Medical Aspects of Disability

A Handbook for the Rehabilitation Professional

4th Edition
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4th Edition

Steven R. Flanagan, MD
Herb Zaretsky, PhD
Alex Moroz, MD, FACP
Editors
To my family, friends, and especially Lou for their understanding, support, and inspiration.

Steven R. Flanagan

To my wife, Diane, for her love, inspiration, extraordinary support, and cherished friendship; to my daughter, Lauren; my son, Andrew; my son-in-law, Lee; and to my grandchildren, Alec, Will, and Jake—each of whom is a constant source of joy and love in my life.

Herb Zaretsky

To Justin the Fair, to Ryan the Noble, to Marina the Guide, to Vitya the Giver, to Eduard the Youngheart, and to my students and residents.

Alex Moroz

The editors also wish to acknowledge the tireless dedication and invaluable assistance of Linda Yuen-Moy in the timely preparation of this textbook.

The Editors
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Introduction

The manner in which health care will be delivered in the future remains uncertain in nearly all fields of medicine, particularly Physical Medicine and Rehabilitation (PM&R). Despite increasing efforts to establish evidence-based practices in PM&R, economic and political forces continually challenge the delivery of care to people with disabilities. This fourth edition of Medical Aspects of Disability has been substantially updated from previous editions to reflect advancements in medical care for specific disabling conditions as well as changes in forces that impact the delivery of that care. Chapters in the fourth edition have either been substantially updated by previous authors or completely rewritten by new contributors, including Social Work in Physical Medicine, Stroke, The Computer Revolution—Disability and Assistive Technology, Chronic Pain, Traumatic Brain Injury, Complementary and Alternative Medicine, Rehabilitation in Burns, Disabling Conditions Seen in AIDS and HIV Infection, and Spinal Cord Injury. While some previous chapters were eliminated, several new topics were added to reflect the changing face of rehabilitation medicine and disability, including The History of Rehabilitation, Geriatric Rehabilitation, Challenges and Opportunities for Quality in Rehabilitation, Limb Deficiency, Organ Transplantation and Rehabilitation, Musculoskeletal Disorders, and Future Directions of Rehabilitation Research. Our contributors are among the most widely respected authorities in their respective fields so that we can present our readers the most useful and updated information on the vast array of disabling conditions afflicting millions of people and how they are best addressed and impacted by our current health care system. Our primary goal in this latest edition is to provide health care professionals, teachers, and students a useful and updated handbook that addresses the many conditions and topics that impact people with physical, developmental, and cognitive disabilities. In that sense, the editors are confident that this newly revised and updated fourth edition will be a valuable resource.

Steven R. Flanagan, MD
THE HISTORY OF REHABILITATION

The history of rehabilitation is fraught with acrimony, contention, and eventual triumph. Prior to the evolution of physical medicine and rehabilitation (PM&R) as an organized field and profession, individuals unfortunate enough to be suffering from a physical affliction were left to their own measure and often labeled as a cripple, an invalid, or worse.

The first known medical document was discovered in Egypt and dates back to 2000 BC. This document is known as the Edwin Smith Surgical Papyrus (named after the American Egyptologist who purchased the treatise in 1862). The treatise describes the general sentiment of how most disabilities were treated, which could be summarized as sparse at best. For spinal cord injuries, treatment options were nonexistent and this injury was often deemed “an ailment not to be treated” (Donovan, 2007). Unfortunately, treatments for spinal cord injuries and other causes of disabilities did not advance for thousands of years. Most patients with disabilities were treated by their families or in religious establishments until the latter part of the 20th century (Ohry, 2004). In fact, General George Patton (1885–1945), who is famous for many highly successful campaigns in World War II, sustained a spinal cord injury shortly after returning from the war. It is said that he was well aware (likely from seeing injured soldiers first hand) that there were no cures or efficacious treatments available and thus he refused all treatments. Patton died in the hospital (Donovan, 2007). It was Alexander Fleming’s discovery of penicillin that greatly decreased deaths from infections, including those seen in spinal cord injury care, and a host of other disabilities that revolutionized all of medicine, including PM&R (Donovan, 2007).

Ancient Egyptians had a life expectancy of only 36 years and high-speed injuries were nonexistent. However, the ancient Egyptians, Greeks, and Romans sustained many fractures and slowly advanced various treatment options. Once again, the initial data come to us from the Edwin Smith Papyrus that outlines several fracture treatments. Compound fractures were considered to have a poor prognosis, but simple fractures of the upper extremity were often reduced by traction and had a favorable prognosis (Brorson, 2009).

It was not until the early 1900s that rehabilitation as a profession and field of study started to become more organized and gain some traction, even though it was initially viewed in large part as quackery (Opitz, Folz, Gelfman, & Peters, 1997). The struggle for legitimacy continued during much of the early years as the field developed. For a fascinating and complete account of the political, social, and medical aspects of the rise of the field of PM&R, the reader is referred to a 1997 edition of the Archives of Physical Medicine and Rehabilitation (Folz, Opitz, Peters, & Gelfman, 1997; Gelfman, Peters, Opitz, & Folz, 1997; Opitz et al., 1997; Peters, Gelfman, Folz, & Opitz, 1997).
In studying the history of rehabilitation there are two prominent figures to be considered, Frank H. Krusen, MD, and Howard A. Rusk, MD. Drs. Krusen and Rusk were essential in creating the scope of the field as it is known today. Dr. Krusen's (1898–1973) interest in rehabilitation was shaped by personal experience. While working in his first year of surgical residency training, he was infected with tuberculosis (Opitz et al., 1997). He spent 5 months in a sanitarium, during which time he recognized that he and other patients were becoming physically deconditioned, causing them to become increasingly more dependent on the institution for care. It was then that he came up with the idea of physical rehabilitation with an emphasis on social reintegration, physical reconditioning, and vocational rehabilitation as essential components of convalescence, ultimately becoming his life's work.

The American Medical Association (AMA) did not initially view physical rehabilitation favorably. It was not until 1939 that the first scientific paper on rehabilitation was accepted in a medical journal (Opitz et al., 1997). Dr. Krusen experienced great resistance from several groups that organized against him. His most significant opponents were in the fields of orthopedics and pediatrics as well as in the National Foundation for Infantile Paralysis (whose director, Catherine Worthingham, PhD, PT, was a past president of American Physical Therapy Association) (Gelfman et al., 1997). Many were concerned about the use of the word “rehabilitation” in this developing specialty because it was felt to have a place in many other disciplines. Orthopedists and pediatricians were worried about encroachment on their practice whereas physical therapists were concerned that rehabilitation physicians would impinge on their autonomy as independent practitioners (Gelfman et al., 1997). However, Dr. Krusen's intellect, organizational skills, political ties, and interpersonal skills eventually triumphed over these groups, and on September 5, 1944, the American Congress on Physical Therapy changed its name to the American Congress of Physical Medicine (Folz et al., 1997). The medical journal by the Congress also changed its name from the Archives of Physical Therapy to the Archives of Physical Medicine (Folz et al., 1997).

Dr. Howard Archibald Rusk (1901–1989) had a similar insight as Dr. Krusen. Although he is often mistaken as a physiatrist, Howard Rusk was an internist who organized comprehensive medical rehabilitation departments in Army Air Corps hospitals during World War II (Gelfman et al., 1997). While working in medical rehabilitation, he noticed that the soldiers were becoming deconditioned and bored during their convalescence. Rusk organized academic class work and physical exercise during the soldiers' hospitalization. He also emphasized interdisciplinary teams and psychosocial functioning in addition to physical and vocation rehabilitation (Gelfman et al., 1997). Through his work, soldiers regained physical fitness and were able to return to active duty at a faster pace while experiencing significantly lower rates of hospital readmission. He also included military training as part of the academic course work provided to the soldiers to enhance their performance when they returned to active duty. For example, he organized replicas of German planes to cycle over the soldiers' hospital beds to assist in identifying them when they returned to the battlefield (Rusk, 1977).

Rusk was also a pioneer in the concept and implementation of early mobilization after illness or injury. He conducted experiments to analyze the impact of returning to activity quickly after surgery and the initial findings were favorable. This success spurred further research.

When he completed his military service, he petitioned the AMA to start residencies in medical rehabilitation. The AMA deferred to the Council on Physical Medicine because of the similarities of the two fields (Gelfman et al., 1997). Dr. Krusen also recognized the close association and with their backing, the AMA Council on Physical Medicine approved a motion to change the residencies to a combination of PM&R (Gelfman et al., 1997). Dr. Rusk, who is generally recognized as the “father of comprehensive rehabilitation,” went on to teach and train physicians across the United States and throughout the world, including Russia, Korea, China, and Vietnam.
Just as World War II shaped Rusk’s views and thoughts on rehabilitation, the wars in Afghanistan and Iraq have also profoundly influenced the field in recent times. With many soldiers returning from combat with amputations and traumatic brain injuries (TBI), there has been an increase in research and development in these areas. As described throughout this textbook, the reader will learn of recent advances in the care and rehabilitation for people with conditions such as limb loss and TBI resulting from these conflicts.

“Physical rehabilitation in its essence is the preservation and restoration of function” (anonymous) (Haig, Nagy, Lebreck, & Stein, 1995). A significant portion of the U.S. population lives with physical disabilities. Rehabilitation is a process aimed at enabling people with disabilities to reach and maintain their optimal physical, sensory, intellectual, psychological, vocational, social, and functional potential. Rehabilitation provides people with disabilities the tools they need to attain greater independence. The World Health Organization (WHO) estimates that 10% of the world’s population experience some form of disability or impairment. The number of people with disabilities is increasing due to population growth, aging, emergence of chronic diseases, increasing motor vehicle use, and medical advances that preserve and prolong life. The most common causes of impairment and disability include chronic diseases such as diabetes, cardiovascular disease, cancer, traumatic injuries, mental impairments, birth defects, malnutrition, HIV/AIDS, and other communicable diseases. These conditions are creating overwhelming demands for health and rehabilitation services (World Health Organization, 2005). Managing these conditions is one of the biggest challenges our health care system faces as we move through the 21st century. People are living longer yet the percentage of them living with chronic diseases has increased significantly over the last two decades. “Over 133 million Americans have at least one chronic disease. With proper care, the onset and progression of these diseases can be better contained and controlled for many years. In addition to the suffering and early death they can cause, these chronic conditions cost a staggering $1.7 trillion yearly” (www.barackobama.com, 2009a).

As the health care system changes and the ability to provide care across a long continuum is being remolded, effective communication between rehabilitation team members becomes increasingly more essential. Thus, the medical rehabilitation model consists of a core group of medical professionals who comprise a comprehensive team to evaluate and treat people to best meet their needs, with communication between members occurring on a regular basis. The interdisciplinary team involves a large number of disciplines that are lead by rehabilitation physicians (Figure 1.1). The physician usually determines which team members should be involved in the care of a particular patient, noting that all disciplines are not always required or involved at the same time. Each discipline plays an integral role in the patient’s recovery and includes:

- Child life therapist
- Creative art therapist
- Horticultural therapist
- Nutritionist
- Occupational therapist
- Pastoral care
- Patient
- Physiatrist/physician
- Physical therapist
- Psychologist
- Rehabilitation engineer
- Rehabilitation nurse
- Social worker
- Speech and language pathologist
- Therapeutic recreational specialist
- Vocational counselor.
Below is a brief description of the most common team members.

The patient is by far the most important member of the interdisciplinary team and should be involved in all decisions regarding his/her care. If the patient (or the designee, if the patient is incapable of participation) is not included or is not in agreement with the plan of treatment, rehabilitation is unlikely to succeed.

Occupational therapists (OT) are professionals who help promote health and enhance independence in the performance of activities of daily living (ADLs) for people with disabilities. Occupational therapists assess people's skills and limitations regarding ADLs and use meaningful and purposeful activities in addition to specialized equipment and adaptive aids to promote independent function.

Physical therapists (PT) are professionals who provide services to patients with physical impairments, functional limitations, disabilities, or changes in function and health resulting from injury or disease. PTs assess and treat bed mobility, the ability to move from place to place (e.g., wheelchair to bed), ambulation skills, balance, strength, range of motion, and function.

Physiatrists are physicians specializing in the field of PM&R and leading the rehabilitation team. After reviewing the history and performing the physical examination, the physiatrist prescribes the rehabilitation program and provides medical treatment to people with disabilities.

Psychologists are clinicians who assess patients' cognitive status and mental health. Psychologists help emotionally distressed patients adjust to life that has changed due to injury or illness and provide therapy to improve cognitive performance when necessary.

Therapeutic recreational specialists (TRS) are trained and certified to provide treatment, education, and recreational services to help people with illnesses and disabilities develop.
leisure activities that enhance their health, functional abilities, independence, and quality of life.

Rehabilitation nurses (RN) are clinicians responsible for monitoring patients’ medical status including, but not limited to, vital signs, skin integrity, and sleep status. Rehabilitation nurses also evaluate the patient’s mental state, medication usage and effectiveness, pain, and bowel and bladder function and provide essential education to both patients and their families.

Speech-language pathologists (SLP) are clinicians who assess the patient’s ability to communicate by both spoken and written language in addition to evaluating swallowing ability, which is often impaired following brain injury. They provide treatment to improve both communication skills and ability to safely swallow food and liquids.

Social workers (SW) assess patients’ psychosocial status, including their living situations, support system, and financial status. They assist patients by helping them cope with social issues that impact their life, particularly as they pertain to their disability, in addition to dealing with their personal and professional relationships.

Vocational rehabilitation counselors (CRC) assess a patient’s ability to return to work or to previous activities enjoyed. Vocational counselors determine the jobs that are best suited to their patients via interviews, evaluation of their abilities, and selected tests.

PATIENT EXPERIENCE

A patient’s experience varies depending on the setting in which rehabilitation is being provided. For example, services provided acutely after injury, in an acute inpatient rehabilitation hospital, subacute rehabilitation facility, or outpatient venue have unique characteristics and regulations that dictate the type and intensity of treatment provided. Services can also vary within each setting with individual rehabilitation centers often offering highly specialized programs to meet the needs of the patients they serve. After the onset of an adverse medical event, a patient will usually be taken to an acute care hospital. After to once patients are medically stabilized, they leave the acute care hospital and may be transferred to an acute rehabilitation facility if they can participate and benefit from intensive therapy. A common element for patients destined for acute rehabilitation is that their lives have been altered physically, psychologically, and often spiritually by the experience.

Imagine for a moment that your ability to walk, dress, and even comprehend a loved one’s speech has been suddenly lost because of an acute medical event such as stroke or TBI. Now you find yourself in a medical center with a team of individuals working with you to restore what previously was taken for granted.

The above scenario is quite typical for patients in need of acute rehabilitation following a sudden illness or injury and outlines some key points. In most acute inpatient rehabilitation facilities, bedside rounds attended by representatives of the team occur daily. This is a time to review daily progress, receive updates on medical status and medication changes, review issues that occurred overnight, and answer questions from the patient or their significant others. This is also an opportunity to get the patient’s feedback, review team goals, discuss discharge planning, and get information on the patient’s preferences.

The team conference is a gathering of the various disciplines that are working with patient, and typically occurs weekly in acute inpatient settings. This conference, usually lead by the physician, will include updates on the patient’s medical condition, functional changes, progress toward patient goals, unusual occurrences, discharge planning, and modification of desired or expected goals. In addition to setting individual goals that are specific to each discipline, the team will create and review goals that cross disciplines, such as community mobility that requires the use of mass transportation. Discussions will also focus on planning for discharge, which may include the need for continued medical, nursing, and rehabilitation care. Potential
barriers to discharge will be reviewed, including access to and within the patient’s home and
the availability of others to assist in their care once in the community. Ongoing rehabilitation
is often needed after discharge, which may be provided at home, as an outpatient, or at a
subacute facility. Subacute rehabilitation is provided in a skilled nursing facility (SNF), but at
a lower intensity with about 1 hour of therapy given daily, as opposed to acute rehabilitation
where at least 3 hours of daily therapy is provided.

Family meetings are typically arranged by the social worker or case coordinator and
include the physician and many of the team members. The psychologist is often present at
these meetings as family dynamics are often explored. When possible and appropriate, the
patient is included in this meeting. This is a good opportunity to problem solve discharge
planning issues and make arrangements for the next level of care. Many factors are consid-
ered, such as the availability and adequacy of family and community support and the provi-
sion of continued needed care.

Conditions seen for rehabilitation include, but are not limited to, persons who have suf-
fered from the following:

- Traumatic brain injury
- Stroke
- Multiple sclerosis
- Limb loss
- Sports injury
- Vestibular disorders
- Spinal cord injuries
- Developmental delay
- Parkinson’s disease
- Muscular dystrophy
- Cerebral palsy
- Amyotrophic lateral sclerosis.

Patients requiring rehabilitation often have complex medical, psychological, and social
needs that warrant a coordinated and interdisciplinary approach. The definition of the inter-
disciplinary team “refers to activities performed towards a common goal by individuals from
a group of different disciplines” (Melvin, 1980). The members of the interdisciplinary team
need to be skilled not only in their specific discipline, but in others as well to be effective
interdisciplinary team members. The goal should be “to accomplish an outcome which is
greater than each functioning separately” (Keith, 1991). This also requires considerable edu-
cation for the patient, their families, and significant others.

CONTINUUM OF CARE

As health care reform progresses, the delivery of services provided throughout the contin-
umum of care is changing. The current model in the United States can provide all aspects of
rehabilitation care in various settings, noting that the intensity of services in these practice
settings varies. All rehabilitation professionals are available throughout the continuum of
care that is described below. National, state, and local laws determine who is authorized to
provide these services.

Acute Care

It is provided in a hospital setting. The patient is typically admitted following an acute injury,
medical occurrence, or for a surgical procedure. Length of acute hospitalization is often only
a few days, and patients are routinely discharged to another level of care or to their homes
when medically stable.
Inpatient Acute Licensed Rehabilitation Program

Patients admitted to acute rehabilitation facilities require around-the-clock medical care but do not require the level of medical service provided in an acute care hospital. These patients are usually transferred to acute rehabilitation after medical stability has been achieved in an acute hospital. These patients should tolerate at least 3 hours of therapy services daily (inclusive of PT, OT, and/or SLP), require both acute nursing care and physician availability 24 hours a day, and have the ability to make timely functional improvements.

Subacute Rehabilitation

Subacute rehabilitation provides care that is less intense than in acute rehabilitation, but patients continue to manifest potential to improve their functional skills through rehabilitation. Patients are generally required to tolerate only 1–2 hours of daily therapy, but must still require acute nursing care 24 hours a day and periodic physician care.

