not ultrasound, only large changes would have been detected. Treated patients also noted symptom improvements. However, while the symptom improvements were statistically significant at 8 weeks, they did not differ from the placebo group by the end of the study.

While Caine's study demonstrated the application of antiandrogens in BPH, it raised more questions than it answered. Unfortunately, a phase III trial was done when neither the correct dose or the appropriate duration of administration were known. Extrapolation from the canine data suggests that Caine's study employed too low a dose (< 5 mg/kg) for too short a period (< 24 weeks). More recent studies with androgen deprivation using LHRH compounds confirms that one needs a minimum of 4–6 months to achieve maximum reduction in prostate-gland size [13, 14]. The most appropriate dose for BPH is still unknown because no one has reported dose-ranging studies with flutamide.

Despite these shortcomings, Caine did show the potential of flutamide in patients with BPH. Toxicity was low but gynecomastia or mastalgia occurred in 7 of 15 patients. No patients reported loss of potency.

Because of the increased interest in medical therapy for BPH, an industry-sponsored, randomized, controlled study of flutamide was initiated. Patients were randomized to either 750 mg of flutamide/day (250 mg tid) or placebo. Stone *et al.* enrolled 84 patients (42 placebo, 42 flutamide) and analyzed changes in prostate volume, uroflow rates and symptom scores [15].

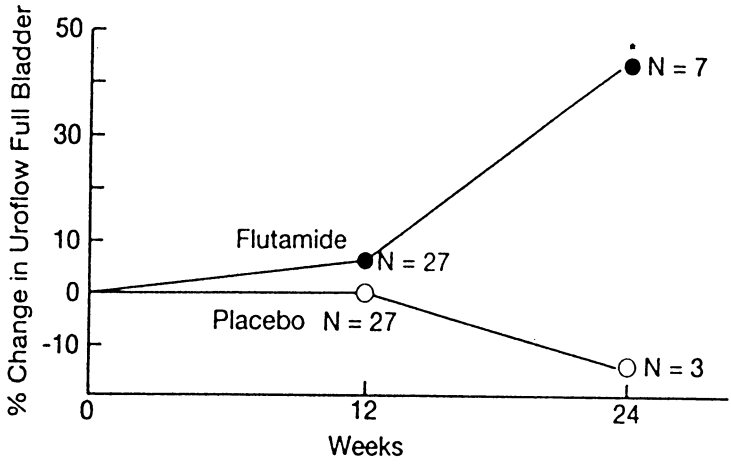

Fig. 4. Median percent change in full-bladder overflow at twelve and twenty-four weeks ($p < 0.05$). (From Urology 1989; 34:66.)

He noted significant improvements in all parameters in the treated group. Prostate volume decreased a median of 18% by 3 months and 41% by 6 months. Uroflow increased by 35% in the treated group, while no improvement was noted in the patients on placebo. Both groups had a 50% improvement in overall symptom scores (Figs. 3, 4).

As might be expected, there was a significantly higher proportion of adverse reactions in the flutamide group. For the most part, these side effects were mild and did not cause patients to drop out of the study. While 53% noted some breast pain or gynecomastia, only one patient (3%) said this was more than mild. Four patients noted diarrhea (11%) and again only 1 (3%) said this was more than mild. No patients complained of impotence or decreased libido after taking flutamide.

A more recent report analyzed the effect of flutamide on prostate volume, prostate-specific antigen and testosterone in men with BPH [16]. In 11 patients, who received flutamide for 6 months, prostate volume decreased from a mean of 101 cm^3 to 66 cm^3 (mean decrease 35%) and serum PSA decreased from 10.7 ng/ml to 3.8 ng/ml (mean decrease 65%). These changes occurred despite an increase in serum testosterone from a mean of 336 ng/dl to 518 ng/dl (mean increase 58.3%) (Fig. 5). Thus, despite an increase in testosterone, flutamide was able to continue a state of androgen deprivation. Side effects were similar in this study, 36% complained of mild gynecomastia and one patient reporting a decrease in potency.

There is compelling evidence that flutamide eventually may be an important agent in treating BPH. However, as newer antiandrogens such as Casodex or Zanoterone become available for clinical study, they may replace flutamide. These compounds are reported to have greater potency, improved

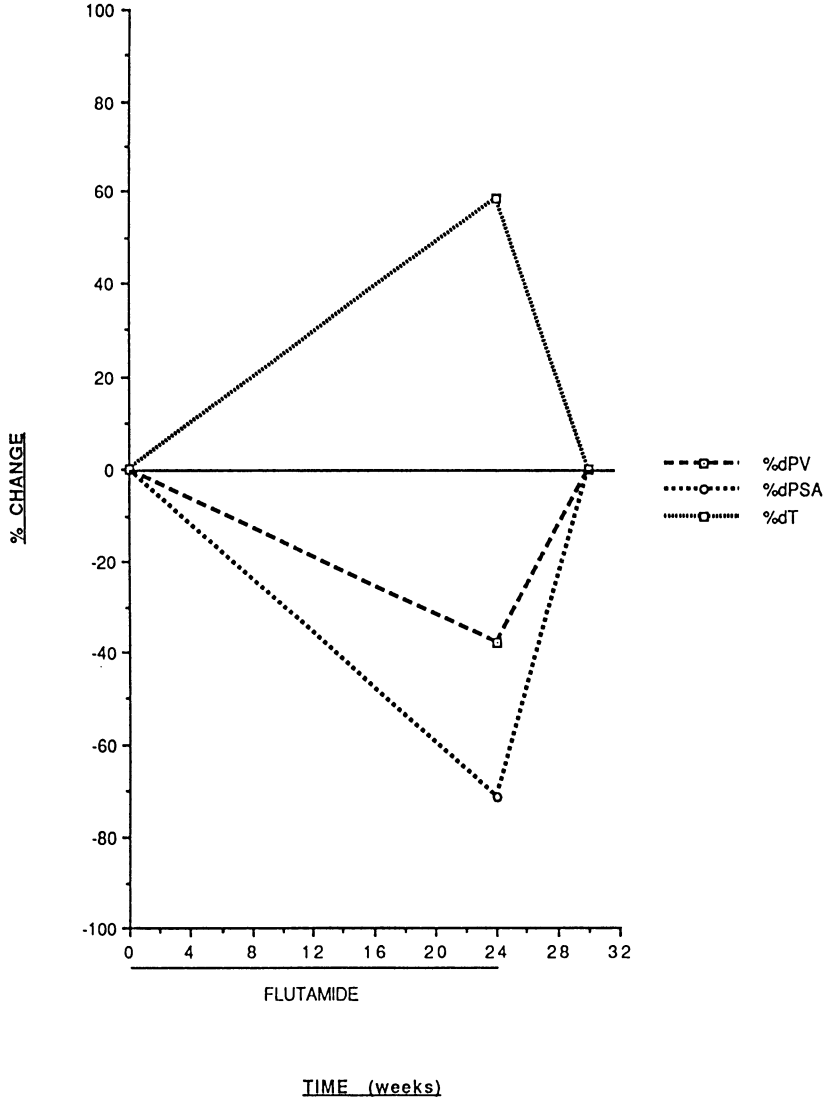

Fig. 5. Change in prostate volume (PV), prostate specific antigen (PSA) and testosterone (T) in men with BPH while on flutamide (750 mg/day) and after drug discontinuation.

tolerance, longer half-life and to be less likely to raise LH levels when compared to flutamide [17]. Whether these or other newer agents will be as effective as flutamide in treating BPH and have less toxicity, will be determined by clinical trials.

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CHAPTER 58

Non-medical alternative therapy in BPH

STEVEN A. KAPLAN

Over the past few years, the urologic literature has described a host of new and innovative techniques in the management of BPH. This paper will review the highlights of nonmedical alternative therapies being used in Europe and in North America. Many of these technologies are in their infant stages and we should temper our enthusiasm until long term follow-up is available. However, given that caveat, it is worthwhile reviewing some of the early encouraging results.

1. Heat therapy
   (a) hyperthermia
      - transrectal
      - transurethal
   (b) thermal therapy
2. Prostatic stents
   (a) springs
   (b) Wallstent
   (c) titanium stent
   (d) biodegradable and thermoexpandable stents
3. Balloon dilation
   (a) one balloon (Dowd)
   (b) two balloon
      - ASI
      - AMS
4. Transurethral laser incision of the prostate (TULIP)

Heat therapy

Currently, hyperthermia is being evaluated as a non-surgical treatment of benign prostatic hyperplasia. Preliminary clinical studies using both transurethral and transrectal applicators have demonstrated varying subjective and objective response rates [1–4]. One of the issues that has not been addressed adequately is predicting, *a priori*, which group of these patients will benefit

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from this modality. Furthermore, because of the paucity of randomized, placebo-controlled studies, the urologic community have shown a great deal of skepticism regarding the ultimate role of hyperthermia in treating symptomatic prostatism.

Why use heat?

Many investigators have reported the toxic effects of heat on cancer cells. In 1866, Busch reported the antitumor effects of hyperthermia after he noted the regression of a histologically proven sarcoma after a high fever caused by erysipelas [5]. Whole body, regional and local hyperthermia are employed routinely in oncology today, principally as an adjuvant to radiation [6, 7]. The rationale for this approach is that tumor cells in the S-phase of division are exquisitely sensitive to heat but resistant to ionizing radiation [6, 7].

Tumors are relatively vascular deficient and therefore poorly equipped to dissipate the destructive effects of temperatures above 42 °C. In theory, benign prostatic hyperplasia (BPH) is such a tumor. A consequence of relative vascular deficiency is the inability to vasodilate under the influence of heat with an increased incidence of both tumor vessel and tissue death. However, it should be emphasized that there is no literature to support this theoretical premise in BPH and normal prostate tissue

Recently, Rigatti *et al.* reported the histologic changes associated with transrectal hyperthermia [8]. These include a diffuse inflammatory infiltrate with particular increase in lymphocytes. In addition, there is a large increase in neovascularization. This appearance is much more significant in BPH tissue than in associated 'normal' prostate. However, irreversible cellular damage was never seen.

Using microwaves to deliver heat

The recent urologic literature has many studies describing transrectal and transurethral hyperthermia, microwave therapy and transurethral thermal therapy. To be precise, hyperthermia refers to heat delivered by microwaves to a temperature of < 45 °C. These microwaves can be delivered via a transrectal or transurethral route. In contrast, thermal therapy refers to heat generation of > 45 °C. This degree of heat may be delivered by microwaves via a transurethral route (a full discussion of this modality will be presented in another article in Contemporary Urology). Even higher temperatures can be delivered by using lasers, such as the TULIP or ultrasound waves. This has important treatment ramifications because hyperthermia does not cause pain and does not result in extensive tissue destruction. In contrast, higher temperatures are associated with both pain and more widespread parenchymal destruction.

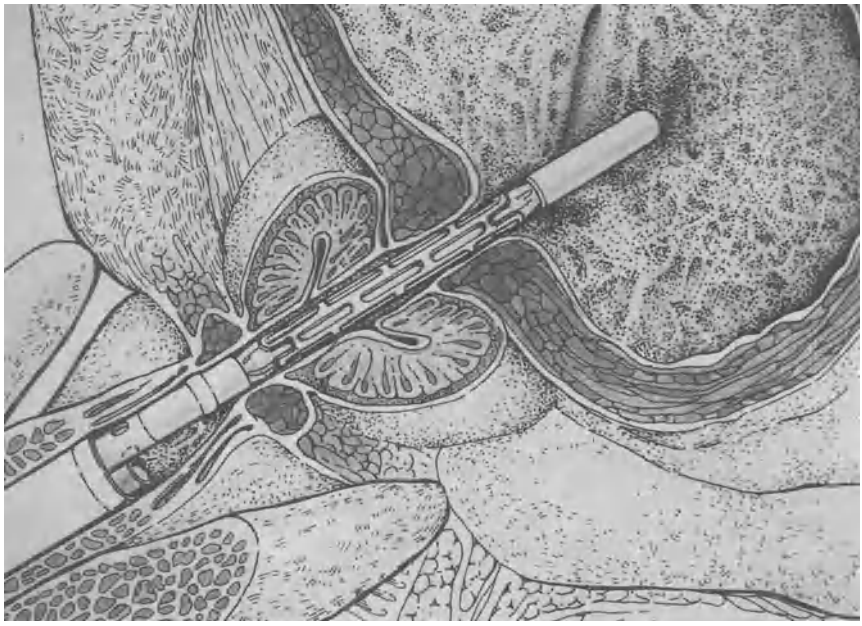

Fig. 1.

Microwaves (waves with an electromagnetic frequency over 200 MHz) are generated by specially designed applicators. Different applicators have been designed to deliver microwave energy to various parts of the body. In urology, coaxial antennae (dipoles or helical coils) have been designed for placement within the rectum or urethra. Helical coils have more even heat distribution and are used commonly in transurethral applicators. Other components of the transrectal hyperthermia device include a cooling system around the applicator. This ensures that the rectum is protected from direct heat injury. Transurethral hyperthermia has no cooling systems and in this modality there is a 'urethral burn'. The premise of transurethral thermal therapy is that with simultaneous urethral cooling, higher 'prostate' temperatures can be delivered.

One of the physical principles of heat distribution is that it is distance dependent, that is, the further away the target tissue is from the microwave applicator, the lower the temperature distribution (Fig. 1). Roehrborn *et al.* noted that in a dog treated with a transurethral catheter, a temperature of 43 °C was recorded in the periurethral prostate [9]. However, there was a 1° drop in temperature per 3 mm distance from the catheter. This suggests a limited treatment zone of 1 cm around the periurethral prostate. Devonec *et al.* reported on interstitial thermokinetics in humans using a transurethral microwave applicator [10]. Temperatures of 44 °C were noted at a distance

of 15 mm from the urethra. In addition, there was destruction of tissue from 5 to 15 mm from the urethra with no evidence of rectal injury. However, the power used in that study was 35 watts, which is relatively high when compared to transrectal hyperthermia. Recently, Astrahan *et al.* reported on the interstitial temperature measurements of prostatic and rectal tissue in 5 patients undergoing transurethral hyperthermia (BSD Medical) [2]. They noted that temperature decreased by a rate of 6 °C/cm. Although intraurethral temperature reached 48 °C in one patient, the interstitial temperatures remained within safe levels. However, there was inadequate temperature distribution 1 cm beyond the applicator.

Two questions raised regarding the use of transrectal hyperthermia in the treatment of BPH are: (1) whether there is a uniform and safe temperature distribution within the prostate; and (2) whether the heating profile is confined solely to the target tissue, i.e. the prostate. At Columbia-Presbyterian, we attempted to map the interstitial thermal distribution in the prostate during hyperthermia treatments [11]. Under local anesthesia and ultrasound guidance, a transperineal 3-point thermocouple (TC) was placed into various areas of the prostate in 15 patients. Prostatic-urethral-TC distance ranged from 1–3 cm. A urethral catheter containing a 5-point, linear-array TC was placed and the balloon inflated so that the proximal point was at the bladder neck and the remaining points located at 1 cm intervals along the prostatic urethra. Power (25 watts) was delivered via a transrectal microwave applicator with simultaneous cooling of the rectal mucosa (between 12 and 14 °C). Treatment was delivered for 60 minutes and temperatures recorded. In the prostatic substance, a maximal temperature (T_{max}) of 45 °C was observed during the heat-up phase and decreased as the vasoactive response occurred. Temperature along the prostatic urethra varied between 40–43 °C and never exceeded 44 °C. A similar distribution of temperature was registered at the TC points in the prostatic substance. The anticipated thermal dose of 41.5 + 1 °C for 60 minutes was achieved in the prostatic substance as measured by the interstitial sensors and those in the prostatic urethra sensors. The results suggest that TRTT delivers a uniform and safe distribution of heat in both the prostatic substance and urethra (Fig. 2). In our experience, as well, thermal distribution is clearly related to distance from the applicator dipole Theoretically, therapeutic temperatures (> 43 °C) are being delivered when the AU distance is > 1 cm but < 2.5 cm (Fig. 4)

Does hyperthermia work?

Previous authors proposed transrectal hyperthermia for cancer of the prostate and BPH using intracavitary applicators with microwave dipole antenna [12, 13]. Yerushalmi *et al.* added a water-circulating system to cool the rectal wall while simultaneously heating the prostate [14].

There have been numerous reports of the efficacy and safety of hyperther-

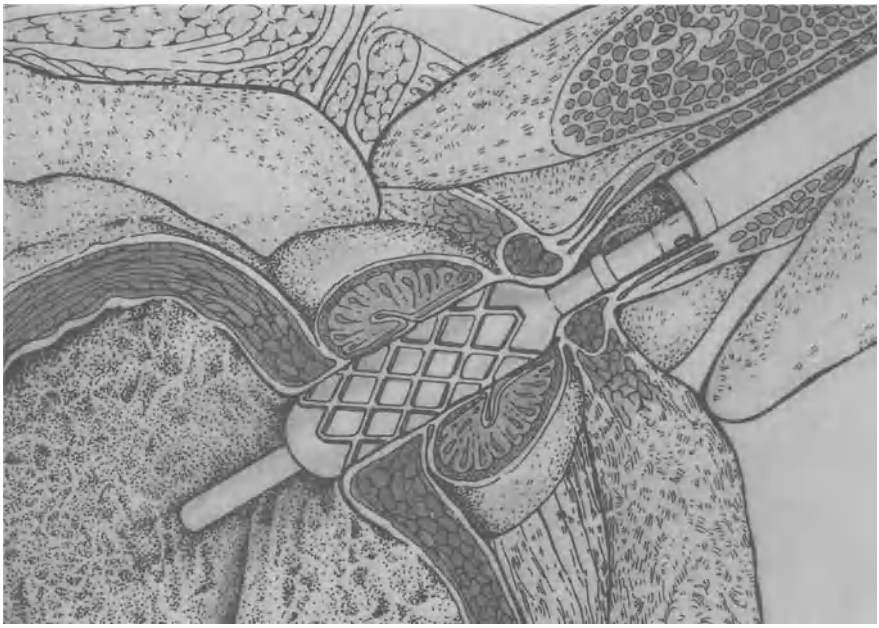

Fig. 2.

mia in the management of BPH. One caveat is that there are few long-term, placebo-controlled studies using this therapeutic modality. Sapozink *et al.* reported on their initial experience in 21 patients with BPH using transurethral hyperthermia [4]. Microwave frequencies were set at either 630 or 915 MHz using fixed-length antennae. Patients were treated for 5 consecutive weeks (2 per week) at 72-hour intervals with power averaged at 48 watts. Patients experienced significant improvement in uroflow and nocturnal frequency and were categorized as having a good/better objective response in 89% of objective scores and 71% in subjective scores. Of note, patients pretreatment flow was only moderately impaired, which may suggest a less symptomatic group. In addition, most patients experienced side effects during treatment varying from urethral pain (43%) to bladder spasm and hematuria (71%), although none persisted after treatment.

Baert *et al.* reported their experience using the BSD-300 in 15 poor surgical-risk patients with BPH [3]. A modified helical antenna was used to deliver power. Patients showed marked subjective improvement and statistically significant improvement in uroflow, residual urine and prostate size. Of note, the mean prostate size was only 29 cm^3. Perhaps previously reported failures were in relatively larger prostate glands. All patients experienced side effects during therapy and 3 had persistent perineal pain.

Yerushalmi *et al.* reported on 29 patients with BPH who underwent trans-

rectal hyperthermia (Technomatix) [14]. Treatments varied in number between 6 and 15. They reported a regression in the size of the prostate (by digital palpation), improvement in symptoms and 8/11 patients, who started in urinary retention, were catheter-free at the termination of treatment. No objective parameters were measured and no complications were reported. More recently, Van Erps *et al.* reported on 60 patients treated in a similar fashion to those in this study [15]. Objective improvement was demonstrated in 21 patients (35%) and subjective improvement in 41 (68%). Of note, there were no complications during or after treatment. There was no change in the size of the prostate or in PSA values. Lindner *et al.* also noted no changes in PSA values in 18 patients treated with transrectal hyperthermia [16].

There have been numerous reports on the efficacy of another type of transrectal hyperthermia device, the Prostothermer (Biodan). Watson *et al.* reported a 30% reduction in post-void residual volumes in 30 patients with BPH who were given 6 treatments [17]. Although the majority had subjective improvement, only 25% had improvement in uroflow. However, all patients described the procedure as uncomfortable or painful causing two patients to withdraw. Knapp and Newman reported that, in 18 patients treated, there was a $> 50\%$ improvement in 61% of patients [18]. In addition, 50% of patients had improvement in symptom score, post-void residual and bladder-neck-opening pressure. Finally, long-term usage of the Prostothermer has resulted in few long-term complications. Of 435 patients treated between 1986 to 1989, only 29 (6.6%) had transient complications ranging from hematuria (1.4%) to UTI (1.4%).

Zerbib *et al.* conducted a prospective, randomized study comparing transrectal hyperthermia treatments (Biodan) versus sham [19]. Treatments were done once per week for 5 weeks at 43 °C. Although no definitive results were published, there was a clear objective and subjective advantage to the treatment group versus sham. This is the only paper which has addressed the possible placebo effect of this modality. In contrast, Fabricius *et al.* reported that, in a placebo-controlled study using transrectal thermal therapy (Primus), there was minimal objective differences between the 2 groups, although subjective differences did exist [20]. Other treatment regimens, including pharmacologic manipulation with alpha-blockers, anti-antiandrogens and 5 alpha-reductase inhibitors have demonstrated placebo effects ranging from 30–65%.

Strohmaier *et al.* using the Prostothermer in 30 patients with BPH reported no beneficial effect [21]. Patients received 8 treatments (2 per week for 4 weeks), and various parameters were measured including symptoms, uroflow, prostate volume and residual volume. Subjective improvement was reported in 54 of patients and only 1 patient had improvement in uroflow. Of note, this group of patients had a relatively low symptom score and a flow rate of 10.9 ml/sec before therapy and may represent an *a priori* mildly symptomatic group of patients who may not derive as much benefit as a more symptomatic one.

We have used transrectal hyperthermia in 24 patients with BPH [22]. As part of their initial workup, all patients had preoperative symptom-score analysis, synchronous video/pressure/flow urodynamic and transrectal measurement of both prostate size as well as applicator-to-urethral (AU) distance. The Primus prostate treatment machine (Technomatix, Belgium) was used to deliver transrectal hyperthermia. The Primus system includes an IBM-compatible PC with a safety hardware and software system, 2450 MHz microwave (MW) generator, eight-channel thermocouple (TC) thermometry system, closed-loop, water-cooling system with platinum resistor, and a rectal applicator with built in TC and circulating surface cooling.

