Papers and Originals

Depression*

HENRY MILLER,† M.D., F.R.C.P., D.P.M.

Brit. med. J., 1967, 1, 257-262

The brief of the Morison lecturer is to deal with a neuro-psychiatric topic, and my choice of subject is based on the fact that although depressive illness is ubiquitous it often escapes recognition, with distressing and sometimes disastrous results for the patient. My account will be personal and idiosyncratic: it is based on experience acquired in the management of more than 2,000 such cases during nearly two decades of private consultant and general hospital practice.

I hope it will not surprise you that a physician and neurologist should choose a psychiatric subject. Specialization is essential to the advance of medicine, but we should beware of taking it too seriously. The boundaries of the various specialties are matters of expediency rather than logic. Where paediatrics end and medicine begins in a hospital may depend on nothing more fundamental than the length of the patient, and what is regarded as geriatric on his need for a long-stay hospital bed—while, as for the contemporary chest physician, he is after all merely a historical accident we owe to the chemotherapeutic conquest of tuberculosis. The psychiatrist is no exception. He deals not with a specific group of diseases but with any illness that is characterized by psychiatric or, more bluntly, mental *symptoms*—a brief that covers the whole of medicine. The patient presenting with a confusional state may be suffering from any one or more of several hundred pathophysiological disturbances, of which uraemia, liver failure, hypercapnia, bronchogenic cancer, encephalitis, and vitamin-B₁₂ deficiency are but a few. In other words, the psychiatrist should not only first be a physician but ideally a superlative physician.

I must add in parenthesis that for this reason the current psychiatric tendency to side-step the rigorous basis of training in internal medicine that is the only excuse for memberships of Royal Colleges and such exercises, and to choose the softer option of segregation into a college of symptomatologists, is as regrettable as it is remarkable. It is a retrograde step that will blight the specialty's aspirations to scientific respectability, and cannot fail to perpetuate the deplorable anomaly of two classes of psychiatric physician.

Psychiatry is of course not only medicine but without doubt the most difficult of all the branches of medicine. It is concerned with neurology at its highest level—*neurology without physical signs*—where disturbed cerebral function is manifest not in the easily elicited and fairly objective physical evidence of the neurological clinic but in the subtler fields of altered mental processes and changes in behaviour. Imagine for a moment, if you can, the cardiologist deprived of his physical signs as well as his formidable battery of ancillary investigations, and dependent for his final diagnosis entirely on the patient's account of his symptoms and his observed behaviour. What sort of classification of cardiovascular disease

would he have achieved, and how accurate would his diagnosis be? Yet this is the psychiatrist's everyday task, and psychiatric symptomatology is infinitely less tangible than that of circulatory disturbance.

Developments in Depressive Illness

The developments of the past 30 years in the field of depressive illness, and especially of its treatment, have great theoretical as well as practical importance. They are crucially relevant to the central concept of psychiatry as an integral part of medicine, centred primarily in the general hospital. This is *our* solution to the contemporary problem of replacing and revivifying the traditionally autonomous discipline of mental hospital practice. It is, however, in contrast with the situation in the United States, where psychiatry is widely regarded as a psychotherapeutically orientated "office" specialty. This transatlantic situation reflects, of course, the present economic organization of American medicine, and finds its philosophical justification in a widely and passionately held view that psychiatric disorders originate predominantly from psychological causes, and can be effectively treated by the psychological methods of the office interview. Such a view is seen at its most characteristic in the psychoanalyst's highly wrought psychological determinism, which relates all current psychiatric disturbances to antecedent psychological events. Psychoanalysis firmly attributes depression to the patient's deprivation of love by loss of its object; this induces regression to oral sadism, with its component of self-destructive impulses. Since the acutely depressed patient was coping satisfactorily with these elemental forces until the onset of his illness a few weeks ago, and since we can be reasonably certain that the taking of appropriate tablets will speedily transform his suicidally depressive behaviour to normal we may perhaps be excused some lingering scepticism regarding their aetiological significance.

Classification

The definition and classification of depressive illness presents a perennial problem. This concerns especially the distinction between exogenous and endogenous depression—between depressions that can reasonably be regarded as reactive to the environment and those that seem to have their origins within the patient.