Skilled Nursing Facility

These facilities have distinct beds that allow patients the opportunity to recuperate for an extended period of time with some therapy services on a daily basis. These designated beds can also be within a freestanding acute licensed rehabilitation hospital, a freestanding long-term care facility, or a freestanding skilled rehabilitation hospital. Patients treated in this setting have fewer acute medical needs than either acute or subacute rehabilitation. It is typically targeted at older, postacute patients who may not be able to tolerate the intensity of acute rehabilitation but who have the capacity for functional recovery.

Home-Based Therapy

Home therapy is provided to patients who need continued rehabilitation but no longer require care within a hospital, a subacute facility, or a SNF. Patients are typically considered homebound and are therefore incapable of participating in outpatient rehabilitation programs.

Outpatient Therapy

Outpatient services are provided to those patients who no longer require hospital-based therapies and who are not homebound. Services are designed to provide either general rehabilitation to a wide group of individuals or more specialized care to specific groups of patients. Depending on the individual needs of the person being served and the specific discipline prescribed, outpatient therapy is typically provided two to three times per week per discipline. The number of sessions and frequency of treatment depend on the amount of treatment needed and the patient’s progress.

Wellness and/or Prevention Centers

These are centers that are often within community fitness centers, health clubs, or a health care facility. Their goal is to educate, instruct, and promote the practices of wellness and prevention of illness or injury. A physiatrist and other rehabilitation professionals often refer individuals to these centers after they have had a course of a more traditional rehabilitation.
Comprehensive Day Treatment Programs

Comprehensive day rehabilitation programs have the goal of preventing long-term institutionalization while providing a daily program of activities. Some comprehensive day rehabilitation programs provide restorative services and are geared toward achieving specific therapeutic endpoints within a defined period of time, with the goal of living a more independent life in the community. Some common types of day treatment programs include brain injury day treatment programs, adult day treatment programs, and dementia day treatment programs. These programs often provide some degree of respite for full time care providers of severely disabled individuals. If these programs were otherwise not available it would require many individuals be institutionalized due to the level of care they require.

World Health Organization (WHO)

In addition to the various settings designed to assist the patients in recovery, there are also organizations that work on a large scale to improve the lives of people who require rehabilitation services. One such organization is the World Health Organization (WHO). WHO’s role in the area of disability and rehabilitation is to enhance the quality of life and promote and protect the rights and dignity of people with disabilities through local, national, and global efforts. It is estimated that 650 million people live with disabilities around the world. To enhance the quality of life and to promote and protect the rights and dignity of people with disabilities the key focus is the following:

- Advocacy
- Data collection
- Medical care and rehabilitation
- Community-based rehabilitation
- Assistive devices/technologies
- Capacity building
- Policies
- Partnerships (World Health Organization, 2005).

DISABLEMENT MODELS

The WHO and other groups have been instrumental in creating models to understand function and disability, which are better known as “disablement models.” One of the earliest theories in rehabilitation, and the most familiar, concerns the consequences of disease and injury, that is, disablement, and how they integrate the medical and social models of practice. In the medical model, disability is viewed as a “characteristic or attribute of the person, which is directly caused by disease, trauma, or other health condition and requires some type of intervention provided by professionals to ‘correct’ or ‘compensate’ for the problem.” In the social model, disability is viewed as a “socially created problem and not as an attribute of the person.” In the social model of disability, the underlying problem is created by an unaccommodating or inflexible environment brought about by the attitudes or features of the social and physical environment itself, which calls for a political and physical response or solution (Jette, 2006). The combination of the medical and social model subsequently is the biopsychosocial model. It attempts to integrate both models of disability. This is the key framework of the disablement model that is widely used today.

Rehabilitation medicine experts have been struggling with the concepts and language that describe disablement for decades. Nagi in the 1960s and the WHO in the 1980s were among the major contributors to the literature of rehabilitation medicine (Table 1.1).
Nagi’s disablement model has its origins in the early 1960s as part of a study of disability commissioned for the Social Security Administration (SSA) and his work on conceptual issues related to rehabilitation. Nagi designed a framework that differentiated between four distinct yet related phenomena that he considered basic to the field of rehabilitation. He referred to these as active pathology, impairment, functional limitation, and disability. His conceptual framework has become known as Nagi’s disablement model.

Jette, 2006

The World Health Assembly developed a common language and framework to understand and describe similar concepts of rehabilitation. The WHO’s model of the International Classification of Impairments, Disabilities and Handicaps (ICIDH) (Jette, 2006) was completed in the early 1980s and differentiated health conditions into impairments, disabilities, and handicaps. Each model works to try to provide a language and a structure to define disablement (Figure 1.2).

The WHO model, currently known as the International Classification of Functioning, Disability and Health (ICF), was not endorsed by the World Health Assembly at the United Nations until 2001, after major revisions from the initial document were made. The intent in the development of the ICF as a disablement model was to provide professionals in the field of rehabilitation medicine a universal, standardized disablement language. One of its goals is to provide a scientific basis for understanding and studying health and health-related disability throughout the world. This common language was designed to help with research, care, and provision of services throughout the world.

**RESEARCH**

This is an exciting time for research in rehabilitation. Many challenging unanswered questions need to be resolved. It is always a challenge to conduct a well-designed study, and in rehabilitation, there are several added hurdles. First, there are many team members with overlapping responsibilities. Second, there are many types of disabilities and a multitude of different treatments occurring simultaneously (e.g., surgical, pharmaceutical, various

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**TABLE 1.1 Disablement Concepts and Definitions**

<table>
<thead>
<tr>
<th>Nagi</th>
<th>ICF</th>
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<tbody>
<tr>
<td>Active pathology—interruption or interference with normal processes and effort of the organism to regain normal state</td>
<td>Health conditions—diseases, disorders, and injuries</td>
</tr>
<tr>
<td>Impairment—anatomical, physiological, mental, or emotional abnormalities</td>
<td>Body function—physiological functions of body systems</td>
</tr>
<tr>
<td>Functional limitation—limitation in performance at the level of the whole organism or person</td>
<td>Body structures—anatomical parts of the body</td>
</tr>
<tr>
<td>Disability—limitation in performance of socially defined roles and tasks within a sociocultural and physical environment</td>
<td>Impairments—problems in body functions or structure</td>
</tr>
</tbody>
</table>

Activity—the execution of a task or action by an individual

Activity limitation—difficulties an individual may have in executing activities

Participation—involvement in a life situation

Participation restriction—problems an individual may experience in involvement in life situations

An Introduction to Key Topics and Issues

therapies, and medical management). In addition, it is also difficult to isolate how much of
an impact rehabilitation has versus the effect of time alone on recovery.

Length of stay defines how long a patient remains in the hospital. Currently, there is a lack of
good quality scientific data to show what the ideal length of stay should be to most efficiently
benefit individuals with various conditions. A patient’s progress and change in functional
status give important individual information when determining length of stay. However, the
ideal length of stay for various conditions and presentations is largely unknown.

Until optimal length of stay data are clearly delineated, it is likely that inpatient rehabilita-
tion lengths of stay will continue to decrease. Whereas it is certainly initially less costly to
have shorter lengths of stays, it remains unclear whether patients receive maximum benefit
or if an early discharge potentially leads to greater disability and cost over time. The current
fiscal climate appears to beckon for continued length of stay reductions and this will likely
continue until research can show that there is a point of diminishing returns.

Disease-specific research in rehabilitation also holds great promise. For example, what is
the etiology of Parkinson’s disease and multiple sclerosis? Can these and other conditions be
prevented? If we understand the disease process better, we can develop more effective inter-
ventions or prevent them altogether. There are many exciting research questions to answer in
the next decade. The answer to these and many other questions will have a profound infl u-
ence on rehabilitation care and quality of life for generations to come.

A specific type of research relates to outcomes achieved by a group of patients receiving
care from a defined group of health practitioners. Outcome data are becoming a more com-
mon means of assessing the effectiveness of health care including medical rehabilitation.
Outcome measures allow an organization to measure its performance over time and compare
its performance with others in the region and the nation.

Many types of outcomes, such as patient satisfaction, can be assessed. These data points
are used to analyze how patients report their overall satisfaction with those health care pro-
fessionals and organizations that provided their care. For example, Press Ganey® is a popular
and widely used patient satisfaction tool. This and other similar tools have been found to
be valid and reliable and allow comparisons of patient satisfaction between medical centers throughout the country that use the same tool. However, one difficulty with these types of data is that they are obtained by patients voluntarily agreeing to complete a survey, which often includes a majority of those that are either highly satisfied or highly dissatisfied, potentially skewing the results.

Another commonly used outcome assessment is the Functional Independence Measure (FIM®), which measures patient’s progress and burden of care. The FIM® is considered a PM&R industry standard and measures a patient’s improvement (or regression) across several standardized domains such as length of inpatient rehabilitation, abilities in locomotion, transfers, dressing, bathing, cognition, and bowel and bladder function. FIM® data can be combined among specific diagnostic groups within a particular rehabilitation organization that can be compared with similar patients in other organizations. This type of benchmarking provides a means to compare the magnitude of outcomes a particular rehabilitation organization has on a specific group of patients against others in their immediate area, their state, or even the country. This information can then be used to highlight exemplary care or identify problem areas that may be addressed through quality improvement initiatives.

Outcome data have lead to a critical assessment of inpatient length of stay. Length of stay for inpatient rehabilitation has continually decreased over the last two decades. For example, in the early 1990s many patients had more than 30 days of continual inpatient care. Today, the average patient stays only 2 weeks. As mentioned previously, there is every indication that the length of stay will continue to decrease until acute rehabilitation organizations can show a shorter length of stay leads to a worse outcome as compared to a longer length of stay.

ACCREDITATION

The accreditation process is a systematic means of evaluating a program against specific standards from an outside body. During the accreditation process, an outside agency is hired to review either an entire medical center or specific programs within the medical center. There are several accreditation bodies that pertain to rehabilitation. Two of the largest and most renowned are the Committee for the Accreditation of Rehabilitation Facilities (CARF®) and the Joint Commission®.

CARF takes a consultative approach to accreditation and focuses primarily on the patient’s experience. The CARF survey ensures the health and safety of the persons served (the term used to denote patients or clients) are maintained and that the persons served are benefiting from the service. CARF also looks to establish exemplary care by sharing best practice ideas and innovations across multiple rehabilitation centers. The CARF accreditation process is a systematic means of ensuring quality, value, and optimal outcomes (CARF Medical Rehabilitation Standards Manual July 2010–June 2011, 2010).

CARF surveys are voluntary in that each rehabilitation organization desiring accreditation must request it. Once requested, CARF provides a set of standards that must be met to become accredited and informs the organization in advance of when the survey will occur. All CARF surveyors are actively employed experts in the field. Numerous standards are analyzed in terms of conformance (meeting the intent of the standards). In addition, feedback is given to raise the level of quality of the program. One of CARF’s tenements is transparency and the sharing of ideas and resources. Therefore, if an exemplary practice is being implemented in a medical center, CARF will ask permission to share this practice at a national conference and/or other rehabilitation centers that may benefit from it. The goal of CARF is for organizations to achieve exemplary status where persons served are receiving maximal benefit from the services.

The Joint Commission has a larger scope and looks not only at the rehabilitation services of a medical center but the entire hospital as well. The Joint Commission will come unannounced to a facility and conduct an extensive and systematic review to ensure patient safety and quality of care.
The process of preparing for accreditation itself tends to improve quality. A detailed review of current practices and comparison to the standards outlined by the accreditation bodies helps to identify areas of deficiency and areas of strength in an organization.

The State Department of Health is a regulatory body with great scope and its own standards. The State Department of Health can come unannounced to conduct an investigation of a hospital or section of a hospital. This can be in response to a patient complaint, a patient procedure error, an unexpected medical error, billing inquiries, part of a quality check, or other indicators that a particular state monitors.

NEW AREAS OF REHABILITATION AND CURRENT CONCEPTS

Assistive Devices/Technologies

Assistive devices and technologies such as wheelchairs, prostheses, mobility aides, hearing aids, visual aids, and specialized computer software and hardware improve mobility, hearing, vision, and communication capacities. With the aid of these technologies, people with a loss in functioning are able to enhance their abilities and are better able to live independently and participate in their communities.

In many low-income and middle-income countries, only 5–15% of people who require assistive devices and technologies have access to them because their production is low and often of limited quality. There is a scarcity of personnel trained to manage the provision of such devices and technology, especially at the provincial and district levels. In many settings, where access might be possible, costs are prohibitive (Eldi & Parkin, 2005).

The Assistive Technology Act of 1998, defines these devices as “any item, piece of equipment, or produce system, whether acquired commercially, modified, or customized, that is used to increase, maintain, or improve the functional capabilities of individuals with disabilities” (Eldi & Parkin, 2005). Accessing this equipment and technology is often a critical component to successfully reintegrating many individuals to their communities, home, school, and work lives.

The Convention on the Rights of Persons with Disabilities (Articles 20 and 26), The World Health Assembly resolution WHA58.23, and the United Nations Standard Rules on the Equalization of Opportunities for Persons with Disabilities all highlight the importance of assistive devices. States are requested to promote access to assistive devices and technologies at an affordable cost and facilitate training for people with disabilities and professionals and staff working in habilitation and rehabilitation services. (www.who.int/violence_injury_prevention, 2009b)

DISASTERS, DISABILITY, AND REHABILITATION

“Disasters have an impact on disability, by disproportionately affecting persons with existing disabilities and by creating a new generation of persons with disabilities who will be in need of rehabilitation services. In settings where resources are limited, the impact of disasters on these groups of people can be long term and far reaching” (World Health Organization, 2005). Local and institutional emergency preparedness has become more of a recognized need, in which rehabilitation professionals must be actively involved.

As these issues arise, the impact on individuals with disabilities can be addressed by rehabilitation professionals who are readily available to aide them. Some issues preferentially affecting those with a disability during a disaster may include the following:

- Persons with disabilities are often more at risk of injury or abandonment
Many persons with disabilities lose their assistive devices, including artificial limbs, crutches, hearing aids, and glasses.

Rehabilitation infrastructure is often disrupted during a disaster because care providers are often diverted, cannot reach the individuals in need whom they care for, or are injured themselves. Therefore, individuals with special needs are left in even greater need.

Future of Rehabilitation

It is difficult to predict the future of rehabilitation but trends that are apparent today are likely to change the landscape of future practice. It is clear, for example, that there will be a greater demand for provision of care that is based on scientific evidence, as third-party payers are increasingly demanding proof of treatment efficacy. It will also become necessary to clearly demonstrate the optimal time period for rehabilitation, otherwise length of treatment will likely continue to decrease. In addition, acute inpatient rehabilitation is labor intensive with many disciplines providing care. Unless it can be shown that more team members with specific skills sets can improve outcomes it is unlikely that the model will remain the way it is (Strasser, 1997).

However, there is hope and many exciting new initiatives are taking hold. For example, safe patient handling programs are a new frontier for rehabilitation. Rehabilitation professionals often have a high rate of injury secondary to the physical tasks required to assist disabled patients (e.g., lifting patients and helping them move). One way of improving this is by using specialized equipment to lift and move patients without the risk of injury to the staff. This initiative has benefits for patients as well. Some medical centers are using ceiling harnesses to safely keep patients upright, which also allows safe, early ambulation and mobilization. The patients who would normally take several staff members to walk with are now able to bear weight and practice functional skills without the risk of injury from a fall.

Robotics is an area that has seen tremendous growth recently. The implantation of cerebral electrodes in the patient with a spinal cord injury is being studied now with great promise to decrease the burden of care on themselves and their support systems (Gelfman et al., 1997). Prosthetic limbs have also seen tremendous advancements thanks in large part to new computer-controlled technology that can readily adapt to a changing environment and the unique demands of various situations (Blakeslee, 2009).

After thousands of years of slow advancement, rehabilitation has recently shown tremendous growth. The rehabilitation team is active in many different models throughout the world today. Patients are benefitting from advancing technologies, accrediting bodies, research studies, and the use of a common language. Rehabilitation is a field rich with history, exciting in the moment, and full of possibilities.

REFERENCES


A clinician should view human immunodeficiency virus (HIV) infection as a spectrum of illness ranging from the primary infection to a relatively asymptomatic stage that in turn progresses to an advanced stage known as the acquired immunodeficiency syndrome (AIDS). HIV is caused by one of two human retroviruses HIV-1 or HIV-2. HIV-1 is the more common causal agent worldwide and tends to lead to more rapid immune deficiency. Both viruses can be transmitted through sexual exposure, through contact with blood or other body fluids, vertically from mother to child, or via breast milk.

The Centers for Disease Control and Prevention estimate that there are approximately 1.1 million people living with HIV/AIDS in the United States, with more than 50,000 new infections occurring annually (Bradley & Verma, 1996). Major risk groups continue to be men who have sex with men and injection drug users, but high-risk heterosexual contacts accounted for 32% of transmitted HIV infections in 2007 (CDC, 2009). The burden of HIV infections falls disproportionally on minority populations, with African Americans comprising 51% of the total cases, on the basis of the 2007 data.

The hallmark of HIV disease is a profound immunodeficiency resulting from progressive quantitative and qualitative deficiency in the subset of T lymphocytes known as T-helper, or CD4+, cells. Virtually any cell in the body that expresses the CD4 molecule on its cell surface can get infected with the HIV virus, although two major coreceptors, CCR5 and CXCR4, need also to be present to promote efficient HIV entry into the T cell.

Laboratory diagnosis of HIV infection is usually accomplished by detecting HIV antibodies using a highly sensitive enzyme immunoassay (EIA) and a confirmatory Western blot test that detects antibodies to HIV antigens of specific molecular weights. With the exception of patients who may be presenting with very early HIV infection, prior to the development of HIV antibodies, the combination of a positive EIA and confirmatory Western blot is considered the gold standard for the diagnosis of HIV infection.

For HIV-infected patients, measurement of the CD4+ T-cell count and the level of plasma HIV RNA replication (also known as their viral load) are considered as part of routine evaluation and monitoring. The CD4+ T-cell count provides information about the present immunological status of the patient, with the viral load predicting the likely future immunological health of the patient. More specifically, CD4 counts will help prognosticate which complications an infected individual is at greatest risk of developing, along with guiding the use of available prophylactic medications to help prevent infections. The viral load is also used to assess a patient’s adherence to and the effectiveness of a given antiretroviral regimen. The
goal of therapy is to maximally suppress the measurable plasma HIV to below the lower limit of detection of the viral load assay.

A complete discussion of the clinical manifestations of HIV infection is beyond the scope of this chapter, but severe and disabling conditions associated with HIV become more common as the patient’s CD4 count declines as the illness progresses. The key elements in treating symptomatic complications of HIV disease are simultaneously achieving control of HIV replication through the use of combination antiretroviral therapy and implementing therapies directed at curing or mitigating the disabling HIV-associated conditions.