Twenty-one patients completed the study (mean follow-up 6.7 months). There was a significant reduction in symptom score ($> 50\%$) in 14 patients (67%) and Q_{max} increased from 5.9 ml/sec to 12.4 ml/sec at 1 month, 12.7 ml/sec at 3 months and 13.2 ml/sec at 6 months. Twelve patients (57%) had both a $> 50\%$ decrease in symptom score and a concomitant $> 50\%$ increase in uroflow (excellent result). Of the 6 patients who failed therapy: 5 had prostate volumes > 85 grams; 4 had voiding detrusor pressure < 40 cm H_2O; 5 had AU distance of > 2.5 cm. In contrast, of the 15 patients who had an excellent or good response, none had a prostate volume of > 60 grams or a voiding detrusor pressure of < 50 cm H_2O and the AU distance was < 2.5 cm. Of those patients who completed therapy, 5 (24%) had gross hematuria, which resolved within 48 hours after placement of a urethral catheter (treatment #1) and 3 (14%) complained of transient dysuria. No infections were associated with this treatment. In addition, there was no evidence of rectal complications.

Of interest, maximum uroflow improved in the first month of treatment with little change over the next 6 months. This is in contrast to transurethral microwave therapy where there is little change initially but steady improvement over the ensuing months. It may be that transrectal hyperthermia causes no tissue destruction and minimal edema. Therefore, 'no period' of healing is needed and any uroflow changes would occur almost immediately. In contrast, transurethral hyperthermia does cause a more extensive inflammatory reaction and therefore requires a longer period before maximal improvement.

There are a number of potential reasons for the varied results reported using transrectal hyperthermia. The most obvious are patient selection and method of treatment. In our experience, patients were moderately to severely symptomatic. In addition, great care is given to proper applicator placement. To ensure that the transrectal applicator is propped against the prostate, the applicator rests on a level that angulates the applicator anteriorly and a Foley catheter with a 70 ml balloon is inserted with the applicator with the balloon inflated to further insure appropriate placement. Given the small margin of heat distribution, with both transurethral and transrectal applicators, it is important to keep to a minimum the space between the applicator and prostate. The depth of insertion is based on transrectal ultrasound identifica-

tion of the distance from the mid-prostate to the anal verge. Simple placement of the applicator without these precautions may contribute to outcome differences.

Certain patients may be poor candidates for transrectal hyperthermia. Based on temperature distribution and AU distance, those with large prostates and/or AU distance of > 2.5 cm may be destined for a poor response. However, it is difficult to discern, during treatment, which patients will fail. In this series, patients received 10 treatments. It remains unclear whether some patients would benefit from more treatments at higher temperature.

In conclusion, the role of hyperthermia in the management of BPH remains to be defined. It seems clear that both transurethral and transrectal applicators deliver safe temperature distributions when operated at standard operating parameters. The temperature gradient is much steeper with the transurethral applicator. In addition, both systems have achieved significant objective and subjective improvement in some patients with BPH. Side effects, although usually transient, are much more common with transurethral applicators. Long-term, follow-up studies with consistent treatment parameters are needed to ascertain: (1) the optimal treatment regimen, that is, the number of treatments; (2) durability of response; and (3) the preferred route of delivery. Until these issues are addressed, the urologic community should view hyperthermia as investigational and use cautious optimism when recommending these measures to patients with BPH

Prostatic endoprostheses

Of all the new therapeutic alternatives under investigation for the management of symptomatic prostatism, prostate stents make the greatest intuitive sense to urologist. The notion of implanting a device, transurethrally, to 'open up' the prostatic urethra is inherent to basic urologic management of prostate obstruction. There has been considerable enthusiasm for, and early encouraging results with prostate endoprostheses particularly in elderly or debilitated patients with benign prostatic hyperplasia (BPH) who often have multiple contraindications to surgical removal of bladder outlet obstruction [23]. Often these patients are destined for long-term, indwelling bladder catheterization, which often is accompanied by multiple sequelae including urinary tract infection and sepsis, uremia and renal insufficiency. In addition, these patients require close monitoring and frequent catheter changes with inconvenience to the patient and increased medical costs. This section will provide an up-to-date review of the use of endoprostheses in the prostatic urethra.

Table I. Prostatic urethral prostheses

Spirals
(1) Prostakath
(2) Urospiral
Self expandable stents
(1) Superalloy mesh (Wallstent)
(2) Stainless steel (Gianturco)
Balloon expandable
(1) Intra-prostatic device (titanium)
On the horizon
(1) Intraurethral Stent
(2) Biodegradable (PLLA)
(3) Thermoexpandable (TiNi)

Endoprostheses in medicine

Other specialities particularly vascular surgery have applied this basic concept, that is, placement of a stent through a stenotic lumen, for the past two decades. In 1969, Dotter *et al.* used a coilspring in the popliteal artery [24]. More recently Bucx *et al.* have done successful stenting of coronary arteries, although stringent anticoagulation is necessary [25]. Self-expandable stents of stainless steel (Wallstent) were used to treat stenoses or occlusions in 26 iliac and 15 femoral-popliteal artery lesions of 31 patients. The indications were complex lesions, including residual stenoses and dissections after percutaneous procedures or previous surgery in the iliac artery lesions, and long-segment (mean, 13.5 cm) occlusions with inadequate response to percutaneous recanalization in the femoropopliteal artery lesions. In the iliac-artery group, after stent placement, 96% of the lesions were patent at a mean follow-up of 16 months, while in the femoropopliteal artery group, in 11 patients, only six had patent stents at 7–26 months [26]. Others have reported greater success in larger diameter vessels [27]. Finally, Foerster, Hoepffner and Domschke have reported success in 80% to 90% patients with plastic biliary endoprostheses to relieve malignant obstructive jaundice. They recommended that because of the comfort, a completely indwelling endoprosthesis should be offered to all palliatively treated tumor patients, and external-internal catheters should be reserved for those few patients who return with occluded endoprostheses [28].

Endoprosthesis in urology

Many endoprostheses (Table I) have been proposed and investigated in a host of urologic disorders; these include urethral strictures, detrusor-external sphincter dyssynergia and prostatic obstruction. A multicenter European

group [29] reported on the use of the Wallstent in 71 patients with bulbar urethral strictures Fifty patients had previous urethral dilatations, 68 had optical urethrotomies. The stent always was placed distal to the external urethral sphincter. Subjectively, 68 of 71 patients were satisfied with the results. Flow rates improved from 6 ml/sec to 18 ml/sec at 8 months. Retrograde urethrography in 27 patients done at least 3 months post stent insertion revealed patency of the urethra. At 12 months, 23 stents were covered with a smooth epithelium with no infection or encrustation. The most common side effects included perineal discomfort, which occurred in most patients but was usually self limiting. Persistent bleeding occurred in 4 patients during the first 3 months. Leakage of urine was noted in 28 patients at 3 months secondary to pooling in the urethra of serous discharge. In the majority of patients, this resolved. In 1991, Parra reported success with a titanium stent in 5 patients with recurrent posterior urethral strictures [30]. Four have had unobstructed voiding with no evidence of incontinence. McInerney *et al.* reported on the use of the Wallstent in 22 patients with spinal cord-injury and documented detrusor external sphincter dyssynergia. Fifteen patients achieved complete voiding after placement of one stent; 3 developed bladder-neck obstruction after stenting, but in one of these cases this resolved after incision of the bladder neck. Placement of these stents was predicated on the desire for future fertility; that is, the stent was placed distal to the verumontanum.

Prostate spring – Prostakath

A prostatic stent or spiral was first described by Fabian in 1980 [32] and many subsequent modifications include the Prostakath (Engineers and Doctors A/S Copenhagen, Denmark). The stainless-steel stent is coated with 24-carat gold, which prevents encrustation. The outside diameter is 21 F and it comes in four lengths: 4.5, 5.5, 6.5 and 7.5 cm. The straight portion consisting of multiple spiral loops remains in the prostatic urethra and the most proximal portion extends through the bladder neck into the bladder. The distal portion consists of a 2 cm straight segment traversing the membranous urethra and two spiral loops in the bulbar urethra. It is important to note that the spiral does not become epithelialized.

The Prostakath can be placed under direct vision or under ultrasound guidance. Vincente *et al.* reported on 49 patients (40 with BPH, 7 with prostatic carcinoma and 2 patients with 'sclerosis' of the bladder neck), who were followed for 22 months after cystocopic insertion. There was normal voiding in 74%, decrease post-void residual in 88.5% and flow rates between 6 to 12 ml/sec in 60% of the cases [33].

In a multicenter study from Finland, 75 patients underwent placement of the Prostakath (80% under ultrasound guidance). A good or excellent result was noted in 50% of patients, while 8 remained in urinary retention. Three

patients required removal because of urinary-tract infection [34]. Yachia *et al.* inserted the stent in 26 men, who were poor operative risks [35]. The treatment was successful in 20 (77%). All 20 were able to void satisfactorily. Four of the 20 resumed sexual activity, which previously had been prevented by indwelling catheters. Two patients, who had delayed prostatic surgery because of fear of impotence, were able to empty their bladders properly and to remain sexually active. Subsequently, three patients had surgery, two after anticoagulant therapy could be stopped and one after renal function improved. The stent caused no difficulties during surgery. Four patients, who had the stent for 12 months, had no difficulties. Sixteen of the 18 patients, who had indwelling catheters and infected urine before insertion, had sterile urine after relatively short courses of antibiotic treatment. Short-term stent complications were incontinence or urinary retention. These were treated by repositioning the stent. After insertion, frequency of urination disappeared spontaneously or was treated with anticholinergic drugs. In six patients, severe frequency required stent removal and insertion of an indwelling catheter. All patients had slight to mild dysuria immediately after surgery but this eventually disappeared [35].

Nordling *et al.* [36] used ultrasound guidance for stent insertion and reported that the *in-situ* position was maintained at three months in 82% of patients. Some patients are more prone to stent migration because of the length or the configuration of the prostatic urethra.

Porges urospiral

Miller *et al.* [37] had success in 67% of 36 patients, who had endoprostatic helicoplasty using a similar device, the Porges Urospiral. Failure was more common in patients with chronic retention. In addition, 8 patients had incontinence. In a Turkish study, 18 patients were all able to void after stent insertion. However, 44% had persistent urinary-tract infection and 55% of cases had upward migration of the stent [38].

Self-expandable stents

Wallstent

The UroLume Wallstent (American Medical Systems), a biomedical superalloy prosthesis woven in a tubular mesh, is produced in various diameters and lengths. It is stable when expanded and will not suffer elastic recoil. It is preloaded in a special delivery system which allows direct visualization of the prosthesis and the urethra throughout the entire insertion. As the UroLume is deployed from the delivery system, it expands to a diameter of 14 mm. Its elastic properties and radial force of the prosthesis prevent migration.

Fig. 3.

The stent can be placed under spinal, caudal or local anesthesia with a prostate block and IV sedation. In our experience, a saddle block has been particularly effective with minimal patient discomfort or morbidity. The length of the prostatic urethra is calibrated using a standard ureter stent or a calibration catheter. A deployment tool places the stent (2 or 3 cm in length) under direct vision (Fig. 3). In patients with longer prostatic urethras, an overlapping stent can be used. This device, which is 21 F in diameter, holds the stent in a compressed state. As the stent is released, it expands to its full diameter and length. In our own experience and that of others, one of the keys to successful placement is that no portion of the stent should protrude through the bladder neck into the bladder or distally beyond the verumontanum. Chapple *et al.* [39] used the Wallstent in 12 patients with prostatic outflow obstruction. All were at high risk for surgery and 11 were treated successfully, with a follow-up of 1 to 11 months (median 9). The majority of patients (11 of 12) were satisfied; the procedure provided a quick, safe and effective alternative to conventional surgical treatment. In this series, the stent was delivered using combined ultrasound and endoscopic control under local anesthesia. The procedure was well tolerated, the stent was covered with epithelium by 6 to 8 months, yet it allowed easy removal within the first 4 to 6 weeks should the need arise. In that series, mean flow rate improved to 13.4 ± 4.7 ml/sec. All patients had postoperative urgency

which usually resolved within 4–6 weeks. However, in one patient, these symptoms persisted, consistent with *de novo* detrusor instability.

The same group updated their experience in 54 patients. The majority demonstrated marked objective and subjective improvement, but in 5 stents had to be removed [40]. Harrison and Souza [41] reported a similar experience in 30 patients with outflow obstruction. Most had retention of urine and were unfit for conventional surgery. The prostatic stent was readily inserted under local anesthesia and relieved obstruction in 80% of patients with acute retention.

Finally, McLoughlin *et al.* [42] reported that all 19 patients in urinary retention were able to void spontaneously after placement of the Wallstent. Similarly, in a high percentage of patients, postoperative urgency (79%) resolved within 8 weeks. Subsequently, the same group reported that, in 21 patients, endoprostheses were placed under fluoroscopic guidance. The procedure was technically successful in all patients, although one required a second stent 2 months later [43]. One patient developed a urethral stricture in the 12–16 month follow-up period. After stenting, one developed epididymoorchitis and one septicemia and these were treated successfully with antibiotics.

In the United States, Oesterling in 1991 [44] used the Wallstent in a different population, those with moderate symptoms yet relatively healthy. In 24 men, (ages 62–77), symptom scores decreased from 13.1 to 4.8. Urinary flow rates increased from 9.6 ml/sec to 20.1 ml/sec. Post-void residual volume decreased from 107 ± 74 ml to 32 ± 14 ml. There were no cases of infection, encrustation, erosion or migration. Similarly he noted that the majority of patients have postoperative urgency, which resolves over time. An ongoing multicenter trial is investigating the use of the Wallstent in patients with symptomatic prostatism.

Gianturco stent

A self-expanding metal device, the Gianturco stent, has been studied in the prostatic urethras of dogs [45]. This stainless-steel stent differs from the Wallstent in that it has greater spacing between each of the interstices, is inserted with a stent pusher and is 1.5 cm in diameter. There was no epithelial overgrowth and marked infiltration of lymphoids cells. No data is available on its efficacy in humans.

Balloon expandable stents

Intra-prostatic stent (titanium)

Titanium has excellent biocompatibility and a long history of safety as a biomaterial for both dental and orthopedic implants. It is particularly useful

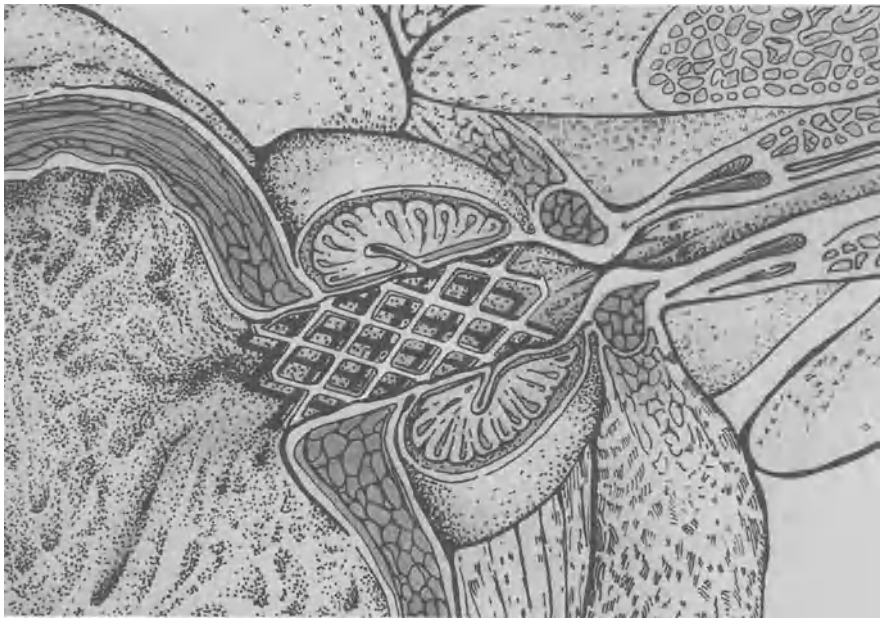

Fig. 4.

where stresses are moderate to low and where a long-term implant is intended. The Intra-prostatic stent, when expanded, is 11 mm in diameter and is available in lengths ranging from 12 to 65 mm in 4 mm increments (Fig. 4). The stent is placed cystoscopically under local anesthesia and sedation. As with the Wallstent, a calibration catheter is inserted cystoscopically and the prostatic urethra is measured from the bladder neck to the external urethral sphincter under direct vision. The elongated stent is mounted on an insertion catheter, which can be adapted to a special urethroscopic sheath. The stent is expanded in the prostatic urethra by inflating the balloon on the insertion catheter to 130 PSI (or 9 ATM) for 30 seconds. The position of the stent can be confirmed cystoscopically or by ultrasound; stent position can be adjusted using grasping forceps through the cystoscope.

From England, Kirby *et al.* [46] reported that 28/32 patients in acute urinary retention were able to void satisfactorily after placement of the Intra-prostatic stent. Asymptomatic urinary-tract infections were noted in 8 patients. In a recent update of their data, 36/42 patients in retention were able to void spontaneously with a mean peak flow rate of 10.5 ml/sec.

Recently, in a multicenter, cooperative study (the initial United States experience with the Intra-prostatic stent) 44 patients (ages 60–93) had a symptom-score analysis and uroflow was measured as part of their initial workup [47]. Patients were seen at 1, 3, 6 and 12 months after stent insertion.

The anesthesia included 3 general, 17 spinal or epidural, 10 intravenous sedation and 14 with intraurethral xylocaine only.

All patients were able to void spontaneously within 36 hours after stent insertion. Symptoms scores decreased from 16 to 4, 7, 5 and 5 at 1, 3, 6 and 12 months, respectively. Peak uroflow increased from 7 ml/sec to 13, 11, 11 and 13 ml/sec at 1, 3, 6 and 12 months, respectively.

Of the initial 44 patients, 5 died from their underlying disorder (all voiding satisfactorily with the stent in place) and 17 had uneventful stent removal (10 technical and 7 treatment failures). Technical failures were secondary to inaccurate positioning or improper stent sizing. Of the 34 patients with proper placement of the stent, 29 (85%) had improved symptom scores and uroflow. Transient hematuria was noted in 41 patients (93%) and usually resolved within 48 hours.

On the horizon

Intraurethral catheter

Researchers in Israel have developed an intraurethral catheter as an alternative to long-term indwelling catheters. Nissenkorn and Lant [48] placed 83 intraurethral catheters (IUC) in 65 patients between 1988 and 1990. All insertions were done under local anesthesia and in an outpatient setting. The IUC was left in place from 1–61 weeks (mean 19.4 weeks). All patients were able to void freely, were continent and had no residual urine. In 3 patients unresolved urinary tract infection required removal of the IUC. In addition, patients, who were sexually active before catheter placement, continued normal ejaculations with the IUC in place.

Biodegradable stents

A biodegradable spiral stent, which does not need to be removed is composed of poly-L-lactide (PLLA) with a length of 15 mm and diameter of 0.7 mm, was implanted into 14 male rabbits. No calcifications were noted and the stent was completely absorbed at 14 months. This early data suggests that this material may hold promise for urinary-tract stents [49].

Thermoexpandable stent

A stent made of an equiatomic intermetallic compound NiTinol (a titanium-nickel alloy) has had early encouraging results in 8 patients. The stent can change from one configuration to another at different temperature. A Ni-Tinol thread of 0.85 mm diameter is mounted on an insertion catheter as a coil with a diameter of 21 F. Flushing the catheter with 45 °C water makes the coil expand to 35 F and the insertion catheter is then removed. If the

stent requires removal, the coil can be irrigated with water at 15 °C, which softens the metal and allows the coil to be removed as a string. Of the initial 8 patients 4 had stent migration during the procedure while 4 remain for a minimum of 6 months with satisfactory voiding [50].

Conclusions

The use of stents to bridge the prostatic urethra has been greeted with considerable enthusiasm. Based on initial results, it seems clear that this technology will have a lasting impact on how we treat some patients with BPH. In our experience, the optimal patient has been the frail elderly patient in urinary retention. Others have advocated endoprostheses, particularly, the prostatic spiral as 'stress tests' to determine how patients will fare after definitive prostatectomy [51].

However, future innovations particularly the use of biodegradable materials, should make the prostatic stent more attractive to a greater segment of the BPH population. Future studies will help the urologist to select: (1) the appropriate clinical setting for the prostate stents; and (2) what type of stent to use.

Balloon dilation

If Shakespeare were a urologist and alive today, he might ponder this: "To balloon dilate or not to balloon dilate, that is the question". A modern addendum would also include, "Does it work?" The following summary will present the rationale and results of several studies using balloon dilation to treat symptomatic prostatism. It is by no means complete or definitive, however, there is evidence that some patients do benefit from this modality.

The history of balloon dilation is interesting. The initial metal dilator of Mercier who first proposed this modality in 1844, was modified by Deisting in 1950. In 324 patients, the latter reported an immediate success rate of 95.3%. Symptomatic improvement was maintained in 85% of patients after 8 years. With modern transurethral technology, the popularity of prostate dilation declined. However, in the late seventies and early eighties, advances were made in interventional radiologic techniques in vascular obstruction and biliary and gastrointestinal strictures. In 1984, Burhenne, a radiologist and Klein, a urologist, dilated the prostatic urethra with an angioplasty catheter. Others, such as Casteneda and Reddy, used a radiographic technique to position the balloon with the prostate. Three balloon catheters, have been extensively studied.

(1) transcystoscopic balloon catheter, first described by Klein (Advanced Surgical Intervention, Inc). The kit requires a special sheath measuring catheter and the various lengths of dilating balloons. Theoretically, this

system affords the best dilation of the bladder neck and prevents retrograde ejaculation.

(2) Dowd balloon (one-balloon system) is inflated with a direct palpation nodule. The Dowd balloon catheter system (Microvasive) has been advertized as the most efficient balloon catheter system because 'one balloon fits all'. However, its detractors note that dilation is ineffective particularly in very short prostatic urethras. In addition, retrograde ejaculation, as proposed by Dowd, is the best measure of the success of the dilation.

Finally, (3) a two-balloon catheter system (advocated by Reddy) has a fixating balloon distal to the external urethral sphincter (American Medical Systems). Its major theoretical advantage is prevention of balloon migration.

It is beyond the scope of this paper to describe in detail the various techniques of each balloon insertion, however, the following summarizes the most recent data on each of these balloon catheters:

Two-balloon, transcystoscopic balloon catheter

The clinical evaluation of all investigators using this balloon catheter system was begun in 1988. Data from 10 centers have been collected on 122 patients with a follow-up of up to 24 months. Analysis included symptom scores (maximum total score of 27) and peak uroflow rates. Table II presents: (1) age distribution; (2) balloon length distribution; (3) average symptom score improvement; (4) average symptom score; and (5) peak uroflow improvement. Percentage of patients with success, defining 'success' as a minimum of 50% symptomatic improvement, the success rate at 3, 6, 12, 28 and 24 months are 84%, 88%, 88%, 78% and 69% respectively. These data parallel the improvement rates in a symptom scores seen after TURP. Others, such as Goldenberg and Klein reported similar results with this catheter in smaller series.

