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EDITORIAL

The scientific status of electro-convulsive therapy[1]

Electro-convulsive therapy (ECT) has been available for just over 40 years, whereas neuroleptic drugs have recently celebrated their 25th anniversary. Yet much more is known of the magnitude and scope of effectiveness, the mechanism of action, and even the adverse effects, of neuroleptic drugs in the treatment of schizophrenia than of electro-convulsive therapy in depression. Research on drug therapy of schizophrenia has advanced rapidly in the past 15 years while clinical research on ECT has progressed little. Until recently, basic research on possible mechanisms of action was also very limited.

It seems unlikely that this state of affairs presages the demise of convulsant therapy as a major treatment modality. Despite criticisms from a number of sources, most psychiatrists remain convinced that ECT has a unique place in the treatment of depression. Yet it is an entirely empirical treatment. In this respect it is far from unique in medicine; but it must be unusual for a treatment to remain widely used and so little understood for so long a period.

Advances in understanding mechanisms of action are desirable but many purely clinical questions remain unanswered. The Department of Health and Social Security and the Royal College of Psychiatrists are ascertaining the extent to which ECT is now used in British hospitals. It seems possible that a number of smaller projects, if properly designed, could provide answers to some outstanding questions concerning the scope and indications for this treatment. Such answers might substantially influence current practice, based as it is on information from trials carried out when antidepressant medications were relatively new, and to a large extent upon the individual clinician's intuition.

EFFECTIVENESS IN DEPRESSION

In an attempt to obtain an overall view of the effectiveness of ECT in comparison with other therapies, Wechsler *et al.* (1965) summarized 153 studies published between 1958 and 1963 in American, British and Canadian journals, involving a total of 5864 patients. They present the figures shown in Table 1.

Since many studies were uncontrolled, and these studies showed higher rates of improvement than those with a control group, these figures almost certainly exaggerate the effectiveness of antidepressant treatments, including ECT. More cogent perhaps is the contrast which these authors were able to demonstrate in the findings of studies dealing with depressions of recent onset and those which included mainly chronic depressions (but also some schizophrenic patients) (see Table 2). The superiority of both drugs and ECT over placebo is much less in the latter group.

No firm conclusions can be drawn from a literature survey. Patient selection is uncontrolled and many studies in which ECT was compared directly with other treatments included small numbers of patients. The soundest basis for an assessment of the efficacy of ECT are 2 major controlled trials completed in the early 1960s. The first (Greenblatt *et al.* 1962, 1964), in the United States, included 281 patients, and the second (Medical Research Council, 1965), in the United Kingdom, included 259 patients. Both were multicentre studies and included groups treated with placebo, imipramine and a monoamine oxidase inhibitor, as well as ECT. The age range of the American study (16–70 years) was wider than of the MRC trial (40–69 years), and it seems likely that the range of clinical features qualifying for admission (including groups labelled psychoneurotic depressive reaction, and

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Table 1.

	No. studies	Mean % improvement
MAOIs	76	50·4
Tricyclics	55	64·8
Placebo	25	23·2
ECT	9	72·0

Table 2.

	Mean % improvement	
	Depressions of recent onset	Chronic depressions
All drugs	61·7	31·9
Placebo	23·7	20·7
ECT	86·1	36·7

Table 3.

	Greenblatt *et al.* (1964) moderate to marked improvement (%)		MRC (1965) no or only slight symptoms (%)
ECT	92	ECT	71
Imipramine 200–250 mg daily	74	Imipramine 200 mg daily	52
Placebo	69	Placebo	39
MAOI:		MAOI:	
Phenelzine 15–60 mg daily	79	Phenelzine 60 mg daily	30
Isocarboxazid 40–50 mg daily	56	—	—

schizophrenic reaction depressed as well as manic depressive, depressed and involutional psychotic reaction) was also somewhat broader in the American trial. The treatment period was longer in the American trial (8 weeks including at least 9 ECT in the ECT group) than in the MRC trial (3½ weeks, including 4–8 treatments). These differences must be borne in mind, but a comparison of the main findings at the end of the treatment period is instructive (Table 3).

In the American trial ECT was superior to each of the other treatments and placebo at the 1 % level of significance or beyond, and in the UK study ECT was superior to imipramine (on the above assessments) at the 5 % level and to other treatments at a higher level of significance.

