RESEARCH AND TREATMENT APPROACHES TO DEPRESSION

Ma-Li Wong and Julio Licinio

Depression is a major cause of disability worldwide, but we know little about the underlying fundamental biology. Research is hindered by the difficulties of modelling a disorder of higher cognitive functions in animals. Depression can be understood as the interaction of genetic susceptibility and environmental factors; however, current classifications are purely descriptive. The complexity of this field is best approached by rigorous explorations of known candidate systems in conjunction with the use of genomic tools to discover new targets for antidepressants and to predict therapeutic outcomes.

DSM-IV
American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders Fourth Edition.

CYCLOTHYMIA
A mild form of bipolar disorder, characterized by recurring episodes of hypomania and depression.

ANHEDONIA
Loss of interest or pleasure in almost all activities.

MORBIDITY
The incidence or prevalence of a disease in a population.

Clinical Pharmacology Program, Laboratory of Pharmacogenomics, Neuropsychiatric Institute, Brain Research Institute, Gonda Neuroscience and Genetics Research Center, University of California, Los Angeles, School of Medicine, Los Angeles, California 90095-1761, USA.
Correspondence to M.-L.W. and J.L.
e-mails: mali@ucla.edu; licinio@ucla.edu

> "Grief and fear, when lingering, provoke melancholia."
>
> Hippocrates, 460–377 BC

μελαγχολια (melancholia, from the Greek, 'black bile') is the only condition whose original name survived from the Hippocratic classification of diseases based on the four humours. Hippocrates thought that melancholia was caused by the humour 'black bile' and that treatment should consist of purging and removing of blood. In the contemporary classification of psychiatric disorders (DSM-IV)[1], melancholia is defined as a subtype of major depression. Major depression, in turn, is a diagnostic category within the mood disorders, which also include dysthymia (chronic intermittent minor depression), CYCLOTHYMIA, and bipolar disorder (manic–depressive illness).

How do we now approach depression, a condition that has been identified since antiquity but is still conceptualized as a common and complex disorder of unknown aetiology? How is depression different from ordinary sadness? Why is it still a syndrome without an established set of biological correlates? Why do we not know more about depression in the light of recent advances in molecular biology, genomics and proteomics?

A triad of symptoms clinically characterizes depression: low or depressed mood, ANHEDONIA and low energy or fatigue. Other symptoms, such as sleep and psychomotor disturbances, pessimism, guilty feelings, low self-esteem, suicidal tendencies, and food-intake and body-weight dysregulation, are also often present. The disease is more prevalent in women — the female:male ratio can be as high as 5:2. Typically, the course of depression is recurrent; patients go through periods with symptomatic episodes and periods of recovery. However, ~17% of patients have a chronic unremitting course[2]. Because each of its symptoms is not qualitatively different from experiences all of us have at some points in our lives, depression is frequently not detected or misdiagnosed. In a recent Swedish study, 10.1% of patients in a gynaecology clinic suffered from previously unrecognized major depression[3]. In a geriatric primary care setting in Rochester, New York, 6.5% of patients had untreated major depression[4]. The distinction between depression and everyday sadness is based on the unrelenting nature of depression and the accompanying disability. The DSM-IV classification requires that symptoms be present 'nearly every day for two weeks' before the diagnosis of major depression can be made.

The prevalence of depression is consistently high worldwide, and is associated with considerable MORBIDITY and mortality. Community surveys in Europe show a one-year prevalence of 9.3% in Finland[5], and a six-month prevalence of 8% in Italy[6] and 1.4% in rural Bavaria, Germany[7]. In Japan, a survey[8] of first-year university students showed an astonishing one-year prevalence of up to 53.4%. A detailed and well-controlled

Table 1 | **Lifetime and annual rates and onset age for major depression, ages 18–64 years***

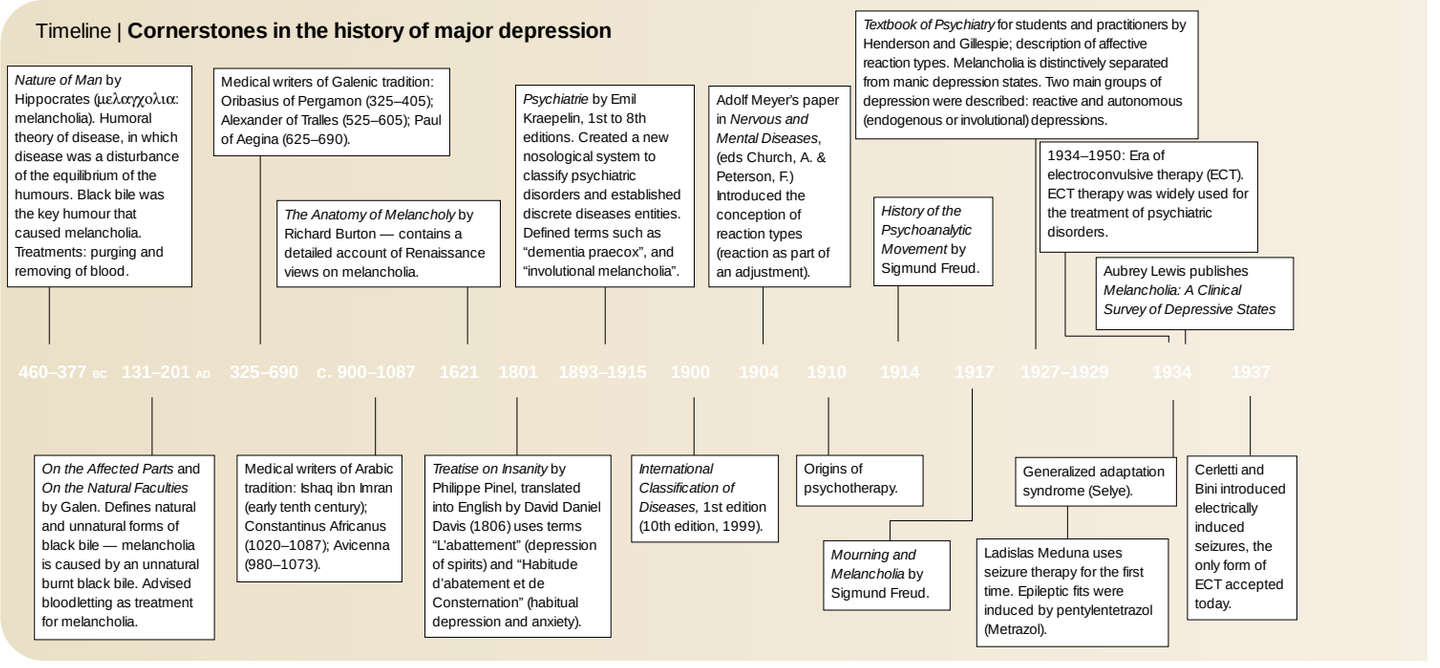
Country	Annual rate per 100 (SE)	Lifetime rate per 100 (SE)				
		Overall	Females	Males	Female ratio	Mean age at onset in years (SE)
United States	3.0 (0.18)	5.2 (0.24)	7.4 (0.39)	2.8 (0.26)	2.6 (0.11)	25.6 (0.30)
Edmonton, Alberta, Canada	5.2 (0.45)	9.6 (0.60)	12.3 (0.93)	6.6 (0.73)	1.9 (0.13)	24.8 (0.52)
Puerto Rico	3.0 (0.49)	4.3 (0.59)	5.5 (0.91)	3.1 (0.72)	1.8 (0.29)	29.5 (1.19)
Paris, France	4.5 (0.65)	16.4 (1.16)	21.9 (1.80)	10.5 (1.39)	2.1 (0.16)	29.2 (0.52)
West Germany‡	5.0 (1.13)	9.2 (1.50)	13.5 (2.46)	4.4 (1.56)	3.1 (0.39)	29.7 (1.18)
Florence, Italy	Not available	12.4 (1.33)	18.1 (2.16)	6.1 (1.40)	3.0 (0.26)	34.8 (1.12)
Beirut, Lebanon	Not available	19.0 (1.76)	23.1 (2.63)	14.7 (2.25)	1.6 (0.19)	25.2 (1.00)
Taiwan	0.8 (0.09)	1.5 (0.12)	1.8 (0.19)	1.1 (0.16)	1.6 (0.17)	29.3 (1.04)
Korea	2.3 (0.22)	2.9 (0.24)	3.8 (0.38)	1.9 (0.29)	2.0 (0.18)	29.3 (0.88)
Christchurch, New Zealand	5.8 (0.70)	11.6 (0.96)	15.5 (1.51)	7.5 (1.14)	2.1 (0.18)	27.3 (0.58)

