setting of cerebral disease. As so frequently happens in diagnostic problems, a reliable history of the patient almost decides the issue. In a true depression the history will reveal that until recently the patient was going about his life in a normal way, showing no intellectual impairment of memory, or of grasp, or initiative, until the fairly rapid onset of a depressive mood and gloomy outlook. When such a history is obtained one is very unlikely to be dealing with a senile dementia or other organic disorder. Even though the patient's appearance may be more apathetic than depressed, and the depressive ideas are stereotyped and grotesque, the correct diagnosis is probably endogenous depression. Cases with clouding of consciousness may present difficulties. Here again the development of the condition is the best guide; if it is of recent onset and has evolved with rapidity, some degree of clouding is quite consistent with affective disorder, provided there is nothing to suggest a cerebrovascular lesion. In the case of an organic disorder the history will reveal a slow, insidious onset of negative symptoms such as impairment of memory, disorientation, blunting of emotion, and deterioration of habits; such symptoms have been noticeable in the usual case for many months before he comes under observation. In most cases of organic disorder, moreover, the depressive symptoms are ill-sustained, shallow, and fragmentary.

That this distinction is not only of theoretical interest but has its basis in the natural history of the illness is shown by the results of Roth's follow-up of patients over 60 years admitted to a mental hospital because of apparently senile psychoses: within six months of admission more than 60% of cases with affective psychosis were discharged; of the truly senile psychotics, almost 60% were dead: the proportion of patients still in hospital was 27% and 33% respectively. Before the introduction of physical treatments over half the patients with affective disorder were still in hospital six months after admission and only about a third were discharged, but the pattern of outcome was even then very different from that of the two main organic disorders of old age—senile and arteriosclerotic psychosis. When the patients were followed up two years after admission the patterns of outcome remained distinct; the "peak" is seen in the same column as at six months for each group. In the case of affective disorder, discharges reach about 65%, while in senile psychosis, by this time, over 80% of the patients have died.

These findings have recently been confirmed by a follow-up study of similar material, aged 65 and over, at the Crichton Royal: 45 out of 64 patients diagnosed as cases of senile or arteriosclerotic dementia had died after two years, only two patients lived at home, as invalids, while 17 out of 33 depressives were at home and socially recovered (O'Connell, 1954).

To sum up: with the increase of life-span in the general population, not only the probability of degenerative cerebral changes has increased, but also the prevalence of depression for which we fortunately have some effective remedy.

Summary

Depression as a psychiatric symptom is probably the most common complaint of psychiatric patients to-day. During the last twenty years it has become more frequent as the presenting symptom of neurosis, and this has aggravated the diagnostic problem.

For rational therapy the reactive, neurotic form of depression has to be differentiated from the endogenous depression with little or no environmental aetiology. Physical treatment methods, especially convulsive therapy, can rapidly relieve depression in many patients. This treatment has to be based on an aetiological diagnosis and combined with other measures adapted to the special circumstances of the case.

Many patients suffering from periodic indigestion, "bilious attacks," and other intestinal complaints are,

in fact, suffering from recurrent depression, as are some cases diagnosed as "hysteria." Finally, the differential diagnosis of depression in the elderly from senile dementia and arteriosclerosis is of great value in the treatment and disposal of geriatric patients.

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PROGNOSIS OF DEPRESSION WITH ELECTRICAL TREATMENT

BY

D. L. C. THOMAS, M.D., D.P.M.

*Late Senior Registrar, Psychiatric Department,
St. George's Hospital*

A factual study has been made of the effects of electrical treatment on 338 cases of depression, in the hope of being able to answer more precisely the sort of questions that are legitimately asked by patients, their relatives, and doctors about (1) the probable length of stay in hospital, (2) the number of treatments likely to be necessary, (3) the chances of recovery, and (4) the likelihood of recurrence. This has necessarily involved secondary considerations of the different response to treatment and therefore different prognosis of various types of depressive illness.

The 338 cases were given electrical treatment for depression in the wards of the psychiatric unit attached to St. George's Hospital. Thirty-one of these showed schizophrenic or paranoid features or a history of previous manic or hypomanic attacks in addition to the depressive illness itself. It is with the remaining 307 that this paper is primarily concerned. None of these patients was certified, though some were certifiable, and it must be accepted that the conditions treated in this unit are probably less severe than many that are seen in mental hospitals. Owing to the fact that up to two years ago there were few beds available for men, there were more female cases than male. Of the 307 patients, 219 were women and 88 were men. Out-patient electrical treatment was available, but the clinical condition in each case was severe enough to warrant admission.