The classical German psychiatrists of the nineteenth century thought there was a clear qualitative difference between these two types of illness. Many subsequent observers have questioned this view, quoting the occasional development of depressive illness of endogenous pattern after psychological stress, and regarding this as merely a more severe illness than reactive depression but one essentially of the same nature.

* Morison lecture delivered at the Royal College of Physicians of Edinburgh on 14 October 1966.

† Professor of Neurology in the University of Newcastle upon Tyne.

Unfortunately some of the standard psychiatric texts can easily confuse the inexperienced reader in this connexion. Depression is usually classified among the affective disorders. Often, however, these also include states of anxiety, and, although outlines are blurred and anxiety may coexist with depression, the classical anxiety state is a disorder distinct from depression, with a different prognosis and requiring a different kind of management.

Kraepelin's integral view of mania, depression, and involutional melancholia as "manic-depressive insanity" stands on firmer theoretical ground, but few accounts make it clear how far the scene is dominated by depression. By comparison mania is a clinical rarity, and, though we are all prone to swings of mood, their progression to the psychotic intensity of classical manic-depressive illness is rarely encountered outside institutional practice. Depression, like the poor, is with us always. Indeed, I am often inclined to think that few of us can expect to go through life without experiencing at least one depressive episode—though whether either we or our physicians will recognize its nature is perhaps another matter.

Here I feel I must declare my own position in the matter of classification. The condition to be discussed is that now generally known as *endogenous depression*, and in my opinion it is as near to a clinical entity as almost any disease in internal medicine. It may lack the clear-cut definition of trigeminal neuralgia, but its claim to the title is at least as good as that of acute appendicitis—another banal disease of which the cause still escapes us—and in a typical case its diagnosis is no more difficult. I regard endogenous depression as a pathophysiological disturbance of "organic," or more accurately "physiogenic," origin—though the exact nature of the disturbance is unknown—distinct both from exogenous depression and from the traditionally psychogenic anxiety-state. The validity of this view rests chiefly on a number of incontrovertible clinical considerations. Firstly, the symptomatology of endogenous and that of exogenous depressions are different. Secondly, they affect a different type of patient: the endogenous depression strikes a stable, or, more rarely, rather cyclothymic subject, while reactive depression affects the inadequate or unstable personality. Familial predisposition is much more often evident in endogenous than in reactive cases.

Endogenous depression usually comes out of the blue and without any evident cause. When it follows emotional stress—as it very occasionally does—the stress is usually major or catastrophic, such as the tragedy of bereavement or something comparable, and the patient's appearance and physical condition bespeak a significant physiological somatic disturbance. In any case, endocrine changes and certain types of physical illness are more frequent and characteristic precursors. Endogenous depression is unresponsive to environmental changes or to the removal of the apparent cause of the episode. The latter measure usually leads to rapid improvement in the exogenous disorder, and indeed such a condition may be palpably directed to achieve some desired end, ranging from the return of an errant spouse to escape from the consequence of embezzlement.

But the most convincing definitions in medicine are often operational, and it is here that the distinction is unequivocal. The rapid response of the large majority of cases of endogenous depression to electric convulsion therapy or to antidepressive drugs, and the poor response of most exogenous cases to such measures, clinches the distinction and makes nonsense of the view that this is nothing more than one of severity. Otherwise we are left with the improbable conclusion that the milder cases of this illness fail to respond to a form of treatment that speedily and predictably cures nearly all patients more severely affected by it. The recent successes of antidepressive treatment have established depression, in the sense I am using it here, as a physical illness treatable by physical means, and they have made psychopathological speculations on its nature as irrelevant as they are unconvincing. Furthermore, they have

opened the way to a rational if still empirical psychiatry with enormously important implications for the future.

Epidemiology

There can be little doubt that it is within the scope of geographical pathology to make great contributions to our understanding of disease, but it is also not unfair to comment that up to the present time it has raised more questions than it has answered. Even where such studies deal with diseases that are well defined pathologically, as well as clinically, the collection of truly comparable data presents remarkable difficulties. At their simplest, these concern differences in both the quantity and quality of medical care in the communities under consideration, and the many factors that determine whether or not a patient ever comes under medical surveillance.

