

Select Psychiatric and Psychological Considerations

Henry Olders
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Introduction

The behavioral implications of this chapter fly into the face of tradition. If we are to make progress in the cancer-related fatigue syndrome, we have to be willing to examine the facts and think radically. Dr. Henry Olders' pioneering work in fatigue, sleep, and depression in cancer patients makes this chapter rich in new and challenging insights. In this presentation, Dr. Olders uses the "thought experiment" technique presented in Chapter 2.¹ Furthermore, his logic exemplifies the type of scientific inquiry proposed in the *Principia* (as related in Chapter 1) by Isaac Newton.

Among the disease- and treatment-specific conditions involved in the cancer-related fatigue syndrome (CRFS) are some that present a special opportunity in the field of oncological psychiatry. Complex metabolic, nutritional, pharmacological, lifestyle, genetic, and psychosocial issues challenge the clinician's ability to assess and appropriately intervene. The potential for psychiatry's contribution to the understanding and treatment of some aspects of the CRFS is only beginning to be appreciated.

A number of psychiatric conditions are of special concern in the context of the CRFS. On one hand, they may relate directly to the enigma of fatigue in cancer, such as the problem of differentiating and treating depression from fatigue. On the other hand, they may relate indirectly to the problem of the CRFS when the diagnosis and treatment of cancer threaten and overwhelm homeostatic coping mechanisms in vulnerable individuals. These threats, added to other compromises in patients, contribute to emotional exhaustion or counterproductive health belief practices. Examples include the effects of cognitive changes, depression, anxiety, prior trauma, and alterations in sleep patterns that frequently occur with the CRFS.

There are some excellent resources available on psychiatric conditions in cancer. Rather than reviewing what has already been well covered elsewhere, readers would better be served by a referral to other articles and books listed in the Resources section (Breitbart, 1995; Breitbart and Holland, 1988; Breitbart and Holland, 1993; Breitbart and Passik, 1993; Holland and Rowland, 1989; Kazak et al, 1996; Razavi and Stiefel, 1994). The present chapter focuses on topics that are less well known, but specifically significant to some components of the CRFS. Relatively little is mentioned in the literature about screening in oncology clinics, sleep disturbances, sleep-activity relationships, cognitive deficits resulting from cancer

and its treatments, and the effect of traumatic life experiences on patients' responses to cancer. There are also new possibilities in pharmacological as well as behavioral interventions.

There are frequent questions about how much rest people with cancer should get, activity-rest issues, and how long people should nap. This chapter presents surprising insights on the traditional "get more rest" advice. Lay readers will find the comments surprising, clinicians will discover pearls of wisdom to pass along to their patients, and researchers should find the comments a stimulating basis for work in these areas.

—M. L. W.

Dr. Winningham: Dr. Olders, it is clear that cancer fatigue, or the CRFS, is different from tiredness experienced by healthy people or even the fatigue resulting from vigorous activity. Could you explain how cancer fatigue differs from other forms of fatigue?

Dr. Olders: The fact that a whole book can be devoted to the topic of fatigue in cancer testifies to its importance. Not only is it the most distressing symptom experienced by many cancer patients, but also it may interfere with self-care more than any other symptom.

I would like to make something clear: Fatigue is clearly not limited to cancer. It is also a significant issue in other medical illnesses and is often the chief reason why patients are unable to work. Here are some examples: Fatigue affects nearly 80% of patients with rheumatoid arthritis (Mahowald et al, 1989) and 68% with primary biliary cirrhosis (Cauch-Dudek et al, 1998). In the chronic fatigue syndrome, 28% of patients described their fatigue as being so severe that they became bedridden, able to do virtually nothing (Buchwald, Sullivan, and Komaroff, 1987). Complaints of tiredness and fatigue are universal during the initial weeks of Epstein-Barr viral infection (Guilleminault and Mondinir, 1986). Twenty percent of unemployed patients with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) reported that fatigue was largely responsible for the need to stop working (Darko et al, 1992). Most patients with chronic fatigue syndrome are unable

About the Contributor

When Henry Olders's service chief in consultation-liaison psychiatry at the Sir Mortimer B. Davis-Jewish General Hospital in Montreal asked him in 1995 if he were interested in being the liaison psychiatrist with the oncology department, he was unable to answer right away. Having lost his wife to colorectal cancer only three years earlier, he knew that daily contact with cancer patients would be sure to stir up painful feelings. But he felt also that what he had learned as witness to her courageous battle with her illness, her success at warding off depression, and the indomitable spirit that made it possible to accept her pain and fatigue while seeking (and finding!) something positive in every trial and setback, was something that he wanted to communicate to others. He finally concluded that fear of his own feelings should not stand in the way of helping relieve suffering by setting up a psycho-oncology clinic at the "Jewish."

to continue with full-time work, and many receive some form of disability payments for an extended period (Abbey and Garfinkel, 1991).

