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CHAPTER 1

Depression Casts a Long Shadow

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Depression is a disorder of mood that affects a person's capacity to think clearly; undermines motivation to act; alters intimate bodily functioning, such as sleeping and eating; and leaves a person feeling stranded in the midst of searing mental pain and suffering he or she feels unable to do anything about. Each individual suffers alone, yet when we consider how many people suffer from depression, the figures are staggering. Based on data from both hospital and community studies, such mood disorders are among the most prevalent psychiatric conditions, a finding that is remarkably consistent all over the world. Recent epidemiological data from roughly 14,000 people, surveyed across six European countries, found that 17% of the population report some experience with depression in the past 6 months. When looked at more closely, serious major depression accounted for 6.9%, with minor depression accounting for 1.8%.[1] The remaining 8.3% of participants complained of experiencing depressive symptoms but did not view them as interfering greatly with either their work or social functioning. These numbers are closely comparable to rates reported in both Canadian[2] and U.S. samples.[3] At these levels, family physicians can expect to see at least one person with a significant depression during each day of clinical practice. When people are asked about their experiences with depression over longer periods of time, at any one time, 6.6% of the U.S. population have experienced clinical depression in the past year,[4] and between 18 and 22% of women and 7 and 11% of men will suffer a clinical depression during their lifetime.[5]

What is this depression? In its common usage the term suggests that one is "feeling down" or "blue," yet this characterization misses the

essential "syndromal" nature of the clinical disorder; that is, it consists of a combination of elements rather than a single feature. Clinical depression (sometimes also called "major depression") is a state in which persistent depressed mood or loss of interest occurs with other reliable physical and mental signs, such as difficulties sleeping, poor appetite, impaired concentration, and feelings of hopelessness and worthlessness. A diagnosis of depression is given only when a number of these elements are present at the same time, for at least 2 weeks, and are shown to interfere with a person's ability to perform his or her day-to-day activities.

Those who have been depressed know that there is no single face to the disorder, no single feature that tells the whole story. Some consequences of having depression are easier to recognize by the sufferer, including low mood and lack of concentration. Others may be harder to recognize because their main effects reduce the patient's ability to interact with loved ones and other family members, for example, lack of energy and preoccupation with negative themes and ideas. One of the most obvious tolls that depression exacts is increased risk for suicide. Suicide risk increases with each new episode, and there is a 15% chance that patients suffering from recurrent depression severe enough to require hospitalization will eventually die by suicide.[6] Depression is also rarely observed on its own. The most likely additional problem is anxiety.[7] The chances of a person with depression, for example, also suffering from panic disorder are 19 times greater than the odds of someone without depression experiencing panic.[8,9] Increased odds are also reported for simple phobia (nine times greater) and obsessive–compulsive disorder (11 times greater).

One of the most surprising and disturbing aspects to emerge from community-based surveys of depression and other mental illnesses is the low rate of mental health services use. There is a strange irony here. People with the most prevalent mental disorder are among the least likely to seek treatment. Of those seeking treatment, only 22% actually see a specialist for their problem and receive adequate treatment.[5] The failure to obtain care, especially in the case of depression for which effective treatments exist, has developed into an important public health issue. One response to this has been publicity to educate the public about the symptoms of depression and available treatment options. Depression screening days, now common in many hospitals, have helped to reduce the stigma associated with this disorder by portraying it as a legitimate medical/psychological condition with well-documented clinical features.

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Another change that has occurred in our understanding of depression over the past 20 years has been appreciation of the degree of disability associated with the disorder. In addition to the emotional pain and anguish suffered by those who are depressed, evidence suggests that the level of functional impairment is comparable to that found in major medical illnesses, including cancer and coronary artery disease. At the time we started this work, the work of Kenneth Wells and his colleagues had gone far in revealing many of the hidden costs and the nature of the social burden due to depression. For example, when we measure disability in terms of "days spent in bed," many people would be surprised to find that depressed patients spent more time in bed (1.4 days per month) than patients with lung disease (1.2 days per month), diabetes (1.15 days per month), or arthritis (0.75 days per month). Only patients with heart disease spent more time in bed (2.1 days per month).[10] As one might assume, the ripple effect of "bed days" on productivity at work is considerable. Workers suffering from depression have five times more work-loss days than do their healthy counterparts,[11] and depression is one of the most common causes of extended work absence in white-collar employees.[12]

The impact of these findings, as they entered the literature in the late 1980s and early 1990s, was that many people changed their views on the magnitude of the problem of depression. A World Health Organization projection for the year 2020 confirms these early warnings: Of all diseases, depression will impose the second-largest burden of ill health worldwide.[13] At the time we came together to consider the best treatment approach, depression was fast becoming the major challenge within the field of mental health.