In psychiatry these difficulties are magnified by the absence of a clear dividing line between the normal and the pathological, by the subjective nature of diagnostic formulation, and by differences in terminology. For reasons such as these any generalization in this difficult field can be nothing more than tentative.

The paucity of hard facts makes speculation easier and indeed virtually irresistible. My African colleagues, for example, never tire of reminding me that, while schizophrenic illness is ubiquitous, depression is uncommon in the native African, and states of excitement much more frequent. Unfortunately, their smiling attribution of this difference to our sunless climate is belied by the frequency of depressive illness in India.

At a more parochial level a relative predilection of depressive illness for the female, for members of the Jewish race, and for the solidly built, is well authenticated. In striking contrast with schizophrenia, the condition seems to affect the middle and upper classes more than social classes IV and V. Here at least two factors are operative: schizophrenia in a family spells social decline, while the innate seriousness and obsessionality often found in those prone to depressive illness may actually promote social advancement.

Aetiological Factors

In this connexion the first point that strikes us is the frequency of a history of depressive illness, and much less frequently of mania or hypomania, in the families of affected patients. Even under the conditions of ordinary consulting-room practice such a history is elicited in more than three-quarters of all cases, and this is certainly an underestimate. Closer study of affected families favours the dominant inheritance of a genetic susceptibility that may or may not at some time express itself as overt illness.

A great deal has been written about the personalities of patients prone to depression. Like most such studies these are rather unsatisfying, dealing with the subjective assessment of immeasurable qualities and lacking any "normal" standard of reference. However, the problem is an important one, and here I would make three observations. The first is that endogenous depression rarely affects the feckless inadequate patient whose history reveals a repeated pattern of escape from life's difficulties through symptoms often regarded by psychiatrists as psychoneurotic, and sometimes by the rest of us as bogus. Secondly, the illness strikes often and most dramatically in an unexpected way at the stable, energetic, extroverted, middle-aged "success." Thirdly, it also frequently affects the equally worthy subject of a chronically depressive personality—the kind of patient who has soldiered on effectively but unhappily for many years, and perhaps throughout life, subdued in manner and often gloomy in outlook.

If we consider the factors that precipitate depressive breakdown, with or without evident personal or familial loading,

the influence of tangible physical factors is impressive. We have all seen a previously normal patient plunged into serious depression, often of considerable duration, by influenza, hepatitis, mononucleosis, or head injury; and today puerperal insanity is more frequently a depressive episode than the toxic-confusional state that often followed less expert obstetric management. Whatever the connexion of involuntal melancholia with the menopausal contraction of sexual function, the frequent relationship of depression to endocrine function and disturbed metabolism is inescapable. Not only is amenorrhoea a feature of some severe illnesses of this nature, but there are other patients who present a microcosm of agitated depression, sometimes of psychotic intensity, with every menstruation, while endogenous depression may be symptomatic of Cushing's syndrome, steroid therapy, or vitamin-B₁₂ encephalopathy.

The occasional provocation of endogenous depression by overwhelming emotional stress has been mentioned, but its infrequency should be emphasized. Depressive illness does not usually spring from grief, from which in most instances recovery is rapid. The tendency of patients and their families to attach illness of all kinds to antecedent events is familiar, and depression is often attributed in this way to banal agencies either in the recent or more improbably in the remote past. But an acute depressive illness cannot reasonably be regarded as a result of those 30 years of conscientious overwork so often endowed with aetiological significance by the patient's admiring family, while his own frequent attribution of his illness either to sins long past or to inherent personal unworthiness is clearly a symptom rather than a cause of his illness. The less severely affected patient often regards the puzzling symptoms of his depressive symptoms as an inevitable concomitant of advancing years.

Clinical Features

Endogenous depression is one of the commonest illnesses in medicine. Since it causes an enormous amount of chronic ill-health and social inefficiency, and since it threatens life through an ever-present tendency to suicide, its early recognition is of paramount importance. Many cases are never recognized, and in others diagnosis is delayed long after the true position would have been clearly evident to any reasonably informed observer. This is doubly important, not only because modern treatment is extraordinarily effective, but because even before treatment is instituted the distressed patient is enormously helped by the realization that he has at last encountered a doctor who understands the nature of the trouble and is confident of his ability to cope with it.

The cardinal feature of depression of endogenous type is its totality. It involves the entire person. Mood, thinking, and physical and mental activity are all depressed.

