Delirium in Hospitalized Elderly

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THE POPULATION'S AGING has brought increasing attention to the special problems that face the elderly. In addition to memory impairment, acute medical problems and psychiatric symptoms create burdens on caregivers and influence the risk of institutionalization.[1-5] Acute confusional states (delirium) typify the complex interactions of physical illness, cognitive dysfunction, and behavior change.

Although delirium was known to the ancients (Celsus coined the term) and has occupied the attention of psychiatrists since the nineteenth century,[6-10] physicians have been accused of ignoring this condition, to the detriment of their patients. Thus, Engel and Romano wrote, "It is a curious fact that while most physicians have a strong bias toward an organic etiology of mental disturbances, at the same time they seem to have little interest in, and, indeed, often overlook, delirium."[8]

Delirium is probably increasing in frequency among hospitalized patients as an increasingly older and sicker population inhabits our general medical and surgical wards.[10] Its close association with a vast spectrum of illnesses makes it the province of the general internist. Yet the subject remains relatively neglected in the general medical literature. The purpose of this article is to review the literature on delirium, with emphasis on methodologic issues as well as practical management.

TERMINOLOGY AND CLINICAL DESCRIPTION

Liston identified over 30 terms used in recent literature to denote delirium; a partial listing is given in Table 1.[11] Such nomenclature has made it difficult to review work published prior to 1980 since it is not certain that authors are referring to the same clinical entity.[12] The 1980 publication of the third edition of the American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM-III) and its recent revision (DSM-III-R) introduced standardized nomenclature and criteria for the diagnosis of delirium (Table 2).[13]

According to DSM-III-R, the primary process in delirium is the reduced ability to maintain attention to the outside world. A patient with delirium has diminished awareness of his or her surroundings, is easily distracted, and follows commands poorly. "Clouding of consciousness" was used to describe this process in the first version of DSM-III, but this ambiguous phrase is no longer used.

The delirious patient's speech is limited, rambling, irrelevant, or incoherent, indicating disorganization of thought. Other behavioral changes include reduced level of consciousness; perceptual disturbances (misinterpretations of stimuli, illusions, or frank hallucinations); sleep–wake disturbances (insomnia, daytime sleepiness); increased or decreased psychomotor activity; disorientation (first to time, then place, and

TABLE 1

Synonyms for Delirium

Acute brain failure	Exogenous psychoses
Acute brain syndrome	Metabolic encephalopathy
Acute cerebral insufficiency	Pseudosenility
Acute confusional state	Reversible cognitive dysfunction
Acute mental status change	Reversible dementia
Acute organic psychosis	Reversible toxic psychosis
Acute organic reaction	Subacute befuddlement
Acute organic syndrome	Toxic confusional state
Agitated confusional state	Toxic delirious reaction
Altered mental status	Toxic encephalopathy
Cerebral insufficiency syndrome	Toxic-metabolic encephalopathy
Dysergastic reaction	Toxic psychosis

TABLE 2

DSM-III-R Criteria for Delirium

Reduced ability to maintain attention to external stimuli and to appropriately shift attention to new external stimuli

Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech

At least two of the following:
- Reduced level of consciousness
- Perceptual disturbances: misinterpretations, illusions, or hallucinations
- Disturbance of sleep-wake cycle with insomnia or daytime sleepiness
- Increased or decreased psychomotor activity
- Disorientation to time, place, or person
- Memory impairment

Clinical features develop over a short period of time and tend to fluctuate over the course of a day

Either one of the following:
- Evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
- In the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder

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then person); and, finally, memory impairment of varying degrees of severity.

Delirium fluctuates over the course of the day and generally becomes worse at night. Another key temporal feature of delirium is its acute onset, occurring over a period of hours to days. Finally, DSM-III-R mandates that specific organic etiologies be demonstrated or presumed to underlie the disturbance.

According to Geschwind, the global disorder of attention is unique to delirium and needs to be distinguished from unilateral spatial neglect due to cerebrovascular disease, deliberate lack of cooperation, and distraction caused by depression or other factors.[14] He argued that the manifestations of delirium are logical results of the loss of selective attention, whose function is to maintain coherence of thought, orientation to surroundings, and organization of memory and perception.

Not all authors accept this broad formulation. Victor and Adams, for instance, prefer to limit the term delirium to acute confusional states characterized by heightened alertness, an increased responsiveness to stimuli, vivid hallucinations, psychomotor agitation, and autonomic nervous system arousal.[15] Delirium tremens is the prototype of these states. Acute confusional states with reduced alertness and decreased psychomotor activity are classified as a separate entity. Victor and Adams justify the separate classification of hyperactive and quiet confusional states by postulating that different mechanisms underlie each entity.

At present, however, our knowledge of the underlying mechanisms of delirium (see below) is quite limited. Until further research can uncover distinctions, the broad definition of delirium in DSM-III has the advantage of accommodating a wide variety of manifestations, including "quiet" delirium, which appears to be most common in the aged.[16]

DIAGNOSIS

As reflected in DSM-III-R criteria, the diagnosis of delirium is a clinical one based on direct observation of the patient, collateral sources of information, and awareness of the patient's baseline mental state and current physical problems. Attempting conversation with the patient is often sufficient to reveal wandering attention and easy distraction (e.g., need to repeat instructions). The content of speech may reveal thought disorganization and perceptual problems. Changes in psychomotor activity, including lethargy, may be directly observed during the day, but nighttime agitation may be known only to the nursing staff. Nursing notes can provide invaluable documentation of behavioral disturbances that are otherwise missed by physicians. Family members or companions to the patient are needed to identify preexisting cognitive and behavioral problems and to delineate the time course of the present decline. Finally, the physical examination may reveal myoclonus and asterixis, which are considered pathognomonic of delirium, although most often the primary findings are those of the illness or illnesses that precipitated delirium.[16]

Although these signs of delirium can often be noted in the course of a standard history and physical, incorporating formal mental status testing into the evaluation may uncover subtle disturbances of attention, orientation, and memory that might otherwise be missed. Mental status testing also provides the opportunity to assess progress or deterioration through serial testing and to differentiate chronic from acute problems if cognitive assessment was performed in the outpatient setting prior to the onset of acute illness.

Several brief, easily administered mental status questionnaires have been developed, including the Mini-Mental State Exam (MMSE) and the Cognitive Capacity Screening Exam (CCSE).[17, 18] No evidence suggests that one is clearly superior to any other.[19] The MMSE takes about 10 minutes to administer and provides a screening assessment of orientation, recall, attention, calculation, language, and constructional abilities. Despite this breadth of coverage, the physician should not rely solely on the MMSE or any other brief instrument to diagnose delirium, primarily because such tests fail to capture key features of delirium (attention deficit, rapid onset, and fluctuating course). The MMSE and other short mental status tests are relatively insensitive to mild impairment and may have poor specificity in some hospital settings.[20, 21] In one trial of the MMSE on general medical ward patients, there was a sensitivity of 87%, a specificity of 82%, and a positive predictive value of 61% when compared with a psychiatrist's judgment on the presence of delirium or dementia.[21]

The basic clinical assessment of delirium can be supplemented by psychomotor testing and electroencephalopathy (EEG). Psychomotor testing measures the attention deficit that is of primary importance in the delirious state. Screening instruments that have been used in clinical settings include the trail-making test,[22] which is a timed test of number connection, and the hand-held tachistoscope, a portable apparatus for measuring the time needed to perceive a brief visual stimulus.[23]

The trail-making test correlates with arterial ammonia concentration and other measures of hepatic encephalopathy.[24, 25] In a recent survey of delirium among liver transplant candidates, the trail-making test achieved a sensitivity and specificity of 92% and 73%, respectively.[26] However, the usefulness of the trail-making test in other medical settings has not yet been demonstrated, and performance may potentially be affected by physical impairments unrelated to the delirious state.

Abnormally prolonged perception times measured by the hand-held tachistoscope have nearly 100% sensitivity for delirium, but a specificity of under 50%, due to the confounding effect of physical and sensory impairment commonly found in elderly patients.[27] As a result, this test has significant limitations for the study of delirium in hospitalized elderly.

Finally, EEG has been advocated by many investigators in the diagnosis of delirium.[26,29-31] Early work of Engel and Romano revealed nearly universal EEG changes in delirium, including diffuse slowing, low-voltage fast activity, and progressive disorganization of rhythms as patients deteriorate.[31] Low-voltage fast activity predominates in hyperactive, aroused delirium such as delirium tremens. In contrast, generalized slowing is the major finding of "quiet" delirium. Commonly both EEG manifestations coexist.[28] In anticholinergic delirium, there is close correlation between clinical state and EEG. Reversal of delirium with cholinesterase inhibitors returns the EEG pattern to normal.[32] Other EEG patterns have been described, including spike and slow wave (triphasic) complexes in a variety of metabolic encephalopathies, and epileptiform activity in cases of barbiturate or sedative-drug withdrawal.[33] However, the underlying medical condition responsible for delirium usually cannot be determined from the EEG pattern.[34]

These findings have led investigators to conclude that EEG changes are particularly useful in the differential diagnosis and confirmation of delirium.[29] However, in the studies that have been reported, all the patients had definite clinically diagnosed delirium and severe metabolic or central nervous system insults. Formal evaluation of sensitivity and specificity in general medical settings is lacking. In individual patients, particularly the elderly, the EEG probably has less practical value. Some degree of EEG slowing is found in many elderly,[35] and can be pronounced in dementia,[35-37] so one would expect a low specificity for this diagnostic tool. Furthermore, the EEG pattern may change without producing a clearly abnormal result within a given individual as he or she become delirious.[28] Serial testing has been advocated to improve sensitivity and circumvent this shortcoming, but is not practical in acutely ill patients. Finally, bedside recordings made in medically ill patients frequently show artifacts.[33]

In conclusion, the diagnosis of delirium remains a clinical one. The value of the clinical interaction was demonstrated by Anthony and colleagues,[27] who found that a non-psychiatrist's observation of the patient's "global accessibility' (i.e., attentiveness and ability to follow directions) had better sensitivity and specificity (both over 90%) compared with a psychiatrist's standardized clinical diagnosis than either the MMSE or a tachistoscope. The internist, therefore, should be able to diagnose delirium with the tool he finds most familiar: the medical interview supplemented by mental status testing. More sophisticated testing should be reserved either for research purposes or the occasional confirmation of an uncertain diagnosis.

