Recent Advances

Psychiatry

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Psychiatric illness stands out as having a rich multifactorial aetiology. This makes it unreasonable to expect massive advances because of the complexity of studies needed to understand it. Acknowledging the multifactorial nature of psychiatric illness, over the past year researchers have tried to consolidate information about different disorders—for example, by studying environmental aspects of the more biological conditions and biological aspects of the traditionally more environmental disorders—and in drawing up treatment protocols.

Schizophrenia

There have been some promising developments in the treatment of schizophrenia, with both pharmacological and psychological interventions. It is now recognised that the atypical neuroleptic drug clozapine is effective in 30-60% of patients with schizophrenia who do not respond to conventional neuroleptics.^{1,2} As up to 2% of patients treated with clozapine develop agranulocytosis, obligatory blood monitoring has been introduced, which can be a considerable obstacle to compliance for many chronically psychotic patients.

The introduction of clozapine in Britain in 1990 was followed by the release of another atypical neuroleptic, risperidone, in 1993. The clinical effects of these drugs have stimulated investigations into the neurochemistry of schizophrenia and are leading to the formulation and testing of different hypotheses to explain the disorder's complex phenomenology.

Conventional neuroleptics are presumed to exert their effect through blockade of dopamine D₂ receptors. Clozapine has a more complex pharmacology, with a lower occupancy of D₂ receptors and higher occupancy of D₁ receptors than conventional neuroleptics,^{3,4} in addition to potent blockade of 5HT₂ receptors. The finding that clozapine also selectively binds to the D₄ receptor led to speculation about the role of this receptor in the aetiology of schizophrenia. There is, however, no difference between patients who respond to clozapine and those who do not respond in the distribution of alleles for the D₄ gene,⁵ which suggests that clozapine's antipsychotic activity is not merely a result of its activity at the D₄ receptor. These findings reveal the inadequacy of a simplistic dopamine hypothesis to explain the aetiology of schizophrenia and the therapeutic effect of neuroleptic drugs.

Many patients with schizophrenia exhibit delusional beliefs, often with a paranoid theme, which can lead them to engage in irrational or self destructive behaviour. In most cases delusions respond to antipsychotic drugs, but some patients remain chronically deluded despite intensive pharmacotherapy. It is well recognised that psychosocial and family interventions

Recent advances in psychiatry

- New atypical neuroleptics clozapine and risperidone are useful in treating schizophrenia
- Cognitive behaviour therapy techniques help patients cope with delusional beliefs
- Serotonergic neurotransmitters are important in the aetiology of obsessive-compulsive disorder
- Education programmes for professionals and public have been developed about depression and a consensus statement for treatment has been introduced
- Second line strategies for "treatment resistant depression" include lithium augmentation and electroconvulsive therapy
- An animal model has been produced to investigate the amyloid hypothesis of Alzheimer's disease
- Genetic risk factors of Alzheimer's disease include the e2 allele on chromosome 19; the e4 allele seems to be protective
- A multifactorial aetiological model helps in understanding child sexual abuse within the context in which it occurred
- A supervision register has been introduced for patients with severe mental illness at risk of violence, suicide, or severe self neglect

can reduce the rate of relapse for schizophrenia,⁶ but it now seems that individual psychotherapy may also help patients to modify or cope with delusional beliefs. The techniques used in this type of work are derived from cognitive behaviour therapy. Over a series of sessions patients are encouraged to systematically review the start of their symptoms and are questioned in detail to identify faulty reasoning.⁷ Patients learn to monitor their psychotic symptoms and to develop coping strategies, including changing attention, relaxation techniques, and modifying behaviours which exacerbate psychotic symptoms. Efforts are also made to educate patients about their illness and to provide them with an acceptable explanation about the origin of their symptoms, with the aim of destigmatising the illness and improving compliance.

These techniques have been evaluated in a study that compared a cognitive behaviour therapy intervention designed specifically for psychotic patients with a non-specific problem solving therapy.⁸ Both treatments were effective in reducing psychotic symptoms (compared with the control period, when the patients were

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on a waiting list), but the cognitive behaviour therapy produced the greater reduction in symptoms. The patients had maintained the improvement six months later. The treatment has a drop out rate of up to half, but if the results of this study are replicated at other centres individual psychotherapy will probably, resources permitting, become part of the standard treatment for patients with chronic psychotic symptoms.

