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Lecture

Treatment of Depression
The Relevance of Research for Clinical Practice*

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My aim in this lecture is to review a wide range of published studies on the treatment of depression. I want to look at these with one major clinical question in mind: given the range of treatments available, which treatment should be chosen for which patient? In July 1985 a report, published as a special supplement to the *American Journal of Psychiatry*, called for more research on this topic:

> "As the number and diversity of the effective drugs and psychosocial interventions expand, clinicians will increasingly want objective, reliable criteria with which to match the patient to the optimal treatment modality and to monitor the response." (Institute of Medicine, 1985)

I wish to examine the extent to which this aim may already have been achieved. To establish some reasonably firm conclusions, I will also need to look to a lesser extent at the degree to which the treatments are effective.

I have chosen this topic for several reasons. The honour of an invitation to deliver the Maudsley Lecture encourages a certain internal deliberation about a suitable subject. Treatment is a central activity for the psychiatrist: it is the main reason why the world wants his existence. However, this is not the occasion for a straightforward practicum of treatment. As a research topic, much of my own work over 25 years has been concerned with prediction of response and indications for therapeutic choice in depression.

As a second major theme, I want to illustrate the place of research in relation to clinical practice. I will synthesise many studies to draw conclusions about specific treatments. In doing so I will try to illustrate the value of treatment trials, and, particularly, to explore the two-way process by which clinical insight informs the genesis of good studies, and in turn sound methodological investigations are essential for firm conclusions about clinical treatments.

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Causative models and therapeutic modalities

Treatment of depression also allows one to illustrate a fundamental principle in psychiatry: the value of multiple approaches. Akiskal & McKinney (1975), in a review, described ten partially overlapping models of depression, ranging from impaired monoaminergic neurotransmission to loss of the meaning of existence. They covered five broad areas – psychoanalytic, behavioural, sociological, existential and biological. These explanatory models need not be regarded as antithetical, but all may converge on a final common pathway. All the evidence indicates that causation of depression is multifactorial. No single factor is of overwhelming importance, except possibly in bipolar disorder, where there may be single genes of major effect. Otherwise depression has many causes, with an amalgam of genetic make-up, early environment, physical factors and recent social stresses. One should not make an artificial dualistic separation between the biological and the psychological, since psychosocial stresses are mediated via the brain.

In a disorder of complex aetiology it would seem unlikely that a single form of therapy would serve all cases. The social, the biological, the psychological, are as valid as approaches for treatment as for causation, and for theoretical models. The eclectic therapist will assign importance to all three modalities, and he or she will be careful not to infer a particular cause from a particular therapeutic response. For drugs and for psychological approaches I will show detailed evidence, since there have been many studies. As a social psychiatrist I would like to be able to deal equally thoroughly with social aspects of treatment, such as family support, rehabilitation and environmental manipulation. Unfortunately these have been less subject to controlled evaluation. Probably one of the most powerful treatments for severe depression is admission to hospital: many clinicians and biological depression researchers will have had the experience of watching a psychotically depressed patient improve markedly after admission to a supportive ward milieu, while drug treatments or electroconvulsive therapy (ECT) are being withheld. Equally, for mild depression

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there are probably major supportive effects from out-patient assessment by a psychiatrist, with the unusual experience of spending up to an hour reviewing in detail one's recent problems and life-history to a sympathetic listener.

Methodological requirements

We need also to consider the methodological requirements for conclusive studies. The essential test for efficacy and for specificity is the controlled trial. Many studies in the past have adopted a single group predictive design. One takes a mixture of depressed patients, treats them for six weeks with a single antidepressant, rates them at beginning and end of treatment, and then examines by some statistical technique to see what characteristics at the beginning distinguish those who have done well and badly on the treatment. Although such studies may drop useful hints, this design is not enough.