TABLE 3
Differential Diagnoses of Delirium

Diagnosis	Distinguishing Features
Functional psychosis	Onset prior to age 40 Chronic, relapsing course Auditory hallucinations characteristic Bizarre and systematic delusions Intact sensorium and orientation Myotonus/asterixis absent EEG usually normal
Delirious mania	History of prior manic episodes Family history of bipolar disorder Responds to lithium
Dementia	Insidious onset, chronic course Alertness and attention intact until final stages
Organic delusional syndrome	Prominent delusions without attentional difficulties
Organic hallucinosis	Prominent hallucinations without attentional difficulties
Organic amnestic syndrome	Impaired short- and long-term memory with intact attention, abstract thinking, judgment, and personality
Ictal confusion (nonconvulsive status epilepticus)	Occurs in known epileptic patients Associated movements (eyelid flutter, rhythmic facial or arm movement, staring, automatisms) Characteristic electroencephalogram Responds to antiepileptic medication

DIFFERENTIAL DIAGNOSIS

Delirium is often mistaken for functional psychosis.[16,30,38,39] Furthermore, other organic mental disorders may possess some of the behavioral features of delirium, such as memory impairment, hallucinations, or delusions, without having abnormal attention and awareness. Finally, nonconvulsive seizures can mimic delirium. Features that distinguish these diagnoses from delirium are summarized in Table 3.

Functional psychosis, in contrast to delirium, generally has its onset in early adult life, usually before age 40. Beyond that age, a sudden change in behavior should prompt suspicion of delirium.[40] Other features that distinguish functional psychosis from delirium are the character of the hallucinations (typically auditory in psychotic patients), delusions (often bizarre and highly systematic in the schizophrenic and paranoid disorders), and sensorium (generally intact in functional disorders if the patient cooperates with testing).

Physical signs of delirium, such as myoclonus, asterixis, and EEG changes, are absent.

Occasionally, acute psychiatric illnesses more closely simulate delirium; "pseudodelirium" has been coined to denote these states.[41] Carlson[42] and Bond,[43] for instance, reported that untreated mania can progress to a state resembling delirium, with distractibility, insomnia, lability, confusion, disorientation, and hallucinations. Patients with "acute delirious mania" usually have a history of bipolar affective disorder, or have a family history of mania. Furthermore, this disorder lacks a discernible organic cause and responds to standard therapy for manic-depressive illness.

Dementia, like delirium, can have prominent memory and cognitive deficits, but has an insidious onset and chronic course and is stable over short periods of time. The demented remain attentive and aware of their environment until very advanced stages.[6, 10 16, 30] Delirium can superimpose upon dementia, in which case features of both coexist, and improvement in cognition occurs when the precipitants of delirium are treated. Some "reversible dementias" are probably examples of such superimposed deliriums.[1]

DSM-III-R recognizes several other organic mental disorders that exhibit some of the features of delirium without the global attention deficit: organic delusional syndrome, organic hallucinosis, and organic amnestic syndromes. Delusions, commonly persecutory, have been associated with dementia, drug toxicity, and medical illness.[44] Among a geriatric referral population, 37 of 100 demented elderly had delusions.[45] These patients were generally not disoriented and were more functionally competent than the nondelusional patients. Organic hallucinosis refers to the hallucinations, usually visual, occurring in a variety of other physical conditions, such as ophthalmologic disease, neurologic disorders, and sleep disturbances.[46] Last are organic amnestic syndromes (e.g., Korsakoff's psychosis) present with prominent perceptual or memory disturbances, but not the other criteria for delirium.[13]

Acute prolonged confusion can sometimes be a manifestation of a seizure rather than delirium.[47] In a study of patients in a general hospital, Dunne found 22 cases of nonconvulsive status epilepticus over a two-year period, comprising almost 20% of patients presenting with status epilepticus.[48] Eighteen of these patients presented with "absence status" — confusion, disorientation, partial responsiveness, and subtle rhythmic movements of the eyes, face, or jaw. Generalized EEG abnormalities were seen. Both clinical and EEG abnormalities responded to antiepileptic medication. Much less common (four cases) was "complex partial status," which presented with a cyclical pattern of unresponsiveness, mimicking the waxing and waning progress of delirium. However, staring, automatisms, and EEG abnormalities with a temporal lobe focus served as distinguishing features.[49] Most reports of both varieties of nonconvulsive status epilepticus involve patients with known epilepsy, but de novo presentations in the elderly have been reported and can be easily mistaken for delirium.[47]

TABLE 4

Characteristics and Rates of Confusion from Studies of Hospitalized Elderly

Reference	Population	Definition of Confusion	Monitoring	Rate of Confusion
Rosin and Boyd, 1966[50]	Geriatric ward ($n = 169$)	Not given	Not specified	18% incidence during stay
Hodkinson, 1973[51]	Geriatric ward ($n = 588$)	Abnormal mental test, duration less than 2 weeks	Testing at 2-week intervals	24% prevalence on admission, 16% incidence during stay
Lowy et al., 1973[52]	All ages ($n = 65$)	Organic brain syndrome	Test within 48 hours of admission	None had organic brain syndrome
Bergmann and Eastham, 1974[53]	Age over 65 ($n = 100$)	Not given	Interview on admission	16% prevalence on admission
Henker, 1979[54]	Psychiatry consults	Acute brain syndrome (DSM-II)	Request for consultation	0.74% of all adult admissions
Seymour et al., 1980[55]	Age over 70 ($n = 68$)	Abnormal mental test, duration less than 1 week	Admission and 1-week testing	16% prevalence on admission
Chisholm et al., 1982[56]	Age over 60 ($n = 99$)	Not given	Daily assessment by unit nurse	56% developed confusion
Gillick et al., 1982[57]	All ages ($n = 429$)	Not given	Twice-weekly chart review	Confusion in 30% of patients 70 years old or older
Warshaw et al., 1982[58]	Age over 70 ($n = 279$)	Not given	Single assessment	31% point-prevalence
Fields et al., 1986[59,60]	All ages ($n = 115$)	MMS score less than 24	MMS on admission and discharge	20% cognitively impaired on admission
Cameron et al., 1987[61]	All ages ($n = 133$	DSM-III delirium	Psychiatric examination of all patients	13.5% prevalence on admission, 3.3% incidence during stay

TABLE 5

Outcomes of Confusion from Studies of Hospitalized Elderly

Reference	Population	Definition of Confusion	Outcome	Comparison Group	Mortality Ratio
Roth, 1955[68]	Psychiatric, age over 60 ($n = 38$)	Acute clouding of consciousness	40% of patients dead at 6 mo	Psychiatric patients	1.6
Kay, et al., 1956[69]	Psychiatric, age over 60 ($n = 107$)	Delirium or dementia	57% of patients dead at 12 mo	Psychiatric patients	3.0
Guze and Cantwell, 1964[70]	Consults, all ages ($n = 117$)	Acute or chronic brain syndrome	17% of patients died in-hospital	Hospital patients	4.6
Guze and Daengsurisi, 1967[71]	As above ($n = 262$)	As above	11.4% of patients died in-hospital	Matched controls	2.0
Hodkinson, 1973[51]	Geriatric ward ($n = 186$)	Abnormal test score, duration less than 2 weeks	25% of patients dead at 1 mo	Cognitively intact patients	2.0
Bergmann and Eastham, 1974[53]	Medical ward, age over 65 ($n = 16$)	Not given	37.5% of patients died in-hospital	Cognitively intact patients	2.2
Rabins and Folstein, 1982[72]	Consults, all ages ($n = 48$)	Delirium diagnosed by psychiatrist	23% of patients died in-hospital	Demented patients	5.8
Weddington, 1982[73]	Consults, all ages ($n = 15$)	DSM-III delirium	33% of patients dead at 3 mo	Depressed patients	16.5
Trzepacz et al., 1985[74]	Consults, all ages ($n = 77$)	DSM-III delirium	25% of patients dead at 6 mo	Demented patients	3.7
Black et al., 1985[75]	Psychiatric, all ages ($n = 543$)	DSM-III organic mental disorders	9.4% of patients dead at 2 yr	Population mortality	3.02 (men) 4.10 (women)
Fields et al., 1986[60]	Medical ward, all ages ($n = 23$)	MMS score less than 24	17% of patients died in-hospital	Cognitively intact patients	3.4
Cameron et al., 1987[61]	Medical ward, all ages ($n = 20$)	DSM-III delirium	65% of patients died in-hospital	Nondelirious patients	19.7

INCIDENCE AND PREVALENCE IN GENERAL MEDICAL PATIENTS

Few studies report the rates of delirium as defined in DSM-III. Nearly a dozen studies have been published on rates of "confusional states" in medical patients (Table 4). Some report separately the prevalence of delirium upon admission to the hospital and its incidence over the course of hospitalization among patients who had stable mental status on admission. When both prevalent and incident rates are combined, it appears that approximately 25% or more of elderly patients on medical wards are at risk for delirium, although rates range from less than 1% to over 50%. These studies are difficult to compare because of several factors:

Definitions of Confusion. In some reports, chronic and acute confusional states are not distinguished.[50, 57-60] Acute confusion may be defined simply as an observed change in mental status score,[51, 55] or other behaviors may be included in the criteria.[54, 56, 61]

Study Population. The target population may be all hospital admissions, or only those over a certain age. One study in a relatively young population yielded no cases of delirium.[52]

Referral Bias. A study that focused on patients seen by consulting psychiatrists reported acute brain syndrome in less than 1% of adult admissions. Patients seen in consultation tend to be more flagrant cases or particular management problems, but represent only a fraction of delirium.[54]

Ascertainment Bias. Physicians recognize cognitive impairment less than 50% of the time compared with standard mental status screening tests.[18, 62-65] Of 20 cases of DSM-III-diagnosed delirium in one study, only one case was identified as such by housestaff.[61] Nurses, perhaps because of their closer contact with patients, are much more likely to identify signs of delirium. Reviewing charts of patients seen by psychiatric consultants in a general hospital, Perez[66] found physicians indicated possible delirium in only 34% of cases. Nurses, on the other hand, recorded signs of delirium (restlessness, confusion, disorientation, and disruptive behavior) in 93% of patients with this condition. The highest rates of delirium, exceeding 50% among elderly admissions, have been recorded in studies relying on assessments by unit nurses.[56, 67]

PROGNOSIS OF DELIRIUM

The studies summarized in Table 5 confirm the association of delirium with increased mortality. Both in-hospital and post-discharge mortality rates of patients with delirium are significantly higher than those of patients with other psychiatric diagnoses[68, 69, 72, 73]; overall hospital admissions[70]; cognitively intact patients[51, 60, 61]; population controls[75]; and hospital patients matched for age, sex, and diagnosis.[71]

Prognostic comparisons of delirium patients with control groups reveal a wide range of results, with mortality ratios from under 2 to almost 20, and short-term

mortality rates from 10% to 65%. Divergent criteria for confusional states, biases introduced when only referred patients are studied, variable length of follow-up, and differing patient-care settings and control groups probably account for such wide variation.