It should be noted that the patients did not receive electrical treatment alone. In all cases, psychotherapy, sedation, and an occupational programme were given according to their needs; nor were the social problems arising directly or indirectly from these illnesses disregarded. In particular, the help of the nursing staff was invaluable. These factors were invariably present, however, and do not invalidate the results from electrical treatment itself.

Diagnosis

The diagnosis and assessment of prognosis of these patients were not made by any one psychiatrist, but there is an approximate conformity as all cases are discussed among the three consultants and registrars on the staff of this unit. The diagnostic groupings are those commonly used in psychiatry. These, and indeed all other diagnostic terms, have been criticized by different writers—for example, Lewis (1934)

and Hobson (1953)—on the grounds that they are not constant enough or are not used with sufficient uniformity. But such criticism may be considered excessive, and it is believed that there is in fact a consensus of opinion concerning the use of diagnostic terms. Partridge (1954) indicates clearly the meaning that has been attached to the diagnosis of the cases under discussion here. The diagnoses were:

Endogenous depressions	149
" " " with agitation	18
" " " hysterical symptoms	31
" " " anxiety and tension	18
" " " hypochondriasis	15
" " " obsessional symptoms	9
Involuntal	50
Reactive	17

The mention of hysterical symptoms refers to their association with the depression regardless of whether they were features before the illness or not. The same is true of the other additional symptoms of anxiety, tension, obsessionalism, and hypochondriasis. Most of the patients with marked hypochondriasis fell into the involuntal age period, but not all.

Reactive depression, as used here, indicates a syndrome, precipitated by outside events, in which preoccupation with such events was prominent, and characterized by variability of the depression and other symptoms and by an absence of endogenous features. It does *not* refer to depressions of endogenous type precipitated by environmental circumstances.

So far as could be judged from the notes and from personal knowledge, the initial diagnosis had not been altered in the light of the effects of treatment. This point is of importance in view of the very different ways in which these groups behave.

Method of Study

The records of 307 cases were studied in detail, particularly with regard to the number of electrical treatments given, their spacing, the clinical response, and the stay in hospital. These immediate results are given below.

The case material was then studied with a view to finding (a) any significant differences between the diagnostic subgroups in their response to treatment; (b) any indications of the minimum length of time that a patient should be kept in hospital to guard against relapse; and (c) the chances of recurrence after recovery or improvement.

The rate of recurrence was investigated by finding what happened over a period of twelve months immediately following one month after the end of the initial course of treatment. Those patients who had been readmitted or were still attending the out-patient department were followed up by interviews. The remainder were followed up by letter, designed to elicit such concrete evidence of recurrence as shown by their having required further electrical treatment, leucotomy, or admission to a mental hospital or having committed suicide. This provided a yardstick against which the various types of depressions could be measured relative to each other.

In general it was found that out of 307 cases 213 recovered or were much improved (69%). A further 85 were improved (28%), and 9 were unchanged (3%). The average number of treatments required for patients whose recovery was straightforward was 5.7. The average stay for these 69% who recovered or were much improved was 44 days.

Difference Between Diagnostic Subgroups

Cases with reactive depression did least well, while those endogenous depressions with hysterical and obsessional symptoms did less well than other endogenous forms (Table I).

It may be added that the number of treatments and the duration of stay required for those cases in which progress was straightforward were slightly greater in the involuntal depressions than in the other forms: 6 treatments as against 5.2, and just over seven weeks as against just under six weeks.

TABLE I.—*Response to Treatment*

Diagnostic Subgroup	Recovered or Much Improved	Total
Endogenous depression	120 (81%)	149
Agitated	12 (67%)	18
Involuntal	34 (68%)	50
Depression with hysterical symptoms	14 (45%)	31
" " anxiety and tension	12 (67%)	18
" " hypochondriasis	10 (67%)	15
" " obsessional symptoms	5 (56%)	9
Reactive depression	6 (35%)	17
Total	213 (69%)	307

Minimum Length of Stay after Treatment

It is an observed fact that a certain number of those patients who made an initial improvement or recovery with electrical treatment later relapse quickly while still in hospital. (For our present purposes the word "relapse" or interruption of recovery is used to indicate that the patient has needed further electrical treatment within four weeks of his initial course. The word "recurrence" is used to indicate any worsening of the state calling for further electrical treatment, readmission, or admission elsewhere, or resulting in suicide, and occurring *more than four weeks* after the end of the initial course of electrical treatment.)