Sleep Disturbance

The almost pathognomic clinical feature of endogenous depression is a *distinctive pattern of sleep disturbance*. It is true that sleep is normal or even excessive in a tiny minority of cases of serious depression, and that in some others the sleep disturbance is uncharacteristic. In typical depressive insomnia, however, the patient gets off to sleep without difficulty, but this is interrupted and ultimately terminated by awakening in the early hours of the morning. In the worst cases there may be no sleep at all, or it may be broken after a couple of hours.

Except because of pain or respiratory obstruction, organic disease rarely causes sleeplessness. One of the commonest day-to-day problems of clinical neurology concerns the evaluation of headache, and whether or not this portends structural intracranial disease. In this connexion the most important single question concerns the patient's sleep habits, and especially any recent change in them. Symptomatically the headaches

of neurosis, depression, and brain tumour may be indistinguishable. But few neurotic patients admit to sleeping well, and here the difficulty is in getting over to sleep, "because my brain is so active"; the flattering nature of the explanation is worth noting. In contrast, the depressive patient may go to sleep almost as soon as his head touches the pillow, but his sleep is broken, often with almost monotonous regularity at the same hour of the early morning.

Feeling of Illness

The second feature to which I would draw your attention is that *the patient with depression feels ill, looks ill, and is ill*. Often he does not volunteer depression as a presenting symptom, and he may even deny frank depression of spirits, though this is usually admitted on questioning. More consistent is a loss of well-being, a loss of zest, of drive, and feeling. Such patients will often say that they have lost all normal feelings for their families. On the other hand, they may be near to tears the whole time, and break down in a paroxysm of weeping at a mildly sentimental television programme. The patient is apathetic and easily exhausted, and all his activities have contracted. My colleague, Dr. Robert Orton, has coined the excellent aphorism that the neurotic gives up his work, while the depressive abandons his pleasures. Such a patient will awaken at 5 a.m., panic-stricken and wondering how possibly to get through the day's work in the office or in the home, but will manage by a great effort to cope adequately—though not to his or her own satisfaction—and then fall into bed exhausted in the early evening, hobbies, pleasures, and social life abandoned.

Other Features

The third point to which I would draw attention is that in all but the mildest cases there is *evidence of physiological disturbance*. Loss of appetite and weight, and failure of sexual interest, are almost invariable. Constipation is common, and may lead to a suspicion of growth in the large bowel.

The fourth feature of *diurnal variation* is characteristic though not invariable. Most patients are worst in the mornings and improve in the evenings, especially after taking a little alcohol. This is of course another illustration of the fact that psychiatric reactions represent in essence an exaggeration or caricature of normal behaviour. The hilarious breakfaster always has difficulty in finding an appropriate audience, and surliness behind the morning paper is traditional. However, in a depressed patient consistent improvement in mood during the course of the day is a good positive sign that the condition is endogenous.

Attitude of Mind

The patient's attitude to his illness is also of considerable importance. In most cases *feelings of inadequacy or self-reproach* are evident. The patient will often say that he is "letting everybody down," or is "not pulling his weight." He is convinced he is not doing his job properly, though those with whom he works will often stress his continuing conscientiousness and hard-bought efficiency. In contrast the neurotic patient tends to be disgruntled, convinced that he is doing his job well despite being unscrupulously exploited, and plaintively or aggressively insistent that medical attention has done him more harm than good. It is not surprising that most doctors feel an immediate sense of sympathy for the depressive patient, even if they do not recognize the nature of his illness. This is in contrast to the attitude of irritation often evoked by the importunate chronic neurotic too obviously labouring the severity of his disabilities.

