1. **Overview: The Neuroanatomy of Cognition**

Assessment of dementia requires a set of skills and knowledge that span several clinical domains. The clinician should be familiar with normal aging, brain anatomy, brain pathology that produces dementia and common disorders that mimic dementia. Clinicians should combine basic clinical evaluation skills with other disease-specific assessments to provide accurate high-quality dementia assessments. The symptoms of dementia are divided into cognitive, functional, and psychiatric. Cognitive symptoms include intellectual deficits such as amnesia or aphasia. Functional impairments include inability to perform common activities of daily living (ADLs) while psychiatric manifestations include behavioral and psychological symptoms of dementia (BPSD).

The proper assessment of dementia requires that the clinician understand the four or five most common diseases that produce cognitive loss in the elderly as well as the neuroanatomy of cognition, four or five medical problems that mimic dementia, and basic assessment strategies that capture essential information. The average dementia assessment requires approximately one hour; however, this process can be broken into several segments. A careful examination is accurate in 90% of cases when performed by a knowledgeable clinician. The value of laboratory studies or sophisticated brain imaging is ancillary rather than diagnostic.

Recent advances in the understanding and treatment of dementia underscore the importance of adequate assessment. New treatments for Alzheimer’s disease are most effective when employed in the earliest stages of the disorder. Scientists are exploring the boundary between age-related memory impairment and dementia for ways to better distinguish those individuals who will later develop significant cognitive impairment. The pharmaceutical industry is developing over 70 medications for specific types of dementia. Clinicians will be tasked to distinguish common types of dementia for appropriate therapeutic interventions.

2. **The Functional Neuroanatomy of Language and Memory**

Specific cognitive functions are assigned discreet brain regions to process this information. For example, the left anterior frontal lobe, i.e., Broca’s area, is assigned the task of motor speech. Dysfunction of this cortical segment may produce expressive aphasia. The proper function of expressive speech depends on three factors: 1) the presence of intact circuits within the inferior frontal cortex, 2) the appropriate balance of ascending cholinergic and catecholaminergic projections that facilitate frontal lobe transmission, and 3) the integrity of subcortical loops that process information through the basal ganglia, thalamus, and other structures to maintain frontal lobe function and tone.

A second model is sensory processing. The accurate interpretation of spoken word requires proper function of sensory organs that provide raw sensory input to primary auditory processing centers in the transverse temporal gyrus of the temporal lobe. The encoded electrical signal is then transferred to the association cortex in the superior temporal gyrus for interpretation and final integration of the auditory message with other sensory data in the multimodal association cortex of the temporal pole. These circuits depend upon ascending catecholaminergic projections for proper synchronization and function.
A third basic function is memory that includes recent and remote data. The human brain is flooded with sensory information, e.g., telephone conversation, events on the drive to work, etc. The human brain, like the home PC, has a workstation and a hard disc. The workstation is an analogous to short-term recall, while hard disc is analogous to long-term memory. Long-term memories are stored over broad neural networks, while short-term memory is processed through the human hippocampus. The neurobiology of long-term memory is poorly understood in humans. Short-term recall, i.e., memories lasting 5-15 minutes, operates through human hippocampus. The hippocampus receives a piece of auditory information from the auditory association cortex which projects to a very specific destination along the length of the hippocampus, i.e., a 3.5cm tubular structure in the mesial temporal lobe. The data is transmitted into cortex adjacent to the hippocampal formation, an area termed the “entorhinal cortex” where it is relayed into a series of circuits within the hippocampal structure and back to the temporal lobe for temporary storage. The proper function of this circuit is dependant upon intact neurons in the temporal lobe as well as the hippocampus and intact catecholaminergic projections that facilitate memory. The hippocampus contains a wide range of receptors including NMDA, i.e., excitotoxic, steroid, cholinergic, adrenergic, and others. This diversity of receptors explains how many drugs and injuries can produce memory problems. For example, hippocampal neurons are quite sensitive to hypoxia and hypoglycemia, and severe clinical occurrences can produce memory dysfunction.

3. Cognitive Screening

The mini mental status examination (MMSE) is the basic screening instrument for intellectual function in persons over the age of 65. This 30 point inventory samples a wide range of intellectual functions. One MMSE item requires the recall of three words after five minutes. This simple task actually samples multiple cortical circuits because the individual must first hear the three words, and then understand those words. The examinee must commit those words to short-term memory and then have the expressive ability to repeat those words after five minutes. This simple task requires: 1) proper sensory function, 2) proper interpretation of the words, 3) registration of the information, 4) retrieval from memory, and 5) speaking the words back to the instructor.

Registration is distinct from memory. Registration indicates that the person is capable of getting the three words into the workstation via a sensory port, while memory implies that the three words were loaded onto the workstation and retained for five or ten minutes. The mini mental status examination tests both registration and short-term recall. Registration is when the person is given the three words and asked to repeat them back. Memory is when the person is asked five or ten minutes later whether they can remember the three after they are engaged in other intellectual tasks.

