Reviews in Medicine

Psychiatry

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Introduction

The field of clinical psychiatry is very large and includes a number of specialities of which the principal ones relate to children and adolescents, the elderly, legal offenders, substance abuse, mental handicap and psychotherapy. Here are reviewed recent publications relating to four topics: Parkinson's disease, clozapine, neuroleptic malignant syndrome and human immunodeficiency syndrome. They have been chosen in the hope that they are of interest to the general physician and surgeon as well as to the general psychiatrist.

Psychiatric aspects of Parkinson's disease

For more than 60 years clinicians have recognized that mental disturbances are not uncommon in Parkinson's disease (PD). Some of these disturbances have well-known causes such as the unwanted effects of anticholinergic drugs and of dopamine agonists used to treat the disorder, but the relationships of the major psychiatric syndromes – particularly dementia and depression – to PD are still not well understood, in spite of much research in this field.

Some of the problems hindering advances in our understanding have been given prominence in the recent literature. First of all imprecise criteria often have been used in diagnosing PD, dementia and depression.^{1,2} Apart from idiopathic PD – the subject of this review – parkinsonism may be a feature of other neurological diseases, such as Alzheimer's disease (AD) (but only if the basal ganglia are involved) and progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and of head injury and bilateral subcortical vascular disease; in these conditions, dementia may be observed in addition to the parkinsonian extrapyramidal symptomatology.¹ In addition, these dementing disorders, particularly AD, may coexist with PD.³ Secondly, the symptoms of PD may be

confused with both depression and with dementia; the mask-like faces with little or no tendency to smile, the monotonous speech, and the stooped posture may give an appearance suggesting depression of mood, while PD may cause so much difficulty with verbal communication, perseveration and apparent apathy, that it may give rise to an inappropriate suspicion of dementia.⁴⁻⁶ Depression itself may lead to a misdiagnosis of dementia, particularly in the elderly where depressive 'pseudodementia' is often observed. Thirdly, confusional and delirious states, especially when mild or moderate in intensity and due to anti-parkinson medication, may be misdiagnosed as dementia.^{2,3}

Recently, to try to overcome these difficulties, clinical research into the prevalence and correlations of mental disturbances in PD has increasingly tended to use strictly defined criteria to diagnose dementia and depression – particularly the criteria in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) or its revised version (DSM-III-R) published by the American Psychiatric Association. However, an important criterion of dementia in DSM-III and DSM-III-R is interference with social functioning and/or work by the intellectual disabilities. In some cases of PD where there is interference, it is not always possible to decide whether this is due to disturbances in the mental state or to the direct effects of the motor disturbances.² The Present State Examination (PSE) – a structured interview during which psychiatric phenomena are rated – has also been used. In one recent study of depression and cognitive impairment in PD from the National Hospital, Queen Square,⁴ the investigators paid particular attention to ensuring that apparently psychiatric symptoms were not manifestations of parkinsonism or of the effect of drugs used in treatment; in fact, they found that certain syndromes – generated from the analysis of the raw PSE data by the CATEGO computer program – such as 'affective flattening,' 'slowness,' 'self-neglect,' 'lack of energy,' 'hypochondriasis' and 'visual hallucinations' – need not be considered further since in all cases they could be attributed,

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either directly or indirectly, to the symptoms of parkinsonism or to the effects of treatment.

Further methodological problems in investigating dementia associated with PD are due, first, to lack of sufficient information about the distribution of brain pathology in the general population² and, secondly, to controversy over the recently introduced dichotomy of 'cortical' and 'subcortical' dementia. It is generally agreed that PD is characterized by degenerative changes in the substantia nigra, i.e. depigmentation, neuronal loss, and gliosis, with the invariable presence of Lewy bodies (eosinophilic hyaline inclusions) in the cytoplasm of some of the neurones that remain.¹⁻³ This is in contrast to the pathology of AD, which typically consists of senile neuritic plaques, intraneuronal neurofibrillary tangles, neuronal loss and granulovacuolar degeneration in the cerebral cortex, particularly in the hippocampus and neocortex.¹⁻³ But, although PD and AD appear to be quite distinct, both as regards the appearance of the lesions and their distribution in the brain, this is not altogether correct. Thus, Lewy bodies are not unique to PD: they sometimes occur in other conditions and indeed may be observed occasionally in the otherwise normal cortex of elderly subjects; AD lesions may also be found in the cortex of healthy mentally normal old people and, in cases of AD in the basal ganglia where they may give rise to symptoms of parkinsonism.¹ Certainly, cases of PD with dementia may be found at autopsy to have no AD lesions,³ but in some cases of PD, typical changes of AD may be seen in addition to those of PD.³ It has been suggested that what is required to determine the relative contribution of the two types of lesion to the dementia is a representative autopsy series in which patients were evaluated prospectively for dementia, and that until this information is available, there will still remain uncertainty.²