The findings of these 2 studies are similar and establish ECT as a highly effective treatment of depressive illness that appears to be acting more rapidly than what most clinicians would regard as adequate doses of imipramine. Although there are trials (e.g. Fahy *et al.* 1963; Mcdonald *et al.* 1966) in which ECT has been compared with a tricyclic antidepressant and has not been found significantly better (although both treatments were superior to placebo), the numbers of patients were substantially smaller than in the 2 major trials and the differences were in favour of ECT. In a non-randomized comparison of ECT, imipramine and placebo, Wittenborn *et al.* (1962) concluded that imipramine might influence more aspects of behaviour than ECT, but such an advantage has not been documented in more strictly controlled comparisons. Of some interest are the results of a study reported

by Wilson *et al.* (1963) and analysed in 2 parts: in the first phase ECT was found to be superior to imipramine 150–200 mg daily; in the second phase, when the dose of imipramine was increased to 250 mg daily, the response to these 2 treatments was similar. The numbers of patients were insufficient to draw firm conclusions, but the findings do raise the possibility that there are regimes of tricyclic medication which can produce results similar to those achieved with ECT.

In general, the findings of other studies do not challenge the conclusions of the major studies that ECT has therapeutic effects in depression which are at least as good as those produced by other treatment methods and that the onset of the effect of ECT is more rapid. At the same time it should be emphasized that all those trials of ECT which have included such a group have shown substantial remission rates on placebo alone. For example, in the MRC (1965) trial the differences between ECT and other treatments diminished with length of follow-up, although the interpretation of these differences was complicated by the addition of other treatments after completion of the initial trial period.

MECHANISM OF THE ANTIDEPRESSANT EFFECT

It is widely assumed that it is the induction of convulsion which is responsible for the therapeutic effect. This question is of academic interest and also of practical importance since it seems highly likely that many of the adverse effects stem from the passage of current and the induction of fit. Therefore, if the treatment is to continue to be widely used on an empirical basis, it seems important to establish beyond all reasonable doubt what are and are not the essential ingredients. Clinicians need only remind themselves of the case of insulin coma therapy to realize that empirical treatments can be widely adopted, and accepted as self-evidently beneficial, before the real long-term benefits and hazards have been established in careful controlled studies. Although the major studies reviewed above demonstrate the effectiveness of the ECT procedure in depressive illness beyond reasonable doubt, it has to be considered that the therapeutic effect, or some part of the effect, is unrelated to the passage of current and the induction of fit.

Earlier attempts to establish this point by comparing ECT with 'pseudo-ECT' (i.e. anaesthesia without the shock, or with the shock modified in some way to avoid a fit) have yielded equivocal findings:

(*a*) Miller *et al.* (1953) compared ECT with anaesthesia alone, and with anaesthesia followed by sub-convulsive shock, in 40 patients with chronic schizophrenia, and observed no differences in response to the 3 treatments.

(*b*) Ulett *et al.* (1956) compared ECT with photoconvulsive and subconvulsive photic stimulation, and a control group, in 84 patients with a variety of depressive and schizophrenic symptoms. All patients were apparently sedated but not anaesthetized, and patients given photic stimulation were also given intravenous injections of the convulsant hexazol. There were rather large differences between groups in pre-treatment ratings, but improvement scores were greater in the photoconvulsive and ECT groups than in the other 2 groups. However, a χ^2 comparison of the ECT and placebo groups failed to reveal significant differences either at completion of the treatment or at follow-up (Costello, 1976).

(*c*) Brill *et al.* (1959) compared ECT administered in 3 different ways (without anaesthesia, with succinylcholine, and with thiopentone) with anaesthesia induced either by thiopentone or nitrous oxide (i.e. with anoxia), in 97 patients with schizophrenic and depressive reactions. Many patients were judged to be improved after each of these treatments but there were no significant differences between treatments. This remained true when the 30 patients with depression were separated from those 67 with schizophrenic illnesses.

(*d*) Cronholm & Ottosson (1960) compared 3 types of convulsive therapy in 65 patients with episodes of endogenous depression: (i) convulsions provoked by supraliminal stimulation, (ii) convulsions provoked by stimulation just above the convulsive threshold, and (iii) convulsions elicited by electrical stimulation but modified by intravenous lidocaine which reduces the duration and

spread of seizure activity. It was argued that if therapeutic activity were dependent upon the convulsion it would be less in group (iii) than in the other 2 groups, whereas if it were dependent upon electrical stimulation *per se* the effect would be greater in group (i) than in groups (ii) and (iii).

