Depression in late life: psychiatric-medical comorbidity

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The links between late-life depression and the medical comorbidities that are often associated with it can be divided into two paths. The path from medical illness to depression reflects general mechanisms related to stress, disability, and loss, as well as more specific physiological mechanisms, including those related to subclinical cerebrovascular disease, adverse drug effects, and endocrine/metabolic effects. Similarly, the path from depression to medical illness includes general mechanisms related to self-neglect, decreased adherence to medical treatments, maladaptive health-related behaviors, and, possibly, more specific physiological mechanisms including those related to altered endocrine and autonomic functions. In the clinical context, these two paths can interact to constitute a vicious cycle. With further research, it should be possible to translate current understanding in these areas into advances in both basic knowledge and treatments that could initiate virtuous cycles with beneficial effects for both mental and physical health.

Keywords: *major depression; vascular depression; chemically induced depression; hypercortisolemia; heart rate; cytokine*

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The 1991 National Institutes of Health (NIH) Consensus Statement on the Diagnosis and Treatment of Late-Life Depression[1] noted that the hallmark of depression in the elderly was its co-occurrence or comorbidity with medical illness. The theme of comorbidity, the interaction between mental and physical health in late life, has been one of the major areas of recent research in geriatric psychiatry. In this, geriatrics has led advances in an area of general importance. Although the coexistence of medical illness and depression is less common in younger individuals, psychiatric-medical comorbidity is important throughout the life span; in fact, its impact may be greater in younger adults. At this time, the most general conclusions from the available literature must be that medical illness can be both a cause and a consequence of depression, and that treatment of depression, regardless of the clinical context in which it occurs, can have a positive effect on quality of life, functioning, and health. Moreover, current knowledge in this area should serve to guide further research to develop novel treatments, improve the effectiveness of established treatments, and provide insight into pathogenic mechanisms.

Psychiatric-medical comorbidity is important at several levels. Pragmatically, it can affect the recognition, diagnosis, treatment, and delivery of care for patients with depression. More conceptually, it can affect the mechanisms responsible for the pathogenesis of depression and for its impact as a multisystem disease. Among the early findings that established geriatric psychiatry as an important field of scientific inquiry were those of Stenstedt,[2] Hopkinson,[3] and Mendlewicz[4] demonstrating that elderly patients with depression could be divided into two subgroups, early-onset depressives, whose late-life depression was a recurrence of a disorder that had its initial onset earlier in life, and late-onset depressives, for whom depression began for the first time in late life. These groups differed in terms of family histories and

genetic risk for depression, with an excess of depression among first-degree relatives for the early-onset depressives. In contrast, the late-onset depressives had an excess of other factors, especially chronic medical illness, suggesting that physical illness could play an important role in the pathogenesis of those depressions that occur for the first time in later life.

Although these findings have had an enormous impact on subsequent research, identification of the path from physical illness to depression represents only one of the factors linking depression and medical illness. Another body of work has demonstrated the importance of the mirror image path, that proceeding from depression to medical illness. In his prospective study of a cohort of college students from the 1940s, Vaillant found that there was an association between depression and chronic, disabling illnesses in his subjects when they reached their seventies.[5] However, contrary to what one may have expected, he found that this association could be explained by the increased incidence of chronic disease and disability among those who, earlier in life, had exhibited evidence of depression. This finding reinforces epidemiological findings suggesting that patients with depression exhibit a higher subsequent incidence of diabetes[6] and an increased number of first myocardial infarctions,[7-11] as well as clinical research findings that women with depression experience an accelerated rate of osteoporosis.[12] Also relevant may be findings suggesting that a history of depression is a risk factor for Alzheimer's disease.[13,14]

The research demonstrating the importance of depression as an antecedent of medical illness was conducted in populations of aging rather than aged individuals. Among the elderly, the most salient issues may not be related to the initial incidence of either depression or disabling disease, but, instead, to how existing disorders affect each other. Evidence that established physical illness can affect the clinical course of depression comes, for example, from observations that depression may be more persistent among those patients with cardiac disease than several other chronic diseases,[15] and that it may be more resistant to antidepressant treatment in frail elderly patients for whom disabling medical illnesses have led to protein-calorie malnutrition than among individuals who are more fit.[16] Viewing the paths in the opposite direction, there is also evidence from multiple sources that depression can affect the clinical course of established medical illnesses by presenting barriers to convalescence and recovery, increasing disability, cognitive impairment, pain, and related symptoms.[17] These findings can be summarized with the unifying hypothesis that depression amplifies the morbidity and disability associated with medical illnesses; they suggest that the recognition and treatment of depression in the presence of other medical illnesses can serve as a form of secondary prevention that can decrease the impact of these conditions.[18]