The remainder of this chapter will describe and discuss specific conditions that may create disability in persons infected with HIV.

**PERIPHERAL NEUROPATHIES**

It is estimated that nearly one third of people with HIV/AIDS experience some degree of peripheral nerve damage. Peripheral neuropathy is the most common neurological complication in these patients. For patients with HIV/AIDS, peripheral neuropathy can be caused by the virus itself, by medications used in the treatment of HIV/AIDS, or as a result of opportunistic infections. The symptoms of peripheral neuropathy that patients usually experience include uncomfortable sensations that are often described as burning, stiffness, prickling, tingling, or numbness. Patients often note a loss of feeling in the toes and soles of the feet. Sometimes the nerves in the fingers, hands, and wrists are also affected. This pattern of symptoms is referred to as a “stocking-glove” distribution, which is characteristic of peripheral neuropathy. Although relatively uncommon, symptoms may progress above the ankles or wrists; this indicates more severe nerve damage.

**Distal Sensory Polyneuropathy**

The most common form of peripheral neuropathy in this patient population is distal sensory polyneuropathy (DSP) (Cornblath & McArthur, 1988). There are two forms of DSP in HIV patients: one which is associated with the HIV disease itself and the other which is an antiretroviral-induced toxic neuropathy.

DSP, like most peripheral neuropathies, typically causes symptoms of painful or uncomfortable paresthesias. Symptoms may include allodynia, a painful response to a stimulus which is not typically painful, pins and needles sensation, burning discomfort, and/or numbness, which usually begins in the feet and progresses proximally into the legs. DSP has been found to be more common in the late stages of HIV disease when the disease is advanced and generalized wasting and cachexia may be present. The clinical presentation of antiretroviral-induced neuropathy is similar to that associated with DSP, directly related to HIV infection. The exact mechanism of DSP is not known; however, when associated with antiretroviral treatment, the underlying mechanism is thought to be related to mitochondrial toxicity caused by these agents. Among the pharmacological treatments, nucleoside analogues such as abacavir, didanosine, lamivudine, and stavudine are most commonly associated with this neuropathy. Loss of sensation may result, placing the affected individual at risk for injury to the skin of the affected area and related soft tissue or bone infections. In addition, loss of sensation places the affected individual at increased risk for falls and related injuries.

With regard to treatment, the practitioner should search for nutritional or metabolic deficiencies as these may contribute to the development of neuropathy. Treatment is primarily symptomatic and may include various medications to dampen the intensity of the uncomfortable sensations. These include medications such as tricyclic antidepressants, anticonvulsants, and other typical and atypical pain medications. Experimentally, pathogenesis-based approaches have shown promising results, such as highly active antiretroviral therapy (HAART) (Dwyer,
Mayer, & Lee, 1992). Recombinant human nerve growth factor has also been used experimentally with significant improvement in patients’ pain (Engsig et al., 2009).

**Necrotizing Vasculitis–Associated Neuropathy**

Necrotizing vasculitis has been described in patients with HIV (Garstang, 2002). This condition is an immunologically induced process causing an inflammatory reaction and necrosis in the vasa nervorum, the blood vessels that nourish the peripheral nerves. The resulting clinical syndromes may include a distal symmetrical neuropathy or a mononeuritis multiplex, which results from damage to multiple individual nerves. Distal neuropathy, the most common clinical manifestation of vasculitic neuropathy, is usually painful and associated with weight loss and myalgia. CD4 counts are usually below 600/ml. This type of neuropathy is relatively rare and affects 0.1–0.3% of patients with AIDS. The clinical course can be monophasic; however, patients often have relapses. In many patients, there is an overlap with the presence of hepatitis B or C and cryoglobulinemia may be present as well. An evaluation for opportunistic infections associated with vasculitis such as cytomegalovirus (CMV), *Mycobacterium tuberculosis*, fungi, and parasites should be performed. The diagnosis of necrotizing vasculitic neuropathy is made by nerve and muscle biopsies, which reveal inflammatory cell infiltrates and necrosis of blood vessels. The therapy presents a particular problem as most immunosuppressive or cytotoxic agents regularly used to treat vasculitis are contraindicated in HIV, though corticosteroids, IV γ-globulin, and plasmapheresis have been used successfully in combination with antiretroviral treatment (Gonzalez-Duarte, Robinson-Papp, & Simpson, 2008).

**MUSCLE DISORDERS**

Severe muscle wasting from repeated infections, malignancy, malabsorption, and nutritional deficiency often accounts for weakness and disability seen in patients with HIV/AIDS. Such wasting is characterized by loss of lean body muscle mass and is associated with weakness. Although weakness may be associated with nervous system involvement from infections or immunologically mediated neuropathies in these patients, the possibility of a primary skeletal muscle disease should not be overlooked as several skeletal muscle disorders causing weakness have been identified in HIV-infected patients.

**Myopathy**

In a review of almost 5,000 HIV-infected patients, myopathy was present in 0.2% (Griffiths, 2004). The affected patients typically present with myalgias, muscle tenderness, and symmetric proximal muscle weakness with a predilection for the lower extremities. Patients may rarely encounter myopathy as the presenting manifestation of HIV infection, or it may occur in the setting of already established AIDS. Unlike neuropathy, the development of myopathy does not correlate with the degree of immunosuppression or the level of CD4+ T cells in the circulation.

HIV-associated myopathies include polymyositis and dermatomyositis, zidovudine (AZT) myopathy, rhabdomyolysis, nemaline rod myopathy, HIV wasting syndrome, myopathy associated with local neoplasm, and myopathy associated with local infection. Opportunistic muscle infections are encountered in untreated patients, whereas treated patients are more likely to develop inflammatory myopathies or drug-induced muscle involvement.

In early HIV infection, polymyositis and dermatomyositis or nemaline rod myopathy may occur. Polymyositis and dermatomyositis are immune mediated and are similar in presentation to patients who do not have HIV. Symptoms are usually generalized and include
progressive muscle weakness that develops gradually and tends to affect proximal muscles such as those in the hips, thighs, shoulders, upper arms, and the neck. Nemaline rod myopathy is characterized by slowly progressive weakness and muscle wasting which may be autoimmune in nature (Haas et al., 2004). Later in the disease process, AZT-related myopathy may occur (Hall et al., 2008). Under this condition, patients present with proximal muscle weakness, myalgias of the calves and thighs, and easy fatigability. In the later stages of HIV disease, myopathy may be caused by a local infection or from neoplasm, such as lymphoma or Kaposi’s sarcoma. In the setting of an infection, affected muscles become painful and swollen; fever and fatigue may be present as well.

Treatment of HIV-related myopathy is based on its etiology. Polymyositis and dermatomyositis are treated with corticosteroids. Patients who are unresponsive to steroids are often treated with an alternative immunosuppressant, such as azathioprine, cyclosporine, or methotrexate. Intravenous immunoglobulin treatments may help some people who are also unresponsive to other immunosuppressants. Patients with nemaline rod myopathy also respond to corticosteroid treatment (Horberg et al., 2008). In AZT myopathy, the offending medication is discontinued and alternative medications are substituted. Muscle enzymes and muscle strength usually return to normal within a few months after AZT is discontinued.

**HIV-Associated Neuromuscular Wasting Syndrome**

This syndrome includes neuromuscular clinical manifestations, such as progressive myopathy and a rapidly progressing sensorimotor polyneuropathy. In HIV-associated neuromuscular wasting syndrome (HANWS), patients present with progressive weakness, weight loss, and metabolic abnormalities such as elevated serum lactate and liver function tests. Neurological manifestations vary, as there is a spectrum of pathologies. Many patients exhibit features of demyelination clinically, which is caused by loss of myelin that surrounds the axons that normally increases the speed of nerve condition. However, the majority of patients have primarily axonal pathology, caused by direct involvement of the nerve. The axonal form of this syndrome has a worse prognosis than the demyelinating form. When elevated serum lactate develops in the setting of therapy with nucleoside reverse transcriptase inhibitors, there is a high likelihood that HANWS will develop. Systemic symptoms may include nausea, vomiting, abdominal distention, weight loss, and hepatomegaly (abnormal increase in the size of the liver), which are associated with a rapidly ascending motor weakness that develops over days to weeks. This syndrome may mimic Guillain-Barre syndrome, and it can result in respiratory failure and death (Griffiths, 2004).

The pathogenesis of HANWS in HIV-infected patients is likely to be multifactorial, and may result from a combination of mitochondrial and immunological mechanisms caused by HIV disease; though HAART therapy may contribute as well. Although a majority of patients present with axonal alterations, intravenous immunoglobulin or plasmapheresis could be considered as possible treatment options with the prevalence of demyelination. The treatment of HANWS is controversial, and important, because it is a potentially fatal syndrome. It is therefore important to interrupt HAART therapy in such cases. The reintroduction of HAART then becomes quite challenging; other treatment options should be considered.

**SPINAL CORD DISEASES**

**Vacuolar Myelopathy**

Vacuolar myelopathy is the myelopathy most commonly associated with HIV; it is a slowly progressive painless spastic paraparesis, with sensory ataxia and neurogenic bladder and bowel. Histopathologically, vacuolar myelopathy is characterized by prominent vacuolar changes in the ascending and descending tracts of the spinal cord, with a particular affinity...
for the thoracic region (Figure 2.1). This type of myelopathy is only clinically symptomatic in about 5–10% of AIDS patients. Most patients who develop this disease die within 6 months of developing related symptoms. This typically occurs during the later stages of HIV infection, when other neurological problems may be present as well, including peripheral neuropathies, dementia, and opportunistic central nervous system and peripheral nervous system infections or malignancies. Vacuolar myelopathy is not typically fatal but rather a cause of significant disability (Jose, Saravu, Jimmy, & Shastry, 2007).

There is no specific treatment that has been proven to be effective for vacuolar myelopathy. Treatments are symptomatic and aimed at relief of typical symptoms of myelopathy including spasticity, neurogenic bladder and bowel, and improving function with multidisciplinary rehabilitation.

**Infectious Myelitis**

Infectious myelitis in patients with HIV may result from a variety of different etiologies. The involvement of the spinal cord in patients with HIV can be caused either by HIV itself or other opportunistic infections. These infections may be bacterial, viral, or fungal in nature.

Varicella zoster is one of the viruses associated with HIV in many cases. Varicella zoster myeloradiculitis in patients with HIV sometimes involves related encephalitis as well. Varicella myelitis usually involves the posterior horns of the spinal cord because the infection spreads from the dorsal root ganglia through the posterior roots. Patients often note burning pain and hypersensitive skin, which is then followed by the characteristic rash. The blistering rash
follows a dermatomal pattern, which appears as a band-like pattern on the skin. The lesions will eventually crust over and heal later. The duration of a typical outbreak usually takes 3–4 weeks for full resolution. Motor weakness may accompany the typical sensory symptoms. Treatment includes pain medications as well as antiviral agents and oral corticosteroids.

Bacterial infections causing myelitis tend to be rare in HIV patients; the most common such pathogen is *M. tuberculosis*. Tuberculosis (TB) is the most common opportunistic infection worldwide affecting HIV-infected persons and is the most common cause of death in patients with AIDS. Involvement of the spine by TB is known as Pott’s disease. The signs and symptoms of Pott’s disease include back pain, fever, night sweats, weight loss, and focal neurological deficits determined by the level of spinal involvement and paraspinal masses. In adults, the lumbar region is the most commonly involved. Treatment includes long-term multidrug antituberculosis therapy. Surgery may occasionally be indicated to prevent progressive neurological decline or spinal deformity. Overall, the prognosis for recovery is excellent with a recovery rate of more than 90% with appropriate treatment (Kalichman, Heckman, Kochman, Sikkema, & Bergholte, 2000).

**HTLV-1 Myelopathy**

Human T-cell lymphotropic virus type I (HTLV-1) is a virus commonly found in the Caribbean and is transmitted through sexual, parenteral, and maternal routes. Risk factors for infection with this virus include intravenous drug use, promiscuous sexual activity, and the presence of HIV disease. HTLV-1 myelopathy is found in a small percentage of patients infected with the virus and causes pyramidal, spinocerebellar, and spinothalamic tract injury. The clinical manifestations of HTLV-1 myelopathy include a slowly progressive spastic paraparesis, segmental sensory abnormalities, urinary dysfunction, and back pain. HTLV-1 is diagnosed based on clinical suspicion and is confirmed with laboratory testing demonstrating HTLV-1 antibodies in the serum and cerebrospinal fluid (CSF). Magnetic resonance imaging of the spinal cord may show abnormalities in the periventricular white matter tracts. There is no long-term disease-altering treatment available for this disease, and potential treatments including corticosteroids, cyclophosphamide, AZT, and vitamin C have been ineffective. Plasmapheresis has also been tried with minimal success (Kalichman et al., 2000). The mainstay of treatment, as with vacuolar myelopathy, involves the symptomatic treatment of associated conditions, prevention of secondary complications such as falls, pressure ulcers, and urinary tract infections, and the rehabilitation interventions to maximize function and preserve independence for as long as possible.

**BRAIN DISORDERS**

**Progressive Multifocal Leukoencephalopathy**

Progressive multifocal leukoencephalopathy (PML) is a fatal viral disease characterized by progressive inflammation of the white matter of the brain at multiple locations. This disease typically occurs in patients who are immunocompromised, most commonly in patients with HIV or AIDS. PML is caused by a virus called the John Cunningham (JC) virus. Antibodies to the JC virus are actually found in a large percentage of the general population. In healthy individuals though, the virus typically remains latent and harmless. JC virus produces disease only when one’s immune system is severely compromised. Research has shown that the effect of HIV on brain tissue enables viral activation in the brain, which results in the clinically detrimental effects. The symptoms and signs of PML result from the loss of white matter in many areas of the brain (Figure 2.2). PML is a demyelinating disease, which results in a slowing of nerve conduction. Patients experience symptoms that include weakness or
Disabling Conditions Seen in AIDS and HIV Infection

paralysis, dysarthria, impaired vision, and cognitive dysfunction. Patients affected with PML typically deteriorate very rapidly; the average survival of HIV patients with PML is about 6 months. There is no known cure for PML; however, patients have been able to survive longer when treated with HAART (Power, Boisse, Rourke, & Gill, 2009). Other antiviral medications have also been studied as possible treatment options; however, more research is required in this area.

CMV Encephalitis

CMV belongs to the family of herpes viruses. CMV infection is endemic; the majority of adults with HIV have evidence of previous CMV infection when blood work for antibodies is performed. CMV encephalitis is a disease typically diagnosed based on clinical suspicion in HIV-infected patients who have a history of infection with CMV disease. These patients present with a clinically progressive encephalopathy, and imaging studies often reveal the evidence of ventriculitis. The diagnosis is then confirmed with polymerase chain reaction (PCR) testing and CSF cultures revealing presence of the virus. CSF-PCR is the diagnostic test of choice.

CMV encephalitis, when associated with HIV infection, can vary in the way in which it presents clinically. Patients who have ventriculoencephalitis suffer an acute onset and rapid deterioration characterized by confusion and lethargy. The cranial nerves may also be affected causing focal neurological deficits. Other medical problems that may be associated with CMV encephalitis include myelitis, retinitis, esophagitis, neuropathy, and adrenal insufficiency.

FIGURE 2.2 Axial T2-weighted image of the brain in an HIV-infected patient with progressive multifocal leukoencephalopathy who presented with behavioral changes as his initial manifestation of HIV infection. Arrows indicate multiple areas of abnormal signal change within the brain. (Photo courtesy of Rona Woldenberg, MD.)
If CMV encephalitis is not treated, it typically progresses to death in a period of days to weeks. The treatment consists of ganciclovir, foscarnet, or cidofovir. Patients are usually treated with induction doses initially and then continued on maintenance doses of medication (Robinson-Papp & Simpson, 2009).

**Dementia**

HIV-associated dementia produces a wide spectrum of disabilities that range from reduced work efficiency and quality of life to complete dependence for self-care. The HIV virus enters the central nervous system very early in the disease process. HIV-associated dementia is thought to arise from an HIV-induced defect in immune cellular signaling that produces neuronal damage in the brain (Said & Lacroix, 2005).

The clinical syndrome known as the AIDS dementia complex (ADC) is one of the most common and clinically important central nervous system complications of late HIV infection. ADC includes behavioral changes, cognitive dysfunction, or brain-related motor impairment, that is not directly attributable to a specific etiologic agent such as PML or CMV. It is quite common for patients with HIV to have deficits in cognition, including in areas such as memory, concentration, problem solving, and mood. These symptoms may be present in different stages of severity. Because ADC is a diagnosis of exclusion, it is important to consider multiple etiologic possibilities, including the possibility of cognitive impairment caused by medications. For example, Efavirenz has been associated with multiple CNS side effects, including impaired concentration (Simpson & Bender, 1988).

Prior to the advent of treatment with HAART, dementia was associated with a high mortality and was seen in many patients before their death. The incidence of dementia in HIV has declined with HAART treatment; however, the prevalence has remained the same, as persons with HIV live longer. Treatment with HAART has even been found to reverse some of the neurological deficits caused by HIV. HAART also delays the onset of dementia in HIV, though it does not seem to prevent the onset of cognitive impairment.

The treatment of HIV-associated dementia is with HAART combined with an aggressive treatment of related psychiatric disorders that may be present. For example, patients who present with depression along with dementia should be evaluated for the need for antidepressant medications. The commonly used antidepressants in patients with HIV include citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. The treatment of concomitant depression not only results in improvement of mood but also better adherence to the patient’s antiretroviral medication regimen (Simpson, Citak, Godfrey, Godbold, & Wolfe, 1993).

**Psychological Conditions**

The introduction of HAART changed the lives of patients with HIV dramatically. Before HAART treatment was available, patients with HIV suffered from extremely poor health characterized by a downward spiral of negative medical events, which dramatically affected life span, as well as quality of life. Patients often became very depressed as they began to lose their jobs and sources of income because of the severity of their illness. With the introduction of HAART, the life expectancy for patients with HIV has been prolonged, and their overall health has improved, which has obvious psychological benefits. Occasionally, the disease is less likely to result in disability. However, the importance of psychologists and mental health professionals remains critical in patients with HIV. Patients with HIV often experience social and psychological distress and require mental health intervention to address these important issues. Patients may suffer from various psychological conditions, including depression, anxiety, panic attacks, and adjustment disorders. The stigma associated with HIV infection alone is a psychological burden to those individuals with HIV and...
Disabling Conditions Seen in AIDS and HIV Infection

AIDS. These patients, as a result, often have higher rates of suicide when compared with the general population. In one study that evaluated the psychological status of HIV patients in New York City, significantly more persons with HIV disease exhibited suicidal behavior as compared with patients with an unknown HIV serostatus (Wu, Zhao, Tang, Zhang-Nunes, & McArthur, 2007). Psychological support is therefore critical in HIV patients, and families and friends should be included as part of the support system. It is important for mental health providers to allow the patients to share their feelings and experiences in order to help them remain optimistic and maintain hope throughout the course of the disease. The different services that should ideally be available for these patients include crisis intervention, individual psychotherapy, family interventions and support, support groups, and treatment for those with substance abuse. Those who counsel these patients should have a good understanding of the different psychosocial aspects involved with HIV and the social aspects involved with HIV-associated disability.