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EARLY OPTIMISM ABOUT THE TREATMENT OF DEPRESSION

With depression as the problem, where was the answer likely to be found? The truth was that by the end of the 1980s, there were a number of ways to combat depression. Antidepressant drugs, first discovered and used in the 1950s, had been refined to the point that a number of them had amassed decisive evidence for their efficacy. Most of these drugs targeted brain neurotransmitter function (the chemical messengers that allow neural impulses to cross from one nerve fiber to another at their junctions,

or *synapses*). They worked by increasing the efficiency of the connections between brain cells and making greater quantities of neurotransmitters, such as norepinephrine or serotonin, available at the synapse.[14] Although how exactly this occurs remains in doubt, there is evidence to suggest that some drugs block the reuptake of neurotransmitters by other cells, whereas others actually stimulate nerve cells to release more neurotransmitter. By the end of the 1980s, antidepressants had become, and still remain, the frontline treatment for clinical depression.[15] However, there are alarming indications that for mild to moderate depression, they are not any more effective than an inert placebo,[16] and that even if they are effective, for some people (for reasons we don't yet understand) they begin to lose their power after 1 or 2 years of continuous treatment.[17]

By the late 1980s, psychological treatments of depression were also starting to come into their own. There were at least four broad approaches to the problem, all of which were structured and time-limited. Each had some degree of empirical support. Behavioral approaches emphasized the need to increase depressed persons' participation in reinforcing or pleasure-giving activities,[18] while social skills training corrected behavioral deficits that increased depressed persons' social isolation and rejection.[19] Cognitive therapy[20] brought together a number of behavioral and cognitive techniques, with the joint aim of changing the way a person's thoughts, images, and interpretation of events contribute to the onset and maintenance of the emotional and behavioral disturbances associated with depression. Finally, IPT[21] stressed that learning to resolve interpersonal disputes and changing roles would alleviate depression. Cognitive and interpersonal therapies came to be seen as "gold standards" in psychological treatment, largely because support for these interventions reflected three important features that are still rare in psychological treatment research: The therapies were tested in multiple studies in different centers; they used clinical patients who met standard diagnostic criteria for depression; and when evaluated against antidepressant medication, their efficacy was judged to be equivalent.[22]

With all these treatments for depression available, surely the problem had been solved. Unfortunately, as treatments for current depression demonstrated their efficacy, research showed that a major contributor to prevalence rates across the world was the *return* of new episodes of depression in people who had already experienced one episode. The scope of the problem had changed.

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DEPRESSION AS A CHRONIC, RELAPSING CONDITION

Why had this aspect of depression not been noticed before? First, because much of the data on which our understanding of depression was based came from studies conducted in the earlier part of the 20th century. At that time, the first onset of serious clinical depression tended to be late middle age, so the opportunity to see longer patterns of recurrence did not exist. Decade by decade, as the second part of the century unfolded, a different pattern emerged, with the first onset of depression being seen earlier and earlier, until the average age of onset had fallen to the mid-20s, with many people experiencing their first episode during adolescence. The tragic effect of earlier onset is that there is now a whole lifetime to observe what happens after a single episode of depression—and the newer research studies started to tell a different and disturbing story.

Second, we had not realized how recurrent depression could be because there had been no studies in which patients who recovered from the disorder had been followed and evaluated at regular intervals. Only with this type of information can there be a complete understanding of how depression waxes and wanes over the life cycle, and how its natural course develops. Such studies allow us to calculate the likelihood of *spontaneous remission* (in which a person gets better without treatment) and to evaluate the relative costs of using treatments that carry significant risks or side effects against the costs of leaving depression untreated. There was little in the way of hard data on these issues until the mid-1980s. Now, newer studies identified patients once they were no longer depressed, then followed them over 1- to 2-year intervals.

One of the first such studies, conducted by Martin Keller and colleagues in 1983,[23] followed 141 patients diagnosed with major depressive disorder for 13 months and reported that 43 (33%) had relapsed after having been well for at least 8 weeks. Clearly, patients in recovery faced a major challenge in maintaining their health and the gains of treatment. All the research since that time has told a similar story: that at least 50% of patients who recover from an initial episode of depression will have at least one subsequent depressive episode,[24] and those patients with a history of two or more past episodes will have a 70–80% likelihood of recurrence in their lives.[6] Up to this point, mental health professionals distinguished between "acute" conditions (short-term) and "chronic" conditions (long-term, lasting over 2 years), noting that some depressions might *appear*

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acute, but many depressed people who recover remain "chronic" in the sense of increased, long-term vulnerability. In a widely quoted review, Judd concluded that "unipolar depression is a chronic, lifelong illness, the risk for repeated episodes exceeds 80%, patients will experience an average of 4 lifetime major depressive episodes of 20 weeks' duration each" (p. 990).[25] Findings such as these have helped to shape the current consensus that relapse and recurrence following successful treatment of depression are common, debilitating outcomes (see Figure 1.1[26]).