*Figures standardized to US age and sex distribution. ‡Data from former Federal Republic of Germany (West Germany) based on ages 26 to 64 years. (SE, standard error) (Adapted with permission from REF. 9 © (1996) American Medical Association.)

cross-national epidemiological study examined lifetime rates of depression in ten countries[9] (TABLE 1). Weissman and colleagues suggest that the wide range in rates across countries might indicate that variations in culture or in risk factors could affect the expression of the disorder. The estimated lifetime prevalence in the United States is 21.3% in women and 12.7% in men[10].

Depression costs the US economy, directly and indirectly, over 43 billion dollars per year[11], and it is a leading cause of disability worldwide[12]. Suicide, which is usually a consequence of depression, is the eighth leading cause of death in the United States. The rate of suicide is even more alarming when it is examined as a function of age. Suicide is the sixth leading cause of death in the 5–14 age group, the third leading cause of death in the 15–24 age group, and the fourth leading cause of death in the 25–44 age group[13]. It seems that the incidence of major depression is increasing and that the onset of this condition occurs at a younger age now than in previous generations. The one-year prevalence in a Swedish high-school group of 2,300 was 11.4%, with a female–male ratio of 4:1. The most common manifestation of depression in that sample was a chronic course of more than one-year duration[14]. Gerald Klerman defined the current era as the "age of melancholy"[15].

Several lines of evidence indicate an important contribution of depression to medical morbidity. Depressed patients have an increased risk of premature death when compared with control subjects[16,17]. Epidemiological studies point to heart disease as one possible explanation for the decreased life expectancy, as depression is an independent risk factor for cardiovascular disease. It



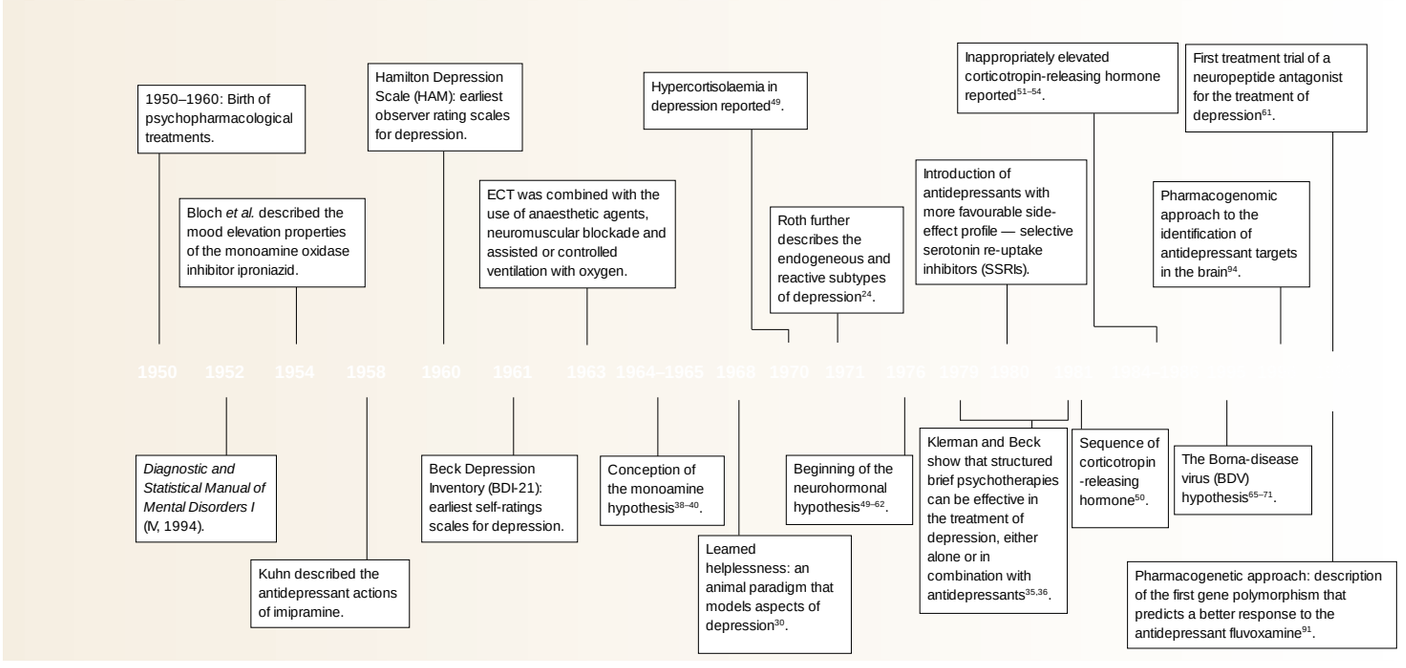
increases the risk of myocardial infarction more than fourfold after controlling for both medical risk factors and other psychiatric diagnosis[18]. In myocardial infarction, depressive symptoms increase medical and psychological morbidity and mortality even after controlling for the severity of coronary disease[19]. It has also been associated with decreased bone mineral density. Premenopausal 41-year-old women with past or current depression have bone mineral densities that are equivalent to those of healthy 70-year-old women[20].

Although the description of depression can be traced back to Hippocratic writings, our current understanding of this disorder emerged in the second half of the nineteenth century. Emil Kraepelin's formulations of psychiatric disorders took into consideration clinical and anatomical concepts (TIMELINE), and he classified depression as a disease. By contrast, in the same historical period, Freud viewed depression as the manifestation of internalized anger or loss. Freud's concept seemed to stem from early Hippocratic writings, as cited in the epigraph of this article. Freudian thought profoundly influenced generations of psychiatrists, particularly in the United States. Interestingly, some parts of the Freudian hypothesis were experimentally tested only very recently. For example, the work of Lerer and colleagues, published in 1999, showed that the loss of a parent before age nine (early parental loss) is a highly significant predictor of depression later in life[21]. The same study indicated that depression was significantly more associated with parental divorce than with the death of a parent and that loss of a mother had a more profound effect on outcome than loss of a father. Freudian thinking has been criticized in recent years, but it seems that at least this aspect of his theory was correct after all[22].

From a historical perspective, there have been large swings in the classification pendulum, ranging from very descriptive-based strategies, such as those of Kraepelin and the American Psychiatric Association, to interpretative-based approaches, such as Freud's. In most of Northern Europe, Asia and Latin America, the Kraepelinian, descriptive approaches have always prevailed because Freudian analytic thinking never became as strongly entrenched in the academic psychiatry of those countries as it did in the United States (except for France, where the influence of Freudian thinking has also been substantial). Additionally, the distinct conceptual approaches from two British groups have had a great effect in this field. The Maudsley group, represented by Aubrey Lewis and colleagues, promoted a continuum model from anxiety syndromes, to mild, moderate and severe psychotic depression[23]. By contrast, the Newcastle group, represented by Martin Roth and colleagues, classified these manifestations of depression in a categorical manner, separating them into distinct groups. Martin Roth and the Newcastle group further contributed to the understanding of clinical manifestations through their work characterizing endogenous and reactive subtypes of depression[24].