In general, groups (i) and (ii) showed significantly greater improvements than group (iii). The results were therefore interpreted as consistent with the hypothesis that the convulsion is the essential element. The Cronholm & Ottosson result has often been regarded as the most convincing evidence for this viewpoint. However, there are aspects in the design of this study which make the conclusions less certain than would otherwise be the case. Although in the summary of their paper the patients are described as being allocated at random to the 3 treatments, the description of the procedure reveals that this was not so. Initially, patients were allocated alternately (i.e. not according to a random procedure) to groups (ii) and (iii). After 2 years it was decided to add group (i) (with supraliminal stimulation) and this group was then filled until it had reached the size of groups (ii) and (iii). Subsequently, patients were again allocated in sequence (i.e. not according to a random procedure) to the 3 groups. Although the authors present evidence that the 3 groups were comparable in initial severity, the design does allow for the entry of a systematic bias and cannot be regarded as blind. Moreover, 4 patients who relapsed after having been studied on one occasion were taken back into the trial.

(*e*) Robin & Harris (1962) reported that a group of 15 patients treated with ECT (bi-weekly, number not stated) and placebo tablets improved to a significantly greater extent, as assessed on a number of the components of the Hamilton rating scales and a global outcome assessment, than 16 patients treated with 'pseudo-ECT' and imipramine (dose not stated). However, few details of the conduct and analysis of this trial are presented and behaviour rating scales apparently did not distinguish between the groups.

Thus, while the findings of the studies of Cronholm & Ottosson (1960) and Robin & Harris (1962) are consistent with the view that the electrically induced convulsion is an important element in the therapeutic process, neither study is decisive and the negative findings of Brill *et al.* (1959), who did find a therapeutic effect in their rather heterogeneous group of patients but found it unrelated to the convulsion, remain to be explained.

Two recent studies have attempted to resolve this issue:

(*a*) Freeman *et al.* (1978) randomly allocated 40 patients judged to be suitable for ECT to either 2 real ECTs or 2 'pseudo-ECTs'. Subsequently, all patients received real ECT. The dependent variables were ratings after the first 2 treatments and at weekly intervals thereafter, and the number of ECTs judged necessary by the independent clinician. The findings were that the group treated with real ECT showed significantly more improvement on some, but not all, rating scales after 2 treatments, and were judged by the clinician to require fewer subsequent treatments to achieve a satisfactory response. Thus, the results were interpreted by the authors as demonstrating the superiority of the procedure including the convulsion.

However, interpretation of this study is complicated by the fact that treatment was discontinued for reasons other than a satisfactory response in 6 of the 20 cases treated initially with real ECT and only 2 of 20 of those treated with 'pseudo-ECT'. Since in the former group in 2 cases treatment was discontinued by the clinician's decision that the response to ECT was unsatisfactory (a possibility apparently not allowed for in the design), and 2 further cases refused further treatment because they felt it was not helping them, it appears that the assessment of the trial based on number of subsequent real ECTs required cannot be taken as decisive. The difference in ratings observed after 2 treatments are interesting, but it is surprising that significant differences between the groups were not observed at subsequent assessments. Clinical lore, and some trials in which serial assessments have been made (e.g. Cronholm & Ottosson, 1960; Herrington *et al.* 1974), suggest that the beneficial effects of ECT are rather slow to emerge.

(*b*) Lambourn & Gill (1978) randomly allocated 32 patients with depressive psychosis to unilateral pulse ECT (inducing a bilateral convulsion) and to a simulated procedure including anaesthesia but omitting the electrical stimulus. Outcome was assessed after 6 treatments (administered thrice

weekly) and again 1 month later by the Hamilton (1960) rating scale, and was also assessed globally by the referring clinician, and in terms of subsequent treatments (ECT or antidepressants) required. The Hamilton overall ratings revealed no significant differences either after 6 treatments or 1 month later. One individual item (hypochondriasis) showed a significant change in favour of the ECT group and one (middle insomnia) a change in favour of the simulated ECT group. Neither the referring doctors' global assessment nor additional treatment distinguished the 2 groups.