Some recent studies have challenged the basic model of Stenstedt, Hopkinson, and Mendlewicz. Lyness and coworkers studied a sample of elderly patients hospitalized for depression and found comparable measures of physical illness in those with early- and late-onset disease.[19] Although their findings appear inconsistent with earlier distinctions between early- and late-onset depressions, it is important to note that more than a generation elapsed between these studies, and that the relative contribution of the path that extends from medical illness to depression versus that which extends from depression to medical illness may well vary over time as a result of cohort effects, increases in longevity resulting from changes in lifestyles and medical care, and advances in the treatment of both medical and mental illnesses. Another challenge to this model comes from studies of patients with one specific type of comorbidity: major depression as it coexists with Alzheimer's disease. Here depression is, in fact, associated with an excess of depression among first-degree relatives, suggesting that depression in Alzheimer's disease occurs among those who are at increased genetic risk.[14,20-23] These findings suggest that the mechanisms linking depression with other disorders may differ between conditions, and that specific studies of the associations between depression and commonly occurring comorbidities may be of value.

Studies of the mechanisms underlying the increases in mortality associated with depression have also led to apparent conflicts between findings. Investigations of patients after myocardial infarction have consistently found a robust association between depression and decreased survival, which remains significant after controlling for the severity of the underlying cardiac disease.[23-26] However, findings in frail elderly patients in nursing homes have been less consistent. Although all investigations in this area have found that major depression is associated with decreased survival,

there has been controversy about the extent to which this can be attributed to depression itself or to the associations of both depression and mortality with more severe medical illness[27-29]; differences between studies may depend upon the nature of the control groups and the methods that were used to control for the extent of medical illness. More generally, one might expect findings in this area to depend upon the context and the population under investigation. In a population such as patients with a recent myocardial infarction, where depression may predispose patients to sudden death, it may be relatively easy to test for the extent to which depression directly contributes to mortality. However, in other contexts, such as long-term care populations, where depression may accelerate a more continuous pattern of deterioration and decline leading to death, the analytic problems are more complex. If one evaluated the mechanisms by which depression increased mortality early in the process, before it had led to significant deterioration, one might find a direct effect of depression. However, if one studied the same effects later during the course of the patients' illnesses, when depression had already made a substantial contribution to decline, it might no longer be possible to find effects of depression that would remain significant after controlling for the severity of medical illness. This discussion suggests that the mechanisms responsible for the consequences of depression, as well as those responsible for its causes, may differ between clinical settings and comorbid conditions.

Although knowledge in this field has advanced primarily through explorations of unidirectional models for the links between mental and physical health in late life, those interested in this area from a clinical, financial, or policy perspective should recognize that the most valid models must be bidirectional. Depression and medical illness in late life are linked through complex reciprocal mechanisms in which pathology in one domain can accelerate deterioration in the other. These interactions can constitute a vicious cycle that can, in some cases, begin early in life and end in premature death. Recognition of these linked mechanisms is important because of their implications for prevention and treatment; recognition and treatment of depression can initiate a virtuous cycle that may not simply improve mental health and quality of life, but also prevent physical decline.

Evaluating the associations between medical illness and depression

As discussed above, observed relationships between mental and physical health can depend upon the cohort studied, the setting, and the population from which study samples are drawn. Additional problems arise in studies designed to investigate the associations of depression with specific disorders and to evaluate underlying mechanisms. These arise because medical illnesses can lead to depression through the additive or interacting effects of a number of mechanisms. Some are general and are associated with factors such as the experience of disability, pain, stress, loss, or impaired self-esteem as a result of medical illness. Other more specific mechanisms may involve disease-related structural abnormalities in brain, or physiological abnormalities that affect the brain or the periphery. Any observed associations of depression with measures or correlates of physical illness could reflect general as well as specific mechanisms. Therefore, research must always include some type of control for these nonspecific effects of disease.

Another complication occurs in case of concomitant multiple disorders. Disabling chronic illnesses accumulate with aging such that middle-aged and "young-old" individuals often suffer from a single disorder, but the "old-old," most often, suffer from many. Investigations into the mechanism of association between mental and specific diseases or physiological abnormalities in homogeneous populations of younger individuals are less likely to be obscured by the presence of multiple, potentially interacting abnormalities, but they may miss mechanisms that arise specifically out of such interactions. Moreover, the problems associated with choosing control conditions are, perhaps, greatest in the presence of multiple disorders. In probing mechanisms, the salient questions are not whether specific disorders or abnormalities are associated with depression, but whether the associations remain significant after controlling for general mechanisms. One strategy may involve use of summary measures of comorbidity or illness burden that rely upon clinical judgments or information available from medical records. However, available instruments differ in the dimensions of illness considered, and there is no consensus as to what should be measured in rating illness severity. An alternative approach may be to use disability as a control measure. For example, in evaluating the theory that cerebral microvascular disease may

predispose patients to depression, it may be reasonable to compare patients with hypertension and diabetes, disorders that may lead to depression via such mechanisms, with comparably disabled control subjects with osteoarthritis, a disorder that may lead to depression by primarily noncerebral mechanisms; however, such comparisons would be made difficult by differences between disorders in the nature of the disability and their meaning to the patients.