In any patient who improves or recovers on treatment with an antidepressant, a number of different elements may contribute to the response. First, it may have been spontaneous, reflecting the natural history of the disorder. Spontaneous remission is probably not uncommon. It is clear from historical accounts that severe melancholia in the nineteenth century did in due course remit: the recognition of this remission contributed to Kraepelin's delineation of manic depressive disorder by its course. Modern high prevalence and episode rates for mild depression in the community make it clear that much of this disorder remits without ever being recognised or treated.

Secondly, many other treatment processes are also at work in a patient who receives an antidepressant, such as the social effects of ventilation, support, and hospital admission already referred to, and the effect of receiving an inert placebo. The placebo group in drug trials controls for everything except the specific effects of the chosen antidepressant treatment. The limited evidence available (Paykel *et al*, 1975) suggests that the effects of the placebo itself are in fact quite weak, but the effects of other non-specific treatment factors are probably quite powerful. The specific effects of the drugs are not very large. In placebo-controlled trials in depression, as a rule only 20–30% more recoveries occur on active treatment than on placebo.

When predictor analyses of response only examine the change in a group of subjects given the single treatment under investigation, improvement is an amalgam of the above factors, and it is not possible to say to which element significant predictors are related. If one wants to say that a certain treatment is indicated for a specific patient, one needs to focus on the specific effect of the treatment, i.e. the magnitude of the difference between improvement on this drug and on placebo or alternative treatment. One needs to show that this difference is greater in the patient group under consideration than it is for other treatments which might be given instead. This requires a controlled trial against placebo or an alternative treatment. Probably the best technique is the factorial design with two-way analysis of variance of treatments by classification subgroups where one seeks a significant interaction term indicating that differences between the two treatments are of different magnitude in different patient groups (Paykel, 1988).

I will now look for this kind of efficacy and any groups specifically responsive to five classes of treatment: ECT, monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, dynamic psychotherapy, and cognitive therapy.

Electroconvulsive therapy

ECT is the oldest of the current antidepressant treatments. It illustrates one earlier pathway between clinical care and research – clinical innovation, in which research designs followed much later. The clinical innovation followed a mistaken and accidental road that seems almost classical for new treatments in psychiatry. Von Meduna's use of chemical convulsions was based on the belief that epilepsy protected against schizophrenia; the truth, at least for temporal lobe epilepsy, turns out to be the reverse. He, and Cerletti and Bini, used convulsive therapy for the wrong disorder: its most useful place is in depression.

It is easy to feel that if dramatically effective treatments came along in psychiatry, controlled trials would no longer be necessary, and of course they played no part in the introduction of ECT. It is therefore interesting that in the long run they became necessary, in response to public questioning of the value of the treatment.

Among the most remarkable of studies have been the six recent blind comparisons of ECT and simulated ECT carried out in Britain. The first of the studies (Lambourn & Gill, 1978) showed virtually no benefits and the Northwick Park study (Johnstone *et al*, 1980*a*) found effects that were less strong than might have been expected, but the remaining studies showed strong treatment effects among groups of relatively severely ill in-patients (Freeman *et al*, 1978; West, 1981; Brandon *et al*, 1984; Gregory *et al*, 1985).

It is instructive to ask why the studies differed in their findings. One possibility is that the negative study was the only one to use ECT applications that were unilateral and brief pulse. There is some evidence that

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sine wave applications are more effective than brief pulse, at least when delivered at low energy (Robin & de Tissera, 1982), and more clearcut evidence that bilateral ECT is more effective than unilateral (D'Elia & Raotma, 1975; Abrams & Fink, 1984; Sackeim *et al*, 1987), probably because induction of convulsions is more reliable.