'Subcortical dementia' is a term introduced in 1974 to denote a type of dementia with a pattern of mental deficits distinct from that seen when there is extensive damage to the cerebral cortex – so-called 'cortical dementia'; protagonists of its use, such as Cummings and Benson,⁷ state that it is caused by diseases of the basal ganglia and hemispheric white matter tracts. It is characterized by cognitive slowing (bradyphrenia), impairment of executive function (which includes the ability to shift from one idea to another, the ability to predict the consequences of behaviour and the construction of serial goal-directed activities), impairment of the recall of memories (but not recognition or registration), visuospatial deficits, depression of mood and the absence of delusions. The similarity between the impairment of executive function and the effects of frontal lobe lesions has been noted by a number of workers, and has been attributed to

defective dopaminergic connections between the basal ganglia and the frontal cortex.^{1,2} Subcortical dementia is said to occur in a variety of conditions: PD, Huntington's chorea, progressive supranuclear palsy, idiopathic basal calcification, Wilson's disease, AIDS dementia complex, multiple sclerosis and infectious and vascular conditions affecting the subcortical region.⁷ In contrast, dementias seen in cortical disorders such as AD and Pick's disease are said to be characterized by more severe memory dysfunction with difficulty in encoding as well as impairment of recall, by apraxia, by spatial disorientation, and by disturbances in language such as dysphasia, dysgraphia, agnosia and acalculia.^{1,7} This classification of dementias has, however, been questioned widely: the overlap, both in the distribution of brain pathology described above and in the clinical features of the two syndromes^{1,2,8,9} suggest that the validity of the distinction has not been demonstrated unequivocally and that there is little reason to continue using the term 'subcortical dementia'.⁹

A most informative study from Johns Hopkins University describes a consecutive series of 105 patients with idiopathic PD attending a neurology clinic who underwent independent neurological and psychiatric examinations.^{10,11} The neurological examination included the use of rating scales for the severity of the symptoms of parkinsonism, and disability was assessed by rating activities of daily living. The psychiatric examination included the PSE, the General Health Questionnaire (GHQ), and quantitative measures of depression (i.e. the Hamilton Rating Scale for Depression and the Beck Depressive Inventory), and of cognitive impairment (the Mini-Mental State Examination – MMSE). Psychiatric diagnosis was based on the PSE data using DSM-III criteria. Social function was also quantified.

Major depressive episode was diagnosed in 41 of the 105 patients, while in another 20 patients a diagnosis of minor depression was made (based on DSM-III criteria for dysthymic disorder, excluding the two-year duration criterion.) The diagnosis of depression (major or minor) did not correlate significantly with the severity of the symptoms of parkinsonism, although there was a trend in that direction. Patients with major depression were significantly more disabled than other patients and more often had a past history of depression. Of the 105 patients in the series, 38 had predominantly unilateral symptoms of PD – 19 had mainly right sided symptoms and 19 were affected mainly on the left side. Those affected mainly on the right were more significantly depressed than the others and were more often diagnosed as cases of major or minor depression. They also had significantly lower scores on the MMSE, indicating more cognitive impairment. Thus depression in PD appears to be

related to structural and/or biochemical changes in the left basal ganglia. The significance of the lateralizing effects on MMSE scores is not clear since MMSE ratings were also inversely related to a significant extent to age, to duration of PD and to disability.

The Queen Square study,⁴ to which reference has been made, used the PSE and the MMSE to assess the mental state of 40 patients with PD. A substantial number of patients were noted to have at least some neurotic symptoms, particularly depression of mood and impairment of interest and concentration, but only four patients could be diagnosed, on ICD-9 criteria, as suffering from mental illness: two were diagnosed as neurotic depression (ICD-9 code 300.4), one as anxiety state (300.0) and one as phobic state (300.2), a prevalence not significantly different from that found in the general population, and much lower than that reported in the Johns Hopkins study.^{10,11}

Level of disability was assessed using a questionnaire on activities of daily living and by scoring the performance of patients on tasks such as climbing stairs and doing up buttons. The physical symptoms of PD were also quantified. The PSE score of psychiatric disturbance correlated significantly with the degree of disability and also with low scores on the MMSE (i.e. with cognitive impairment).

Other recently reported studies of depression and dementia in patients with PD include two (one retrospective and one prospective) from Columbia University, New York,¹² and one (of dementia only) from Milan.¹³ In each of these the diagnoses of dementia and of depression were based on DSM-III criteria. In the three series there were, respectively, 339, 115 and 147 unselected patients with Parkinson's disease. The prevalence of dementia was 10.9%, 27.0% and 14.3% and that of depression (in the first two series only) was 51% and 23.5%. Dementia was related significantly to age and to the severity of the physical disability.

Thus, although the findings from different studies are sometimes at variance with one another, there does appear to be sufficient to conclude that patients with PD do become depressed and demented more often than in the general population. Whether or not the dementia, the depression and the parkinsonism have a common biological mechanism is still a matter for speculation.

