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The Long-Term Outcome of Depressive Illness

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One hundred and forty-five patients with primary depressive illness admitted to a university hospital between 1966 and 1970 were followed up an average of 15 years later. Adequate data were obtained on 133 (92%) of the 145. During the follow-up period, 7% of the 133 had suicided, 12% had remained incapacitated by illness and only 20% had remained continuously well. Patients for whom the index admission was not their first were especially likely to be readmitted during the follow-up period. Patients with endogenous depression, none of whom developed schizophrenia during the follow-up period, were more likely to need readmission than patients with an index diagnosis of neurotic depression. In all other respects the prognosis for the two types of depression was the same, with considerable morbidity evident in both.

In his book *Anatomy of Melancholia* published in 1621, Robert Burton proposed a dual classification of depression. In one group the depression was viewed as being of cerebral or somatic origin, and in the other the melancholia was believed to be related to psychological causes such as a morbid preoccupation with love, scholarship, or religion. The recognition and definition of manic–depressive psychosis by Kraepelin (1913) provided greater precision to this bimodal view, and the distinction of endogenous from neurotic cases of depression was widely accepted.

In Britain this division was perhaps most clearly described by Gillespie (1929), in spite of the fact that he had been a pupil of Adolph Meyer, who discounted Cartesian dualism and any kind of precise classification. Meyer preferred to call syndromes "reaction types", one group being "the thymergastic reactions in which depressive states may appear as reactions (protective, at any rate in intentions designed to withdraw the individual from an ill adjusted situation)" . . . "the dominant affect may be not sadness but anxiety" (Meyer, 1922 *cit*. Lewis, 1934*a*).

At the Royal Society of Medicine in 1926, Mapother, clearly influenced by Meyer, read a paper that was described by the chairman, Dr Buzzard, as controversial and provocative. On the basis of his clinical observations, but lacking any factual evidence, Mapother stated that in manic–depressive psychosis, "We are dealing with a merely quantitative deviation, that the disturbance consists in a response similar in kind to that which like circumstances might provoke in us but morbidly prolonged or disproportionate or disastrous in degree." Not only neurotic depression but anxiety states were regarded as "merely one of the numerous subdivisions of the manic depressive group." Mapother considered that there were mild or neurotic cases and severe or psychotic cases. This was challenged by Buzzard, who considered that mild or moderate forms of manic–depressive psychosis were very common; he added that "the distinction between the two conditions, although sometimes difficult, was of fundamental importance in regard to prognosis and treatment as well as in the interests of academic accuracy" (Mapother, 1926).

At this time Lewis was Mapother's deputy at the Maudsley Hospital. Lewis conducted a detailed study of 61 patients and submitted his results for a doctorate of the University of Adelaide. His thesis was subsequently published *in toto* in *The Journal of Mental Science* (Lewis, 1934*a*,*b*, 1936). His conclusions provided apparent confirmation of Mapother's views, and as joint authors of the section on Psychological Medicine in Price's *Textbook of Medicine* (Mapother & Lewis, 1937), they summarised these maintaining that there was every gradation between the mild neurasthenic depressive and the grossly deluded melancholic who craved death, adding "There is no need to try to diagnose affective psychosis from psychogenic depression, cyclothymia, anxiety depression, neurasthenia or involutional melancholia." The introduction of electroconvulsive therapy had little influence on this concept, as, in general, clinicians gave this form of treatment only to severe cases of depression. Consequently, the question of classification remained academic and the unitarians and bimodalists went their own ways in relative peace.

It was the introduction of antidepressant drugs in 1959 that disturbed the truce. It seemed necessary to establish which clinical features were related to drug response in order to predict which patients could expect recovery. It so happened that at this same time computers became available, allowing the much easier application of multivariate analysis to

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clinical data. The time was ripe for a reconsideration of the classification of depressive illness. Indeed, Lewis (1938) had been optimistic in this regard – "No doubt increasing knowledge will bring an improved, eventually, even a stable classification based on aetiology and pointing, it may be hoped, to treatment." In fact, as is so often the case in medicine, treatment antedated knowledge of aetiology and indeed has made its own contribution to classification. Recent genetic studies suggest that Lewis's optimism may soon be realised.

Following the publication of a paper entitled "The independence of neurotic and endogenous depression" (Kiloh & Garside, 1963) and one by Carney *et al* (1965) with virtually identical findings and conclusions, the interest in this very old topic was rekindled. These, and most of the subsequent, studies have used semiotic and prognostic approaches, as indeed did Lewis, who concluded that neither symptoms nor outcome provided any evidence of a qualitative distinction between cases of "melancholia and mild neurasthenic depression". It is of interest, though, that when Lewis's data were subjected to a principal components analysis, a bipolar component was identified differentiating between endogenous and neurotic items. The distributions of the component scores indicated that there were two separate clusters of patients, one mainly endogenous and the other neurotic (Kiloh & Garside, 1977).