REFERENCES


Evidence suggests that approximately 10–15% of community-residing persons in the United States, aged 65 and older, may be afflicted with Alzheimer’s disease (AD) or closely related dementing illnesses of late life (Evans et al., 1989; Katzman, 1986). Presently, it is estimated that in the United States more than 5 million persons aged 65 and older and approximately 200,000 persons younger than 65 years have AD (Executive Summary, Alzheimer’s Association, 2009). At the other end of the demographic spectrum, half of persons older than 85 years in the United States are believed to have AD. More specifically, in the United States, dementia, secondary to AD, in entirety or in part in the great majority of cases, affects about 30% of community-residing persons between 85 and 89 years of age and about 50% of those in the community between 90 and 94 years of age. For community-residing U.S. persons 95 years or older, nearly 75% are found to have dementia (Graves et al., 1996; Montine & Larson, 2009). Worldwide, it has been estimated that more than 24 million persons have AD (Ferri et al., 2005). The prevalence of AD approximately doubles every 5 years after the age of 65 in developed nations and every 7 years in developing nations (Larson & Langa, 2008; Lobo et al., 2000).

In the United States, AD is the fourth leading cause of death in the elderly, after heart disease, cancer, and stroke. AD is the single major cause of institutionalization of aged people in the United States and in many other industrialized nations in the world. Studies have indicated that a large majority of approximately 1.5 million residents in nursing homes in the United States manifest a dementia syndrome generally associated with AD (Chandler & Chandler, 1988; Rovner, Kafonek, Filipp, Lucas, & Folstein, 1986). In addition, the institutional or “semi-institutional” burden of AD, depending upon the precise definition of institutionalization, is truly much greater. Approximately 1 million persons in the United States reside in assisted living facilities, which are “depicted as residential settings for cognitively intact older people with functional limitations” (Kaplan, 2005). In a study of 22 such facilities in Maryland, approximately two thirds of these persons have been found to have dementia, and the great majority of these persons with dementia were found to have AD (Rosenblatt et al., 2004). These statistics may be applicable to the broader U.S. assisted living population. The dimensions of the institutional burden associated with AD are even more striking when it is noted that well under 1 million persons are in U.S. hospitals at any particular time.

Pre-AD conditions add further to the true burden of the disease. For example, approximately 15% of persons aged 65 and older in the United States have mild cognitive impairment (MCI)
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(Executive Summary, Alzheimer’s Association, 2009). This condition, which is a precursor of overt AD, is associated with a decrease in performance in complex occupational and social tasks (also referred to as executive activities), as well as a generalized decrement in cognitive performance and an increased susceptibility to delirium (Gauthier et al., 2006). MCI is also associated with a decrease in balance and coordination (Franssen, Souren, Torossian, & Reisberg, 1999). These MCI-related disabilities likely have considerable economic, social, and medical consequences, the dimensions of which are largely uncharted. In addition, a pre-MCI condition, termed subjective cognitive impairment (SCI), is now increasingly recognized as an early antecedent of eventual AD. Very subtle cognitive and functional changes appear to occur in this SCI stage of eventual AD, which have unknown consequences, apart from heralding an eventual decline to MCI and, ultimately, the dementia of AD (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). However, it is clear that large proportions of older persons take a variety of medications, nutriceuticals, vitamins, and other substances in an effort to mitigate their perceived symptoms, and the economic costs associated with this self-prescribing are very considerable (Reisberg, Franssen, Souren, Kenowsky, & Auer, 1998; Reisberg & Shulman, 2009).

The course of AD has been described in increasing detail over the past several years. The cognitive, functional, and behavioral concomitants at each stage of the illness can presently be described in detail (see Figure 3.1). The clinically observable symptomatology of AD dramatically changes in form from the earliest manifest deficits to the most severe stage; therefore, recognition and differentiation of the stages of this illness is imperative for proper diagnosis, prognosis, management, and treatment. Progressive cognitive changes that occur are manifest in concentration, recent memory, past memory, orientation, functioning and self-care, language, praxis ability, and calculation, among other areas (Reisberg, London, Ferris, et al., 1983; Reisberg, Schneck, Ferris, Schwartz, & de Leon, 1983). Characteristic behavioral symptoms are also a frequent component of AD (Finkel, 1996; Finkel & Burns, 2000; Kumar, Koss, Metzler, Moore, & Friedland, 1988; Lyketsos et al., 2000; Reisberg, Franssen, Sclan, Kluger, & Ferris, 1989; Rubin, Morris, Storandt, & Berg, 1987). These behavioral symptoms peak in occurrence at various points in the course of AD and subsequently recede in magnitude and frequency with the progression of the disease. A comprehensive view of the nature and progression of these cognitive, functional, and behavioral changes is critical for the optimization of residual capacity and the identification and management of excess disability in these patients.

An outline of global cognitive, functional, and behavioral changes in normal aging and progressive AD is provided in the Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982), outlined in Table 3.1 and described in greater detail in the following sections.

GLOBAL DESCRIPTION OF NORMAL BRAIN AGING AND AD

Seven major, clinically distinguishable, global stages from normality to most severe AD have been described (Reisberg et al., 1982; Reisberg, Sclan, Franssen, et al., 2008). These stages and their implications are as follows:

Stage 1: No Cognitive Impairment—Diagnosis: Normal

No objective or subjective evidence of cognitive decrement is seen. A significant proportion, although possibly only a minority, of persons more than age 65, fall within this category (Blazer, Hays, Fillenbaum, & Gold, 1997; Brucki & Nitrini, 2008; Gagnon et al., 1994; Jonker, Geerlings, & Schmand, 2000; Reinikainen et al., 1990; Tobiansky, Blizard, Livingston, & Mann, 1995; Wang et al., 2000). The prognosis is excellent for continued adequate cognitive functioning (Geerlings, Jonker, Bouter, Ader, & Schmand, 1999; Kluger, Ferris, Golomb, Mittelman, & Reisberg, 1999; Reisberg, Shulman, Torossian, et al., 2010).
**Stage 2: Subjective Cognitive Decline Only—Diagnosis: SCI**

Many persons older than 65 years have subjective complaints of cognitive decrement such as a subjective perception of forgetting names of people they know well or of forgetting where they placed particular objects such as keys or jewelry. These subjective complaints may be elicited by comparing the person’s perceived abilities with perceptions of their performance 5–10 years previously.

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**FIGURE 3.1** Typical time course of normal brain aging, mild cognitive impairment associated with Alzheimer’s disease, and the dementia of Alzheimer’s disease. AD - Alzheimer’s disease; CDR - Clinical Dementia Rating (Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993); FAST - Functional Assessment Staging (Reisberg, 1988; Sclan & Reisberg, 1992); GDS - Global Deterioration Scale (Reisberg et al., 1982; Reisberg et al., 1988); MMSE - Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975); Mod AD - Moderate Alzheimer’s disease; Mod Sev AD - Moderately severe Alzheimer’s disease. *Stage range comparisons shown between the CDR and GDS/FAST stages are based upon published functioning and self-care descriptors. **Numerical values represent time in years. For GDS and FAST stage 1, the temporal values are subsequent to the onset of adult life. For GDS and FAST stage 2, the temporal value is prior to onset of mild cognitive impairment symptoms. For GDS and FAST stage 3 and above, the values are subsequent to the onset of mild cognitive impairment symptoms. In all cases, the temporal values refer to the evolution of Alzheimer’s disease pathology. All temporal estimates are based upon the GDS and FAST scales and were initially published based upon clinical observations in Reisberg (1986). These estimates have been supported by subsequent clinical and pathological cross-sectional and longitudinal investigations (e.g., Bobinski et al., 1995; Bobinski et al., 1997; Kluger et al., 1999; Prichep et al., 2006; Reisberg & Gauthier, 2008; Reisberg et al., 1996; Reisberg et al., 2010; Wegiel et al., 2008). The spacing in the figure is approximately proportional to the temporal duration of the respective stages and substages, with the exception of GDS and FAST stage 1, for which the broken lines signify abbreviated temporal duration spacing for this normal adult condition which lasts approximately 30–50 years. ***MMSE scores are approximate mean values from prior published studies. †For typical adult psychometric tests. Copyright © 2007, 2009 Barry Reisberg, MD. All rights reserved.
## TABLE 3.1  **Global Deterioration Scale (EDS) for Age-Associated Cognitive Decline and Alzheimer’s Disease (AD)**

<table>
<thead>
<tr>
<th>GDS Stage</th>
<th>Clinical Characteristics</th>
<th>Diagnosis</th>
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</table>
| 1         | No subjective complaints of memory deficit  
No memory deficit evident on clinical interview | Normal |
| 2         | Subjective complaints of memory deficit, most frequently in following areas:  
(a) forgetting where one has placed familiar objects  
(b) forgetting names one formerly knew well  
No objective evidence of memory deficit on clinical interview  
No objective deficit in employment or social situations  
Appropriate concern with respect to symptomatology | Subjective cognitive impairment |
| 3         | Earliest subtle deficits  
Manifestations in more than one of the following areas:  
(a) person may have gotten lost when traveling to an unfamiliar location  
(b) coworkers become aware of person’s relatively poor performance  
(c) word and/or name-finding deficit become evident to intimates  
(d) person may read a passage or book and retain relatively little material  
(e) person may demonstrate decreased facility remembering names upon introduction to new people  
(f) person may have lost or misplaced an object of value  
(g) concentration deficit may be evident on clinical testing  
Objective evidence of memory deficit obtained only with an intensive interview  
Decreased performance in demanding employment and social settings  
Denial begins to become manifest in person  
Mild to moderate anxiety frequently accompanies symptoms | Mild cognitive impairment |
| 4         | Clear-cut deficit on careful clinical interview  
Deficit manifest in following areas:  
(a) decreased knowledge of current and recent events  
(b) may exhibit some deficit in memory of one’s personal history  
(c) concentration deficit elicited on serial subtractions  
(d) decreased ability to travel, handle finances, etc.  
Frequently no deficit in following areas:  
(a) orientation to time and place  
(b) recognition of familiar persons and faces  
(c) ability to travel to familiar locations  
Inability to perform complex tasks  
Denial is dominant defense mechanism  
Flattening of affect and withdrawal from challenging situations occur | Mild AD |

*Continued*
### TABLE 3.1 Continued

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<tr>
<th>GDS Stage</th>
<th>Clinical Characteristics</th>
<th>Diagnosis</th>
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<tr>
<td>5</td>
<td>Patient can no longer survive without some assistance</td>
<td>Moderate AD</td>
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<td></td>
<td>Patient is unable during interview to recall a major relevant aspect of their current life, e.g.:</td>
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<td></td>
<td>(a) their address or telephone number of many years</td>
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<td></td>
<td>(b) the names of close members of their family (such as grandchildren)</td>
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<td></td>
<td>(c) the name of the high school or college from which they graduated</td>
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<tr>
<td></td>
<td>Frequently some disorientation to time (date, day of the week, season, etc.) or to place</td>
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<td></td>
<td>An educated person may have difficulty counting back from 20 by 2s</td>
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<tr>
<td></td>
<td>Persons at this stage retain knowledge of many major facts regarding themselves and others</td>
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</tr>
<tr>
<td></td>
<td>They invariably know their own names and generally know their spouse's and children's names</td>
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<td></td>
<td>They require no assistance with toileting or eating, but may have difficulty choosing the proper clothing to wear</td>
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<tr>
<td>6</td>
<td>May occasionally forget the name of the spouse upon whom they are entirely dependent for survival</td>
<td>Moderately severe AD</td>
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<td></td>
<td>Will be largely unaware of all recent events and experiences in their lives</td>
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<td></td>
<td>Retain some knowledge of their surroundings; the year, the season, etc.</td>
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<tr>
<td></td>
<td>May have difficulty counting by 1s from 10, both backward and sometimes forward</td>
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<td></td>
<td>Will require some assistance with activities of daily living:</td>
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<td></td>
<td>(a) may become incontinent</td>
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<td></td>
<td>(b) will require travel assistance but occasionally will be able to travel to familiar locations</td>
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<td></td>
<td>Diurnal rhythm frequently disturbed</td>
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<td></td>
<td>Almost always recall their own name</td>
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<td></td>
<td>Frequently continue to be able to distinguish familiar from unfamiliar persons in their environment</td>
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<td></td>
<td>Personality and emotional changes occur. These are quite variable and include:</td>
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<tr>
<td></td>
<td>(a) delusional behavior, e.g., patients may accuse their spouse of being an imposter; may talk to imaginary figures in the environment, or to their own reflection in the mirror</td>
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<td></td>
<td>(b) obsessive symptoms, e.g., person may continually repeat simple cleaning activities</td>
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<td></td>
<td>(c) anxiety symptoms, agitation, and even previously nonexistent violent behavior may occur</td>
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<td>(d) cognitive abulia, e.g., loss of willpower because an individual cannot carry a thought long enough to determine a purposeful course of action</td>
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Apart from the occurrence of complaints of cognitive impairment with, what appears to be seemingly “normal aging,” these complaints may also occur with other, frequently more serious common conditions in the elderly, notably, MCI, dementia and depression. Persons with comparatively benign complaints associated with this stage can usually recall the names of two or more primary school teachers, classmates, or friends and are oriented to the time of day, date, day of week, month, season, and year (although, of course, occasional minor errors may occur). They also display normal recall when queried about recent events and normal concentration and calculation abilities, for example, when asked to perform serial subtractions of sevens from one hundred. The terminology “subjective cognitive impairment” has been suggested for this condition (Reisberg, Prichep, Mosconi, et al., 2008). The American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, refers to this condition under the more inclusive category of “age-related cognitive decline” (American Psychiatric Association, 1994). Clinical interview reveals no objective evidence of memory deficit, and there are no deficits in employment or social situations. However, physiological studies have shown clear, significant decrements in persons with these symptoms in comparison with age-matched subjects free of subjective complaints. For example, a recent study found an 18% decrement in cerebral metabolism in a particular brain region, the parahippocampal gyrus, as well as significant metabolic decrements in some other brain regions, in older persons with SCI in comparison with age-matched subjects who were healthy and free of SCI (Mosconi et al., 2008). Significant increases in urinary cortisol levels have also been reported in SCI subjects in comparison with age-matched control subjects (Wolf, Dziobek, McHugh, et al., 2005).

Current data from prospective longitudinal study indicates that these subjective impairments are in most cases a harbinger of subsequently manifest cognitive impairments after an average of about 7.5 years (Prichep et al., 2006; Reisberg & Gauthier, 2008). The total duration of this stage has been estimated to be an average of about 15 years prior to the onset of more overtly manifest impairments such as those associated with MCI (Reisberg, 1986; Reisberg & Gauthier, 2008). Although medications, nutriceuticals, and nostrums are frequently taken for these perceived deficits, largely in order to prevent further decline, there is no convincing evidence of their efficacy in treating the symptoms of this stage at the present time.
Stage 3: Mild Cognitive Decline—Diagnosis: MCI

This now widely recognized condition was first described, and subsequently named, in association with the GDS (Reisberg et al., 1988; Reisberg, Ferris, Kluger, et al., 2008). Various subsequent definitions of MCI have been proposed (e.g., Petersen et al., 1999; Petersen et al., 2001); however, current consensus definitions are consistent with the original GDS descriptions of the MCI entity (Gauthier et al., 2006; Winblad et al., 2004). MCI is a condition in which subtle deficits in cognition and cognition-associated functioning occur. Subtle evidence of objective decrement in complex occupational or social tasks may become evident in various ways. For example, the person may become confused or hopelessly lost when traveling to an unfamiliar location; relatively poorer performance may be noted by coworkers in a demanding occupation; persons may display overt word- and name-finding deficits; concentration deficits may be evident to family members and upon clinical testing; relatively little material may be retained after reading a passage from a book or newspaper; and/or an overt tendency to forget what has just been said and to repeat oneself may be manifest. A teacher who had routinely recalled the names of all of the students in his class by the end of a semester now may have difficulty recalling the names of any students. This same teacher may, for the first time, begin to miss important appointments. Similarly, a professional who had previously completed hundreds, perhaps thousands, of reports in the course of her lifetime now, for the first time, may be unable to accurately complete a single report. The person may lose or misplace objects of value. Mild to moderate anxiety is frequently observed and is an appropriate reaction to the awareness of impairment.

The prognosis associated with these subtle but objectively identifiable symptoms varies. In some cases, these symptoms are the result of brain insults, such as small strokes, which may not be evident from the clinical history, neurological examination, or neuroimaging findings. In other cases, symptoms are due to subtle and perhaps not clearly identifiable psychiatric, medical, and neurological disorders of diverse etiology. These symptoms are benign in many of the subjects who report them. However, in most cases, where other conditions have been ruled out in terms of etiology, these symptoms do represent the earliest symptoms of subsequently manifest AD. The mean true duration of this stage as a precursor of subsequently manifest mild AD has been estimated to be approximately 7 years (Reisberg, 1986). A review of 19 longitudinal studies found that the “overall conversion rate” (of MCI subjects per annum) was 10%, with large differences between studies (Bruscoli & Lovestone, 2004). They noted that self-selected clinic attendees had the highest conversion rates. In a rigorous 4-year prospective study of otherwise healthy subjects, fulfilling the exclusionary criteria for probable AD at baseline (except for the presence of dementia), MCI subjects declined at a rate of 17.8% per year to dementia, a rate quite similar to the 14.3% per annum change which would be anticipated from a stage which lasts approximately 7 years (Kluger, Ferris, Golomb, Mittelman, & Reisberg, 1999).

However, subjects commonly present with these symptoms well into this stage, and mild AD frequently becomes manifest after a much briefer period (Bowen et al., 1997; Daly et al., 2000; Devanand, Folz, Gorlyn, Moesller, & Stern, 1997; Flicker, Ferris, & Reisberg, 1991; Morris et al., 2001; Petersen et al., 1999; Tierney et al., 1996). Presently, no pharmacological agents have been approved for preventing further decline or in treating cognitive impairments in MCI.