Dowd and Smith

In 1990, Dowd and Smith reported their results in 50 men, ages 49–89 with a 1–4 month follow-up. Patients varied between those who electively pursued this therapeutic alternative, those who were at high risk for future surgery and had complex medical problems, and those who were poor risk patients who required relief of bladder-outlet obstruction. More than 50% of patients were discharged less than 24 hours after procedure. Twenty-three patients (46%) had excellent results; an additional 13 patients had acceptable results. The remainder went onto TURP or had suprapubic tube left in place.

Table II. Balloon dilatation

Author/ Date	# of Patient	F/U month *s*	F/U range	Success *s* *Sx*	Success Q_{max}	Tech.	Brand
Klein Prob. in Urology July 1989	22	> 6	N/R	80%	N/R	Cyst.	ASI
Klein J. Urol Vol 4,1990	22	> 12	> 12	62%	N/R	Cyst.	ASI
Goldenberg J. Urol July, 1990	42	6	1–12	74%	N/R	Cyst.	ASI
Dowd Urol Clin Nor Amer Aug. 1990	50	N/R	1–41	72%	46%	Palpa.	Micro
Daughtry Urology Sept. 1990	55	10	1–26	84%	79%	Fluoro	Medit.
Wasserman Radiol. 1990	70	16.2	6–36	70%	54%	Fluoro	Medit. AMS
Goldenberg Urology Times April, 1991	39	12	N/R	82%	N/R	Cysto	ASI
Klein World J. Urol 1991	53	N/R	3–12	64%	N/R	Cysto	ASI
ASI Clin. Report Apr. 1991	122	N/R	> 12	88%	N/R	Cysto	ASI

Two balloon catheter (AMS)

Reddy has the largest experience with this catheter system. In 44 patients, symptoms and flow rates improved significantly. Sixteen per cent of patients were considered failures and underwent subsequent TURP.

In conclusion the advantages and disadvantages of balloon dilation can be summarized as follows:

Advantages

(1) simplicity
(2) minimal hospitalization and convalescence
(3) less expensive

Disadvantages

(1) effect is unpredictable
(2) only effective in smaller prostates
(3) not well reimbursed
(4) placebo effect. No placebo studies have compared balloon dilation with a larger 90 F balloon catheter

In conclusion, balloon dilation remains to be established as a reasonable therapeutic alternative. Long-term, placebo-controlled studies are required to evaluate this technique as a viable therapeutic alternative. However, early results have been encouraging and, in addition, the use of larger balloons may improve the results noted. We must, however, maintain a healthy caution when evaluating all alternative therapies.

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PART FOURTEEN

Ethical issues

CHAPTER 59

Advance directives for health care*

BARBARA MISHKIN

Introduction

Advance directives for health care are legal documents that give instructions for dealing with treatment decisions in the event of subsequent incapacity. They are similar to organ-donor cards; they provide specific instructions to family, friends, and health-care providers about how one's body should be treated in specific situations. While an organ-donor card provides instructions for the recovery and use of organs and tissues following death, an advance directive for health care appoints someone to make health-care decisions if the patient is incapable of making or expressing a choice when a treatment decision must be made, and/or provides instructions about treatments that should, or should not, be applied in the event of terminal illness or incurable condition.

There are two kinds of advance directives: living wills and healthcare powers of attorney (more accurately, durable powers of attorney for health care). While living wills may be more familiar and were the first to be recognized by state law, healthcare powers of attorney are more flexible and, for a variety of reasons, are the preferred form. Some states – and many individuals – have tried combining the two but, due to the legal restrictions on situations in which living wills can be used, a combination living will/healthcare power of attorney must be drafted carefully to assure its effectiveness in all situations for which its use is intended.

It is important to emphasize that, in the United States, advance directives do not create rights; they merely provide a mechanism for implementing rights already established through case law, state statutes, and the constitutions of the United States and the individual states.

Because living wills came first historically, this paper describes them first and then describes healthcare powers of attorney, stating briefly the advantages and disadvantages of each. Next, it will describe new developments in

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federal law and finally identify the potential effects of increased use of advance directives on organ donation

Living wills: instructions for 'death with diginity'

It is a principle in American law that "every human being of adult years and sound mind has a right to determine what shall be done with his own body, and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages".[1] Nevertheless, some physicians have been reluctant, and some have refused to withdraw or withhold life-sustaining treatment, partly because they feared legal liability.

In the mid 1970s, cancer patients and their families began to search for ways to stop the administration of aggressive therapies which were often toxic and, when the patient was clearly beyond restoration to normal health, provided little or no benefit. Often it proved difficult to persuade the medical establishment to cease invasive interventions even when patients made it clear that they preferred death with dignity.

Although patients and their families sometimes sought court relief, judicial appeals can take so long that the patients often died – still attached to respirators and tubes – before the legal question was resolved. Courts faced with such cases would hear them anyway on the theory that the situation was capable of repetition yet, because of the circumstances, would evade review unless a patient was strong enough to outlive the judicial process.[2]

Gradually, courts made it clear that the right to refuse life-sustaining treatment applied equally to patients with chronic conditions declining respirators, dialysis, and artificial nourishment.[3]

More difficult was the case of patients so compromised by illness or dementia that they could not make or express a choice at the time a treatment decision was needed. To avoid long, costly and public trials, commentators suggested that people write 'living wills' to express to their family and physicians their intent to forego life-sustaining treatments in the event of terminal illness.[4]

Typically living wills instruct physicians not to prolong the dying process and to provide only treatments necessary to maintain comfort, dignity, and personal hygiene. Because such documents developed out of concern for cancer patients, generally the documents – as well as the statutes that give them legal validity – do not become effective until one or two physicians have certified in writing that the patient is terminally ill. Thus, a living will could not be used in patients with chronic conditions, such as kidney failure, progressive dementia, or permanent loss of consciousness.

A living will would not have helped either Karen Ann Quinlan or Nancy Cruzan. Karen Ann Quinlan suffered respiratory arrest at age 21, and lived for nine years in a persistent vegetative state *after* her parents won the right to remove her respirator.[5] Similarly, 25-year-old Nancy Cruzan suffered anoxia as a result of an automobile accident in January 1983, and lived in a

persistent vegetative state until December 1991 when her parents finally were permitted to have artificial nourishment withdrawn.[6]

Also living wills were designed as directives for treatment refusal; but not everyone wants to refuse treatment. Some want to keep fighting to the end. Others, even those with terminal illness, wish to hang on until a particular event occurs;[7] and those who work with hospice patients know how often dying patients are able to accomplish that goal. It soon became apparent that a more flexible document would be better – one that permits instructions about particular treatments that would be acceptable, and others that would not, under certain circumstances. Even better would be the ability to appoint an agent with clear legal power to make health-care decisions on behalf of the patient. Better still, of course, would be a document in which one could do both: assign decision-making authority and provide instructions for treatment. Such a document is the healthcare power of attorney.

Healthcare powers of attorney: for appointing agents and providing instructions

Powers of attorney are documents through which one may give legal authority to another to act in a particular capacity, e.g., to manage investments or sell a house. Under English law as received in the United States, however, the power delegated to an agent terminates automatically if the individual delegating the power (the 'principle') becomes incompetent.[8] To overcome this problem, the states enacted laws permitting powers of attorney to be 'durable', so that they would endure even if the maker's competency did not. Every jurisdiction in the United States now has such a law.[9] To make a power of attorney durable, one must include a provision stating either that it "will not be affected by my incapacity" or that it "shall take effect upon [i.e., at the time of] my incapacity".

As concern about ability to control health-care decisions increased in response to highly publicized cases (such as *Quinlan* and *Cruzan*), states began to pass legislation creating or recognizing powers of attorney designed specifically for making healthcare decisions. By the fall of 1991, over one-half of the states had enacted such statutes.[10]

Health-care powers of attorney have a number of advantages over living wills. First, they can be used whenever a patient lacks capacity to make a health-care decision, whatever the reason. Thus, powers of attorney can be useful even in situations that are not life-threatening but in which legally valid consent may be sought, e.g., if an elderly patient with dementia needs dental surgery or an invasive diagnostic test, or if surgeons discover an unanticipated problem during surgery that could be remedied easily during the operation.

Second, they are legally recognized in every U.S. jurisdiction, whereas four states still have not enacted laws recognizing living wills.[11] Third, by appointing a proxy decisionmaker or agent, powers of attorney assure that

there will be someone to speak for the patient and, if necessary, to assert the patient's rights. Since it is impossible to foresee and provide instructions for every health problem that might occur and for every new therapy that might be developed, one cannot write instructions in advance that will apply clearly to every situation. An agent, legally empowered to speak for the patient, can be important in resolving questions and ambiguities.

Finally, as already indicated, powers of attorney are not just for refusing treatment; they can be used as well for directing that all appropriate treatments be provided, or for authorizing certain treatments and declining others.

It is important to put specific instructions in a power of attorney (to the extent one has any in mind) in addition to designating an agent, in order to provide guidance to the agent and providers of care. In addition, in some states (such as Missouri, Maryland, and New York), an agent may not order certain treatments withheld or withdrawn unless the power of attorney expressly includes a directive or specific authority for the agent to do so.

The patient self-determination act: federal prodding for education of patients, doctors, and others

Despite the heightened public awareness of the issues and the accelerating response of the courts and state legislatures, few people in the United States had prepared advance directives for health care by the late 1980s.[12] Worse, few hospitals had established procedures for asking about advance directives or documenting their existence in patients' records.[13] According to one survey, only 4% of U.S. hospitals had such procedures in place in 1989.[14] As a result, an advance directive could be ignored by hospital personnel unaware of its existence or unfamiliar with their own state laws and court decisions on the subject.

A particularly graphic account of the final hospitalization of a dialysis patient, who was subjected to CPR and other invasive therapies against her explicit, written instructions and over the vigorous objections of her mate, dramatically demonstrated the need for widespread education of practitioners and administrative personnel.[15] Accumulating case law and anecdotal evidence demonstrated the equally important need to educate patients and their families – in other words, the community at large.

One person who noticed these needs was John Danforth, Republican Senator from Missouri. Although he is an outspoken 'right to life' advocate on the question of abortion, he recognized the distinction between that issue and the right of adults to control their health care. An Episcopal priest, former assistant chaplain of the Memorial Sloan-Kettering Cancer Center, and former Attorney General of the state of Missouri, Senator Danforth drafted the Patient Self-Determination Act and introduced it on October 17, 1989 – the day after the incumbent Attorney General of Missouri filed his *Cruzan* brief in the United States Supreme Court.[16]

> Commenting on the need for the legislation, Senator Danforth observed: Common law dictates that competent patients always have a right to refuse any and all treatment for themselves, even if doing so would certainly hasten death. . . . And a patient should not lose that right if he or she becomes comatose or unconscious and terminally ill or otherwise unable to make decisions. . . .
>
> Advance directives encourage people to discuss and document their views of life-sustaining treatment in advance. They uphold the right of people to make their own decisions. And they enhance communication between patients, their families, and doctors, easing the burden on families and providers when it comes time to decide whether or not to pursue all treatment options.

The bill, co-sponsored by Democratic Senator Moynihan of New York, was enacted in 1990 and became effective on December 1, 1991.[17] A companion bill was introduced in the House of Representatives by Sander Levin of Michigan.

The Patient Self-Determination Act requires every hospital, nursing home, home-health agency, hospice, and health maintenance organization (HMO) or similar prepaid health plan that receives payments through Medicare or Medicaid, to give every new patient or enrollee written information about their right to make health-care decisions, their right to refuse medical treatment, and their right to create advance directives for health-care. In addition, all such health-care providers must provide copies of their own written policies and procedures for implementing those rights. They must ask each patient being admitted to care, and each new HMO enrollee, whether he or she has signed an advance directive and must document the existence of any advance directives in the patient's medical record. In addition, providers must ensure compliance with state laws about advance directives. Finally, they must educate their physicians, staff, patients, and the community at large about advance directives.

Health-care providers may not require an advance directive as a condition either for admission or for the provision of care, nor may they discriminate based on the presence or absence of an advance directive. If a provider cannot implement an advance directive as a matter of conscience, that limitation must be disclosed to patients at the time of admission or enrollment.

Although neither the Patient Self-Determination Act nor the implementing regulations address how to determine a patient's capacity to make health-care decisions, many of the state laws concerning advance directives provide guidance.[18] Typically they require written certification of incapacity by one or two physicians (sometimes, by one physician and another licensed practitioner, such as a clinical psychologist) before an advance directive may be invoked. To fulfill their obligation to ensure compliance with state law, therefore, providers must learn what their state requires and develop forms and procedures for meeting those requirements.

The Act has had the salutory effect of prodding state governments (often working in collaboration with state bar associations and medical societies) to develop clear and accurate descriptions of their state law on advance directives and to distribute packages of informational materials to all of the health-care providers in the state. Those packages have been used to inform members of the community as well as to educate the physicians, nurses, social workers, clergy, and volunteers who work in health-care facilities and agencies. As a result, the number of individuals who create advance directives should increase dramatically over the next few years, as should the appropriate responses on the part of physicians, nurses and administrators.

Potential effects on organ donation

While it is too soon to see any effects on organ donation resulting from the increased use of advance directives, at least two outcomes are possible. On the one hand, enhanced awareness and availability of advance directives could increase the number of persons making anatomical gifts. Several states have included provisions for organ donation in their statutory forms for healthcare powers of attorney.[19] In other states, organ-procurement organizations could request that organ-donor information and cards be included in the packages of materials being distributed by state agencies to individual health-care providers.

At the same time, the number of suitable donors may decrease as a result of increased use of advance directives requiring that artificial life support be withheld or withdrawn. Patients, who might otherwise continue on ventilators to the point of brain death, may be removed from life-support pursuant to a living will or as requested by an agent appointed under a healthcare power of attorney. This likely would render their organs useless for transplantation. In addition, patients declining aggressive life-support may be cared for at home or in a nursing facility rather than in a hospital, thus making prompt removal of organs difficult if not impossible.

Since advance directives provide instructions about health care during life, and anatomical gifts do not take effect until death has occurred,[20] a directive to withhold or withdraw life-sustaining treatment will predominate in the absence of explicit instructions to the contrary. Thus, it will not be possible to maintain artificial respiration in order to preserve organs for transplantation in the face of an advance directive to forego life-sustaining treatment.

On balance, the heightened awareness of advance directives should increase the number of organ donors if state agencies and health care providers can be persuaded to include information about anatomical gifts with the materials about living wills and healthcare powers of attorney that must be distributed to all adult patients.

Notes

1. *Schloendorff v. New York Hospital*, 211 N.Y. 125, 129–130, 105 N.E. 92, 93 (1914) (Cardozo J.), quoted with approval, *Cruzan v. Missouri Dept. of Health*, 110 Sup. Ct. 2841, 2847 (1990).
2. See, e.g., *In re Conroy*, 486 A. 2d 1209 (N.J. 1985); *Eichner v. Dillon*, 426 N.Y.S. 2d 517 (App. Div. 1980) *modified in*, *In re Storar*, 420 N.E.2d 64 (N.Y. 1981) *cert. denied*, 454 U.S. 858 (1981); *Satz v. Perlmutter*, 379 So. 2d 359 (Fla. 1980); *In re Spring*, 405 N.E. 2d (1980).
3. *In re spring* 405 N.E. 2d 115 (Mass. 1980) (dialysis); *Satz v. Perlmutter*, 362 So. 2d 160 (Fla. Ct. App. 1978), *aff'd*, 379 So. 2d 359 (Fla. 1980) (respirator); *Application of Lydia Hall Hospital*, 455 N.Y.S., 2d 706 (1982) (dialysis); *Bartling v. Superior Court*, 163 Cal. App. 3d 186, 209 Cal. Rptr. 220 (Ct. App. 1984) (respirator); *In re Hier*, 464 N.E. 2d 959, review denied, 465 N.E. 2d 261 (Mass. 1984) (feeding tubes); *In re Application of Plaza Health and Rehabilitation Center*, (Sup. Ct., Onandaga Co., N.Y. Feb. 2, 1984) (feeding tubes).
4. Modell W. A 'Will' to Live (Sounding Board). N Engl J Med 1974; 290:907. See also Bok S. Personal directions for care at the end of life. N Eng J Med 1976; 295:367.
5. *In re Quinlan*, 355 A. 2d 647 (N.J. 1976), *cert. denied*, 429 U.S. 922 (1976); Society For the Right To Die, Right-To-Die Court Decisions, New York:The Society 1986; N.J.1–2.
6. *Cruzan v. Director, Missouri Deparatment of Health*, 110 S.Ct. 2841 (1990); Nancy Beth Cruzan, 1957–1990. Society For The Right To Die Newsletter 1991 (Spring); 10.
7. See, e.g., National Hospice Organization. Decisions in Hospice. Arlington (VA):National Hospice Organization, 1985:14.
8. President's Commission for the Study of Ethical Problems in Medicine. Deciding to Forego Life-Sustaining Treatment. Washington: U.S. Gov't. Printing Office, 1983; 145–147. The historical purpose was to protect people from agents who might act to their detriment, once they are unable to revoke a power of attorney.
9. See generally, Mishkin B. A Matter of Choice. 2nd rev. ed. Washington: American Association of Retired Persons (AARP), 1992.
10. Id., Table 1; see also, Society for the Right to Die (now, Choice In Dying). Refusal of Treatment Legislation. New York: The Society, 1991 and annual updates.
11. Id., Table 2. States without living will legislation are Massachusetts, Michigan, New York and Pennsylvania.
12. According to a survey conducted in 1988 by the American Medical Association, only 15% of respondents had prepared living wills. The survey was cited by Justice Brennan in his dissenting opinion in *Cruzan*, 110 S.Ct. at 2875, n.21.
13. U.S. Congress, Office of Technology Assessment. Life-Sustaining Technologies and the Elderly. Washington:U.S. Gov't. Printing Office, 1987; 33.
14. McCloskey E. The Patient Self-Determination Act. Kennedy Institute of Ethics J 1991; 1(2):163–169.
15. Schucking E. Death at a New York Hospital. Law, Med. & Health Care 1985; 13(6):261–268.
16. *Congressional Record*. October 17, 1989; 153:S.13566.
17. Omnibus Reconciliation Act (OBRA) of 1990, Pub.L. 101–508, §§ 4206, 4751, codified at 42 U.S.C. §§ 1395cc(f) (Medicare) and 1396a(w) (Medicaid).
18. See qenerally, Mishkin B. Determining The Capacity For Making Health Care Decisions. In Billig N., Rabins P, editors. Issues in Geriatric Psychiatry. Basel:Karger 1989; 151–166.
19. See, e.g., Cal. Civil Code § 2500; Ga. Code § 31-36-10 (1991); Idaho Code § 39-4505; Ill. Ann. Stat. Chap. 110-1/2, § 804-10 (Smith-Hurd Supp. 1991).
20. Mishkin B. A Matter of Choice. *supra* n. 9, Chapter III(c).

CHAPTER 60

The Oregon health plan

MARK GIBSON

I want to discuss the challenge of developing and maintaining equitable health care resource allocation policies in an era of limits. I want to talk not only about the problem and how it evolved, but particularly about how we can work together to find solutions to it. I want to put the Oregon Health Plan into its proper context – not in itself a definitive solution, but rather a political strategy – a process to achieve consensus on the policy objective and principles of reform and a framework in which such reform can take place.

The current U.S. crisis dates back to 1964 when President Johnson signed into law two dramatic amendments to the federal Social Security Act: Medicaid and Medicare. While the objective of this legislation was access to health care, it was not universal access. It focused on the needs of certain groups of Americans who were perceived as facing the greatest barriers to access. The government was responding to an immediate problem but not in the context of any comprehensive longterm policy. Thus, Medicaid and Medicare are based not on a policy of universal access but on a policy of access based on category.

Medicaid is a program not for all poor people but only for certain 'categories' of poor people. To be eligible for the Medicaid program one must fit into a congressionally designated 'category', such as families with dependent children or the blind or disabled. Just being poor is not enough. Poor men and women without children are ineligible even though they may be deeply impoverished.

Medicare, on the other hand, is a federally administered 'entitlement' program for those in the category 'over the age of 65'. It is not 'means-tested', which means that everyone over the age of 65 receives publicly subsidized health care regardless of whether they are impoverished or retire on $2 million a year.

Nonetheless, these two programs, along with the growth of private employment-based insurance policies, gave most Americans access to some form of third-party insurance coverage. But because universal access was never the policy objective, many people fell through the obvious gaps in this

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public/private financing system. But because of our fee-for-service reimbursement system, which allowed us to cost shift, most of these people were still treated and the costs simply shifted to someone who could pay, by increasing either their insurance premiums or their bills.

Widespread third-party insurance coverage and the ability to cost shift created the illusion that health care was free, since both providers and consumers were insulated from the true cost of treatment decisions. Consumers began to expect, not just access to the health care system, but to everything the system had to offer, including the latest 'high tech' and even experimental procedures. Providers, on the other hand, could enjoy the luxury of employing all treatments available, regardless of cost, as long as some potential benefit, however slight, might result.

Not surprisingly, this system encouraged dramatic and unchecked escalation in costs and, as a result of these astronomical cost increases, the major third party payers – the government and employers – began to look for ways to shield themselves from what was becoming a serious financial liability by adopting a variety of strategies: adding or increasing copayments and deductibles; dropping coverage; cutting provider reimbursement rates; and changing Medicaid income eligibility levels – essentially 'redefining' the poor for accounting purposes and throwing some people off the program altogether in order to maintain the benefit for others. Nationally, the average Medicaid eligibility is now less than 50% of the federal poverty level, which means that, in most states, a family of three making more than $5600 per year is considered too wealthy to qualify for state medical assistance.

So, in 1992, if you don't have public or private health insurance or considerable personal wealth, you are likely to lose access to the health-care system, squeezed into a growing coverage gap, either because you can't find a provider, who will see you, or because you avoid or delay seeking treatment out of concern for how to pay for it. Today this gap contains around 35 million Americans, the majority of them workers and their dependents.

The most obvious consequence of this 'non-system' is the rationing of health care in America: premature infants dying from respiratory distress because their mothers did not receive prenatal care; children dying of treatable spinal meningitis; young adults in diabetic coma, with lobar pneumonia, with serious wound infections – all because they delayed seeking treatment because they did not know how they would pay for it.

Such are the salient features of the current, federally created, health-care system – developed piecemeal and in response to the needs of specific interest groups, without the benefit of any long-range comprehensive policy objective, and unguided by a clear set of principles. In fact, the 'policy' implied by the current system is this: (1) not all citizens in need are entitled to medical services and procedures – including those of proven value and effectiveness; (2) need and ability to pay are not necessary considerations in determining eligibility for public assistance; and (3) the working poor although not entitled to healthcare assistance themselves, should be required through their taxes

to subsidize health care for others, many of whom are capable of paying their own way.