ECT was the target of the earliest predictor studies of specific antidepressant treatments. Hobson (1953) constructed a predictor index in which the items were very similar to those distinguishing psychotic and neurotic depressives, although he did not adopt that terminology. Since then, a moderately large number of studies have concluded that psychotic depressives show better response (Paykel, 1979), the main dissenting study being that of Abrams *et al* (1973). All these studies were without control groups and did not conform to the design I have advocated. One study which did do so was the Massachusetts collaborative study (Greenblatt *et al*, 1964). In this controlled trial, non-blind with respect to ECT, breakdown by diagnosis showed, among manic depressive illnesses (bipolar and unipolar in modern terminology), 78% markedly improved on ECT as opposed to 37% on placebo; among involutional psychoses 85% against 25%; for psychoneurotic depressive reactions, 77% against 83%. In addition, the Northwick Park study (Clinical Research Centre, 1984) in subsequent analyses found that the superiority of active ECT was mainly in patients with depressive delusions.

Published studies of ECT almost exclusively involve in-patients in the severely ill range. Among such patients, ECT does appear to be more effective than tricyclic antidepressants and MAO inhibitors. There have in fact been a number of non-blind randomised comparative trials with random assignment (Paykel, 1979). Among nine comparisons with tricyclic antidepressants, six found ECT better overall, while three studies found equal drug effects. Among comparisons with MAO inhibitors, the superiority is even more striking, with ECT more effective in all five studies (Greenblatt *et al*, 1964; Medical Research Council, 1965; Kiloh *et al*, 1960; Hutchinson & Smedberg, 1963; Stanley & Fleming, 1962). No study has found drug treatment more effective overall than ECT. This shows a pattern which is frequently found in surveying therapeutic trials in psychiatry: two treatments are found equal or treatment A is found better than treatment B, but rarely or never is B better than A. What this usually indicates is some, although limited, superiority of A over B: it shows up in some situations with some samples but not in others.

Monoamine oxidase (MAO) inhibitors

With the MAO inhibitors the link between clinical practice and research was different: a story of drugs introduced just before the beginning of the era of controlled trials in psychiatry, and of the insight of a charismatic clinician as to their specific place slowly being subjected to controlled testing by others with some confirmation. The clinician who first crystallised a view of the selective clinical place of MAO inhibitors was William Sargant. His ideas first clearly emerged in a paper by West & Dally (1959), who described a syndrome of atypical depression. There have been many subsequent papers.

Three different meanings have really been assigned by different authors to the term atypical depression (Paykel *et al*, 1983). One is the idea of marked anxiety and phobic symptoms, either accompanied by depression, or assumed to have some relation to an underlying depression as indicated, for instance, by diurnal variation. This has included the influential views of Tyrer (1976).

The second meaning is what Pollitt (1965) describes as reversed functional shift, i.e. depression with a diurnal pattern of evening worsening, insomnia of early rather than late kind or increased sleep, increased appetite and weight, all in the direction opposite to the physiological changes said to characterise endogenous depression. In the USA Donald Klein, another charismatic clinician, who conducts controlled trials to test his insights (Liebowitz *et al*, 1988), assigns principal importance to these features.

A third meaning of atypical depression, at one time common in the American Literature (Robinson *et al*, 1974), was that of non-endogenous depression in general. This usage has gradually dropped out in the last ten years.

These three meanings identify different groups of patients. In a sample of out-patient depressives we collected a large amount of diagnostic data on many different subclassificatory systems (Paykel *et al*, 1983). We examined the relationships between different diagnostic systems, using separate criteria for the three aspects of atypical depression. The three separate criteria tended to select quite different patients. We had to conclude that the concept of atypical depression was imprecise. It would be better to specify which aspect was to be emphasised.

The best evidence on the efficacy of MAO inhibitors is for phenelzine. Among seventeen controlled trials against placebo in depression (Paykel, 1989) ten have shown the drug to be clearly superior to placebo, three have been doubtfully positive, and four failed to show drug superior to

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placebo. For isocarboxazid, three trials have shown superiority over placebo and three have failed to. For tranylcypromine, two studies have been positive, one equivocal, and one negative (Paykel, 1989). This is less impressive than for ECT or for tricyclic antidepressants. There are also a number of positive studies in phobic disorders.