The fact that fatigue is so prominent in so many illnesses suggests that much of the fatigue experienced by cancer patients may be the result of having a serious illness. Certainly we need to consider those common elements when we address cancer fatigue.

Dr. Winningham: I'm glad to hear you say that. Chapter 1 in this book also suggests this approach. It is interesting that many of the individuals who initially present with one of the illnesses you mentioned are told they are depressed. I have had patients who told me they were *relieved* to have a diagnosis of cancer because they had been told they were crazy!

Dr. Olders: Fatigue is common and distressing in many medical conditions. It also figures prominently in the complex of symptoms of psychiatric affective disorders, whether major depression, dysthymic disorder, or bipolar depression.

The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) of the American Psychiatric Association (1994) includes the criterion "fatigue or loss of energy nearly every day" in its criteria for major depressive episode, and "low energy or fatigue" as a criterion for dysthymic disorder. The World Health Organization (1992) in its International Diagnostic Classification (ICD-10) includes the following in its description of a depressive episode: "In typical depressive episodes of all three varieties described below (mild, moderate, and severe), the individual usually suffers from depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity. Marked tiredness after only slight effort is common."

One of the problems is that various instruments used to aid in diagnosing depression consider fatigue an important component. For example, the Zung Self-rating Depression Scale (SDS) assesses the symptom "increased and unexplained fatigue" with the question "I get tired for no reason," which can contribute up to 4 points out of a total of 80 points.

A degree in electrical engineering (University of Waterloo, Ontario, 1970) and several years working as a computer systems engineer prior to studying medicine and then psychiatry at McGill University in Montreal comprise the backdrop to Henry's fascination with the biology of brain functioning. This background is particularly useful in his practice and research on interventions for treating cancer fatigue and depression by modulating rapid eye movement (REM) sleep.

Father of four and grandfather to three, Henry is happily remarried and fully occupied with family, work, singing in a community choir, lessons in ballroom dancing, and running with the "Wolf Pack." He nevertheless tries to find time for computer programming an artificial neural network to help diagnose psychiatric and neurological disorders.

The Beck Depression Inventory (BDI) includes 2 questions out of 21 that address fatigue: one about tiredness; the other about ability and motivation to work. The Hamilton Depression Scale permits a clinician to assess a patient's degree of depression; 2 questions, worth up to 6 points out of a possible 64, tap decrease in work and activities due to fatigue, as well as loss of energy and fatigability.

Dr. Winningham: For years, cancer fatigue was ignored because we didn't seem to realize how devastating it was, we thought it was depression, or thought it was an unavoidable part of cancer and cancer treatment. Could you address this?

Dr. Olders: Given that the fatigue associated with cancer and other serious illnesses may be indistinguishable from the fatigue of depression, it would be reasonable to explore whether illness-related fatigue may actually be a mild form of depression, perhaps a partial depressive syndrome that might occur in individuals who are *not predisposed* to develop a full-blown depression. If this is a reasonable hypothesis, then one might attempt to determine whether there are factors or circumstances associated both with depression and with fatigue in cancer and other illnesses.

Dr. Winningham: Wait a minute! For years we've been saying, "It's depression." More recently, we've been saying, "It's fatigue," and trying to get people to understand cancer fatigue. Now you're suggesting it may, indeed, be depression? You have defined your premises by alluding to the difficulty we have in discriminating fatigue from depression based on the DSM-IV diagnoses and the depression inventories. But what about the sleep disturbances, particularly insomnia, reported in cancer patients? Couldn't the fatigue experience in cancer be linked to insomnia?

Dr. Olders: Insomnia, defined as difficulty falling asleep or staying asleep, as well as hypersomnia, sleeping excessively, are common in patients with cancer, in other illnesses, and in depression. Fatigue and insomnia are reported to be closely linked in cancer (Grayden, 1994; Nail et al, 1991; Sarna, 1993) and during cancer treatment (Irvine et al, 1994). Fatigue and insomnia are also linked in people who have had heart attacks (McCorkle and Quint-Benoliel, 1983), who are receiving hemodialysis (Brunier and Graydon, 1993), and who suffer from rheumatoid arthritis (Mahowald et al, 1989). They are also linked in chronic fatigue syndrome patients, of whom 81% had at least one sleep disorder, most frequently sleep apnea (44%) and idiopathic hypersomnia (12%) according to one study (Buchwald et al, 1994). It may even be that you don't need cancer or another serious illness to experience crippling fatigue: Insomnia may be enough. Spielman, Saskin, and Thorpy (1987) found that insomnia patients have the same levels of fatigue as fibrositis syndrome patients.