Experience from the University of Pennsylvania's National Institute of Mental Health (NIMH)-supported Intervention Research Center provides an example of the complexities involved in drawing conclusions about the specificity of the associations between depression and medical illness in geriatric populations. As described previously,[30,31] this study evaluated residents (average age 85 years) from a large urban nursing home and congregate apartment facility at 2 weeks after their admission (or at the anniversary of their admission) with a series of measures. For the findings summarized in *Table I,* cognitively more intact individuals with a score on the Blessed Information-Memory-Concentration Test less than 13 were evaluated with a modified Schedule for Affective Disorders and Schizophrenia (mSADS) interview and the Geriatric Depression Scale (GDS) and were classified at their initial interview and after 1 year as euthymic, dysphoric (with persistent sadness or anhedonia on the mSADS or GDS score >10), or as experiencing a major depressive episode. Disability was evaluated using the Physical Self-Maintenance Scale (PSMS) of Lawton and Brody. Medical comorbidity was evaluated with the Cumulative Illness Rating Scale (CIRS), as previously described[32]; this scale uses clinician judgments to measure the severity of disease in each of 13 systems and 2 summary measures, the mean score across systems, and the number of systems with at least moderate disease severity. For evaluating changes over a 1-year period, subjects were considered to decline if they had incident dysphoria or depression or if they worsened from dysphoria to major depression. The study sample at

Indicator	Correlation with disability (r; n=420-480)	Association with depression F (2, 478)	Association with 1-year decline F (1, 224)
PSMS	–	65.098***	4.423*
Mean CIRS	0.322**	12.347***(a)	2.553
No. of CIRS systems > mild	0.352**	8.284**(a)	2.480
Cardiac	0.159**	1.241	4.237*(a)
Hypertension	-0.005	2.371	3.093
Vascular	0.168**	4.711**(a)	2.735
Respiratory	0.155**	2.132	0.280
EENT	0.102*	2.882	2.521
Upper GI	0.123*	3.739*(a)	0.341
Lower GI	0.022	5.573**	0.552
Hepatobiliary	0.089	4.372*	1.327
Renal	0.158**	1.171	2.820
Other GU	0.130**	0.539	1.694
Musculoskeletal	0.251**	1.517	1.169
Neurological	0.376**	6.796**(a)	0.922(b)
Endocrine/metabolic	0.124**	4.849	0.539

*P<0.05; **P<0.01; ***P<0.001. (a) no longer significant after controlling for disability; (b) significance emerges after controlling for disability; Abbreviations: CIRS, Cumulative Illness Rating Scale; EENT, eye, ear, nose, and throat; GI, gastrointestinal; GU, genitourinary; PSMS, Physical Self-Maintenance Scale.

Table I. Associations between medical illness and depression in patients with Blessed IMC (Information-Memory-Concentration) score <13.

baseline consisted of 480 individuals, 55.3% euthymic, 29.7% dysphoric, and 15.0% with major depression. Over the 1-year period, the affective status of 27 of 226 subjects (11.9%) for whom follow-up data were available, declined.

As shown in *Table I,* depression was associated with summary measures of physical illness and with disability. Among the systems probed, there were associations of depression with vascular disease, upper gastrointestinal disease, lower gastrointestinal disease, hepatobiliary disease, neurological disease (primarily stroke and parkinsonism) and endocrine-metabolic disease (primarily diabetes). However, after controlling for disability, the associations with summary measures of medical illness were no longer statistically significant, and the only associations between depression and disease in specific systems were those with lower gastrointestinal and endocrine-metabolic systems. In stepwise logistic regression models that considered the systems that had univariate associations with depression, any depression (dysphoria or major) was found to be associated (model χ^2=19.292; *P*=0.0002) with upper and lower gastrointestinal and neurological disease, while major depression was associated (model χ^2=17.72; *P*=0.0005) with lower gastrointestinal, neurological, and endocrine-metabolic disease. After controlling for disability, any depression was associated (χ^2=5.471; *P*=0.0193) only with upper gastrointestinal disease, while major depression was associated (χ^2=11.909, *P*=0.0026) with lower gastrointestinal and endocrine-metabolic disease.

Higher levels of disability and cardiac disease at the initial assessment were associated with worsening of affective status over a 1-year period. However, after controlling for disability, the association between cardiac disease and worsening depression was no longer significant, and a new association between neurological disease and worsening depression emerged. In contrast, none of the variables tested was associated with persistence versus improvement over a 1-year period in those who were depressed at their initial assessments.