No mainstream politician in America could be elected by openly endorsing such a policy. But since, in the process of developing the current system, objectives and principles were never clearly articulated, these inequitable and indefensible policies were enacted into law. Neither the politicians nor the interest groups were ever required to defend or to be accountable for them.

Two other points need to be emphasized. Our experience over the past four years has convinced us that any effort to deal with this problem – whether in Oregon or Washington, D.C. – will succeed only if it addresses two fundamental issues: a recognition of fiscal limits and the need for clear accountability in health care resource allocation decisions.

Most of us are aware that there is a limit to the level of taxation the public will tolerate. And while unquestionably health care for the poor is a governmental responsibility, it is by no means the only one and, as health-care costs increase, states must either raise taxes or cut other programs – such as education, housing, and transportation, which themselves may have a direct bearing on health.

Thus the health-care budget, like any other budget, is ultimately finite, and an explicit decision to allocate money for one set of services means that an implicit decision has also been made not to spend money on other services. That, in essence, constitutes the rationing of health care, and legislative bodies do it every budget cycle. But it is rationing done implicitly, and for which there is no accountability.

The usual fiscal process, for example, allows public policy makers to take credit for 'saving the life' of a highly publicized child, who needs an organ transplant while assuming no accountability for the 40,000 American children who die each year before their first birthday. The only difference is that the 40,000 are not on the nightly news – they are invisible, even though many of them die preventable deaths as a result of implicit social and legislative decisions.

By contrast the Oregon Health Plan requires policy-makers to make health-care, resource-allocation decisions explicitly, to weigh the overall social costs and benefits involved, and assume clear accountability for the decisions themselves and for their consequences.

Our success to date in Oregon is due to two factors. First, we broke the health-care debate into four fundamental questions – (1) 'Who is Covered?' (2) 'What is Covered?' (3) 'How is it Financed?' and (4) 'How is it Delivered? ', – and used this 'matrix' as the framework for our decisionmaking process. Second, we have been operating from a common policy objective and from a consensus on a set of principles, which has guided our reform efforts.

Knowing what you want the reform to accomplish is the essential first step and it is amazing how many 'reformers' – including many of our national candidates and lobby groups – have never defined their policy objective.

What are we trying to accomplish? Is the objective to guarantee all citizens access to health care? Or is it to keep all citizens healthy? Obviously it is or should be the latter, and if the objective is to keep people healthy, we must recognize that health care is not necessarily synonymous with health. Health care is but a means to an end – not an end itself.

Infant mortality, for example, reflects more than just a lack of prenatal care. It also reflects environmental problems, housing problems, teenage pregnancies, and the enormous problem of substance abuse. We cannot improve the health of our nation if, for example, we continue to spend money only on the medical complications of substance abuse, yet ignore the social conditions which lead to addiction in the first place. And that means investing in things like education, housing, environmental programs, income maintenance, and economic opportunity. But as health-care costs increase, it becomes ever more difficult to make significant investments in these other social areas which would keep America far healthier.

Prior agreement on the policy objective of the Oregon Health Plan, then, allowed us to develop not simply a healthcare policy, but a health policy: an integrated approach in which resource allocations for health-care are balanced with allocations in related areas, which also affect health.

Establishing a common policy objective, however, is not enough. To achieve that objective, a series of incremental explicit choices must be made within the decision matrix. Each of the four questions can be answered in a number of different ways and, associated with it, each choice has a different set of political and policy implications and a different effect on a diverse set of political stakeholders representing vested and often conflicting interests. To insure that these interests remained focused on the broad policy objective – and to make sure that this focus transcended their narrower concerns – we did not start with a completed 'plan' but rather with a consensus on a set of principles that would guide the reform effort.

Among them were: (1) since health care is one of the important factors affecting health, all citizens should have universal access to a basic level of care; (2) there must be a credible process to determine what constitutes a 'basic' level of care; (3) this process must be based on criteria that are publicly debated, reflect a consensus of social values, and consider the good of society as a whole; (4) eligibility for a public subsidy must be based on financial need; and (5) there must be a mechanism to establish clear accountability for both resource allocation decision and for their consequences.

Thus, the Oregon Health Plan did not need to be 'sold' to the interest groups but rather emerged from them, moving through the decision matrix along the path of (political) least resistance, which remained consistent with the agreed-upon objective and the principles.

This has allowed a consistent course of action to be maintained over time because its incremental elements can be evaluated, not by the extent to which they are 'unfair' to one interest group or another, but rather by the

extent to which they represent a sequence of steps in a larger comprehensive strategy in which all interests are fairly represented and which will, in the long run, be more equitable and effective.

The development and implementation of our plan spanned the 1989 and 1991 legislative sessions. We started with the premise that everyone should have access to the health-care system. We recognized that Medicaid reform by itself is not enough. People in poverty constitute only about one third of those who are losing access to the health-care system. We realized that if we didn't solve the access problem of the 'working uninsured' as well as the access problems inherent in the current Medicaid program, the management of this problem would continue to be virtually impossible.

Thus, to the question 'who is covered?' Oregon has answered 'everyone' – universal access. SB 27 extended Medicaid eligibility to all persons below the federal poverty level, thus establishing a definition of the poor based strictly on need as opposed to category. SB 935 mandated comparable employment-based coverage for those with a family income above the federal poverty level, thus bringing the 'working poor' into the system.

With these two bills, we also answered the question of 'how financed?' We established the policy that society, through general tax revenues, was responsible for those living in poverty, and those with incomes above the federal poverty level would receive workplace-based coverage with the costs shared between the employer and the employee.

To ensure that an affordable insurance product will be available as small employers begin to assume their responsibility under the Plan, the legislature passed SB 1076, which enacts significant reforms in the small group insurance market including guaranteed issue, guaranteed reissue, prohibition of pre-existing condition exclusions, and price controls on small group insurance premiums. This is significant legislation which will force small-group insurance carriers to compete on the basis of price, product, and quality – not on the basis of avoiding risk.

By guaranteeing that virtually everyone in the state will have access to the health-care system, we have significantly shifted the debate from *who is covered* to *what is covered*, and created a framework for beginning to evaluate the effectiveness and appropriateness of the actual services we are buying with our health-care dollars.

This observation has an important implication for the development of public policy. Since it is the cost of the 'benefit' package for those who have health insurance that lies at the root of the problems, which are systematically excluding people from the system, a consideration of what constitutes a 'benefit' must play a significant role in resolving this crisis. This means that individual medical services must be evaluated on the basis of their efficacy and cost-effectiveness.

To determine the nature of Oregon's 'benefit' package, SB 27 established a Health Services Commission, an 11-member body appointed by the Governor and confirmed by the Senate and consisting of five primary-care phys-

icians, a public health nurse, a social worker, and four consumers. The Commission was charged with reporting on a comprehensive list of health services ranked in priority from most to least important, judged by criteria of clinical effectiveness and social values.

To carry out its charge, the Commission developed a method based on the prioritization of medical 'condition/treatment pairs'. The condition/treatment pairs were gleaned from two widely recognized classifications of treatment and diagnosis: the Physicians' Current Procedural Terminology (CPT-4 codes) and the International Classification of Disease (ICD-9 codes). The determination of clinical effectiveness was based on a literature search and on the input of panels of physicians, who were asked to provide certain clinical information about each condition/treatment pair in their respective areas of practice. Oregon physicians gave over 7000 hours of volunteer time to this effort.

The Commission also developed an extensive, broad-based, public outreach that integrated into the process the values society felt should be used to guide health-care, resource-allocation decisions. Under the auspices of an organization called Oregon Health Decisions, 47 townhall meetings, involving over 1000 citizens, were held around the state to generate this kind of input.

On February 21, 1991, after 18 months of work, the priority list was completed. It consists of 709 condition/treatment pairs divided into 17 categories. The categories are prioritized based on the Commission's interpretation of the social values generated from the public-involvement process. Within each category, the ranking of the condition/treatment pairs reflect the benefit likely to result from each procedure, the duration of the benefit, and the cost.

Services in the highest category were for acute fatal conditions where treatment prevents death and returns the individual to their previous health state (such as an appendectomy for appendicitis). Because of the high value placed on prevention by those participating in the community-outreach process, the category of maternity care (including prenatal, natal, and postpartum care) and that of preventive care for children ranked very high. Dental care and hospice care also ranked high as a direct result of the outreach process. At the bottom of the list were categories of services for minor conditions, futile care for terminally ill patients, and services that had little or no effect on health status.

The final priority list was given to an independent actuarial firm, which determined the cost of delivering each element on the list through managed care – a partial answer to the question 'how delivered?' The list and its accompanying actuarial data were given to the legislature on May 1, 1991.

SB 27 prohibits the legislature from altering the order of the priorities as established by the Health Services Commission, so in May and June of last year, the Joint Ways and Means Committee, starting at the top of the list, determined how much could be funded from available revenues and what

additional revenues would be needed to fund an acceptable 'basic' package. In this way, the question 'what is covered?' is linked directly to the reality of fiscal limits.

The old options of cutting provider reimbursement to below cost or changing eligibility levels were not available to the 1991 legislature. Reimbursement already had been determined by the actuary, and the state could no longer arbitrarily 'ration people' for reasons of budgetary expediency. Everyone retained coverage: universal access. Instead, the debate centered on the level of that coverage – on the answer to the critical question: 'what is covered?' – on what we as a society are willing to fund and thus guarantee, to all of our citizens.

Because the Committee did not have infinite resources, it was clear that increases in the health-care budget must come at the expense of other programs such as education, housing, or corrections. This enabled the legislature to begin to develop an overall health policy – a policy that recognizes that health can be maintained only if resources in a number of related areas are responsibly balanced. Because of the priority list, because the tools of implicit social rationing have been statutorily eliminated, and because it was clear what services would be included by incremental increases in expenditure level and what services would not be included, the legislature now is clearly and inescapably accountable not just for what is funded in the health-care budget, but also for what is not funded – a major departure from the current system.

The 1991 Oregon legislature appropriated $33 million dollars in new revenue, which funded all condition/treatment pairs through line 587 on the list of 709. The resulting benefit package, with its strong emphasis on preventive care, is eminently defensible. It covers virtually all current Medicaid mandates, including all preventive and screening services, as well as a number of important services not required by Medicaid including: dental services, hospice care, prescription drugs, routine physicals, mammograms, most transplants, and physical and occupational therapy. This benefit package serves as the minimum standard not only for the Medicaid program but also for the 300,000 Oregonians who will come into the system on the employer side by 1995, at which point we hope it will become the base standard for all policies written in the state.

At this time we are awaiting word from the Health Care Financing Administration to which we have applied for the Title XIX waivers necessary to implement the program and remain optimistic that they will be granted very soon. Let me emphasize again, however, that the Oregon Health Plan is not a substitute for definitive federal action. Until a national solution is enacted, however, it represents a significant improvement over the *status quo* and addresses the immediate health needs of Oregonians, which we can and should not have to wait for future Congressional action.

The greatest contribution offered by the development of the Oregon Health Plan, then, is that it has served as a forum to force the debate on

the uncomfortable yet inescapable issues that must be addressed if we are to succeed: limits, accountability, and a consistent, defensible policy guided by principle and conviction, not politics and expediency.

Beyond that, it has powerfully and effectively dispelled the 'conventional wisdom' which sadly dominates our nation's capitol – the view that the range and diversity of the various political stakeholders makes meaningful change politically impossible. Through the development and enactment of this proposal, we have demonstrated that these groups can be brought together in common cause.

Reforming our health-care system is difficult, but not impossible. We can do it if we are willing to be honest with ourselves; willing to be accountable to the public; willing to set aside narrow self-interest and to embrace reform based on policy and principle so that we and our children and all who follow us can share in a future that will continually recommit itself to the next generation.

CHAPTER 61

Stopping dialysis – different views

C. KJELLSTRAND

A common cause of death in dialysis patients in North America is the stopping of dialysis. In Canada, approximately 20% of such deaths are due to discontinuation of treatment, second only to cardiac events, which are responsible for 35% of all deaths. In the USA, stopping dialysis is responsible for approximately 15% of deaths, secondary to cardiac causes – 50% – and infection – 20% [1, 2]. Australia [3] reports similar figures, but figures from Europe are lower [4]. In the West, stopping treatment is directly related to age, while in Japan [5] it is inversely correlated with age (Fig. 1).

Two facts are obvious. First the startling difference between statistics in Japan and those from the West. Secondly, stopping treatment is a more common event in North America and Australia than in Europe. However, in Europe, twice as many patients on dialysis commit suicide as in North America. Thus EDTA reports that approximately 1% of all patients in Europe kill themselves compared to 0.4% in Minnesota [4, 6].

Risk factors for stopping dialysis

In the West, we have recognized several risk factors that predict death from stopping dialysis. There appears to be no difference in risk factors between men and women, but the incidence of stopping treatment in whites was more than twice that in blacks [7]. In persons under 60 years of age, discontinuation of dialysis is 3–5 times as common in diabetics as in non-diabetic patients [6]. Pre-existing disease is a major risk factor: among those who will die as a result of stopping dialysis, artheriosclerotic heart disease, peripheral vascular disease, cancer and COPD at the start of treatment is twice as common as in those who die of other causes [8]. No one has established the relative influence of age and these diseases that obviously covariate. In the patients over 70 years of age, discontinuation of dialysis, the most common cause of death, is responsible for almost 40% of all deaths [6, 7]. While pre-existing diseases often lead to discontinuation of dialysis, emerging complications do not seem to do so. Among our diabetic patients, 16% discontinued dialysis

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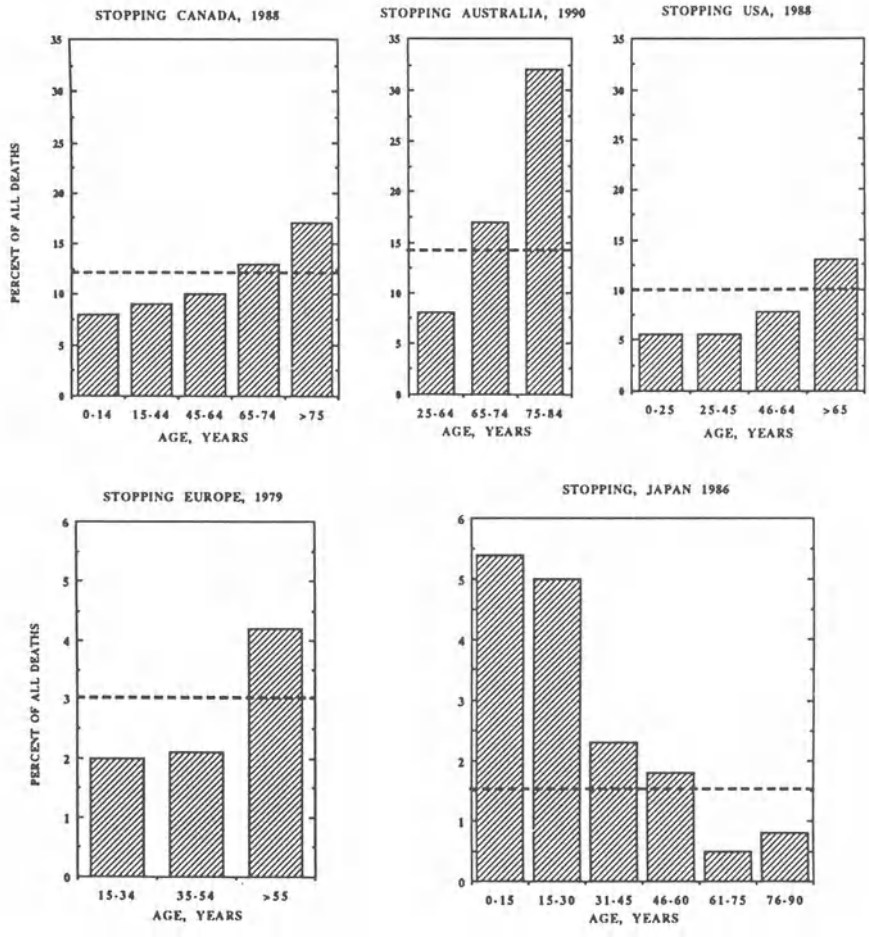

Fig. 1. Stopping treatment as a cause of deaths reported by several large dialysis patient registries [1–5]. Figures are expressed as percent of all deaths.

when they became blind; however, 7% of those who died of other causes also became blind. Similarly, although 2% of the patients who died because dialysis was stopped had amputations, 5% of those who died of other causes also had this procedure [6].

Old age, white race, and the presence of degenerative diseases when starting dialysis are the most common risk factors that predict death from discontinuation of dialysis.

Differences in view of discontinuation or use of life support

Although sex and mode of dialysis do not appear to be risk factors for discontinuation, patients of the two sexes and on different modes of dialysis differ in the frequency that they consider stopping. In one study 90% of men had considered stopping treatment, while only 50% of the women had. Similarly, 90% of those on hemodialysis and only 60% of those on CAPD had considered stanning dialysis [9]. In another study, more white patients than black considered discontinuation of dialysis [10] and more young patients with life-threatening disease wanted life support than older patients [11].

Concerning comparisons of the views of patients, their families and physicians, Seckler *et al.* [12] interviewed 70 patients with severe chronic diseases – heart disease, arthritis, psychiatric disease, chronic lung disease and others, and asked the patients, their physicians and their relatives whether they thought the physician should do cardiopulmonary resuscitation in the event of cardiac arrest (a) in the current state of health or (b) if the patient developed dementia. While there was close agreement between patients and their relatives (68% for dementia, 88% for current state of health) there was less agreement between the physician and patients (59% and 72%, respectively). In general, the family tended to overtreat the patient while the physicians were more inclined to give less treatment than the patient wanted. A study of patients who had survived cardiac arrest and cardiopulmonary resuscitation reached different conclusions. Of patients who survived and said that they were happy with the decision to be resuscitated, there was a 73% agreement between physicians and patients. In 27% of cases the physician was wrong in concluding that the patient did not want resuscitation. However, almost the same proportion was found in the patients who did not want resuscitation. Among these patients, the physicians erroneously thought that 63% wanted resuscitation and that only 7% did not. Age has not been carefully explored as a factor in choice of life support. Of 18 survivors of cardiopulmonary resuscitation, 6 of 9 under age 60 thought that it was right to have been resuscitated. However, only 2 of 9 patients over the age 60 thought that it was a good decision, and 7 believed it was a misfortune to have been resuscitated [13–15].

Molzahn, studying quality of life in dialysis patients, concluded that physicians overrated quality of life while nurses underrated it. Nurses thought that patients were unhappy because of poor sex life or poor family relations, while the patients themselves were disturbed chiefly by diet and travel restrictions, and some of them had difficulties doing household chores [16].

We tried to investigate how close the agreement was between those patients who were competent and died when they chose to stop dialysis, and incompetent patients whose family and physicians together decided to withdraw treatment [17]. In 155 patients who died when dialysis was stopped, 66

were competent and 66 incompetent, while in 23 competency could not be ascertained. We compared the competent and incompetent patients for 23 factors: age, sex, diagnosis, duration of disease and all these factors evaluated together, the year when the decisions were made, the site of dialysis (home, peripheral or in-centre), the type of dialysis, the time the patient had been on dialysis, where they lived, at home or in an institution, what support they had by friends and family members, how long it took the patient to die, where the patient elected to die and the presence of 10 emerging complications in major organ systems. Overall, the two groups of patients were similar. They differed in only three factors: more often than not the patients who were competent died at home, while those who were incompetent usually died in a hospital. The incompetent patient had many more emerging complications than the competent patient. With time, more commonly the family, rather than the physician took charge and initiated discussion concerning stopping dialysis in the incompetent patient. We concluded that, in the dialysis patient, families and physicians make decisions that are similar to those that the patient would have made for himself, and that these decisions can be safely left in the hands of the treatment team and the families.

Does participation in discontinuation discussions harm surviving relatives?

We evaluated this possibility by sending letters to 144 family members of patients who had died when dialysis was stopped. Of these, 50 letters were returned 'address unknown', 94 appeared to have reached the addressee, and 54 (57%) were returned [18]. In general, relatives felt no anger and as they looked back at it, were comfortable with the decision. Only one relative seemed to have been hurt by the decision, but this was due to family conflicts. The relatives judged that the physician and residents had been helpful in making the decision and that once the decision was made, the nurses and social workers had been particularly helpful in the patient's care. Of the patients, 26 – most of them on home dialysis – had discontinued treatment for no medical reason when dialysis seemed to be going well [19]. In these cases, the relatives showed the most anger and discomfort, and believed that the treatment staff had not been helpful in either getting involved or in making the decision. These decisions lead to no lasting ill-effects on surviving family members.

Follow-up of families of neonates who die when life support is withdrawn give similar results [20].

How the process can be improved – talking to patients

Cohen *et al.* found that only 10% of dialysis patients had discussed discontinuation with the nephrologist, and only 25% had discussed the issue with a family member [9]. This finding is similar to Lo's, who interviewed 152

patients with cancer, angina, chronic heart failure, COPD, chronic renal failure and other serious medical problems. He found that 55% had discussed discontinuation of life support with a relative and 15% with a friend, but only 6% had discussed it with a physician. Of those with severe disease, two-thirds did not want life support. Of these, 79% wanted their relatives to decide if treatment should be discontinued should they become incompetent and 13% thought the physician should decide. While only 29% of the elderly wanted life support, 57% of the young wanted it. While only 6% of these patients had had a discussion with their physicians, 90% wanted the physician to bring the topic up. After the discussion with Lo and his team, 71% of the patients felt that they had better control, 53% felt relieved, and 53% felt better cared for [11]. Twenty-two percent felt nervous, 16% were sad and 6% felt like giving up. There seems to be a latent desire to discuss the subjects of life support which physicians do not raise. The physician's own fear of death may explain why the subject is not brought up. Evaluating the fear of death, Feifel found that this fear was particularly pronounced in physicians, compared to non-medical people. He also found that, in medical students the fear of death slowly increased as they went through medical school [21, 22].

Shagal and his associates studied the use of advance directives in 150 dialysis patients [10]. They asked three questions:

(i) If the patient develops dementia should dialysis be stopped? On this, patients were evenly divided, 50% said yes, 50% said no. More black than white patients wanted to continue treatment.

(ii) If advance directives are written, how closely should caregivers follow them? Fifty percent of the patients thought their advance directives should be followed to the letter while 50% of the patients wanted to give a lot of leeway to decision-makers.

(iii) What factors should the directives consider? The patients gave equal consideration to pain, quality of life dignity, the chance of new treatment and religious beliefs.

Gorbien and co-workers investigated health perceptions and the wish for advance directives in 106 old (> 60 years) and 83 young (< 60 years) dialysis patients [23]. Of these patients one half had not considered end-of-life decisions. Only 11% had had such discussions and 83% had made no statements regarding intensity of care. Although one-half of the patients were familiar with advance directives, and 31% of the old believed treatment plans should be made, only 19% had made such directives. They failed to prepare ahead because they did not feel ill (41% of the older patients expected to live > 10 years longer) and many simply were not interested.