Damage at any point in the sensory, memory, or expressive language centers can produce dysfunction. Either damage of intrinsic neurons or disruption of crucial neuromodulators, e.g., acetylcholine, within the circuit can produce dysfunction. The screening instrument will not identify the level of disruption but rather dysfunction of the circuit. Sophisticated neuropsychological testing may detect the precise level of dysfunction that produces specific symptoms, e.g., failure to remember three words at five minutes.
Information must pass through the hippocampus to enter memory. Damage to intrinsic hippocampal neurons, diminished amounts of essential neuromodulators, e.g., norepinephrine or serotonin, as well as excessive stimulation or blockade of intrinsic hippocampal receptors, e.g., alcohol-induced NMDA receptor dysfunction, may produce memory dysfunction. The failure to remember three items that are properly registered may result from: 1) depression that lowers hippocampal serotonin and norepinephrine, 2) delirium that disrupts other hippocampal transmitter systems, 3) hypoxia that over-stimulates NMDA receptor and damages intrinsic hippocampal circuits, as well as 4) any degenerative disease such as Alzheimer’s or diffuse Lewy body that damages hippocampal or parahippocampal neurons. Disorders that damage multiple components to the system probably impacts memory greater than disorders that damage isolated units.

Similar complex circuits exist for almost every type of cognitive processing and damage to these circuits produce core symptoms of dementia, including amnesia, aphasia, apraxia, and agnosia.

4. Basic Elements of Clinical Assessment

The clinical assessment of dementia begins with a careful detailed clinical history to determine the precise features of intellectual loss. Dementia produces three categories of symptoms: 1) cognitive or intellectual, 2) functional, and 3) psychiatric or behavioral that predicts the level of functional disability. The sequence of symptom development and the timing of clinical features are helpful but not diagnostic. Many older persons fail to recognize memory impairment as a problem and attribute their memory dysfunction to old age. Most affected older individuals with mild dementia recognize their loss of intellectual functions in the early stages. Clinicians should inquire about specific behavioral problems, e.g., forgetting to shut off the stove, cooking from cards rather than from memory, forgetting important conversation, etc., to assess short-term recall problems. Clinicians should assess the duration of symptoms by inquiring as to when the person last felt like their “old self”. The longitudinal history is essential to determine other medical conditions that might be contributory to cognitive loss, e.g., memory problems for about two years coinciding with a stroke or heart bypass surgery, etc. Abrupt onset memory problems are unusual in persons with Alzheimer’s disease and other possible causes, e.g., delirium and depression, should be considered when significant cognitive decline occurs over a period of weeks to several months. Abrupt cognitive decline can be recognized following the death or disability of a caregiver who was compensating for the mild dementia of their spouse or loved one, e.g., Papa was covering up for Mama’s memory troubles. The appearance of depressive symptoms that coincide with the onset of memory problems may reflect dementia with depression or depressive pseudo-dementia. The clinician must establish the timing and sequence of each symptom to judge cause and effect. The appearance of other psychiatric symptoms concurrent with memory problems suggests dementia other than Alzheimer’s disease, e.g., diffuse Lewy body disease.

Problems of language and complex motor skills are often the second symptom to present following memory problems. Open-ended questions such as “do you ever have trouble getting words that folks are saying” or “do you have trouble with your words” allow patients to describe both receptive and expressive problems. Expressive problems can be termed “do you ever have trouble with words being stuck on the tip of your tongue?” Most patients fail
to recognize apraxias and the clinicians must ask open-ended questions such as “is your dressing harder or your driving more difficult” to determine whether the individual is experiencing these difficulties. Family caregivers can give more detailed description; however, clinician should begin the assessment by obtaining the first-person account of the patient.

5. **Essential Components of Past Psychiatric History in the Diagnosis of Dementia**

The past psychiatric history is a key component to the dementia assessment. A past history of substance abuse or depression provides important diagnostic clues about etiology or potential complications. Individuals with a past history of depression may have a recurrence with depressive pseudodementia and these individuals are more at risk for depression during the course of their cognitive decline. Individuals with substance abuse, especially alcoholism, may suffer from alcohol-induced dementia.

The eliciting of psychiatric symptoms requires delicacy and sensitivity because most older persons are concerned about being labeled as “crazy”. Direct closed-end questions like “do you ever hear voices or see things” usually produces an immediate negative response. A more oblique approach such as “do your ears ever bother you” or do your eyes play tricks on you” can be prefaced by comments such as “many older persons have trouble with their eyesight and their hearing”.

6. **Essential Components of Past Medical History in the Diagnosis of Dementia**

The past medical history is important for risk factors such as hypertension, heart disease, diabetes, vitamin deficiencies, or thyroid disorder – conditions that may complicate or mimic dementia. A past history of strokes, seizures, or head trauma is important information about the neurological status of the individual. A history of concurrent weakness, neuropathy, or abnormal cranial nerve function diminishes the likelihood of Alzheimer’s disease. The relationship of cognitive symptoms to health events will alert the clinician to any cognitive complications produced by health problems, e.g., cerebral anoxia following cardiac arrest or hypoglycemia.