To some extent depressive symptomatology is coloured by a patient's underlying tendencies and personality structure. Though I have never encountered a case of classical paranoia, I have met many people, both professionally and socially, whose excessive tendency to attribute their difficulties to the shortcomings of others justifies their categorization as paranoid. Again, we are all paranoid, but some are more paranoid than others. The paranoid individual afflicted by depression will often show an accentuation of these tendencies, the commonest pattern being to blame the spouse—presumably the most accessible object. But the tendency of depression to intensify basic personality features is not limited to paranoid feelings. Hypochondriasis is often a lifelong attitude of mind. It may sometimes reach malignant proportions, especially in the middle-aged and elderly, without any convincing evidence of definable mental illness. Often, however, the background of such an intensification is a depressive illness, the symptoms of which may lie deeply buried under a thick hypochondriacal dressing. It is well known also that obsessional subjects are prone to depression, and this may sometimes express itself in a combination of agitation and obsessional-compulsive activity. As a syndrome apparently *sui generis*, obsessional hand-washing is one of the most terrible and intractable afflictions in medicine, but I have several times seen it reach alarming proportions in a middle-aged patient, whose previous tendencies in this direction had been trivial, in the presence of a recent depressive illness of no great apparent severity. In each instance the addiction to hand-washing and similar compulsions faded away in a few weeks with control of the depressive state.

Clinical Variants

Most of the clinical features so far described are common in some degree to most cases of endogenous depression, but there is another important criterion in this connexion, as well as several clinical variants worthy of special mention.

The first variable concerns *the patient's level of activity*. This could be envisaged as a continuous scale, at one end of which is the retarded patient, so slowed-down in body and mind that he sits hunched and immobile in his hospital chair gazing vacantly into nothing, unresponsive and unwilling to feed himself or make a movement. At the other extreme is the agitated depressive—often a middle-aged woman—agonizingly distressed, tortured by a combination of apprehension and despair, and so restless that she cannot remain in the house and feels impelled to go out and roam the streets. Most cases fall somewhere between these two extremes, and an assessment of how much agitation and how much retardation are present is of some importance, since it may influence the choice of drug.

Involucional Melancholia

I have said that the typical patient with agitated depression is a middle-aged woman, and I have mentioned the same pattern of reaction in connexion with the larval psychoses of the menstrual cycle. Agitated depression is in no sense restricted to the female patient, but it is often a feature of what is traditionally known as *involucional melancholia* in patients of either sex, and this concept deserves mention. Evidence for the existence of involucional melancholia as a distinct entity, and as anything more than a form of endogenous depression, is dubious. Depressive illness is certainly commoner in later life than in earlier years, and often affects older patients whose previous history reveals no hint of previous trouble. Most such depressions have a good prognosis, but they are often severe and florid. Anxiety, agitation, and hypochondriasis are common, the last sometimes reaching delusional intensity, with unshakable convictions such as those of blocked bowels. The

elderly patient is often preoccupied with death, and convinced, against all objective evidence, of his abject poverty. Many of them manifest ideas of reference, and some experience horrifying hallucinations, which may impart an almost schizophrenic flavour to their illnesses. The risk of suicide is greater in these agitated patients than in retarded cases. In some less severe instances hypochondriasis dominates the picture, and its depressive basis may be missed, while irrelevant investigations for structural disease are repeated by a succession of baffled doctors. Sometimes the patient's behaviour is disordered or suggestive of hysteria; the development of such symptoms for the first time in later life nearly always implies either depression or organic brain disease.

In many instances the illness of a patient with agitated involucional melancholia goes unrecognized. Passing from doctor to doctor in a frenzied attempt to obtain relief from her distress, she is regarded either as nothing more than psycho-neurotic or else as merely a bloody-minded importunate woman. Often her querulous hostility deters the physician even from eliciting the careful history that will mark out her impossible behaviour as having a beginning months or years previously, and as evidence of a radical change rather than an inherent personality defect. To recognize such behaviour as evidence of illness is to be more than halfway to curing it.

One intriguing variation on this theme is the syndrome of malignant house-changing. Here a middle-aged woman with restless agitation attributes her distress to her living conditions, or to some aspect of her home that demands removal of the household elsewhere. Some minor inconvenience, cheerfully tolerated for years, comes to acquire an increasing and ultimately obsessive importance. I have known a patient drag her exhausted family and bewildered husband through four or five removals in a couple of years before somebody had the percipience to give her antidepressive drugs.

The depressive personality also deserves further comment. These are sometimes charming people, and socially admirable in the restricted sphere determined by the limitations of their available energy. They are often obsessively conscientious, and their gentle and perhaps ironic pessimism is not invariably punctuated by periods of more intense and frankly depressive gloom. However, it may be only when such an episode has demanded antidepressive treatment that the chronic depressive feels really fit and lively, and realizes how long he has been unwell. Some such patients require lifelong treatment. With daily drugs they are happy and efficient citizens, without them neurasthenic semi-invalids.

