

Aetiology and pathology of clinical depression

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Clinical depression affects one in five people at some time in their lives. This, the first part of the special feature on depression, discusses its causes, symptoms and pathology



Depression is fast becoming a substantial public health concern, with the continuing rise in its prevalence. The World Health Organization (WHO) predicts that by 2020, depression will become the second leading cause of DALYs (disability adjusted life-years) lost worldwide, after ischaemic heart disease. About 20 per cent of the population will develop a depressive episode at some point in their lives, with up to 85 per cent of patients having more than one episode. Further, one in 10 patients with depression will commit suicide, and up to 20 per cent of patients with depression will have symptoms for two years or more (chronic depression).¹

These startling predictions contrast with the perception of the lay public. Perhaps even more worrying is that the knowledge of health professionals and their attitude towards depression are at odds with the WHO projections. This can be seen in the fact that despite the availability of effective treatments, only a quarter of primary care patients receive adequate pharmacological cover when treatment is initiated. It is crucial that patients receive effective treatments, since suboptimal treatment can be associated with patients developing chronic disease. It is noteworthy that guidelines and educa-

tional programmes have generally not been successful in improving the management of depression, despite there being over 45 separate treatment guidelines for depression in the UK. This suggests that there are major deficiencies in the attitudes of health professionals towards depression.

There is arguably one central belief that is proving to be a major barrier to successful therapy. This is the belief that depression is not a brain disorder but "a problem of the mind" occurring in the context of an understandable cause and thus not within the realm of conventional medical expertise. Such a view has evolved because little is known about the physiology of normal human emotion regulation and also because, like most psychiatric disorders, a quantifiable pathology has been difficult to identify. The term "depression" is a misleading label, being frequently used to denote emotional experiences ranging from normal sadness to a pathological condition. Given this, it is not surprising that pharmacological interventions are seen as an admission of weakness, shame or a psychological crutch that should be used for as short a period as possible.

both psychiatric and non-psychiatric.

Panel 1 (p220) provides examples of conditions in which depressed mood can be found. For non-psychiatric conditions, the presence of other symptoms and results from investigative tests will usually indicate the correct primary diagnosis. In a similar vein, attributing a psychiatric cause to a depressed mood requires the presence of other symptoms found in the syndrome, and is not a diagnosis reached by excluding other causes.

DIAGNOSIS

Psychiatry itself had previously confused matters by the way that depression was diagnosed and classified. Depression was classified as being either reactive/neurotic or endogenous.

Neurotic depression was described as being mild, related to particular stressors for the individual, associated with a lot of anxiety and less amenable to drug therapy. Endogenous depression was regarded as being more severe, unrelated to life stressors, characterised by specific symptoms and more amenable to drug treatment.

This classification system has been abandoned because its validity is questionable. For example, studies found that the occurrence of a stressful event before the onset of depression did not reliably predict a reactive/neurotic depression or response to any

SYMPTOMS

The feeling of depression, or a pervasive, continually lowered mood is a symptom and can be found in a number of diagnoses,

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Panel 1: Some conditions in which there is lowered mood

Endocrine disorders
Hypothyroidism
Cushing's syndrome
Addison's disease
Metabolic disorders
Diabetes mellitus
Porphyria
Neurological diseases
Parkinson's disease
Cerebrovascular disease
Cerebral tumours
Dementias
Huntington's disease
Multiple sclerosis
Hypertensive disorders
Antihypertensives
Antimalarials
Psychiatric disorders
Depressive disorder
Manic depressive disorder
Post-psychois depression
Personality disorders

particular type of treatment.² Further, reactive depression does occur without an identifiable precipitating event. As a result of these findings, diagnostic classifications such as the 'International classification of diseases' 10th edition (ICD-10) and the 'Diagnostic and statistical manual of mental disorders' 4th edition (DSM-IV), an American system, have been developed.^{3,4}

In both of these classifications (see Table 1, p221), a diagnosis of depression is made from the presence of a number of specific symptoms, or a syndrome, for a minimum of two weeks. It therefore relies on one of the most fundamental medical skills, that of recognising patterns of symptoms. This is unlike modern medical diagnostic practice as it is not based on specific pathology, does not have characteristic findings on investigative tests and does not even suggest the need for specific treatments. There is also no importance placed on any apparent immediate cause in making the diagnosis.