The definition of delirium highlights its association with physical illness, but few studies have attempted to control for illness severity. Guze originally reported a 4.6-fold increase in mortality among hospitalized patients with organic brain syndrome.[70] Repeating his analysis on the same patients, but with controls matched for age, sex, and diagnosis, he demonstrated only a two-fold increase,[71] indicating possible confounding by underlying illnesses. More recently, Fields and coworkers reported a multivariable analysis that included measures of illness severity. In their study, higher in-hospital morality rates among patients with cognitive impairment appeared to be explained by their greater illness severity and comorbidity, with no significant independent effect of delirium.[60] However, the authors raised concerns about Type II error, as only 23 impaired patients were identified.

Mortality appears to be higher in patients with delirium because the presence of delirium indicates significant underlying medical problems. However, it is still possible that delirium serves as a marker for impaired homeostasis in the elderly and may have prognostic value independent of the usual markers of illness severity. Unfortunately, lack of reliable measures of illness severity for general medical ailments[76] has hampered the search for these associations.

When dealing with the elderly, endpoints other than mortality assume greater importance since quality of life is often valued more than mere quantity. Data on such endpoints are scant. Some authors hypothesize that the stress of delirium can affect the psychological well-being of patients following its resolution,[77] and may potentially result in major depression or posttraumatic stress syndrome,[78] but large prospective studies have not addressed these outcomes.

Abnormal mental status may predict functional outcomes such as dependence in activities of daily living and institutionalization. Lamont,[79] in a review of 205 general hospital discharges, found that acute or chronic confusion predicted discharge to nursing facilities. Similarly, in a review of 70 demented patients admitted because of behavioral disturbances (half of whom had delirium or drug intoxication), only 24% were able to return home after discharge.[80] Despite the failure to distinguish delirium from other confusional states, these studies suggest that confusion in the hospital identifies a population in need of long-term care following hospital discharge.

Finally, the definition of delirium implies potential reversibility. Bedford[8] initially reported that following an episode of delirium, confusion resolved within one month in 82% of his patients, and by six months in 94%. Other studies show a less optimistic outlook. Morse,[82] for instance, noted minor degrees of cognitive impairment at the time of discharge in half of the patients suffering postoperative delirium. The possibility of "occult dementia" was not addressed. More recently, in a study of general medical patients,[59] 50% of cognitively impaired subjects had persistent deficits three months after discharge. The presence of criteria for delirium (as opposed to dementia) did not predict improvement in mental test scores.

It is widely conjectured that delirium, properly treated, leads to full recovery and that transition from delirium to dementia is rare. Patients who fail to recover completely may have had unrecognized dementias unmasked by hospitalization for acute illness.[1, 10] Alternatively, chronic decline may begin at the time of an initial acute confusional episode. There is a need, therefore, to test prospectively the hypothesis that an episode of delirium can be the initial manifestation of dementing illness.

MECHANISMS OF DELIRIUM

Although a syndrome as clinically diverse as delirium might be expected to have a multitude of putative neurochemical mechanisms, only a handful of etiologic hypotheses have been advanced. By far, the most compelling of these is the anticholinergic hypothesis, which is supported by the following observations:

1. Minimal impairment of cerebral metabolism produced by hypoxia or hypoglycemia can significantly impair synthesis of acetylcholine.[83,84]
2. Anticholinergic intoxication can produce behavioral and EEG manifestations of delirium that can be reversed with cholinesterase inhibitors such as physostigmine or tetrahydroaminoacridene.[32, 85]
3. Correlations are reported between cognitive decline and serum anticholinergic activity measured by radioreceptor assay in a number of settings, including post-cardiotomy delirium[86]; delirium following general surgery[87]; post-ECT confusional states[88]; cognitive decline in schizophrenic patients receiving psychotropic medications[89]; and delirium occurring in intensive care.[90]
4. The loss of cholinergic cells that occurs in Alzheimer's disease[91, 92] provides an analogy to the cognitive dysfunction of delirium.

The risk of anticholinergic toxicity is high in the elderly as so many medications have such activity, including antipsychotics, antidepressants, anti-parkinsonian agents, certain sedative-hypnotics, and antihistamines. Anticholinergic drugs are readily available over the counter as cold remedies, allergy formulations, and sleeping pills. Nearly 60% of nursing home residents and 23% of ambulatory elderly are prescribed drugs with anticholinergic properties. Many take three or more such agents concurrently, further enhancing

the risk of toxicity.[93] In addition, many classes of drugs not ordinarily viewed as having anticholinergic binding can produce delirium that is reversible with physostigmine. Meperidine, cimetidine, and ranitidine are examples of such agents.[94-97] In some instances, post-receptor mechanisms may be involved. For instance, lithium in toxic concentrations inhibits cyclic GMP formation, an intracellular "second messenger" formed after agonist binding to muscarinic receptors.[98]

Only limited data exist for mechanisms other than the anticholinergic hypothesis. Among the earliest explanations of delirium was stress-induced cortisol hypersecretion, in effect, a self-induced "steroid psychosis."[16] Recent investigations of post-operative delirium reveal prolonged increases in circulating cortisol as well as disruption of the normal circadian rhythm of cortisol secretion, changes that are absent in non-delirious postoperative patients.[99] This may reflect the stress of physical illness associated with delirium rather than an etiologic mechanism.

Beta-endorphin levels also rise in postoperative delirium,[99] although not in alcohol withdrawal.[100] Endogenous opiates have been linked to mental illness, but the data are far from consistent[101] and their role in delirious states remains conjectural.

Biogenic amines are speculated to play a role in delirium due to withdrawal states. The levels of norepinephrine and metabolites are increased in blood and cerebrospinal fluid of alcoholics in withdrawal,[102] not surprising since autonomic hyperactivity characterizes the state. Since delirium in the elderly usually does not manifest autonomic activation, the generalizability of this finding is uncertain.

Finally, peripheral mediators of the inflammatory and immune responses may have central nervous system effects that contribute to the clinical picture of delirium. Endogenous pyrogen (interleukin-1), for instance, produces EEG slowing and sleep when injected into rabbit ventricles.[103] Whether these animal data are generalizable to humans remains to be demonstrated.

CAUSES AND SETTINGS OF DELIRIUM

The DSM-III-R criteria for delirium require the presence of organic factors underlying the disturbance. Often, physical illness whose primary locus is outside the central nervous system is the precipitant of delirium. Potential causes of delirium include virtually any medical diagnosis.[40] In addition, delirium may be a complication of therapy or diagnostic procedures.[104-108] Finally, the elderly often have nonspecific presentations of diseases. Life-threatening conditions such as myocardial infarction, for instance, may present initially as acute mental status change without other obvious symptoms or signs.[109-110]

The spectrum of illnesses that are reported to cause delirium reflect highly prevalent conditions. Flint[111] identified cerebrovascular accident, heart failure, and pneumonia as the most common etiologies of acute confusional states in the elderly. Infections were the most common causes of acute confusional states among general hospital admissions.[112] In a review of neurologic consultations for delirium, Moses reported that drug effect, fluid or electrolyte disturbance, and hypoxia or hypotension were the leading identifiable causes of delirium. Only 8% of patients in this study had delirium due to a primary neurologic event.[107] In nearly half, a clear etiology for delirium could not be identified.

In addition to acute medical illnesses, medications, prior dementia, cerebrovascular disease, malignancy, environmental stressors such as sensory deprivation, sensory impairment, and homeostatic challenges such as surgery all interact to produce a multifactorial etiology for delirium. This complexity explains why relatively few studies have attempted to enumerate the causes of delirium among their patient populations.

Drugs

Drug toxicity is a leading cause of delirium in hospital settings.[107, 112] It is not possible in this paper to review all the potential pharmacologic precipitants of encephalopathy. According to Lipowski, "Practically every drug listed in the pharmacopeia may occasionally induce delirium in a susceptible individual."[16] Lists of drugs that cause mental status changes are available,[113] and side effects of confusion are reported in standard drug references.[114]

Drugs may induce delirium when present in toxic serum levels as a result of excessive ingestion or impaired clearance, or when present in therapeutic or nontoxic levels in susceptible patients.[115] The major classes of drugs implicated in delirious states are anticholinergic agents[32, 35, 116]; narcotic and nonnarcotic analgesics, including nonsteroidal antiinflammatory agents[96, 117-120]; sedative-hypnotics[121-123]; steroids[124-126]; H_2-receptor blockers[94, 95, 97]; antibiotics[127-130]; cardiovascular drugs,[131, 132] and antihypertensives.[133, 134] Not all drugs within a particular class have the same propensity to produce delirium. Meperidine, for instance, produces central nervous system excitatory effects, including restlessness, myoclonus, and mood changes, more frequently than other opiates due to the accumulation of the metabolite, normeperidine.[135] Benzodiazepines in therapeutic doses only rarely produce paradoxical agitation and confusion, except in the setting of withdrawal.[16, 121] However, short-acting agents, such as triazolam, have been more commonly linked to acute confusional and amnestic states. This may be because their rapid clearance produces a withdrawal state shortly after a single dose,[136] or because of an excitatory effect of the triazolo side-group.[137]

Study of drug-induced delirium is complicated by the multiple medical problems that delirious patients possess. In cases of antibiotic-associated delirium, for instance, it may be difficult to determine whether infections or drugs led to the acute confusional states. Strict criteria for the assessment of adverse drug reactions are available,[138, 139] but have only been used in the assessment of chronic cognitive impairment,[140] and not for delirium.