At present, major depression is defined as a disorder, on the basis of the results from the United States–United Kingdom diagnostic project[25] and the National Institute of Mental Health collaborative study of the psychobiology of depression[26]. The results of these projects supported the distinction of unipolar (depression) and bipolar (manic–depressive) disorders, which is reflected in the recent editions of the DSM-IV[1] and in the International Classification of Diseases (ICD-10)[27].

A mild but chronic and disabling manifestation of depression that had been previously conceptualized as a personality disorder (depressive personality disorder) is now classified in the DSM-IV as a distinct mood disorder — dysthymia. The work of Akiskal was instrumen-



Box 1 | Classification categories for depression

- **Onset: early, postpartum, late**
- **Clinical course: single episode, recurrent, chronic**
- **Severity: mild, moderate, severe**
- **In remission: partial or full**
- **With/without psychotic features: mood congruent or incongruent**
- **With/without catatonic features**
- **With atypical features**
- **With melancholic features**
- **Seasonal pattern**
- **Secondary to medical illness**

tal in moving dysthymia from a personality disorder to a pharmacologically treatable type of mood disorder[28].

A key problem in diagnosis that has baffled non-psychiatrists is the fact that the elaborate classification systems that exist today are solely based on the subjective descriptions of symptoms. Such detailed phenomenology includes the description of multiple clinical subtypes (BOX 1); however, there is no biological feature that separates one subtype from another. It is well known that different diseases can show similar clinical manifestations and also that the same disease can manifest itself differently in different patients. For example, precocious puberty can be caused by various diverse and unrelated genetic defects and environmental factors, and hepatitis B can manifest itself in forms as diverse as acute hepatitis, chronic active hepatitis, cirrhosis of the liver or hepatocarcinoma, or it can be fully asymptomatic. In clinical research on depression, some related fundamental questions remain unanswered. Is each subtype of depression the result of different biological abnormalities? Or are they merely different manifestations of the same underlying disease process? Such basic aspects about the nature of depression have yet to be clarified because we still lack an unequivocal understanding of the biology of this disorder.

Animal models

A main obstacle for depression research is the fact that this condition affects higher cognitive human processes such as motivation and self-esteem, which cannot be easily modelled in animals. Although existing animal models for depression involve the induction of pain, fear or loss, it is unclear whether they really model the same disorder that affects humans, or if they are solely representations of the effects of stress, pain or deprivation. Nevertheless, conditions such as LEARNED HELPLESSNESS can, as proposed by Seligman, model at least some features that are disrupted in depression[29–31]. Additional models that are reminiscent of aspects of depression include bond disruption (offspring–mother separation) in non-human primates[32] and in rodents[33], and chronic dominance–subordination relationships between male rats in a seminatural situation. In this model, Blanchard and Blanchard showed that male subordination reduces longevity and produces a pattern of behavioural changes that are very similar to the defences elicited by predatory exposure. They proposed that many of those changes are equivalent to certain behavioural features of clinical depression[34].

Treatments

Despite the strengths of animal studies, it is unclear to what extent they model the human disorder. Because of the difficulties for modelling in animals a disorder that involves higher human emotions, a key approach to research on depression has been the study of the effects of antidepressants. It has been proposed that understanding the pathways and mechanisms that underlie antidepressant treatments can substantially advance our understanding of depression.

Currently accepted methods of treatment have been described as early as 1937, with the introduction of electroconvulsive therapy (ECT), which is an often used and very efficacious treatment of severe melancholia. Although psychoanalysis was never shown by scientific methods to be effective, the studies of Beck and Klerman successfully documented that brief, structured psychotherapy is an effective treatment for depression[35,36]. Structured psychotherapy modalities, particularly COGNITIVE–BEHAVIOURAL or INTERPERSONAL types, have a significantly positive outcome as a sole treatment for mild cases or, in combination with antidepressants, in moderate to severe cases.

Pharmacological treatments were serendipitously discovered in the mid-1950s and helped to revolutionize our understanding of neurotransmitters and their receptors. The Nobel Prize awarded to Julius Axelrod in 1970 recognized his discoveries on the mechanisms that regulate the production of noradrenaline in nerve cells and the mechanisms that are involved in the inactivation of this transmitter[37]. Noradrenaline levels seem to be abnormal in depression and are affected by antidepressant treatment. Moreover, MONOAMINE OXIDASE (MAO) inhibitors and TRICYCLIC DRUGS can be effective antidepressants. Antidepressants are in fact a heterogenous group of drugs that act primarily by increasing the availability of monoamines at the synaptic cleft. Understanding their pharmacology has provided the means for the formulation of the monoamine hypothesis of depression. It has also broadened the approach of developing new drugs, such as the selective serotonin reuptake inhibitors that have less side effects but are not more efficacious than previously available tricyclic drugs.

Mechanisms

The monoamine hypothesis. Developed out of a meticulous research effort in modern psychiatry, the monoamine hypothesis (also known as the biogenic amine hypothesis) was an early milestone in the field of depression. Under this hypothesis, depression was postulated to reflect a deficiency or imbalance in noradrenaline[38,39] or serotonin[40]. These conclusions were based on observations that several antidepressant drugs increased synaptic concentrations of noradrenaline or serotonin, and that reserpine, a catecholamine-depleting drug, could cause depression-like symp-

LEARNED HELPLESSNESS
A cessation of the attempts to reach a goal as a consequence of the idea that rewards are not contingent on the attempts. Learned helplessness is accompanied by motivational and emotional deficits that have been proposed to model certain aspects of depression.

COGNITIVE–BEHAVIOURAL PSYCHOTHERAPY
Form of psychotherapy that aims to strengthen self-esteem and provide the patient with support and understanding. Cognitive–behavioural psychotherapy emphasizes the analysis of the problems at hand, and the definition of concrete goals and solutions so that the patient can recognize progress.

INTERPERSONAL PSYCHOTHERAPY
Form of psychotherapy used for the treatment of depression, which explores the relationships between the patient and other people, particularly around the time when the depression began, and uses the difficulties in those relationships as a treatment focus.

MONOAMINE OXIDASE
Enzyme located on the outer mitochondrial membrane, which catalyses the hydrolysis of biogenic amines such as catecholamines and serotonin.

TRICYCLIC DRUGS
Molecules that inhibit biogenic amine reuptake, therefore prolonging the period during which these neurotransmitters are active at the synaptic cleft.

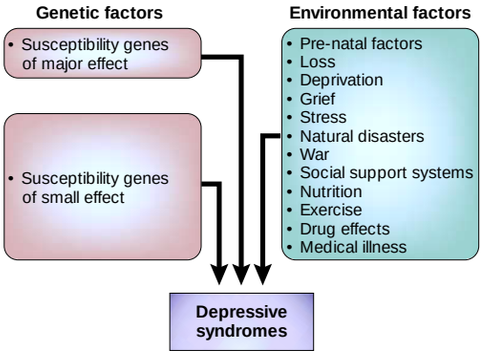


Figure 1 | **A conceptual approach to depression.** Available evidence consistently indicates that neurobiological substrates underlying depression phenotypes are the outcome of a combination of genetic and environmental factors.

toms[38,39]. Catecholamine depletion by dietary methods has also been shown to induce a relapse of depressive symptoms[41–43]. Subsequent variations of the monoamine hypothesis were supported by animal research, including the findings that antidepressants effectively treat learned helplessness.