It should be noted that the symptoms selected to define the syndrome are based largely on consensus opinion. In addition, the amount of time that should have lapsed before a diagnosis can be made has been set arbitrarily and does not, for example, indicate whether treatment is justified on the basis of meeting minimum criteria. Both systems are structured so that they code the pattern of occurrences of the symptom complexes, such that patients may have single depressive episodes, have several episodes making up a depressive disorder or have a pattern of episodes of depression interspersed with episodes of pathologically elevated mood (manic episodes) making up

a bipolar affective disorder. The two systems differ in that ICD-10 provides guidelines in making a diagnosis, whereas DSM-IV is more explicit in the symptoms required to make a diagnosis. However, both systems allow the coding of somatic symptoms, psychotic symptoms, and other illness characteristics. Two advantages of these classification systems are the standardisation of diagnostic practice and a more accurate description of syndromes.

Standardisation of diagnostic practice The systems standardise diagnostic practice across the field of psychiatry and across countries. Previously, diagnostic practices varied considerably between, for example, Europe and the United States, making it difficult to ascertain if differences in the prevalence of depressive disorders were due to true variations in the prevalence of syndromes across regions or simply the result of differing diagnostic practices. ICD-10 and DSM-IV have been tested for reliability across regions and between countries. This has major benefits for research and development, including research carried out by the pharmaceutical industry.

Increased accuracy of descriptions The systems allow a more accurate description of the syndromes by allowing the different types of symptoms found in depression to be explicitly specified (eg, psychotic symptoms, somatic symptoms) and by allowing the specification of duration and severity.

It has to be stressed that these systems are only descriptive and have been designed to be free of any assumptions regarding aetiology or pathology.

— AETIOLOGY

Depression is a broad and heterogeneous psychiatric disorder that affects people of all ages, from childhood to old age. It varies in severity and duration, and there is a difference in incidence between the sexes. It is therefore unlikely that there is only one cause of depression. Rather, its aetiology is multifactorial, with contributions from factors such as genetic predisposition, the influence of early childhood experiences, the possible effects of psychosocial adversity, and biological and physiological effects of other physical diseases. Moreover, although many people do believe that depression is caused by a biochemical imbalance, the fact that there is not a single "biochemical imbalance rectifier" drug indicates that there is more than one final common pathway involved in the biochemical aetiology of depression.

It can therefore be said that a variety of factors can contribute to the predisposition to depression or precipitate depression. Nevertheless, it is not yet possible to deter-

mine the precise effect that these factors have on neurochemical function.

Genetic influence It has been recognised for over 50 years that mental disorders, including mood disorders, aggregate in families. By means of twin studies and studies of adopted children, the genetic contribution to affective disorders has been established. In twin studies, for example, concordance (the appearance of the same condition in both twins) is 80 per cent for bipolar disorders and 60 per cent for recurrent depression.⁵ The most representative figure for heritability is about 60 per cent for all severe affective disorders.⁶

However, it is not clear exactly what is inherited. For example, because of the possible role of serotonin in the treatment of depression, the finding of a difference in the polymorphism of a gene involved in serotonin transport in patients with depression was greeted with enthusiasm.⁷ However, this finding has been difficult to replicate subsequently, possibly suggesting the involvement of multiple genes in conferring a predisposition. Depression is therefore unlikely to be caused by a single faulty gene, but is a multifactorial disorder like diabetes and hypertension.

Early childhood environment If identifying the influence of genetics on the aetiology of depression has its difficulties, these are dwarfed by the challenges faced in trying to identify the influence of an individual's early life experiences on his or her predisposition to affective disorders.

For example, much research has been carried out on investigating the importance of the parent-child relationship, particularly parental deprivation. An influential study by Brown et al argued that the loss of the mother before the age of 11 years was associated with a greater risk of adult depression, suggesting a direct causal link.⁸ This has, however, been difficult to confirm, given that a parental loss can occur in the context of widely varying social environments which can have their own influences.

Recently, the only clear evidence suggests that lack of adequate parental care may be a developmental risk factor for adult depression.⁹

Age of onset Recent research illustrates the heterogeneous aetiology of depression. There is increasing evidence that late onset depression (usually defined as first occurring after the age of 65) may have a more vascular aetiology than early onset depression.¹⁰ This is based on the observation that patients with late onset depression show evidence of more vascular-related brain changes on magnetic resonance imaging (MRI), such as so-called white matter hyperintensities (discrete high intensity signals in white matter on MRI) which, post-mortem, are found to be

sclerotic lesions around the vasculature. This coincides with the observation of increased treatment resistance, increased mortality from cardiovascular disease and significant cognitive impairment in those with depression in later life, suggesting the presence of a disease process.¹¹ If this is found to be true, it could open up the possibility of using vascular agents in the treatment of depression in the elderly.