On the surface, this connection between fatigue and insomnia seems self-explanatory. After all, if you don't get enough sleep, *of course* you'll be tired. As my teenage daughter says, "Duh!" But many people with fatigue seem to get lots of sleep: Bipolar depressed patients often have hypersomnia, yet complain of fatigue; chronic fatigue syndrome patients spend more time in bed and nap more than normal, healthy people (Sharpley et al, 1997). Insom-

nia also is closely linked to depression. Insomniacs had four times the rate of affective disorder and double the rate of anxiety disorder compared to the general population (Schramm et al, 1995).

Part of the problem may be terminology. Although the dictionary definitions for *tiredness* and *fatigue* are similar, and bear no relationship to drowsiness or sleepiness, these terms are frequently used interchangeably, by lay people (Carskadon, Brown, and Dement, 1982) as well as by researchers (Moldofsky, 1992; Nofzinger et al, 1991). For example, Martikainen and coauthors (1992) wrote, "Tiredness may take the form of sleepiness." According to Glaus (1993), on aspect of fatigue is the "dull, sleepy" factor. The Piper Fatigue Self-Report Scale include "sleepy" and "drowsy" as fatigue sensations (Piper et al, 1989). The idea that fatigue may be caused by insufficient sleep (Jamar, 1989) may spring from this confusion in terminology. So it is entirely possible that individuals with poor sleep who also have fatigue will interpret their tiredness as being caused by insufficient sleep and attempt to increase their sleep. Insomnia may even contribute to *causing* depression. In a study involving almost 8,000 community respondents, people who still had insomnia a year after an initial interview were 40 times more likely to be depressed. This last finding (Ford and Kamerow, 1989), that insomnia may trigger depression, is particularly difficult to reconcile with other findings about the connection between sleep and depression. For example, sleep deprivation is used to treat depression, but sleeping afterward causes the depression to return (Wiegand et al, 1987). Excessive sleep is found in patients with bipolar depression, in young depressed patients, and in patients with seasonal affective disorder (SAD). If insomnia truly represents insufficient sleep, then one would expect depressed people to sleep less, not more, than normal people.

Dr. Winningham: Taking this a step farther, are you suggesting that insomnia, depression, and excessive sleep may be related?

Dr. Olders: What if, contrary to what most people believe, insomnia (or at least, the most common form known as primary or psychophysiological insomnia) actually is the result of trying to sleep *more* than one needs (Chambers and Keller, 1993)?

What is known is that insomniacs get into bed early, stay in bed late, and nap (Spielman, Saskin, and Thorpy, 1987). They spend *more time in bed* than normal subjects (Middelkoop et al, 1996), they underestimate the amount they actually sleep (McCall and Edinger 1992), but they sleep as much as normal people (Pace-Schott et al, 1994). The amount of daytime sleep is directly related to sleeping problems (Bazargan, 1996). In fact, voluntarily extending sleep is known to cause insomnia (Aserinsky, 1969). Conversely, *reducing time in bed* is a very effective treatment for insomnia (Bliwise et al, 1995; Spielman, Saskin, and Thorpy, 1987) even when it is due to chronic pain (Morin, Kowatch and Wade, 1989).

Following this line of reasoning, we can see that insomnia and hypersomnia are similar in that both represent excessive sleep. The finding that depressed people are likely to have either hypersomnia or insomnia is not contradictory. It is possible that the element of

Figure
11.1

A Historical Perspective on Getting Up Early

The quotations and proverbs that follow suggest that for hundreds of years, the emphasis was on early rising. The earliest recorded reference to “early to bed” appeared in 1639.