This discussion demonstrates that the specific relationships observed between mental and physical health can depend strongly upon the assumptions and methods used in analyses. From a broad and pragmatic perspective, the findings on the baseline associations between depression and endocrine-metabolic disease and between cardiac disease and worsening of depression over a 1-year period are compatible with models suggesting a relationship between depression and vascular risk factors. The findings on gastrointestinal disease are similar to those found by Zubenko and colleagues in a psychiatric inpatient setting,[33] and suggest the salience of autonomic effects (see below). More critically, however, the results of analyses that control for disability emphasize the principle that findings can depend critically upon methodology.

Medical illnesses as causes for depression: specific mechanism

Vascular mechanisms

As summarized by Alexopoulos and colleagues,[34] a growing body of recent research has focused on cerebrovascular mechanisms for the onset of late-life depression. This line of investigation began with the empirical findings by Coffey and others[35] that late-life depressives, most often those with late-onset disease, exhibited an excess of subcortical and deep white matter hyperintensities on magnetic resonance imaging (MRI) scans, consistent with the hypothesis that depression in late life could be a manifestation of subclinical cerebrovascular disease. The accumulating findings allowed both Alexopolous and his coworkers[36,37] and Krishnan and his colleagues[38] to propose that vascular depression may be a specific subtype of late-life depression that could be defined either in terms of MRI findings or the presence of specific medical comorbidities; they also suggested that clinical features associated with vascular depression might include increased anhedonia, psychomotor retardation, and loss of insight, but decreased agitation and guilt. Although evidence that cerebrovascular mechanisms can account for a significant component of the depressions that arise in late life is accumulating, a number of questions remain, primarily about the specificity of the associations.

From a formal perspective, it is important to question whether the MRI findings associated with depression are, in fact, directly involved in its pathogenesis or whether they are an indirect index of the severity of underlying diseases that could lead to depression through other paths. Other questions about specificity follow from empirical findings. These include questions about the nature of the lesions based upon observa-

tions that comparable MRI findings can occur in younger and physically healthier patients with bipolar disease.[39,40] Moreover, Lyness and coworkers reported a lack of association between cerebrovascular risk factors and depression in a comparison of psychiatric inpatients with normal controls.[41] Finally, although Kumar and colleagues reported an association of depression with subcortical and deep white matter hyperintensities, and have used regression models to demonstrate a path from physical illness through MRI findings to depression, they were not able to relate the MRI findings specifically to disorders associated with increased risk for cerebrovascular disease rather than more general measures of medical illness burden.[42] Interestingly, in addition to these findings, they found independent associations of depression with measures of cerebral atrophy, suggesting that depression may result from separable vascular and neurodegenerative mechanisms.

Other questions relate to the specificity of the effects of MRI findings. As might be expected from electroencephalographic findings that the relevant lesions can disrupt interconnections between cortical areas,[43] there is evidence that they can be associated with multiple forms of morbidity, including disturbances of gait and balance[44,45] and cognitive deficits,[46] especially deficits in executive functions, as well as depression. These findings raise questions about whether the association between MRI lesions and depression is a direct effect or an indirect manifestation of disability or dysfunction related to other effects.

The suggestion that vascular depressions are associated with symptoms consistent with frontal system deficits, and the observed association of MRI lesions with executive deficits suggests the need for further studies on the diagnosis of late-life depression. Although the differential diagnosis of depression and dementia has received extensive attention in both the research and the practice literature, there has been little discussion about the overlap or distinction between depression and frontal lobe syndromes. The association between vascular pathology and executive deficits together with evolving questions about the associations of both with depression suggest the importance of research designed to optimize the discrimination between these syndromes and to ensure that observed associations are not inflated by confounding of case identification.

There have been proposals about the neuroanatomic circuits that may be the substrate for the pathogenesis of depression in individuals with subcortical and deep white matter hyperintensities on MRI scans,[47] and there have been preliminary attempts to map the relevant lesions.[48] It is possible that larger-scale studies that map the MRI-located lesions in vulnerable patients with and without depression may be informative about the neuroanatomic basis for vascular depressions. However, before such studies can be designed, it will be necessary to obtain further information on the nature of the association between brain lesions and depression. Mapping may be straightforward if the association between depression and strategically placed lesions is direct, immediate, and inevitable. However, mapping would be more complex if vascular depression occurred within a biopsychosocial matrix in which patients with significant lesions were at increased risk for depression, but where stress and loss still act as precipitants for the onset of depressive episodes, and social support still acts as a buffer.