Obsessive-compulsive disorder

Obsessive-compulsive disorder classically presents as a combination of senseless repetitive rituals (compulsions) and intrusive repetitive thoughts (obsessions). The importance of neurobiological factors in the aetiology of this disorder is suggested by the observed increase in obsessive-compulsive symptoms after head injury and encephalitis. Structural brain imaging has failed to reveal consistent abnormalities in patients with the disorder, but recent functional imaging studies show a consistency that is unusual in the functional imaging studies of other psychiatric disorders. Positron emission tomography in patients with obsessive-compulsive disorder who were not receiving drugs showed increased cerebral blood flow in the orbitofrontal cortex and the dorsal parietal cortex and decreased cerebral blood flow to the caudate nucleus compared with controls.⁹ These findings are consistent with previous studies with positron emission tomography, which reported increased metabolic activity in the frontal cortex. Relevance to the psychopathology of obsessive-compulsive disorder has been shown in studies that induced obsessive-compulsive symptoms in patients undergoing positron emission tomography. It has been possible to show a close relation between severity of symptoms and cerebral blood flow in the orbitofrontal cortex, basal ganglia, hippocampus, and cingulate gyrus.^{10,11} Two elegant studies have compared the results of positron emission tomography before and after treatment. One of these found that improvement in obsessive-compulsive symptoms correlated with changes in caudate metabolism and that these changes were present in patients treated with either drugs or behaviour therapy.¹² The other study also showed a correlation between reduction in symptoms and decrease in orbitofrontal metabolism.¹³ One interpretation of these findings is that obsessive-compulsive symptoms may be the result of an abnormally functioning neurological circuit encompassing the orbitofrontal cortex, cingulate gyrus, and caudate nucleus.¹⁴ This hypothesis is open to testing and refinement with further functional imaging and neuropsychological studies.

Investigations of the neurochemistry of obsessive-compulsive disorder highlight the role of abnormalities in serotonergic neurotransmitters.¹⁵ Controversy

over the superiority of antidepressants with specific serotonergic agonist activity over other antidepressants has now concluded in favour of serotonergic drugs. Some of the evidence that supports this conclusion comes from an unlikely source: a study of the treatment of a type of obsessive-compulsive disorder in dogs known as canine acral lick (excessive licking of paws or flanks, which can produce ulcers and infection) showed clear superiority in serotonergic drugs (clomipramine and fluoxetine) over non-serotonergic antidepressants.¹⁶ A meta-analysis of studies of treatment for obsessive-compulsive disorder concluded that behaviour therapy, clomipramine, and fluoxetine were all effective.¹⁷ In view of the lower risk of relapse after effective behaviour therapy, however, this should still be considered the first line treatment.

Depression

Attempts to raise the profile of depression among professionals and the public have resulted in consensus statements,^{18,19} and public education programmes such as the "defeat depression campaign" run by the Royal College of Psychiatrists in Britain.²⁰

General practitioners still do not diagnose up to half of cases of depression, and, of those patients who receive treatment, 80% have ineffective doses for less than the minimum required course while 60% of patients who recover do not receive preventive drug treatment.²¹ These findings prompted the International Committee for the Advancement of Neuroscience and Psychiatry to issue a consensus statement on the long term management of depression. The key message is that, with a first episode of depression, a course of antidepressants should continue for six months and stopping the treatment sooner is likely to lead to a return of depression in up to 60% of cases.

Over the past year researchers have attempted to consolidate knowledge about other aspects of the management of affective disorder. Goodwin, analysing the results of studies on bipolar illness, found that over half of new episodes, especially of mania, occurred within three months of stopping treatment with lithium.²² He concluded that psychiatrists should not introduce lithium for the prophylactic treatment of bipolar illness until both the doctor and the patient understand that the drug must be used for a minimum of two years.

Treatment of depression may be helped by knowledge of the course of the illness in subjects with different temperaments. Double depression (acute illness superimposed on background depression) is associated with a dysthymic temperament, while cyclothymic depression (depression fluctuating with a normal or elated mood) is associated with a cyclothymic temperament.²³ It seems that these two types of depression respond to different treatments, traditional antidepressants being suitable for double depression and mood stabilisers such as lithium being particularly useful in cyclothymic depression.