The question of relapse is important in deciding how soon after treatment a patient may legitimately be discharged. If discharged too soon, readmission or treatment as an out-patient becomes necessary; if a patient is kept unnecessarily long, his time and a hospital bed are wasted. Opinions collected from other sources regarding the minimum necessary time of stay varied from fourteen to twenty-eight days.

At this hospital the policy of giving a routine number of treatments is not practised, but the patient is treated according to his clinical condition. As a general rule, three treatments are given in the first week and two in each subsequent week as may be necessary. In studying the case notes it was assumed, therefore, that if there had been at any point an interval of seven days or more without treatment then resumption of electrical treatment after that time indicated that the patient had relapsed. It was found that, out of the total of 307 cases, 81 patients fell into this "relapse" or "interrupted recovery" category. Table II shows the number of patients relapsing in this way and the number of days that had elapsed before resumption of the treatment.

TABLE II.—*Time Between Last E.C.T. of Initial Course and First Relapse E.C.T. (81 Cases)*

Days after Cessation of Initial Course of E.C.T.																									
Day:	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26						
No.:	10	14	11	8	6	4	8	3	4	1	3	2	1	2	2	1	—	—	—	—	—	—	—	—	—

It will be seen that the great majority of relapses had occurred by the fourteenth day after the end of the initial course of treatment, and that relapses after the sixteenth day occurred in only 13 out of the total of 307 patients. Of these last 13 cases six had actually relapsed some time before their electrical treatment was resumed: two of them had refused further treatment on first relapsing, one had prematurely discharged himself, two were on leave over Christmas and had preferred to stay it out, and one had had his treatment delayed on account of chest symptoms. It is felt that these six should be excluded from the group of 13 patients who relapsed after the sixteenth day. Of the remaining seven, one was a chronic depressive who relapsed repeatedly, another had a coexisting organic dementia, one was shown by later events to be a misdiagnosed malingerer prepared to have further electrical treatment in order to stay in hospital, and two received their last treatment more or less as a pat of encouragement before departing for the rehabilitation centre for which their tenuous improvement called. Thus it seems fair to say that only a doubtful seven cases out of a total of 307—that is 2%—have needed further

	Relapse—Recurrence									
Endogenous depression ..	2	3	1	1	1		3	5	8	
Agitated ..				1				1	1	
Involutional ..		4		1				8	8	
Depression with hysterical symptoms ..										
Depression with anxiety and tension ..				1	1	1		1	2	3
Depression with hypochondriasis ..			1					1		1
Depression with obsessional symptoms ..			1	2				1	2	3
Reactive depression ..										
Total								6	18	24

In general, 50 cases out of 219 had shown recurrence within twelve months (23%). The rate of recurrence in the diagnostic subgroups is shown in Table V. It will be seen that recurrence was more frequent in agitated depression, involutional depression, and depression with hypochondriasis.

The principal finding, however, was arrived at only after detailed comparison of those cases that recurred with those that had relapsed while in hospital. It was then observed that when recovery on first admission had been smooth and sustained there was less tendency to recurrence than when recovery had not been smooth but had been marked by relapse. Of the 219 cases investigated for recurrence 160 had shown a smooth and uninterrupted recovery; in 59 the recovery had been interrupted by relapse. Of the 160 cases which had not relapsed on first admission, only 26 had recurred within a year; but of the 59 cases which had relapsed on first admission no fewer than 24 had recurred within a year. This result has high statistical significance and strongly suggests that relapse during the first admission is a bad prognostic sign which makes the chance of recurrence within a year two and a half times as great as if that relapse had not occurred. Detailed findings are shown in Table VI.

It may be noted that, in the group that did not relapse during first admission, recurrences were shown by only 2 out of 40 men, but by 24 out of 120 women. While superficially striking, this difference has bare statistical significance.

It might at first be thought that as depressions with hypochondriasis and involutional depressions have a special tendency to relapse and to recur, their relative preponderance in the group that relapsed during first admission might have weighted the figures so as to encourage a false conclusion that relapse is related to recurrence. But this is not so, as will be seen by reference to Table VII. This shows that, if involutional depressions and depressions with hypochondriasis are both excluded, there is still a relation between

TABLE VII.—*Showing that Recurrence Within the Year, Which is High in the Relapse Group, is Not Due to the Involutional and Hypochondriacal Cases which also Have a High Recurrence Rate (see Table V) and which Relatively Preponderate in the Relapse Group*

	Non-Relapse Group		Relapse Group	
	No Recurr.	Recurr.	No Recurr.	Recurr.
Involutional melancholia + hypochondriasis	19	8 (30%)	11	11 (50%)
Remainder	115	18 (14%)	24	13 (35%)
Total	134	26 (16%)	35	24 (41%)

relapse during first admission and recurrence in the remainder of the cases. In fact, the recurrence rate in those cases that relapsed during first admission is still two and a half times as great as in those in which improvement was smooth and sustained.