Difficulties in Evaluation

The multiple and florid physical symptoms often seen in agitated depression are usually recognizable as such, but when a single persistent physical complaint, such as headache or abdominal pain, is a feature of depressive illness its evaluation may be difficult. In many such cases a suspicion of serious structural disease remains in the mind of the physician, but is not convincing enough to justify the battery of ancillary tests that would be necessary to clear the physical ground completely. In such cases there is much to be said for giving a six-week trial of antidepressive treatment, and then reviewing the situation. Often the improvement in local symptoms is so striking that further investigation is unnecessary and a longer period of antidepressive treatment clearly indicated. Another category of cases is that in which the patient's physical symptoms have a structural basis, but evoke much more disablement than can be justified by the objective findings. A good example of this is spondylosis. Everybody over 50 has spondylosis, and nearly everybody over 50 has occasional pain and disability on this score. Sometimes this reaches a periodic crescendo on a purely physical and local basis, but such increased disablement is often due to a superadded

depression. Many of the patients who walk the streets in cervical collars would probably be better off with amitriptyline.

The differentiation of depression from dementia in the aged patient is often difficult. The severely depressed patient is too retarded, too inattentive, and too preoccupied with his misery to give proper attention to formal psychological tests, and even in expert hands the distinction may be impossible. Furthermore, both elements may be present, the mildly demented patient presenting to his doctor with frankly depressive symptoms. Again, a therapeutic trial is the best diagnostic test. When we were dependent on electric convulsion treatment we were reluctant to use this test in such circumstances, because of the risk that some permanent deficit might be left—as it sometimes was—by the disturbance of memory that follows this type of treatment, especially in the elderly patient. No such problem arises in the case of drug therapy. The clinical improvement induced by amitriptyline in patients of this type may be dramatic, often confirming that even where a nucleus of dementia remains most of the patient's overt disability was in fact depressive.

Suicide

Depressive illness is the most important cause of suicide, not only because of its frequency, but because the disorder is nearly always curable and the disaster often avoidable. Sometimes, of course, the quietly depressed individual commits suicide before seeking medical attention, and even before his family appreciates that he is ill. In other instances of that small minority of depressive illnesses that are entirely intractable to medical, physical, and even surgical treatment, the psychotic urge to self-destruction is so powerful as ultimately to evade every precaution.

All too often, however, the depressive suicide is tragically unnecessary. Often the evening paper describes such an incident in a patient due to attend hospital "for an x-ray examination," or who had just been negatively investigated for "stomach trouble." Most such cases arise from a professional failure to appreciate the true nature of the patient's symptoms. I recall the case of a 22-year-old woman who developed palpitations and sleeplessness 10 days after the birth of her first child. She became obsessively preoccupied with the condition of her heart, and was referred to a physician, who screened her, carried out an electrocardiogram, and reassured her as to the absence of any organic disease. She went home and put her head in the gas oven, leaving her husband with a motherless 3-week-old child.

Every patient with endogenous depression is a potential suicidal risk. Most patients will answer quite unaffectedly if they are asked in a straightforward manner whether they have contemplated suicide, and evasiveness on this account implies suicidal intention. Unwillingness on the part of the physician to ask this question under these circumstances is out of place.

Like most of those who have worked in this field, I too have had my tragedies, and one important lesson I have learned is that even where serious organic disease is present a coincident endogenous depression may represent a more serious immediate threat to the patient's life than the physical disorder, and should have priority in treatment. It is also important to remember that the recovering patient is often at greater risk than the severely retarded depressive. Suicide within a few days of discharge from hospital after clinical improvement is all too frequent.

Treatment

Electric Convulsion Therapy

The treatment of depressive illness has been revolutionized by electric convulsion therapy and antidepressive drugs. Except

for a minority of intractable cases, the stay of one or two years in a mental hospital, so often necessary in the past, is no longer required. Most can be treated as outpatients, and many others with a brief stay in a general hospital.

