

A Brief Synopsis of Select Neurological Disorders

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Disorders Considered

- Four neurological disorders are examined to illustrate pathological conditions that can develop related to course material
 - Myasthenia Gravis
 - Multiple Sclerosis
 - Parkinson's Disease
 - Alzheimer's Disease

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Neurological Basis

- The neural bases of three of the four diseases are well understood
 - Myasthenia Gravis
 - Multiple Sclerosis
 - Parkinson's Disease
- The causes are **not** understood for any of these diseases
 - we know what happens but not why it happens
 - only the symptoms are treated not the diseases

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Neurological and Psychiatric Symptoms

- Two of the diseases involve primarily motor function – Myasthenia Gravis & Multiple Sclerosis
- One is usually viewed as a motor disorder but may have an important psychological component – Parkinson's Disease
- One is primarily a cognitive disorder but can have profound emotional disturbances – Alzheimer's Disease

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Treatment Effectiveness

- Effective treatments have been developed for two of these diseases - Myasthenia Gravis & Parkinson's Disease
- For one disease there is some progress in slowing its progression - Multiple Sclerosis
- For one of these diseases there is no effective treatment, despite the fact that 50% of those over age 85 develop the disease - Alzheimer's Disease

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The Role of Psychologists

- For the diseases that are largely motor disturbances - Myasthenia Gravis, Multiple Sclerosis: psychologists help the patient adjust to their personal limitations and to cope with the stress associated with any progressive neurological disorder
- For the diseases with prominent psychological disturbances - Parkinson's Disease, Alzheimer's Disease: psychologists play a more critical role directly treating the psychological disturbances of the illness

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Myasthenia Gravis

- A disease where the immune systems attacks and destroys acetylcholine receptors at the neuromuscular junction, resulting in muscular weakness
 - *ocular myasthenia gravis*: restricted primarily to ocular-motor system
 - *generalized myasthenia gravis*: widespread destruction of the neuromuscular junction including the ocular-motor system
- The cause is unknown, but it appears to be an autoimmune disorder involving the thymus

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Myasthenia Gravis: Incidence

- Onset usually between the ages of 20 and 40 years but can occur at any age
- About 0.01% U.S. population affected
 - < age 40 years: 75% women
 - > age 40 years: 60% men
- About 12% of the infants born to women with myasthenia gravis have a syndrome called *neonatal myasthenia* caused by antibodies passively crossing the placenta – the syndrome usually last only several days to a few weeks

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Myasthenia Gravis: An Orphan Disease?

- Some diseases are so rare that it's not economically feasible for pharmaceutical companies to invest in treatment research and development (e.g., about 28,000 cases of myasthenia gravis exist in the United States)
- The Orphan Drug Act (1983) defines orphan products as ones used to treat diseases or conditions affecting fewer than 200,000 people in the United States
 - special grants, tax incentives, and patent protection are available for developing drugs to treat the conditions included on the FDA's list of orphan diseases
 - 47% of these diseases affect fewer than 25,000 people in the United States; some have fewer than 100 patients

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Myasthenia Gravis: Symptoms

- Ptosis
- Diplopia
- Muscle fatigue after exercise
- Other indicators
 - antibodies for the acetylcholine receptor are present in the serum
 - 50% incidence for the ocular form of the disease
 - 90% incidence for the generalized form of the disease

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Myasthenia Gravis: Diagnosis

- Neurological examination
 - presenting symptoms
- Diagnosis is confirmed by using a short-acting (< 5 minutes) cholinesterase inhibitor (edrophonium) to reverse the presenting symptoms – patients should show an immediate, short-lived improvement

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Myasthenia Gravis: Diagnostic Procedure

- Over stimulation of the neuromuscular junction (e.g., nerve gases such as sarin, organophosphate insecticides) can produce the same symptoms, so it's critically important to exercise care in performing this diagnostic procedure – the addition of the cholinesterase inhibitor would exacerbate some conditions (i.e., cholinergic crisis)
- "A syringe is loaded with 10 mg [edrophonium]; 2 mg is given IV, and if no reaction occurs within 30 sec, the rest is injected. If the patient has myasthenia gravis, muscle function improves suddenly and briefly. The test can also differentiate between myasthenic and cholinergic crisis: Patients with myasthenic crisis improve, but those with cholinergic crisis worsen. Because dangerous cardiorespiratory depression can occur, facilities to maintain respiration and atropine (as an antidote) must be available during the test. [from the *Merck Manual* online edition]"