A recent report¹⁴ described seven depressed patients with PD. The extrapyramidal symptoms and the depression in each patient were rated before, during and after a course of electroconvulsive therapy (ECT) (the average was 7 treatments). The mood improved in every case and the physical symptoms became much less intense in five. This anti-parkinson effect of ECT has been reported previously;¹⁵ it may be distinct from the anti-

depressant action, because improvement may be noted in the parkinsonism much before the depression starts lifting, but it may last for years before the signs of PD return. Marked improvement of PD in a patient whose mania was treated by ECT has also been reported.¹⁶ Although ECT has almost only been used in PD where it is indicated for the treatment of affective disturbance, it has been suggested that it may be worth trying for its anti-parkinson action in patients with intractable or drug-resistant PD.¹⁵

Clozapine

Clozapine is a dibenzodiazepine derivative with apparently greater antipsychotic activity than other neuroleptic agents and a lower propensity for extrapyramidal side effects (EPS). It has evoked great interest during the past two years although, in fact, it was originally synthesized in 1960 and first shown to have antipsychotic activity in 1966.¹⁷ It was marketed in Europe in 1975, but withdrawn from general use after psychiatrists in Finland reported 16 cases of agranulocytosis (with eight deaths) due to the drug. For some years clozapine was used extremely cautiously on selected patients, with frequent monitoring of the white cell count, but it then became clear that the agranulocytosis was reversible when the drug was stopped and that it could be prevented in most patients. Recently, it has been approved both by the US Food and Drug Administration and by the UK Committee on Safety of Medicines.¹⁸

A multicentre double-blind trial in the United States¹⁹⁻²¹ involved 268 schizophrenic patients who were allocated a 6-week course of either clozapine or a combination of chlorpromazine and benztropine (the benztropine was administered to mask the EPS of the chlorpromazine). The patients were selected on the basis that they had not responded to at least three previous courses of antipsychotic agents given in adequate dosage for at least 6 weeks on each occasion; these agents had to be representative of at least two different chemical classes (i.e. phenothiazines, butyrophenones, thioxanthenes, benzamides, diphenylbutylpiperidines etc.). In addition, before entering the trial each patient had failed to respond to a 6-week course of haloperidol (up to 60 mg/day or more) plus benztropine mesylate (up to 6 mg/day). One hundred and twenty six patients completed the course of clozapine (up to 900 mg/day), while 139 completed the course of chlorpromazine (up to 1800 mg/day) and benztropine (up to 6 mg/day.) The trial clearly demonstrated that clozapine was a much more powerful antipsychotic drug than chlorpromazine, both for positive symptoms of schizophrenia (hallucinations, suspiciousness, unusual thought con-

tent, etc.) and for negative symptoms (emotional withdrawal, blunted affect etc.); 30% of the clozapine-treated group improved to a clinically useful extent compared with only 4% of chlorpromazine-treated patients. There was a drop-out rate of 12% of clozapine-treated patients and 13% of chlorpromazine patients due to severe side effects, protocol violation, lack of cooperation etc. There were significantly fewer EPS with clozapine than with chlorpromazine.

Other recently published studies^{22–26} also indicate that clozapine is often effective in the treatment of schizophrenics resistant to standard neuroleptics, and that it tends to improve negative as well as positive symptoms.

There is abundant evidence that clozapine causes much less EPS than do conventional neuroleptics.²⁷ In a survey of a number of studies on a total of more than 1300 patients, the prevalence of extrapyramidal EPS was 0–20% for clozapine, 0–40% for chlorpromazine and 40–85% for haloperidol and other neuroleptics. With clozapine, acute dystonic reactions have not been observed, but akathisia and drug-induced parkinsonism are sometimes seen. Clozapine may be indicated in patients who show undue sensitivity to conventional neuroleptics. The low prevalence of EPS is possibly related to the observation that clozapine binds better to the dopamine (D2) receptors in the mesolimbic region than to those in the nigrostriatum, and to the finding that it does not cause catalepsy when given to rodents. Tardive dyskinesia (TD) does not seem to be a side effect of clozapine; indeed, there is some evidence that established TD due to previous neuroleptic administration may become less intense when clozapine is administered as the sole antipsychotic drug. In a study of 30 patients with TD who took clozapine for at least 12 weeks, there was no worsening of the TD in any patient, while 40% improved in the first 6 months to the point where no symptoms of TD could be detected.²⁸ Complete remission occurred particularly where there had been prominent dystonia. In another study,²³ 5 of 11 patients with moderate to severe TD showed a remarkable improvement on clozapine, while no patient's condition deteriorated.