In these studies there was not a very strong relationship between response and defined subtype, but there was a clear relationship to treatment setting. All except one of the studies showing drug–placebo differences have been in out-patient samples; all the negative studies have been carried out on in-patients. Studies in day patients or mixed patients have tended to be equivocal. The most likely explanation would be that this reflects diagnostic subtype, since out-patients tend to be less severely ill and more neurotic in symptom pattern. Some re-evaluation may be needed here since most of the in-patient trials were early studies, using doses and treatment periods that were relatively low by modern standards.

We conducted a controlled trial of phenelzine, amitriptyline and placebo in out-patient depressives and mixed anxiety depressives. Overall we found clear drug effects for both drugs, with surprisingly little difference between them. On depression measures amitriptyline was minimally superior to phenelzine and on anxiety measures phenelzine was minimally superior to amitriptyline. These differences between the drugs, although in the predicted direction, were weak (Rowan *et al*, 1982).

We also undertook a series of two-way analyses of covariance with the various kinds of atypical depression as the second factor in the design (Paykel *et al*, 1982). Subclassifications based on presence or absence of additional anxiety symptoms gave some interactions, although they were not very strong. Phenelzine tended to be superior to placebo in those depressives with an admixture of anxiety but not in those depressives without anxiety. However, amitriptyline was effective in both groups. Neither of the other two views of atypical depression gave significant interactions with drug response.

Overall the findings of this study suggested some selectivity of MAO inhibitors in patients showing anxiety, but the difference was weak. In this mildly ill, neurotic and somewhat anxious group of depressives, usually not regarded as showing much benefit from tricyclic antidepressants, amitriptyline was clearly superior to placebo, and did not show any particular selectivity.

These weak differences between tricyclics and MAO inhibitors are consistent with other recent studies. Ravaris *et al* (1980) found only weak differences between amitriptyline and phenelzine, with phenelzine having more effect on anxiety measures. Davidson *et al* (1986), analysing patients from a number of studies, found weak trends for better effects of MAO inhibitor rather than tricyclic where a precipitant was present and, contrary to expectation, in the absence of agoraphobia. There were also some inconsistent predictors in the two sexes.

Liebowitz, Klein, Quitkin and colleagues have found stronger differences (Liebowitz *et al*, 1988). Selecting patients with reversed functional shift, they found phenelzine most effective; imipramine was less so, although better than placebo. Examining subgroups within this selected sample, they unexpectedly found that superiority of both phenelzine and imipramine to placebo was largely confined to patients with spontaneous panic attacks and/or hysteroid dysphoric features. Davidson *et al* (1988), in a comparative trial of isocarboxazid and placebo, found the drug more effective in endogenous depressives but also in patients with reversed functional shift, in anxious and in hostile depressives. In general these studies suggest some convergence of anxiety and reversed functional shift, but still the overall impression is of weak differences.

Taken overall then, a general conclusion for MAO inhibitors would be that they are weakly selective for anxiety and reversed functional shift, but the differences from tricyclics are not sufficiently strong to guide treatment choice consistently. Since tricyclics are safer and easier to use, the logical place for MAO inhibitors is as a second choice where tricyclics have failed and ECT is not indicated.

It remains possible that there is some other variable, rather than clinical symptom subtype, which predicts a better response to MAO inhibitors. Most clinicians are used to having some patients under their care who seem to respond only to this class of drug, and previous good response is probably the best indication for use as first choice. Supporting this view, Pare & Mack (1971), comparing outcome in patients who in successive episodes had received antidepressants of the same type or of different type, found a significant tendency for consistent response in the same direction, i.e. good or bad, with the same class of drug, and inconsistent responses across different kinds of drug. They also found some consistency in responses among relatives. This was a small study which needs repeating, but it does support the view that there are some specific response factors which might be related to biochemical variables only weakly reflected in symptom pattern.