*As the olde englysshe proverbe sayth in this wyse,
who soo woll ryse erly
shall be holy helthy and zely.*
(zely = happy, fortunate)
Wynkyn de Worde,
A Treatyse of Fysshynge wyth an Angle, 1496

Diluculo surgere saluberrimum est.
(to rise early is very healthy)
William Lily (ca. 1468–1522),
Latin Grammar, 1513

*At grammar-scole I lerned a verse, that is this,
Sanat, sanctificat, et ditat surgere mane.
That is to say,
Erly rysyng maketh a man hole in body, holer in
soule, and rycher in goodes.*
Anthony Fitzherbert (1470–1538),
The Book of Husbandry, 1523

*Six hours in sleep, in law's grave study six,
Four spend in prayer, the rest on Nature fix.*
Sir Edward Coke (1549–1634)

*To business that we love we rise betime,
And go to 't with delight.*
William Shakespeare (1564–1616),
Antony and Cleopatra

*Ryse you earely in the morning,
for it hath propertyes three:
Holynesse, health, and happy welth,
as my Father taught mee.*
Hugh Rhodes, *Boke of Nurture*, 1577

*Earley to bed and earely to rise,
makes a man healthy, wealthy, and wise.*
John Clarke (1596–1658),
in *Paroemiolgoia Anglo-Latina*, 1639

*One hour's sleep before midnight is worth
two hours after.*
John Rays (1627–1705),
A Compleat Collection of English Proverbs, 1670

Plough deep while sluggards sleep.
Benjamin Franklin (1706–1790), maxim
prefixed to *Poor Richard's Almanac*, 1757

The early bird catches the worm.
unknown

*My formula for success?
Rise early, work late, strike oil.*
J. Paul Getty

insomnia that triggers depression may be excessive sleep. By extension, if fatigue is itself a form of depression, then excessive sleep may also trigger fatigue.

Dr. Winningham: Help me with something: We hear a lot today about people who are overworked and sleep deprived. Is this a modern phenomenon? In the days before electric lights, didn't people go to bed earlier and get up later? Isn't it likely that throughout the ages, most people got more sleep every night?

Dr. Olders: I don't believe that people necessarily slept a great deal more in years past than they do today. Consider the sixteenth-century maxim by Sir Edward Coke (see Figure 11-1): “Six hours in sleep, in law's grave study six, Four spend in prayer, the rest on Nature fix.” Here's another from the eighteenth century: “Six hours sleep for a man, Seven

for a woman, And eight for a fool." If people went to sleep at sunset, in the summertime when nights are short at high latitudes, they would get little sleep. What is more likely is that many people stayed up past sunset for much of the year, using the light from the stars, the moon, or a cooking fire for social gatherings with music making and storytelling. The more intense light provided by candles, gas, and now electricity is necessary for the evening activities of only a very few people, even today. And those activities (chiefly reading) are optional in any case.

Daytime sleepiness, other than the normal sleepiness in the early afternoon, may be a sign that the person is getting insufficient sleep. But it could also be a side effect of medication, or a symptom of narcolepsy or sleep apnea. It is certainly possible, and even likely, that many people in the United States and Canada are getting insufficient sleep in general. But these are people who are burning the candle at both ends, who are often highly productive and lead full, energetic lives. They are unlikely to listen to the message to get more sleep. The people who take this message to heart are the fatigued insomniacs who are already getting more sleep than they need!

Dr. Winningham: If you have had the right amount of sleep, shouldn't a person awaken in the morning "bright-eyed and bushy-tailed" as the saying goes? Isn't morning sleepiness a sign of insufficient sleep?

Dr. Olders: I rarely come across people who feel clear and alert when they first wake up. Usually, people feel very sleepy, and it may be that this sleepiness increases the longer you have slept! If people are sleepy when they first awaken (for me, until I'm actually drinking my first coffee), they may interpret their sleepiness as tiredness, and decide that they haven't had enough sleep. If they sleep in, they will have overslept, and they will encounter sleep difficulties that night (Helmus et al, 1996).

Dr. Winningham: Could you briefly clarify, then, what you would use as criteria for sleep disturbance?