Three different explanations have been put forward for this beneficial effect on TD. First, that TD is suppressed by clozapine in the same way as by other neuroleptics, but this is unlikely because withdrawal of clozapine does not lead to a recurrence of TD as would be expected if this were the mechanism. Secondly, that clozapine neither alleviates nor aggravates TD, and that there is a natural tendency for the abnormal movements to lessen with time; and thirdly, that clozapine has a direct therapeutic effect on TD. Since both the dose and the length of time that clozapine is administered are

important for improvement to take place, it seems likely that clozapine has a direct therapeutic effect. Consistent with this is the observation that clozapine seems to benefit the abnormal movements of Huntington's chorea, and of essential and parkinsonian tremor.²⁷

Agranulocytosis is the most important adverse effect of clozapine. In the US multicentre trial²⁰ no cases were noted; however, leucopenia (white blood count < 3900/mm³) was observed in 4.9% of patients receiving clozapine and in 3.3% of patients receiving chlorpromazine. In another report the authors estimated a cumulative incidence of agranulocytosis over 52 weeks of treatment with clozapine of approximately 2%.²⁸ The cause is uncertain, but an immune basis seems possible since antibody in IgM fractions has been identified in the serum of patients whose agranulocytosis is attributable to clozapine. Recovery is the rule when the drug is withdrawn. The most risky period for developing the condition appears to be between 6 and 18 weeks after clozapine is started; hence the recommendation that clozapine should only be given to patients who have not responded to (or have been intolerant of the EPS of) conventional neuroleptics, and who have no history of leucopenia. It has been suggested that if there is no clear sign of improvement 6 weeks after starting clozapine, the drug should be discontinued. In the UK the manufacturers make it a condition of supplying the drug that white blood counts are carried out every week for the first 18 weeks of treatment and every 2 weeks thereafter.³⁰

Other side effects of clozapine have been noted by all investigators. European studies^{31,32} emphasize delirium, hypotension, tachycardia, fever, a well marked increase in liver enzyme activity and grand mal fits, all of which may necessitate the withdrawal of the drug. Sialorrhoea, sedation, nausea and vomiting and respiratory depression may also require that the drug is stopped. In the US, where the practice is to start with a small dose of clozapine (25–50 mg/day) and to increase the dose gradually, over the course of one or two weeks, side effects appear to be less of a problem. Clozapine does not seem to cause hyperprolactinaemia, gynaecomastia or amenorrhoea, as do other antipsychotic agents, presumably because the dopamine receptors in the tubero-infundibular region are not blocked by the drug.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a complication (sometimes fatal) of antipsychotic drug therapy, in which muscular rigidity is associated with fever, autonomic disturbances and altered consciousness. In severe cases rhabdomyolysis with

myoglobinaemia and acute renal failure may occur, and autopsy may show evidence of a toxic myopathy similar to that described in malignant hyperthermia.³³ It was first reported by Delay and his colleagues 30 years ago who described two cases among 62 patients who were being treated with haloperidol.³⁴ Until 1980 only 60 cases had been published, but a further 256 examples were reported to the literature between 1980 and 1987.³⁴ The condition is now better known and more frequently recognized, but it may be considerably underdiagnosed.

Diagnosis and prevalence

Criteria for diagnosis differ between investigators. Keck and his colleagues^{35,36} require that three operationally defined criteria be met for a definite diagnosis to be made. First, there must be hyperthermia, i.e. the body temperature must be at 38.0°C or more with no apparent cause other than NMS. Secondly, severe extrapyramidal symptoms (EPS) must be present as evidenced by two or more of the following disturbances: lead-pipe muscular rigidity, pronounced cogwheel rigidity, sialorrhoea, oculogyric crises, retrocollis, opisthotonos, trismus, dysphagia, choreiform movements, dyskinetic movements, festinant gait, and flexor-extensor posturing. Thirdly, there must be two or more of the following autonomic disturbances: hypertension (at least 20 mmHg rise in the diastolic blood pressure above the baseline level), tachycardia (at least 30 beats/minute above baseline), tachypnoea (at least 25 respirations/minute), prominent sweating, incontinence. Other features of the condition include clouding of consciousness (delirium, mutism, stupor or coma), leucocytosis (15,000 white blood cells or more per mm³), and a serum creatine kinase (CK) level of more than 1000 U/l.

Other workers give slightly different criteria: Adityanjee and his colleagues³⁷ insist on the presence of an altered sensorium in addition to muscular rigidity, hyperthermia and autonomic dysfunction; the criteria of Rosebush and her colleagues^{38,39} do not include autonomic disturbance as an essential criterion, but state that elevated levels of muscle enzymes in the blood are 'the biochemical hallmark of the disorder.' Serum CK levels are, however, raised in a wide variety of disorders; isoenzymatic fractionation shows that when the enzyme derives from muscle (as in NMS) it is almost entirely MM. Reliance for the diagnosis of NMS should not be placed on serum CK levels, as they may be raised in acute psychotic states when there is intense isometric muscular activity (as in dystonic reactions or with the use of restraints), or when intramuscular injections are given; 2 cases of raised serum CK levels have been reported where

neuroleptics were given orally.⁴⁰

That the criteria for diagnosis of NMS vary is indicated by a survey on 256 cases reported between 1980 and 1987³⁴ which found a few cases where body temperature was normal, or where there was no muscle rigidity, or no autonomic changes, or no rise in serum CK or white cell count. Since then patients have been reported where there is no fever or no clouding of consciousness^{37,41} or no rise in serum CK.⁴² This sort of finding has given rise to the idea that NMS can vary in intensity along a spectrum from very mild or atypical cases or formes frustes at one end to severe full-blown cases at the other.^{37,41}