Social stress and life events Of all factors, social stress and life events have always appeared to be the most important in causing depression. Since the 1960s, a large amount of research has been carried out into the role of life events (defined as recent major changes in the individual's socio-economic situation) and social stress in the development of depression.

The evidence available indicates that the risk of depression increases following stressful life events, but many other causative and modifying factors also come into operation. It is also important to bear in mind that although many people undergo considerable distress following life events, relatively few develop overt clinical depression and fewer still come to the attention of a psychiatrist. Thus Cooke¹² found that the population attributable risk (an estimate of the proportion of the disorder caused by life events) for life events in depression was about 40 per cent, indicating that although life events were important, the greater part in determining if an event is followed by depression was attributable to a combination of other factors.

The effects of psychosocial stress are of particular importance because of the heuristic association with biological systems, particularly with the hypothalamic-pituitary-adrenal (HPA) axis which is known to exhibit a number of differences in patients with depression. This is examined in the next section.

Neuroendocrine changes Although a number of endocrine systems have been found to have altered function in depression, the greatest focus has been on the HPA axis, as it is the main endocrine stress system in humans and its ability to become active is essential in

Table 1: The ICD-10 and DSM-IV classification systems for depression^{3,4}

Classification	Symptoms of a depressive episode
ICD-10	Typical features for a period of around two weeks:
Examples:	1. Depressed mood
F32.x =	2. Loss of interest and enjoyment
Depressive episode	3. Reduced energy or increased tiredness
F33.x = Recurrent depressive disorder	4. Reduced activity
x specifies severity	Other common symptoms
	Reduced concentration and attention
	Reduced self-confidence and self-worth
	Guilt and unworthiness
	Bleak and pessimistic regarding the future
	Self-harm or suicidal ideas
	Disturbed sleep
	Reduced appetite
	Somatic symptoms
	Low mood may vary over the course of the day
	Motor activity may be slowed or increased
	Sexual appetite may be reduced
	Patient may lose weight
	Loss of interest and unreactivity of mood may be present
	Psychotic symptoms (usually hallucinations or delusions) may be present in severe depression. Determination of the severity of depression is based upon a clinical judgement involving the number, type and severity of symptoms
DSM-IV	Criteria for a depressive episode:
Examples:	1. At least five of the following for at least two weeks, and representing a change from previous function. One symptom must be either depressed mood or loss of interest/pleasure
296.2x = Major depressive disorder (MDD), single episode	Depressed mood for most of the day, nearly every day
296.3x = MDD, recurrent	Reduced interest or pleasure
x specifies severity or remission	Significant weight loss or gain or appetite change
	Insomnia or hypersomnia
	Psychomotor agitation or retardation
	Fatigue or loss of energy
	Feeling of worthlessness or inappropriate guilt
	Reduced concentration or indecisiveness
	Recurrent thoughts of death or suicidal thoughts or actions
	2. Do not meet criteria for mixed episode
	3. Symptoms cause significant distress or impairment
	4. Not due to direct physical effects of substances or general medical condition (eg, hypothyroidism)
	5. Not better accounted for by bereavement

adapting to chronic stress. It is well established that patients with depression often have abnormalities of the HPA axis, which are manifested in the form of hypercortisolism and adrenal hyperplasia.

These changes are more prevalent in depression with somatic-type symptoms and appear to depend on the patient's state.

These changes resolve on recovery from depression. Moreover, at a higher level on the axis, there appears to be a blunted response in depressed patients to the effect of corticotropin releasing hormone in stimulating the release of corticotropin.

HPA is also under the control of a variety of neurotransmitters, including serotonin, noradrenaline, acetylcholine and opioids. These are of obvious interest, given the therapeutic effects of monoamine-enhancing drugs in the treatment of depression. There is the suggestion that the common antidepressants exert their effect by modulating the HPA axis. However, the results of activating these receptor systems on the HPA axis in depressed patients have proved difficult to interpret because of the abnormalities that have already been demonstrated in the HPA axis.

Nonetheless, the HPA axis is still of considerable interest on a variety of fronts. Raised levels of cortisol in animal models have been found to be associated with neuronal damage, particularly within the hippocampus.¹³ If depressed patients also exhibit hypercortisolism, it is reasonable to expect that hippocampal change will be present in depressed patients.