Tricyclic antidepressants

Tricyclic antidepressants lie squarely in the controlled trial era. Discovery was rapidly followed by a model placebo-controlled trial carried out in Britain

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(Ball & Kiloh, 1959). From the point of view of efficacy, they are well-evaluated drugs. A useful review was published by Morris & Beck (1974). Surveying the limited selection of tricyclic antidepressants then available in the USA, they found 93 comparative trials against placebo. This gives some idea of the relentless effort that goes into drug evaluation nowadays. Among these, 61 showed drug superior to placebo and 32 failed to do so. There will be more positive studies of additional drugs by now, so the evidence for efficacy is impressive. Some of the negative studies can be attributed to poor trial technique, such as short treatment periods, low doses and unsatisfactory outcome measures. Some undoubtedly reflect the limited benefit obtained from these drugs.

The view that tricyclics are particularly effective in endogenous depression has an impressive lineage, going back as early as the intitial open studies by Kuhn, and the first controlled trial. However, a critical look at the controlled trials published in the 1960s suggests that, although the effect may have been a little better in endogenous depressives, there was evidence of benefit in neurotic depressives (Paykel, 1979). Certainly there have been many trials, in which a tricyclic was superior to placebo in samples characterised as neurotic or reactive (Ball & Kiloh, 1959; Wittenborn *et al*, 1962; Uhlenhuth & Park, 1964; Covi *et al*, 1974; Friedman, 1975; Paykel *et al*, 1982).

The more recent literature regarding delusional depression also suggests a poor response to tricyclics and better to ECT or neuroleptics (Perry *et al*, 1982). It would appear that the most severe endogenous or psychotic depressives do not respond very well to tricyclics. There may be a curvilinear relationship in which the best response is shown by patients with the endogenous symptom pattern but moderate severity. This was found in two studies by Coppen and colleagues, using the Newcastle Scale (Rao & Coppen, 1978; Abou-Saleh & Coppen, 1983).

There is increasing evidence that tricyclics are superior to placebo when neurotic states other than depression are present. Marks (1983) reviewed a number of studies showing tricyclics to be superior to placebo when obsessional neurosis or agoraphobia were present. The obsessional studies depend mainly on one drug, clomipramine, with a more serotoninergic action, but the studies in agoraphobia have employed more standard drugs. Two important studies including a spectrum of anxious and depressed patients have not received the attention they deserve. Johnstone *et al* (1980*b*) treated such patients with amitriptyline, diazepam or placebo. Amitriptyline was consistently superior to placebo while diazepam showed only weak effects, even in patients with predominant anxiety. Kahn *et al* (1986) carried out a similar study with imipramine, chlordiazepoxide or placebo, with similar findings.

We examined effects of tricyclics in mild depression by means of a controlled trial in general practice. Depressives identified in general practice were treated for six weeks with amitriptyline or placebo double blind (Paykel *et al*, 1988; Hollyman *et al*, 1988). Mean initial total scores on the 17-item Hamilton Rating Scale for Depression were a little below 15, confirming the relative mildness of the sample. Differences started to appear surprisingly early and at two weeks had reached significance. By six weeks highly significant differences had appeared on a wide variety of typical depressive symptoms, with amitriptyline impressively superior to placebo.

To examine for responsive subgroups we carried out a series of two-way analyses of covariance, using as the second factor a variety of classifications from the literature. Significant interactions were relatively few, indicating fairly strong and consistent drug effects across most subgroups. Subgroups failing to give rise to interactions included demographic variables, history of chronicity, and endogenous versus neurotic depression.

Only in one area, severity, were there interactions. Active drug was beneficial to Research Diagnostic Criteria major depressives, with clear superiority over placebo. Minor depressives improved equally on drug and placebo. On initial Hamilton score we divided the sample into three groups: the most mild, with Hamilton scores below 13, those intermediate, with initial scores 13 to 15 and the relatively more severe, comparable with psychiatric out-patients. It was only the very mildly ill patients who showed no benefit from active drug: there were considerable drug–placebo differences for the two other patient groups, and again the effect was to produce final scores from amitriptyline close to those of the mildly ill.