Some reports indicate that the diagnosis of NMS is sometimes made where no neuroleptic (in the generally accepted meaning of the word) has been taken by the patient. One such patient⁴³ developed the condition while receiving phenelzine 45 mg/day, lithium carbonate 800 mg/day, L-tryptophan 1 g/day, diazepam 6 mg/day and trizolam 0.25 mg/day, while the Committee on Safety of Drugs⁴⁴ has stated that of 17 reports received by July 1986, there was one fatal case due to clomipramine and one non-fatal case due to dothiepin. In most cases however, there is a clear temporal relationship between the start of the neuroleptic administration and the beginning of the NMS, and between the withdrawal of the neuroleptic and recovery. Of 136 cases reported between 1980 and 1987, where time of onset of NMS was indicated in relation to the start of neuroleptic medication, 16% began within 24 hours of the start, 30% within 48 hours, 66% within one week and 96% within 30 days.³⁴ Two more recent cases with onsets of 16 hours and 18 hours have been reported.^{45,46}

The close relationship in time between recovery from NMS and withdrawal of neuroleptic medication is shown in a survey of 65 cases, untreated by dopaminergic agents or by dantrolene, which reported the interval between withdrawal of the neuroleptic and recovery from NMS: 23% recovered within 48 hours, 63% within 2 weeks and 97% within one month.³⁴

In view of the varying criteria for diagnosis, it is not surprising that the frequency with which NMS is reported among patients receiving neuroleptics also differs markedly between observers. Recent estimates include a prospective study⁴⁷ of 1470 in-patients in a private psychiatric hospital in Massachusetts during the course of one year, all of whom had been given neuroleptic medication. Only one patient (0.07%) developed NMS; this very low incidence was possibly attributable to the relatively low dose of neuroleptics prescribed: the maximum dose of haloperidol and of trifluoperazine was 40 mg/day, while that of chlorpromazine was 550 mg/day.⁴⁷ Other reports indicate an incidence varying in different series

from 0.02% to 3.2%;³⁴ the average seems to be about 1–2%.

Risk factors

Since only a very small proportion of patients receiving neuroleptics develop NMS, Keck *et al.*³⁶ studied 18 patients with NMS and compared them with 36 controls who had also been treated with neuroleptics, but had not developed this complication. They found that among patients with NMS, the drug dosage tended to be higher (both mean and maximum doses) and that there was a greater tendency for an increase in dose before the onset of NMS. There was evidence of greater psychomotor agitation and of a larger number of intramuscular injections in the NMS subjects. Psychiatric diagnosis, the chemical class and the potency of the neuroleptic were all unimportant. Other workers^{34,48} have suggested that the use of haloperidol is particularly associated with the development of NMS, but it is probable that this is due to the relatively high dose of haloperidol administered in comparison with other drugs. It has already been noted that the prevalence of NMS was particularly low in a hospital where low-dosage neuroleptics were used.⁴⁷ A past history of NMS clearly increases the likelihood of NMS,³⁴ but there is controversy about differences in risk between high and low potency drugs, and between depot and oral preparations; it is also unclear whether the concomitant use of lithium increases the prevalence.

Mortality rates

In a review of 202 cases reported between 1959 and 1987⁴⁸ it was found that the mortality rate of cases published before 1980 was 27.7%, while for the periods 1980–1983 and 1984–1987 the rates were 22.6% and 11.6% respectively. In a recently reported series of 24 episodes in 20 patients between 1981 and 1987 no fatalities occurred.³⁸ The fall in death rate over the past decade seems to be due to the earlier recognition of the disorder and hence to quicker withdrawal of the neuroleptic responsible, and to the better intensive care facilities and the use of specific therapeutic agents (dantrolene and dopamine receptor agonists).³⁴ NMS induced by haloperidol, sulpiride or thioridazine seem to have a lower mortality rate than when other neuroleptic drugs are responsible, particularly when haloperidol is used alone. Myoglobinaemia or acute renal failure carries a mortality rate of about 50%.⁴⁸

Differential diagnosis

A number of conditions may produce a clinical picture similar to that of NMS.³⁸ These include

infections (particularly when the picture is complicated by the presence of neuroleptic-induced EPS), the toxic effects of other drugs (e.g. anticholinergic agents), neuroleptic heat-stroke and status epilepticus.^{34,38} Anticholinergic intoxication resembles that due to atropine and is characterized by dry flushed skin, dryness of the mouth, tachycardia, widely dilated unreactive pupils and delirium, with relief of symptoms by one or two intravenous injections of 1 mg physostigmine. Neuroleptic heatstroke⁴⁹ is caused by the same mechanisms as heatstroke in general (usually during unaccustomed heat, especially where there has been severe exertion) aggravated by neuroleptic-induced neurotransmitter blockade of hypothalamic dopaminergic thermoregulatory pathways. Rhabdomyolysis, myoglobinaemia and acute renal failure occur rarely and only when one of the factors is severe exertion. There is very high fever, but no muscle rigidity or sweating. The mortality rate is much higher than that of NMS, but treatment (hydration and cooling) is very effective. The two most important conditions in the differential diagnosis, however, are malignant hyperthermia and lethal catatonia.