The concept of vascular depression has already been of value to the field of psychiatry by stimulating research and critical thinking in the area of psychiatric-medical comorbidity. Given the complexity of the problem and the limitations in available methods for research in accessible patient populations, the next steps in developing this model should, perhaps, be pragmatic. Research on vascular depression has, thus far, suggested the importance of advancing the differential diagnosis of depression and frontal lobe syndromes in elderly and medically ill patients. Studies of the mediators and moderators of the associations between depression, risk factors for cerebrovascular disease, and depression are also important. Although such studies will be necessary to allow the design of mapping experiments as described above, their more immediate value may be in determining the extent to which there may be individuals with vascular lesions or risk factors without current mood disorders who may be at high risk for depression, and who may benefit from preventive interventions. The most critical next step, however, may be to confirm and follow up on early findings that suggest that vascular depressions may be associated with differential responses to specific treatments.[49]

Drug toxicity

The risks and costs of adverse drug effects in the elderly were emphasized in a 1995 General Accounting

Office report.[50] The literature on psychiatric side effects was comprehensively reviewed in a book by Brown and Stoudemire[51] and the problem from a lay and personal perspective was described by Fried.[52] One indication of the scope of the problems can be provided by review of the medications discussed as potential causes of depression within the current literature. *Table II* summarizes those agents discussed in papers indexed in MEDLINE over the past 10 years under the headings "depression" or "depressive disorder" and the subheading "chemically induced." An estimate of the significance of adverse drug effects as causes of depression can be derived from the work of Patten and coworkers[53] who studied a series of medical inpatients for association between the incidence of depressive symptoms and prescription of any of six classes of medications (β-blockers, histamine H_2 receptor blockers, corticosteroids, sedative hypnotics, calcium-channel blockers, and angiotensin-converting enzyme inhibitors) and reported that 56% of the depressive symptoms occurring in the population could be attributable to use of these agents. Although this estimate is provocative, it must be viewed with caution. As with the other potential pathogenic mechanisms, the study of adverse drug effects must control for potential biases; most important may be the possibilities of confounding by indication, where the apparent relationships of medications with symptoms may, in fact, reflect associations with the disorder that is being treated, rather than a true adverse drug effect. A recent critical review[54] summarized this area by noting that most of the literature consisted of case reports, and that there were relatively few empirical studies. Nevertheless, it concluded that corticosteroids, certain calcium-channel blockers, and digoxin have been associated with depression by replicated, well-conducted studies. In addition, it suggested that the literature is sufficient to warrant suspicion about antihyperlipidemic agents, angiotensin-converting enzyme inhibitors, sedative hypnotics, psychostimulants, and certain hormonal agents. It concluded that the potential association between β-blockers and depressive symptoms remains controversial, and that there was no substantial evidence that L-dopa or histamine H_2 receptor blockers cause depression. Clearly, this is an area in which further research is needed.

Historically, this area has been dominated by research related to biogenic amine theories of depression as a conceptual model. The suggestion that medications that affect aminergic systems can cause depression was key to the development of these theories of depression almost two generations ago. Nevertheless, the empirical evidence in support of these associations remains marginal. Although the suggestion that reserpine can cause depression is now primarily of historic interest,

Anticonvulsants
Phenobarbital
Phenytoin
Topiramide
Vigabatrin
Antihyperlipidemic agents
Antiparkinsonian agents
Cardiovascular agents
Angiotensin-converting enzyme inhibitors
β-Blockers
Calcium-channel blockers
Clonidine
α-Methyldopa
Hormonal treatments
Anabolic steroids
Contraceptive agents (oral and depot)
Corticosteroids
Gonadotropin-releasing hormone antagonists
Progesterone
Tamoxifen
Migraine treatments
Cinarizine
Flunarizine
Oxetorone
Sumatriptan
Others
Antipsychotic agents
Baclofen
Benzodiazepines and sedative hypnotics
H_2-blockers
Interferon
Metoclopramide
Nonsteroidal anti-inflammatory drugs
Ofloxacin
Ondansetron
Psychostimulants
Retinoids
Tramadol

Table II. Medications discussed as possible causes of affective toxicity; 1989-1999.

it is still important to take a critical perspective and to ask whether reports of this association were adequate in distinguishing between depression and extrapyramidal symptoms. Recent reviews agree that the evidence to support the hypothesis that β-blockers can cause depression remains controversial.[54,55] More generally, the vascular depression hypothesis, with its suggestion that hypertension can itself be a risk factor for depression, raises questions about whether any apparent associations between depression and relevant antihypertensive medications may an example of indication bias, with symptoms related to the sequelae of hypertension rather than to the direct effects of medication.

