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Overview of the field

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Abstract

Clinical descriptions of depression date back to antiquity. Scientific investigations of mood disorders started only 150 years ago. An historical overview of depression leads into today's knowledge that depressive disorders are common, serious, and sometimes life-threatening and that their effects are persistent and costly. Depressive disorders have a high prevalence, around 5% in the general population, with at least 20% of patients suffering with chronic conditions, such as cardiovascular disease and diabetes. Neuroimaging technology provides unprecedented opportunities for elucidating the neurobiological correlates of mood disorders. Neuroimaging studies of primary mood disorders have identified neurophysiologic abnormalities in the orbital and medial prefrontal cortex (PFC), the amygdala, and the related parts of the striatum and thalamus. There has been a revolution in our understanding of the pathogenesis of depression, with recent work demonstrating, among others, the critical impact of stress. There is an abundant evidence from family, twin, and adoption studies that genetic factors play an important role in the etiology of affective disorders. A variety of hormonal abnormalities, such as altered levels of cortisol, growth hormone, or thyroid hormones, indicate the existence of endoctrine disturbances. Despite the initial findings of immunosuppresion in depression, some studies have indicated that immune activation could also be present and might even play a role in the onset of depressive symptoms. Neurotrophic factors are among the growth factors that have been studied for their role in the adult nervous system. Despite advances in the pharmacotherapy of depression, only one third of patients respond favorably to antidepressant drugs. One third do not respond at all, and in clinical trials, at least one third respond to placebo. There is clearly an urgent need for novel antidepressants.

1. History

Literary and clinical descriptions of depression—the mental, bodily, and spiritual state that in previous eras was called melancholia—date back to antiquity, as do speculations about the relationship of those emotional states to health and illness and to the human condition. Scientific investigations of affective disorders, however, are only a century old or two. During the 19th century, clinicians, and especially the French clinicians Falret and Ballenger [1], observed the alternation of depressed and elated states in the same individual. However, it was Kraepelin [2] who brought the diverse states together under his unifying concept of "manic-depressive insanity."

The clinical picture of manic-depressive insanity was first described and classified by Kraepelin [2]. Kraepelin's interpretation was modified by Bleuler [3]. Subsequently, various workers in the field have changed the concept further [4,5].

A turning point came in the early 1950s with the development of new psychopharmacologic agents. The pattern response to several classes of therapeutic drugs proved consistent with Kraepelin's categories. In particular, the response patterns separated the so-called functional psychoses into schizophrenia, paranoia, and other disorders of thinking, which were found to respond to neuroleptics, and the disorders of affect, which responded to either lithium, in the case of manic states, or to tricyclics, in the case of depressive states. Although there is an overlap among classes of drugs, the general pattern of response follows the separation of the major functional psychoses proposed by the generation of Kraepelin [2] and Bleuler [3].

Depressive disorders are common, serious, and sometimes life threatening. Their effects are persistent, debilitating, and costly. Depression causes significant suffering,

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disability, and social dysfunction, frequently leading to disruption of normal daily activities for both the patient and the immediate family. Depressed patients struggle to recover, often over several months or even years, and in many, the illness takes a chronic, recurrent, and remorseless course. As well as a high morbidity, depression carries substantial mortality, not only for suicide but also from other causes. The economic burden of depression on society is considerable and is comparable to that of other major illnesses such as coronary heart disease. However, because depression is often not properly recognized, almost half of all patients who contact primary care health services [6] are believed to have a current depressive disorder [6]. The condition generally begins to affect people at a relatively young age. It exacts high costs over a long period and places a particularly heavy burden on employment productivity. Depressive disorders are now widely recognized as a major public health problem, not least by the World Health Organization [6].

2. Epidemiology

Depressive disorders have a prevalence of approximately 5% in the general population. This proportion increases to around 10% among people who contact their general health services for any reason [6]. The prevalence of depressive disorders is known to rise considerably among those who have chronic physical illnesses. Thus, at least 20% of patients with chronic conditions, such as cardiovascular disease or diabetes, suffer from depressive disorders, although the formal diagnosis is made in only a small proportion [7,8]. The lifetime prevalence of depression is as high as 20% in the general population worldwide, with a female-to-male ratio of about 5:2 [6]. We have to assume that only about one third of patients with depression are diagnosed and treated—perhaps because their symptoms often are not sufficiently different from the usual everyday complaints to attract diagnostic attention. Typically, the course of the disease is recurrent and most patients recover from major depressive episodes. However, in a substantial proportion of the patients, the illness becomes chronic, and after 5 and 10 years of prospective follow-up, 12% and 7% of them, respectively, are still depressed [9]. In patients who do recover, there is a high rate of recurrence, and it has been found that approximately 75% of patients will experience more than one recurrence of major depression within 10 years [10,11].

Another very important aspect of depression is the high rate of comorbidity with other psychiatric disturbances. Anxiety, especially panic disorder, is often associated with affective disorders, whereas the magnitude of the association with alcohol or drug abuse, although important, is less pronounced [12,13].