Malignant hyperthermia consists of a group of inherited disorders where, in response to the administration of certain volatile anaesthetic agents (such as halothane) or of muscle relaxants (particularly succinylcholine), there is a rapid rise in body temperature and muscular rigidity. Thus the condition tends to occur after surgical operations (or electroconvulsive therapy) involving the use of muscle relaxants and anaesthesia. Some patients who are susceptible to the condition show an abnormality in muscle obtained by biopsy: the muscle will contract *in vitro* in concentrations of halothane or caffeine which have little effect on muscle from normal subjects. In one study⁵⁰ the past history of 20 patients with NMS and of their first-degree relatives was investigated retrospectively: no cases of malignant hyperthermia were found, even though a number of the patients and their relatives had had ECT or surgical procedures involving agents known to precipitate the condition. This suggests that malignant hyperthermia is aetiologically distinct from NMS. These findings are consistent with those of another recent study⁵¹ where the *in vitro* muscle contraction test was found to be negative on tissue obtained from 8 patients with NMS and from 10 controls, in contrast to the positive results on 10 patients known to be susceptible to malignant hyperthermia.

Cases of lethal catatonia have been reported in the psychiatric literature for more than 150 years. The condition is characterized by the sudden onset of intense psychomotor excitement, continuing day and night, associated with mounting fever, tachycardia, profuse sweating, dehydration and cloud-

ing of consciousness. Catatonic and other abnormal movements are seen. The patient becomes progressively exhausted and the condition has a mortality of about 60%. A series of 292 cases reported between 1960 and 1985 has been analysed⁵² and the authors came to the conclusion that lethal catatonia is a syndrome which may develop in association with both functional and organic illnesses and that NMS may be a neuroleptic-induced form of the condition. Indeed 65 of the 292 cases appeared to have followed the use of neuroleptics. Other workers^{53,54} maintain that lethal catatonia and NMS are two separate, though similar, conditions and that often they can be differentiated clinically. For example, lethal catatonia may have a premonitory phase of about two weeks, during which the patient may show emotional withdrawal and depressive symptoms and may complain of various physical discomforts, while the presence of marked anxiety, of choreiform stereotypy, or of delusional thinking or hallucinatory experiences favours the diagnosis of lethal catatonia.

Treatment

Immediate withdrawal of all neuroleptic medication, and general measures (preferably in an intensive care unit), including the correction of dehydration and, if there is a high fever, cooling the patient, are important in all cases, and there is good evidence that the use of specific agents, such as dantrolene and dopamine agonists, produces better results. On reviewing 67 cases of NMS reported between 1977 and 1987, where there was adequate information about the diagnosis and response to treatment, the investigators⁵⁵ found that without specific therapy, the mean duration between the onset of treatment and the beginning of clinical improvement was over 6 days and that the time to complete resolution was an average of 15 days. The addition of bromocriptine or dantrolene reduced the time before any improvement was noted to 1–2 days and the time to complete resolution of the disorder to 9–10 days.

Dantrolene is a direct acting muscle-relaxant and is given by mouth in doses up to 100 mg four times daily, or intravenously, 1 mg/kg body weight at a time. Dopamine agonists, particularly bromocriptine (5–30 mg/day), but also levodopa (100–800 mg/day) and amantidine (100–400 mg/day) are used on the basis that NMS is due to neuroleptic-induced central dopamine receptor blockade. They have the disadvantage of possibly aggravating the underlying psychosis for which the neuroleptic was prescribed.

Benzodiazepines are also much used, presumably because of their centrally-mediated muscle relaxing effects. Nifedipine in a single dose of 20 mg

taken sublingually led to a remarkable improvement within 2 hours in one case of NMS.⁵⁶

Reintroduction of antipsychotic medication

With recovery from NMS it is often possible to reintroduce antipsychotic medication without relapse. This is important because withdrawal of neuroleptics (and the use of dopamine agonists) may be followed by a return of or an increase in psychotic symptoms. Rosebush and her colleagues⁵⁹ describe their experience of 15 patients in which re-introduction was attempted. Thirteen (87%) were eventually able to take antipsychotics again, although in some cases repeated efforts had to be made. Five settled on carbamazepine and in each of these cases the interval between resolution of the NMS and the successful reintroduction of medication was 2 weeks or more. The other 8 patients tolerated various neuroleptic drugs, sometimes the same as that which originally precipitated NMS. In another review series of 47 cases, reintroduction of neuroleptics was achieved without trouble in 33 (70%).³⁴

Psychiatric aspects of infection with the human immunodeficiency virus (HIV)

Soon after the recognition by the Centres for Disease Control (CDC) of a new acquired immune deficiency syndrome, its psychological and psychiatric aspects began to receive increasing attention, and now many scores of articles on the mental state of patients infected with HIV-1 are published each year. (This review refers only to HIV-1 infections; the psychiatric manifestations of infection with HIV-2 have yet to be determined.) A review of the literature on the psychiatric aspects of HIV infection up to the end of 1987⁵⁷ covered a wide range of topics; here, some of those topics will be brought up to date.