From the perspective of the early part of the 21st century, it is easy to forget that this emphasis on recurrence was quite new at the time. Up to the late 1960s and early 1970s, the focus had been on developing more effective treatments for acute depression. Relatively little attention was paid to a patient's ongoing risk. This new research signaled the need to take into account the risk of relapse that remained during recovery, when making decisions about the type of treatment to offer.

Keller's data suggested a large difference in prognosis between patients with no history of depression and those with at least three previous depressive episodes. These two groups relapsed at significantly different rates—22% for "first timers" versus 67% for patients with a history of three or more episodes. Patients recovering from their first episode of depression were shown to be at a critical juncture in the developmental course of their disorder. They "have a substantial probability of prompt

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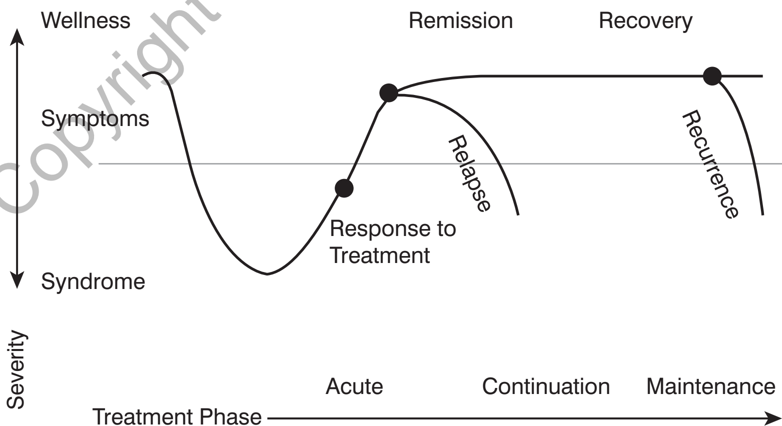

FIGURE 1.1. Depression as a chronic relapsing condition.

relapse, and should they relapse, they have approximately a 20% chance of remaining chronically depressed" (p. 3303).[23] As later data from a 5-year follow-up of patients with chronic and nonchronic affective disorder suggested,[27] those who relapse very soon after recovery are the ones whose depression becomes a long-lasting condition.

Distinguishing among patients on the basis of the number of past episodes continues to be one of the most reliable predictors of future depression, bearing out Keller's earlier observations. While the threshold in Keller's study was set at three past episodes, now the more common cutoff is two episodes. It is important to note that the principle of separating these two groups on the basis of their risk for relapse is still endorsed. In fact, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) of the American Psychiatric Association[28] qualifies the diagnosis of major depressive disorder with the term "recurrent" for those patients with a history of at least two depressive episodes.

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HOW COULD DEPRESSIVE RELAPSE AND RECURRENCE BE PREVENTED?

With a clearer view of the burdens that depression imposes on its sufferers came a corresponding urgency to develop treatments that might help. Because major depression was now seen to be a recurrent disorder, it seemed imperative to look at ways of expanding the types of care offered to patients. The evidence seemed to suggest that if one relied on medication, there was a need for a longer-term approach.

Although the conclusion was not wholly welcome to those uncomfortable with long-term administration of medication, the evidence implied that a clinician should continue to prescribe antidepressants after depressed patients had recovered from the episode for which they sought help in the first place. What sort of study could be used to test the necessity of such continuation treatment?

The answer is a study in which all patients receive the same medication until they have recovered, and are then randomly allocated either to a condition in which the active drug is swapped for a placebo (an inert pill) or one in which they continue to receive the active drug. (Patients agree beforehand to participate in such a study but do not know the group

to which they are assigned.) That is what Glen and his colleagues did in a seminal study in the 1980s. All patients were allocated to receive drug or placebo once they had got better on the active drug. The results were clear: Some 50% of the patients who were switched to the placebo became depressed again, compared to only 20% of the patients treated with active medication.[29]

One feature of this result was particularly important. Glen and colleagues found that depression came back much more quickly than would be expected if it were a new episode. This suggested that patients were experiencing not a new episode (a "recurrence"), but the worsening of a previously controlled episode that had not yet run its course (a "relapse"). The more general implication of this result was that although individuals suffering an episode of depression might feel better after taking antidepressant medication, if they stopped the medication before the episode had run its course, they risked rapid relapse.