Thirty years of research have revealed some serious gaps and limitations in the monoamine hypothesis[44]. For example, studies on noradrenaline spillover in plasma and cerebrospinal fluid documented increased noradrenaline output in depression[45,46]. Moreover, drugs that target monoamines affect these neurotransmitter systems within hours of initial treatment. Consequently, the monoamine hypothesis does not fully explain why antidepressant effects only occur after several weeks of daily treatment. Theories that postulate long-term changes in receptor sensitivity have unsuccessfully tried to bridge this gap[47]. It is now believed that changes in brain gene expression that are elicited after chronic treatment might underlie the effects of antidepressants (see section on pharmacogenomics).

Box 2 | **Stress and depression: epiphenomenon or pathophysiology?**

The term "stress" was introduced to biology by Selye, who, in 1936, described the generalized adaptation syndrome that occurs in reaction to adverse situations[96]. The stress response has two main effectors — the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system — both of which are dysregulated in the depressed state but are normalized during remission. The nature of the association between stress and depression has been an area of intense debate[97]. Those who are sceptical that there is any causal association between the two states point out two facts. First, it is expected that a depressed patient would be stressed, but this could be simply an epiphenomenon — a result and not a cause of depression. Second, there is no specificity in the association between stress and depression; chronically stressed individuals have been described to be more susceptible to a wide array of medical and psychiatric disorders. On the other hand, the most convincing evidence for a possible pathophysiological role of stress systems in depression has been provided by the following three sets of findings. First, antidepressants directly downregulate HPA function in rodents and humans[98–100]. Second, antagonism of corticotropin-releasing hormone attenuates behavioural, neuroendocrine and autonomic responses to stress in primates[101], and was effective in the treatment of depressed patients in a limited pilot study[62]. Third, increased noradrenaline concentrations are elevated in the cerebrospinal fluid throughout the day and night, even during sleep, which suggests that such dysregulation of a stress-related system is primary and not merely a reaction to depressed mood[46].

Neuropeptides. Although anxiety disorders, such as panic disorder and simple phobias, have been classified separately from mood disorders since the late 1970s (ICD-9 and DSM-III), there is considerable overlap in symptomatology between anxiety states and depression. Rating scales for depression and anxiety contain common factors[48]. Clinical and biochemical features of depression, especially of the melancholic subtype, closely resemble those that occur during acute stress (BOX 2). The response to stress is accompanied by the activation of the sympathetic nervous system and the hypothalamus–pituitary–adrenal (HPA) axis. In the face of persistent stress, continued activation of these central systems could lead to a final common pathway, resulting in failure to maintain homeostasis. Sustained activation of the sympathetic nervous system has been identified in major depression[46]. Moreover, hypercortisolaemia has been one of the most reproducible biological findings in major depression, although it is nonspecific and non-universal[49]. The characterization of corticotropin-releasing hormone (CRH)[50] has greatly assisted testing of the hypothesis that elevated cortisol levels fail to adequately suppress CRH in depressive states. Indeed, the hypothesis that increased CRH bioactivity results in hypercortisolaemia in depression has been supported by clinical research findings[51–54].

Gold and colleagues have proposed that various depression subtypes could be associated with differential levels of CRH activity. Whereas the melancholic subtype (characterized by increased anxiety, insomnia and weight loss) might be associated with increased central CRH function, these authors have hypothesized that depression subtypes that show atypical features such as fatigue, hypersomnia and hyperphagia might actually have decreased CRH activity and consequent decrements of HPA function. Therefore, decreased central levels of the arousal-producing neuropeptide CRH might explain the decreased levels of activity, increased fatigue, hypersomnia and increased food intake that are observed in patients with atypical features[55,56].

Our understanding of neuropeptide systems that are involved in the pathophysiology of major depression continues to grow. Dysfunctions in growth hormone, in the thyroid axis, in opioid receptors and in substance P have all been described[57,58]. Augmentation of antidepressant treatment with thyroid hormone is an accepted approach to the treatment of refractory major depression[59,60]. Substance P is involved in the neurobiology of pain. In addition, substance P is expressed in regions of the central nervous system (CNS) that are important for the regulation of affective behaviour and is activated as a neurochemical response to stress.

Substance P antagonism has been used as an effective antidepressant treatment[61]. Such successful use of a neuropeptide antagonist represented a paradigm shift in our approach to the treatment of depression. Subsequently, antagonism of CRH was reported in a small pilot study as a successful treatment of depression[62]. It remains to be seen whether these approaches will be used in the clinic and whether they will indeed represent an improvement over existing drugs.

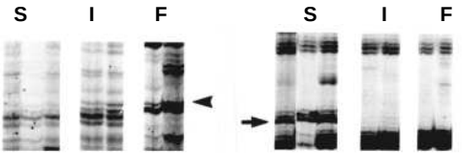


Figure 2 | **Differential displays comparing RNAs from saline (S)-, imipramine (I)- or fluoxetine (F)-treated rats.** Total RNA was extracted from hypothalami of animals treated with the different drugs for two months. Autoradiograms of amplified α-[^{35}S]-dATP-labelled PCR (polymerase chain reaction) products after electrophoresis in 6% polyacrylamide gels are shown for two different primer combinations that identified one upregulated (arrowhead) and one downregulated (arrow) fragment in the groups treated with antidepressants.

Nevertheless, the results from these studies have supported the idea that neuropeptides are a key element in the biology of depression and have given us the opportunity for novel antidepressant treatment strategies that go beyond the monoamine hypothesis.

Circadian regulation. Abnormalities in the circadian regulation of sleep, temperature and activity cycles have been described in major depression[63]. Short latency to the onset of rapid-eye-movement sleep, as well as early-morning awakening seem to reflect a phase shift of the biological clock. Moreover, sleep deprivation and exposure to bright white light ameliorates depressive symptoms by correcting this phase shift. Sleep deprivation causes a short-lived remission of depression and light therapy is an effective treatment for seasonal affective illness[64].

Infectious agents. Borna-disease virus (BDV) is a neurotrophic, single-stranded enveloped RNA virus that persistently infects birds, rodents and primates[65]. Infection causes disturbances in behaviour and cognitive functions but can also lead to a fatal neurological disease and there has been considerable interest in the hypothesis that BDV infection is associated with depression. Positive reports include descriptions of BDV antibodies[66] and viral genomic transcripts in patients with recurrent depression[67], the isolation of infectious BDV from mononuclear cells of patients[68], and the detection of BDV antigen and RNA in human autopsy brain samples from patients with depression[69]. However, there are also several negative reports that show no association of BDV with depression[70,71]. Only detailed, carefully controlled, prospective studies will determine if BDV infection can be a cause of some forms of depression.

Neuroimmune mediators. A logical way to search for a mechanism of disease is to look at all existing types of pathological process and to see which one is most compatible with the clinical course of the disorder. If one looks at the clinical evolution of depression, one sees that the disorder advances along a variable course with long periods of full recovery between periods of depression. But depressive stages can also happen more and more often until a severe and unremitting course is reached. Among the mechanisms of disease (which include atrophy, necrosis, degeneration, inflammation and neoplasia), inflammation can best explain the highly variable, waxing and waning course of depression. A focus of our laboratory has therefore been the study of genes that encode inflammatory mediators in the brain and their relationship to depression. It should be kept in mind, however, that alternative theories could explain the clinical course of depression, a condition in which genetic substrates interact with environmental factors and the ageing process to result in specific clinical manifestations (FIG. 1).