Stage 4: Moderate Cognitive Decline—Diagnosis: Mild AD

Clinical interview at this stage reveals clearly manifest deficits in various areas, such as concentration, recent and past memory, orientation, calculation, and functional capacity. Concentration deficit may be of sufficient magnitude that patients may have difficulty subtracting serial 4s from 40. Recent memory may be affected to the degree that some major events of the previous week are not recalled, and there may be superficial or scanty knowledge of current events and activities. Detailed questioning may reveal that the spouse’s knowledge of the patient’s past is superior to the patient’s own recall of his or her personal history, and the patient may confuse the chronology of past life events. The patient may mistake the date
by 10 days or more but generally knows the year and the season. The patient may manifest decreased ability to handle such routine activities as shopping or managing personal and household finances.

Psychiatric features that may be prominent in this stage include decreased interest in personal and social activities, accompanied by a flattening of affect and emotional withdrawal. These behavioral changes are related to the person’s decreased cognitive abilities rather than to depressed mood. However, they are frequently mistaken for depression. True depressive symptoms may also be noted but are generally mild, requiring no specific treatment. In cases where depressive symptoms are of sufficient severity to warrant treatment, a low dose of an antidepressant is frequently effective in reducing affective symptoms. At this stage patients are still capable of independent community survival if assistance is provided with complex but essential activities such as bill paying and managing the patient’s bank account. Denial is the dominant defense mechanism protecting the patient from the devastating consequences of awareness of dementing illness.

The diagnosis of probable AD can be arrived at with confidence in this stage. It is possible to follow patients through the course of this stage, whose mean duration has been estimated to be approximately 2 years (Reisberg, 1986; Reisberg, Ferris, Franssen, et al., 1996). The cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) have been approved for treating the symptoms of AD in this stage and appear to slow cognitive decline.

**Stage 5: Moderately Severe Cognitive Decline—Diagnosis: Moderate AD**

Cognitive and functional deficits are of sufficient magnitude that patients can no longer survive without assistance.

Patients at this stage can no longer recall major relevant aspects of their lives. They may not recall the name of the current president, their correct current address or telephone number, or the names of schools they attended. Patients at this stage frequently do not recall the current year and may be unsure of the weather or season. Concentration and calculation deficits are generally of sufficient magnitude as to create difficulty in subtracting serial 4s from 40 and possibly even serial 2s from 20. Patients at this stage retain knowledge of many major facts regarding themselves and others and generally require no assistance with toileting or eating, but they may have difficulty choosing the appropriate clothing to wear for the season or the occasion and may begin to forget to bathe regularly unless reminded.

Psychiatric symptoms in this stage of moderate AD are in many ways similar, although generally more overt, than those noted in mild AD. The patient’s denial and flattening of affect tend to be more evident. True depressive symptoms, with mild to moderate mood dysphoria, may occur. Anger and other more overt behavioral symptoms of AD, such as anxieties, paranoia, and sleep disturbances, are frequently evident. Paranoid and delusional ideation peak in occurrence at this stage, with almost 75% of patients exhibiting one or more delusions. Such delusions as people stealing the patient’s belongings or money, that one’s house is not one’s home, or that one’s spouse is an impostor, are common. Aggressivity may include verbal outbursts, physical threats and violence, or general agitation. Depending on the nature and magnitude of the psychiatric symptomatology, treatment with an antidepressant or an antipsychotic medication may be indicated. When the latter is used, the dictum for the treatment of psychosis in the elderly applies: “Start low and go slow.”

Patients who are living alone in the community at this stage require at least part-time assistance for continued community survival. When additional community assistance, such as day care or home health aides, is not feasible or available, institutionalization or a more protective environment such as an assisted-living facility may be required. Patients who are residing with a spouse frequently resist additional assistance at this stage as an invasion of their privacy and home. The duration of this stage is approximately a year and a half (Reisberg, 1986; Reisberg, Ferris, Franssen, et al., 1996). The cholinesterase inhibitor medications have been approved for the treatment of AD symptoms at this stage. Another class of pharmacological treatment, which has been shown to be efficacious in slowing the
course of AD in this stage, is glutamatergic antagonist treatment. Memantine, the first and only medication in this more recently developed class of agents, is believed to reduce the glutamate-induced excitotoxicity caused by presynaptic neuronal injury. Memantine reversibly blocks glutamate transmission postsynaptically at the \(N\)-methyl-\(d\)-aspartate receptor. A pivotal study has indicated that memantine slowed the progression of AD in this stage and the subsequent stage by about 50% in terms of cognitive and functional outcomes (Reisberg, Doody, Stöffler, et al., 2003). A subsequent study has indicated that the effects of memantine remain robust and may even be enhanced, when memantine is given in combination with the cholinesterase inhibitor, donepezil (Tariot et al., 2004).

**Stage 6: Severe Cognitive Decline—Diagnosis: Moderately Severe AD**

Cognitive and functional deficits are of sufficient magnitude as to require assistance with basic activities of daily living.

Recent and remote memories are increasingly affected. Patients at this stage frequently have no idea of the date and may occasionally forget the name of the spouse upon whom they are dependent for survival but usually continue to be able to distinguish familiar from unfamiliar persons in their environments. Patients know their own names but frequently do not know their correct address, although they may be able to recall some important aspects of their domicile, such as the street or town. Patients have generally forgotten the schools they attended but recall some aspect of their early lives, such as their birthplace, their former occupation, or one or both of their parents’ names. Concentration and calculation deficits are of such magnitude that patients with moderately severe AD frequently have difficulty counting backward from 10 by ones and may even begin to count forward during this task.

Agitation and even violence frequently occur in this stage. Language ability declines progressively so that by the end of this stage speaking is impaired in obvious ways. At this point in the late sixth stage, stuttering and word repetition are common; patients who learned a second language in adulthood sometimes revert, to a varying degree, to their childhood language; other patients may use neologisms, or nonsense words, interspersed to a varying degree in the course of their speech.

In this stage, emotional and behavioral problems generally become most manifest and disturbing, with 90% of patients exhibiting one or more behavioral symptoms (Reisberg, Franssen, Sclan, et al., 1989). A fear of being left alone or abandoned is frequently exhibited. Agitation, anger, sleep disturbances, physical violence, and negativity are examples of symptoms that commonly require treatment at this point in the illness. Low doses of so-called atypical antipsychotics may be useful for many patients. Side effects can be avoided if the medication is titrated upward with intervals of weeks between dosage adjustments. Present efficacy data on the treatment of these symptoms are most compelling for the atypical antipsychotic risperidone (Brodaty et al., 2003; De Deyn et al., 1999; De Deyn et al., 2005; Katz et al., 1999).

However, the dosage of antipsychotic medications given by clinicians and the titration schedules used by clinicians are frequently much higher and many times more rapid than those which are recommended. For example, for risperidone, the recommendation for treatment is as follows:

In terms of pharmacological treatment of behavioral and psychological symptoms of dementia (BPSD) symptomatology, the clinical adage “start low, go slow” applies. For risperidone treatment, this rule translates into an optimal starting dose of 0.25 mg daily. Although clinical circumstances dictate the schedule of dosage titration, an optimal clinical response is not achieved for many weeks on any particular dosage of medication. Also, extrapyramidal side effects may not peak until a patient has been on a particular dosage of medication for as long as 6 months (Stephen & Williamson, 1984). Therefore, ideally, the clinician should endeavor to leave a patient on a particular dosage of medication for many weeks before further dosage
adjustments. The exigencies of particular situations, of course, will frequently not permit this time luxury in dose adjustments, and clinicians will frequently need to make rapid dosage adjustments. However, the clinician should also be prepared to adjust medication dosage downward as well as upward in response to particular patient needs and the emergence of side effects. After some months of treatment, a steady-state dosage of approximately 0.25–1 mg of risperidone daily is frequently effective in controlling BPSD symptoms. (Reisberg & Saeed, 2004)

In clinical trials of atypical antipsychotic medications in the treatment of BPSD in AD patients, dosages considerably greater than these recommended amounts titrated over a much more rapid time interval have been used. For example, in the study of Katz et al. (1999), dementia patients with BPSD were randomly assigned to treatment with placebo or 0.5, 1.0, or 2 mg/day of risperidone for 12 weeks. The mean age of the patients was 83 years, and 96% of the patients had moderately severe or severe AD as evidenced by Functional Assessment Staging (FAST) (Reisberg, 1988) scores of ≥6a and Mini-Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975) mean scores of 6.6. When a meta-analysis was used to review the results of this and similar studies, an increased mortality associated with atypical antipsychotic medication used in dementia patients was found (Schneider, Dagerman, & Insel, 2005). This finding of Schneider et al. (2005) resulted in the U.S. Food and Drug Administration “black boxing” with a warning of “Increased Mortality in Elderly Patients with Dementia-Related Psychosis” antipsychotic medications used for the treatment of BPSD. This warning states in part that: “Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of … 1.6 to 1.7 times the risk in placebo-treated patients” (PDR Network, 2009, p. 2683). The warning also notes that the increased mortality is due to varied causes, of which most were related to cardiovascular (heart failure or sudden death) or infectious (such as pneumonia) factors. The Schneider et al. (2005) study and subsequent studies (eg., Wang et al., 2005) have also found an increased mortality associated with the treatment of BPSD (psychosis) in dementia patients with so-called “typical” antipsychotic medications (e.g., haloperidol). In general, the risk of mortality has been found to be greater for “typical” than so-called “atypical” (e.g., risperidone) antipsychotic medications, although one major study found no difference between the two classes of antipsychotic medication in terms of mortality (Kales et al., 2007).

Unfortunately, even more recently published studies of antipsychotic medications in dementia such as the CATIE-AD Study Group report (Schneider et al., 2006) continue to begin with higher dosages of medication than those suggested by Reisberg and Saeed (2004). For example, the Schneider et al. (2006) published study (which was embarked upon in April, 2001) used a starting dose of risperidone of 0.5 mg.

In summary, with respect to the treatment of BPSD symptoms in dementia patients (primarily persons with AD), current consenses have concluded that treatment with antipsychotic medications, approached judiciously, continues to be a necessary option. In the words of a 2008 consensus “there is insufficient evidence to suggest that psychotropics other than antipsychotics represent an overall effective and safe, let alone better, treatment choice for psychosis or agitation in dementia” (Jeste et al., 2008).

In the moderately severe AD stage, the magnitude of cognitive and functional decline, combined with disturbed behavior and affect, make caregiving especially burdensome to spouses or other family members. They literally must devote their lives to helping patients who often can no longer even recall their name, much less appreciate in all the ways which may be desired, the kindness and care being provided. The caregivers’ burden may be alleviated, for example, through regular participation in a dementia caregivers’ support group, utilization of day care and respite centers for patients, or utilization of home health aides, either part-time or full-time. Clinical experience suggests that if behavioral disturbances are not successfully managed, they become the primary reason for institutionalization, and successful management of the disturbances can postpone this need. The mean duration of this stage...
is approximately two and a half years (Reisberg, 1986; Reisberg, Ferris, Franssen, et al., 1996). Memantine has been approved for treatment of AD in this stage and does appear to be useful in slowing the progression of cognitive and functional decline (Reisberg, Doody, Stöffler, et al., 2003; Tariot, et al., 2004; Winblad & Poritis, 1999). In 2006, donepezil became the first and still the only cholinesterase inhibitor approved for treating symptoms in this stage.

Stage 7: Very Severe Cognitive Decline—Diagnosis: Severe AD

A succession of functional losses in this stage results in the need for continuous assistance in all aspects of daily living. Verbal abilities are severely limited early in this stage, to approximately a half-dozen different intelligible words during the course of an average day, frequently interspersed with unintelligible babbling. Eventually, only a single word remains: commonly “yes,” “no,” or “OK.” Subsequently, the ability to speak even this final single word is largely lost, although the patient may utter seemingly forgotten words and phrases in response to various circumstances for years after meaningful, volitional speech is lost. It is important to recognize that although the patient may no longer be capable of speaking, thinking capacity remains. Test measures originally developed for infants are able to demonstrate continuing thinking capacities of the patient (Auer, Sclan, Yaffee, & Reisberg, 1994). Although agitation can be a problem for some patients at this stage, psychotropic medication can generally be reduced as this stage progresses and ultimately discontinued.

Memantine has been approved for treating the symptoms (cognitive and functional) of AD patients in this stage. However, only one published memantine study has included these patients. That study (Winblad & Poritis, 1999) did investigate memantine’s efficacy in institutionalized, primarily nursing home-residing patients. However, very few of the patients in the Winblad and Poritis study were in this final, severe AD stage. Therefore, there is very little current information regarding the role of memantine in this final stage of the disease.

Donepezil is the only cholinesterase inhibitor approved for the treatment of AD at this stage. The pivotal trial of Winblad et al. (2006) included 61 randomized and treated patients with a FAST stage of 7a or greater (25% of the study population). Hence, fully a quarter of the subjects in this pivotal trial had little or no remaining speech. In addition, 23 randomized and treated subjects were losing the ability to ambulate independently (FAST stage 7c). Hence, the most robust pivotal trial data for any medication in the treatment of persons in this final stage of AD at the present time is that available for donepezil treatment. However, even this trial had a requirement of a minimum MMSE score of 1 at entry. Since most stage-7 subjects, even in the early part of stage 7, have MMSE scores of zero (bottom), even this study of Winblad et al., (2006) included relatively cognitively less impaired final stage AD subjects (Reisberg, 2007).

Nursing homes or similar care facilities may be better equipped than spouses for the management of patients in this stage. If family members maintain the patient at home, round-the-clock health care assistance may be necessary to manage incontinence and basic activities of daily living such as bathing and feeding. Human contact continues to make a great difference in the quality of life of a patient, whether in the home or in an institution. A loving voice, attention, and gentle touch are important for the patient’s emotional and physical well-being. As described subsequently, movement and physical activity are particularly important.

AD patients who survive until some point in the severe stage generally die from pneumonia, traumatic or decubital ulceration, or a less specific failure in the central regulation of vital functions. Although approximately half of all patients who reach this stage are dead within 2–3 years, patients may potentially survive for 7 years or longer in this final stage.

FUNCTIONAL CHANGES IN AD

Understanding the progression of AD from the standpoint of change and deterioration in functional abilities is of great importance to both clinicians and families. In terms of a primary diagnosis, as well as differential diagnosis, it is useful to determine whether the nature
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of the dementia is consistent with uncomplicated senile dementia of the Alzheimer type, because dementing processes associated with other causes frequently proceed differently from AD in terms of functional progression. Knowledge of the functional progression of AD can assist in this differential diagnostic process and, additionally, in identifying possible remediable complications of the illness. Furthermore, even the most severe AD patients can be assessed in terms of a functional level when all traditional mental status and psychometric assessment measures produce uniform bottom (zero) scores (Reisberg, Franssen, Bobinski, et al., 1996; Reisberg, Wegiel, Franssen, et al., 2006b). Functional assessment is presently capable of producing a detailed, meaningful map of the entire course of AD and, from the standpoint of physical rehabilitation, is extremely important in describing the AD patient’s level of incapacity and areas of residual capacity.

Requirements for the management of AD fall into two categories: those relating to the patient and those relating to the primary caregiver. It is essential for the benefit of both that management advice be appropriate to each stage of the illness.

**Functional Description of AD**

A practical diagnostic and assessment tool, the FAST of AD (Reisberg, 1988; Sclan & Reisberg, 1992) permits identification of the stages of characteristic decline in functional activities in AD and their estimated duration (outlined in Table 3.2). Because of their utility, these FAST stages of AD are mandated for usage for certain purposes by the Center for Medicare Services in the United States, as well as in certain international jurisdictions (Health Care Financing Administration, 1998). These stages of functional deterioration in AD correspond optimally with the GDS stages described above. Table 3.2 indicates the approximate corresponding mean MMSE scores for each of the FAST stages and substages (Folstein et al., 1975). Research has indicated strong relationships between progressive functional deterioration assessed on the FAST and progressive cognitive deterioration in AD (e.g., Pearson correlation coefficients of ~0.8 or greater between MMSE and FAST scores have been reported [Reisberg et al., 1984; Sclan & Reisberg, 1992]). Therefore, the relationships shown between FAST and MMSE scores are approximations of likely findings in individual patients, although there is variability. Functionally, the late stages of AD can be subdivided into stages 6a–e and stages 7a–f. Consequently, a total of 16 functioning stages can be recognized, that describe in detail the characteristic changes which occur with the progression of AD. In uncomplicated dementia of the Alzheimer’s type, progression through each of the functional stages described below occurs in a generally ordinal (sequential) pattern (Sclan & Reisberg, 1992).

**Stage 1: No Objective or Subjective Functional Decrement**

The aged subject’s objective and subjective functional abilities in occupational, social, and other settings remain intact, compared with prior performance. The prognosis is excellent for continued adequate cognitive functioning.

**Stage 2: Subjective Functional Decrement but No Objective Evidence of Decreased Performance in Complex Occupational or Social Activities**

The most common age-related functional complaints are forgetting names and locations of objects or decreased ability to recall appointments. Subjective decrements are generally not noted by acquaintances or coworkers, and complex occupational and social functioning is not compromised.

When affective disorders, anxiety states, or other remediable conditions have been excluded, the elderly person with these symptoms can be reassured with respect to the relatively benign prognosis for persons with these subjective symptoms.
**Stage 3: Objective Functional Decrement of Sufficient Severity to Interfere With Complex Occupational and Social Tasks**

This is the stage at which persons may begin to forget important appointments, seemingly for the first time in their lives. Functional decrements may become manifest in complex psychomotor tasks, such as ability to travel to new locations. Persons at this stage have no difficulty with routine tasks such as shopping, handling finances, or traveling to familiar locations, but they may stop participating in demanding occupational and social settings. These symptoms, although subtle clinically, can considerably alter lifestyle. When psychiatric, neurological, and medical concomitants apart from AD have been excluded, the clinician may advise withdrawal from complex, anxiety-provoking situations. Because patients at this stage can still perform all basic activities of daily living satisfactorily, withdrawing from demanding activities may result in complete symptom amelioration for a period of years.