AIDS dementia complex

HIV is neurotropic and may enter the central nervous system (CNS) early in the infection. When it does cause CNS symptoms, these are likely to include disturbances typical of those seen in non-focal brain disorder in general, particularly delirium and dementia, or in less severe cases, impairment of cognitive and intellectual abilities. Direct involvement of the brain (meningo-encephalomyelitis) may occur during the HIV seroconversion illness, with transient clouding of consciousness, confusion and, sometimes mood disturbance, but the main syndrome (i.e. dementia, which is included in Group IVb of the CDC's classification of HIV-related illnesses) occurs later in the illness.⁵⁷

The American Academy of Neurology AIDS Task Force⁵⁸ has recently pointed out that although various terms for this dementia have been used, e.g. 'subacute encephalitis', 'HIV encephalopathy', 'AIDS encephalopathy' and 'AIDS dementia complex', they are, in fact, all equivalent. The term 'AIDS dementia complex' (ADC) is now more widely used than the others; it was introduced in 1986 by a group of workers at the Memorial Sloan-Kettering Cancer Center in New York. Recent papers from this group have elaborated on their original observations.⁵⁹⁻⁶²

By definition, patients with ADC do not have intracranial opportunistic infections or neoplasms; nor is there any evidence of encephalopathy due to severe renal, pulmonary, or hepatic disease. Post-mortem, a variety of lesions in the brain are seen, but the presence of multinucleated giant cells containing the virus (seen in a minority of patients only) appears to be more specific than the others. Although it is generally held that ADC is due to the direct effect of the virus on the brain tissue, this has not been proved conclusively, and it has been suggested that the syndrome may be immunologically mediated or that it is due to a pathogen other than HIV.⁶³

Patients with ADC have a moderate or severe dementia, conforming to DSM-III criteria, usually of insidious onset, and associated with motor dysfunction (incoordination, ataxia and slowness) and with behavioural disturbances, such as social withdrawal, reduced spontaneity and apathy in the absence of significant depression. In practice, the diagnosis of ADC is made partly by exclusion, i.e. dementia and motor disturbance in a patient infected with HIV in the absence of any cause other than ADC. Conditions to be excluded are intracranial opportunistic infections and neoplasms and metabolic disturbances severe enough to cause an encephalopathy. The majority of patients with ADC have cortical atrophy, revealed by computerized tomography (CT) or by magnetic resonance imaging (MRI), and p24 HIV-1 core protein antigen and the virus may be found in the cerebro-spinal fluid.

The dementia is described as 'subcortical',⁶¹ in which slowing of both mental and motor function is prominent. Price and Brew⁶¹ have devised a staging scheme of ADC, based on level of functional disability and interference with activities of daily living. Stage 1 (mild) is characterized by the patient's ability to perform all but the more demanding aspects of work or activities of daily living and by the ability to walk without assistance; nevertheless there is unequivocal evidence of functional intellectual or motor impairment. Patients who have the characteristics of stage 4 (end stage) are nearly vegetative; intellectual and social comprehension and output are at a rudimentary level;

there is near or absolute muteness, and there is paraparesis or paraplegia with urinary and faecal incontinence. Stage 2 (moderate) and stage 3 (severe) are intermediate between stages 1 and 4; for research purposes stage 0 is defined as normal mental and motor function, and stage 0.5 (equivocal/subclinical) is characterized by mild motor signs with absent, minimal or equivocal symptoms.

Because the diagnosis is made partly by exclusion, the exact frequency of the condition is not clear: the Memorial Sloan-Kettering Cancer Center group estimate that at least two-thirds of HIV-infected patients develop some degree of ADC (i.e. stage 1 or more) with additional numbers in stage 0.5.⁶¹ Guilloff *et al.*⁶⁴ have reported a series of 122 deceased patients who had been diagnosed as cases of AIDS at a hospital in Central London; the investigators paid special attention to patients with major neurological disturbances. Progressive intellectual impairment was prominent both clinically and socially in 12 patients; 9 of these were considered to have ADC (associated in two with myelopathy.) Seven had CT scans of which 5 showed cerebral atrophy; post-mortem examination showed multinucleated giant cell encephalitis in three. Thus in this series of 122 patients with AIDS, the prevalence of ADC was 7.3% and that of other causes of dementia 2.4%. Two of the demented patients in this series (one of the cases of ADC and myelopathy and a case of multi-infarct dementia with vasculitis and chronic basal meningitis) had neurological symptoms as the presenting condition.⁶⁵

Portegies *et al.*⁶⁶ have reported a series of 196 cases of AIDS associated with neurological symptoms and seen by them in Amsterdam between October 1982 and December 1988. Of these 196 patients, 40 were diagnosed as ADC, giving a frequency of just over 20% – this would have been less if AIDS patients without neurological involvement had been included in the total. Before ADC was defined in 1986, dementia was diagnosed using DSM-III criteria, but retrospectively it was found that, since all the cases so diagnosed had motor symptoms, the criteria for ADC were also satisfied. Thus both the London series⁶⁴ and the Amsterdam series⁶⁶ find ADC less frequently than the group of workers at the Memorial Sloan-Kettering Cancer Center. Portegies *et al.*⁶⁶ also reported that when zidovudine became available in Holland on May 1st 1987 it was administered to a total of 89 patients in the series; of these, two (2.3%) developed ADC. In striking contrast, 38 (i.e. 36%) of the 107 patients who did not receive zidovudine developed ADC.