These findings are consistent with another study in the literature. Stewart *et al* (1985) found desipramine to be superior to placebo when major depression was present, both with and without melancholia, but not dysthymic disorder. It was also effective in patients with initial Hamilton scores of 14 to 18 but not in those with scores of 13 and under (Stewart *et al*, 1983).

The real conclusion about tricyclic antidepressants appears to be that they are truly broad spectrum antidepressants, effective across quite a wide range of depressions, extending to clearly non-endogenous and relatively mild disorders, although with a floor level for severity, and also well into the spectrum of anxiety disorders. They make a good first choice where medication is to be used: the indication is the

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presence of an established depressive syndrome of all but very mild severity.

Psychotherapy

With the dynamic psychotherapies we extend into another area of clinical-research interrelationship: that of the fierce and dogmatic therapeutic debate where research, rather surprisingly, acts as the peacemaker. Historically drugs and psychotherapies have often been diametrically opposed, with proponents of each arguing that the other was at best limited and at worst harmful. Each was opposed to combined therapy, drug therapists arguing that psychotherapy merely stirred up feelings that made the patients feel worse: psychotherapists that drugs fixated the patients on symptom and somatic issues.

The controlled studies have all come out of the USA and it is interesting that the earlier ones were funded by the Psychopharmacology Research Branch, that part of NIMH which supported drug trials. They were really successful transplants of the methodology of drug trials to psychotherapy.

The first Yale–Boston collaborative study (Paykel *et al*, 1976) was a continuation study of amitriptyline versus withdrawal in depressed women, half of whom were assigned to receive once weekly individual psychotherapy from social workers and the other half once monthly low contact. Psychotherapy did not lower the relapse rate but had a clear effect in improving social adjustment and interpersonal relationships. Psychotherapy was only effective after eight months' treatment, and only in patients who had not dropped out because of earlier relapse, so that the best benefits were from the combination.

Using acute treatment with amitriptyline or placebo with and without conjoint marital therapy, Friedman (1975) found that marital therapy improved marital relationships with a little benefit on symptoms also; amitriptyline had much more effect on symptoms. Again, combination was best. In a third study Covi *et al* (1974) found little effect from group therapy, but this study lacked social adjustment measures and there were hints of effects on the limited measures which were incorporated.

A further study from Yale and Boston used amitriptyline, individual psychotherapy from psychiatrists, both treatments, or no treatment and found a different pattern (DiMascio *et al*, 1979). Drugs and psychotherapy both had effects in improving symptoms. The combination produced the most improvement.

These studies all suggested that psychotherapy was of value, but in the first three it was primarily for interpersonal relationships and social maladjustment and drugs were more effective for the symptoms of depression. The split between symptoms and social effectiveness was exactly what had been suggested many years before by Jerome Frank and his colleagues (Parloff *et al*, 1954). All found that drugs and psychotherapy worked well in combination to produce the maximum benefit.

The most recent study is the large collaborative study in which depressed out-patients were randomly assigned to receive imipramine, interpersonal psychotherapy of the kind used in the Yale–Boston studies, cognitive therapy, or placebo (Elkin *et al*, 1985). This was an expensive study and great care was taken over training. Some results have been reported at meetings, but not yet published. Overall, the three active measures produced benefit compared with placebo, although cognitive therapy was a little the weaker of the three. The benefit was on the same symptom measures. This study gives food for considerable thought. It suggests that drug, a dynamic psychotherapy and a cognitive behavioural one, can all produce similar improvement in symptoms. Perhaps a pathway can be altered at various points along the way to produce a final common consequence.