Another method of investigating this nosological issue is to study the natural history of depressive illness. It is this approach that has been used by Lee & Murray (1988) and by ourselves.

Lee & Murray (1988) report on the 18-year follow-up of the cohort of patients studied by Kendell (1968), who at the time felt that there was no clear division into psychotic and neurotic groups. The results of Lee & Murray stress the morbidity and mortality that occurred in the 18 years, due in part to the emergence of other psychiatric diagnoses. Patients whose symptoms placed them at the endogenous or psychotic end of the Kendell continuum did especially poorly; certainly, they did less well than earlier studies would have suggested.

This present report concerns another cohort of depressive patients, studied by the present authors during 1966–70 and carefully diagnosed as to whether the symptoms and treatment response during the index episode satisfied the criteria for either endogenous or neurotic depression. They were followed for a similar period of time as the Kendell cohort.

Method

One hundred and forty-five patients suffering from depressive illnesses admitted to a university teaching hospital in Sydney, Australia, between 1966 and 1970 were included. Complete details of how patients were identified, interviewed and diagnosed are given in Kiloh *et al* (1972*a*). The results of those studies have been published (see Kiloh *et al*, 1972*b*; Andrews *et al* 1973; Kiloh *et al*, 1974). Attempts were made to follow up all patients at 2, 5, and 15 years. This report is primarily concerned with the final follow-up.

The 145 depressives comprised 39 males and 106 females, 97 of the 145 being in hospital for the first time for depressive illness. An endogenous type of depression (ED) was diagnosed in 69 (48%), and neurotic depression (ND) in 76 (52%) in terms of the criteria established by Kiloh & Garside (1963). One hundred and thirty-three (92%) of these patients were traced to death (29% had died) or to their current whereabouts. Seventy-two per cent of the survivors were interviewed, but in 17 cases information could only be obtained from relatives or from medical records. Corroborative data were also obtained from relatives or medical records for one-third of the cases interviewed in person. The cause of death for the 42 who had died was obtained either from medical records or from the coroner's reports, and estimates of the morbidity in the years preceding death was obtained from medical records and from close relatives. Twelve of the 145 patients either refused interview or could not be traced. Thus this report is based on the 133 cases (92%) on whom adequate follow-up data were obtained.

At the final follow-up, subjects received a short form of the SADS interview that covered questions related to the depressive scales, in addition to other questions that were relevant to the present study. On the basis of the assembled data from the three follow-up interviews, a life chart was constructed for each patient that identified all times when the patient was ill or in hospital with a psychiatric condition.

The analysis of results was deliberately modelled on the report of Lee & Murray (1988) and with their permission data from their report are included in the tables for comparison.

Results

The age, sex and social class of the 133 patients on whom long-term follow-up data are available were examined. The 67 patients with neurotic depression were significantly younger (only 15% were over 50 years), but did not differ in

TABLE I
Length of index admission

Length of admission	*Endogenous depression* (%)	*Neurotic depression* (%)	*Total* (%)	*London total*[1] (%)
Less than 4 weeks	26	60	43	80
4–16 weeks	72	37	55	
17–52 weeks	2	3	2	14
More than 52 weeks	0	0	0	6

ND *v.* ED: $\chi^2 = 24.89$, d.f. = 3, $P < 0.001$
Sydney *v.* London: $\chi^2 = 12.32$, d.f. = 2, $P < 0.01$

1. Lee & Murray (1988).

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TABLE II
Details of unnatural deaths

Diagnosis	*Sex*	*Age at death*	*Years after discharge*	*Method*
Neurotic depression	F	46	0.1	Overdose of drug
Neurotic depression	F	33	0.9	Bromide
Endogenous depression	F	56	1.3	Carbon monoxide
Endogenous depression	F	51	2.3	Not known
Neurotic depression	M	29	3.1	Amylobarbitone
Neurotic depression	F	39	4.9	Pentobarbitone
Endogenous depression	F	66	6.6	Pentobarbitone and alcohol
Neurotic depression	F	32	9.3	Amylobarbitone
Endogenous depression	F	65	12.9	Drowning

sex or social class from the 66 patients with endogenous depression, 64% of whom were over 50 years at the time of the index admission. The length of the index admission is shown in Table I. Patients diagnosed as suffering from neurotic depression spent less time in hospital than those with endogenous depression. The period spent in hospital was significantly shorter than for the London sample.