Comparison of these 2 trials allows few firm conclusions to be drawn. While the study of Freeman *et al.* (1978) was interpreted as showing that even 2 real ECTs have a significantly better effect than 2 simulated ECTs, the Lambourn & Gill study with an apparently stronger design (6 real against 6 simulated ECTs) and follow-up at 1 month gives no support at all to this view. It might be argued that the use of unilateral rather than bilateral stimulation is a critical factor. However, bilateral convulsions were observed in their real ECT series by Lambourn & Gill, and such an interpretation would challenge the view of Cronholm & Ottosson that the convulsion is an important element in the therapeutic effect. It has been suggested (Freeman, 1978) that the patients in the Lambourn & Gill study were less depressed than those in the study of Freeman *et al.* (1978). However, pre-treatment Hamilton ratings in the 2 studies do not support this view. Thus, the findings of the Lambourn & Gill study do raise serious questions not only about the mechanism of action of ECT but also its efficacy in the form in which it is commonly administered. Not the least interesting of the findings is the magnitude of the overall improvement (a reduction in Hamilton score to 58 % after 6 simulated ECTs and to 19 % of pre-treatment values 1 month after the end of the trial) in patients receiving no electrical shock.

It is sometimes argued (e.g. Kendell, 1978) that the fact that other methods of inducing a convulsion, e.g. by flurothyl (Laurell, 1970) or by photo-convulsant methods (Ulett *et al.* 1956), are also effective in the treatment of depression suggests that the convulsive activity, rather than any other component of the procedure, is the therapeutic element. However, what has been demonstrated is that these other therapies in certain circumstances are not significantly less effective than ECT, and this is not necessarily the same thing as to demonstrate that by themselves they have antidepressant activity. This is certainly a possibility, but it is in any case not difficult to suggest elements other than the convulsion which these procedures have in common with ECT which may be relevant to the therapeutic effect. For example, Lowinger & Dobie (1969) have described how, at least in an outpatient setting, response to placebo appears to be influenced by expectations of staff concerning the effects of treatment. When staff believe that high dose treatment is being given, patients on placebo tablets appear to do better. Expectations presumably determine the subsequent intensity of staff involvement in assessment and therapy.

ANIMAL EXPERIMENTS

At the same time that there has been a quickening of interest in the mechanism of action in depression there has been increasing interest in the effects of repeated convulsions in animal experiments. While such experiments may not directly illuminate the antidepressant effect, they do make it plausible that treatments which parallel the clinical mode of administration have specific behavioural and neurochemical effects. For example, Modigh (1975) observed that, after a course of 7 daily electroconvulsive shocks, but not after a single shock, mice show increased locomotor activity when this was assessed 3 and 6 days after the last shock. Groups of mice showed enhanced locomotor responses to the drugs apomorphine and clonidine, agonists of the post-synaptic dopamine and noradrenaline receptors respectively, after reserpine pre-treatment. These results are interpreted as suggesting that electroconvulsive shock enhances the sensitivity of catecholamine receptors or of some structure associated with these receptors. Similar findings were reported by Evans *et al.* (1976) with respect to the stimulating effects of a combination of tranylcypromine and L-dopa, which might be expected to activate catecholaminergic mechanisms, and also with a combination of L-tryptophan and tranylcypromine, which probably acts mainly upon serotonergic processes. In this case also a post-synaptic

site of action was suggested by the finding that enhanced responsiveness following electroshock was elicited by 5-methoxy-*N*-*N*-dimethyltryptamine, an agent which may be a serotonin receptor agonist.

These experimentally induced changes resemble the therapeutic effect in that they occur only following a succession of spaced shocks, and also in that they do not occur with peripheral electrical stimulation or with a series of shocks at hourly intervals (Costain *et al.* 1978). Similar changes are seen following convulsions induced by flurothyl (Green, 1978).

It has become possible to examine whether these changes occur at the level of the receptor with the development of ligand-binding assays. Cross *et al.* (1979) found that neither dopamine nor serotonin receptors showed significant changes in number following repeated spaced electroshock treatment in rats. Dopamine and serotonin turnover are probably unchanged (Modigh, 1976; Evans *et al.* 1976), but there may be a sustained increase in noradrenaline turnover (Modigh, 1976). The mechanism of this effect and its relationship to the behavioural changes observed in animal experiments remains to be determined.