In the absence of any well-established laboratory markers, animal models, or models of pathogenesis that could serve as a basis for screening, the only way to approach this area is through empirical research in patient populations. Those adverse drug effects that are most common, most acute, and most severe may be identified during the process of drug development. Most side effects, however, are identified only after medications are approved for use. The sensitivity for the detection of adverse effects of drugs used in clinical practice depends strongly upon the base rate of the symptoms in the population at risk. In general, the high rates of depression in patients who require treatment for medical illnesses will make it difficult to detect the medication-related depressions. One exception, where depression as a possible drug side effect was identified through direct clinical observation, may be with therapeutic use of interferon, where the frequency of severe depression temporally related to treatment has suggested a specific effect.[56,57] More representative may be suggestions of an association between depression and the use of cholesterol-lowering drugs and angiotensin-converting enzyme inhibitors, where suggestions about toxicity developed from epidemiological studies. For the former, concerns about depression and other psychiatric side effects developed out of research showing that, although reductions in cholesterol levels were not associated with decreases in all-cause mortality, they were accompanied by fewer cardiovascular deaths but more deaths related to accidents and self-injury.[58] For the latter, suggestive findings include those derived from prescription asymmetry studies, in which the order of prescribing antidepressants and the target drug are evaluated as an approach for controlling for confounding by indication.[59] The hypothesis that angiotensin-converting enzyme inhibitors may cause depression may appear surprising in light of earlier reports that hypertensives treated with such agents exhibited better quality of life than those treated with other agents such as α-methyldopa.[60] This suggests another possible confound. On the basis of earlier research, practitioners may have believed that angiotensin-converting enzyme inhibitors were less likely to cause depression than other agents, and may have been biased to prescribe them preferentially to patients at increased risk for depression; this, in turn, could have led to spurious associations in subsequent studies.

Oslin has described a pilot study of a method that evaluates the effects of medications on the day-to-day variation of positive and negative affects in normal volunteers; inclusion of such measures in early clinical trials of the safety of new drugs could, in principle, improve the sensitivity for the early detection of affective toxicity.[61] However, a more general method for identifying the medications that may cause depression may be through studies of the associations between medication use and observations or records of psychiatric symptoms, subsequent prescription of psychotherapeutic medications, or use of mental health services. One beneficial effect of the increasing organization of health care systems may be the development of additional sources of data for such studies. However, beyond the initial identification of agents that may cause depression, it will be necessary to control for potential confounding factors and to estimate effect sizes before it is possible to use pharmacoepidemiological findings either to guide clinical practice or to provide insight into pathogenic mechanisms.

Hormonal and cytokine-mediated mechanisms

There is an extensive literature suggesting associations between even mild or subclinical hypothyroidism and the pathogenesis of depression and decreased responses to antidepressant medications.[62,63] Recently, Seidman and Walsh have reviewed evidence that decreased testosterone activity in hypogonadal men may lead to depressive symptoms.[64] This, together with earlier findings suggesting that decreases in testosterone in aged men were most marked in those with chronic disease and disability,[65] suggests that decreased androgen levels may mediate some of the behavioral and affective changes associated with medical illness in late life.

There has also been interest in the possibility that depression and related symptoms in patients with medical illness may be mediated via the neuropharmacological effects of inflammatory cytokines such as interleukin -1β, tumor necrosis factor α (TNF-α), and interleukin-6. At present, however, knowledge in this area is relatively rudimentary. Current research on Alzheimer's disease is investigating the possibility that intracerebral inflammation may play a role in initiating or maintaining the process of neurodegeneration.[66,67] Although some studies have found measures of inflammatory activity or increases in the activity of proinflammatory cytokines in the periphery, the pathological processes associated with the progression of Alzheimer's disease are presumed to be operative within the brain. Theories of inflammatory processes in Alzheimer's disease have stimulated research on the possible therapeutic or preventive effects of corticosteroids and nonsteroidal anti-inflammatory drugs, including recently developed cyclooxygenase (COX) 2 inhibitors.

Hypotheses about depression are less developed, and more divergent. Maes has proposed that dysregulation of immune and inflammatory processes may be basic components of the pathophysiology of depressive disorders.[68-71] They have reported that apparently healthy, mixed-age adults with depression exhibit evidence for increased cytokine-mediated activities and for the activation of acute-phase processes. They probed the interactions between cytokine systems and the hypothalamic-pituitary-adrenal axis (HPA), and suggested that increased cytokine activities may drive the HPA axis and may underlie the hypercortisolemia found in subpopulations of patients with depression. Most basically, the central element of their hypothesis is that the increased cytokine activity and the activation of acute-phase or inflammatory processes in depression is a regulatory abnormality characteristic of depression, rather than a reflection of medical illness.

An alternative hypothesis for a role of cytokines in the pathogenesis of depression is based upon concepts of "sickness behavior."[72-75] According to these models, infection, inflammation, or tissue injury can activate inflammatory processes and induce cytokines that can act locally or systemically to regulate homeostatic responses. Some of these responses, including those that involve acute-phase processes, occur in the periphery, while others involve (direct or indirect) actions of cytokines on the central nervous system. Some of these central nervous system–mediated effects, such as fever, are physiological, while others are behavioral. The latter include a number of nonspecific behaviors associated with illness and injury such as decreased exploratory activity, decreased sexual activity, anorexia, and changes in sleep structure. Studies of the behavioral pharmacology of the cytokines in experimental animals demonstrate that they can, in fact, cause these behaviors; however, questions remain about the mechanisms through which the induction of cytokines in the periphery can cause centrally mediated effects. Nevertheless, this hypothesis proposes that depression can occur when cytokine-mediated processes are induced by illness or injury, and that the depressions that arise through these mechanisms are pathological variants of normal and adaptive sickness behaviors.