The immune system is a key mediator of brain–body interactions[72,73]. Immune mediators such as cytokines influence various key CNS functions that are dysregulated in major depression — sleep, food intake, cognition, temperature and neuroendocrine regulation[74,75]. The biology of specific brain cytokines has been the topic of recent reviews[76,77]. Administration of INTERLEUKIN 1β (IL-1β) in the CNS produces stress-like effects on behaviour, monoamine neurotransmitters, HPA activity and immune function[78,79]. IL-1β potently stimulates hypothalamic CRH production and HPA activation[80,81]. IL-1β is also a regulator of the serotonin transporter gene[82]. In addition, peripheral cytokines are key regulators of bone metabolism and are likely to be involved in cardiovascular disease. Activation of peripheral cytokines has been documented in depressed patients[83]. We have shown that the central and peripheral cytokine actions are integrated but differentially regulated[84]. It is therefore conceivable that whereas brain cytokines might be implicated in the pathophysiology of major depressive disorder, peripheral cytokines might be involved in its additional consequences, such as cardiovascular disease and decreased bone mineral density[85].

Genetics. Major depression is a familial disorder in which first-degree relatives carry a threefold increase in risk when compared to the general population. It does not show classic Mendelian inheritance that could be attributable to a single gene. It has therefore been classified as a genetically complex disorder, much like heart disease, hypertension, diabetes and cancer[86]. However, in spite of an enormous amount of work in this area, at present there are no linkage or association genetic findings that have been adequately confirmed and accepted[87]. Genetic studies have supported the hypothesis that genetic and environmental influences contribute to familial aggregation of the disorder. Major depression has an estimated heritability of 31–42%, which is much lower than the 70% heritability estimated for schizophrenia and bipolar disorder[88]. However, when patients are assessed longitudinally and an error of measurement is incorporated into a structural equation model that includes two occasions of measurement, the estimated heritability of depression is shown to be about 70%. More than half of what were considered environmental effects seemed to be heritable factors when two assessments were used to reflect measurement error. On the basis of these findings, Kendler *et al.* have proposed that major depression as assessed over the lifetime might be a rather highly heritable disorder of

IINTERLEUKIN-1β
Signalling molecule involved in the inflammatory response that can act as an endogenous pyrogen.

POLYMORPHISM
The simultaneous existence in the same population of two or more genotypes in frequencies that cannot be explained by recurrent mutations.

DIFFERENTIAL DISPLAY
A method for the rapid, accurate and sensitive detection of altered gene expression between different cell populations. The method is based on the amplification of 3′-terminal portions of messenger RNAs and resolution of these fragments on a DNA sequencing gel, allowing for the direct comparison of most of the mRNAs between related cells.

SERIAL ANALYSIS OF GENE EXPRESSION
A method for the analysis of gene expression that converts polyadenylated messenger RNA into complementary DNA by reverse transcription. Oligonucleotide 'tags' are then hybridized to the cDNA, ligated to form concatemers that are amplified by PCR, and finally cloned and sequenced. The number of tags present indicates the prevalence of the gene, therefore providing a quantitative profile of cellular gene expression.

Box 3 | Key issues in the pharmacogenetics of antidepressants

Clinical

- **Excessive expectations**
- **Retrospective versus prospective studies**
- **Sample size**
- **Confidentiality**
- **Individual and family informed consent**
- **Genetic background**
- **Ethnic stratification**
- **Community consultation**
- **Continual versus categorical outcome measures**
- **Correctly assigning phenotypes**
- **Choice of drugs and treatment strategy**
- **Treatment compliance**
- **Placebo responses**
- **Environmental contributions to treatment outcome**
- **Shared environment**

Molecular genetics

- **Genome-wide single nucleotide polymorphism (SNP) mapping**
- **Candidate genes**
- **Allele frequencies**
- **Antidepressant-related gene discovery**
- **SNP discovery**
- **Functional characterization of polymorphisms**
- **Examination of many SNPs in a few genes**
- **Examination of a few SNPs in many genes**
- **Coding versus non-coding polymorphisms**
- **Functional versus non-functional polymorphisms**
- **Considering haplotypes**
- **Statistical approaches to multiple comparisons**
- **Determining small effects in the context of multiple comparisons**

moderate reliability, rather than a moderately heritable disorder of high reliability[89].

The role of gene–environment interactions in depression can be best conceptualized as genetic vulnerability that might be expressed in response to life events that are stressful to the vulnerable individual. In a comprehensive review of existing data, Sullivan *et al.* have concluded that recurrence best predicts familial aggregation, and that major depression is a complex disorder that does not result from either genetic or environmental influences alone but rather from both[88]. It is interesting to see that seven decades of scientific work support Aubrey Lewis's statement[23] made in 1934 that the contribution of environmental and constitutional factors was "not an 'either–or' problem" (FIG. 1).

The search for molecular substrates underlying the inheritance of psychiatric disorders has been a challenge for geneticists and has not resulted in any universally accepted findings. Considering the concerted effort to identify susceptibility loci by the National Institute of Mental Health, it is expected that current research will yield results in the next few years. The next generation of genetic studies will benefit from recent advances such as genome-wide scans, large sample sizes, better-characterized cohorts and the availability of high-density genome-wide markers.

TOTAL GENE EXPRESSION ANALYSIS
A procedure that aims to elucidate entire gene expression patterns for a given tissue or cell. It requires a complex series of steps that involve multiplex PCR, complementary DNA cloning, *in vitro* transcription, cDNA construction, sequencing gel analysis and quantification.

DNA MICROARRAY
Device used to interrogate complex nucleic acid samples by hybridization. Microarrays make it possible to count the number of different RNA or complementary DNA molecules that are present in the sample of interest as a preparative stage for their subsequent characterization.

Future approaches

Pharmacogenetics. A major hindrance in clinical treatment is our inability to know *a priori* what antidepressant would be best suited for a specific clinical case. At present, several groups worldwide are trying to overcome that obstacle by searching for genetic POLYMORPHISMS that might be predictive of treatment response. A rational candidate for association studies of antidepressant treatment response is the serotonin transporter, which is the initial target of selective serotonin reuptake inhibitors. Lesch *et al.* have identified a functional polymorphism in the upstream regulatory region of the serotonin transporter gene that affects transcriptional efficiency[90]. This polymorphism has been associated with the antidepressant effects of the selective serotonin reuptake inhibitors[91,92], and also with the positive effects of sleep deprivation, which is an effective but short-lasting non-pharmacological treatment of depression[93].

Although a full discussion of pharmacogenetics is outside the scope of this article, we believe that it might be useful to identify key points that are related to emerging studies in this area. First, however, there should be a word of caution. The promise of identifying an individual's likelihood of responding to a treatment is of enormous clinical and economic importance, but is it a realistic expectation? We might identify the likelihood of treatment response but it might not be feasible to determine with certainty at the individual level whether a person will respond to a drug. Research approaches to this area are fraught with complex issues that require careful consideration (BOX 3).

Pharmacogenomics. It is clear that our insufficient understanding of the pathophysiology of major depression has constrained our ability to improve antidepressant therapies. The limiting factor in the development of new treatments for depression is the paucity of novel targets. The sequencing of the human genome has fostered an unprecedented development of new technologies. High-throughput technologies that can simultaneously examine the expression of thousands of genes have served as the foundation for the new field of pharmacogenomics. Pharmacogenomic tools, such as DIFFERENTIAL DISPLAY, SERIAL ANALYSIS OF GENE EXPRESSION (SAGE), TOTAL GENE EXPRESSION ANALYSIS (TOGA), MICROARRAYS and high-throughput PCR (polymerase chain reaction) are now being applied to the study of the genomic effects of antidepressants.