LONG-TERM EFFECTS

Few controlled studies have examined the long-term effects, whether beneficial or adverse, of electroconvulsive therapy. The possible long-term benefits of ECT are emphasized by an analysis of follow-up studies of depression (Avery & Winokur, 1976) in which series of patients treated with convulsive therapy are compared with groups treated with antidepressant drugs and with neither ECT nor antidepressant medication. Avery & Winokur combine an analysis of the literature with the results of their own retrospective study to support the argument that the increased mortality of depressed patients can be reduced by convulsive or adequate antidepressant treatment. In these authors' own study the mortality of the group treated with ECT was significantly lower in a 3-year follow-up than that of groups who received inadequate antidepressant therapy or no antidepressants and no ECT. Non-suicidal deaths and particularly myocardial infarctions were significantly more frequent in the inadequately treated group, and the differences were greater among men and in the older age groups. Avery & Winokur (1978) also found that suicidal attempts were less frequently seen in patients treated with ECT than in those treated with antidepressants, and this was true in patients both with and without a history of suicidal attempts.

Concern about the possible adverse effects of ECT has focused on whether a component of the well-known impairment of memory persists in the long term. Assessment of this possibility is complicated by the observation (Sternberg & Jarvik, 1976) that memory functions are impaired by depression itself and improve with improvements in mental state. Some memory deficits which follow ECT may be attributable to inadequate response rather than to the effects of treatment itself. Thus, Cronholm & Ottosson (1963) found that patients who showed the most improvement following ECT experienced least subjective memory impairment.

Memory impairment is probably related to the number of shocks given. Squire & Miller (1974) found that the ability to retain new material for 24 hours was more impaired after the fourth than after the first shock treatment. After a number of shock treatments there is an impairment of ability to recall events from the remote past (Squire, 1975) and this impairment does not change in the 24 hours following the last treatment.

The question of the precise duration of objective memory loss following ECT, and the possibility that there may be relatively long-term or even permanent losses, has been too little investigated. Some of the difficulties mentioned above of separating deficits attributable to depression from those due to ECT, the difficulty of assessing premorbid performance, and the problem of obtaining appropriate control groups, may account for discrepancies in the literature. Thus, Bidder *et al.* (1970) estimated that performance had returned to pre-ECT levels within 30 days, but Halliday *et al* (1968) presented evidence for a deficit on some non-verbal learning tasks at 3 months. In an attempt to answer this question, Squire & Chace (1975) applied a battery of tests of delayed and remote memory to groups

of patients who had received bilateral and unilateral ECT or other treatments for depression 6–9 months previously. They obtained no evidence for specific learning deficits attributable to ECT, although persons who had received bilateral ECT rated their memory as impaired significantly more often than did those in other follow-up groups. The authors suggest that this may indicate either that the subjects were aware of a deficit below the level of sensitivity of the tests, or that the experience of bilateral ECT had made the subjects more alert to subsequent memory failures, and thus led them to underestimate their memory abilities. The objective tests were selected for their range and sensitivity in testing memory functions and the results are, in general, reassuring. However, some disquieting findings remain. Thus, Cronin *et al.* (1970) found that unilateral non-dominant ECT produced less impairment than either bilateral or unilateral dominant ECT on the modified word learning test and the Wechsler memory scales; these differences were as marked 4–6 weeks after a course of 8 ECTs as after the eighth treatment. In a study of the cognitive status of patients who had been subjected to cingulotomy, Teuber *et al.* (1976) found that the subjects who had previously received more than 50 ECTs were more impaired than those who had received either no ECT or who had received less than 50 previous ECTs on tests of verbal and non-verbal fluency, delayed alternation, tactual maze learning, and some other recall and recognition tests. It is possible that those who had received more ECT were suffering from more severe illnesses, but these data draw attention to the importance of further investigations of the effects of repeated courses of ECT.

OUTSTANDING ISSUES

The largest and most carefully conducted studies have demonstrated ECT to be a most effective and rapid treatment of depressive illness. However, examination of the literature reveals that the widely held view that the convulsion is a necessary component of the therapeutic effect has never been unequivocally established. The importance of this issue is re-emphasized by the apparently contradictory findings of 2 recent studies, and is highlighted by recent advances in neurochemistry which have made possible detailed investigations of the effects of repeated electroshock on neurotransmitter function. A comparison of the clinical and chemical effects of therapeutically active drugs and ECT could substantially elucidate the mechanisms of affective change.