Most of these studies did not report analyses directed towards the question of who responds best to which therapy. All were conducted in out-patients and they do not permit conclusions regarding severely ill in-patients. The second Yale–Boston study did analyse by Research Diagnostic Criteria subtypes of major depression. Amitriptyline showed the best effects in RDC endogenous depressives: psychotherapy in situational depressions (Prusoff *et al*, 1980). Endogenous depression is defined in the RDC in terms of symptom pattern, situational depression in terms of social stress, so the two are not mutually exclusive. Analyses of the NIMH collaborative study reported so far do not show clear selectivity for interpersonal psychotherapy.

Probably the best guidelines at the moment are that psychotherapy is appropriate for tackling psychodynamic and interpersonal problems when these are present. It is best combined with antidepressants: it may produce some symptoms remission, at least in the milder patients. Combination with drug therapies is highly desirable. Clinically it is often unproductive to use psychotherapy in the more severely ill until symptom remission due to drugs or ECT makes it possible.

Cognitive therapy

Cognitive therapy is the Yuppie of the antidepressant therapies: a child of the 1970s, verbal, exciting, a little

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pushy, perhaps riding for a fall. Again, its introduction has depended on a charismatic clinician, Aaron Beck. Controlled evaluation appeared early in its history, reflecting a birth well within the controlled trial era. A recent review (Dobson, 1989) identified 21 controlled trials, but not all were very informative in design. Studies in clinically depressed samples (out-patient or general practice) are particularly useful. Five studies, including the NIMH collaborative study, have made comparisons with drug (Rush *et al*, 1977; McLean & Hakstian, 1979; Blackburn *et al*, 1981; Murphy *et al*, 1984). All found the two approximately equally effective on symptom measures: sometimes cognitive therapy was a little more effective than drug: sometimes, as in the NIMH collaborative study, a little less. A sixth study (Teasdale *et al*, 1984) found it as effective as GPs' routine treatment. A recent study (Beck *et al*, 1985) found cognitive therapy plus drug no better than cognitive therapy alone.

Again, samples were out-patients with mild to moderate rather than severe illnesses, so conclusions must be limited to such patients. Most of the studies have had too small samples to look for responsive subgroups. In the NIMH collaborative study analyses reported so far, benefit from cognitive therapy was mainly in the more mildly ill among the patients studied, with drug and interpersonal therapy more effective in the moderately ill.

The ultimate place of cognitive therapy is not yet clear. Cognitive therapists with whom I have discussed it tend to feel that it is not useful in chronic, and resistant cases, and that the sort of patients who do well are also those who respond well to drugs. In this case its place would be limited to those who are reluctant to take antidepressants: cognitive therapy involves a lengthy treatment process for up to 16 weeks: drug therapy is cheaper and less intrusive, with much less investment of patient and therapist time. It is quite likely that briefer or even largely self-help methods of cognitive therapy will be developed.

There is an intriguing further finding: some evidence that cognitive therapy may cut down the rate of relapse, which can be quite high after drug therapy. Three studies which compared tricyclic antidepressant with cognitive therapy in initial treatment have found on follow-up for 6–24 months that relapse rates were much lower in the cognitive therapy group than in those who received tricyclic antidepressant (Hollon *et al*, 1984; Simons *et al*, 1986; Blackburn *et al*, 1986). The differences were substantial, from 66%–78% on drug to 12%–25% on cognitive therapy. Each study included a group receiving combined therapy, and in two of the three studies (Hollon *et al*, 1984; Blackburn *et al*, 1986) they also had low relapse rates. Two other follow-ups (Kovacs *et al*, 1981; Beck *et al*, 1985) have failed to find this benefit for relapse rates.

These findings require replication and extension. Samples of patients in naturalistic follow-ups may not be comparable: different patients may respond to drugs and to cognitive therapy. Drug continuation would make a better comparison than the relatively early drug withdrawal that has occurred in some of the studies. If the findings are sustained, cognitive therapy will have a major place in those depressives prone to relapse.