Another example in which knowledge about the nature of a depressive illness might affect the treatment is the maternity blues. Interest is now focused on progesterone, Harris *et al* having shown that maternal mood in the days immediately after delivery is related to the withdrawal of naturally occurring progesterone.²⁴ In future this might mean that treatment with progesterone would decrease the severity of the blues.

In spite of the increased range of antidepressant drugs available, patients with "treatment resistant depression" continue to challenge clinicians. Evidence has been accumulating in support of alternative second line treatment strategies—for example, the addition of lithium to an antidepressant. Results from the

Treatment resistant depression*

Biological correlates

- Unrecognised medical illness
- Endocrine or metabolic disorder
- Neoplastic, immune mediated disorder
- Neurological disorder

Clinical correlates

- Insufficient antidepressant dose
- Inadequate trial length
- Misdiagnosis or comorbid psychiatric condition
- Other medical condition
- Interaction with concomitant drugs
- Compliance issues

*From Homig-Rohan M, Amsterdam JD. Clinical and biological correlates of treatment resistant depression: an overview. *Psychiatric Annals* 1994;24:220-7.

Positron emission tomography data superimposed on a magnetic resonance imaging scan from a patient with obsessive-compulsive disorder showing a positive correlation between symptom intensity and right cerebral blood flow in the left hippocampus (a), right inferior frontal gyrus (b), right putamen and globus pallidus (c), right thalamus (d), left cuneus (e), and left posterior cingulate gyrus (f)

first large controlled trial of lithium augmentation of fluoxetine or lofepramine showed a significant increase in response to treatment in the lithium augmentation group compared with the group given antidepressant only, provided subjects received adequate doses of lithium.²⁵ Another option is to use electroconvulsive therapy, to which at least half of patients with treatment resistant depression will respond.²⁶

Understanding depression requires knowledge of psychosocial factors too. Kupfer, arguing that antidepressant drugs had long term benefit in preventing recurrent episodes of depression, also found that monthly psychotherapy had a modest but significant prophylactic effect.²⁷

Alzheimer's disease

Severe dementia affects up to 5% of people aged over 65 and 20% of people aged over 80. With the increasing number of elderly people in the population, the number of sufferers will grow. Interestingly, the incidence of Alzheimer's disease, of both early and late onset, has been reported to be three times higher in first degree relatives of sufferers.²⁸ Most cases, however, occur sporadically, and similar concordance rates occur in monozygotic and dizygotic pairs of twins. The best model to explain the segregation analyses for patterns of familial clustering remains transmission of one or more autosomal dominant genes with reduced penetrance, together with a multifactorial genetic environmental background.

Neuropathological studies are still investigating the amyloid cascade hypothesis as a model of the pathogenesis of Alzheimer's disease. Controversy continues over whether deposition of amyloid is central to the pathological process.^{29,30} The strongest argument in favour of the amyloid hypothesis was the identification of pathological mutations in the gene for amyloid precursor protein that alter processing of the protein and make deposition of amyloid more likely.^{31,32} Until recently lack of an animal model hampered research, but Games *et al* have now reported the production of transgenic mice that express high concentrations of human mutant amyloid precursor protein and progressively develop many, but not all, of the pathological hallmarks of Alzheimer's disease (tests for cognitive dysfunction in the mice are still needed).³³ Use of transgenic mice should help in understanding the pathogenesis of the disease and might, in the long term, be suitable for testing therapeutic compounds.