The major outstanding issues for research on ECT are:

(i) The question of whether the fit is indeed the critical component of the therapeutic effect as suggested by Cronholm & Ottosson, or whether, as suggested by the work of Brill *et al.* (1959) and Lambourn & Gill (1978), other components of the procedure make a substantial contribution.

(ii) The possible long-term psychological effects of ECT.

(iii) The question of whether the effects of ECT are qualitatively different from those of available antidepressant medications. Further studies should include comparison of the treatments both with respect to the rapidity of the short-term response and, in view of the data recently presented by Avery & Winokur (1976, 1978), with respect to the long-term mortality from suicide and other causes.

(iv) The long-standing, but unanswered, issue of whether there are certain types of depression which respond only to ECT.

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REFERENCES

Avery, D. & Winokur, G. (1976). Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. *Archives of General Psychiatry* **33**, 1029–1037.

Avery, D. & Winokur, G. (1978). Suicide, attempted suicide, and relapse rates in depression: occurrence after ECT and antidepressant therapy. *Archives of General Psychiatry* **35**, 749–753.

Bidder, T. G., Strain, L. J. & Brunschwig, L. (1970). Bilateral and unilateral ECT. Follow-up study and critique. *American Journal of Psychiatry* **127**, 737–745.

Brill, N. Q., Crumpton, E., Eiduson, S., Grayson, H. M., Hellman, L. I. & Richards, P. A. (1959). Relative effectiveness of various components of electroconvulsive therapy. *Archives of Neurology and Psychiatry* **81**, 627–635.

Costain, D. W., Grahame-Smith, D. G. & Green, A. R. (1978). Relevance of the enhanced 5-hydroxytryptamine behavioural responses in rats to electroconvulsive therapy. *British Journal of Pharmacology* **62**, 394P.

Costello, C. G. (1976). Electroconvulsive therapy: is further

investigation necessary? *Canadian Psychiatric Association Journal* **21**, 61–67.

Cronholm, B. & Ottosson, J. -O. (1960). Experimental studies of the therapeutic action of electroconvulsive therapy in endogenous depression. *Acta Psychiatrica Scandinavica* Suppl. 145, **35**, 69–101.

Cronholm, B. & Ottosson, J. -O. (1963). The experience of memory function after electroconvulsive therapy. *British Journal of Psychiatry* **109**, 251–258.

Cronin, D., Bodley, P., Potts, L., Mather, M. D., Gardner, R. K. & Tobin, J. C. (1970). Unilateral and bilateral ECT: a study of memory disturbance and relief from depression. *Journal of Neurology, Neurosurgery and Psychiatry* **33**, 705–713.

Cross, A. J., Deakin, J. F. W., Lofthouse, R., Longden, A., Owen, F. & Poulter, M. (1979). On the mechanism of action of electro-convulsive therapy: some behavioural and biochemical consequences of repeated electrically induced seizures in rats. *British Journal of Pharmacology* (in the press).

Evans, J., Grahame-Smith, D. G., Green, A. R. & Tordoff, A. F. C. (1976). Electroconvulsive shock increases the behavioural responses of rats to brain 5-hydroxytryptamine accumulation and central nervous system stimulant drugs. *British Journal of Pharmacology* **56**, 193–199.

Fahy, P., Imlah, N. & Harrington, J. (1963). A controlled comparison of electroconvulsive therapy, imipramine and thiopentone sleep in depression. *Journal of Neuropsychiatry* **4**, 310–314.

Freeman, C. P. (1978). How does ECT work? *Lancet* ii, 893–894.

Freeman, C. P., Basson, J. V. & Crighton, A. (1978). Double-blind controlled trial of electro-convulsive therapy (ECT) and simulated ECT in depressive illness. *Lancet* i, 738–740.

Green, A. R. (1978). Repeated exposure of rats to the convulsant agent flurothyl enhances 5-hydroxytryptamine and dopamine mediated behavioural responses. *British Journal of Pharmacology* **62**, 325–331.