During the follow-up period there were nine (7%) deaths due to suicide or probable suicide, eight female and one male, five among patients with neurotic depression and four among patients with endogenous depression. Suicide occurred 6 weeks to 15 years after the index episode. The details are displayed in Table II. Deaths from suicide had affected a similar proportion (10%) of the London sample over a similar time period. In contrast to the London sample, there were no other deaths among patients under the age of 50, and of the 33 'natural' deaths in those over 50, 17 were recorded as being from cardiac causes and six were from cancer.

Outcome was assessed in three ways. Readmission was one criterion. The proportion readmitted during the follow-up period, and an associated statistic, the time by which 50% of the cohort had been readmitted for depression, are displayed in Table III, together with the comparable London data. Patients with endogenous depression had significantly higher risks of readmission than patients with neurotic depression. In both diagnoses, patients whose index admission was not their first psychiatric admission were at greater risk of readmission than patients identified during their first admission. In fact, these factors were additive, and in both the Sydney and London samples, 50% of patients with endogenous depression in whom the index admission was not the first were readmitted within 2 years.

TABLE III
Proportion readmitted in the 16 years after index episode by diagnosis and history of previous admission, and time by which half the cohort would have been readmitted (50% risk in years)

	Sydney		*London* [1]	
	16-year proportion	50% risk in years	16-year proportion	50% risk in years
All patients	0.56	9.6	0.60	7.5
By diagnosis				
Endogenous depression	0.63*	4.3	0.73	3.5
Neurotic depression	0.49*	>17	0.47	>20
By index admission				
First admission	0.47*	>17	0.51	14.5
Subsequent admission	0.68*	4.3	0.75	3.0
By diagnosis and index admission				
ED, first admission	0.50	14.3	0.65	5.0
ED, subsequent admission	0.75	1.9	0.84	2.0
ND, first admission	0.46	>17	0.39	>25
ND, subsequent admission	0.61	4.7	NK	NK

1. Lee & Murray (1988).
* $P<0.05$, Lee Desu statistic.

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TABLE IV
Outcome according to clinical criteria, and according to Lee–Murray criteria

	Endogenous depression (%)	*Neurotic depression (%)*	*Total (%)*	*London total*[1] *(%)*
Clinical criteria				
Recovered and continuously well	26	14	20	18
Recovered with subsequent attacks	58	70	63	63
Always incapacitated or death by suicide	17	17	17	19
ED *v.* ND: $\chi^2=6.0$, NS				
Sydney *v.* London: $\chi^2=0.22$, NS				
Lee–Murray criteria				
Very good	36	42	39	17
Moderate, no readmission	14	18	16	22
Moderate, readmission	41	28	35	37
Very poor	9	12	11	25
ED *v.* ND: $\chi^2=2.4$, NS				
Sydney *v.* London: $\chi^2=15.08$, d.f. $=3$, $P<0.01$				

1. Lee & Murray (1988).

Outcome was next assessed according to the customary clinical criteria of dividing patients into those who recovered and were continuously well following discharge, those who recovered in part or in whole but had subsequent attacks, and those who remained incapacitated or who suicided. These results are given in Table IV. Only one-fifth of the patients had no recurrence of depression, but 8% were always incapacitated and 9% committed suicide. Patients with endogenous depression did not differ from patients with neurotic depression on these outcome measures, nor did the Sydney patients differ from the London patients in this respect.

Lastly, patients were scored on operational outcome criteria established by Lee & Murray (1988); their system is summarised as follows. A very good outcome meant that a patient lost no further time from work, had less than a year on medication and was not readmitted. There were two levels of moderate outcome: first, not satisfying the criteria for a good outcome but not readmitted, and second, not satisfying the criteria for a poor outcome but being readmitted. A poor outcome meant that the patient had suicided, had developed schizophrenia, was incapacitated throughout follow-up, was in hospital during more than two-thirds of the follow-up years, or met three or more of a list of other poor outcome endpoints. The results of this classification of outcome are displayed in the second part of Table IV. Patients with neurotic depression did not have a significantly better outcome than patients with endogenous depression, but, irrespective of diagnosis, patients experienced a better outcome than did the patients in the London sample. As the patients with neurotic depression were significantly younger than the patients with endogenous depression, membership of outcome categories, particularly in regard to readmission risk, was explored by diagnosis within age groups. There was no suggestion that the age of patients at index admission affected prognosis.