Conclusions: research and clinical practice

I have tried to summarise many efficacy studies all directed, at least in part, to the question of which specific treatment is indicated for which kind of patient. One of the tasks which I set myself was to see if the aspiration of matching patient and treatment choice had already been achieved. The answer is "yes, to some extent". The broad outlines of who responds best to which treatment are already clear, and tend to confirm long-held beliefs, but there is much variation between individuals and when one applies the criteria for choice to the single patient, there is not high predictability, particularly for the more resistant patients. We are left with some guidelines for first choice and for combining drug and psychological treatments, but the recognition that not uncommonly a less obvious second choice is necessary.

A more general implicit conclusion is that modern treatments are effective. Prior to the introduction of ECT, although the old accounts indicate that patients did improve and recover, the spontaneous course might be quite a long one, and in-patient acute wards were fairly accustomed to the long stay in hospital of persisting psychotic depressives. Nowadays, even if we do need better treatments, even if chronicity does occur and relapse is often a problem, the majority of depressives show considerable improvement within a few weeks or, at the most, months of starting treatment. Severe resistant depression is the exception.

One of my aims has been to illustrate the relationship of therapeutic research and clinical practice. One theme which clearly emerges is the change over the years in the processes by which new treatments become established. In earlier times in psychiatry, and presumably for many centuries in the history of medicine, the process was one of individual treatment innovation. Innovators were striking, often charismatic, personalities. Dramatic

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effects were expected but rigorous proof not demanded nor the requirement for its demonstration appreciated. Within depression, ECT and the older dynamic psychotherapies followed this path. The introduction of the earlier drug treatments showed some similarities with this process but it was rapidly overtaken by the need for controlled trials.

There is a remarkable contrast between the earlier innovations and the careful, measured, and perhaps rather plodding evaluation which precedes the introduction of a new antidepressant today, with all its formal panoply of governmental regulatory oversight. A historian might pay special attention to the place of cognitive therapy, introduced by a charismatic innovator, free of the somewhat limiting constraints which would have accompanied the development of a new drug, yet evaluated by controlled trials from the beginning, because of the scientific climate of the time.

Controlled trials have a special place in what I have said. There have been various criticisms over the years of this methodology. Surely it is rather dull? Is it ethical? Is it misleading because of selection factors? Is it unnecessary because there are other ways of seeing if a treatment works, such as comparisons with experience before the introduction of the new therapy? A good trial has several elements, including random assignment, double blindness, sensitive assessment measures, appropriate data analyses. Among these it is the random assignment to groups treated at the same time with different treatments which is most crucial. The contribution of controlled trials in producing clear-cut answers for the therapist has been extremely high and it remains essential. Outcome measures are too unreliable, effects of bias and expectation too strong, and effects of treatments on the whole too weak in psychiatry, to do without them. Trials are sometimes belittled by researchers as dull and unimaginative. I would rather praise this essential work.

With respect to the specific treatments, the conclusions of this review of a relatively large number of studies, although they have challenged in one or two places earlier cherished beliefs, have tended to confirm modern clinical practice. If, like Molière's *Bourgeois Gentilhomme*, we have discovered that we have always spoken prose, that is not surprising, because the pathway between research and clinical practice is a two-way street. Research confirms clinical practice because clinical practice has been modified by research, and research questions shaped by clinical practice. A very large volume of research has gone into the generation of even tentative conclusions about the place of specific treatments. In treatment studies no single study can be relied on as a definitive example of the revealed truth: findings vary from study to study, depending on the detailed variations in treatments, patients, assessment and analyses. Taken together the studies do in the long run make a consistent picture.

My concluding point must be to highlight the interdependence of research and clinical practice. Therapeutic research can only be relevant when it is anchored in the major questions of clinical practice. Clinical care depends for its advance, and for its validation, on a foundation of painstaking therapeutic research.

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