Other findings were that, independently of relapse during first admission, involutional depressions and depressions with hypochondriasis have a special tendency to recurrence. Age

TABLE VIII.—*Findings in Relation to Age*

	Av. No. of Days Before Treatment	Av. No. of Days After Treatment	Av. Total Stay in Days	Av. No. of E.C.T.	Average Age	Average Ages			
						Recov.	Much Impd.	Impd.	No Change
No relapse, no recurrence	10	15	40	5.3	46	46.2	45.5	45.5	45
No relapse, but recurrence	7	18	45	5.6	53	58.2	50.2	50.75	242
Relapse no recurrence	8.5	12	57	7.7	46.5	46.4	48	41	249
Relapse and recurrence	8	16	61.5	8	44.5	40	48	44.1	50

Average stay in hospital before treatment: depression with hysterical features, 10.4 days; reactive depression, 10.9 days.

appears to have little significance except in the group that did not relapse but nevertheless showed recurrence, in which agitated depressions, depressions with hypochondriasis, and involutional depressions predominated; these were the more elderly cases (Table VIII). Age, however, was prognostically less important than the occurrence of relapse, as shown by the fact that the average age of the group that both relapsed and showed recurrence was the lowest of the four groups.

Finally, the degree of recovery achieved did not influence the chances of recurrence (Table IX). In brief, 23% of cases recurred within twelve months, regardless of the de-

TABLE IX.—*Showing that Patients who Recover, or are Much Improved, Have the Same Chance of Recurrence During the Year as do the Remainder*

	No Recurrence	Recurrence		Total
		No.	%	
Recovered or much improved	120	37	24%	157
Remainder	49	13	21%	62

gree of recovery achieved. Recurrence was commonest in agitated depression, involutional depression, and depression with hypochondriasis. There was some association between age and recurrence on that account. Of much greater prognostic consequence, however, was the finding that relapse during the course of previous treatment was statistically related to recurrence, and appeared to make the chances of the latter two and a half times greater than if relapse had not occurred.

Cases with Schizophrenic and Paranoid Features

There remain 31 cases; of these 12 showed depression with schizophrenic or paranoid features, 16 had shown mania or hypomania in addition to depression, and 3 were entirely anomalous. Neither the group with manic features nor the anomalous cases were such as to lend themselves to statistical study, and for our present purposes they have been omitted.

Of the 12 cases of depression with schizophrenic or paranoid features, 11 recovered or were much improved, and only 1 recurred, although one case was untraced (Table X).

TABLE X.—*Results in Cases with Schizophrenic and Paranoid Features*

	Schizophrenia } with Paraphrenia } Depression		Depression with Schizophrenic/Paranoid features	
	Initial Result	Recurrence after 1 year	Initial Result	Recurrence after 1 year
<i>Straightforward Group</i>				
Recovered	..	2	2	..
Much improved	..	2	4	1
Improved	..	2	1	..
Unchanged	..	2	..	..
Total	7	6	7	1
<i>Relapse Group</i>				
Recovered	..	1	4	..
Much improved	..	1	1	..
Improved	..	1	..	Untraced
Unchanged	..	1	..	..
Total	3	2	5	..
Grand total	10	8	12	1

Comparison of these figures with a separate series of 10 frankly schizophrenic patients with marked depressive admixture shows that the latter did less well in that 8 out of the 10 showed recurrence within twelve months. The numbers are small, but the difference (by the exact methods) is highly significant, and suggests that depressions with paranoid or schizophrenic symptoms behave in much the same way as depressions with less ominous features.

Summary

Of 307 cases of depression given electrical treatment, 69% recovered or were much improved, 28% were improved, and only 3% were unchanged.

Reactive depressions did least well; endogenous depressions with hysterical or obsessional symptoms did less well than other forms. Of endogenous depressions without special features, 81% recovered or were much improved. Involutional depressions, depressions with hypochondriasis, and agitated depressions reacted similarly.

Patients whose recovery was smooth stayed between five and six weeks and averaged 5.4 treatments. Involutional depressions with smooth recovery stayed seven weeks and needed an average of six treatments.

In 26% of all cases the recovery was not smooth or sustained. This "relapse" or "interruption of recovery" is of prognostic significance as regards recurrence.