Dementia

Demented elderly are at risk for acute behavioral changes both at home and in institutional settings. Studies have linked cognitive impairment on admission to the hospital with higher risk for subsequent acute confusion.[65, 67, 112] Radiologic evaluation of patients with acute confusional states often reveals chronic structural brain diseases, such as cortical atrophy and infarction.[141] Finally, sudden onset of disturbed behavior in patients with known dementia is often due to delirium. O'Connor, for instance, reported that almost half of elderly demented patients admitted to a psychogeriatric unit because of disturbed behavior had either acute medical illness or drug toxicities underlying their deterioration.[80]

Oncology

Cancer patients have been found to have a high prevalence of adjustment disorders, depression, and delirium.[141, 143] Consulting psychiatrists have also noted high rates of delirium and other organic mental disorders among referred oncology patients, up to 40% in one survey.[144] Such patients may be misdiagnosed as "depressed" by the referring physicians.[145] Furthermore, delirium is often a preterminal event.[146] One study of 106 patients reported a 67% in-hospital mortality rate for delirious cancer patients, compared with 5% mortality for non-delirious cancer patients.[145]

Etiologies for delirium in cancer patients cover a wide range of medical illnesses and drugs. Only rarely are central nervous system metastases implicated.[144] Chemotherapy has been associated with cognitive impairment,[147, 148] although this may be an unmasking of prior dementia.[149] Finally, narcotic analgesics are often used to control the pain of widespread cancer. Whereas in young patients receiving narcotics, sedation is commonly observed, older patients more frequently manifest delirium.[117]

Cerebrovascular Diseases

Dunne found that of 661 patients presenting with stroke, 19 (3%) had predominantly acute mental status changes.[150] Other neurological signs were absent or minimal and thus were easily missed, but careful neurological examinations, CT scans, or autopsies confirmed recent strokes. Most lesions were right-sided cortical infarctions, usually in the middle cerebral artery territory,[150] similar to prior case reports.[151-153] Less commonly reported are left-sided posterior cerebral artery territory infarctions,[154] right thalamic infarctions,[155] and medial temporo-occipital infarctions.[156, 157] The resemblance to delirium may be due to involvement of cortical attention centers.[14]

Sensory Deprivation

The experiences of explorers, shipwrecked individuals, and prisoners of war testify to the behavioral effects of prolonged periods of social and sensory isolation, which include disorientation, hallucinations, delusions, and depression.[158] Early experiments demonstrated that normal subjects deprived of orienting stimuli develop similar abnormalities, as well as EEG slowing.[159]

Behavioral effects of sensory deprivation have been seen in clinical settings (e.g., poliomyelitis patients treated in tank-type respirators and intensive care unit patients).[16] Wilson found that postoperative delirium in an intensive care unit without windows was twice that in one with windows.[160] However, it was not certain whether patients in the two settings were comparable, or whether nursing ascertainments of confusion were similar.

Nocturnal delirium ("sundowning") is believed to be related to sensory deprivation. Cameron produced delirium by placing demented patients in a dark room during the day.[161] He hypothesized that orientation to surroundings in cognitively impaired patients was more dependent upon vision than is that in normal individuals who can better remember location and time. He demonstrated in an uncontrolled study that his patients' spatial images of their surroundings deteriorated rapidly with blindfolding.

Sundowning has not been systematically studied in hospital settings. Acute illnesses that themselves can produce delirium confound analysis of the separate effect of nocturnal sensory deprivation among general medical patients. Chronic-care settings, on the other hand, are better suited for studies of sundowning and sensory deprivation. In one study of nursing home patients, Evans found that 11 of 89 subjects (12%) regularly developed nocturnal confusion.[162] These patients were more cognitively impaired and had resided in their rooms for shorter periods of time than controls. Medications and sensory impairments were not different from those in controls, and sundowners appeared to have fewer ongoing medical problems. It is not certain, however, whether these patients would have met DSM-III-R criteria for delirium.

These data suggest that nocturnal sensory deprivation is not sufficient alone to account for delirium. Prior cognitive impairment, a recent change in environ-

ment, and coexisting metabolic stress appear to be necessary cofactors.

Sensory Impairment

Visual and hearing impairments affect as many as 40% of hospitalized elderly.[58] Although delirium has been related to such impairments,[163] only one prevalence study[51] showed a small excess of visual and auditory impairment in acutely confused geriatric patients. Furthermore, both chronic cognitive impairment[164] and social isolation often accompany sensory loss.[165] These variables, rather than sensory ability per se, may account for the predisposition to delirium.

Sensory impairment may also lead to hallucinations in the elderly without necessarily producing delirium. Charles Bonnet first described the relationship of visual impairment to hallucinations in 1760, and recent reports confirm his original observation.[166-169] Berrios found visual hallucinations in 30% of 150 geropsychiatric referrals.[169] Patients with hallucinations were more likely to have delusions and eye disorders, but were not more cognitively impaired than controls.

Thus, sensory impairment is common in hospitalized elderly, but its relationship to delirium is not clear.[6] Poor vision or hearing facilitates the formation of hallucinations, misperceptions, and delusions, but may not be responsible for the global attention deficit that is the hallmark of delirium. Research on clinical sensory deprivation is hampered by the difficulty in separating the effect of sensory deprivation from those of other variables such as physical illness, drugs, psychologic stress, dementia, immobilization, and social isolation.[159]

Postoperative Delirium

Most instances of "postoperative psychosis" in the elderly are believed to be cases of delirium and can be diagnosed using DSM-III-R criteria.[170-174] Delirium is one of the most frequent diagnoses made by consultant psychiatrists in surgical settings,[175] and can manifest subtly, such as with a mood disturbance that might be mistaken for depression.[172] Postoperative delirium leads to prolonged hospital stays, higher mortality, and greater need for long-term care after discharge.[174, 175]

Studies of the incidence and prevalence of delirium in surgical settings share the same methodologic difficulties discussed previously (Table 6). In addition, the variety of surgical procedures creates problems of comparison. Delirium has been reported to occur in 5 to 15% of postcatarectomy patients,[176] for instance, but in over 50% of elderly patients undergoing hip surgery.[67, 174] Trends in surgical practice also influence rates of delirium. A fall in the rates reported for postcardiotomy delirium, for instance, has been attributed to shorter times spent on cardiopulmonary bypass and to improved hemodynamic monitoring.[177, 178] In general surgical settings, rates of delirium appear to be between 10 and 15%.[171, 179]

The etiology of delirium in the postoperative setting is multifactorial. Morse, in comparing 60 cases of postoperative delirium with controls matched for age, sex, and type of surgery, found that metabolic abnormalities, cardiovascular complications, infections, intoxications, polypharmacy, preoperative sensory disturbances, and dementia were more prevalent among cases.[170] Prolonged procedure time and emergency surgery were also more common among delirious pa-

TABLE 6

Rates of Postoperative Confusion in Recent Prospective Studies of Elderly

Reference	Population	Definition of Confusion	Monitoring	Rate	Risk Factor(s) for Confusion
Millar, 1981[171]	Elective surgery, age over 65 ($n = 100$)	"Clouding of consciousness" and disorientation	Interview and daily review of nurses' notes	14%	Medical complications, use of morphine
Seymour and Pringle, 1983[179]	General surgery, age over 65 ($n = 258$)	Not given	Not specified	9.7%	Male sex, advanced age
Williams et al., 1985[67]	Hip fracture, age over 60 ($n = 170$)	Behaviors cited by unit nurses	Daily ratings by nurses	51.5%	Age, poor performance on preop mental status test, pre-injury function
Calabrese et al., 1987[178]	Coronary bypass, ages 40–75 ($n = 59$)	DSM-III	Pre- and postoperative neuropsychologic testing	6.8%	Not examined
Gustafson et al., 1988[174]	Hip fracture, age over 65 ($n = 111$)	DSM-III	Daily observations	28%	Anticholinergic drugs, age, dementia, depression, hypotension

tients. In a prospective study of 100 elderly patients undergoing elective general surgery, postoperative confusion was associated with medical complications of surgery and with greater use of opiate analgesics.[171]

Among cardiac surgery patients, postoperative complications, low cardiac output, severity of preoperative illness, preoperative organic brain disease and depression, and time spent in the ICU have been reported to be associated with delirium.[179-183] In patients undergoing hip surgery, age, preoperative mental status, prior functional level, use of anticholinergic drugs, and depression were predictors of delirium.[67, 174] Thus, both preoperative chronic illnesses and postoperative complications contribute to delirium.

In contrast, the choice of anesthetic appears to have little effect on postoperative delirium. One early report noted that epidural anesthesia produced less decline in mental status among patients undergoing hip surgery.[184] However, patients in this study who underwent general anesthesia had lower postoperative Po_2 and received larger doses of atropine than those undergoing epidural anesthesia. Subsequent studies of hip surgery patients revealed no difference in risk of delirium between general anesthesia and epidural anesthesia.[185, 186]

Alcohol and Sedative Drug Withdrawal

Abrupt withdrawal from alcohol and other sedative drugs may produce a wide spectrum of psychiatric manifestations ranging from irritability, tremor, sleep disturbance, and autonomic arousal to a full-blown hyperactive delirium.[187, 188] Alcohol abuse is frequently overlooked by clinicians caring for the elderly,[189] yet alcohol-withdrawal delirium appears to be as common in elderly alcoholics as in their younger counterparts,[190] and has higher mortality in the aged—up to 27% in one series.[191]

Sedative–hypnotic drugs, particularly benzodiazepines, are commonly used by the elderly. In one small prospective study, abrupt discontinuation of benzodiazepines was associated with nearly a fourfold increased risk for confusion and disorientation. Of interest, none of the confused patients demonstrated autonomic manifestations of withdrawal.[121] This atypical presentation of sedative drug withdrawal makes recognition of the problem more difficult.