In terms of the DSM–III, the patients with endogenous depression would have been labelled as suffering from either bipolar disorder or major depression with either melancholia or psychotic features. In contrast, cases diagnosed as suffering from neurotic depression would have met the criteria for major depression without melancholic or psychotic features, or for dysthymic disorder or adjustment disorder with depressed mood. During the follow-up period, none of the cases originally diagnosed as suffering from endogenous depression developed other psychiatric illnesses, but one, who had had earlier admissions in another hospital for paranoid schizophrenia, again became paranoid and eventually suicided, although it seems likely that a reported worsening of the depression was responsible for her gassing herself. Seven of the neurotic depression cases were rediagnosed during subsequent episodes, two to generalised anxiety disorder, four to major depression recurrent with melancholia, and one to bipolar disorder depressed type. The present investigators have always accepted that endogenous depression can be mild but still distinguishable from neurotic depression. A review of the index admission case-notes gave no reason to doubt that the five neurotic depression patients who subsequently developed endogenous depression complied with the criteria for neurotic depression during their index admission. They were not just mild cases of endogenous depression at that time. When treatments were reviewed, 12 of the 66 endogenous depression patients had been given lithium as a prophylactic against further attacks of depression.

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Discussion

A cohort of patients admitted to hospital with either endogenous or neurotic depression was followed up over 15 years. When compared with patients with endogenous depression, patients diagnosed as suffering from neurotic depression were younger, had shorter index admissions, and were less likely to be re-admitted to hospital. In the longer term, however, they were equally likely to experience further episodes of illness and to commit suicide. Furthermore, they were just as likely to be as incapacitated by their illness. When compared with the London cohort, the Sydney sample experienced a similar suicide rate, but did not show the excess of deaths before 50 that afflicted the London group. The Sydney patients had shorter index admissions, but the readmission rates for the two samples were not dissimilar. Application of the Lee & Murray operational criteria of outcome showed a higher proportion of Sydney patients with a very good outcome and fewer with a very poor outcome than in the London group.

Lee & Murray found that a poor outcome was associated with position on the Kendell neurotic–psychotic continuum of scores. The assumption of a continuum might have led Kendell, like Lewis before him (see Kiloh & Garside, 1977), to diagnose some patients with psychotic symptoms as suffering from depression when they were, in fact, depressed as part of a schizophrenic or schizoaffective disorder. A number of Kendell's patients with psychotic depression were subsequently rediagnosed as suffering from schizophrenia, whereas none of the Sydney cohort of patients with endogenous depression was rediagnosed as having schizophrenia. From the data in Table III and in the second part of Table IV, it appears that the neurotic depressives in Sydney experienced a similar course to the neurotic depressive patients in London, and the differences in outcome between the two cohorts are attributable to the improved outcome of the endogenous depression patients in Sydney, since their risks of readmission were lower and the final outcome, as judged by the Lee–Murray criteria, was better. Whether appropriate diagnosis during the index episode resulted in more effective treatment is not known; certainly, time in hospital was shorter, and one in five were placed on lithium in an attempt to prevent further attacks.

We have always advocated the value of distinguishing between the diagnoses of endogenous and neurotic depression. In the present data, patients with neurotic depression spent less time in hospital during the index admission and were less likely to be readmitted, yet at follow-up they were just as likely to have died from, or have remained incapacitated by, their depression as patients with endogenous depression. We would see these data as supporting a different course for each illness; that is, an episodically severe course for endogenous depression and a more low-grade and chronic course for neurotic depression. But over the years there was no difference in overall severity, and both varieties of depression appear to produce the same amount of despair and disability.

Being admitted to a university hospital for an episode of depression would seem to be a relatively innocent event: treatment of the acute illness is effective, and time spent in hospital only a matter of weeks. These present results, and those of Lee & Murray, paint a different picture of the long-term outlook after admission to hospital for depression. Only one-fifth will remain continuously well, and about the same proportion will always be incapacitated or end their life by suicide. Depressive illness that is severe enough to lead to hospital admission may thus be a condition with a serious prognosis. One might argue that persons who require admission to hospital are especially likely to be vulnerable to chronic disability. However, Vaillant & Schnurr (1988) reviewed a cohort of young men who were initially psychologically well: 45 years later, 90% of those who had ever had an episode of depression were in the worst outcome category. They did less well than men with alcoholism and personality disorder. The prognosis of depressive illness in general may thus be more serious than is commonly realised.

After discharge from hospital, the patients in both these cohorts were free to seek continued treatment from whomever they chose. In both England and Australia, treatment from general practitioner or psychiatrist was available at minimal cost, and the antidepressant drugs could be prescribed at very low cost. Restricted access to care was therefore not a factor in generating the poor outcome. Whether energetic long-term follow-up and the appropriate use of lithium, tegretol, long-term antidepressant drugs or leucotomy would have improved outcome is not known. The profession is confident about the management of acute episodes of depressive illness and of treatment-resistant chronic depression (Quality Assurance Project, 1983). We now need to develop some method for the continued expert care of patients who have had a second admission for depression, since in the present data few factors, apart from prior hospital admission, seem to be of prognostic import.

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