Of the 81 (26%) cases "relapsing" during treatment, 74 did so between eight and sixteen days after the end of their first course of treatment and only 7 after the sixteenth day—that is, 98% of patients could have been discharged by the sixteenth day after treatment without risk of relapse. Those cases that "relapsed" in hospital needed 2.4 more treatments on an average. There was a special tendency to this form of relapse in the involutional group (46%).

Of 228 patients whose progress was followed over a period of thirteen months from the end of treatment, 23% showed recurrence.

The rate of recurrence was higher in cases of involutional depression, agitated depression, and depression with hypochondriasis (38%, 41%, and 33% respectively). Recurrence bore no relation to the degree of recovery achieved by treatment.

The recurrence rate in all cases is closely related to the "relapse" rate while under treatment, irrespective of the diagnosis. Such recurrence rate is *not* attributable to the frequency in this group of involutional cases, although these happen to have the highest "relapse" rate.

Of those who "relapsed" while in hospital—that is, needed further E.C.T. after a period of seven days or more without it—41% showed recurrence within thirteen months, as opposed to 16% of those with an uninterrupted recovery. This interesting prognostic finding seems not to have been recorded before.

I would like to thank Dr. D. Curran for suggesting this paper, Dr. Curran and Dr. M. Partridge for their help with its composition and for their generously offered suggestions, and to Dr. Fraser Roberts for his advice and for making available his expert statistical knowledge.

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Sir Isaac Pitman and Sons, Ltd., announce that, as from October 1, they have taken over the Lippincott range of medical books. They will now publish these books throughout the world, except in the U.S.A., Canada, Australia, and the Philippines. A new company, Pitman Medical Publishing Co., Ltd., has been formed to take charge of this arrangement, and also to take over Pitman's own medical books.

RAPID ESTIMATION OF THE SERUM VITAMIN B₁₂ LEVEL BY A MICROBIOLOGICAL METHOD

BY

RONALD H. GIRDWOOD, M.D., Ph.D.
F.R.C.P.Ed., M.R.C.P.

(From the Department of Medicine, University of Edinburgh)

In a previous investigation attempts to measure the serum level of vitamin B₁₂ by its ability to support the growth of the organism *Lactobacillus leichmannii* were unsatisfactory (Girdwood, 1953a). This was because the diluted, heated serum not only of normal persons but also of those with pernicious anaemia was capable of maintaining the growth of the test organism. It was concluded that this activity was due, not to vitamin B₁₂ itself, but possibly to desoxyribosides of thymine, guanine, and hypoxanthine.

While these observations were awaiting publication, Rosenthal and Sarett (1952) in New Orleans described a method for estimating the serum vitamin B₁₂ level, using *L. leichmannii* as the test organism, and with it they found in normal subjects that the level was of the order of 80–420 µg./ml. The technique adopted by these workers differed in several ways from my own, notably in that the serum was treated with an acetate buffer of pH 4.6. In the earlier investigations I had used either no buffer or a phosphate buffer of pH 6.8. The American workers measured their results by titrating the acid produced by the organisms after incubation for sixty-five to seventy-two hours, whereas I carried out photoelectric measurements of the growth of the organisms after incubation for sixteen hours. Since the apparent serum vitamin B₁₂ levels thus obtained by Rosenthal and Sarett (1952) were much lower than my own figures, it was decided to carry out further investigations.

Most of the data concerning the serum level of vitamin B₁₂ have been derived from measurement of the growth of the protozoon *Euglena gracilis* (Hutner *et al.*, 1949; Ross, 1950; Mollin and Ross, 1953). This method is easy to carry out when the necessary apparatus is available, but its advantage to the clinician is lessened by the fact that results are not available within a week.

The workers at New Orleans have kindly kept us informed of their findings with the *L. leichmannii* assay and have recently published the results of their investigations (Unglaub *et al.*, 1954), which, unlike my own, have concerned the value of the *L. leichmannii* assay in differentiating between the serum of a pernicious anaemia patient and that of other persons. My aim has been to obtain even more rapid readings by incubating the inoculated mixture of serum and culture medium for only sixteen hours.

Material and Methods

Unless otherwise stated, the pernicious anaemia patients were typical cases in relapse. In referring to patients with other forms of megaloblastic anaemia, the term "megaloblastic" is used only where the marrow was similar to that of untreated pernicious anaemia. The controls included approximately equal numbers of non-anaemic persons and of people with non-megaloblastic anaemia.

Into a sterile container was put 20 ml. of blood, which was allowed to clot. The preparation of the serum for