### TABLE 3.2  Functional Assessment Stages (FAST) and Time Course of Functional Loss in Normal Aging and Alzheimer’s Disease (AD)

<table>
<thead>
<tr>
<th>FAST Stage</th>
<th>Clinical Characteristics</th>
<th>Clinical Diagnosis</th>
<th>Estimated Duration in AD(^a)</th>
<th>Mean MMSE(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No decrement</td>
<td>Normal adult</td>
<td>29–30</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Subjective deficit in word finding or recalling location of objects</td>
<td>Subjective cognitive impairment</td>
<td>15 years</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Deficits noted in demanding employment settings</td>
<td>Mild cognitive impairment</td>
<td>7 years</td>
<td>24–27</td>
</tr>
<tr>
<td>4</td>
<td>Requires assistance in complex tasks, e.g., handling finances, planning dinner party</td>
<td>Mild AD</td>
<td>2 years</td>
<td>19–20</td>
</tr>
<tr>
<td>5</td>
<td>Requires assistance in choosing proper attire</td>
<td>Moderate AD</td>
<td>18 months</td>
<td>15</td>
</tr>
<tr>
<td>6a</td>
<td>Requires assistance in dressing</td>
<td>Moderately severe AD</td>
<td>5 months</td>
<td>9</td>
</tr>
<tr>
<td>b</td>
<td>Requires assistance in bathing properly</td>
<td>Moderate severely AD</td>
<td>5 months</td>
<td>8</td>
</tr>
<tr>
<td>c</td>
<td>Requires assistance with mechanics of toileting (such as flushing, wiping)</td>
<td></td>
<td>5 months</td>
<td>5</td>
</tr>
<tr>
<td>d</td>
<td>Urinary incontinence</td>
<td></td>
<td>4 months</td>
<td>3</td>
</tr>
<tr>
<td>e</td>
<td>Fecal incontinence</td>
<td></td>
<td>10 months</td>
<td>1</td>
</tr>
<tr>
<td>7a</td>
<td>Speech ability limited to about a half-dozen words</td>
<td>Severe AD</td>
<td>12 months</td>
<td>0</td>
</tr>
<tr>
<td>b</td>
<td>Intelligible vocabulary limited to a single word</td>
<td></td>
<td>18 months</td>
<td>0</td>
</tr>
<tr>
<td>c</td>
<td>Ambulatory ability lost</td>
<td></td>
<td>12 months</td>
<td>0</td>
</tr>
<tr>
<td>d</td>
<td>Ability to sit up lost</td>
<td></td>
<td>12 months</td>
<td>0</td>
</tr>
<tr>
<td>e</td>
<td>Ability to smile lost</td>
<td></td>
<td>18 months</td>
<td>0</td>
</tr>
<tr>
<td>f</td>
<td>Ability to hold head up lost</td>
<td></td>
<td>12 months or longer</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{a}\)In subjects without other complicating illnesses who survive and progress to the subsequent deterioration stage.

\(^{b}\)MMSE = Mini-Mental State Examination score (Folstein et al., 1975). Estimates based in part on published data summarized in Reisberg, Ferris, de Leon, et al. (1989) and obtained in Reisberg, Ferris, Torossian, et al. (1992).

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Stage 4: Deficient Performance in the Complex Tasks of Daily Life
Aspects of decreased functioning from former levels are apparent. At this stage, shopping for adequate or appropriate food and other items is noticeably impaired. The person may return with incorrect items or inappropriate amounts of a certain item. The individual may have difficulty preparing meals for family dinners and may display similar deficits in the ability to manage complex occupational and social tasks. Family members may note that the patient no longer is able to balance the checkbook, no longer remembers to pay bills properly, and may make significant financial errors. Persons who are still able to travel independently to and from work may not recall names of clients or details of their employment duties. Because choosing clothing, dressing, bathing, and traveling to familiar locations can be adequately performed at this stage, persons may still function independently in the community, although supervision is often useful.

Maximizing the patient’s functioning at this stage is the goal of the family and health care professionals. Financial supervision and structured or supervised travel should be arranged. Identification bracelets, ID cards, or clothing labels with a name, address, and telephone number may be useful for unusually stressful situations where anxiety or other factors further impair the person’s capacities.

Stage 5: Incipient Deficit in Performance in Basic Tasks of Daily Life
At this stage, persons with AD can no longer satisfactorily function independently in the community. The person not only requires assistance in managing financial affairs and marketing but also begins to require help in choosing the appropriate clothing for the season and the occasion. The person may wear obviously incongruous clothing combinations or wear the same clothing day after day unless supervision is provided.

At this stage, some patients develop anxieties and fears about bathing. Another functional deficit that frequently becomes manifest at this stage is difficulty in driving an automobile. The patient may slow down or speed up the vehicle inappropriately or may go through a stop sign or traffic light. Occasionally, the person may have a collision with another vehicle for the first time in many years. The person with moderate AD may be sufficiently alarmed by these deficits to voluntarily discontinue driving. Sometimes, however, intervention and coercion are necessary from family members or even from the patient’s physician or licensing authorities. A useful strategy for the physician is to arrange for an automobile driving retest.

It is important that functional abilities be maximized. Persons at this stage are still capable of putting on their clothing with minimal guidance once it has been selected for them. They are also capable of bathing and washing themselves, even though they may have to be cajoled into performing these activities. A supportive environment that provides adequate stimulation, in addition to adequate protection, is desirable. It is important that the person continue to engage in and practice skills in which they remain capable.

Stage 6: Decreased Ability to Dress, Bathe, and Toilet Independently
Throughout the course of stage 6, which lasts for approximately two and a half years and encompasses five substages, increasing deficits in dressing and bathing occur. In addition to not being able to choose the proper clothing, early stage-6 patients develop difficulties in putting on their clothing properly (stage 6a). Other dressing difficulties include putting on street clothing over night clothing, putting clothing on backward or inside out, and putting on multiple and inappropriate layers of clothing. The patient may also have difficulty zipping or buttoning their clothing or tying their shoelaces. More overt dressing difficulties develop as this stage progresses and the patient requires increasing assistance in dressing.

A bathing difficulty that becomes apparent at this stage is a decreased ability to adjust the temperature of shower or bath water (substage 6b). Subsequently, taking a bath or shower without assistance becomes increasingly problematic, ultimately with difficulty getting into and out of the bath and washing properly. Fear of bathing may develop, combined with
resistance to bathing. This fear of bathing sometimes precedes actual difficulties in handling the mechanics of bathing.

Later in the course of this stage, patients begin to have difficulties with the mechanics of toileting: initially, they may forget to flush the toilet, dispose of toilet tissue improperly, and clean themselves inadequately (stage 6c).

Subsequently, urinary incontinence begins (stage 6d), followed by fecal incontinence (stage 6e), both of which appear to be the result of decreased cognitive capacity to respond appropriately to urinary or fecal urgency. Assisting the patient to use the toilet often helps to forestall and remediate incontinence. Anxieties regarding toileting are frequently noted in stage 6c prior to the actual development of incontinence. Patients may go to the toilet repeatedly even in the absence of a true need for elimination.

Motor capacity deficits also become notable during stage 6. Walking becomes more halting and steps generally become smaller and slower, but the ability to ambulate is still maintained. Because orientation in space is affected, patients may approach a chair and sit down with greater difficulty. Patients may also require assistance in walking up and down a staircase.

Full-time home health care is frequently useful at this time, and it may be appropriate or necessary to discuss nursing home placement with the caregiver and family members. Management strategies and supportive techniques must be developed to assist the patient in bathing, dressing, and toileting, as well as in minimizing the emotional stress of the caregiver.

Stage 7: Loss of Speech and Locomotion
This final stage of AD is marked by decreased vocabulary and speech abilities. Speech becomes increasingly limited from a vocabulary of a half-dozen different intelligible, purposeful, and meaningful words (stage 7a) to at most a single distinguishable purposeful word that may be uttered repeatedly (stage 7b). Eventually, speech becomes limited to babbling, unintelligible utterances, and occasional, intelligible, random utterances.

Prior to the loss of ambulatory ability, patients may exhibit a twisted gait, take progressively smaller and slower steps, or lean forward, backward, or sideways while walking. Eventually, the ability to walk unassisted is lost with the progression of AD (stage 7c). It should be noted that after the loss of speech ability, the ability to walk is invariably lost. However, AD patients, for various reasons, especially excess disability, are susceptible to the loss of ambulation from the beginning of the final 7th AD stage, as well as subsequently.

Approximately a year after ambulatory ability is lost, the ability to sit up without assistance (such as lateral chair rests) is also lost (stage 7d). Subsequently, the abilities to smile (stage 7e) and to hold up the head independently (stage 7f) are also lost. At this point, babbling and grasping may still be observed, and patients can still move their eyes, although familiar persons or objects are apparently no longer recognized. Approximately 3–4 years after the onset of stage 7, generally after the loss of ambulatory ability, many patients die. However, some patients survive in this stage for 7 years or longer. Pneumonia, which is often associated with aspiration, is a frequent cause of death.

Full-time assistance at home or in an institution is a necessity at this stage, and as AD patients are increasingly well cared for, it is likely that more will survive to these final sub-stages of the illness.

FEEDING CONCOMITANTS OF AD
Progressive changes in the ability to prepare meals and in feeding skills have been observed in AD patients and enumerated in accordance with the corresponding GDS and FAST stages (Reisberg et al., 1990). These “Feeding Concomitants of Alzheimer’s Disease” are outlined in Table 3.3. The progression of these disturbances in meal preparation and self-feeding,
as with the progression of deterioration in cognitive and functional abilities, appears to be characteristic of AD.

**BALANCE AND COORDINATION**

Although it is clear from the preceding description of functional losses in AD that balance and coordination are eventually lost with the progression of the illness process, these aspects are actually very early changes, coincident with the advent of MCI and mild AD. For example, a detailed study indicated that tandem walking, foot-tapping speed, hand pronation and supination speed, and finger-to-thumb apposition speed all decreased significantly in MCI subjects in comparison with normal elderly controls (Franssen et al., 1999). Additional decrements were noted in mild AD subjects.

Another study has demonstrated that complex motor and fine motor measures can be just as robust markers of MCI and mild AD as a cognitive psychometric battery (Kluger et al., 1997). These observations of motor and equilibrium changes in MCI and AD are consistent with neuropathological observations of robust clinicopathological correlations with cerebellar atrophy in AD (Wegiel et al., 1999).
RIGIDITY AND CONTRACTURES

In the latter stages of AD, rigidity becomes increasingly manifest (Franssen, Kluger, Torossian, & Reisberg, 1993; Franssen, Reisberg, Kluger, Sinaiko, & Boja, 1991). Initially, this rigidity is of a paratonic type, for example, elicited in response to an irregular motion of an extremity, such as an irregular movement of an elbow. Later, the rigidity becomes increasingly evident. Figure 3.2 depicts the emergence of paratonic rigidity in AD. Although infrequently manifest in patients with mild AD (i.e., GDS stage 4), approximately 50% of patients with moderate AD (GDS stage 5), 75% of patients with moderately severe AD (GDS stage 6), and virtually all patients with severe AD (GDS stage 7) manifest at least a mildly detectable form of paratonic rigidity. Figure 3.3 illustrates the methodology for the elicitation of this paratonic rigidity by the clinician.

One probable result of this increasing rigidity is the development of contractures (Figure 3.4). Contractures are irreversible deformities of joints, limiting range of motion. In a study by Souren, Franssen, & Reisberg (1995), a contracture was defined as a limitation of 50% or more of the passive range of motion of a joint, secondary to permanent muscle shortening, ankylosis, or both. Souren et al. found that contractures meeting this definition were present in 10% of moderately severe AD patients with incipient incontinence (i.e., AD patients at FAST stages 6d and 6e). In severe AD, contractures are very common. Forty percent of incipient averbal AD patients (FAST stages 7a and 7b) manifested contractures and 50% of incipient nonambulatory AD patients (FAST stage 7c) manifested these deformities. By late stage 7, that is, in immobile patients (FAST stages 7d–f), 95% of AD patients manifested these deformities. Furthermore, at all stages, when contractures occurred, they generally were present in more than one extremity. Specifically, the great majority of patients with contractures (69%) had contractures involving all four extremities. All but one of the 39 patients found to have contractures (97%) had at least two limbs affected. By limiting mobility, contractures predispose patients to further morbidity, such as decubital ulcerations. One third of the patients with contractures in the study of Souren et al. (1995) had decubital ulcerations, either noted by direct patient observation or in the patient’s medical record.

There is evidence based upon patient observations that contractures may be prevented until very late in the course of AD by maintenance of patient activities, stretching, other movements, and, especially, specific range of motion exercises of all joints including the hands and fingers.

DIFFERENTIAL DIAGNOSTIC IMPLICATIONS OF THE CHARACTERISTIC FUNCTIONAL COURSE OF AD

Cognitive and functional deficits in patients with AD characteristically follow the progression outlined in the preceding sections. However, other disorders frequently associated with the presence of dementia do not necessarily follow this characteristic pattern. It has been observed that the characteristic pattern of functional loss in AD is useful in differential diagnosis (Reisberg, 1986; Reisberg, Ferris, & Franssen, 1985). Common functional presentations of non-AD dementing disorders are outlined in Table 3.4. For example, normal-pressure hydrocephalus (NPH) commonly presents with gait disturbance as the earliest symptom, antedating any overt cognitive disturbance. In NPH, this ambulatory disturbance is commonly followed by urinary incontinence. Only subsequently, after the advent of ambulatory disturbance and urinary incontinence in NPH, may cognitive disturbances become manifest. As summarized in Table 3.2, the sequence of functional loss in AD is very different. In AD, overt cognitive disturbance precedes urinary incontinence, which in turn precedes ambulatory loss.
II: Disabling Conditions and Disorders

Paratonia response, % of subjects

<table>
<thead>
<tr>
<th>Rating</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 2</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Rating ≥ 3
Rating ≥ 5
Rating = 7

FIGURE 3.2 Percentage of subjects with increased paratonic rigidity in normal aging and Alzheimer’s disease of progressively increasing severity. The graph depicts the percentage of subjects showing paratonia as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of activity. Paratonic rigidity, defined as stiffening of a limb in response to contact with the examiner’s hand and an involuntary resistance to passive changes in position and posture, was graded according to the amount of passive force necessary to elicit it. A rating of 1 denotes an absence of paratonic rigidity, whereas a rating of 7 indicates that minimal passive force is required for elicitation of the sequence. Further detail regarding the scoring procedure can be found in Franssen, E. (1993). Neurologic signs in aging and dementia. In A. Burns (Ed.), Aging and Dementia: A Methodological Approach (pp. 144–174). London: Edward Arnold. Source: Data and figure are from Franssen, E. H., Reisberg, B., Kluger, A., Sinaiko, E., & Boja, C. (1991). Cognition independent neurologic symptoms in normal aging and probable Alzheimer’s disease. Archives of Neurology, 48, 148–154.

FIGURE 3.3 In the final stages of Alzheimer’s disease, patients manifest increasing rigidity. Rigidity is evident to the examiner in the Global Deterioration Scale (GDS) stage 7 patient upon passive range of motion of major joints such as the elbow. Copyright © 1999 Barry Reisberg, MD.
Creutzfeldt-Jacob disease is a rare form of rapidly progressive dementia that presents with ambulatory disturbance as the earliest symptom in approximately one third of cases. In AD, the ambulatory disturbance is a much later event. The two conditions also may be distinguished temporally. The course of AD extends over many years, as outlined in Table 3.2, and is frequently much slower than the relatively rapid course of the acute and subacute forms of Creutzfeldt-Jacob disease.

Multi-infarct dementia, or dementia associated with an overt, large infarction, may produce speech disturbance as the only symptom. Alternatively, the infarction may produce urinary incontinence as the major overt manifestation. Commonly, ambulatory loss may be the major sequela of a stroke. Clearly, the evolution of functional losses in AD follows a very different and much more stereotyped pattern (as outlined in Table 3.2). As shown in Table 3.4, the evolution of functional disturbance in dementia associated with multiple infarctions may follow a very different course from that which is characteristic of AD.

Depression is a psychiatric disturbance associated with mood dysphoria and other symptoms. Among these other symptoms are negativity and subjective complaints of cognitive impairment. Occasionally, the depression produces a dementia-like syndrome that is potentially reversible when the underlying mood disturbance is treated. This potentially reversible dementia syndrome of depression, formerly called pseudodementia, does not necessarily follow the functional course outlined in Table 3.2. For example, as outlined in Table 3.4, depression may be accompanied by a refusal to dress and bathe as a result of the patient’s negativity. However, the patient may be able to point to exactly the clothes he or she wishes to wear. In AD, the loss of ability to pick out clothing properly precedes the loss of ability to put on one’s clothing properly.

As outlined in Table 3.4, dementia associated with hyponatremia or other electrolyte disturbances, CNS metastases, and other conditions all may follow a course markedly at variance with the course of AD as outlined in the FAST.