Suicide is estimated to account for approximately 0.9% of all of the world's deaths [6]. About 4000 people kill themselves each day worldwide, and more than 30 000 kill themselves each year in the United States alone [6]. To put the figures into perspective, the total number of deaths from suicide is the same as the total number of deaths from malaria worldwide [6] Depression is probably the most important risk factor for suicide; two thirds of all suicides are committed by people suffering from depressive disorders [6]. About 21% of patients with recurrent depressive disorders will attempt suicide and, unfortunately, many will be successful [6].

Depressive disorders cause more disability than most chronic physical disorders, with the possible exception of myocardial infarction. Thus, many patients with depression experience a degree of disability more severe than that caused, for example, by diabetes or osteoarthritis [6].

World Health Organization and the World Bank have calculated how many years of life will be lost owing to disability related to depression. Taking the world as a whole, the disability associated with depressive illness results in the loss of almost 13 million years of life each year [14]. This figure can be easily translated into terms of economic loss and human loss and suffering.

3. Pathophysiology

Neuroimaging technology provides unprecedented opportunities for elucidating the neurobiological correlates of mood disorders. Functional imaging tools such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging have enabled in vivo characterization of the "metabolic and blood-flow patterns" in normal and pathological emotional states. Neurochemical imaging techniques using PET, SPECT, and magnetic resonance spectroscopy provide in vivo quantitative analysis of neuroreceptor pharmacology, dynamic neurotransmitter function, and molecular biology. Structural magnetic resonance imaging permits assessment of regional morphology and morphometry in primary psychiatric disorders, and localization of pathology in psychiatric syndromes arising secondary to brain lesions.

Neuroimaging studies of primary mood disorders have identified neurophysiologic abnormalities in the orbital and medial prefrontal cortex (PFC), the amygdala, and the related parts of the striatum and thalamus [15]. Some of these abnormalities appear mood state dependent and are located in regions where cerebral blood flow increases during normal and other pathological emotional states. Differences in regional blood flow between depressed and control subjects may thus implicate areas where changes in physiological activity mediate or respond to the emotional, behavioral, and cognitive manifestations of major depressive episodes. Other abnormalities persist after symptomatic remission in primary mood disorders and are found in areas where postmortem studies demonstrate reductions in cortical volume and histopathologic changes [16]. Evidence from brain mapping, lesion analysis, and

electrophysiologic studies of human beings and experimental animals suggests that these areas may modulate emotional behavior and stress responses. Dysfunction involving these regions is thus hypothesized to play a role in the pathogenesis of depressive symptoms. Together, these findings implicate interconnected neural circuits in which dysfunction may result in the emotional, motivational, cognitive, and behavioral manifestations of mood disorders.

There has been a revolution in our understanding of the pathogenesis of depression, with recent work demonstrating, among others, the critical impact of stress [17]. Within the brain, the interrelated roles of the hippocampus, amygdala, and PFC are being clarified [17]. Stress-induced changes in the hippocampus allow the amygdala—the major system involved in emotive responses to stimuli—to become dominant, in the sense that there is an associated downgrading of some aspects of PFC function [18]. In rats, acute stress blocks long-term potentiation in the hippocampus and its projections to the frontal cortex (anterior cingulate cortex) [19]. These effects on plasticity are reversed by antidepressants [20]. These brain areas are precisely the specific regions that show changes in patients with long-term depression, when assessed by means of imaging studies and postmortem histology.

In depression, there is frequently reduced blood flow in frontal areas and prolonged and repeated depression is associated with marked atrophy in cortical regions and hippocampus [20]. Postmortem studies have shown reductions in neuronal size and neuronal and glial density in the orbitofrontal cortex and the dorsolateral frontal cortex [21]. Histomorphologic studies show that glial and neuronal density is reduced in the PFC (particularly the dorsolateral PFC) in major depression, and a reduction has also been found in glial cells in the subgenual frontal cortex, an important projection area for the hippocampus and the amygdala [22].

It has been reported recently that in depressed patients, the volume of the orbitofrontal cortex is markedly reduced (32%), with a corresponding reduction in blood flow [23]. Blood flow is restored (particularly in specific areas of the anterior cingulate cortex) after successful antidepressant therapy [24]. Interestingly, blood flow was restored in exactly the same brain areas in patients who responded to placebo, showing that the effects were not just a pharmacological coincidence, but a real change associated with the improvement in mood.

There is an abundant evidence from family, twin, and adoption studies that genetic factors play an important role in the etiology of affective disorders [25]. There is strong epidemiological evidence for a genetic contribution, especially in bipolar disorders, and heritability is estimated to be as high as 80% [25]. However, the inheritance does not follow the classical Mendelian pattern, which suggests that a single major gene locus may not—or at least only in few families—account for the increased intrafamilial risk for the disorder [26]. A more likely model is that of a complex disorder, which postulates that several genes of modest effect interact with each other or with a variety of environmental factors to increase familial susceptibility to the disorder [26].