The studies of the Gorbien team, Shagal *et al.* and Lo and co-workers between patients on dialysis and those in need of other types of life support have obvious discrepancies.

Clearly, we need education of physicians, patients and their relatives.

It appears evident that legislation in the United States that enforces the use of advance directives will encourage physicians and patients to discuss

these issues. This movement will lead to a feeling of better control, relief and care among the patients.

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CHAPTER 62

Exclusion of old patients from dialysis in the USA, Canada and Sweden

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Acceptance for dialysis is rising everywhere in the world (Fig. 1) and there is no levelling in sight. On the contrary, in the USA, which accepts more than twice as many patients as all other countries, except Japan, the curves seem to rise steeply. Because there is levelling off and because the rise exceeds many times the increase in the population, there is an obvious unmet demand for dialysis everywhere.

Because the median age of patients at time of acceptance to dialysis is increasing [1–3], it is clear that in the last decade the increase is due almost exclusively to older patients. Thus, in Canada, as elsewhere, almost all of the additions to the dialysis population during the 1980s represent an increase in patients over the age of 65 (Fig. 2). Taken together, these two observations suggest that rationing dialysis by age has taken place and is continuing.

Nowadays there are few contraindications to dialysis. In my view, the only medical ones are: (i) a life expectancy of less than 6 months [12]; (ii) dementia, which renders patients unable to understand the benefits of dialysis; (iii) patients who do not wish to have the procedure. When in doubt, patients should be dialyzed for one or two months because it takes this time for a dialysis patient to stabilize [4]. If in doubt, make an agreement with the family and patient to do dialysis on a trial basis, of a limited duration; then one can stop dialysis easily if the patient does not benefit [5].

Who does not get dialysis?

Calculations and projections of the need for dialysis are done chiefly on the basis of retrospective studies of the trajectory of acceptance to dialysis, i.e. these consider only treated patients. However, one needs to know how many patients have died of uremia, i.e. those not treated. Fig. 3 illustrates this for the Province of Alberta, Canada. It shows the number of patients accepted for dialysis during the 1980s and the patients classified as having died of diseases leading to end-stage renal disease according to the International

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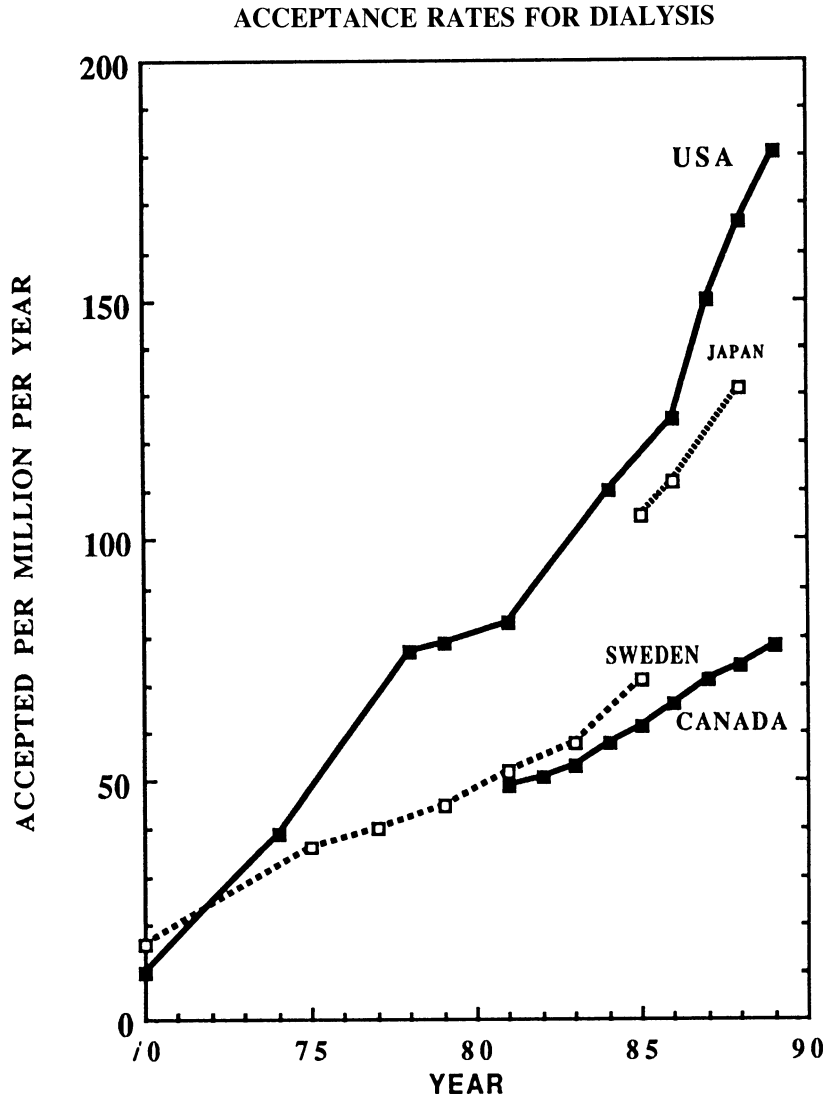

Fig. 1. Acceptance rate for dialysis per million population per year in USA, Japan, Sweden and Canada. The curves are increasing everywhere; there is no levelling is sight. It is paradoxical that, as we accept more patients, the curves become steeper. Clearly, the dialysis need is not saturated anywhere.

Classification of causes of death:

250.4	Diabetic nephropathy
403–404	Hypertensive nephrosclerosis
581–589	Nephritis/nephrosis
590–599	Chronic pyelonephritis
600	Other chronic renal disease
750	Congenital renal disease

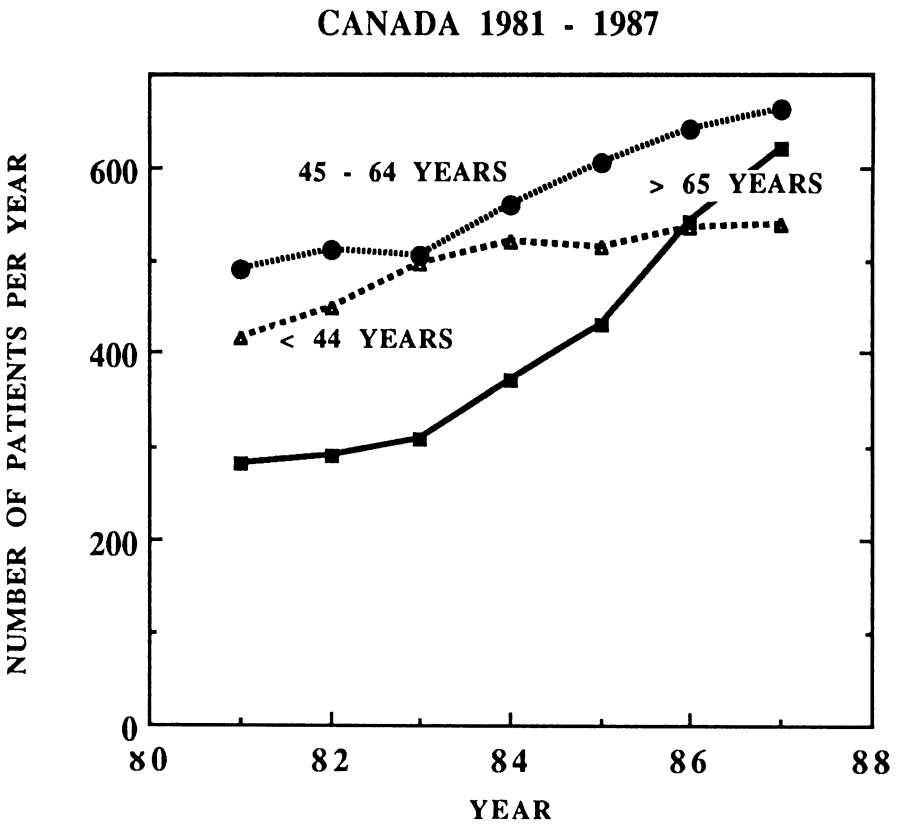

Fig. 2. Total number of patients accepted for dialysis per year in Canada from 1981–1987. While acceptance rates for patients below age 65 have increased only 25%, they have increased over 100% in those over age 65 and continue to increase. More older patients will be accepted for dialysis in the future.

We published details of such an approach earlier [6–8].

We obtained death certificates from Alberta Department of Health and a list of patients accepted for dialysis from the Canadian Organ Replacement Registry [2]. The same statistical information was obtained from Sweden for the year 1985, the last year that country has reliable statistics for dialysis [5–7]. Network 7, now Network 11, responsible for collecting this information for HCFA, provided the number of patients accepted for dialysis in Minnesota and the death certificates were specially obtained from the Minnesota Department of Health.

Patients accepted for dialysis were divided by the number of patients who died of uremia according to death certificates, plus those starting dialysis:

$$\text{Accepted percent} = \frac{\text{Began dialysis} \times 100}{\text{Began dialysis} + \text{Died from ESRD}}$$

These data were analyzed by age group.

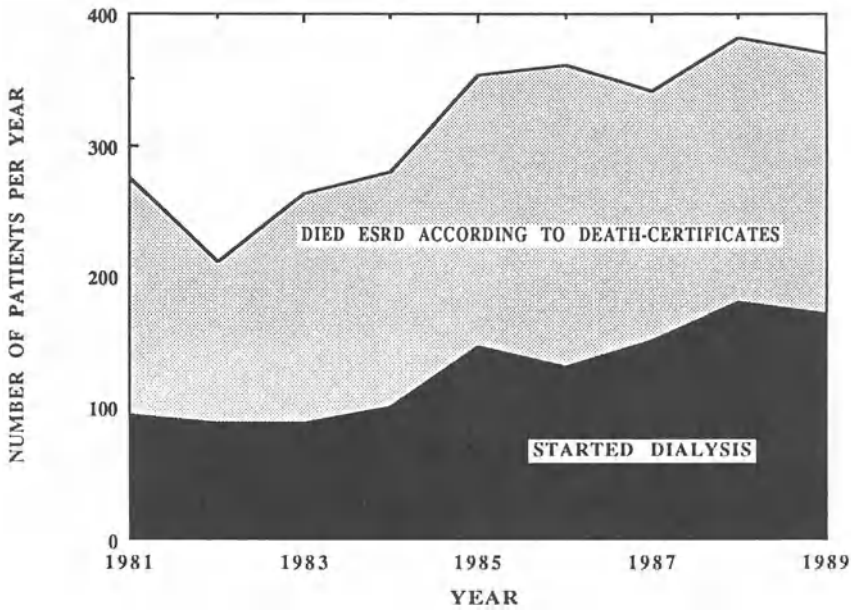

Fig. 3. Patients who died of end-stage renal disease (ESRD) or started dialysis in Alberta from 1981–1989. The number who started on dialysis has increased from approximately 90 to 180 per year. According to death certificates still more patients die of end-stage renal disease. Together, Figs. 1–3 indicate that many more patients in Alberta can benefit from dialysis.

The Alberta data were for the years 1986–1989, those from Minnesota for the years 1987 and 1988, and those from Sweden were for 1985. The total number of patients threatened by death from ESRD and accepted for dialysis in Minnesota and Alberta are shown in Fig. 4. Obviously, in Minnesota, many more patients are threatened by death from ESRD but also many more are accepted for dialysis than in either Alberta or in Sweden. Because the population of Sweden (9 million) is approximately twice that of Minnesota (4.5 million) and that in turn is twice that of Alberta (2.3 million), the figures can be directly compared because the number of years included are 1, 2 and 4 respectively. This is evident when comparing Fig. 4 (total number of patients) and Fig. 5 (patients per million population/pmp).

Fig. 6 divides those patients into age groups. In Minnesota, kidney diseases appear to be more common in all age groups except the youngest, but are particularly common in the very old patients.

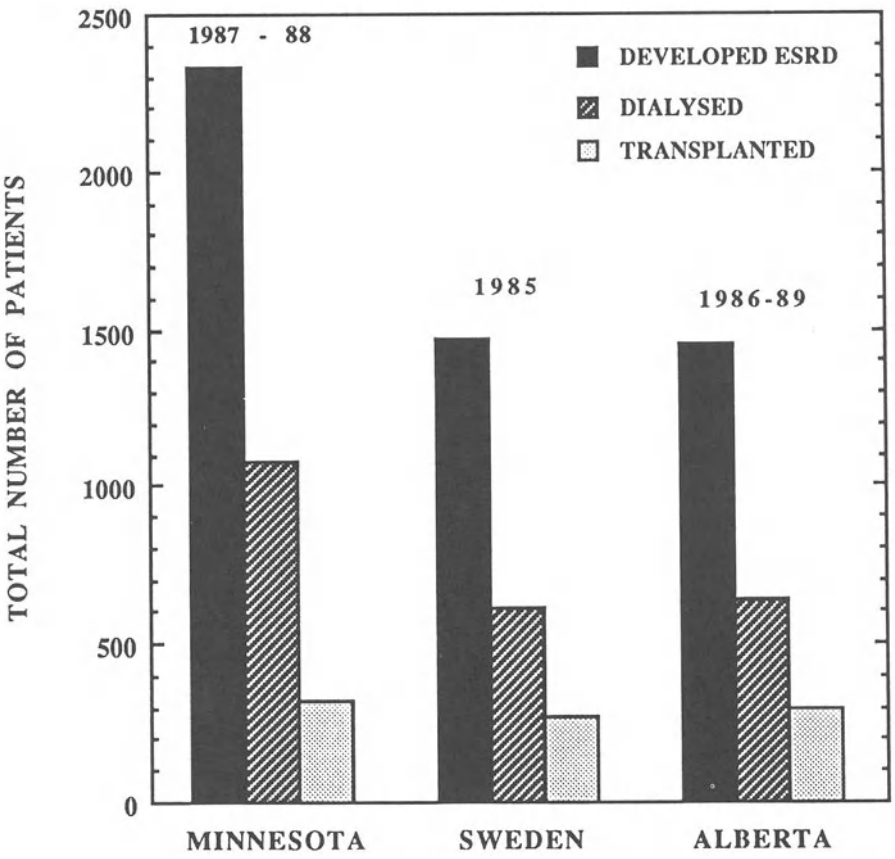

Fig. 4. The number of patients who started dialysis during a 4–year period in Alberta, a 2–year period in Minnesota and a 1–year period in Sweden. These figures indicate that more patients develop ESRD in Minnesota than in the other regions but there is still a large unfulfilled need everywhere.

The chance of receiving dialysis in the various regions

Concerning the chance of receiving dialysis in the various regions (Fig. 7), all three regions accepted almost all young and middle-aged patients between age 16 and 44. However, patients in Minnesota have a slight advantage compared to those in Alberta and Sweden. In all regions, only 40% of candidates in the age group 0–15 years, receive dialysis, because children or newborns with multiple malformations who are dying of renal failure are not offered dialysis. Also, most patients in the age group 45–64 years of age

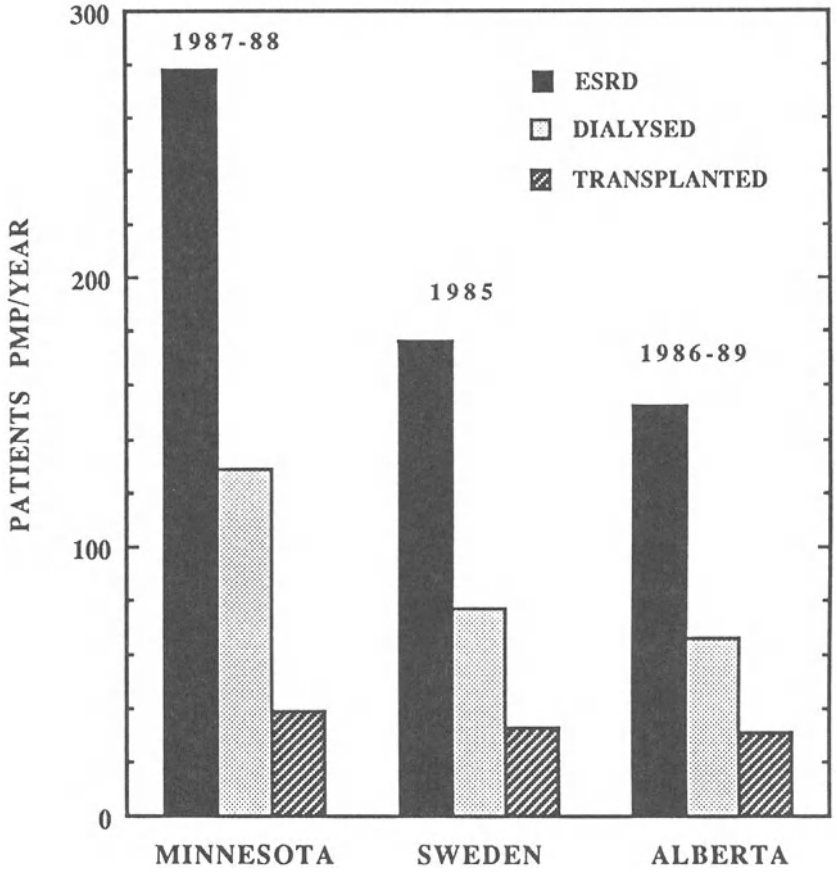

Fig. 5. The data in Fig. 4 expressed as per million population per year still yields the same conclusions. More patients in Minnesota develop end-stage renal failure and there are still large gaps in dialysis facilities in all areas.

receive dialysis, but again the acceptance rates are higher in Minnesota than other places. All three regions accept less than one-third of those over 65 years of age for dialysis.

Dividing the percentage of patients in Alberta and Sweden who receive dialysis by the percent chance of receiving dialysis for the same age group in Minnesota, one can compare the generosity of dialysis acceptance in Minnesota to that in Alberta and Sweden (Fig. 8). Among the very young, acceptance rates appear to be better in Alberta and Sweden, but fewer patients are accepted in these areas for all other age groups, and acceptance

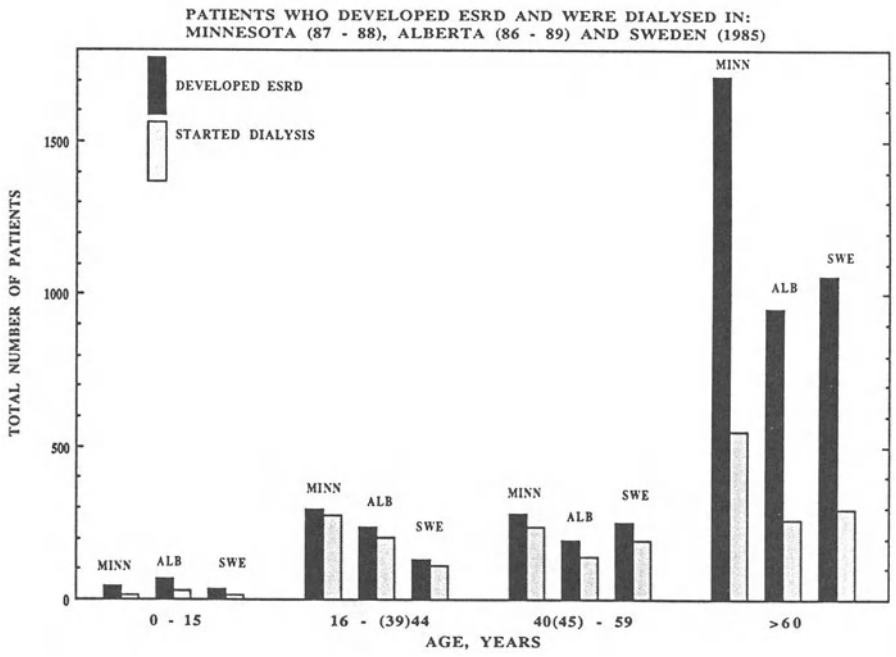

Fig. 6. The number of patients who developed ESRD or started dialysis in Minnesota (Minn), Alberta (Alb) and Sweden (Swe) make it obvious that renal diseases are conditions of the old. Renal disease is almost 30 times more common over the age of 60 than below age 15. Below age 59, most patients now start dialysis but it appears that in all areas, many patients older than 60 still die of renal disease without being offered dialysis. The different age limits are due to differences between the Swedish age ranges (from 16 to 39 and 40 through 59) and Alberta and Sweden with the same age ranges: 16–44 and 45–59 being used,

depends upon age. From age 15 through age 59, Swedes and Albertans have 85–90% chance of receiving dialysis compared to those living in Minnesota. Over the age of 60, it drops to 80%.

This figure indicates that many older patients still appear to die of end-stage renal failure and unless acceptance is limited by economic constraints, the acceptance rates per million in all three areas will continue to rise precipitously as in the past.

How accurate are death certificates?

Death certificates are not accurate and this is illustrated in Fig. 9. Four physicians read the charts of 150 patients from the Stockholm dialysis region who died in the year 1985. Death certificates for these patients stated that the cause of death was chronic renal failure. Of these patients, 38% died of causes other than renal failure, 9% died of acute renal failure, 13% were on

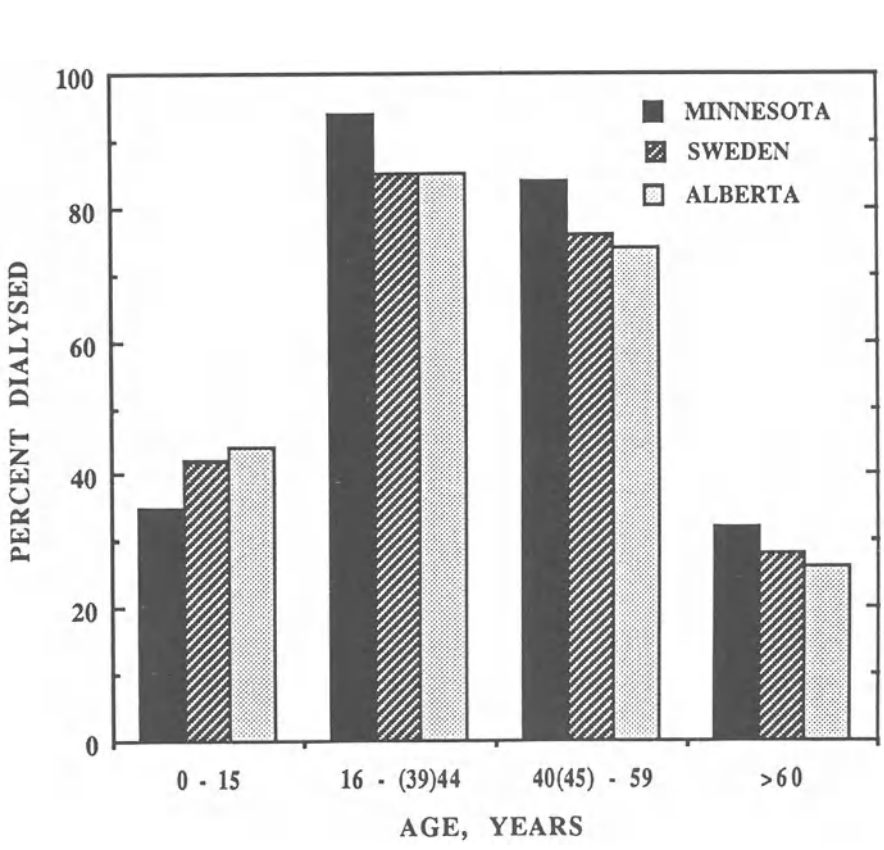

Fig. 7. The percentage of dialyzed patients in the three regions shows that in each area almost all patients between 16 and 59 receive dialysis. On the contrary, many patients younger than 16 do not. This is almost exclusively due to the fact that many babies with multiple malformations are assigned renal diseases as cause of death on certificates but the presence of other malformations would make it impossible to offer them dialysis (unpublished observation). In the age range > 60, less than one-third of the patients receive dialysis. In all age ranges over age 16, more patients are accepted in Minnesota than in Sweden or Alberta.

dialysis at the time of death and 40% of these patients died of chronic uremia. Thus the incidence of false-positive death certificates is 60%. However, there are also false-negative certificates, i.e. patients who died of chronic renal failure but were certified under another disease. Investigators have concluded that the false-positives appear to be approximately equal to the false negatives [5, 10, 11]. No one has established whether Swedish, US and Canadian physicians classify deaths in a similar fashion. We are now studying this matter.