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Myasthenia Gravis: Treatment

- Cholinesterase inhibitors manage the symptoms of the disease
- Corticosteroids and immunosuppressive drugs may be useful to retard the autoimmune response
- Thymectomy is helpful in patients with the generalized form of the disease
 - after thymectomy 80% go into remission or require lower cholinesterase-inhibitor doses

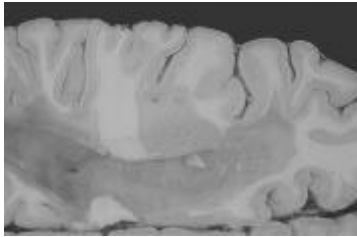
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Multiple Sclerosis

- A slowly progressive neurological disease characterized by patches of demyelination in brain and spinal cord
 - affects only oligodendrocytes not Schwann cells
 - significant neural recovery often occurs during periods of spontaneous remission
- The cause is unknown and the course is highly variable

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Multiple Sclerosis: Postmortem Analysis



brain photograph courtesy of the University of Utah Medical School

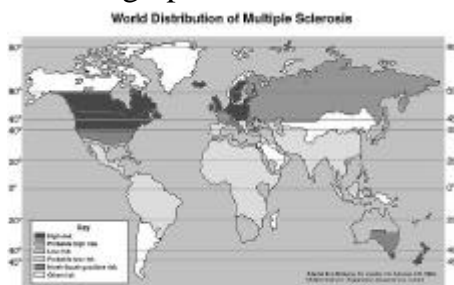
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Multiple Sclerosis: Incidence

- Onset usually between the ages of 20 and 40 years
- Women affected more often than men
- Prominent regional clusters found throughout the world, suggesting environmental influences
 - > 0.03 to 0.13% incidence in northern tier
 - geographic location appears to have no effect after age 15 years

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Multiple Sclerosis: Geographic Distribution



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Multiple Sclerosis: Symptoms

- Early symptoms may include
 - paresthesias
 - weakness in an arm or leg
 - visual disturbances
 - minor gait disturbances
 - vertigo
 - difficulty in speaking
 - neuropathic pain
 - mild emotional disturbances

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Multiple Sclerosis: Symptoms

- Advanced symptoms can include
 - pronounced difficulty moving
 - severe visual impairment or even blindness
 - severe neuropathic pain
 - pronounced cognitive and emotional disturbances

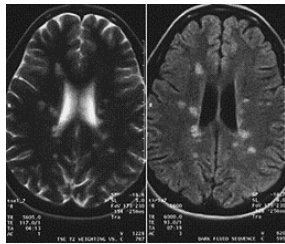
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Multiple Sclerosis: Diagnosis

- Neurological examination
 - presenting symptoms
 - exclusion of other disorders
- MRI may reveal plaques or lesions around demyelinated neurons
- Visual evoked potentials (VEP) may be especially valuable for early diagnosis
 - delayed VEPs are indicative of demyelination

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Multiple Sclerosis: MRI Visualization of Plaques



MRI image courtesy of the Siemens Medical Systems

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Multiple Sclerosis: Treatment

- Disease often shows long periods of remission (sometimes > 10 years) when significant recovery can occur
- Corticosteroids are usually prescribed during active periods
- β -interferon appears helpful in preventing relapse and in delaying progression of the disease

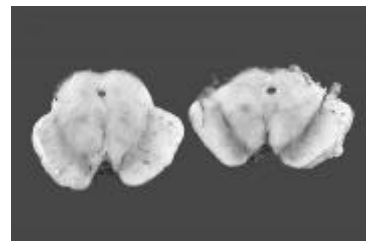
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Parkinson's Disease

- A slowly progressive neurological disorder caused by the loss of dopamine-containing cells in the nigrostriatal pathway
- Prominent symptoms involve motor function
 - psychiatric complications may also occur
 - may have a poorly understood motivational component