Molecular genetic studies not only offer the possibility of unraveling the gene or genes responsible for heritability, but will also enhance our insights into the pathophysiological mechanisms of the conditions under investigation.

A variety of hormonal abnormalities, such as altered levels of cortisol, growth hormone, or thyroid hormones, indicate the existence of endocrine disturbances, especially dysfunctions in the hypothalamic-pituitary-adrenal (HPA) axis and/or the regulation of thyroid function. The consistent finding that a significant subpopulation of depressed patients hypersecrete cortisol during the depressed state, but not after recovery, led to intensive investigation and analysis of the HPA system.

Despite the initial findings of immunosuppression in depression, some studies have indicated that immune activation could also be present and might even play a role in the onset of depressive symptoms [27]. This hypothesis is reinforced by the finding of increased plasma cytokine and acute phase protein concentrations in the blood of depressed patients [28].

Neurotrophic factors are among the growth factors that have been studied for their role in the adult nervous system. Of these endogenous proteins, brain-derived neurotrophic factor and neurotrophin-3 have been shown to promote the function and the growth of 5-hydroxytryptamine (5-HT)–containing neurons in the adult brain [29]. Chronic, but not acute, infusions of these substances have impressive effects on serotonergic neuronal growth and regeneration, and further induce sprouting of 5-HT nerve terminals [29]. Accordingly, depression may result from dysfunctions in the areas of the brain that are modulated by systems such as the frontal cortex, hippocampus, amygdala, and basal ganglia. It is also well known that these areas are highly sensitive to the effects of stress, possibly explaining the adverse impact of life events on depression. Thus, many different factors could lead to a selective or generalized dysfunction in these brain areas, accounting for the apparent heterogeneity of depression.

4. Pharmacotherapy

Despite advances in the pharmacotherapy of depression, only one third of patients respond favorably to antidepressant drugs. One third do not respond at all, and in clinical trials, at least one third respond to placebo. There is clearly an urgent need for novel antidepressants.

It has also become clear that the serotonin reuptake inhibitors (SSRIs) are no more effective than the earlier tricyclic antidepressants, although their side effects are different. Sexual dysfunction may be a key factor in the depressed state, and the deleterious effects of SSRIs on sexual

function are a major disadvantage. Overall, suicide rates are scarcely affected by the availability of antidepressants unless major efforts are made by general practitioners to detect and obtain treatment for patients found to be suicide risks.

The fact that elevated serotonin levels are not associated with any significant improvement in one third of depressed patients given SSRIs suggests that the underlying cause of the condition is not being treated. Indeed, some of the effects of SSRIs may be attributable to drug-induced changes in personality traits, rather than changes in mood [30]. Adding noradrenaline uptake inhibition (eg, with venlafaxine or duloxetine) has caused a modest increase in effectiveness of SSRIs, but at the price of increasing cardiovascular side effects, particularly rises in systolic blood pressure [31]. Taking another serotonergic approach, agonists of 5-HT_{1A} receptors such as buspirone can markedly increase 5-HT release [32]. But buspirone has only limited effectiveness in depression, and no other major therapies have evolved from this approach, despite many drugs undergoing clinical trials [33]. The use of SSRIs has been extended to treatment of anxiety states and related disorders, but with no improvement in efficacy over older drugs such as the benzodiazepines (although the side effects of SSRIs replace those of benzodiazepines) [34].

5. The future

In general, the pharmaceutical industry's approach to drug development is to take the latest scientific techniques (such as genetics, high-throughput screening, and receptor imaging) and then to apply them to a disease. In the future, the order of the approach will be reversed, with the disease and the patients' needs coming first. The technology will then serve as a means to this end. It is necessary, first, to gain a deeper understanding of the physiological mechanisms at work, both in healthy individuals and during disease processes. Then, and only then, should new technologies be brought into play to help us to create and test active compounds. This disease-related approach is a better way to discover and develop well-designed and carefully targeted drugs, with significantly improved clinical efficacy. I also believe that the new discoveries concerning neuronal plasticity, and the significant morphological and functional changes among cells and specific brain systems, require a reordering of our investigative priorities. Disease states should be examined at a higher level, rather than concentrating on single biochemical mechanisms or on the enhancement or repression of neurotransmitters. Psychiatric and neurological disease should be addressed at a cellular and systemic level, with the aim of reversing pathological changes within the brain and restoring normal form and function.

In this supplement of *Metabolism*, various aspects of depression are discussed by outstanding authors. We shall see that today, we already have in hand the tools, the technologies, and the methodologies that will allow us to understand better how the brain works, as well as the mechanism and the pathophysiology of depression. There is a strong basis for hope that in the near future, it will be possible to control, treat, and even prevent this pervasive and disabling disease.

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