As discussed above, it is possible to distinguish between two distinct cytokine-related theories of depression, one in which the induction of cytokines occurs spontaneously as a result of regulatory deficits intrinsic to the depressive illness, and the other in which they arise in the context of medical illness. These models may, however, be poles in a continuum. For example, cytokine-mediated processes initiated by illness could, in principle, remain activated after illness as a result of a failure in restorative mechanisms. Alternatively, regulatory abnormalities may allow for the extensive induction of cytokines by minor illness or injury. Thus, it is possible to propose a series of plausible cytokine theories of depression. The important question is, of course, whether there is empirical evidence to support any of them.

Observations from our center that depressions associated with high levels of disability and low levels of serum albumin (a negative-acute phase reactant as well as a marker for protein-calorie nutritional status) constituted a treatment-relevant subtype of depression less likely to respond to nortriptyline treatment than other depressions, led us to investigate the sickness behavior hypothesis in the long-term care setting. Thus far, however, our findings have been negative. The low serum albumin in depression appears to be a marker for subnutrition rather than for acute-phase processes. Moreover, pilot studies (n=36 to 60) have found a modest association between plasma levels of TNF-α and self-reports of appetite loss, but no relationship between plasma levels of TNF-α, interleukin-1β, or interleukin-6 and measures of depression. Thus, our findings on appetite disturbances are consistent with

the hypothesis that cytokine-associated sickness behavior can occur in an elderly chronic care populations, but our data do not support the suggestion that this mechanism can explain a significant component of the depressions seen in this population. Had these exploratory studies found correlations between cytokine activities and depression, it would have been necessary to conduct further studies to determine if the cytokines were directly associated with the affective and behavioral symptoms or whether they were indirect measures of the severity of illnesses that led to depression through other mechanisms; however, in the absence of correlational findings, questions about mechanisms are not relevant.

A recent report by Dentino and colleagues[76] provided additional insight into this area. In a large-scale study of 1732 elderly individuals (mean age 77.6 years) living in the community, they found a statistically significant correlation (Spearman r=0.06) between log-transformed plasma levels of interleukin-6 and measures of depression. Subsequent regression analyses demonstrated that this effect remained significant in models that considered other biological variables, measures of self-care deficits, and self-rated health. Unfortunately, although this study found an association between depression and stroke, a history of fracture, and arthritis, and an earlier report of research on this study sample[77] found associations between plasma levels of interleukin-6 and cancer, heart attack, and high blood pressure, this report did not control for medical comorbidities. Thus, this report does not allow the distinction between models in which the association of depression and interleukin-6 is a reflection of their common links with medical illness, and those in which it arises independently.

The most significant conclusions from the work of Dentino et al,[76] however, may follow from the quantitative findings reported. The magnitude of the observed correlation coefficient indicates that less than 0.4% of the variance in depression in the population can be attributed to variability in (log-transformed) interleukin-6 levels. Thus, this report demonstrates that interleukin-6–related mechanism can account for, at most, a small component of late-life depressions. Although these mechanisms cannot explain a substantial proportion of the late-life depressions that occur in the community, the statistically significant correlations may provide a rationale for further studies in specific populations in which the associations may be more robust. However, even in such settings, plasma levels of circulating cytokines may not be a sensitive indicator of relevant processes. Furthermore, it would be difficult for observational studies to distinguish between direct effects of cytokines and correlations that may occur because both depression and cytokine-related processes arise from illness. Therefore, the most rigorous research in this area, as well as the most clinically relevant, may be to test pharmacological treatments that target cytokine-related mechanisms for depression and related behaviors in carefully selected patient populations.

Depression as a cause of medical illness

The mechanisms leading from depression to the onset or worsening of medical illness are as complex as those operative in the other direction. Here too, observed effects may be related to both general and specific mechanisms. General mechanisms can include the effects of self-neglect, poor nutrition, agitation, decreased physical activity, and lack of adherence with treatments required for medical conditions. Other mechanisms can be related to the sleep disturbances that occur as components of depression, and the association between depression and cigarette smoking.[78] One specific physiological mechanism proposed to account for the excess of osteoporosis in middle-aged women with depression is related to the effects of hypercortisolemia.[12,79] There have also been preliminary suggestions that hypercortisolemia and dysregulation of the HPA axis in depression may lead to cerebral atrophy.[80,81] Although hypercortisolemia could, in principle, lead to immune dysfunction, decreased carbohydrate tolerance, and muscle atrophy, there is no consistent body of evidence to suggest that such effects are operative in individuals with depression. There have also been proposals that depression-related changes in platelet activity[82,83] and heart rate variability[84,85] may be associated with the increased incidence of ischemic heart disease in patients with depression and with depression-related increases in mortality after myocardial infarction. The decreased heart rate variability in depression may be related to decreased parasympathetic (vagal) tone; similar decreases in parasympathetic activity could also account for the association of depression with gastrointestinal disease.[86]