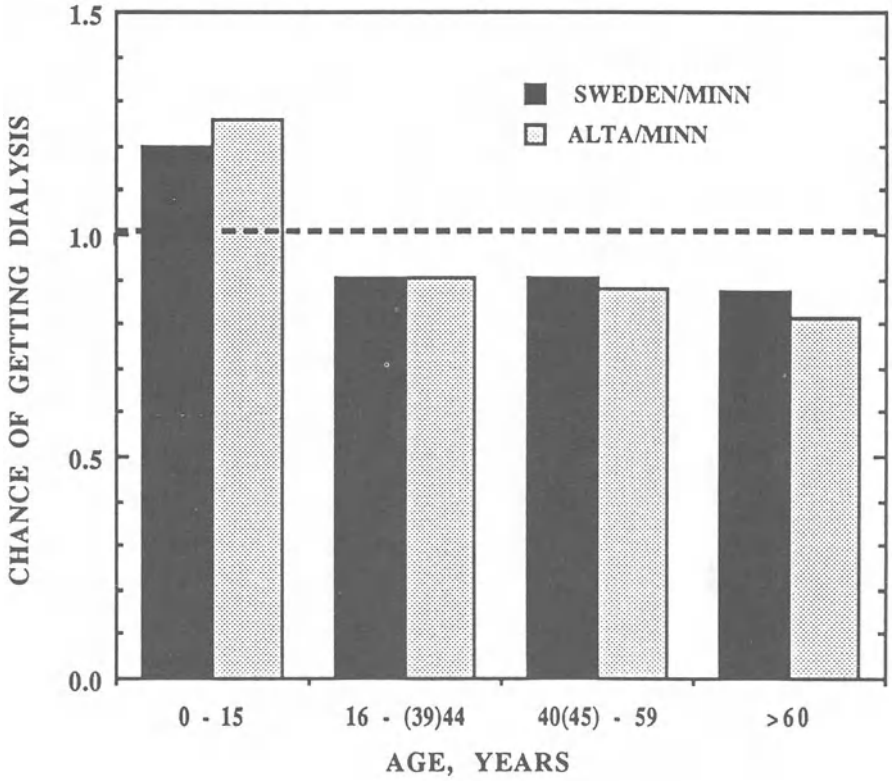

Fig. 8. The chance of receiving dialysis in Sweden and Alberta (Alta) is compared to that in Minnesota. The percentage of patients, who receive dialysis in Sweden or Alberta, was divided by the percentage of patients in the same age range who receive this treatment in Minnesota. These data indicate that the chances of receiving dialysis between the ages 16 and 59 are approximately 90% in Sweden and Alberta compared to Minnesota, but drops to about 80% to 85% over that age range (see text for discussion).

How many patients not offered dialysis would have benefited from this therapy?

The four physicians also examined the records of patients who died of chronic renal failure in Stockholm, to determine whether these patients would have benefited from dialysis. While they agreed on the number of patients who died of chronic renal failure, there was profound disagreement concerning how many would have benefited from dialysis. The Swedish physicians thought that 10% to 20% should have been offered dialysis, the US physician thought that approximately 50% should have been offered a trial of dialysis

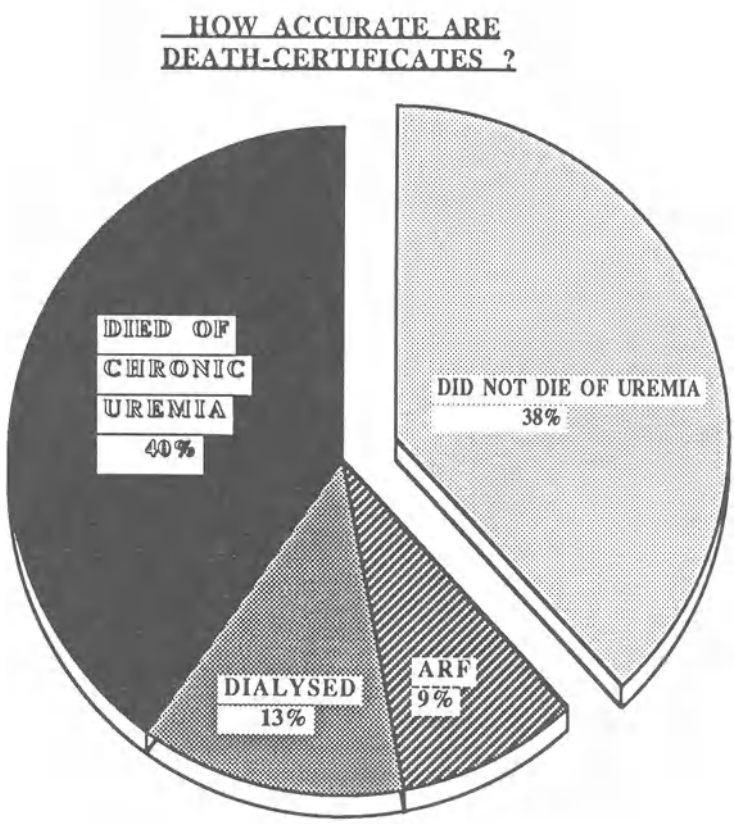

Fig. 9. Information gained from an examination of death certificates for end-stage renal failure in the Stockholm region [9]. Of the patients stated to have died of end-stage renal failure, only 40% died of chronic uremia, 13% had benefited from dialysis, 9% had acute renal failure and 38% did not die of renal disease.

[9]. In a similar study performed in England, the records of 20 patients who needed dialysis but who had difficulty because of age, diabetes, alcoholism, drug abuse or mental retardation, were sent to general practitioners, specialists in internal medicine and nephrology in the United Kingdom and to nephrologists in eastern Europe and the USA. While the general practitioners rejected 46% of the patients, and the internists 43%, the UK nephrologists rejected 29%. The US dialysis physicians rejected 2%! The Eastern European nephrologists rejected 47%. Obviously the system under which one works prejudices one's view [12]. In the United States where funding is secure, patients 'chase' machines as profit from dialysis can be invested in new machines. In Sweden and Canada, and particularly in Britain, where there are severe budgetary restrictions, machines always 'chase' patients. There is a shortage of dialysis facilities and new patients are not particularly

welcome because they put more strain on already strained systems. Not only do physicians shape the system they work under but the system also shapes physicians.

Another way to illustrate this is to study acceptance rates in different regions of Sweden. A review of patients per million population accepted for dialysis in Sweden in 1985 shows an almost 100% variation in acceptance rates between regions. This is due almost entirely to the fact that some regions take many older patients, and others take very few, while all regions seem to take approximately the same number of younger patients [5,8,9]. When these discrepancies were debated in the media, dialysis physicians in the region with the lowest acceptance rates retorted that they accepted everyone who could 'benefit'. The newspaper headline that said "We will not fight for more dialysis places", was accompanied by a photo of their oldest patients, 62 years of age [13].

Similarly, English physicians 'whitewashed' their decision to exclude patients from dialysis by reviewing those who died of end-stage renal failure in a region in England. From this review they concluded that none of the patients, who died without receiving dialysis would have 'benefited' from it [14]. Exclusion from dialysis was based on the fact that some patients did not speak English, or it was difficult to create a vascular access, or they had diabetes. At that time diabetes was a major diagnostic entity in those accepted for dialysis in USA and Northern Europe. An editorial in the British Medical Journal severely criticized the review: "Retrospective benign audits of this kind may have unintended but far reaching consequences. Governments may be encouraged to believe that they have succeeded when they have not, and doctors may think they are not making errors when they still have much to learn" [15].

Medical subterfuge as a cover-up for political decisions

Rationing is a consequence of insufficient resources. If physicians have to ration, the easiest of all factors to use is age. As Wetle has pointed out, in many instances age alone is used as a contraindication for any treatment, rather than the more subtle and more difficult to measure physiological variables [16]. Physicians, when forced to carry macroallocation to the bedside, are put in an impossible ethical situation. It is almost intolerable to deny any patient life-saving treatment if one thinks he could benefit from it. It is much easier to withhold treatment for an imagined physiologic contraindication, which one automatically ascribes as an unavoidable consequence of age. The behavior of English and Swedish physicians indicates this. The conflict at the bedside between beneficence, justice and advocacy for many patients is insoluble [5]. Physicians should never be forced to ration at the bedside but, when they have to, because they are poor advocates for their patients or because of ruthless and corrupt governments, they tend to

betray patients by using 'futility' (the absence of benefit) to cover up rationing (the absence of resources). It is a wonderful tool to get the monkey off one's back and remain a friend to those in power, because exclusion by age alone allows one the illusion of believing that there is no morally hard choice.

Political decisions

In both Canada and Sweden it is easy for the government to decrease funding for dialysis because the government in both countries controls all budgets. In the United States such economics are much more difficult because of the laws governing Medicaid and Medicare. Politicians have difficulty limiting dialysis funding and dialysis has competed successfully for the money. In many ways the American system for funding dialysis has been a happy marriage between ruthless capitalism, where one can earn money on dialysis and reinvest the earnings in more machines to make more money, and socialized medicine, i.e. the government pays for it. So far, the government has not determined a method of controlling access. In Canada and Sweden it is hard to get money for dialysis. First, as the need for treatment grows, one has to fight with the local hospital, which already is strapped for funding. Secondly, once the administration has been convinced, there is a second fight with bureaucrats and politicians who are hesitant to increase any payment for medical care. This is somewhat ironic since polls conducted in both Sweden and the United States indicate that the only thing people are willing to pay more taxes for is the medical system.

Is dialysis expensive?

In all three countries unbelievable waste dwarfs the cost of dialysis. Every other second of the Gulf War cost $34,000, the equivalent of one life-year on dialysis. If these costs had been assigned to dialysis, they would have covered the entire cost of dialysis for the United States from 1990 to 2050. In Canada, some physicians believe that the government has a secret agenda to cut funding for medical care [17]. Servicing the national debt, money paid for unnecessary cars, electronic gimmicks, and funding of friends' businesses would more than pay for all dialyses in this country. Sweden passed a law whereby all Swedes were promised a full salary from time zero when they developed even the most trivial illness. If the Swedes would consent to have a common cold for 48 minutes without any salary payments, that would take care of the total annual cost for dialysis. I know of no economic reason why we cannot offer dialysis to all who need it in all countries, even if there were twice as many ESRD patients as there are at present. No country has gone bankrupt because of medical services.

Should one dialyze the elderly?

Opponents have raised four arguments against dialysis of the elderly.

First, their time is short. Is this true? Of patients under age 30 who are accepted for dialysis in the United States, 60% are expected to survive for a decade, while only 10% of patients over age 65 will survive for 10 years [1]. However, if one divides the life expectancy of persons who do not need dialysis by those of the same age who need dialysis, this fraction decreases with age (Fig. 10). Thus, while the five-year death rate of a dialysis patient younger than age 44 is 20 times that of the general population, it is only double in patients older than age 75. Of course an elderly patient beginning dialysis will not live as long as a younger one, but this cannot be used in an argument against dialysis.

Second, concerning quality of life, studies in Minnesota [18], California [I9], England [20] and Sweden [21] comparing young patients to old have shown that the elderly are much more satisfied and much less stressed by dialysis than the younger patients. There is no reason to exclude old patients because they 'suffer': old kidney patients are happier than young ones.

The third argument, that of economic constraint, was discussed earlier.

Finally, one might argue that the old should defer to the young but this stand is hard to defend. Present dialysis units were built with tax money contributed by people who paid in good faith assuming that they would be cared for when elderly and ill, just as we now pay taxes that are not used until we become old and ill. It is wrong to deny these patients such treatment. The elderly have paid for treatment and we must not withhold it.

Callahan asserts that medicine is now too expensive and must be rationed. He has proposed an age-based schedule describing the services society will offer patients [22]. Although his proposal has the virtue of disinterested intelligence, it is hard to accept a scheme that denies the elderly the use of their tax money for their medical care as anything more than an insurance scam in which politicians cheat the citizens. In any event, the acceptance of such a proposal requires extensive societal discussion; it is not a medical decision. Physicians must never use medical subterfuge for social Darwinism.

Conclusion

Much remains to be done to expand dialysis to the old. All three countries, but particularly Canada and Sweden, have many patients who could benefit from dialysis, and there seems to be no economic reasons why they should not receive this treatment. We need to tell this to bureaucrats and politicians and to press them to make the necessary money available.

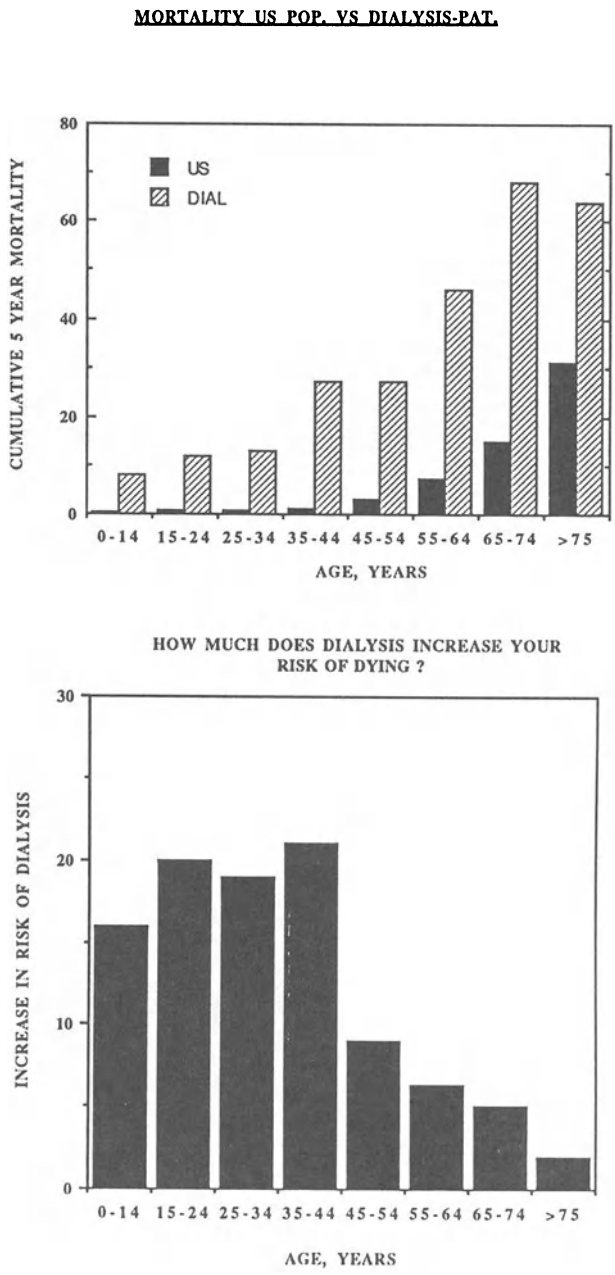

Fig. 10. Comparisons of survival between dialyzed patients (dial) and the US population at large (US). The top half of the figure shows the 5–year mortality calculated on age. Almost no one in the US population below age 54 will die in the next 5 years, but many dialysis patients do. After age 54, there is a steep increase in the chance of dying in the next 5–year period for both the general population and for dialysis patients. The lower half of the graph compares the chance a dialysis patient has of dying in the next 5 years with that of the general population. The risk of dying after starting dialysis decreases markedly with age. While below age 44 the chance of dying on dialysis is 20 times that of the general population, it falls to only twice that if the patient is over 75 years of age.

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CHAPTER 63

Decision to forgo ESRD treatment

NANCY BOUCOT CUMMINGS and PAUL W. EGGERS

The two ESRD treatments of dialysis and kidney transplantation have had a major impact on the nascent field biomedical ethics in the 1960s. The high cost of ESRD treatment and an absolute shortage of transplantable kidneys posed grave problems concerning allocation of scarce resources in the United States until the passage of the ESRD Amendment, PL 92–603 in 1972. The annual cost of dialysis per individual was and remains over twice the average US income and the severe shortage of transplantable cadaver kidneys continues.

Once ESRD treatment was broadly available to entitled Americans, other ethical dilemmas arose. The advent of life-sustaining technologies in general and specifically dialysis called for difficult decisions about their initiation and termination by health professionals as well as by lay people. Dialysis is unique among life-sustaining technologies because most patients with ESRD are conscious and able to evaluate their quality of life and the 'trade-offs' involved in life on a machine. However, studies of quality of life that compare the views of patients with those of professionals often show much dissonance in both directions. Nephrologists and other health professionals involved with dialysis patients may have views vastly different than do patients concerning what constitutes a 'good', 'bearable', or 'unbearable' quality of life [1–4].

A Canadian group [5] that studied ESRD patients on dialysis and after transplantation, found a strong correlation between increased feelings of helplessness and depression and low values of perceived control. The literature [1] concerning quality of life, which includes issues of support systems, adjustment and rehabilitation and special aspects related to home dialysis, confirms many of the observations made about chronic and catastrophic diseases. Thus many patients choose to withdraw from dialysis both among those who have been treated for a relatively long period and those who have had a 'trial' on dialysis and elected not to continue. The reporting of data about withdrawal may be underestimating the size of the problem because some patients can disregard dietary and fluid restrictions with deleterious or fatal consequences.

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The academic field of biomedical ethics began in the mid-1960s when philosophers and theologians became intrigued with the issues raised by allocation of the scarce and costly resources for treatment of chronic renal failure. The Seattle Admissions and Policy Committee were concerned about individual rights. They evaluated medically suitable patients by nonmedical criteria such as sex, medical status, number of dependents, income, net worth, emotional stability, educational background, nature of occupation including past performance and future potential, and references. This 'God Committee' [6] was broadly representative of Seattle's citizenry: a lawyer, a minister, a housewife, a labor leader, a state government official, a banker, a surgeon and two physician advisors.

Ethical considerations

Four ethical principles [7] used frequently in biomedical considerations (and recently named 'principlism') namely: autonomy, beneficence, non-maleficence, and justice provide a useful framework for the assessment of patients' treatment and for withdrawal of treatment. Also in North America there has been a marked shift from the paternalism of former times towards patient autonomy and informed consent.

How do these four ethical principles apply to treatment of ESRD patients? Autonomy allows the independence to make one's own choice, including that of never starting and of discontinuing ESRD treatment. Beneficence ('doing good') is paternalistic if the physician makes the decisions and does not share this with the patient. Non-maleficence is the familiar caveat: *primum non nocere* (first do no harm). Justice is a fairness principle. Consciously or unconsciously, decision makers also consider similar principles: integrity, fidelity, confidentiality, right to privacy, liberty, charity, compassion, respect for persons and for the sanctity of life, and adherence to the 'Golden Rule'.

Five alternatives to the 'principals approach' to bioethics, which are in the germinal process, include phenomenology [8], medical hermeneutics [9, 10], narrative, the 'new casuistry' [12, 13], and virtue [14–16]. Phenomenology describes clinical situations, their relationships and implications for more clinically based ethics. The hermeneutical approach to bioethics interprets moral experience as it relates to health care deliver. The narrative approach uses the patient's 'story' or history. The casuistic mode of moral reasoning uses paradigms from which its proponents derive a carefully though out consensus and reasonable certitude. The virtue approach addresses both individual and community qualities of character.

William May [17] has identified four models which affect treatment decisions: warrior, parent, contractual and covenantal models. Respectively, these models approach medical treatment as: a battle against disease and death; the physician as a parent who knows 'what is best'; the physician and patient (or his/her surrogate) developing an explicit contract in which the

health professional is the contractor and the patient receives the services; and lastly medical-care arrangements as a covenant spelling out mutual commitments. Successful treatment requires that the patient and caregiver have similar views of the goals of treatment and usually this is best achieved within the convenantal model.

In the past several decades, society has moved from a state of awe over medical 'miracles' to one of concern that technology merely prolongs the dying process and even may increases suffering. Increasingly ethicists, the media, policymakers, and the public raise doubts about prolonging life for patients, who are irreversibly unconscious (in a persistent vegetative state [PVS]), or who suffer inordinately. Thus, the foremost issue in the overuse of 'high technology' is that of withholding or withdrawing care. On August 19, 1991, the lead article in the *New York Times Week in Review* was about patients' rights to reject aggressive care [17]. Public concern was evident in the popularity of Derek Humphry's book, *Final Exit*, published by the Hemlock Society; it rose to the top of the New York Times 'How To' best seller list, 25 percent ahead of the next book on the list. The initial printing, 160,000 copies, sold out within a week.

How common is voluntary withdrawal from dialysis? Data of limited accuracy are collected by the Health Care Financing Administration (HCFA) of the U.S. Department of Health and Human Services (DHHS) part of medical and financial data from all beneficiaries. Causes of death include voluntary withdrawal from dialysis, suicide, and hyperkalemia and cardiac deaths, some of which may be due to fluid overload, possibly a hidden 'voluntary' means of withdrawal.

Increasingly, nephrologists face ethical dilemmas on a daily basis, which now intrigue philosophers and theologians. Kidney teams now make a major effort to inform patients concerning all aspects of complex life-support technology so that they can be genuinely informed. Usually they are given the option of withdrawing from treatment, if it becomes too burdensome. Dialysis can sustain life in patients with kidney failure but it has its drawbacks. According to Holden [18],

> Even if an individual patient prefers death to a prolonged illness, the decisions might be denied by the medical team which does not consider death an option and who fear legal entanglements. Dialysis patients who exercise their right to die must do so with many subtle harassments. For a great majority of dialysis patients, a meaningful life is an increasingly reachable goal. Each person should be able to choose and should be assisted in making an independent choice by having adequate information and demonstration of emotional support. The presence of alternatives may tend to reinforce an individual's feeling that life, even with difficulty, is worth living as long as one is in control of the human decision making process.