Other Factors

Other conditions have been associated with delirium, including urinary retention, fecal impaction, new environment, pain, sleep deprivation, and dehydration.[55, 163] The exact relationship of these conditions to delirium can be difficult to ascertain. For instance, sleep deprivation may be associated with delirium because sedative–hypnotic medications used to treat insomnia produce delirium. An alternative possibility is that asleep–wake disturbances may be the initial manifestation of delirium due to another medical illness.[16] Similarly, dehydration may either cause, or be a result of, acute confusion. Delirious patients often have these conditions, but typically other acute medical problems are also present.[192]

MANAGEMENT

The cornerstones of the clinical management of delirium are prompt recognition of the condition, diagnosis and treatment of the specific underlying etiology, management of agitation and disruptive behavior, and provision of general supportive care.[10-12] Managing delirium is one of the most challenging problems facing the physician who cares for the elderly. Prompt recognition and response are vital to return the patient to his or her previous level of functioning. Because of the broad spectrum of potential underlying etiologies, no simple algorithm can substitute for the expertise of the general internist.

The process begins with history, physical examination, mental status testing, interview of capable informants, and review of all recently administered medications. Physicians must vigorously diagnose and treat underlying conditions. Drugs that may produce confusion should be eliminated unless absolutely necessary. Common metabolic problems and fluid/electrolyte disturbances can be ascertained using a modest degree of laboratory testing, and should be corrected without delay.

Many ancillary diagnostic tests, including brain imaging, have been suggested in the evaluation of delirium.[193] No studies have addressed their yield for evaluating mental status changes. Brain imaging often uncovers preexisting central nervous system diseases that may have predisposed to delirium[141, 163]; a comprehensive medical evaluation is still needed to identify the precipitating illness, which usually is outside the nervous system.[107]

The delirious patient can be at times so agitated, assaultive, and disruptive of care that prompt symptomatic control is vital to prevent harm to the patient or others, and to institute evaluation and treatment. The ideal drug for controlling agitation in medical patients should be calming and sedating without causing worsening of delirium. It should abolish psychotic manifestations without anticholinergic or extrapyramidal side effects. A parenteral form should be available. Finally, it should not lead to hypotension, cardiac arrhythmias, or respiratory depression.[12]

No such ideal drug has yet been found. Recommendations have been based on clinical experience rather than controlled trials, and have been influenced by availability and habit. In the past, sedatives such as chloral hydrate were the preferred drugs for control-

ling agitation in medical patients.[194] In the 1960s, the antipsychotic chlorpromazine was the drug of choice despite a relatively high incidence of anticholinergic effects and orthostatic hypotension.[195] Presently, for short-term management of agitation and psychotic features, haloperidol is generally accepted as safe and reliable because it is potent and low in anticholinergic and hypotensive effects. In elderly patients, a dose of 0.5–2.0 mg, repeated in 30 minutes if necessary, appears to be well tolerated, even when given intravenously.[196] Controlled studies, however, do not support the efficacy of haloperidol, or any other neuroleptic, for the long-term management of elderly, agitated patients.[197]

Haloperidol, unfortunately, has strong extrapyramidal effects that can contribute to immobility and falling, and can produce an akathisia that may mimic the restless agitation of delirium.[195] Neuroleptic malignant syndrome (NMS), a potentially lethal disorder consisting of fever, muscle rigidity, altered consciousness, and elevated creatine phosphokinase, is perhaps the most feared complication of the use of haloperidol and similar potent agents.[198] NMS has been reported to occur in the elderly even with short-term use of neuroleptics for delirium and agitative behavior.[199-201] Of particular concern is a recent meta-analysis of published cases that suggested that a rapid increase in neuroleptic dosing for control of acute agitation was a principal risk factor for NMS.[202]

Benzodiazepines are effective in the treatment of drug and alcohol withdrawal, and are useful as adjuncts to haloperidol to blunt extrapyramidal side effects and promote sedation.[196] One protocol used to treat delirium in critically ill patients suggested combining intravenous haloperidol with 0.5–1 mg of intravenous lorazepam, repeated at hourly intervals until the patient is calmed.[203]

Psychotropic agents do not reverse the underlying abnormalities of cerebral function that produce delirium and are contraindicated in patients who are drowsy or unarousable. In effective doses, they may produce delirium themselves. Their use, therefore, should be short-term and limited to those patients whose agitation seriously interferes with their care.

One drug that does specifically address a mechanism of delirium is physostigmine, which, when given slowly in 1- or 2-mg doses intravenously, can temporarily reverse delirium due to central anticholinergic toxicity.[116] A rapid response is virtually diagnostic of anticholinergic intoxication. Physostigmine has a short half-life compared with most anticholinergic drugs, and dosing may need to be repeated at 30-minute intervals, or, alternatively, it can be given as a continuous infusion.[204] The toxicity of physostigmine is due to excessive cholinergic stimulation and includes increased airway secretions, dyspnea, bronchospasm, emesis, diarrhea, abdominal colic, and bradycardia. Cardiac and respiratory monitoring, ideally in an intensive care setting, are mandatory, and cholinergic hyperstimulation can be counteracted with administration of anticholinergic medications, such as glycopyrrolate, that do not cross the blood–brain barrier.[116, 205] Since most cases of anticholinergic toxicity can be treated by removal of the offending agent and traditional supportive care, the use of physostigmine should be limited to severe cases of delirium with stable cardiac and respiratory function.

Supportive care of the delirious patient includes sound medical management, environmental measures, and psychosocial support. Cognitively impaired elderly are at risk for fluid and electrolyte disturbances, aspiration, malnutrition, decubitus ulcers, joint contractures, and other complications of immobility and depressed consciousness.[206] The prevention and management of these conditions are important and are already well described.[207, 208] An important component of general medical management of the elderly is the comprehensive assessment of physical and psychosocial functions. Chronic cognitive and functional impairments are commonly seen in delirious patients,[209] and delirium may be a marker of underlying frailty. Knowledge of the patient's previous functional state can identify those elderly at risk for deterioration during their hospitalization.

Family and staff can optimize the patient's environment by retrieving eyeglasses and hearing aids; minimizing abrupt relocations; providing orienting stimuli such as calendars, clocks, or familiar items from home; and leaving dim lights on at night to decrease frightening illusions.[163] Although bedrails and restraints are commonly used for agitated patients,[210, 211] there is no evidence of their efficacy. Furthermore, vest restraints have caused death from accidental strangulation and may contribute to atelectasis, pneumonia, and decubitus ulcers.[212] However, shortages of personnel, particularly at night, as well as concerns about liability should patients injure themselves, may necessitate restrictive devices.

Other disciplines, such as social work and nursing, should assist in the assessment and management. In particular, long-term care strategies may need to be devised for patients who have become dependent in physical and cognitive function and may not have completely recovered their previous functional levels. Decisions about institutionalization should be made cautiously, however, since the patient's hospital behavior may not accurately reflect function when stable and compensated in a familiar home environment, and delirium may be slow to resolve.

Finally, medical–legal issues may complicate the treatment of delirium. The use of restraints and psychoactive medications in agitated patients constitutes a form of involuntary treatment that is common in general medical hospitals.[213] Although civil commitment procedures are generally used in the involuntary treat-

ment of behaviorally disturbed patients in psychiatry, they are not considered necessary or appropriate for delirium. Since delirium constitutes a true medical emergency, the doctrine of "implied consent" appears adequate to institute diagnostic and therapeutic measures.[214]