The authors attribute this highly significant difference ($P < 0.00001$) to a possible prophylactic effect of the drug. This finding has yet to be confirmed in other studies.

Concern has been expressed that HIV-infected individuals might be cognitively impaired (i.e. subclinically demented or at stage 0.5 ADC) early in the course of the illness. There have been a number of recently reported studies⁶⁷⁻⁶⁹ where various groups of patients (with AIDS, with AIDS-related complex, with persistent generalized lymphadenopathy, and symptom free seropositive individuals) are compared with various controls (seronegative homosexuals and healthy heterosexuals), using batteries of neuropsychological tests to assess various aspects of cognitive ability. In general, these studies indicate some slight impairment of intellectual function, particularly in the later stages of the disease. The clinical relevance of these findings is uncertain at present.

Other organic reactions

Organic mental reactions (dementia and delirium) may be seen in HIV-infected individuals with intracranial opportunistic infections (e.g. toxoplasmosis, candidiasis, cytomegalovirus (CMV) encephalitis, cryptococcal meningitis, progressive multifocal leucoencephalopathy) or neoplasms (primary CNS lymphoma) and in patients with metabolic encephalopathy due to systemic illness.⁵⁷ In the series reported by Guiloff *et al.*⁶⁴ there were three cases of dementia not due to ADC: one had histologically proven CMV encephalitis and one was diagnosed post-mortem as chronic basal meningitis and vasculitis associated with multiple cerebral infarcts; the third case was undiagnosed. Guiloff *et al.*⁶⁴ also noted 15 instances where a metabolic encephalopathy with confusional state was diagnosed; the mental disturbance was related to hypoxia in 7 cases, to dehydration in 4, and there was one case each of drug intoxication, hyponatraemia, hypoglycaemia and hepatic encephalopathy. The mental state of the 15 patients in the series with focal encephalopathies (toxoplasmosis, primary CNS lymphoma etc.) and of the 6 cases of meningitis was not reported.

Functional disorders

These occur commonly in HIV patients, as maladaptive responses to the severe, and sometimes overwhelming, psychological and social pressures arising in the illness. Adjustment reactions (ICD-9 code 309 – adjustment disorder in DSM-III and DSM-III-R), including depressive reactions, anxiety and disturbances of conduct are commonest,

and occur particularly after the patient becomes aware of the diagnosis. They last for some weeks or more; similar disturbances lasting a few hours or days are classified as acute reactions to stress (ICD-9 code 308.) Other reactive disorders include affective disorders, various neurotic disorders, alcoholism and drug abuse, paranoid states and reactive or psychogenic psychoses. Two patients reported by Schaerf *et al.*⁷⁰ became severely depressed and deluded soon after learning that they were seropositive; both responded to ECT.

Vogel-Scibilia *et al.*⁷¹ have tried to determine whether or not HIV infection ever presents as an apparently functional psychosis, on the basis that some other brain diseases (for example, Huntington's chorea) sometimes do. They undertook an extensive computer-assisted search of the literature, published up to March 1988, of all cases of psychosis reported as the initial presentation of HIV infection. They excluded (a) reactive cases, i.e. patients who might have become mentally ill because they knew that they were infected with HIV, (b) patients with recent drug abuse (to exclude cases of drug-induced psychosis) and (c) patients with a history of previous psychiatric disorder (to exclude case where the illness started before infection with HIV.) Nine patients (8 male and one female) satisfied the criteria. The illness of 5 was characterized by paranoid delusions (of whom 3 had auditory hallucinations as well), 3 were manic and one was catatonic. Cognitive changes were not prominent, but 3 patients were noted to have impairment of concentration and memory, one made errors in the serial 7's test and one was disoriented in time. The long-term outcome was poor in that 4 patients died within 6 months. The authors conclude that the illnesses of these patients could be either early manifestations of organic brain disease or be coincidental. On the basis of the known current annual incidence of first episodes of schizophrenia-like illnesses and of the prevalence of HIV seropositivity, they calculated that by chance alone there would be about 750 cases per year in the US of HIV-infected patients with a first episode of a schizophrenia-like illness.

Further cases of psychosis associated with HIV infections have been reported since this study,⁷²⁻⁷⁴ but in only one case⁷² (a homosexual man with an acute schizophrenic illness) was this the presenting illness. Other cases in these reports⁷²⁻⁷⁴ have had schizophreniform and manic illnesses with, on occasions, evidence of cognitive impairment.

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