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Parkinson's Disease: Postmortem Analysis



brain photographs courtesy of the University of Utah Medical School

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Parkinson's Disease: Incidence

- Onset usually appears after age of 40 years
 - mean age of onset 57 years
 - but can begin at any time including childhood when it is termed *juvenile parkinsonism*
- affects 1% aged 50 years and over
- 10% aged 60 years and over may have undiagnosed, early stages of the disease
- about 1½ times more common in women than in men

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Parkinson's Disease: Subtypes

- Primary (idiopathic)
 - unknown origin but **not** induced by obvious stimulus
- Secondary (parkinsonism)
 - related to drugs, stroke, or trauma, other stimuli
- Familial
 - genetically linked
 - accounts for < 20% of the diagnosed cases

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Parkinson's Disease: Symptoms

- Difficulty initiating movement
- Shuffling gait
- “Cogwheel” rigidity
- Tremor at rest
- Advanced stages may include psychiatric complications
 - depression
 - hallucinations
 - paranoia

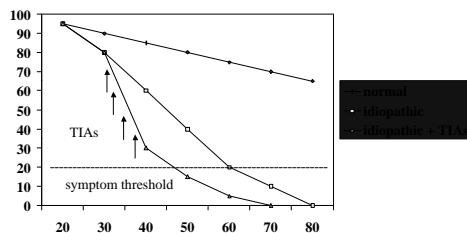
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Parkinson's Disease: Subclinical Profile

- Considerable dopamine loss must occur before the disease is apparent
 - clinical diagnosis is usually made after $\geq 80\%$ loss in striatal dopamine content
 - symptoms may emerge after a 60% reduction in striatal dopamine content
 - animal models usually consider $\geq 90\%$ dopamine depletions necessary to produce effects
- The disease is probably present > 20 years before diagnosis

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Parkinson's Disease: Hypothesized Decline in Dopamine Cells



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Parkinson's Disease: Diagnosis

- Neurological examination
 - presenting symptoms
 - exclusion of other disorders
- Response to levodopa therapy

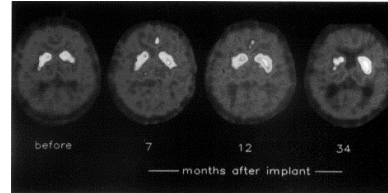
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Parkinson's Disease: Treatment

- Levodopa (L-dopa) therapy
 - usually combined with a peripheral decarboxylase inhibitor (carbidopa)
 - generally very effective for the first 2 to 5 years of treatment after which the on-off effect develops
- Direct-acting dopamine agonists
- Experimental brain surgery
 - lesions (e.g., thalamotomy, pallidotomy)
 - neural tissue implants (e.g., fetal dopamine cells)

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Parkinson's Disease: Treatment – Neural Tissue Implants



Substantia nigra cells were surgically implanted into the right putamen. Note the continued degeneration seen on the contralateral (left) side revealed by the PET.

PET images courtesy of the UCLA School of Medicine, Division of Brain Mapping

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Parkinson's Disease: Treatment Complications

- The on-off phenomenon limits the effectiveness of levodopa therapy
 - may be related to sensitization
 - may be related to continued loss of dopamine cells
 - may produce psychiatric complications
- Some clinicians now recommend direct-acting dopamine agonists as the initial treatment
- The 'psychological' and possible motivational components continue to be largely neglected

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Alzheimer's Disease

- A progressively degenerative neurological disorder leading to dementia with increasing mental confusion, emotional instability, and premature death
- The cause is unknown but amyloid plaques and neurofibrillary tangles are present in the CNS, initially in the hippocampus and later in the cerebral cortex and related structures
- Widespread CNS atrophy is present in advanced cases

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Alzheimer's Disease: Postmortem Analysis

- β -amyloid (protein fragment)
 - insoluble deposits intermingled with portions of neurons and with microglia and astrocytes
- Neurofibrillary tangles
 - twisted microfilaments with abnormal Tau
- Unclear whether β -amyloid or neurofibrillary tangles cause Alzheimer's or are products of the disease (neurofibrillary tangles may be 'aging')
- Advanced stage shows widespread CNS atrophy

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Alzheimer's Disease: Postmortem Analysis