REFERENCES

1. Larson EB, Lo B, Williams ME. Evaluation and care of elderly patients with dementia. J Gen Intern Med. 1986;1:116-126.
2. Greene JG, Smith R, Gardiner M, Timbury GC. Measuring behavioural disturbance of elderly demented patients in the community and its effects on relatives: a factor analytic study. Age Ageing. 1982;11:121-126.
3. Cohen-Mansfield J, Billig N. Agitated behaviors in the elderly. I: A conceptual review. J Am Geriatr Soc. 1986;34:771-721.
4. Cohen-Mansfield J. Agitated behaviors in the elderly. II: Preliminary results in the cognitively deteriorated. J Am Geriatr Soc. 1986;34:722-727.
5. Knopman DS, Kitto J, Deinard S, Heiring J. Longitudinal study of death and institutionalization in patients with primary degenerative dementia. J Am Geriatr Soc. 1988;36:108-112.
6. Lipowski ZJ. Delirium (acute confusional states). In: Vinken PJ, Bruyn GW, Klawans HL, Fredericks JAM, eds. Handbook of Clinical Neurology, revised series, V.2. New York: Elsevier Science Pub. 1985:523-59.
7. Wolfe HG, Curran D. Nature of delirium and allied states. Arch Neurol Psychiatr. 1935;33:1175-1215.
8. Engel GL, Romano J. Delirium, a syndrome of cerebral insufficiency. J Chron Dis. 1959;9:260-277.
9. Berrios GE. Delirium and confusion in the 19th century: a conceptual history. Br J Psychiatr. 1981;139:439-49.
10. Lipowski ZJ. Transient cognitive disorders (delirium, acute confusional states) in the elderly. Am J Psychiatr. 1983;140:1426-1436.
11. Liston EH. Delirium in the aged. Psychiatr Clin North Am. 1982;5:49-66.
12. Wise MG. Delirium. In: Hales RE, Yudofsky SC, eds. Textbook of Neuropsychiatry. Washington, D.C.: American Psychiatric Press; 1987:89-103.
13. Diagnostic and Statistical Manual, third edition, revised. Washington, D.C.: American Psychiatric Association; 1987.
14. Geschwind N. Disorders of attention; a frontier in neuropsychology. Phil Trans R Soc Lond B. 1982;298:173-185.
15. Adams RD, Victor M. Principles of Neurology, 2nd. ed. New York: McGraw-Hill Book Co.; 1981:275-76.
16. Lipowski ZJ. Delirium: Acute Brain Failure in Man. Springfield, Ill: Charles C Thomas, 1980.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-198.
18. Jacobs JW, Bernhard MR, Delgado A, Strain JJ. Screening for organic mental syndromes in the medically ill. Ann Intern Med. 1977;86:40-46.
19. Nelson A, Fogel BS, Faust D. Bedside cognitive screening instruments: a critical assessment. J Nerv Ment Dis. 1986;174:73-83.
20. Kaufman DM, Weinberger M, Strain JJ, Jacobs JW. Detection of cognitive deficits by a brief mental status examination: the cognitive capacity screening examination, a reappraisal and a review. Gen Hosp Psychiatr. 1979:247-255
21. Anthony JC, LeResche L, Niaz U, von Korff MR, Folstein MF. Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. Psychol Med. 1982;12:397-408.
22. Reitan RM. Validity of the trailmaking test as an indicator of organic brain damage. Percept Motor Skills. 1985;8:271-76.
23. Pauker NE, Folstein MF, Moran TH. The clinical utility of the hand-held tachistoscope. J Nerv Ment Dis. 1978;166:126-129.
24. Conn HO. Trailmaking and number-connection tests in the assessment of mental state in portal systemic encephalopathy. Dig Dis. 1977;22:541-50.
25. Conn HO, Lieberthal MM. Assessment of mental state. In: The Hepatic Coma Syndromes and Lactulose. Baltimore: Williams and Wilkins, 1979:169-188.
26. Trzepacz PT, Maue FR, Coffman G, van Theil DH. Neuropsychiatric assessment of liver transplantation candidates: delirium and other psychiatric disorders. Int J Psychiatr Med. 1986;16:101-111.
27. Anthony JC, LeResche LA, Von Korff MR, Niaz U, Folstein MF. Screening for delirium on a general medical ward: The tachistoscope and a global accessibility rating. Gen Hosp Psychiatr. 1985;7:36-42.
28. Pro JD, Wells CE. The use of the electroencephalogram in the diagnosis of delirium. Dis Nerv Syst. 1977;38:804-808.
29. Obrecht R, Okhomina FOA, Scott DF. Value of EEG in acute confusional states. J Neurol Neurosurg Psychiatr. 1979; 42:75-77.
30. Lipowski ZJ. Delirium (acute confusional states). JAMA. 1987;258:1789-92.
31. Romano J, Engel GL. Delirium I: Electroencephalographic data. Arch Neurol Psychiatr. 1944;51:356-377.
32. Itil T, Fink M. Anticholinergic drug-induced delirium: experimental modification, quantitative EEG and behavioral correlations. J Nerv Ment Dis. 1966;143:492-507.
33. Brenner RP. The electroencephalogram in altered states of consciousness. Neurol Clin. 1985;3:615-31.
34. Karnaze DS, Bickford RG. Triphasic waves: a reassessment of their significance. Electroencephal Clin Neurophys. 1984; 57:193-198.
35. Obrist WD. Electroencephalographic changes in normal aging and dementia. In: Hoffmeister F, Mhuller C, eds. Brain Function in Old Age. New York: Springer-Verlag, 1979:102-111.
36. Soininen H, Partanen JV, Puranen M, Riekkinen PJ. EEG and computed tomography in the investigation of patients with senile dementia. J Neurol Neurosurg Psychiatr. 1982; 45:711-714.
37. Giaquinto S, Nolfe G. The EEG in the normal elderly: a contribution to the interpretation of aging and dementia. Electroenceph Clin Neurophys. 1986;63:540-546.
38. Dubin WR, Weiss KJ, Zeccardi JA. Organic brain syndrome: the psychiatric imposter. JAMA. 1983;249:60-62.
39. Daniel DG, Rabin PL. Disguises of delirium. Southern Med J. 1985;78:666-672.
40. McEvoy JP. Organic brain syndromes. Ann Intern Med. 1981;95:212-220.
41. Goldney R. Pseudodelirium. Med J Aust. 1979;1:630.
42. Carlson GA, Goodwin FK. The stages of mania. Arch Gen Psychiatr. 1973;28:221-228.
43. Bond TC. Recognition of acute delirious mania. Arch Gen Psychiatr. 1980;37:553-554.
44. Cummings JL. Organic delusions: phenomenology, anatomical correlations, and review. Br J Psych. 1985;146:184-197.
45. Berrios GE, Brook P. Delusions and the psychopathology of the elderly with dementia. Acta Psychiatr Scand. 1985; 72:296-301.
46. Cummings JL, Miller BL. Visual hallucinations: clinical occurrence and use in differential diagnosis. West J Med. 1987;146:46-51.
47. Ellis JM, Lee SI. Acute prolonged confusion in later life as an ictal state. Epilepsia. 1978;19:119-28.
48. Dunne JW, Summers QA, Stewart-Wynne EG. Non-convulsive status epilepticus: a prospective study in an adult general hospital. Q J Med. 1987;63:117-26.
49. Treiman DM, Delgado-Escueta AV. Complex partial status epilepticus. Adv Neurol. 1983;34:69-81.
50. Rosin AJ, Boyd RV. Complications of illness in geriatric patients in hospital. J Chron Dis. 1966;19:307-313.
51. Hodkinson HM. Mental impairment in the elderly. J Roy Coll Phys Lond. 1973;7:305-317.
52. Lowy FH, Engelsmann F, Lipowski ZJ. Study of cognitive functioning in a medical population. Compr Psychiatr. 1973; 14:331-338.
53. Bergman K, Eastham EJ. Psychogeriatric ascertainment and assessment for treatment in an acute medical ward setting. Age Ageing. 1974;3:174-188.
54. Henker FO. Acute brain syndromes. J Clin Psychiatr. 1979;40:117-120.
55. Seymour DG, Henschke PJ, Cape RDT, Campbell AJ. Acute con-

fusional states and dementia in the elderly: the role of dehydration/volume depletion, physical illness and age. Age Ageing. 1980;9:137-146.
56. Chisholm SE, Deniston OL, Igrisan RM, Barbus AJ. Prevalence of confusion in elderly hospitalized patients. J Gerontol Nurs. 1982;8:87-95.
57. Gillick MR, Serrell NA, Gillick LS. Adverse consequences of hospitalization in the elderly. Soc Sci Med. 1982; 16:1033-1038.
58. Warshaw GA, Moore JT, Friedman SW, Currie CT, Kennie DC, Kane WJ. Functional disability in the hospitalized elderly. JAMA. 1982;248:847-850.
59. Fields SD, MacKenzie CR, Charlson ME, Perry SW. Reversibility of cognitive impairment in medical inpatients. Arch Intern Med. 1986;146:1593-1596.
60. Fields SD, MacKenzie CR, Charlson ME, Sax FL. Cognitive impairment: can it predict the course of hospitalized patients? J Am Geriatr Soc. 1986;34:579-585.
61. Cameron DJ, Thomas TI, Mulvihill M, Bronheim H. Delirium: a test of the Diagnostic and Statistical Manual III criteria on medical inpatients. J Am Geriatr Soc. 1987;35:1007-1010.
62. Gehi M, Strain JJ, Weltz N, Jacobs J. Is there a need for admission and discharge cognitive screening for the medically ill? Gen Hosp Psychiatr. 1980;3:186-191.
63. Cavanaugh SVA. The prevalence of emotional and cognitive dysfunction in a general medical population: using the MMSE, GHQ, and BDI. Gen Hosp Psychiatr. 1983;15-24.
64. Litovitz GL, Hedberg M, Wise TN, White JD, Mann LS. Recognition of psychological and cognitive impairments in the emergency department. Am J Emerg Med. 1985;3:400-402.
65. McCartney JR, Palmateer LM. Assessment of cognitive deficit in geriatric patients: a study of physician behavior. J Am Geriatr Soc. 1985;3:467-471.
66. Perez E, Silverman M. Delirium: the often overlooked diagnosis. Int J Psychiatr Med. 1984;14:181-188.
67. Williams MA, Campbell EB, Raynor WJ, Musholt MA, Mlynarczyk SM, Crane LF. Predictors of acute confusional states in hospitalized elderly patients. Res Nurs Health. 1985;8:31-40.
68. Roth M. The natural history of mental disorder in old age. J Ment Sci. 1955;101:281-301.
69. Kay DWK, Norris V, Post F. Prognosis in psychiatric disorders of the elderly: an attempt to define indicators of early death and early recovery. J Ment Sci. 1956;120:129-140.
70. Guze SB, Cantwell DP. The prognosis in "organic brain" syndromes. Am J Psychiatr. 1964;120:878-881.
71. Guze SB, Daengsurisri S. Organic brain syndromes: prognostic significance in general medical patients. Arch Gen Psychiatr. 1967;17:365-366.
72. Rabins PV, Folstein MF. Delirium and dementia: diagnostic criteria and fatality rates. Br J Psychiatr. 1982;140:149-153.
73. Weddington WW. The mortality of delirium: an underappreciated problem? Psychosomatics. 1982;23:1232-1235.
74. Trzepacz PT, Teague GB, Lipowski ZJ. Delirium and other organic mental disorders in a general hospital. Gen Hosp Psychiatr. 1985;7:101-106.
75. Black DW, Warrack G, Winokur G. The Iowa record-linkage study. II. Excess mortality among patients with organic mental disorders. Arch Gen Psychiatr. 1985;42:78-81.
76. Charlson ME, Sax FL, MacKenzie R, Fields SD, Braham RL, Douglas RG. Assessing illness severity: does clinical judgment work? J Chronic Dis. 1986;39:439-452.
77. MacKenzie TB, Popkin MK. Stress response syndrome occurring after delirium. Am J Psychiatr. 1980;137:1433-35.
78. Blank K, Perry S. Relationship of psychological processes during delirium to outcome. Am J Psychiatr. 1984;141:843-847.
79. Lamont CT, Sampson S, Matthias R, Kane R. The outcome of hospitalization for acute illness in the elderly. J Am Geriatr Soc. 1983;31:282-288.
80. O'Connor M. Disturbed behaviour in dementia — psychiatric or medical problem? Med J Aust. 1987;147:481-485.
81. Bedford PD. General medical aspects of confusional states in elderly people. Br Med J. 1959;2:185-188.
82. Morse RM, Litin EM. The anatomy of a delirium. Amer J Psychiat. 1971;128:111-116.
83. Blass JP, Gibson GE. Carbohydrates and acetylcholine synthesis: Implications for cognitive disorders. In: Davis KL, Berger PA, eds. Brain Acetylcholine and Neuropsychiatric Disease. New York: Plenum Press; 1979;215-236.
84. Blass JP, Plum F. Metabolic encephalopathies in older adults. In Katzman R, Terry RD, eds. The Neurology of Aging. Philadelphia: FA Davis Co.; 1983:189-220.
85. Brizer DA, Manning DW. Delirium induced by poisoning with anticholinergic agents. Am J Psychiatr. 1982;139:1343-1344.
86. Tune LE, Holland A, Folstein MF, Damlouji NF, Gardner TJ, Coyle JT. Association of postoperative delirium with raised serum level of anticholinergic drugs. Lancet. 1981;2:651-652.
87. Miller PS, Richardson JS, Jyu CA, Lemay JS, Hiscock M, Keegan DL. Association of low serum anticholinergic levels and cognitive impairment in elderly presurgical patients. Am J Psychiatr. 1988;145:342-45.
88. Mondimore FM, Damlouji N, Folstein MF, Tune L. Post-ECT confusional states associated with elevated serum anticholinergic levels. Am J Psychiatr. 1983;140:930-31.
89. Tune LE, Straus ME, Lew MF, Breitlinger E, Coyle JT. Serum levels of anticholinergic drugs and impaired recent memory in chronic schizophrenic patients. Am J Psychiatr. 1982; 139:1460-1462.
90. Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. Am J Psychiatr. 1987;144:1218-1220.
91. Bartus, RT, Dean RL, Beer G, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. Science. 1982;217: 408-417.
92. Katzman R. Alzheimer's disease. N Engl J Med. 1986; 314:964-973.
93. Blazer DG, Federspiel CF, Ray WA, Schaffner W. The risk of anticholinergic toxicity in the elderly: a study of prescribing practices in two populations. J Gerontol. 38:31-35.
94. Goff DC, Garber HJ, Jenike MA. Partial resolution of ranitidine-associated delirium with physostigmine: case report. J Clin Psychiatr. 1985;46:400-401.
95. Weddington WW, Muelling AE, Moosa HH. Adverse neuropsychiatric reactions to cimetidine. Psychosomatics. 1982; 23:49-53.
96. Eisendrath SJ, Goldman B, Douglas J, Dimatteo L, van Dyke C. Meperidine-induced delirium. Am J Psychiatr. 1987;144: 1062-1065.
97. Mogelnicki SR, Wallen JL, Finlayson DC. Physostigmine reversal of cimetidine-induced mental confusion. JAMA. 1979;241:826-827.
98. Kanba S, Richelson E. Antimuscarinic effects of lithium. N Engl J Med. 1984;310:989-90.
99. McIntosh TK, Bush HL, Yeston NS, et al. Beta-endorphin, cortisol and post-operative delirium: a preliminary report. Psychoneuroendocrinology. 1985:10:303-313.
100. Brambilla F, Zarattini F, Gianelli A, Bianchi M, Panerai A. Plasma opioids in alcoholics after acute alcohol consumption and withdrawal. Acta Psychiatr Scand. 198;77:63-66.
101. Check WA. Endorphin-mental illness link far from proved. JAMA. 1982;247:570-77.
102. Allen D, Beckmann H, Ackenheil M, Markianos M. Biochemical investigations into the alcoholic delirium: alterations of biogenic amines. Arch Psychiat Nervenkr. 1977;224:129-140.
103. Krueger JM, Walter J, Dinarello CA, Wolff SM, Chedid L. Sleep-promoting effects of endogenous pyrogen (interleukin-1). Am J Physiol. 1984;246:R994-R999.
104. Steel K, Gertman PM, Crescenzi C, Anderson J. Iatrogenic illness on a general medical service at a university hospital. N Engl J Med. 1981;304:636-642.
105. Steel K. Iatrogenic disease on a medical service. J Am Geriatr Soc. 1984;32:445-449.
106. Jahnigen D, Hannon C, Laxson L, LaForce FM. Iatrogenic disease in hospitalized elderly veterans. J Am Geriatr Soc. 1982; 30:387-390.
107. Moses H, Kaden I. Neurologic consultations in a general hospital: spectrum of iatrogenic disease. Am J Med. 1986; 81:955-958.
108. Patterson C. Iatrogenic disease in late life. Clin Geriatr Med. 1986;2:121-136.
109. Pathy MS. Clinical presentation of myocardial infarction in the elderly. Br Heart J. 1967;29:190-199.
110. Bayer AJ, Chadha JS, Farag RR, Pathy MSJ. Changing presentation