Another substance relevant to the pathogenesis of Alzheimer's disease is the glycoprotein apolipoprotein E. A single gene on chromosome 19 encodes for apolipoprotein E and exists in three allelic variants, e2, e3, and e4. In 1987 this region of chromosome 19 was first implicated in familial Alzheimer's disease of late

onset. Both sporadic and familial Alzheimer's disease now seem to be associated with a higher frequency of the e4 allele compared with control groups, suggesting that possession of this allele is a genetic risk factor for the illness.³⁴ On the other hand the e2 allele seems to be protective; subjects aged over 70 who are homozygous for e2 have a smaller risk of being affected by Alzheimer's disease.³⁵

Child sexual abuse

Although studies have identified high rates of child sexual abuse in various community samples in different countries over the past 15 years, we are only now starting to develop ways of understanding its effects. Summarising the literature in 1993, Anderson *et al* stated that it "is common, serious, infrequently reported, the abuser is usually known to the child, and preadolescent girls are at greatest risk."³⁶ The effects of the abuse in children, and longer term in adults, are poorly understood and reflect the lack of a model to explain the consequences of child sexual abuse on victims. Research in the 1980s suggested that there was no specific syndrome in children, while studies on adults found associations with a wide range of psychiatric symptoms, with an increased incidence in clinical populations.^{37,38} However, the severity of the abuse does not seem to relate to the severity of the symptoms, and many victims are asymptomatic.

As more troubled people are "remembering" sexual violations (often under the supportive, encouraging, even coercive influence of therapists who are certain that the evocation and abreaction of such memories is essential for therapeutic success³⁹) researchers have challenged the belief that sexual abuse has a specific aetiological relation to specific syndromes. They have pointed out that rates of sexual abuse do not distinguish clinical, non-clinical, and community groups except in combination with other forms of abuse.⁴⁰

To explain possible consequences of child sexual abuse, we need a multifactorial aetiological model allowing us to understand the event of abuse in the context in which it occurred, looking at the effects of disturbed early family experiences in particular and their impact on the child's overall development. Attachment theory provides one useful conceptual framework for understanding the familial antecedents and long term consequences of sexual abuse.⁴¹ Child sexual abuse may be simply a marker for more general childhood adversity, the effects of the trauma depending on an individual's relationships, social environment, and constitution. Not surprisingly then it is more common in subjects from disrupted families and in those who also report physical and emotional abuse. However, these negative experiences explain only part of the apparent association between child sexual abuse and a range of negative outcomes such as a decline in socioeconomic status, increased sexual problems, and difficulties in intimate relationships.³⁷ We still need more information about the long term outcome in survivors of child sexual abuse and results of intervention, as well as more specific information about different types of abuse, the relationship with the perpetrator, and the context in which the abuse occurred.

Community psychiatry

One of the most important recent publications affecting British psychiatry is the report into the killing of Jonathan Zito in a London Underground station by Christopher Clunis, a patient with schizophrenia.⁴² The Ritchie report was highly critical of the care Clunis received, citing the repeated failure of clinicians to take

seriously Clunis's risk of violence and to accept responsibility for his care in the community after repeated hospital admissions. Clunis's case, along with several other highly publicised cases, attracted attention to the plight of people with mental illness in inner cities, the inadequacy of inpatient resources,^{43,44} and the need to improve the quality of care and supervision of patients in the community.

Part of the government's response to these concerns has been the introduction of the supervision register for patients with a record of severe mental illness who are at risk of violence, suicide, or severe self neglect.⁴⁵ Each patient on the register must be appointed a key worker (usually a community psychiatric nurse) who is trained in risk management and assessment. The key worker and consultant psychiatrist have responsibility for organising regular multidisciplinary review meetings to monitor the patient's progress. The supervision register has been criticised for its vague inclusion criteria and for placing new demands on a hard pressed service without any additional resources.^{46,47} The register may also invite litigation from patients who are aggrieved at being on the register and from victims of violent crime, who may take the view that their assailant should have been on the register or, if the assailant was on the register, that the clinician should have averted the assault.

The supervision register's commitment to a model of high intensity key working is also controversial as there have been few studies in Britain of this form of treatment in the community. There is no clear evidence that the risk of violence or suicide is reduced by assigning a key worker to high risk patients, although patients may benefit in other ways. What little evidence exists suggests that supervising patients in the community, with a heavy emphasis on reducing hospital admissions, may even increase the risk of violent acts.⁴⁸ However much clinicians resent government intrusion into their clinical practice, many will reluctantly agree that the supervision register and its predecessor, the care programme approach, have resulted in focusing services on the neediest patients, improving follow up in the community, and clarifying which members of the multidisciplinary team are responsible for devising and implementing an individual patient's care plan.

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