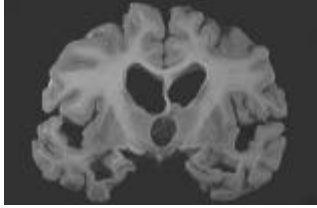


normal advanced Alzheimer's

brain photographs courtesy of the University of Wisconsin Medical School

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Alzheimer's Disease: Postmortem Analysis



*brain photograph courtesy of the
University of Utah Medical School*

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Alzheimer's Disease: Incidence

- Diagnosed cases
 - 10% of the population aged 65 years and over
 - 50% of the population aged 85 years and over
- Number of patients expected to dramatically increase as the population ages
- Delaying the onset of Alzheimer's disease by one or two years would save the U.S. economy billions of dollars annually

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Alzheimer's Disease: Symptoms

- Usually classified into five stages indicating the severity of the disease
- Progressive stages probably mark continued neurological deterioration with the emergence of more severe symptoms

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Alzheimer's Disease: Early Stage Symptoms

- Difficulty learning new information
- Loss of recent memory
- Difficulty 'finding' words
- Abstract thinking & judgment impaired
- Psychological characteristics
 - mood swings
 - personality changes

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Alzheimer's Disease: Intermediate Stage Symptoms

- Severe impairment of recent memory and of learning new information
- Some impairment of long-term memory
- Patients may require assistance with routine activities such as bathing and eating
- Patients may become 'lost' finding their own bedroom or bathroom

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Alzheimer's Disease: Intermediate Stage Symptoms

- Psychological characteristics
 - time-space disorientation
 - wandering
 - agitation
 - hostility
 - uncooperativeness
 - possible physical aggressiveness

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Alzheimer's Disease: Severe Stage Symptoms

- Unable to walk or perform other activities
- Complete loss of remote and recent memory
- Eventually unable to speak

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Alzheimer's Disease: End Stage Symptoms

- Additional motor features may be present
 - spastic movements
 - seizures
- Coma
- Death (usually from infection)

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Alzheimer's Disease: Diagnosis

- Neurological examination
 - presenting symptoms, especially deficits in
 - short-term memory
 - abstract thinking
 - judgment
 - assessment of personality changes
 - exclusion of other disorders
 - continued decline in mental status
 - Alzheimer's disease doesn't show remission – this can be particularly important in distinguishing dementia from delirium

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Symptom Classification: Delirium vs. Dementia

- Both delirium and dementia refer to mental confusion, but the underlying basis for these types of symptoms can be much different
 - *delirium* refers to transitory mental confusion such as that caused by metabolic imbalances, by excessive medication, and by alcohol or other drug abuse
 - *dementia* refers to chronic deterioration of mental function from irreversible neurological damage
- Different diagnosis is important, especially in treating the elderly

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Alzheimer's Disease: Treatment

- Cholinesterase inhibitors are helpful for many patients (three approved by FDA)
- Psychiatric drugs (e.g., antidepressants, antipsychotics) are used to manage some of the psychological disturbances
- Experimental treatments include:
 - vitamins E and C (antioxidants)
 - ginkgo biloba (antioxidant & vasodilator)

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Role of Psychologists in Alzheimer's Disease: Diagnosis

- Short-term memory deficits are among the earliest signs
- Personality changes also occur during early stage

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Role of Psychologists in Alzheimer's Disease: Management

- Helping patient to simplify life style
- Helping patient with simple adaptive strategies to offset mental deterioration
- Helping patient to deal with affective component
 - emotional “swings”
 - depression
 - feelings of hostility

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Role of Psychologists in Alzheimer's Disease: Support

- Preparation of family members for coping with a for progressively deteriorating disease
- Training primary care-givers
- Management of psychological depression that occurs in about 80% of the family members directly caring for the Alzheimer's patient

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Progress Made in Treating These Disorders During the past 25 Years

- **Myasthenia gravis:** thymectomy improves condition in about 80% of the cases
- **Multiple sclerosis:** none except possible usefulness of interferon in extending remission
- **Parkinson's disease:** none except promise of embryonic implants
- **Alzheimer's disease:** some in identifying the
 - limited effectiveness of cholinergic agents
 - recognition of the condition as a “disease”

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