Several features of antidepressant treatments have guided pharmacogenomic approaches. Biochemical effects of antidepressants on monoamine systems occur within a few hours of treatment. By contrast, clinical effects only occur after chronic treatment for at least three weeks. Also, drugs that act on different monoamine systems, such as the selective serotonin reuptake inhibitors and the selective noradrenaline reuptake inhibitors, share the same clinical antidepressant effects. An increasingly popular working hypothesis

is that drugs of various classes have common antidepressant effects after chronic use owing to their ability to regulate transcription of the same set of downstream genes. In 1996, the first identification of new gene transcripts that are equally regulated by chronic treatment with antidepressants of different classes was achieved[94] (FIG. 2). This approach is now being embraced by industry and academia. The scope of this work includes the identification of antidepressant-regulated genes, the functional characterization of those genes and their use in pharmacogenetic studies.

Conclusions

The word 'melancholia' is of Greek origin and is derived from the term black bile (melaina chole), which was known as the melancholic humour. In *Nature of Man*, Hippocrates delineated the four elements of health and disease, and described the humoural theory of diseases. However, more than 24 centuries passed before the introduction of effective treatments for depression. The discovery of antidepressant drugs and the study of their pharmacology have revolutionized the field in the last 50 years. There are now dozens of approved drugs, which belong to four different classes — tricyclic drugs, selective serotonin reuptake inhibitors, MAO inhibitors and miscellaneous antidepressants. Each drug has a success rate of about 60%. When patients do not respond to one drug, they are switched to a different one, usually of a different class, until various classes of antidepressant are tried. At present, the choice of medication is completely arbitrary and often based on their side-effect profile, as there are no uncontested predictors of clinical response to specific antidepressants. Because clinical response only occurs after chronic treatment, well-conducted drug trials usually last 6–8 weeks, followed by a washout period before starting another trial. As a result, highly symptomatic patients can undergo several months of trials until an effective antidepressant is identified. This process is expensive and time consuming, and leads to poor compliance, considerable morbidity and sometimes mortality, as patients can have partial responses that lead to improvement of psychomotor retardation but not of depressive feelings, resulting in increased likelihood of suicide.

Understanding the fundamental biology of major depression has proved to be a challenging scientific problem of enormous clinical relevance[95]. Consequently, pharmacogenetic approaches that lead to the identification of the best antidepressant medication for a patient on the basis of their genetic profile would be of clinical and public health value. Pharmacogenomics brings the promise of much needed improvement in our understanding of molecular mechanisms and pathways involved in the responses to antidepressants. Work on available candidate systems might result in new treatment approaches and might further elucidate dysregulations in neural circuitry[101]. A detailed examination of known candidates, combined with searches for new targets, will result in new insights into the biology of major depression.

Links

FURTHER READING **National Institute of Mental Health**
ENCYCLOPEDIA OF LIFE SCIENCES **Mood disorders**

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, Washington, DC, 1994).
2. Zis, A. P. & Goodwin, F. K. Major affective disorder as a recurrent illness: a critical review. *Arch. Gen. Psychiatry* **36**, 835–839 (1979).
3. Sundstrom, I. M., Bixo, M., Bjorn, I. & Astrom, M. Prevalence of psychiatric disorders in gynecologic outpatients. *Am. J. Obstet. Gynecol.* **184**, 8–13 (2001).
4. Lyness, J. M., Caine, E. D., King, D. A., Cox, C. & Yoediono, Z. Psychiatric disorders in older primary care patients. *J. Gen. Intern. Med.* **14**, 249–254 (1999).
5. Lindeman, S. *et al.* The 12-month prevalence and risk factors for major depressive episode in Finland: representative sample of 5993 adults. *Acta Psychiatr. Scand.* **102**, 178–184 (2000).
6. Dubini, A., Mannheimer, R. & Pancheri, P. Depression in the community: results of the first Italian survey. *Int. Clin. Psychopharmacol.* **16**, 49–53 (2001).
7. Fichter, M. M. *et al.* Prevalence of mental illness in Germany and the United States. Comparison of the Upper Bavarian Study and the Epidemiologic Catchment Area Program. *J. Nerv. Ment. Dis.* **184**, 598–606 (1996).
8. Tomoda, A., Mori, K., Kimura, M., Takahashi, T. & Kitamura, T. One-year prevalence and incidence of depression among first-year university students in Japan: a preliminary study. *Psychiatry Clin. Neurosci.* **54**, 583–588 (2000).
9. Weissman, M. M. *et al.* Cross-national epidemiology of major depression and bipolar disorder. *J. Am. Med. Assoc.* **276**, 293–299 (1996).
A detailed assessment of lifetime and annual rate depression prevalence in ten countries: Canada, France, Germany, Italy, Korea, Lebanon, New Zealand, Puerto Rico, Taiwan and the United States.
10. Blazer, D. G., Kessler, R. C., McGonagle, K. A. & Swartz, M. S. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am. J. Psychiatry* **151**, 979–986 (1994).
11. Greenberg, P. E., Stiglin, L. E., Finkelstein, S. N. & Berndt, E. R. The economic burden of depression in 1990. *J. Clin. Psychiatry* **54**, 405–418 (1993).
Estimates that the total cost of depression in the United States was $43.7 billion per year in 1990.
12. Murray, C. J. L. & Lopez, A. D. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk factors in 1990 and Projected to 2020* (Harvard Univ. Press, Cambridge, Massachusetts, 1996).
13. Murphy, S. L. Deaths: Final data for 1998. *National Vital Statistics Reports (CDC)* **48**, 1–106 (2000).
14. Olsson, G. I. & von Knorring, A. L. Adolescent depression: prevalence in Swedish high-school students. *Acta Psychiatr. Scand.* **99**, 324–331 (1999).
15. Klerman, G. L. in *The Harvard Guide to Modern Psychiatry* (ed. Nicholi, J.) 253–281 (Belknap/Harvard Univ. Press, Cambridge, 1978).
16. Kerr, T. A., Schapira, K. & Roth, M. The relationship between premature death and affective disorders. *Br. J. Psychiatry* **115**, 1277–1282 (1969).
17. Harris, E. C. & Barraclough, B. Excess mortality of mental disorder. *Br. J. Psychiatry* **173**, 11–53 (1998).
18. Pratt, L. A. *et al.* Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation* **94**, 3123–3129 (1996).
19. Glassman, A. H. & Shapiro, P. A. Depression and the course of coronary artery disease. *Am. J. Psychiatry* **155**, 4–11 (1998).
References 18 and 19 report that a history of depression increases the risk of myocardial infarction and the risk of death after infarction.
20. Michelson, D. *et al.* Bone mineral density in women with depression. *N. Engl. J. Med.* **335**, 1176–1181 (1996).
21. Agid, O. *et al.* Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Mol. Psychiatry* **4**, 163–172 (1999).
Shows that loss of a parent (mother more than father) before age nine is a significant predictor of depression later in life.
22. Nemeroff, C. B. The preeminent role of early untoward experience on vulnerability to major psychiatric disorders: the nature–nurture controversy revisited and soon to be resolved. *Mol. Psychiatry* **4**, 106–108 (1999).
23. Lewis, A. J. Melancholia: a clinical survey of depressive states. *J. Ment. Sci.* **80**, 277–378 (1934).
A classic description of depression.
24. Garside, R. F., Kay, D. W., Wilson, I. C., Deaton, I. D. & Roth, M. Depressive syndromes and the classification of patients. *Psychol. Med.* **1**, 333–338 (1971).
25. Gurland, B. Aims, organization, and initial studies of the Cross-National Project. *Int. J. Aging Hum. Dev.* **7**, 283–293 (1976).
26. Katz, M. M., Secunda, S. K., Hirschfeld, R. M. & Koslow, S. H. NIMH clinical research branch collaborative program on the psychobiology of depression. *Arch. Gen. Psychiatry* **36**, 765–771 (1979).
27. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnosis Guidelines* (World Health Organization, Geneva, Switzerland, 1992).
28. Akiskal, H. S. Dysthymia and cyclothymia in psychiatric practice a century after Kraepelin. *J. Affect. Disord.* **62**, 17–31 (2001).
29. Seligman, M. E. Learned helplessness as a model of depression. Comment and integration. *J. Abnorm. Psychol.* **87**, 165–179 (1978).
30. Seligman, M. E., Maier, S. F. & Geer, J. H. Alleviation of learned helplessness in the dog. *J. Abnorm. Psychol.* **73**, 256–262 (1968).
31. Seligman, M. E., Rosellini, R. A. & Kozak, M. J. Learned helplessness in the rat: time course, immunization, and reversibility. *J. Comp. Physiol. Psychol.* **88**, 542–547 (1975).
32. Kalin, N. H. & Carnes, M. Biological correlates of attachment bond disruption in humans and nonhuman primates. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **8**, 459–469 (1984).
33. Plotsky, P. M. & Meaney, M. J. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res. Mol. Brain Res.* **18**, 195–200 (1993).
34. Blanchard, D. C. & Blanchard, R. J. Behavioral correlates of chronic dominance-subordination relationships of male rats