of myocardial infarction with increasing old age. J Am Geriatr Soc. 1986;34:263-66.
111. Flint FJ, Richards SM. Organic basis of confusional states in the elderly. Br Med J. 1956;2:1537-1539.
112. Purdie FR, Honigman B, Rosen P. Acute organic brain syndrome: a review of 100 cases. Ann Emer Med. 1981; 10:455-461.
113. Drugs that cause psychiatric symptoms. Med Letter Drugs Therapeut. 1986;28:81-86.
114. American Hospital Formulary Service. Drug Information 88. Bethesda, MD: American Society of Hospital Pharmacists; 1988.
115. Danielczyk W. Pharmacotoxic psychoses in patients with neurological disorders in old age. Adv Neurol. 1984;40:285-288.
116. Granacher RP, Baldessarini RJ. Physostigmine: its use in acute anticholinergic syndrome with antidepressant and antiparkinson drugs. Arch Gen Psychiatr. 1975;32:375-80.
117. Leipzig RM, Goodman H, Gray G, Erle H, Reidenberg MM. Reversible, narcotic-associated mental status impairment in patients with metastatic cancer. Pharmacology. 1987;35:47-54.
118. Goodwin JS, Regan M. Cognitive dysfunction associated with naproxen and ibuprofen in the elderly. Arthr Rheum. 1982;25:1013-1015.
119. Sotsky SM, Tossell JW. Tolmetin induction of mania. Psychosomatics. 1984;25:626-628.
120. Steele TE, Morton WA. Salicylate-induced delirium. Psychosomatics. 1986;27:455-456.
121. Foy A, Drinkwater V, March S, Mearrick P. Confusion after admission to hospital in elderly patients using benzodiazepines. Br Med J. 1986;293:1072.
122. Paterson JF. Triazolam syndrome in the elderly. South Med J. 1987;80:1425-1426.
123. Berlin RM. Management of insomnia in hospitalized patients. Ann Intern Med. 1984;100:398-404.
124. Glaser GH. Psychotic reactions induced by corticotropin (ACTH) and cortisone. Psychosom Med. 1953;15:280-291.
125. Hall RCW, Popkin MK, Stickney SK, Gardner ER. Presentation of the steroid psychoses. J Nerv Ment Dis. 1979;167:229-236.
126. Ling MHM, Perry PJ, Tsuang MT. Side effects of corticosteroid therapy. Arch Gen Psychiatr. 1981;38:471-477.
127. Kane FJ, Byrd G. Acute toxic psychosis associated with gentamicin therapy. South Med J. 1974;68:1283-1285.
128. Byrd G. Acute organic brain syndrome associated with gentamycin therapy. JAMA. 1977;238:53-54.
129. McCartney CF, Hatley LH, Kessler JM. Possible tobramycin delirium. JAMA. 1982;247:1319.
130. Snavely SR, Hodges GR. The neurotoxicity of antibacterial agents. Ann Intern Med. 1984;101:92-104.
131. Saravay SM, Marke J, Steinberg MD, Rabiner CJ. "Doom Anxiety" and delirium in lidocaine toxicity. Am J Psychiatr. 1987;144:159-163.
132. Trohman RG, Castellanos D, Castellanos A, Kessler KM. Amiodarone-induced delirium. Ann Intern Med. 1988;108:68-69.
133. Gershon ES, Goldstein RE, Moss AJ, van Kammen DP. Psychosis with ordinary doses of propranolol. Ann Intern Med. 1979;90:938-939.
134. Paykel ES, Fleminger R, Watson JP. Psychiatric side effects of antihypertensive drugs other than reserpine. J Clin Psychopharmacol. 1982;2:14-39.
135. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol. 1983;13:180-85.
136. Morgan K, Oswald I. Anxiety caused by a short-life hypnotic. Br Med J. 1982;284:942.
137. Weilburg JB, Sachs G, Falk WE. Triazolam-induced brief episodes of secondary mania in a depressed patient. J Clin Psychiatr. 1987;48:492-493.
138. Kramer MS, Leventhal JM, Hutchinson MB, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I: Background, description, and instructions for use. JAMA. 1979;242:623-632.
139. Hutchinson TA, Leventhal JM, Kramer MS, Karch FE, Lipman AG, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. II. Demonstration of reproducibility and validity. JAMA. 1979;242:633-638.
140. Larson EB, Kukull WA, Buchner D, Reifler BV. Adverse drug reactions associated with global cognitive impairment in elderly persons. Ann Intern Med. 1987;107:169-173.
141. Koponen H, Hurri L, Stenback U, Riekkinen PJ. Acute confusional states in the elderly: a radiological evaluation. Acta Psychiatr Scand. 1987;76:726-731.
142. Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients: psychiatric disorders and cancer patients. JAMA. 1983;249:751-757.
143. Holland JC, Massie MJ. Psychosocial aspects of cancer in the elderly. Clin Geriatr Med. 1987;3:533-539.
144. Levine PM, Silberfarb PM, Lipowski ZJ. Mental disorders in cancer patients: a study of 100 psychiatric referrals. Cancer. 1978;42:1385-1391.
145. Folstein MF, Fetting JH, Lobo A, Niaz U, Capozzoli KD. Cognitive assessment of cancer patients. Cancer. 1984; 53(S):2251-2255.
146. Massie MJ, Holland J, Glass E. Delirium in terminally ill cancer patients. Am J Psychiatr. 1983;140:1048-1050.
147. Silberfarb PM, Philibert D, Levine PM. Psychosocial aspects of neoplastic disease. I: Affective and cognitive effects of chemotherapy in cancer patients. Am J Psychiatr. 1980;137:597-601.
148. Silberfarb PM. Chemotherapy and cognitive defects in cancer patients. Ann Rev Med. 1983;34:35-46.
149. Oxman TE, Silberfarb PM. Serial cognitive testing in cancer patients receiving chemotherapy. Am J Psychiatr. 1980; 137:1263-1265.
150. Dunne JW, Leedman PJ, Edis RH. Inobvious stroke: a cause of delirium and dementia. Aust NZ J Med. 1986;16:771-778.
151. Schmidley JW, Messing RO. Agitated confusional states in patients with right hemisphere infarctions. Stroke. 1984; 15:883-85.
152. Mesulam MM, Waxman SG, Geschwind R, Sabin TD. Acute confusional states with right middle artery infarctions. J Neurol Neurosurg Psychiatr. 1976;39:84-89.
153. Caplan LR, Kelly M, Kase CS, et al. Infarcts of the inferior division of the right middle cerebral artery: mirror image of Wernicke's aphasia. Neurology. 1986;36:1015-1020.
154. Devinsky O, Bear D, Volpe BT. Confusional states following posterior cerebral artery infarction. Arch Neurol. 1988;45:160-163.
155. Bogousslavsky J, Ferrazzini M, Regli F, Assal G, Tanabe H, Delaloye-Bischof A. Manic delirium and frontal-like syndrome with paramedian infarction of the right thalamus. J Neurol Neurosurg Psychiatr. 1988;51:116-119.
156. Medina JL, Chokroverty S, Rubino FA. Syndrome of agitated delirium and visual impairment: a manifestation of medical temporo-occipital infarction. J Neurol Neurosurg Psychiatr. 1977;40:861-864.
157. Medina JL, Rubino FA, Ross E. Agitated delirium caused by infarctions of the hippocampal formation and fusiform and lingual gyri: a case report. Neurology. 1974;24:1181-1183.
158. Soloman P, Leiderman PH, Mendelson J, Wexler D. Sensory deprivation: a review. Am J Psychiatr. 1957;114:357-363.
159. Zubek JP, ed. Sensory Deprivation: Fifteen Years of Research. New York: Appleton-Century-Crofts; 1969.
160. Wilson LM, Dorado E. Intensive care delirium. Arch Intern Med. 1972;130;225-226.
161. Cameron DE. Studies in senile nocturnal delirium. Psychiatr Q. 1941;15:47-53.
162. Evans LK. Sundown syndrome in institutionalized elderly. J Am Geriatr Soc. 1987;35:101-108.
163. Levkoff SE, Besdine RW, Wetle T. Acute confusional states (delirium) in the hospitalized elderly. Ann Rev Gerontol Geriatr. 1986;6:1-26.
164. Applegate WB, Miller ST, Elam JT, Freeman JM, Wood TO, Gettlefinger TC. Impact of cataract surgery with lens implantation on vision and physical function in elderly patients. JAMA. 1987;257:1064-1066.
165. Stevens JM. Some psychological problems of acquired deafness. Br J Psychiatr. 1982;140:453-56.
166. Damas-Mora J, Skelton-Robinson M, Jenner FA. The Charles Bonnet syndrome in perspective. Psychol Med. 1982; 12:251-61.
167. Berrios GE, Brook P. The Charles Bonnet syndrome and the problem of visual perceptual disorders in the elderly. Age Ageing. 1982;11:17-23.
168. Rosenbaum F, Harati Y, Rolak L, Freedman M. Visual hallucina-