Kilner [19] did the first study of decision making in chronic renal failure. He surveyed medical directors of dialysis and of kidney transplant centers in

the United States and had a response rate of 40 and 50%, respectively. He evaluated 16 selection criteria. Dialysis and the transplant-center directors concurred in the following 'very important (selection) criteria'; in descending order of priority those are: medical benefit of treatment, likelihood of benefit, quality of benefit, willingness to co-operate with the treatment regimen, and length of benefit. In circumstances of plenty, there were 11 other criteria of lesser significance: psychological status, age, special responsibilities, required sources, support systems, social value, and scientific progress. Scarcity has a striking impact upon dialysis selection criteria. The percent of center directors who would consider length of benefit increased from 71 if resources were unlimited to 96 if resources are limited; the percent for quality of benefit went from 44 to 97; for ability to pay from 4 to 45 percent; for medical benefit from 62 to 95 percent. The most dramatic shift concerned the age criterion, which went from 10 to 85 percent. If finances were restricted, 43% of directors would consider ability to pay relevant.

Withdrawal from dialysis

The increasing age of patients entering ESRD treatment affects patterns of treatment, of withdrawal from treatment, and of complications because co-morbid conditions increase with age. In the USA, HCFA and the USRDS have demographic data that show the patterns of patients on ESRD programs. Undoubtedly the data on 'withdrawal from dialysis' are underreported because dialysis patients usually are well-informed about the hazards of excessive fluid intake and of potassium. Hence deaths due to these complications may be masked and later attributed to cardiovascular causes rather than reported as instances of 'voluntary' withdrawal from dialysis.

For the period 1987–1989, the USRDS [20] found that 8.51% of deaths were due to withdrawal from dialysis – a percentage representing, on average, 1604 deaths/year. The percentage of deaths in specific groups was distributed as follows: male 7.8%; female 9.35%; black 4.48%; white 10.41%; with increasing age, the proportion rose from 3.5% for those under 20 years to 11.45% for those 65 years of age and over. Also USRDS reported withdrawal from dialysis as 11.2 per 1000 patient years at risk; those under age 20 had only 0.6 deaths per thousand patient years while those 65 years of age and over had 31.5 deaths/1000 patient years. Diabetic patients withdrew from dialysis three times more frequently than did patients whose primary renal disease was hypertension or glomerulonephritis. Further, considering race and age of hemodialysis patients, diabetic patients withdrew from dialysis more frequently in every category analyzed. Also, in the first 90 days, deaths due to withdrawal from dialysis are markedly higher for those between 65 and 74 years of age and for those over 75 years, than for those between 45 and 64 years of age.

Eggers [21] studied voluntary withdrawal from dialysis by evaluating the

20,028 deaths in 1987 that were linked with Medicare hospital stay records (of the total of 22,670 ESRD deaths in 1987, 2642 were in patients covered by other insurance). Fifty-five percent of all deaths were in patients 65 years of age and over. He selected for analysis 71,201 hospitalizations in 1987 and 1986 with an admission date within 365 days of date of death. HCFA death notification forms (No. 2746) were analyzed in two categories: voluntary withdrawal from dialysis or death from another cause. Voluntary withdrawal was directly related to age. No deaths in the youngest group (less than 14 years of age) were reported as voluntary withdrawal, while in the 15–24 age group less than 5% were so classified. In the group 75 years and over, more than 12% of deaths were listed as voluntary. Those withdrawing were less likely (5.9%) to have had no hospital admissions than were those who died from other causes (9.8%). Those withdrawing were slightly more likely to have been hospitalized for neoplasm (12.7%/9.7%), but were not more likely than other deceased to have been hospitalized for diabetes, hypertension, heart disease, congestive heart failure or pneumonia. In those who were hospitalized for mental disorders, 20.5% of deaths were due to voluntary withdrawal compared to 12% among other patients without mental illness. The length of stay per hospital episode was longer for those voluntarily withdrawing from dialysis than for other deceased. The hospital spent about $1200 more on those who voluntarily withdrew from dialysis.

Demographics

In their retrospective study of mortality among dialysis patients, Neu and Kjellstrand [22] reported that 22% of deaths were due to voluntary withdrawal. Withdrawal was equally distributed among patients who were and who were not (mentally) competent to make decisions about termination of dialysis.

In evaluating causes of death among all Michigan dialysis patients from 1980 through 1985, Port [23] noted that discontinuation may be underreported and that there was a "markedly higher withdrawal rate in older, white, and diabetic patient groups, and that during recent years, there has been a striking increase in withdrawal rates even after adjustment for other factors". Of 5208 patients who started ESRD treatment in Michigan during 1980–1985, 282 died and 9.4% of these deaths were due to voluntarily stopping dialysis. This group was made up of 11% women; 8% men; and 12% white, compared to 4% black patients. Between 1980 and 1986, death rates due to stopping dialysis increased by about 60%. Under age 49 years, 0.1 to 3.4% of deaths were due to voluntary discontinuation while, in patients over 80 years of age, 56% of deaths were due to voluntary withdrawal. Port *et al.* speculate that religious and cultural attitudes might explain the difference in withdrawal between white and black patients. Another explanation may be differences in reporting [24].

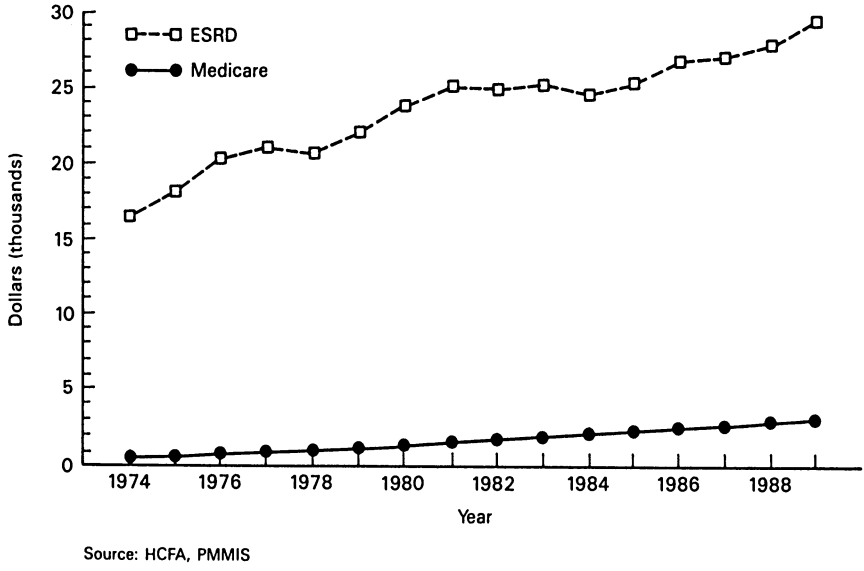

Fig. 1. Medicare and ESRD expenditures (dollars per capita) 1974–1989.

Because the Medical ESRD Program covers 92–95% of Americans and has a detailed data system, which is linked to reimbursement, its Program Management and Medical Information System (PMMIS) provides a reasonably reliable picture of causes of death, if one allows for inaccuracies in diagnoses. This PMMIS data provides an estimate of the importance of voluntary withdrawal from dialysis as a cause of death and a measure of the increase of voluntary withdrawal among older ESRD patients.

In 1989 total Medicare ESRD expenditures in US dollars reached $4.4 billion, which represented 4.5% of the total medicare expenditures of $98.7 billion. In contrast, in 1989 the per capita expenditures for ESRD patients, averaged $29,700 against average per capita expenditures for all Medicare patients of $2937 (Fig. 1).

Over 40% of new patients coming onto the ESRD program last year were 65 years or older. In 1990 19,137 ESRD patients were 65 years and older, a five-fold increase compared to 1978 (Fig. 2). While 10% of all deaths (excluding data missing) were listed as 'voluntary withdrawal', 12.4% of deaths among the 65-and-over group were due to voluntary withdrawal (Table I). Hyperkalemia, suicide, and some cardiac deaths related to fluid overload might be considered as voluntary withdrawal, indirectly. Fig. 3 compares voluntary withdrawal by race, among all ESRD patients and among those 65 years and older. In each racial group, the incidence of voluntary withdrawal by those 65 and over is higher than that for all ESRD patients in the

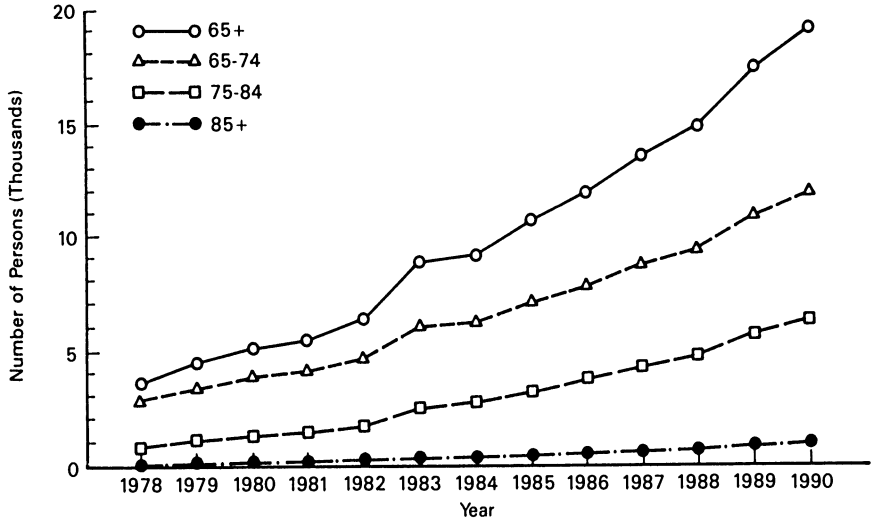

Fig. 2. Medicare ESRD program incidence by age and number of persons 1978–1990.

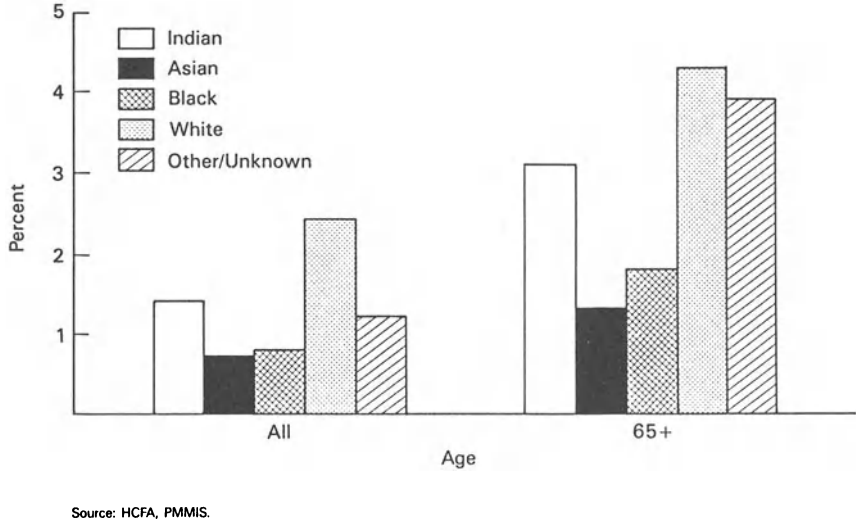

Fig. 3. Voluntary withdrawal from dialysis (within 12 months of onset of renal failure). Medicare ESRD program 1985–1989 incidence cohort by age and race.

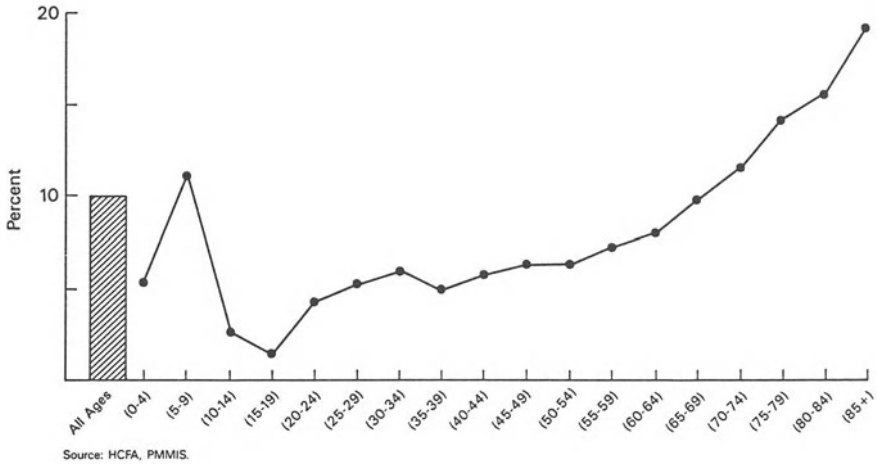

Fig. 4. Voluntary withdrawal as cause of death 1985–1989 incident cohorts percent distribution (excluding missings).

period 1985–19889. While 10% of all ESRD deaths were due to voluntary withdrawal, there is a gradual increase of such deaths by five-year-age cohorts with increasing age. Voluntary withdrawal was the cause of death in 19.2% of persons 85 and older (Fig. 4).

A committee of the Institute of Medicine (IOM) recently studied ESRD and addressed, with other ethical issues concerns about starting and stopping dialysis. This study, Kidney Failure and the Federal Government [25], which was sponsored by the U.S. Congress had three major ethical concerns: acceptance of patients for treatment; termination of treatment; and ethical questions for caregivers who deal with problem patients.

Table I. Death by cause. Medicare ESRD 1985–1989 incident cohort percent distribution (excluding 'missings')

	Cardiac*	Cerebro-Vascular	Septicemia	Hyperkalemia	Voluntary Withdrawal	Suicide	All Other†
All	45.3	6.1	9.3	1.2	10.0	0.2	27.9
0–34	33.6	5.8	10.4	5.2	5.3	0.5	39.2
35–64	45.9	6.1	10.1	1.4	6.9	0.3	29.3
65+	45.9	6.1	8.7	0.7	12.4	0.2	26

* Pericarditis, Acute Myocardiac Infarction, Other.

† Embolism: Air, Pulmonary; Hemorrage: GI, Vascular, Other, Pulmonary Infection; Viral Hepatitis; Infection; Pancreatitis, Accidental: Death, Other; Unknown: Other.

Source: HCFA, PMMIS.

The committee, recognizing this concern (an increasing number of patients with limited survival possibilities and relatively poor quality of life), believes that patient acceptance criteria should be medical, not economic, and based on concern for the best interest of individual patients. They rejected age as a criterion for acceptance for ESRD treatment because they did not consider it to be a predictor of potential benefit for the individual patient. Whatever the age of occurrence, comorbid conditions tend to be 'primary determinants of quality of life and of survival'.

Further the IOM [25] report asserts, "Decision-making about the initiation of treatment should result from informed discussion among the patient, the family, the physician, and other caregivers. ESRD patients usually rate their quality-of-life higher than do 'objective' observers." Patient preferences must be respected in decisions about their care. Often clinical judgment with patients and/or family preferences may indicate that (compassionate) palliative terminal care is more appropriate than life-extending care. The patient's option should not be treatment or abandonment but rather options between different goals of treatment.

The committee recommends that patients, clinicians in adult and pediatric nephrology, and bioethicists should develop guidelines for evaluating patients for whom the burdens of renal replacement therapy may substantially outweigh the benefits. These guidelines should be flexible and encourage the physician to use discretion in assessing an individual patients. Nephrologists and other clinicians should discuss with all ESRD patients their wishes about dialysis, cardiopulmonary resuscitation, and other life-sustaining treatments and encourage documented advance directives.

At a time when he was a member of the New York State Supreme Court, Judge Benjamin Cardozo affirmed the broader right to privacy – a statement that many courts interpreted to include the right to make health-care decisions for oneself. Cardozo declared "Every human being of adult years and sound mind has a right to determine what shall be done with his own body and cannot be subjected to medical treatment without his consent" [26]. This ruling is of special significance because in the second decade of the twentieth century, paternalism and beneficence were the rule in medical practice. The principle of autonomy requires that the patient be allowed to decide if he or she wishes to make a commitment to long-term treatment such as chronic dialysis and whether this commitment is worth the 'trade-off'. Because it is difficult for a patient to comprehend what dialysis may entail, patients may be encouraged to undergo a trial period to see if it will be beneficial; and to allow them the opportunity to adapt to the procedure or even to decide that they do not wish it. The Ann Arbor VA Medical Center, Michigan has an ESRD Committee, which assesses each patient's desire to stop dialysis. Port [23] notes that health professionals are responsible not only to aid patients in rehabilitation, but also to support them and their families if they should wish to withdraw from dialysis. Port adds: "I believe that very rigid criteria for acceptance to chronic dialysis care may be

more harmful by excluding patients who might benefit from therapy than an open acceptance policy that includes the willingness to discontinue dialysis according to a patient's request when there is no hope for reversibility." Oreopoulos, a Canadian nephrologist [27], believes that "when patients have decided to start treatment, we should provide every guarantee that if things do not go well, they can discontinue it." This Canadian group believes it should support the patient whatever decision he makes. If the decision is to withdraw from dialysis, the patient and family are assured that the team will provide appropriate care and comfort including help with costs and insurance.

There are no simple answers to the dilemmas posed by maintenance of life by technological means. Dependency on a machine and upon others is in conflict with individual autonomy. Patients, families, and all health-care professionals need compassion and understanding as they struggle to cope with the complex issues involved in terminating life-sustaining treatments.

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CHAPTER 64

Allocation of scarce resources: justice and rationing of health care

NANCY BOUCOT CUMMINGS

Allocation decisions about health care frequently are made upon factors other than purely medical considerations, albeit subtly, in specified situations and only in certain countries. Two aspects of health-care allocation are germane here: primary health care and treatment of disease; and distribution of cadaver kidneys for transplantation. These represent respectively parameters of macro- and microallocation. Ultimately, no country or society can afford to provide all goods and services for all its members. The United States of America (USA) is the only high income/industrialized country (other than South Africa), which does not have a national health system and/or provide a 'safety net' for at least primary health care for its citizenry. In the face of scarcity it is essential to develop a fair system for distribution of limited resources. Even high-income countries do not have enough resources to provide all the health care possible. Furthermore, it is difficult for those used to relative plenty to understand the necessity or reality of rationing of health care.

If one views the global distribution of health care expenditures and looks critically at the failure of an affluent country – the USA – to provide adequate health care for its people, one realizes that the ethical principle of justice has not been applied equitably. In January 1992, 35.7 million Americans had no health insurance and a comparable number had inadequate medical coverage [1]. Statistics about such parameters of health as infant and neonatal mortality, maternal mortality, prenatal care, and malnutrition indicate that the USA, which provides some of the world's best medical care, does not provide medical care equitably. The World Health Organization (WHO) has outlined nine essential elements of primary health care, namely: (1) adequate food and housing including protection against insects and rodents; (2) water adequate to provide for cleanliness and safe drinking; (3) acceptable waste disposal; (4) provision of antenatal, postnatal care and family planning; (5) adequate infant and child care and nutrition; (6) immunization against the major childhood infectious diseases; (7) prevention and control of locally endemic diseases; (8) elementary medical care of injury and diseases for all;

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(9) ready access to practical and useful knowledge about potential health problems and methods for their prevention and control.

Data from 142 countries gives a picture of the limited funds available for even minimal primary health care in low-income countries. The richest fifth of the world's population has 50 times the income of the poorest fifth [2]. In 1987, public expenditures per capita for health in developing countries was $11, that for the entire world was $162, and that for developed countries was $657 [2, 3]. Thus, tertiary health care, which includes high-technology, life-sustaining methods such as hemodialysis and transplantation that high-income countries take for granted, is far out-of-reach for most low-income countries. There is a roughly linear correlation between GNP per capita and public expenditures on health per capita. In addition to the fact that 'developed' countries have a greater gross national product (GNP) per capita, they spend a greater percentage of their GNP on health-about 4.8%, while 'developing' countries spend 1.6% of their GNP on health [3].

When the United Nations was founded in 1945, it was agreed that, "Everyone had the right to a standard of living adequate for the health and wellbeing of himself and his family, including food, clothing, housing, and medical care and necessary social services. . . . ." [4]. The ethical dilemma inherent in the World Health Organization (WHO) guideline is "How do we provide adequate medical care when resources are limited?"

The United States does not have enough cadaver kidneys for transplantation. UNOS reports that over 20,000 patients are on waiting lists for kidneys while each year fewer than ten thousand kidneys, either living or cadaver become available. Transplant physicians and surgeons, organ-procurement agencies, voluntary health agencies involved with transplantation, and policy makers have tried many innovative approaches to increase the supply of kidneys for transplant. In some low-income countries, living unrelated kidney donors (LURD) have been used as a source of organs for those with money enough to buy a kidney [5, 6]. The purchase of body parts from living donors has aroused major ethical concerns among transplant physicians and surgeons, ethicists, policy makers, clergy, and the public, primarily in high-income countries. Many countries, including the United States, have passed legislation [7] forbidding this practice while transplantation societies have issued a similar *caveat*. Some physicians and surgeons from low-income countries such as India have rationalized the use of LURD kidneys [8–11]. One frequent justification of the commercialism in LURD organ procurement is that the 'donor-for-hire' can earn money for his/her impoverished family.

Resource allocation: generic issues

Two factors should be considered when viewing resource allocation [3]. First, scarcity is inherent in the human condition. Resources rarely are adequate and demands often increase faster than resources. Second, medical care is

not the only or even the chief determinant of health. The resources available for medical care compete with public funds, some of which provide for health and safety such as sanitation, pollution control, police and fire protection, and other societal needs. Political, social, and economic decisions are made about needs such as education, defense, and the costs of operating the government. Decisions about expenditures for health care also compete with private funds, which individuals spend according to their resources and their priorities for food, clothing, shelter, and transportation as well as medical care.

In the allocation of resources, many questions must be asked [3]:

1. Who chooses those who are to make allocation decisions?
2. Do those selected act as individuals, within *ad hoc* groups, or within institutionalized structures?
3. What are the requisite qualifications for the decision makers: – medical competence, equitable representation of society, philosophical or economic or political representation, etc.?
4. Should social worth of competing patients be weighted, and if so, how? The Seattle Admissions and Policy committee faced such issues in the 1960s when its members were forced to decide which of the medically appropriate patients would receive hemodialysis (12).
5. The selection process is so complex that many biomedical ethicists and philosophers recommends a lottery that would adhere to the ethical principle of justice. Others, particularly those in the health-decisions movement, believe that the public must set priorities for health care needs and benefits.
6. Overtly or tacitly these decisions involved demographic and medical criteria. Race, sex, and age may affect decisions that should be made based only on objective medical factors such as comorbid conditions.