in a seminatural situation. *Neurosci. Biobehav. Rev.* **14**, 455–462 (1990).
References 29–34 examine animal syndromes that model aspects of the depression phenotype.
35. Weissman, M. M. *et al.* The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. *Am. J. Psychiatry* **136**, 555–558 (1979).
36. Kovacs, M., Rush, A. J., Beck, A. T. & Hollon, S. D. Depressed outpatients treated with cognitive therapy or pharmacotherapy. A one-year follow-up. *Arch. Gen. Psychiatry* **38**, 33–39 (1981).
References 35 and 36 show that brief, structured psychotherapies are effective in the treatment of depression, and that they can be successfully combined with pharmacological treatments.
37. Nobel Foundation. *Nobel Lectures — Physiology or Medicine, 1901–1970* (Elsevier, Amsterdam, 1970).
38. Bunney, W. E. & Davis, J. M. Noradrenaline in depressive reactions. A review. *Arch. Gen. Psychiatry* **13**, 483–494 (1965).
39. Schildkraut, J. J., Gordon, E. K. & Durell, J. Catecholamine metabolism in affective disorders. I. Normetanephrine and VMA excretion in depressed patients treated with imipramine. *J. Psychiatr. Res.* **3**, 213–228 (1965).
40. Coppen, A. The biochemistry of affective disorders. *Br. J. Psychiatry* **113**, 1237–1264 (1967).
41. Delgado, P. L. *et al.* Serotonin function and the mechanism of antidepressant action. Reversal of antidepressant-induced remission by rapid depletion of plasma tryptophan. *Arch. Gen. Psychiatry* **47**, 411–418 (1990).
42. Miller, H. L. *et al.* Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. *Arch. Gen. Psychiatry* **53**, 117–128 (1996).
43. Charney, D. S. Monoamine dysfunction and the pathophysiology and treatment of depression. *J. Clin. Psychiatry* **59**, 11–14 (1998).
References 41–43 show that noradrenaline- and serotonin-selective probes can potentially identify subsets of depressed patients who might respond differentially to selective noradrenaline or serotonin reuptake inhibitors.
44. Thase, M. E., Frank, E. & Kupfer, D. J. in *Handbook of Depression: Treatment, Assessment, and Research* (eds Beckham, E. E. & Leber, W. R.) 816–913 (Dorsey, Homewood, Illinois, 1985).
45. Veith, R. C. *et al.* Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma noradrenaline kinetics. *Arch. Gen. Psychiatry* **51**, 411–422 (1994).
46. Wong, M. L. *et al.* Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl Acad. Sci. USA* **97**, 325–330 (2000).
References 45 and 46 report increased activity of sympathetic systems in depression.
47. Siever, L. J. & Davis, K. L. Overview: toward a dysregulation hypothesis of depression. *Am. J. Psychiatry* **142**, 1017–1031 (1985).
48. Johnstone, E. C. *et al.* Neurotic illness and its response to anxiolytic and antidepressant treatment. *Psychol. Med.* **10**, 321–328 (1980).
49. Sachar, E. J., Hellman, L., Fukushima, D. K. & Gallagher, T. F. Cortisol production in depressive illness: a clinical and biochemical clarification. *Arch. Gen. Psychiatry* **23**, 289–298 (1970).
50. Spiess, J., Rivier, J., Rivier, C. & Vale, W. Primary structure of corticotropin-releasing factor from ovine hypothalamus. *Proc. Natl Acad. Sci. USA* **78**, 6517–6521 (1981).
51. Gold, P. W. *et al.* Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am. J. Psychiatry* **141**, 619–627 (1984).
52. Nemeroff, C. B. *et al.* Elevated concentrations of CSF corticotropin-releasing-factor-like immunoreactivity in depressed patients. *Science* **226**, 1342–1344 (1984).
53. Holsboer, F., Girken, A., Stalia, G. K. & Muller, O. A. Blunted corticotropin and normal cortisol response to human corticotropin-releasing factor in depression. *N. Engl. J. Med.* **311**, 1127 (1984).
54. Gold, P. W. *et al.* Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. *N. Engl. J. Med.* **314**, 1329–1335 (1986).
55. Gold, P. W., Wong, M. L., Chrousos, G. P. & Licinio, J. Stress system abnormalities in melancholic and atypical depression: molecular, pathophysiological, and therapeutic implications. *Mol. Psychiatry* **1**, 257–264 (1996).
56. Demitrack, M. A. *et al.* Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *J. Clin. Endocrinol. Metab.* **73**, 1224–1234 (1991).
57. Whybrow, P. C. & Prange, A. J., Jr. A hypothesis of thyroid-catecholamine-receptor interaction. Its relevance to affective illness. *Arch. Gen. Psychiatry* **38**, 106–113 (1981).
58. Gold, P. W. & Chrousos, G. P. The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proc. Assoc. Am. Physicians* **111**, 22–34 (1999).
59. Whybrow, P. C., Coppen, A., Prange, A. J. Jr, Noguera, R. & Bailey, J. E. Thyroid function and the response to liothyronine in depression. *Arch. Gen. Psychiatry* **26**, 242–245 (1972).
60. Joffe, R. T. Refractory depression: treatment strategies, with particular reference to the thyroid axis. *J. Psychiatry Neurosci.* **22**, 327–331 (1997).
61. Kramer, M. S. *et al.* Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* **281**, 1640–1645 (1998).
62. Zobel, A. W. *et al.* Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J. Psychiatr. Res.* **34**, 171–181 (2000).
63. Kupfer, D. J., Shaw, D. H., Ulrich, R., Coble, P. A. & Spiker, D. G. Application of automated REM analysis in depression. *Arch. Gen. Psychiatry* **39**, 569–573 (1982).
Documents decreased latency to rapid-eye-movement–sleep onset in depressed patients.
64. Gerner, R. H., Post, R. M., Gillin, J. C. & Bunney, W. E. Jr Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. *J. Psychiatr. Res.* **15**, 21–40 (1979).
65. Lipkin, W. I., Travis, G. H., Carbone, K. M. & Wilson, M. C. Isolation and characterization of Borna disease agent cDNA clones. *Proc. Natl. Acad. Sci. USA* **87**, 4184–4188 (1990).
66. Rott, R. *et al.* Detection of serum antibodies to Borna disease virus in patients with psychiatric disorders. *Science* **228**, 755–756 (1985).
67. Bode, L., Zimmermann, W., Ferszt, R., Steinbach, F. & Ludwig, H. Borna disease virus genome transcribed and expressed in psychiatric patients. *Nature Med.* **1**, 232–236 (1995).
68. Bode, L., Durrwald, R., Rantam, F. A., Ferszt, R. & Ludwig, H. First isolates of infectious human Borna disease virus from patients with mood disorders. *Mol. Psychiatry* **1**, 200–212 (1996).
69. De La Torre, J. C. *et al.* Detection of borna disease virus antigen and RNA in human autopsy brain samples from neuropsychiatric patients. *Virology* **223**, 272–282 (1996).
70. Kim, Y. K. *et al.* Failure to demonstrate Borna disease virus genome in peripheral blood mononuclear cells from psychiatric patients in Korea. *J. Neurovirol.* **5**, 196–199 (1999).