By the late 1980s, many clinicians endorsed the view that it was best to prevent future episodes of depression by prescribing antidepressant medication *prophylactically* (i.e., to prevent the occurrence of a future episode, and not just to treat the existing episode). Clinicians started to distinguish between *acute, continuation*, and *maintenance* use of antidepressant medication to refer to treatment at the different stages of the depression (see Figure 1.1). So prescribing antidepressants with the aim of relieving current symptoms during an episode was called *acute treatment*. Prescribing antidepressants for 6 months beyond the period of recovery from the episode of depression was called continuation treatment, and extending antidepressants for as long as 3 to 5 years following recovery was referred to as *maintenance treatment*. The American Psychiatric Association's current practice guidelines for depression are based on this framework.[30,31]

But note a very important assumption behind these guidelines: that antidepressant drugs do not provide a long-term cure. Their effects do not outlast their use. To put it another way, antidepressants have their effects by suppressing symptoms; they do not target the supposed causes of the episode itself.[32,33] Nevertheless, given that the risk for early recurrence increases with each episode experienced, and that the interval between recurrences tends to shorten over time,[34] it remained important to prevent the return of symptoms in any way possible. For many, the message of this and similar, later studies was clear: To prevent future depression,

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continue the same treatments that worked in alleviating the acute episode of depression.

PSYCHOTHERAPY AS A MAINTENANCE TREATMENT

The gains achieved through extending pharmacological treatment of depression beyond initial recovery were, by the late 1980s, well documented and extremely important. Yet effective alternatives to the continued use of antidepressant medication in the recovery phase were still required. At any given time, such long-term drug treatment is not suitable for a considerable number of people. For example, pregnant women and women who wish to breast-feed their babies are discouraged from taking such medication, as are those undergoing major surgery. Others cannot tolerate the side effects of antidepressants, and still others decline to take the medication. In a study of 155 depressed outpatients, 28% stopped taking antidepressants during the first month of treatment, and 44% had stopped taking their medication by the third month.[35] In general, the proportion of patients that does not take the prescribed antidepressant medication is estimated in the 30–40% range.[36] An online survey of 1,400 patients in the United States, conducted by the National Depressive and Manic–Depressive Association, found that only one-third of patients receiving maintenance antidepressant therapy were satisfied with the quality of their treatment.[37]

Could psychotherapy help? After all, there was evidence that negative life events often precede the return of episodes of depression. Such events often involve losses, arguments, rejections, and disappointments. Surely, then, psychotherapy could play an important role in helping patients manage the interpersonal consequences of these events, thus reducing the risk of recurrence. This was the rationale behind the groundbreaking study of maintenance IPT conducted by Ellen Frank and her colleagues.[38]

What was new about this study was that patients were first treated for their episode of depression with a combination of interpersonal therapy and the antidepressant, imipramine, then continued to receive therapy for 3 years, even though they had already recovered. For patients, the experimental part of the study started once they had recovered from their episode of depression. Results from the Frank and colleagues study showed

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that maintenance IPT significantly extended how long they stayed well. For patients who received maintenance IPT, the average survival time until the next episode was greater than 1 year. By contrast, patients receiving only placebo during the maintenance phase had a depression-free period of only 21 weeks.

These findings spoke directly to central concerns in the field. They demonstrated for the first time that psychotherapy, like antidepressant medication, could reduce the chances that depression would return. Interestingly, patients receiving medication actually stayed well longer than those receiving only maintenance IPT. However, patients on maintenance IPT still did much better than patients receiving only placebo. These findings opened the door to using psychotherapy as a preventive measure and challenged the field to develop theoretical models to clarify which skills depressed patients ought to be taught to prevent relapse.

The finding that IPT could be used in a maintenance format to keep people well was very important, and it was not long before clinicians started to wonder whether other forms of psychotherapy might also be used in this way. The problem was that, at the time, many psychotherapy researchers had put their energies into developing better and more effective treatments for acute depression, and had not considered developing "maintenance" versions of their therapies. If this field was to progress, others would need to do what Frank and her colleagues had done, and begin to examine how best to offer psychological treatments to keep people well once they had recovered.

The possibility of developing a maintenance version of cognitive therapy to parallel the maintenance version of IPT provoked the interest of members of the John D. and Catherine T. MacArthur Foundation's Psychobiology of Depression and Affective Disorders Research Network. The network director, David Kupfer, invited Zindel Segal to explore how to produce such a maintenance treatment. Kupfer was also to play an important role later in the development of our ideas, when he allowed us to stray from our initial brief and to follow our growing feeling that such a maintenance form of cognitive therapy was too narrow an approach. But we are running ahead of our story. We were asked to develop a maintenance version of cognitive therapy, and that is where we started.

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