Resource allocation: some ethical issues

Most analyses of ethical issues about ESRD treatment derive from Western culture and from high-income countries, which can afford the high costs and which tend to place great weight upon the individual and his rights of self-determination. Allocation issues emerged early and were of major concerns in chronic renal failure because of its high cost, beyond the average income of citizens of even high income in developed countries [13]. In the 1960s, after the Quinton–Schribner shunt made chronic hemodialysis possible, the Seattle Admissions and Policy Committee met to decide which medically eligible patients should receive this life-saving treatment. These decisions along with those on the potential for renal transplantation after immunosuppression stimulated the nascent field of biomedical ethics. The high cost of dialysis and the shortage of cadaver kidneys forced society to consider how we can allocate limited resources.

It is imperative to apply the ethical principle of *justice* in order to allocate limited resources fairly. Often seven factors are considered in the fair selection of patients: need, likelihood of success, choices, social worth, responsibility, ability to pay, and constraints. Also, seven groups often are involved in making fair selection decisions: clinicians, patients, families, a committee process, the judicial process, administrative policy, and hospital fiscal policy [14, 15].

Since the passage of the ESRD amendment to the Social Security Act, PL 92–603, in 1972, the United States of America (USA) has provided ESRD coverage for the entitled 92–95% of its population. However, ESRD patients are the only group of US citizens who have such extensive health coverage. The high per capita cost of the ESRD program and the increasing number of entitled patients has made legislators wary of the threatened escalation of cost if the USA were to adopt a national health insurance program. Adequate health insurance was a major issue in the Pennsylvania senatorial campaign when Harris Wofford was elected in November 1991. In the mid-1980s, after a budget crisis, Oregon removed authorization for some transplants under Medicaid. In 1987, when a 7-year old leukemia patient was denied a bone marrow transplant under Medicaid, Oregon [16–18] gained national prominence because of its 'rationing' of health care. Over the past 3–4 years Oregon, grappling with the task of providing a reasonable level of coverage for its citizens, has developed a priority list for medical services; in addition it requires that businesses offer health insurance to employees and has set up a state-run insurance pool to make coverage more affordable. California, Florida, Hawaii, Minnesota and Wisconsin also have developed legislation to cope with the demand for health services. The American media are filled with reports, editorials, and discussions of one of the best health-care systems in the world, yet one which has high neonatal and infant mortality rates, widespread drug abuse and AIDS among other defects.

Looking at Canada, which has in place a functioning national health system produces ambivalent reactions in the USA. The USA faces a crisis in health care because of inadequate coverage of its population by private and/or public funds. The Health Management Quarterly and the Heath Insurance Association of America [1] report that in the USA, employers provide coverage for 68% of the population, Medicaid for 8%, 15% are uninsured, and 9% have some other coverage. A breakdown of the 15%, who are uninsured, indicates that 71% include a fulltime worker family, 14% a part-time worker family, and 15% a nonworker family.

In a poll of the health-care choices of Americans, the Washington Post/ABC [1] found that 44% of US citizens favor a national health plan run by the government and financed by taxpayers, which would cover all Americans; 32% favor a plan that would require the employers to provide coverage for their employees or contribute to a federal fund that would cover all employees; and 20% favor maintaining the current system of private insurance,

Medicare, and Medicaid. As noted earlier, the ESRD program is the only US health service to which almost the entire population is entitled.

To provide a basis for considering some practical changes that would achieve universal health care for the USA, and enable the reader to compare the Canadian and US systems in terms of quality of care and social justice, Mark Gibson, chief of staff to Dr John Kitzhaber, President of the Oregon Senate, provides elsewhere an overview of Oregon's experiment and Dr Martin Barkin, former Deputy Minister of Health for Ontario, has answered some of the questions Americans ask about the Canadian health-care system.

Of the numerous ethical issues in the field of organ transplantation, one of the most prominent is the allocation of donor kidneys, both living-related and cadaver. With lower highway speed limits, stringent seatbelt laws, and efforts to reduce drunken driving, the number of cadaver organs available for transplant has declined despite aggressive public education programs that stress organ donation. The recruitment of organ donors is inadequate to provide the kidneys needed for an increasing numbers of patients on transplant waiting lists.

Efforts to increase the number of cadaver donors have had limited success. Even when potential donor families understand the need for organ donation, emotional reservations often prevent them from donating organs of their relative. While blacks have a higher incidence of ESRD, they do not donate organs proportionally. In a pilot project [19], Callender and colleagues identified three reasons that black respondents gave for not donating kidneys (and for not filling out donor cards): (1) religion or superstition; (2) lack of trust in health-care providers and the suspicion that the potential donor might not receive adequate hospital care; and (3) the potential donor's discomfort at being reminded of death.

In view of the shortage of donor kidneys, many have suggested new types of donors and new means of acquiring kidneys: expanding the age limits for donors, loosening other criteria for kidney harvesting, and a campaign to persuade individual states to enact presumed consent laws. Studies and polls indicate that both health professionals and lay persons support living unrelated donors such as friends and spouses [20, 21]. *Presumed consent* assumes that every person who dies would consent to donate his organs unless he or his family have indicated their unwillingness to donate. Walter Land of Germany reported that, while several European countries have presumed consent laws, they are not enforced rigorously, except in Austria, and that the new European Community will not keep presumed consent. Also a stipend has been suggested for donor families after organ donation but this has raised some controversy because many consider that organ donation is an altruistic act and that payment could be coercive, especially for those who are poor.

A random mail survey of health professionals who most frequently are involved with requesting organ donation by grieving families was undertaken by the Partnership for Organ Donation. In response to the question, "Should

financial incentives be offered to encourage families to donate?" the overwhelming percentage of respondents answered in the negative: 79% (chaplains and critical care nurses); 70% (neurosurgeons and social workers); and 53% (organ procurement coordinators). The "comfort level" in requesting donation under the current system, i.e. without financial incentives, when compared to that with financial incentives changed from an average of about 77% to about 30% among the five groups noted above. This survey indicates that the use of financial incentives may have a negative effect on organ procurement.

Age as a criterion for selecting transplant recipients is controversial as it is for other types of medical treatment [23]. The 1984 Massachusetts Task Force Report [24] recommended that transplantation be made available to those who would benefit the most, especially in terms of post-transplant longevity and the potential for rehabilitation. On the other hand, the Federal Age Discrimination Act of 1975 (codified at 42 USCA 6101 [1985]) prohibits "discrimination on the basis of age in programs or activities receiving federal assistance." In Norway, unlike the United States, transplantation is the treatment of choice for elderly patients. Fauchald *et al.* [25] describe the use of elderly donor kidneys for transplantation and experience with elderly recipients in Norway. If the USA adopted the Norwegian approach, the supply of donor kidneys might increase but the transplant waiting list would lengthen as elderly recipients were entered. Because of the shortage of cadaver kidneys, the transplant community, including organizations such as the American Society of Transplant Surgeons, has agreed that not more than 5% of cadaver kidneys would go to foreign nationals. Usually, foreign kidney-transplant candidates who arrive in the United States with a *bona fide* living related donor (LRD) will be accepted. However, ethical dilemmas arise when foreign patients arrive with a stated living unrelated donor or when the physician suspects that the alleged LRD is not true blood relative. In the debate about treatment of foreign nationals, we might ask whether the principle of justice allows us recognize national borders in the allocation of donor organs.

Summary

Scarcity will continue to be a characteristic of the human condition. Even affluent countries with high GNPs cannot provide all their citizens with all goods and services. Rationing, overt or covert, is a given in health-care allocation. In the USA, rationing proceeds on the basis of ability to pay. Other high-income countries that provide health care for all frequently fix budgetary limits but not for all types of health care. Allocation of resources, and especially of the limited life-supporting services will continue to raise serious ethical issues. It remains important that we make justice a primary element when reaching decisions about the allocation of health services.

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CHAPTER 65

The Canadian health care system

MARTIN BARKIN

Health care: a major issue around the world

Over the past four or five years, virtually every nation in the world has been intensely scrutinizing its health care systems. None has come under more pressure than the US health system. It now stands as the most expensive health care system in the world, yet the one that seems to give its people the least satisfaction.

These feelings were highlighted by the state and federal elections that culminated in the Presidential election of November 1992.

These elections, combined with the cooling of the international political situation as a result of the changes in the former Soviet Union, have now focused America's attention on its domestic issues.

Health care, for reasons which we shall see later, has become one of those key domestic issues. In searching for solutions to the US health care dilemma, it is not unreasonable that Americans should look to Canada.

Many similarities between Canada and the US

These two countries share a common history and the longest and easiest-to-cross border in the world. For more than a hundred years there has been a free exchange of ideas and cultures between them.

Both countries grew more from immigration than from their internal birth rates. As a result both are multicultural and multiracial societies with a significant indigenous native population.

In both countries the health care system has its roots in insurance. Until 1957, in fact, the two health systems were scarcely distinguishable, one from the other.

D.G. Oreopoulos, M.F. Michelis and S. Herschorn (eds), Nephrology and Urology in the Aged Patient, 605–614.

Reasons why the US looks to Canadian health care

Compared to the US, Canada appears to have far lower administrative costs (at least according to the General Accounting Office of the US); it costs 40% less per person, yet covers everyone to the same high standard. Just about every health status indicator in Canada is better than the same health status indicator in the US and by a significant difference.

Even the American business community and the American providers have begun to look to the Canadian system for some of their solutions.

Important differences between Canada and the US

Notwithstanding the many similarities between the two countries, there are several important differences. Perhaps the most significant difference is in the system of government. As we shall see later, this may be the most significant factor that allows Canada's health-care system to thrive and serve its people as well as it does.

There are other important differences, however. Canadians tend more towards the left-wing ideologies and recently have elected three provincial NDP (socialist) governments. Healthcare marketing, while it is not illegal in Canada, is at the very least condemned.

Canadians regard health care as an essential service, like fire, and police services. They do not consider it a commodity to be marketed or sold. Most Canadians remain critical of any human service that runs on a 'for-profit' basis, especially if it is government funded.

Perhaps the most significant cultural difference between the two peoples is found in the highest aspirations of the two countries, as reflected in their fundamental charters.

The US continues to take pride in its belief, "*life, liberty and the pursuit of happiness*". This is an intensely individualistic attribute. In the same place, the Canadian Charter says, "peace, order and good government". It is not that Canadians are averse to having their government do things for them – they only require that government do these things well.

Canadians tend to do things collectively. This collectivity arises from Canada's sparse population scattered over a vast tract of land – the smallest number of people in the largest country among the G7 nations.

Canadian health care universally admired

Canadian health care is extremely popular around the world. A Louis Harris poll found that more British people and Americans prefer the Canadian system than their own. Canadians, on the other hand, take intense pride in their own system. When questioned in a national unity poll about the reasons

for wanting to be Canadian, the vast majority of Canadians responded that their health-care system was an important reason for them to want to be Canadian.

So we have, in Canada, a Churchillian view of health care – like democracy, it may not be perfect, but compared to the available alternatives, it is the one that Canadians prefer above all others.

Important strengths of US health care

It is important, as we examine aspects of the Canadian system that might be applicable to the US, to, at the same time, indicate the important strengths of the US system, which should in no way be compromised by the reforms that inevitably will come.

The US has the finest centers of medical excellence found anywhere in the world. Its reputation for research and innovation makes it the pre-eminent winner of Nobel prizes in medicine in the world today. It has the best and most advanced training. In fact, candidates, both undergraduate and postgraduate, from everywhere in the world, if they can, would prefer to go to the US to round out their advanced training.

The US remains the world leader in advanced technology.

Finally, there is an abundance of the most advanced medical and technological services for those who can afford them.

US has serious health care problems

Too many and the most vulnerable are under or uninsured

Approximately 37 million fall into this category, up from 29 million in 1980. It includes 15–20% of all of those under age 65. One-third of the uninsured are under 18. The plight of the uninsured has been accentuated by the job losses of the recession. The fear of losing health insurance has severely limited the ability of the American worker to change jobs or make other adjustments to the economic restructuring now taking place.

The uninsured use emergency departments for their primary care, they use less prevention, and have almost no prenatal care.

As a result, child health has been the most visibly affected. For example, in Washington, DC a baby dies every 33 hours. Washington's infant mortality of 23.8 per 1000 is twice as high as Cuba's. One-third of its children live in poverty and the majority have not been vaccinated.

It is too expensive for what it does

Health care has now passed 12% of Gross Domestic Product, leaving Americans the highest per capita spenders on health care in the world, notwithstanding the fact that so many are without health insurance. Health care costs 40% more per person than in Canada, 200% more than in the United Kingdom.

Yet the US is fifteenth in male life expectancy, twenty-seventh in cardiovascular health, and twentieth in infant mortality. Although it may be argued that these are social consequences rather than consequences of the deficiency of health care, the degree to which health care consumes national wealth is the degree to which such wealth cannot be diverted to addressing the social dimension of these illnesses.

The cost of health care in the US is unfairly distributed

US health costs tend to fall heaviest on manufacturers and employers, and least on seniors and those in the service industries. In the heavy industries, such as automobile production, the price of health care has become a significant portion of the cost of the product. For example, the price per car for worker health care in the US is greater than the price for steel for that same vehicle. In 1990, General Motors paid $772 per vehicle for health care in the US; it paid about $200 per vehicle for health care in Canada.

Iacocca, the Chairman of Chrysler, expressed it this way: "Other countries put employee health costs into their taxes – we put them into the price of our products. That is not a healthy way to compete in the world market."

It is too expensive to administer

The General Accounting Office (GAO) and several economists have estimated that if the US had the Canadian system, it would save huge sums in the non-health-care dimensions of its health-care systems, specifically: paperwork, red tape, bureaucracy and administrative costs.

The GAO estimate was that $40 billion would be saved in insurance costs, $15 billion saved in physician costs, and $18 billion saved in hospital costs – enough to cover all of the uninsured and have money left over.

Too much is of unverified effectiveness

US epidemiologists, from the east coast to the west coast, provide examples that about one-third of what is done is inappropriate, and another one-third is of doubtful usefulness. At least some of this may be accounted for by

conflict of interest, self-referral, and the general tendency of the US health-care system to market itself.

Americans disagree over merits of national health insurance

Because of these factors, there has been a polarization of opinion in the US over national health insurance. The tally now indicates that about two-thirds of the US citizens, about one-half of Congress and Senators, and such significant influences as the New England Journal of Medicine, the General Accounting Office, The National Association of Children Hospitals and Related Institutions, and the American College of Physicians support national health insurance.

The previous Republican administration, the American Medical Association, the Health Insurance Association of America, and the American Hospital Association remain opposed.

Origins of the Canadian system

The Canadian system of health care was a natural progression for Canada. Its sparse population already had undertaken other collective actions to bring in railroads, airlines, telecommunications, and broadcasting. In 1957, Canadians coalesced their various private hospital insurance plans to create a public hospital insurance system. In 1966, they did the same with the private physician insurance plans to create the public physician insurance system. In 1983, both were combined into a single act – The Canada Health Act of 1983.

The unwritten principles of Canadian health care

Canadian health care is based on two powerful unwritten principles:

- **The first** – care for the few who are ill, paid for by the many who are well-established the principle of insurance as the primary mode of payment.
- **The second** – equality before health care like equality before the justice system – established the single-tier concept in Canadian health care.

Canada is the only country in the world that prohibits a private sector in health care.

The written principles of Canadian health care

These unwritten principles are expressed in the written principles of Canadian health care that are enshrined in The Canada Health Act of 1983.

Public administration

The Act requires that insurance of essential health services must be publicly administered, that is, there cannot, by law, be a secondary private health insurance system in Canada.

Public administration turns out to have a number of significant advantages.

(a) Far *lower administrative costs* than the pluralistic, private-sector-run US system.
(b) The *distribution of costs*, since they are from general taxation, is as fair a distribution as a society can achieve.
(c) Expenditures on health care, since they are from the same pot as expenditures on other social support services, can be *balanced with other expenditures* on these items to create trade-offs that lead to a balanced approach to supporting and sustaining all of the determinants of health. The net effect is that Canada is now rated as number one in the world in terms of quality of life.
(d) Perhaps the most significant advantage, although not yet fully realized, is that a single payer has a very *significant information base* and can use that information for proper epidemiological studies and monitoring of health-care services.

Universality

All patients are covered by virtue of their residence in the country. With a few minor exceptions, no premiums and no co-payments are permitted for essential health-care services.

Portability

Canadians are covered at Canadian rates no matter where they travel in the world. Unfortunately, Canadian rates are insufficient to cover the full cost of health care when Canadians travel to the US, and so the one exception to the Canadian private health insurance restrictions is the permission for supplementary private health insurance to cover the difference between Canadian costs and US costs in the event that Canadians require unexpected health care while they are traveling through the US.

Comprehensiveness

Although The Canada Health Act only specified coverage for doctors and hospitals, various provincial plans have expanded on those services to include drug benefit plans, assistive devices including hearing aids, stomal devices,

wheelchairs, prosthetics, etc., ambulance services, travel from remote areas, long-term care, attendant care, supportive housing for discharged psychiatric patients, etc., etc.

Reasonable accessibility

The Canada Health Act specified that access shall be reasonable, not necessarily unfettered or unqualified. It is around the issue of access that the debate around the sufficiency of the Canadian health care system revolves. For example, in 1989 and 1990, during the shortage of cardiovascular resources in Canada, the ability of the Canadian system to assure appropriate access was called into question. One must recall, however, that the Canadian system is an insurance-based system and if it cannot provide the services, it must pay for them wherever they are delivered. This, in fact, did happen in both Ontario and British Columbia when the resources within those provinces were insufficient to meet the requirements of their patients. But this is not dissimilar from situations which arise for insured patients in sparsely populated mid-western states who have to go to other jurisdictions for highly specialized treatment.

Canadian governments and health care

To understand how Canadian health-care operates so well, it is necessary to understand the Canadian political system, since the two are intimately related.

Canada is divided into 10 provinces and two territories. Under the British North America Act, health care is a provincial matter. The Federal Government's role in health care was to impose federal standards and it used its financial clout to get those standards simply by saying, "Provide health care according to our principles, and we will provide you with supportive funding".

Each province has its own parliamentary democracy. The party that wins the most seats becomes the governing party, and its leader automatically becomes the Premier. This is not like the American system where the President or Governor has an election that is separate from the election of other representatives.

When the government is formed, the Premier creates Ministers from the elected members. Amongst those Ministers is the Minister of Health. That individual has total responsibility for the effective operation of the provincial health-care plan.

At the same time, the opposition parties appoint individuals whose sole responsibility in the legislature is to provide criticism of the work of the

Minister of Health. Thus there is at least one, and usually two, official 'health care critics' in every Provincial Parliament.

Each day that Parliament sits, during question period, the health care critic can, and usually does, ask a question of the Minister concerning certain failures of the health-care system.

This is one of the most important checks and balances within Canadian health care. The concept of ministerial responsibility is inviolate within the Canadian political system.

The other effect, of course, is that each case that is raised in the house becomes a news story. Americans frequently read these news stories and interpret a health care system in distress. Canadians read these news stories and sleep a little more comfortably, knowing that the vigilance of their parliamentary process is continuing to assure a responsive health care system.

Structure of Canadian health care

The Canadian system is similar to that in the US. Ninety percent of its physicians are on fee-for-service; its public hospitals are all under public governance; and there is limited private-sector involvement in the areas of pharmacy, nursing homes, home care, ambulance services and labs.

The Canadian system is more properly characterized as *public insurance for private medicine – it is not socialized medicine.*

Canadian patients can choose their own doctor, and can do so even in capitation systems. They can choose their specialist and choose their hospital.

Hospitals less efficient

Unfortunately, the Canadian system has certain deficiencies particularly in the area of efficiency and streamlining patient throughput. As a result, waiting times can be particularly long. For the most part, however, these waiting lists are stable, indicating that the number of patients coming onto the waiting list is about the same as the number coming off.

Physician incomes comparable

Physician income in Canada is only slightly lower that physician income in the US, even though gross revenues are much lower. The reason for this is the much lower overhead for practicing physicians in Canada. There is a lower cost of billing, much lower cost of maintaining accounts receivable, almost no bad debts and delayed debts, a far lower cost of liability and a very low cost of office procedures since most are carried out in hospitals.

Dark clouds on the Canadian horizon

The recent Canadian recession and the high deficits at both the Federal and Provincial level have produced substantial government reductions in the rate of rise of health-care expenditure. This rapid imposition and fiscal constraints have produced an intense debate over the preservation of Canada's health-care principles, but it is also resulting in rapid reform of Canada's health-care delivery systems.

Common problems in both countries

Both countries have equal difficulty in the appropriate allocation, the numbers, distribution, and mix of health-care human resources, particularly physicians and nurses. Both countries believe they could do better in the areas of health promotion and prevention, and both are working at developing standards and guidelines.

The Canadian healthcare system is beginning to take on certain characteristics of some areas of the American health care systems, as we move to greater regional autonomy and accountability.

One significant change in the Canadian health care system has been a new harmony, particularly between physicians and provincial governments.

Recently, the Ontario Medical Association signed a six-year agreement with the Government of Ontario that provides for orderly establishment of fees that includes binding arbitration when negotiation fails. Moreover, the physicians have joined the government in a high-level joint-management committee in order to manage the rate of growth of health-care costs with physician co-operation, as opposed to imposing such measures on resistant physicians.

Canada has learned from the US

Canada has learned a number of important lessons from its interactions with the US. Canadians believe that they could improve their system by using some of the advanced management techniques, now in use in the US, particularly total quality management. Canadians also believe that some financial incentives would be appropriate.

Canada offers some lessons to the US

While Canadians have learned these lessons from Americans, they believe that Americans could learn some lessons from Canada.

The most significant lesson is that there can be no reform of health care

unless a health-care value system is developed. Canadians believe that their value system is one that guarantees access to health care by the state, and that health care is a public service not a marketable commodity. It is clear that if the same value system prevailed in the US, American creativity would easily address the issues of American health-care delivery.

If, however, the US does not address reform of the US health-care system from a base of common values and chooses to be much more pragmatic, then Canadians offer the following lessons:

- First and foremost, one should begin by simplifying the maze of multiple insurance plans and multiple coverages in order to make interaction with the system less complex. At the same time, all individuals should be covered and this coverage should be portable.
- The second important lesson that Canadians believe can be learned from their experience is that the information systems of a single-payer system are important tools of accountability.
- The final lesson, and the one which Canadians have come to rely on, is that one cannot have a health care system unless there is a publicly accountable individual or body that takes responsibility to assure the integrity of the system and to assure access to health as well as access to health care. For Canadians, this body is its accountable parliamentary system of democracy.

Americans will have to find an equivalent counterpart in their social and economic system.

Conclusions

Canadians have enjoyed a close and harmonious relationship with Americans for more than a century. We have learned and benefited greatly from our close association. We are pleased to share our experiences with the US in the same spirit of mutual respect and support that has characterized our close relationship and opened our borders.

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