In a patient with AD, a variety of coexisting conditions may result in functional disturbances that may occur prematurely or nonordinarily (i.e., out of sequence) in terms of the FAST predictions. Examples of conditions that may be associated with premature (i.e., nonordinal) functional losses in an AD patient are outlined in Table 3.5. For example, if an AD patient is at GDS stage 5 and FAST stage 5 and develops urinary incontinence, this incontinence may,
### TABLE 3.4  Examples of the Order of Functional Loss in Non-Alzheimer Disorders Associated With Progressive or Gradual Onset of Dementia and Characteristic FAST Order of Functional Loss in AD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Pathology or Presumed Etiology</th>
<th>Example of the Order of Functional Loss in Non-AD Disorder&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Equivalent FAST Stage</th>
<th>Order of Functional Loss in AD per FAST</th>
<th>FAST Stages in AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-pressure hydrocephalus</td>
<td>Dilated cerebral ventricles</td>
<td>1. Gait disturbance</td>
<td>7c</td>
<td>1. Loss of ability to perform complex tasks</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Urinary incontinence</td>
<td>6d</td>
<td>2. Urinary incontinence</td>
<td>6d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Loss of ability to perform complex tasks</td>
<td>4</td>
<td>3. Ambulatory (gait) disturbance</td>
<td>7c</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Prion</td>
<td>1. Gait disturbance</td>
<td>7c</td>
<td>1. Loss of ability to perform complex tasks</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Loss of ability to perform complex tasks</td>
<td>4</td>
<td>2. Gait (ambulatory) disturbance</td>
<td>7c</td>
</tr>
<tr>
<td>Multi-infarct dementia</td>
<td>Multiple cerebral infarctions</td>
<td>1. Loss of speech</td>
<td>7a–7b</td>
<td>1. Loss of ability to perform complex tasks</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Loss of urinary incontinence</td>
<td>6d</td>
<td>2. Loss of ability to pick out clothing properly</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Loss of ability to put on clothing</td>
<td>6a</td>
<td>3. Loss of ability to put on clothing without assistance</td>
<td>6a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Loss of ability to bathe without assistance</td>
<td>6b</td>
<td>4. Loss of ability to bathe without assistance</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Loss of ambulatory capacity</td>
<td>7c</td>
<td>5. Loss of urinary incontinence</td>
<td>6d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Loss of ability to pick out clothing (associated with negativity)</td>
<td>5</td>
<td>7. Loss of speech</td>
<td>7a–7b</td>
</tr>
<tr>
<td>Dementia syndrome of depression (&quot;pseudodementia&quot;)</td>
<td>Affective disorder associated with neurotransmitter imbalance</td>
<td>1. Loss of ability to perform complex tasks</td>
<td>4</td>
<td>1. Loss of ability to perform complex tasks</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Refusal to put on clothing (associated with negativity)</td>
<td>6a</td>
<td>2. Inability to pick out clothing properly</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Equivalent FAST Stage.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Pathology or Presumed Etiology</th>
<th>Example of the Order of Functional Loss in Non-AD Disorder</th>
<th>Equivalent FAST Stage</th>
<th>Order of Functional Loss in AD per FAST</th>
<th>FAST Stages in AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia associated with hyponatremia</td>
<td>Electrolyte disturbance</td>
<td>3. Refusal to bathe (associated with negativity) 6b</td>
<td>3. Inability to put on clothing without assistance. 6a</td>
<td>3. Inability to put on clothing without assistance. 6b</td>
<td>6a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Loss of ability to pick out clothing properly 5</td>
<td>4. Inability to bathe without assistance 6b</td>
<td>4. Inability to bathe without assistance 6b</td>
<td>6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Loss of ability to perform complex tasks 4</td>
<td>1. Loss of ability to perform complex tasks 4</td>
<td>1. Loss of ability to perform complex tasks 4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Loss of ability to pick out clothing properly 5</td>
<td>2. Loss of ability to pick out clothing properly 5</td>
<td>2. Loss of ability to pick out clothing properly 5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Loss of ability to dress, bathe and toilet independently 6a–6c</td>
<td>3. Loss of ability to dress, bathe, and toilet independently 6a–6c</td>
<td>3. Loss of ability to dress, bathe, and toilet independently 6a–6c</td>
<td>6a–6c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Loss of urinary and fecal continence 6d–6e</td>
<td>5. Loss of speech 7a–7b</td>
<td>5. Loss of speech 7a–7b</td>
<td>7a–7b</td>
</tr>
<tr>
<td>Dementia associated with diffuse CNS metastasis</td>
<td>Neoplastic diffuse cerebral trauma</td>
<td>1. Loss of ability to perform complex tasks 4</td>
<td>1. Loss of ability to perform complex tasks 4</td>
<td>1. Loss of ability to perform complex tasks 4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Loss of ability to dress, bathe, and toilet independently 6a–6c</td>
<td>2. Loss of ability to dress, bathe, and toilet independently 6a–6c</td>
<td>2. Loss of ability to dress, bathe, and toilet independently 6a–6c</td>
<td>6a–6c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Loss of speech 7a–7b</td>
<td>5. Loss of ambulatory capacity 7c</td>
<td>5. Loss of ambulatory capacity 7c</td>
<td>7c</td>
</tr>
</tbody>
</table>

*The sequences of functional loss shown are typical for normal-pressure hydrocephalus and Creutzfeldt-Jakob disease; the sequence for multi-infarct dementia is one of various common presentations; the sequences in the dementia syndrome of depression, dementia associated with hyponatremia, and dementia associated with diffuse CNS metastasis are previously observed examples of the presentation of these dementias. It should be noted that in some of the non-AD disorders, particularly multi-infarct dementia, the “sequence” described may appear abruptly, rather than over an extended time interval.*

FAST = Functional Assessment Staging.

at this early point in AD, be a remediable complication, perhaps secondary to a urinary tract infection.

Similarly, if a patient with AD at GDS stage 5 and FAST stage 5 develops loss of independent ambulation, this may be the result of a stroke or possibly of a variety of potentially treatable conditions common in the elderly, such as medication-induced parkinsonian symptoms, arthritis, fracture, and so on. Table 3.5 provides an extensive list of causes of premature functional losses in an AD patient, many of which are potentially remediable.

The relationship between the FAST and the GDS, or the FAST and the MMSE, is also useful in the identification of excess functional disability that may be remediable. Specifically, if an

<table>
<thead>
<tr>
<th>Stage</th>
<th>FAST Characteristics</th>
<th>Differential Diagnostic Considerations (Particularly if FAST Stage Occurs Prematurely in the Evolution of Dementia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No functional decrement, either subjectively or objectively, manifest</td>
<td>Anxiety neurosis, depression</td>
</tr>
<tr>
<td>2</td>
<td>Complains of forgetting location of objects; subjective work difficulties</td>
<td>Depression, subtle manifestations of medical pathology</td>
</tr>
<tr>
<td>3</td>
<td>Decreased functioning in demanding employment settings evident to co-workers, difficulty in traveling to new locations</td>
<td>Depression, psychosis, focal cerebral process (e.g., Gerstmann's syndrome)</td>
</tr>
<tr>
<td>4</td>
<td>Decreased ability to perform complex tasks such as planning dinner for guests, handling finances, and marketing</td>
<td>Depression, anxiety neurosis, depression</td>
</tr>
<tr>
<td>5</td>
<td>Requires assistance in choosing proper clothing, may require coaxing to bathe properly</td>
<td>Depression</td>
</tr>
<tr>
<td>6</td>
<td>(a) Difficulty putting on clothing properly (b) Requires assistance in bathing, may develop fear of bathing (c) Inability to handle mechanics of toileting (d) Urinary incontinence (e) Fecal incontinence</td>
<td>(a) Arthritis, sensory deficit, stroke, depression (b) Arthritis, sensory deficit, stroke, depression (c) Arthritis, sensory deficit, stroke, depression (d) Urinary tract infection, other causes of urinary incontinence (e) Infection, malabsorption syndrome, other causes of fecal incontinence</td>
</tr>
<tr>
<td>7</td>
<td>(a) Ability to speak limited to one to five words (b) Intelligible vocabulary lost (c) Ambulatory ability lost (d) Ability to sit up independently lost (e) Ability to smile lost (f) Ability to hold up head lost</td>
<td>(a) Stroke, other dementing disorder (e.g., diffuse space-occupying lesions) (b) Stroke, other dementing disorder (e.g., diffuse space-occupying lesions) (c) Parkinsonism, neuroleptic-induced or other secondary extrapyramidal syndrome, Creutzfeldt-Jakob disease, normal-pressure hydrocephalus, hyponatremic dementia, stroke, hip fracture, arthritis, overmedication (d) Arthritis, contractures (e) Stroke (f) Head trauma, metabolic abnormality, other medical abnormality, overmedication, encephalitis, other causes</td>
</tr>
</tbody>
</table>

FAST = Functional Assessment Staging.
AD patient is notably more impaired functionally, in comparison with the magnitude of the cognitive impairment (e.g., a GDS stage 5 patient who is at stage 6d on the FAST), this is an indication of the likely presence of excess functional disability. For example, the patient may have coexisting arthritis and AD. As a result of the combination of arthritis and dementia, in addition to not being able to handle finances and to pick out clothing without assistance (deficits that occur only because of the patient’s AD), the patient may be unable to dress, bathe, and use the toilet without assistance, the latter resulting in occasional urinary incontinence. The arthritis may or may not be remediable. Similarly, the excess functional disability may or may not be remediable. Interestingly, when excess functional disability occurs in AD patients, it tends to occur “along the lines of the FAST.” It appears that AD predisposes to functional losses outlined on the FAST. When an insult occurs, the closer the AD patient is to the inevitable point of loss of a functional ability on the FAST, the more predisposed the AD patient is to the premature loss of that capacity on the FAST. Not only illnesses but also psychological stressors may produce these premature losses. For example, if an AD patient at GDS stage 6 and FAST stage 6c is moved to an unfamiliar environment, the patient may develop urinary and fecal incontinence that remits when the patient is returned to familiar surroundings. Subsequently, these capacities will, tragically, be lost with the advance of AD.

Knowledge of the FAST progression of AD, in conjunction with the global concomitants, feeding concomitants, and other aspects, also provides invaluable information on the potential for treatment of disability, even in AD that is uncomplicated by the presence of additional pathology. For example, strategies for forestalling incontinence can be contemplated in FAST stage 6c. In FAST stage 6d or 6e, treatment of incontinence requires different strategies, such as frequent toileting. With the advance of deficits in FAST stage 7, strategies and goals for the management of incontinence need to be modified.

Other symptoms in AD, notably symptoms associated with the behavioral syndrome as outlined in Table 3.6, also require treatment. These symptoms are commonly treated with neuroleptics or other psychotropic medications. It should be noted that treatment of these symptoms may also be related to the treatment of functional disabilities. For example, it has been observed that AD patients with excess functional disability in relation to the magnitude of their cognitive disturbances may frequently have particularly marked behavioral disturbances. Conversely, marked behavioral disturbances may be associated with excess functional disability. This excess functional disability may be remediated in part by successful treatment of the behavioral symptoms.

OVERALL MANAGEMENT SCIENCE

As shown in Table 3.7, a very interesting and important aspect of the functional progression of AD is that the order of losses on the FAST is a precise reversal of the order of acquisition of the same functions in normal human development (Reisberg, 1986; Reisberg, Ferris, & Franssen, 1986). Subsequent work has indicated that AD also reverses normal development in terms of other functional parameters such as feeding abilities and figure drawings (Reisberg et al., 1990), as well as cognitively (Auer et al., 1994; Ouvrier, Goldsmith, Ouvrier, & Williams, 1993; Sclan, Foster, Reisberg, Franssen, & Welkowitz, 1990; Shimada et al., 2003).

For example, the MMSE is a well known and widely used cognitive assessment developed for the assessment of dementia patients (Folstein et al., 1975). The MMSE score has shown approximately as robust a relationship to the mental age of children, as it has shown to any noncognitive measure of dementia pathology. Initially, in a study of Australian children, a 0.83 Pearson correlation of the MMSE score to the mental age of children was found (Ouvrier et al., 1993). A subsequent study, in Spanish children, found a 0.76 Pearson correlation between childhood mental ages and MMSE scores, and a 0.80 correlation between MMSE scores and children’s chronological ages (Rubial-Álvarez et al., 2007).

Conversely, a study was conducted in AD patients of a cognitive assessment measure specifically developed for infants and small children, the Ordinal Scales of Psychological...
II: Disabling Conditions and Disorders

TABLE 3.6 Behavioral and Psychological Pathological Symptomatology in Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Paranoid and delusional ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The “people are stealing things” delusion</td>
</tr>
<tr>
<td>The “house is not one’s home” delusion</td>
</tr>
<tr>
<td>The “spouse (or other caregiver) is an imposter” delusion</td>
</tr>
<tr>
<td>The “abandonment” delusion</td>
</tr>
<tr>
<td>The “infidelity” delusion</td>
</tr>
<tr>
<td>Other suspicions, paranoid ideation, or delusions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual hallucinations</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wandering</td>
</tr>
<tr>
<td>Purposeless activity (cognitive abulia)</td>
</tr>
<tr>
<td>Inappropriate activities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aggressivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal outbursts</td>
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<tr>
<td>Physical outbursts</td>
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<td>Other agitation</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Diurnal rhythm disturbance</th>
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<tbody>
<tr>
<td>Day/night disturbance</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Affective disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tearfulness</td>
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<tr>
<td>Other depressive manifestations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxieties and phobias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety regarding upcoming events (Godot’s syndrome)</td>
</tr>
<tr>
<td>Other anxieties</td>
</tr>
<tr>
<td>Fear of being left alone</td>
</tr>
<tr>
<td>Other phobias</td>
</tr>
</tbody>
</table>


Development (OSPD) assessment (Uzgiris & Hunt, 1975). This OSPD test was slightly modified for use in severe dementia patients. The resulting modified-OSPD measurement of cognition (the M-OSPD) showed approximately the same relationship to the FAST stage in stage-6 and stage-7 AD patients (a 0.8 correlation) as is seen between the FAST functional stage and MMSE cognitive assessment in somewhat less severe AD patients who are testable with the MMSE (Auer et al., 1994; Reisberg, Ferris, Torossian, Kluger, & Monteiro, 1992).

Similarly, a widely used intelligence test measure for children, the Binet scale, has been applied to AD patients in FAST stages 5, 6, and 7. A Spearman correlation of −0.85, between the Binet test measure basic age value and the FAST stage, was found (Shimada et al., 2003). This is at least as robust as the relationship between the MMSE and the FAST assessment in dementia patients in the corresponding FAST range (Reisberg et al., 1992).

Table 3.7 illustrates that the FAST stages of AD can be expressed in terms of developmental ages (DAs). Remarkably, so-called developmental infantile reflexes appear to be equally good markers of the emergence of the stage of severe AD, corresponding to a DA of infancy, as the same reflexes are in marking the emergence from infancy in normal development (Franssen, Souren, Torossian, & Reisberg, 1997) (see Figure 3.5). Similar to the findings
### TABLE 3.7  Functional Landmarks in Normal Human Development and Alzheimer’s Disease (AD)

<table>
<thead>
<tr>
<th>Approximate Age</th>
<th>Approximate Duration in Development</th>
<th>Acquired Abilities</th>
<th>Lost Abilities</th>
<th>Alzheimer Stage</th>
<th>Approximate Duration in AD</th>
<th>Developmental Age of AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescence</td>
<td>13–19 years 7 years</td>
<td>Hold a job</td>
<td>Hold a job</td>
<td>3—Incipient</td>
<td>7 years</td>
<td>19–13 years: Adolescence</td>
</tr>
<tr>
<td>Late childhood</td>
<td>8–12 years 5 years</td>
<td>Handle simple finances</td>
<td>Handle simple finances</td>
<td>4—Mild</td>
<td>2 years</td>
<td>12–8 years: Late childhood</td>
</tr>
<tr>
<td>Middle childhood</td>
<td>5–7 years 2.5 years</td>
<td>Select proper clothing</td>
<td>Select proper clothing</td>
<td>5—Moderate</td>
<td>1.5 years</td>
<td>7–5 years: Middle childhood</td>
</tr>
<tr>
<td>Early childhood</td>
<td>5 years 4 years</td>
<td>Put on clothes unaided</td>
<td>Put on clothes unaided</td>
<td>6a—Moderately severe</td>
<td>2.5 years</td>
<td>5–2 years: Early childhood</td>
</tr>
<tr>
<td>Infancy</td>
<td>15 months 1.5 years</td>
<td>Speak 5–6 words</td>
<td>Speak 5–6 words</td>
<td>7a—Severe</td>
<td>7 years or longer</td>
<td>15 months to birth: Infancy</td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td>Speak 1 word</td>
<td>Speak 1 word</td>
<td></td>
<td>b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td>Walk</td>
<td>Walk</td>
<td></td>
<td>c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–10 months</td>
<td>Sit up</td>
<td>Sit up</td>
<td></td>
<td>d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2–4 months</td>
<td>Smile</td>
<td>Smile</td>
<td></td>
<td>e</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–3 months</td>
<td>Hold up head</td>
<td>Hold up head</td>
<td></td>
<td>f</td>
<td></td>
</tr>
</tbody>
</table>

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with neurological reflexes, a leading investigator in neurometabolism, Michael Phelps, has reported remarkable similarities between the pattern of brain metabolic activity in the late-stage AD patient and that in the normal infant brain (Phelps, 2000). These findings, obtained using positron emission tomography (PET) techniques, are very different from the metabolic patterns observed in the normal adult brain.

Neuroanatomic brain changes in AD have also been observed to mirror in various ways, the brain changes in normal human development. In early studies of the neuropathology of AD, Brun and Gustafson (1976) noted that “maximal cortical degeneration occurred in the medial temporal (limbic) area and in the lateral hemisphere” and that other brain regions were notably spared. These brain regions, which were observed to be relatively free of AD-related pathology, were observed to be “mainly the anterior cingulate gyrus and the calcarine and
cortical motor areas (primary projection areas).” The investigators concluded that, “the pattern described may be related to ontogenetic [developmental] features” (Brun & Gustafson, 1976). Subsequently, McGeer et al. (1990), noting the patterns of neuronal loss described by Brun and Englund (1981), and their own PET studies of neurometabolic changes in AD, concluded that the AD neurodegenerative process appears to relate to the pattern and process of brain myelination in normal development (McGeer et al., 1990). They observed that the areas of the brain, which are the last to be myelinated in normal development (and which are therefore the most thinly myelinated) (Flechsig, 1920), appear to be the areas that are the most vulnerable to the pathology of AD in terms of neuronal losses and decrements in cerebral metabolism (reviewed in Reisberg, Franssen, Hasan, et al., 1999). The pattern of neurofibrillary pathology in AD has also been related to the developmental pattern of myelination of the brain in reverse (Braak & Braak, 1991, 1996). Raz (1999) has provided a numerical value for these anatomic relationships between myelination in normal human development and myelin loss in the AD pathological process as seen with neuroimaging. He noted that, “The gradient of vulnerability seems to follow the rules of last (….ontogenetically) in—first out …. the later a region completes its myelination, the greater age-related difference in volume it exhibits, r = .60, p < 0.05” (Raz, 1999). This process by which the degenerative changes in AD, and to some extent other dementias, reverse the order of acquisition of capacities and processes in normal development has been termed retrogenesis (Reisberg, Franssen, Hasan, et al., 1999). The process of myelin loss, which is associated with the retrogenic process occurring in AD, has been termed “arboreal entropy” (Reisberg et al., 2002). “Just as the bark of a tree protects it from … injury and, to some extent, the thicker the bark, the greater the protection, the myelin protects the axon and its neuron. Hence, to some extent, … the thicker the myelin, [and the earlier in development the neuron is myelinated] the greater the protection” (Reisberg et al., 2002).

Interestingly, the retrogenesis process can explain many of the other symptoms and findings in AD, such as the nature of patient behavioral disturbances (Reisberg, Auer, Monteiro, Franssen, & Kenowsky, 1998), and the kind of symptoms that are progressively and invariably lost, such as speaking and walking, in comparison with the kind of symptoms that are more variable, such as the behavioral disturbances (Reisberg, Franssen, Souren, Auer, & Kenowsky, 1998). Most importantly, the retrogenic process provides a rapid appreciation of the general care and management needs of the AD patient at each stage of the disease (Reisberg, Kenowsky, Franssen, Auer, & Souren, 1999) (Table 3.8).

An understanding of the retrogenic process in AD also provides the basis for a detailed management science (Reisberg et al., 2002). This science includes care axioms, care postulates, and care caveats. The care axioms apply to all human beings and to AD patients at all stages (Table 3.9). The postulates are testable hypotheses of AD patient care based on the DA retrogenesis model (Table 3.10). Finally, the caveats are based on acknowledged differences between AD patients and their DA peers (Table 3.11). The combination of these care axioms, postulates, and caveats forms the nascent science of AD management.