71. Tsuji, K., Toyomasu, K., Imamura, Y., Maeda, H. & Toyoda, T. No association of borna disease virus with psychiatric disorders among patients in northern Kyushu, Japan. *J. Med. Virol.* **61**, 336–340 (2000).
References 65–71 report that Borna-disease virus (BDV) might infect a small, but significant portion of patients with depression; however, these findings have not been fully replicated. A causal relation between depression and BDV is at present unclear.
72. Solomon, G. F. Psychoneuroimmunology: interactions between central nervous system and immune system. *J. Neurosci. Res.* **18**, 1–9 (1987).
73. Sternberg, E. M. Emotions and disease: from balance of humors to balance of molecules. *Nature Med.* **3**, 264–267 (1997).
74. Licinio, J., Wong, M. L. & Gold, P. W. Localization of interleukin-1 receptor antagonist mRNA in rat brain. *Endocrinology* **129**, 562–564 (1991).
75. Rothwell, N. J. & Hopkins, S. J. Cytokines and the nervous system II: Actions and mechanisms of action. *Trends Neurosci.* **18**, 130–136 (1995).
76. Van Wagoner, N. J. & Benveniste, E. N. Interleukin-6 expression and regulation in astrocytes. *J. Neuroimmunol.* **100**, 124–139 (1999).
77. Rothwell, N. J. & Luheshi, G. N. Interleukin 1 in the brain: biology, pathology and therapeutic target. *Trends Neurosci.* **23**, 618–625 (2000).
78. Connor, T. J. & Leonard, B. E. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci.* **62**, 583–606 (1998).
79. Weiss, J. M., Sundar, S. K., Becker, K. J. & Cierpial, M. A. Behavioral and neural influences on cellular immune responses: effects of stress and interleukin-1. *J. Clin. Psychiatry* **50**, S43–S53 (1989).
80. Buckingham, J. C., Loxley, H. D., Taylor, A. D. & Flower, R. J. Cytokines, glucocorticoids and neuroendocrine function. *Pharmacol. Res.* **30**, 35–42 (1994).
81. Rivier, C. Effect of peripheral and central cytokines on the hypothalamic–pituitary–adrenal axis of the rat. *Ann. NY Acad. Sci.* **697**, 97–105 (1993).
82. Ramamoorthy, S. *et al.* Regulation of the human serotonin transporter by interleukin-1β. *Biochem. Biophys. Res. Commun.* **216**, 560–567 (1995).
83. Maes, M. *et al.* Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* **9**, 853–858 (1997).
84. Wong, M. L., Bongiorno, P. B., Rettori, V., McCann, S. M. & Licinio, J. Interleukin (IL) 1β, IL-1 receptor antagonist, IL-10, and IL-13 gene expression in the central nervous system and anterior pituitary during systemic inflammation: pathophysiological implications. *Proc. Natl Acad. Sci. USA* **94**, 227–232 (1997).
Shows that central and peripheral cytokine compartments are integrated but differentially regulated: central cytokines are counter-regulated to a smaller extent than peripherally secreted ones.
85. Licinio, J. & Wong, M. L. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol. Psychiatry* **4**, 317–327 (1999).
86. Lander, E. S. & Schork, N. J. Genetic dissection of complex traits. *Science* **265**, 2037–2048 (1994).
87. Fava, M. & Kendler, K. S. Major depressive disorder. *Neuron* **28**, 335–341 (2000).
88. Sullivan, P. F., Neale, M. C. & Kendler, K. S. Genetic epidemiology of major depression: review and meta-analysis. *Am. J. Psychiatry* **157**, 1552–1562 (2000).
Shows that depression is caused by both genetic and environmental factors.
89. Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C. & Eaves, L. J. The lifetime history of major depression in women. Reliability of diagnosis and heritability. *Arch. Gen. Psychiatry* **50**, 863–870 (1993).
Shows that major depression as assessed over one's lifetime might be a rather highly heritable disorder of moderate reliability rather than a moderately heritable disorder of high reliability.
90. Lesch, K. P. *et al.* Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **274**, 1527–1531 (1996).
Discovery of a polymorphism in the regulatory region of the serotonin transporter gene that reduces transcriptional efficiency and might be correlated with anxiety traits.
91. Smeraldi, E. *et al.* Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. *Mol. Psychiatry* **3**, 508–511 (1998).
Proposes that genotyping the serotonin transporter regulatory region might be used as a tool to predict treatment response in depression.
92. Kim, D. K. *et al.* Serotonin transporter gene polymorphism and antidepressant response. *Neuroreport* **11**, 215–219 (2000).
93. Benedetti, F. *et al.* Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. *Am. J. Psychiatry* **156**, 1450–1452 (1999).
94. Wong, M. L., Khatri, P., Licinio, J., Esposito, A. & Gold, P. W. Identification of hypothalamic transcripts upregulated by antidepressants. *Biochem. Biophys. Res. Commun.* **229**, 275–279 (1996).
95. Hyman, S. E. Mental illness. Genetically complex disorders of neural circuitry and neural communication. *Neuron* **28**, 321–323 (2000).
Reviews the complexity of depression genetics.
96. Selye, H. A syndrome produced by diverse nocuous agents. *Nature* **138**, 32 (1936).
In this one-page article, Selye launched the field of stress biology. He showed that the organism had common responses to various types of stressor, and described those responses as much as it was possible using the methods available to him in the 1930s.
97. Chrousos, G. P. & Gold, P. W. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *J. Am. Med. Assoc.* **267**, 1244–1252 (1992).
98. Brady, L. S., Whitfield, H. J. Jr, Fox, R. J., Gold, P. W. & Herkenham, M. Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain. Therapeutic implications. *J. Clin. Invest.* **87**, 831–837 (1991).
99. Brady, L. S., Gold, P. W., Herkenham, M., Lynn, A. B. & Whitfield, H. J. Jr The antidepressants fluoxetine, idazoxan and phenelzine alter corticotropin-releasing hormone and tyrosine hydroxylase mRNA levels in rat brain: therapeutic implications. *Brain Res.* **572**, 117–125 (1992).
100. Michelson, D. *et al.* Chronic imipramine is associated with diminished hypothalamic-pituitary-adrenal axis responsivity in healthy humans. *J. Clin. Endocrinol. Metab.* **82**, 2601–2606 (1997).
References 98–100 show that attenuation of hypothalamus–pituitary–adrenal axis activity is a direct pharmacological effect of antidepressants.
101. Habib, K. E. *et al.* Oral administration of a corticotropin-releasing hormone receptor antagonist significantly attenuates behavioral, neuroendocrine, and autonomic responses to stress in primates. *Proc. Natl Acad. Sci. USA* **97**, 6079–6084 (2000).

Acknowledgements
We are grateful to Kevin Kelly. J.L. is supported by grants from the National Institutes of Health and by awards from the Dana and Stanley Foundations. M.-L.W. is supported by a grant from the National Institutes of Health and by a NARSAD award.