The introduction of both electric convulsion therapy and of effective antidepressive remedies was accompanied by psychiatric homilies on the necessity of combining such measures with "psychotherapy"—a pursuit that resists accurate definition. Such adjurations are of course not surprising, and recall the venereologist's losing battle to sustain the importance of arsenical or bismuth treatment as a necessary prelude to really curing syphilis with penicillin. It is also axiomatic that once a really effective treatment is produced for a disease it becomes a general-practitioner disease. Antidepressive drugs will bring relief to more than three-quarters of all patients with endogenous depression, whether they are administered among the rhododendrons of the Crichton Royal or in a back street in the Gorbals. Most of the depressives referred to formal psychiatrists today are either undiagnosed, half-treated with inadequate dosage, or imipramine-fast. This is not surprising. The recognition of depression may be very difficult, but its treatment is simple enough to be left in many instances to the general practitioner, provided he appreciates the danger of suicide, the importance of adequate dosage over an adequate period, and the need for regular periodic consultations to ensure continued control of symptoms.

The details of antidepressive treatment are too familiar to require repetition. In the hands of some mental hospital psychiatrists the routine employment of electric convulsion therapy continues, sometimes, it seems, merely because the machine is there and the operator is familiar with its use. It still has an important place, but the need for its employment has been reduced by the development of effective drug treatment. It is invaluable in very severe acute depression, where it allays agitation, diminishes the risk of suicide, and makes life more tolerable for the patient and his attendants until the few weeks have passed that are often necessary to establish pharmacological control of his symptoms. It is also used, of course, where drugs have failed. Sometimes it is very effective under these circumstances, but other depressions that resist drug treatment are also unresponsive to physical measures, and furnish that hard core of depressive illness where suicide ultimately follows prefrontal leucotomy, the psychiatrist's and neurosurgeon's last resort. Four out of five cases of endogenous depression respond to antidepressive drugs, and during recent years I have needed to resort to electrical treatment not more than three or four times a year out of an average of about 100 new cases.

The indications for admission to hospital are first a palpable risk of suicide, and secondly severe agitation. Even mildly agitated patients benefit from two or three weeks in hospital at the inauguration of treatment. One reason for this is that they are so disturbed that they may fail to take the drugs at home, or may abandon them, ungenerously attributing their symptoms to the therapy. In the reassuring atmosphere of hospital full dosage can be established, and real or imagined side-effects dealt with. Admission to hospital itself often produces striking improvement before drugs can be effective; the increased agitation that occasionally follows the institution of treatment, especially with imipramine, can be detected at once; and electric convulsion therapy is at hand if need be.

Drugs

We all have our favourite drugs, and in this field, as in others, it is better to know and use a few than to follow every hortation of the morning's blotters. I most often use amitriptyline (Tryptizol), especially in the agitated and elderly patient. Where retardation is conspicuous, imipramine (Tofranil) is perhaps marginally preferable. A sleeping-tablet is usually

necessary, though in severe depression even the most powerful hypnotics may be ineffective until the condition is controlled by antidepressive treatment. Tranquillizing drugs, such as sodium amytal or chlorpromazine, are useful in the early weeks where agitation and anxiety are prominent.

The monoamine oxidase inhibitors have lost some favour, partly because of their well-known side-effects and partly because they are generally less potent in controlling the symptoms of endogenous depression. Nevertheless, there is a borderline type of case where a neurasthenic syndrome—often in a younger patient—lacks some of the classical features of endogenous depression, and yet is distinctly depressive and more clearly “illness” than exogenous depression. This syndrome is closely related to the “endogenous anxiety-state,” and sometimes responds most dramatically to phenelzine (Nardil). I have in mind a distinguished engineer who presented with this picture, and who was transformed within a month by this drug, and told me that he had never felt so fit and active for 10 years. He is still taking it regularly eight years later, having risen to the top of his profession with its assistance. Such patients need to be told that, though we do not know the exact nature of the metabolic disturbance that causes depressive illness, we believe that some such disturbance is the basis of the condition, and that the antidepressive drug is a form of replacement therapy for them analogous with insulin for the diabetic, and just as respectable.

Nature of Depressive Illness

When we consider the genesis of a reaction as discrete and yet as complex as endogenous depression we must think not only of a multifactorial aetiology involving a constellation of “causes” of differing valency, extending from the remotely genetic to the immediately psychological, but also of a chain of successive pathogenetic events. This concept emphasizes the temporal factor in causation, and also opens the door to possible interruption of the chain at several points in its length by different therapeutic manoeuvres.