tions in sane people: Charles Bonnet Syndrome. J Am Geriatr Soc. 1987;35:66-68.
169. Berrios GE, Brook P. Visual hallucinations and sensory delusions in the elderly. Br J Psych. 1984;144:662-664.
170. Morse RM, Litin EM. Postoperative delirium: a study of etiologic factors. Am J Psychiatr. 1969;126:136-43.
171. Millar HR. Psychiatric morbidity in elderly surgical patients. Br J Psych. 1981 1981;138:17-20.
172. Golinger RC. Delirium in surgical patients seen at psychiatric consultation. Surg Gynecol Obstet. 1986;163:104-106.
173. Tune L, Folstein MF. Post-Operative Delirium. Adv Psychosom Med. 1986;15:51-68.
174. Gustafson Y, Berggren D, Brannstrom B, et al. Acute confusional states in elderly patients treated for femoral neck fracture. J Am Geriatr Soc. 1988;36:525-30.
175. Hale M, Koss N, Kerstein M, Camp K, Barach P. Psychiatric complications in a surgical ICU. Crit Care Med. 1977; 5:199-203.
176. Summers WK, Reich TC. Delirium after cataract surgery: review and two cases. Am J Psychiatr. 1979;136:386-391.
177. Heller SS, Frank KA, Kornfield DS, Malm JR, Bowman FO. Psychological outcome following open-heart surgery. Arch Intern Med. 1974;134:908-914.
178. Calabrese JR, Skwerer RG, Gulledge AD, Gill CG, et al. Incidence of postoperative delirium following myocardial revascularization. Clev Clin J Med. 1987;54:29-32.
179. Seymour DG, Pringle R. Post-operative complications in the elderly surgical patients. Gerontology. 1983;29:262-270.
180. Sveinsson IS. Postoperative psychosis after heart surgery. J Thorac Cardiovasc Surg. 1975;70:717-727.
181. Kornfield DS, Heller SS, Frank DA, Edie RN, Barsa J. Delirium after coronary artery bypass surgery. J Thorac Cardiovasc Surg. 1978;76:93-96.
182. Smith LW, Dimsdale JE. Postcardiotomy delirium: conclusions after 25 years? Am J Psychiatr. 1989;146:452-58.
183. Folks DG, Freeman AM, Sokol RS, Govier AV, Reves JG, Baker DM. Cognitive dysfunction after coronary artery bypass surgery: a case-controlled study. South Med J. 1988;81:202-206.
184. Hole A, Terjesen T, Breivik H. Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. Acta Anaesth Scand. 1980;24:279-287.
185. Riis J, Lomholt B, Haxholdt O, et al. Immediate and long-term mental recovery from general versus epidural anesthesia in elderly patients. Acta Anaesthesiol Scand. 1983;27:44-49.
186. Berggren D, Gustafson Y, Eriksson B, et al. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. Anesth Analg. 1987;66:497-504.
187. Khan A, Joyce P, Jones AV. Benzodiazepine withdrawal syndromes. NZ Med J. 1980;92:94-6.
188. Sellers EM, Kalant H. Alcohol intoxication and withdrawal. N Engl J Med. 1976;294:757-62.
189. Hartford JT, Samorajski T. Alcoholism in the geriatric population. J Am Geriatr Soc. 1982;30:18-24.
190. Atkinson RM. Alcoholism in the elderly population. Mayo Clin Proc. 1988;63:825-29.
191. Feuerlein W, Reiser E. Parameters affecting the course and results of delirium tremens treatment. Acta Psychiatr Scand. 1986;73(Suppl 329):120-3.
192. Francis J, Strong S, Martin D, Kapoor W. Manifestations and outcomes of delirium in elderly medical patients. Clin Res. 1989;37(2):311A.
193. Zisook S, Braff D. Delirium: recognition and management in older patient. Geriatrics. 1986;41:67-78.
194. Posner JB. Delirium and exogenous metabolic brain disease. In: Beeson PB, McDermott W, eds. Cecil-Loeb Textbook of Medicine. 12th ed. Philadelphia: W.B. Saunders, 1967.
195. Thompson TL, Moran MG, Nies AS. Psychotropic drug use in the elderly. N Engl J Med. 1983;308:194-99.
196. Menza MA, Murray GB, Holmes VF, Rafuls WA. Controlled study of extrapyramidal reactions in the management of delirious, medically ill patients: intravenous haloperidol versus haloperidol plus benzodiazepines. Heart Lung. 1988;17:238-41.
197. Risse SC, Barnes R. Pharmacologic treatment of agitation associated with dementia. J Am Geriatr Soc. 1986;34:368-76.
198. Guze BH, Baxter LR. Neuroleptic malignant syndrome. N Engl J Med. 1985;313:163-66.
199. Finucane P, Price C, Ghose K. Neuroleptic malignant syndrome in an elderly patient. Br Med J. 1988;296:18.
200. Lieberman A, Pasternack P, Colvin S. The neuroleptic malignant syndrome after open heart surgery: successful treatment with bromocriptine. NY State J Med. 1987;87:362-63.
201. Serby M. Neuroleptic malignant syndrome in Alzheimer's disease. J Am Geriatr Soc. 1986;34:895-6.
202. Shalev A, Munitz H. The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand. 1986; 73:337-47.
203. Adams F, Fernandez F, Andersson BS. Emergency pharmacotherapy of delirium in the critically ill cancer patient. Psychosomatics. 1986;27:33-7.
204. Stern TA. Continuous infusion of physostigmine in anticholinergic delirium: case report. J Clin Psychiatr. 1983;44: 463-64.
205. Baldessarini RJ, Gelenberg AJ. Using physostigmine safely. Am J Psychiatr. 1979;136:1608-9.
206. Harper CM, Lyles YM. Physiology and complications of bed rest. J Am Geriatr Soc. 1988;36:1047-54.
207. Andres R, Bierman EL, Hazzard WR, ed. Principles of Geriatric Medicine. New York: McGraw-Hill Book Co., 1985.
208. Fretwell MD. Management in the acute care setting. In: Kelly WN, ed. Textbook of Internal Medicine, vol 2. Philadelphia: Lippincott, 1989, pp. 2619-22.
209. Francis J, Martin D, Kapoor W. Predictors of delirium in elderly medical patients. Clin Res. 1989;37(2):786A.
210. Robbins LJ, Boyko E, Lane J, Cooper D, Jahnigen DW. Binding the elderly: a prospective study of the use of mechanical restraints in an acute care hospital. J Am Geriatr Soc. 1987;35:290-296.
211. Frengley JD, Mion LC. Incidence of physical restraints on acute general medical wards. J Am Geriatr Soc. 1986;34:565-568.
212. Evans L, Strumpf NE. Tying down the elderly: a review of the literature on physical restraint J Am Geriatr Soc. 1989;36:65-74.
213. Appelbaum PS, Roth LH. Involuntary treatment in medicine and psychiatry. Am J Psychiatr. 1984;141:202-205.
214. Fogel BS, Mills MJ, Landen JE. Legal aspects of the treatment of delirium. Hosp Comm Psychiatr. 1986;37:154-158.