Greenblatt, M., Grosser, G. H. & Wechsler, H. (1962). A comparative study of selected antidepressant medications and ECT. *American Journal of Psychiatry* **119**, 144–153.

Greenblatt, M., Grosser, G. H. & Wechsler, H. (1964). Differential response of hospitalized depressed patients to somatic therapy. *American Journal of Psychiatry* **120**, 935–943.

Halliday, A. M., Davison, K., Brown, M. W. & Kreeger, L. C. (1968). A comparison of the effects on depression and memory of bilateral ECT and unilateral ECT to the dominant and non-dominant hemispheres. *British Journal of Psychiatry* **114**, 997–1012.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

Herrington, R. N., Bruce, A., Johnstone, E. C. & Lader, M. H. (1974). Comparative trial of L-tryptophan and ECT in severe depressive illness. *Lancet* ii, 731–734.

Kendell, R. E. (1978). Electroconvulsive therapy. *Journal of the Royal Society of Medicine* **71**, 319–321.

Lambourn, J. & Gill, D. (1978). A controlled comparison of simulated and real ECT. *British Journal of Psychiatry* **133**, 514–519.

Laurell, B. (1970). Comparison of electric and flurothyl convulsive therapy. II. Antidepressive effect. *Acta Psychiatrica Scandinavica* Suppl. 145, 22–35.

Lowinger, P. & Dobie, S. (1969). What makes the placebo work? A study of placebo response rates. *Archives of General Psychiatry* **20**, 84–88.

McDonald, I. M., Perkins, M., Marjerrison, G. & Podilsky, M. (1966). A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression. *American Journal of Psychiatry* **112**, 1427–1431.

Medical Research Council (1965). Report by Clinical Psychiatry Committee. Clinical trial of the treatment of depressive illness. *British Medical Journal* i, 881–886.

Miller, D. H., Clancy, J. & Cumming, E. (1953). A comparison between unidirectional current nonconvulsive electrical stimulation given with Reiter's machine, standard alternating current electroshock (Cerletti method), and pentothal in chronic schizophrenia. *American Journal of Psychiatry* **109**, 617–621.

Modigh, K. (1975). Electroconvulsive shock and post-synaptic catecholamine effects: increased psychomotor stimulant action of apomorphine and clonidine in reserpine pretreated mice by repeated ECT. *Journal of Neural Transactions* **36**, 19–32.

Modigh, K. (1976). Long-term effects of electroconvulsive shock therapy on synthesis, turnover and uptake of brain monoamines. *Psychopharmacology* **49**, 179–185.

Robin, A. A. & Harris, J. A. (1962). A controlled comparison of imipramine and electroplexy. *Journal of Mental Science* **106**, 217–219.

Squire, L. R. (1975). A stable impairment in remote memory following electroconvulsive therapy. *Neuropsychologia* **13**, 51–58.

Squire, L. R. & Chace, P. M. (1975). Memory functions six to nine months after electroconvulsive therapy. *Archives of General Psychiatry* **32**, 1557–1564.

Squire, L. R. & Miller, P. L. (1974). Diminution of anterograde amnesia following electroconvulsive therapy. *British Journal of Psychiatry* **125**, 490–495.

Sternberg, D. E. & Jarvik, M. E. (1976). Memory functions in depression. *Archives of General Psychiatry* **33**, 219–224.

Teuber, H. L., Corkin, S. & Twitchwell, T. E. (1976). A study of cingulotomy in man. A report to the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research.

Ulett, G. A., Smith, K. & Gleser, G. C. (1956). Evaluation of convulsive and subconvulsive shock therapies utilizing a control group. *American Journal of Psychiatry* **112**, 795–802.

Wechsler, H., Grosser, G. H. & Greenblatt, M. (1965). Research evaluating antidepressant medications on hospitalized mental patients: a survey of published reports during a five-year period. *Journal of Nervous and Mental Disease* **141**, 231–239.

Wilson, I. C., Vernon, J. T., Guin, T. & Sandifer, M. G. (1963). A controlled study of treatments of depression. *Journal of Neuropsychiatry* **4**, 331–337.

Wittenborn, J. R., Plante, M., Burgess, F. & Maurer, H. (1962). A comparison of imipramine, electroconvulsive therapy and placebo in the treatment of depressions. *Journal of Nervous and Mental Disease* **135**, 131–137.