RELATIONSHIP BETWEEN AD’S CLINICAL COURSE AND MANAGEMENT AND ITS OBSERVED PATHOLOGICAL AND BIOMOLECULAR FEATURES

The classical observed pathology accompanying the dementia of AD, as viewed upon microscopic examination of the brain, is extracellular plaques containing a substance called amyloid and intraneuronal neurofibrillary tangles. The amyloid plaques are primarily composed of a protein called β-amyloid. The intracellular neurofibrillary tangles are derived from neuronal microtubules. These microtubules are the “tubes” that are used to transport nutrients and other essential substances through the axonal fibers. The axons can be very long, and the axons degenerate in the absence of this essential neurotubular transport.

As noted earlier, the amyloid protein in the amyloid plaques is mainly composed of β-amyloid protein. This β-amyloid protein, like all proteins, is made up of amino acids. There
### TABLE 3.8 Stages of Aging and Alzheimer's Disease (AD) and Corresponding Developmental Ages (DAs): Care Needs and Care Recommendations

<table>
<thead>
<tr>
<th>GDS Stage</th>
<th>Diagnosis</th>
<th>Developmental Age (DA)</th>
<th>Care Needs</th>
<th>Care Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Adult</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Subjective cognitive impairment</td>
<td>Aged adult</td>
<td>None</td>
<td>Reassurance with respect to relatively benign prognosis</td>
</tr>
<tr>
<td>3</td>
<td>Mild cognitive impairment</td>
<td>Adolescence</td>
<td>None</td>
<td>“Tactical” withdrawal from situations that have become, by virtue of their complexity, anxiety provoking</td>
</tr>
<tr>
<td>4</td>
<td>Mild AD</td>
<td>Late childhood</td>
<td>Independent survival still attainable</td>
<td>Assistance towards goal of maximum independence with financial supervision; structured or supervised travel; identification bracelets and labels may be useful</td>
</tr>
<tr>
<td>5</td>
<td>Moderate AD</td>
<td>Middle childhood</td>
<td>Patient can no longer survive in the community without assistance; needs supervision with respect to travel and social behavior</td>
<td>Part-time home health care assistance can be very useful in assisting the patient’s caregiver. Driving becomes hazardous and should be discontinued at some point over the course of this stage. Family may require guidance in handling patient’s emotional outbursts</td>
</tr>
<tr>
<td>6</td>
<td>Moderately severe AD</td>
<td>Early childhood</td>
<td>Patient requires assistance with basic activities of daily life. Early in this stage, assistance with dressing and bathing is required. Subsequently, assistance with continence becomes necessary as well</td>
<td>Full-time home health care assistance is frequently very useful in assisting the patient’s caregiver. Strategies for assistance with bathing, toileting, and in the management of incontinence should be discussed with the family. Emotional stress in the caregiver should be minimized with supportive techniques</td>
</tr>
<tr>
<td>7</td>
<td>Severe AD</td>
<td>Infancy</td>
<td>Early in this stage assistance with feeding as well as dressing, bathing, and toileting is required. Subsequently, assistance with ambulation and</td>
<td>Full-time assistance in the community home residence or institutional setting is a necessity. Strategies for maintaining locomotion should be</td>
</tr>
</tbody>
</table>

*Continued*
Alzheimer’s Disease

are generally 40–42 amino acids in the β-amyloid protein. This β-amyloid protein is itself derived from a much larger protein, the amyloid protein precursor (APP) protein, which is 365–770 amino acids long. The APP protein is known as a transmembrane protein, because it crosses the cell membrane of the neuron. Part of the APP is outside the neuronal cell membrane, part is inside the neuronal cell membrane, and part of this protein is inside the cell, in the cytosol, the neuronal cell substance. The APP protein is normally cleaved by an enzyme known as α-secretase, which cleaves the APP outside the cell membrane. When α-secretase cleavage occurs, there is no amyloid β (Aβ) produced. Alternatively, the APP is cleaved by another enzyme, the β-secretase enzyme, which is, like the α-secretase, located outside the cell membrane. β-Secretase cleavage is followed by cleavage within the cell membrane by an enzyme known as γ-secretase. The result of this β- and γ-secretase cleavage is the Aβ protein, which is in the plaques in AD. Both aging and AD are associated with increased Aβ protein in the brain (Näslund et al., 2000; Seubert et al., 1992).

### TABLE 3.9 Alzheimer’s Disease (AD) Care Axioms

<table>
<thead>
<tr>
<th>Axiom I</th>
<th>All human beings avoid trauma and humiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axiom II</td>
<td>All human beings seek a sense of accomplishment</td>
</tr>
<tr>
<td>Axiom III</td>
<td>All human beings seek a sense of dignity and self-worth</td>
</tr>
<tr>
<td>Axiom IV</td>
<td>All human beings are social organisms</td>
</tr>
<tr>
<td>Axiom V</td>
<td>All human beings seek praise and acceptance</td>
</tr>
<tr>
<td>Axiom VI</td>
<td>All human beings have the capacity to learn</td>
</tr>
<tr>
<td>Axiom VII</td>
<td>All human beings require love</td>
</tr>
<tr>
<td>Axiom VIII</td>
<td>All human beings have the capacity for happiness if basic needs are fulfilled</td>
</tr>
<tr>
<td>Axiom IX</td>
<td>All human beings have the need for physical movement</td>
</tr>
<tr>
<td>Axiom X</td>
<td>All human beings have the capacity to remember</td>
</tr>
<tr>
<td>Axiom XI</td>
<td>All human beings have the capacity to think</td>
</tr>
<tr>
<td>Axiom XII</td>
<td>All human beings seek to influence their environment</td>
</tr>
<tr>
<td>Axiom XIII</td>
<td>All human beings have a sense of “taste,” i.e., likes and dislikes</td>
</tr>
</tbody>
</table>

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## TABLE 3.10  Alzheimer’s Disease (AD) Care Postulates

<table>
<thead>
<tr>
<th>Postulate</th>
<th>Postulate Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The magnitude of care and supervision required by an AD patient, at a developmental age (DA), is mirrored by the amount of care and supervision required by a child or infant at the corresponding DA</td>
</tr>
<tr>
<td>II</td>
<td>The kinds of activities enjoyed by an AD patient, at a particular DA, are mirrored by the kinds of activities enjoyed by children at a corresponding DA</td>
</tr>
<tr>
<td>III</td>
<td>The capacity of an AD patient to perform in an area of residual expertise is dependent on the patient’s DA</td>
</tr>
<tr>
<td>IV</td>
<td>Previous experiences may determine the kinds of activities enjoyed by an AD patient</td>
</tr>
<tr>
<td>V</td>
<td>The emotional level of the AD patient is dependent on the DA</td>
</tr>
<tr>
<td>VI</td>
<td>Life experiences appropriate to the DA become most relevant for AD patients at any particular stage</td>
</tr>
<tr>
<td>VII</td>
<td>Socialization of the AD patient is dependent on the DA</td>
</tr>
<tr>
<td>VIII</td>
<td>Diversity in children’s and infants’ activities and interests is mirrored in diversity in AD patient’s interests and activities at a corresponding DA</td>
</tr>
<tr>
<td>IX</td>
<td>The emotional changes that occur in AD at a DA are mirrored by the emotional changes observed in children at a corresponding DA</td>
</tr>
<tr>
<td>X</td>
<td>Care settings appropriate to AD patients at a DA are mirrored by care settings appropriate to children at the corresponding DA</td>
</tr>
<tr>
<td>XI</td>
<td>Vulnerability (emotional, physical, and cognitive) of the AD patient at a DA is mirrored by the vulnerability of children at the corresponding DA</td>
</tr>
<tr>
<td>XII</td>
<td>The need of an AD patient for physical movement is mirrored by the corresponding DA</td>
</tr>
<tr>
<td>XIII</td>
<td>Just as one judges development in an infant or child by what the infant or child can do and has achieved, not by what the infant or child cannot do, the AD patient at any particular DA should be assessed in terms of his or her residual skills and accomplishments, what they have learned and relearned, not by what they cannot do</td>
</tr>
<tr>
<td>XIV</td>
<td>The developmental analogy is sufficiently strong to trigger DA-appropriate childhood memories, beliefs, and anxieties in the AD patient</td>
</tr>
<tr>
<td>XV</td>
<td>The language changes of the AD patient are mirrored by the DA</td>
</tr>
</tbody>
</table>

DA = Developmental ages. Copyright © 2002, 2004 by Barry Reisberg, MD. All rights reserved.

## TABLE 3.11  Alzheimer’s Disease (AD) Care Caveats

<table>
<thead>
<tr>
<th>Caveat</th>
<th>Caveat Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Development in infants and children is accompanied by increasing expectations, whereas AD at all stages is accompanied by progressively diminished expectations</td>
</tr>
<tr>
<td>II</td>
<td>AD patients experience developmentally analogous brain changes; however, they do not undergo developmentally analogous physical changes</td>
</tr>
<tr>
<td>III</td>
<td>AD patients can, to some extent, draw upon previously mastered skills, whereas infants and children may not have access to these skills</td>
</tr>
<tr>
<td>IV</td>
<td>AD patients can, to some extent, draw upon previously mastered knowledge, whereas infants and children may not have access to this knowledge</td>
</tr>
<tr>
<td>V</td>
<td>AD patients are older than their DA peers, and old age predisposes to various physical disabilities that influence the life and experience of an AD patient</td>
</tr>
<tr>
<td>VI</td>
<td>AD patients appear to be more prone to rigidity than their DA peers</td>
</tr>
<tr>
<td>VII</td>
<td>AD patients can potentially concentrate on a task longer than infants or children at a corresponding DA</td>
</tr>
<tr>
<td>VIII</td>
<td>AD patients appear to be less fascinated by the world and less inquisitive than infants and children at a corresponding DA</td>
</tr>
</tbody>
</table>

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The neurofibrillary tangles in AD, seen inside the neuron, are composed of paired helical filaments (Kidd, 1963). The major constituent of these paired helical filaments is a protein known as “tau” (Kondo et al., 1988; Wischik, Novak, Edwards, et al., 1988; Wischik, Novak, Thøgersen, et al., 1988). Tau is believed to be a scaffolding molecule, which maintains the structural integrity of the microtubules in the neurons.

The relationship between the clinically observed “plaques and tangles” of AD (including the more recently discovered biomolecular constituents of the plaques and tangles) and the observed behavioral course of AD, described in the preceding sections of this chapter, can presently be elucidated.

As described in the prior sections, remarkably similar patterns between the neurometabolic activity of a late-stage AD patient and those of the infant brain have been noted (Phelps, 2000). In 2002, Reisberg et al., hypothesized that these patterns could be explained if “the most metabolically active regions of the brain in AD ... are the regions which are the most vulnerable in AD” (Reisberg et al., 2002). In 2005, it was found by Buckner et al. that, in fact, the pattern of deposition of amyloid plaques in the brain of AD patients appeared to occur in the regions of the brain that are the most active during the resting, so-called, default state, when the brain is not focused upon any particular activity (Buckner et al., 2005). Hence, there appears to be a direct relationship between the metabolic activity of the brain and a major form of microscopically evident AD pathology, the amyloid plaques, containing β-amyloid.

In 1980, Ferris and associates reported, using the then new PET scanning techniques, that there is a continuous decrease in metabolism in many brain regions, with the advance of the behaviorally evident AD process (Ferris et al., 1980). These findings have been replicated and supported in numerous subsequent studies. This process of continuing neurometabolic loss in AD has been termed “neurometabolic entropy” (Reisberg, Wegiel, Franssen, et al., 2006a). The continuing neurometabolic entropy, affecting first, the most metabolically active brain regions, appears to provide an explanation for the observed neurometabolic retrogenesis seen in AD.

Recent studies have provided an understanding of the mechanisms underlying these metabolic changes in AD. The insulin receptor and the insulin-like growth factor (IGF) receptor signaling pathway play a major role in controlling maximum lifespan and age-associated diseases in all species of multicellular organisms that have been studied, including yeast, worms, flies, and mammals (Puglielli, 2008). Interestingly, a decrease in IGF-1 blood levels occurs with normal aging in a retrogenic-like pattern. Specifically, there is a continuing increase in IGF-1 blood levels from infancy to about 15 years of age and this is followed by a continuing decrease in levels of IGF-1 in the blood, reaching an infant and early childhood level by about age 80–85 (Laboratory Corporation of America, accessed 2003; Reisberg, Wegiel, Franssen, et al., 2006a). These circulating blood changes in IGF-1 levels may be related to currently observed changes in the IGF-1 insulin receptor in aging and AD. A decreased number of neurons are now being reported to express the IGF-1 receptor in AD (Moloney et al., 2010). Also, Moloney et al. are reporting that the IGF-1 receptor is aberrantly distributed in AD, particularly in neurons affected by neurofibrillary tangles, in that it is concentrated intracellularly rather than at the neuronal cell membrane. Related to this, Moloney et al. are reporting decreased insulin receptor substrate levels in AD neurons, and these decrements are localized with the neurofibrillary tangles. Interestingly, in terms of the other major microscopically observed pathology in AD, the β-amyloid, formed in part by γ-secretase cleavage, the same enzyme, γ-secretase, is also being related to the IGF-1 receptor. Specifically, γ-secretase has now been reported to be involved in the proteolysis (breakdown) of the IGF-1 receptor (McElroy, Powell, & McCarthy, 2007).

In addition to direct relationships between the IGF-1 receptor and AD pathology, the insulin receptor is also being directly related to AD pathology. Soluble, Aβ (Townsend, Mehta, & Selkoe, 2007), as well as Aβ oligomers (Zhao, DeFelice, Fernandez, et al., 2008) have been shown to impair insulin receptor function.
The net result of these changes in the IGF-1 receptor and in insulin receptor signaling is that the neurons which degenerate in AD may be more resistant to these signals (Moloney et al., 2010). This resistance is being widely observed, and AD is now frequently referred to as type 3 diabetes (Hoyer, 1998; Steen et al., 2005). As with many changes in biology, the arrows, in terms of etiopathogenesis of metabolic deficits in the brain in AD, appear to point in both directions. The decrease in oxidative metabolism, which occurs in the brain in AD, has been observed to be associated with amyloid accumulation in several studies (Pluta, 2002; Popa-Wagner, Schröder, Walker, & Kessler, 1998; Sinigaglia-Coimbra, Cavalheiro, & Coimbra, 2002).

To fully understand the nature of the pathology in AD, together with associated pathogenic mechanisms, and their relationship to the clinical manifestations of AD, an additional principle must be recognized and addressed. This is that there is a homeostatic, regenerative, developmental, physiological response to the progressive pathology of AD. This regenerative physiological response in AD has many elements, which notably include: (1) there is a reactivation of the cell cycle enzymes in terminally differentiated neurons in AD (reviewed in Reisberg et al., 2002); (2) there is an activation of neurogenesis (new neuron production) in a region of the hippocampus (the dentate gyrus) in AD; (3) the activation of the β-secretase enzyme appears to be associated with a myelin regeneration effect; (4) the activation of γ-secretase may also be associated with a regenerative effect; (5) the production of Aβ may be associated with injury repair in the brain; and (6) the reduction in IGF-1 signaling appears to delay age-associated protein-related toxicity (e.g., from toxic soluble and oligomeric forms of Aβ).

For example, to the extent that the function of the β-secretase enzyme is known, apart from its role in the generation of amyloid β, it plays an important role in cleavage associated with the production of myelin (Glabe, 2006; Willem et al., 2006). Interestingly, IGF-1 also plays a role in myelin production, causing the oligodendrocytes, the myelin producing brain cells, to produce more myelin (Carson, Behringer, Brinster, & McMorris, 1993; Flores et al., 2008). β-Secretase knock-out mice show decreased myelin production and decreased IGF-1 signaling (Hu et al., 2006). Therefore, the β-secretase response in AD appears to be a homeostatic compensation for the decrease IGF-1 activity with aging and AD. Nevertheless, as described above, there are continuing IGF-1 signaling abnormalities in AD, and these can account for the observed myelin arboreal atrophy and myelin retrogenesis seen in AD.

Activation of γ-secretase also appears to be a developmental response to the pathology in AD, in addition to its role in the production of β-amyloid and in the protein breakdown of the IGF-1 receptor. For example, notch, an element of the γ-secretase complex, is involved in signaling, which is “crucial for long-term memory” (Costa, Drew, & Silva, 2005). Also, “the notch pathway has been shown to regulate neurite growth and adult neurogenesis” (Breunig, Silberets, Vaccarino, Sestan, & Rakic, 2007; Costa et al., 2005).

Aβ itself appears to be involved in brain injury repair. Brody et al. (2008) have shown that there is an increase in Aβ in the brain interstitial fluid in the 72-hour period after a brain trauma associated with coma, in the persons who show signs of recovering from a coma. However, this increase in Aβ in the brain interstitial fluid is not seen in the persons with poor signs of coma recovery.

Additionally, the reduced insulin and IGF-1 signaling in AD appears to be, in part, a physiological homeostatic response to toxic proteins produced by the AD process. For example, a recent study showed that reduction in IGF signaling in an Alzheimer mouse model decreased behavioral impairment, neuroinflammation, and neuronal loss (Cohen et al., 2009).

Hence, there is a complex homeostatic, physiological response to the behavioral and biomolecular changes associated with AD. This response can presently provide a good understanding of the nature of the changes seen in AD, including the retrogenic physiological process and the consequent management needs in AD.
CONCLUSIONS

AD is a very common condition in elderly persons, marked by a characteristic cognitive and functional course of disability. Knowledge of this characteristic course is essential for the identification and treatment of excess functional disability and for many other aspects of patient management and care. Proper management and care can alleviate, indeed, even eliminate suffering in the patient and reduce burden in the caregivers of AD victims.

ACKNOWLEDGMENT

This work was supported in part by U.S. Department of Health and Human Services (DHHS) grants AG03051, AG08051, AG09127, and AG11505 from the National Institute on Aging of the U.S. National Institutes of Health; by grants 90AZ2791, 90AM2552, and 90AR2160 from the U.S. DHHS Administration on Aging; by grant NCRRM01 RR0096 from the General Clinical Research Center Program and by Clinical and Translational Science Institute grant 1UL1RR029893 from the National Center for Research Resources of the U.S. National Institutes of Health; by the Fisher Center for Alzheimer’s Disease Research Foundation; by a grant from Mr. William Silberstein; by the Leonard Litwin Fund for Alzheimer’s Disease Research; by the Woodbourne Foundation; and by the Hagedorn Fund.

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