The dementia evaluation includes a careful inventory of all medications including prescribed items, over-the-counter preparations, and any other medicinal substances consumed by the patient. Medications with high anticholinergic profiles worsen confusion in elders. Narcotics and benzodiazepines can produce or worsen confusion in the older person.

7. **Essential Components of Family History in the Diagnosis of Dementia**

The family history provides valuable clues about inheritable disorders such as Alzheimer’s disease and fronto-temporal dementia. The clinician should determine how many family members suffered from dementia, at what age of onset, and how close in the family tree. Clinicians should inquire about autopsy conformation of the clinical diagnosis, as many clinical diagnoses differ from post mortem results.

8. **Essential Components of Social History in the Diagnosis of Dementia**

The social history is important to assess highest level of educational achievement, intellectual lifestyle, and degree of social connectivity. Sedentary, physical or intellectual lifestyle and social isolation, i.e., loneliness, predisposes to early loss of function. Important facts about
caregiver networks must be obtained to determine a home plan for any demented patient. Financial resources, living arrangements, available family are all essential tools in constructing an effective home plan.

9. **The Physical and Neuropsychiatric Examination for Dementia**
   The examination component of a dementia evaluation includes the physical examination, neurological examination, and mental status examination. A basic physical examination is essential to exclude severe cardiovascular or cerebrovascular disease. Patients with alcohol-induced dementia may demonstrate evidence of alcohol-induced, end-organ disease; however, little relationship exists between end-organ damage and cognitive decline. The neurological examination is important because Alzheimer’s disease does not produce focal neurological deficits. Discrete neurological impairment suggests dementia other than Alzheimer’s disease. The mental status examination should include a cognitive screen such as the Folstein mini-mental status examination, as well as an assessment to exclude symptoms of psychosis, anxiety, and depression. Specific depression screens may be helpful or the clinician can perform an individualized assessment.

   Basic laboratory values are performed on all patients to include a comprehensive chemistry panel, thyroid studies, folic acid, B12, and urinalysis. These laboratory values are components to any basic comprehensive physical examination. Specific examinations such as toxicology, heavy metal screens, etc., are only acquired to address specific issues. A plasma homocysteine level may be obtained in place of the folic acid level or in combination with the folate and B12. No blood, urine, or CFS test is available to distinguish Alzheimer’s from normal aging or other dementing illnesses.

   Components of the routine physical examination, such as electrocardiogram, provide valuable information. For example, atrial fibrillation is a risk factor for vascular dementia. A lumbar puncture is only performed to investigate specific concerns such as infection, demyelinating diseases, etc. The EEG is rarely helpful in screening for Alzheimer’s disease or other common dementias; however, this test may be performed when specific issues arise such as the possibility of Creutzfeldt’s disease or dementia with seizures.

   Brain imaging is helpful to address specific issues or distinguish between different types of dementia. Persons with severe cortical atrophy and ventriculomegally almost always suffer from dementia; however, some individuals with sever dementia have normal CT or MRI scans. CAT scans will exclude structural brain lesions such as tumor or assess for large areas of ischemic damage or stroke. The MRI is more sensitive at locating smaller lesions produced by hypertensive small vessel disease as well as white matter damage, e.g., subcortical arteriosclerotic encephalopathy. Most patients with Alzheimer’s disease have loss of hippocampal volume and dilation of the inferior horn of the lateral ventricle during the middle phase of the disease. Functional brain imaging such as SPECT and PET may be helpful for distinguishing localized hypoperfusion that predict specific kinds of dementia, e.g., isolated frontal hypoperfusion in fronto-temporal dementia.

10. **Forming a Diagnostic Opinion**
    The clinician must gather all clinical data and laboratory assessments prior to deciding on a diagnosis. Clinicians do not need to insist on a diagnosis of Alzheimer’s disease with the
patient, but rather can advise the affected individual that many diseases cause memory problems. Patients who ask about the possibility of Alzheimer’s should be provided accurate answers. The end of the diagnostic phase signals the beginning of the therapeutic intervention that includes medications to slow the progress of dementia, treatment of behavioral or psychiatric complications, and education of the family to provide maximum support to the patient and caregiver. The diagnostic process continues over the next several years by comparing the natural history of the patient with the natural history of Alzheimer’s or other types of dementia. Alzheimer patients typically lose two points per year from the mini mental in the early stages, and three points per year in the middle stages. Rapid progression or symptom plateauing suggests some other diagnosis.

11. Confirming a Diagnosis of Dementia
   A post mortem examination of brain tissue is the ultimate diagnostic test. A careful clinical evaluation produces the best diagnostic accuracy in the living patient. Diagnostic precision is high, i.e., 90%, for common dementias such as Alzheimer’s disease or diffuse Lewy body disease. Mixed dementia is most difficult to diagnose.