Such hippocampal change has, in fact, recently been demonstrated, the degree of change correlating with the degree of memory impairment present in the depressed patient.¹⁴ This finding is also of interest from the perspective of developing novel antidepressants. For example, a recent review suggested that antigluco-corticoid drugs may have some form of antidepressant effect in about 67–77 per cent of patients, roughly equivalent to the size of response seen with conventional antidepressants.¹⁵ Such a response was best demonstrated in depressed, hypercortisolaemic patients, suggesting a causal role for HPA dysfunction in some patients.

Neurochemical changes The foremost biochemical theory of depression remains the monoamine deficiency hypothesis. This suggests that depression is due to a deficiency of a monoamine (and mania due to a relative excess). In its original form, it was postulated that brain noradrenaline was the

central amine involved. This was based on the observation that catecholamine-depleting drugs such as reserpine seemed to cause depressive symptoms. This hypothesis was extended when serotonergic enhancing drugs, such as L-tryptophan were found to possess antidepressant properties as well. Despite the proliferation of antidepressant drugs whose principal action involves monoamine systems, the hypothesis is not sufficient to explain the following observations:

- I Most monoamine active drugs have an almost immediate effect on their pharmacological sites, for example, in preventing monoamine reuptake. However, the therapeutic effect of most antidepressant drugs only becomes apparent after chronic administration for about two weeks. It has been postulated that this may be because the drugs cause receptor sensitivity changes on chronic administration. This is referred to as the receptor sensitivity hypothesis
- I It has been difficult to identify clear evidence of monoamine deficiencies in depressed patients, despite evidence that monoamine-enhancing drugs have antidepressant efficacy

The major barrier to investigating possible neuronal biochemical abnormalities in depression has been the lack of direct access to neuronal systems in vivo. Most of the previous studies have examined indirect markers of monoamine function by measuring neuroendocrine responses to monoamine challenge tests, measuring peripheral markers of central function (eg, platelet 5HT binding) or measuring cerebrospinal fluid or blood metabolites.¹⁶

However, modern neuroimaging techniques such as positron emission tomography and single photon emission tomography offer the potential to test specific monoamine hypotheses in vivo. By designing specific receptor or protein ligands, differences in receptor density can be measured. For example, using the competitive dopamine-D₂ receptor-specific ligand, [¹²³I]-3-iodomethoxybenzamide (IBZM,) a number of studies have suggested that dopamine release is reduced in the striatum of patients with depression, the degree of reduction being associated with the degree of psychomotor slowing found in the depressed patient.

PATHOLOGY

Until now, it has been difficult to establish the presence of any functional or structural brain abnormality in those with mood disorders. Part of the problem has been in the relatively poor resolution of established imaging methods such as computed tomography scanning.

A further problem has been the difficulty associated with the accurate measurement of neuronal function in vivo. Over the past 15 years, however, there has been a proliferation of neuroimaging studies in psychiatric disorders. These have led to the following conclusions:

- I Mood disorders are associated with measurable changes in regional brain function compared with controls¹⁷
- I The changes referred to above are different from the changes that occur when non-depressed subjects feel sad
- I It follows from the foregoing that severe depressive disorders are disorders of the brain

A major advance, recently, has been in increasing the resolution of structural imaging, such that it is now possible to measure the size and volumes of discrete brain structures in a meaningful way. This has led to the confirmation that discrete brain structures, particularly the hippocampus, undergo atrophy in patients with depression.¹⁸ This is a finding of significant importance as it supports the hypothesised effects of chronic hypercortisolism in depression. Another study of patients with chronic, treatment-resistant depression suggests that frontostriatal regions of the brain may show atrophy.¹⁹ A further study has indicated that trait (that is, pre-dating illness) changes may be present in the structure of parts of the anterior cingulate in those with familial depression.²⁰

FUTURE DIRECTIONS

The evidence that has been considered suggests that depressive illness, particularly severe and chronic types, may give rise to neurodegeneration. Conventional wisdom suggests that neurodegeneration is irreversible. However, the recent discovery that most antidepressants, including selective serotonin reuptake inhibitors, tricyclics, lithium and electroconvulsive therapy, lead to the production of brain derived neurotrophic factor (BDNF) is now providing an exciting challenge to this notion.

BDNF plays a critical role in the survival, maintenance, and neuronal plasticity of the central nervous system. Together with the recent demonstrations of neurogenesis in regions of the brain, including the neocortex and hippocampus in adult primates (including man), the prospect of therapeutic interventions that could correct pathophysiological disease-related changes has been opened up.

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