It has been well established that a sizable subset of patients with depression exhibit hypercortisolemia. Although there appears to be significant variability in the extent to which this normalizes with treatment and the remission of depressive symptoms, there must still

be questions about the extent to which this heterogeneity is characteristic of subtypes of depression or the effects of different treatments. The associations of depression with decreased heart rate variability and decreased parasympathetic tone are not as well established. Although it is known that treatment with anticholinergic tricyclic antidepressants can increase these effects, there are questions about the impact of other treatments on autonomic functions.

A critical unanswered question for psychiatric research is whether the treatment of depression improves health outcomes. It would clearly be difficult to conduct the large-scale, long-term treatment studies with medical outcomes that would be needed to address this issue most directly. Intermediate goals, based upon the above considerations, may be to explore the extent to which measures of cortisol production and parasympathetic activity could serve as proxy measures for health outcomes in more accessible, shorter-term treatment studies. Although it is always necessary to be cautious about the interpretation of proxy outcome data, such studies could serve heuristic, hypothesis-building functions about the extent to which health outcomes might differ as a function of alternative treatments for depression, or as a function of variations in duration and intensity within treatments.

Conclusion: psychiatric medical comorbidity as a focus for translational research

Clinical studies on the association between depression and medical illness can guide translational research. Clinical studies of the paths leading from medical illness to depression could translate into larger-scale studies of prevention and treatment effectiveness in specific patient populations. They could also translate into more basic studies. The classic findings that chronic medical illness represents a path to depression that is separable from genetic mechanisms suggests that findings from studies on comorbidity will be needed to complement anticipated findings from genetics to provide a comprehensive picture of the mechanisms that can lead to depression. The most important results from studies on the paths from depression to medical illness may be translation into prevention research on the extent to which treatment of depression can preserve health and prevent the accelerated physical decline that is increasingly being identified as a consequence of depression. ❑

Depresion en la edad avanzada : la comorbilidad medico-psiquiatrica

La relación existente entre la depresión en la edad avanzada y las comorbilidades médicas, que a menudo se asocian entre sí, pueden considerarse en dos sentidos. La vía que va desde la enfermedad somática a la depresión refleja mecanismos generales vinculados al estrés, la incapacidad consiguiente y la vivencia de pérdida, así como mecanismos más específicos que comprenden a aquellos relacionados con la enfermedad cerebrovascular subclínica, efectos adversos de los fármacos, y efectos endocrinos y metabólicos. Del mismo modo, la vía que conduce de la depresión a enfermedades médicas incluye mecanismos generales vinculados al descuido de sí mismos, al progresivo desinterés en el cumplimiento con el tratamiento médico, a conductas inadecuadas con respecto a la propia salud, y posiblemente mecanismos fisiológicos más específicos que se relacionan con funciones autonómicas y endocrinas alteradas. En el contexto clínico, estas dos vías pueden interactuar constituyendo un círculo vicioso. Investigaciones adicionales posibilitarían la transposición de la comprensión acutal en estas áreas en progresos tanto en el campo de los conocimientos básicos como en el de los tratamientos, pudiendo generar círculos virtuosos con efectos benéficos tanto en la salud mental como fisica.

La dépression du sujet âgé : comorbidité médicale et psychiatrique

Les liens entre la dépression du sujet âgé et les comorbidités médicales qui lui sont souvent associées peuvent être séparés en deux voies. La première d'entre elles, qui établit un lien entre la maladie somatique et la dépression, est le reflet de mécanismes généraux qui ont trait au stress, à l'incapacité et à la perte d'une fonction ou encore de mécanismes plus spécifiques incluant tous ceux qui ont un rapport avec une maladie cérébrovasculaire infraclinique, les effets indésirables des médicaments, mais aussi des phénomènes endocriniens ou métaboliques. De façon identique, la seconde voie qui va de la dépression à la maladie somatique inclut des mécanismes généraux qui sont liés à l'autodépréciation, à la diminution de l'observance des traitements médicaux et à l'existence de comportements inadaptés, tributaires de l'état de santé. Elle peut aussi inclure des mécanismes physiologiques plus spécifiques qui intègrent ceux témoignant d'altérations des fonctions endocriniennes et de l'autonomie. Dans ce contexte clinique, ces deux voies peuvent constituer un cercle vicieux. De futures recherches devraient permettre de convertir des données disponibles dans ces domaines en avancées aussi bien dans le domaine de la recherche que dans celui des traitements avec, à terme, la création de cercles vertueux capables d'améliorer santé physique et mentale.

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