The consistent patterns of endogenous depression as it affects people of different ages and personalities, and as it arises under the various clinical circumstances I have mentioned, argues that, whatever the proportional contributions of various aetiological factors in a particular case, the syndrome is mediated through a *final common pathway of pathophysiological disturbance*. That this final common pathway itself probably has several stages is suggested by the everyday observation that a patient entirely unresponsive to one antidepressive drug may benefit dramatically from another.

It must be admitted at once that direct evidence of the physiological disturbance that underlies endogenous depression is scanty and inconclusive. Among the physiological deviations reasonably authenticated in depression must be included increased steroid output with elevated plasma cortisol levels and cortisol secretion rates; minor alterations in the metabolism of sodium and other electrolytes; and decreased glucose tolerance. None of these changes can be regarded as specific, and they seem at least as likely to reflect the psychiatric disturbance as to play any part in the chain of causation.

The most exciting clues to the possible physical basis of depressive illness have come from the last 10 years' work in neuropharmacology. They concern the relation of central nervous system catecholamine to sedation and stimulation. The catecholamines *noradrenaline* and *dopamine* and the indole amine *serotonin* have all been studied in this connexion. Noradrenaline is of course the transmitter substance of the peripheral sympathetic nervous system. Though there is no

final proof that it functions similarly in the brain, it seems not unlikely that it is also in some way concerned with central nervous transmission. Noradrenaline is present in high concentration in the hypothalamus, structural lesions of which are often associated with disturbances of mood, behaviour, and appetite. What is now known as the *catecholamine hypothesis of depression* postulates that the condition is due to a lack of noradrenaline (and possibly of the other amines mentioned) in the brain, elation and excitement resulting from an excess.

The evidence favouring this view of affective illness is certainly suggestive. The occasional provocation of severe depression by the sedative and hypotensive drug reserpine is well known: in the experimental animal the administration of this drug causes depletion of cerebral noradrenaline. Conversely, present evidence suggests that in the short term, and in modest dosage, amphetamine releases active noradrenaline from nerve cells and probably also blocks its inactivation. It was, however, the almost accidental discovery of the more-sustained antidepressant effect of the monoamine oxidase inhibitors (discovered accidentally during the treatment of tuberculosis with isoniazid) that stimulated the current explosion of research in this field. These drugs inhibit intracellular deamination, and their administration to animals is followed by increased levels of both cerebral noradrenaline and serotonin. The introduction of imipramine, and the early realization that it was a much more potent antidepressant than any of the monoamine oxidase inhibitors, seemed at first to doom the catecholamine hypothesis. However, it is now known that both imipramine and amitriptyline potentiate the effects of noradrenaline, probably by inhibiting the inactivation normally associated with cellular reabsorption, and perhaps by decreasing cellular or intracellular membrane permeability to this substance.

There are too many gaps in present knowledge for the catecholamine hypothesis to be regarded as proved. In particular, direct evidence of disturbed catecholamine metabolism in depressed patients is inconclusive. As it is sketched above, the hypothesis seems too simple to account for the clinical complexity of the problem, and it is already being elaborated to take further variables into account. There can be no doubt that it is generally compatible with much that we know about depression and its treatment, and it certainly furnishes a convenient frame of reference for both reflection and investigation in this important and absorbing field of medicine.

Summary

Depression is ubiquitous, usually easily recognized, and in most cases rapidly responsive to modern treatment. Nevertheless, cases often escape recognition. The consistent symptomatology of depressive illness of endogenous pattern lends support to the view that it represents a pathophysiological disturbance mediated through a final common pathway, and justifies its acceptance as a disease-entity. Among its more important and commoner clinical features are a characteristic alteration in sleeping habits, objective evidence of disturbed physiology, diurnal variation, and varying degrees of retardation or agitation.

The catecholamine hypothesis of depression postulates a relation between mood and cerebral noradrenaline levels. It is known that these levels can be influenced by such drugs as reserpine, amphetamine, the monoamine oxidase inhibitors, and the newer antidepressive drugs such as imipramine and amitriptyline. The hypothesis cannot yet be regarded as firmly proved, but it is generally compatible with clinical and pharmacological evidence.