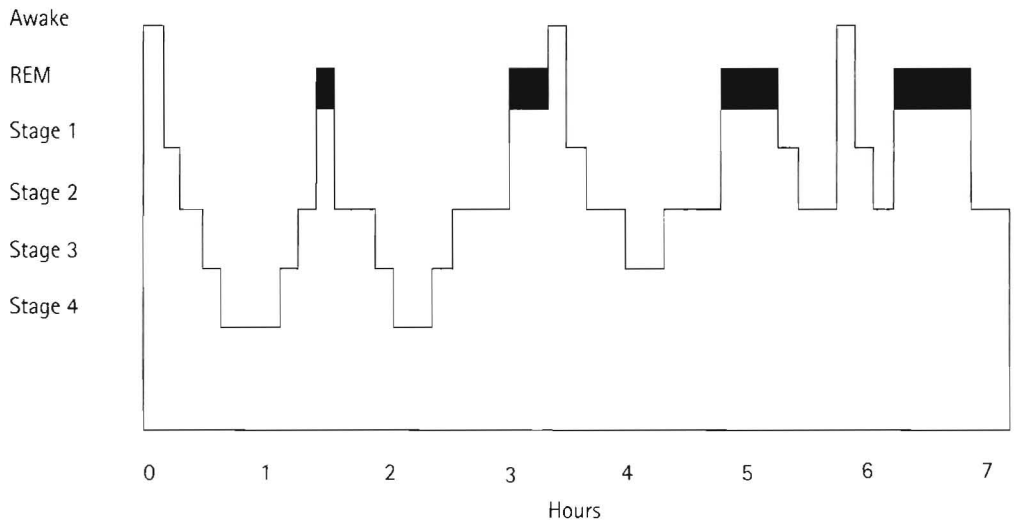
Dr. Olders: I would ask the following questions: Do they have frequent difficulty with falling asleep, staying asleep, or waking earlier than desired? Do they experience distress due to these symptoms? Has there been a significant change in sleep patterns from when they were well, even if they are not distressed about it?

Dr. Winningham: Thank you. Back to the sleep-depression discussion. What mechanisms do you propose may be behind this?

Dr. Olders: Suppose that we accept the hypothesis that excessive sleep could trigger fatigue and even depression in predisposed individuals. Is this due to a particular aspect or characteristic of sleep? Let's look at the data on which we base our assumptions. We know that sleep, when monitored by measuring the electrical signals from the brain and from eye muscles (polysomnography), can be divided into five stages: stages 1 and 2 represent light sleep;

Figure
11.2

REM Sleep as a Function of Diurnal Variations



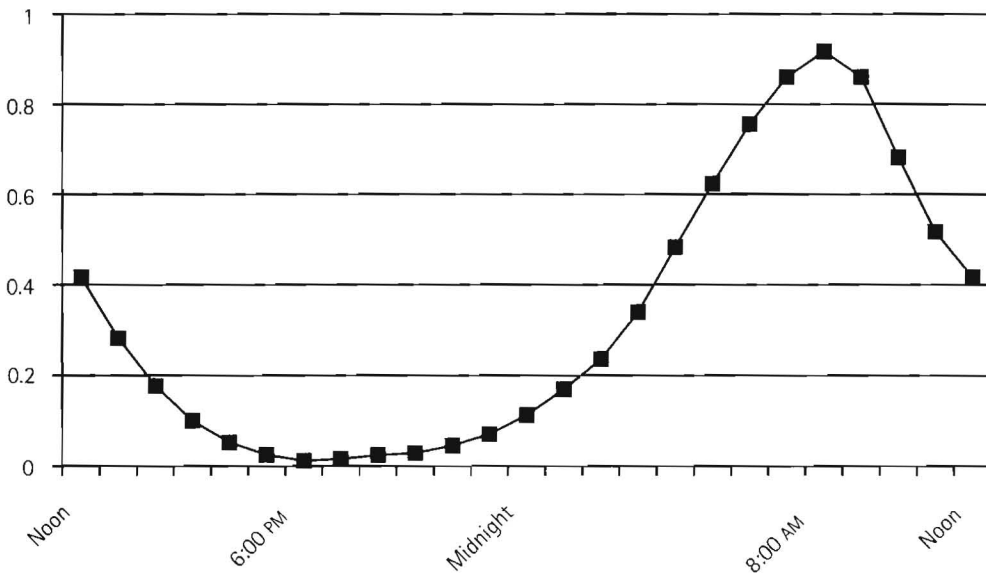
stages 3 and 4, called *slow wave sleep*, are deep restorative sleep; and rapid eye movement (REM) sleep is the last stage.

REM sleep typically starts about 90 minutes after we first fall asleep and recurs periodically throughout our sleep. REM sleep, which occupies about 20% to 25% of our total sleep time, is when we do most of our dreaming. This type of sleep appears to be essential for consolidation of long-term memory in our brains (Karni et al, 1992).

A lot of evidence suggests that REM sleep is linked to depression. For example, REM sleep is increased during depression (Lauer et al, 1995; Nofzinger et al, 1995) and in relapse of depression following successful treatment (Kupfer et al, 1991). Short REM latency and a shift of REM into the first part of the night are also markers for depression (De la Fuente et al, 1992; Lauer et al, 1995). Selective REM sleep deprivation is an effective antidepressant treatment (Klysner, Geisler, and Andersen, 1985). REM sleep is suppressed by antidepressant treatments including tricyclic medications such as nortriptyline and amitriptyline, the newer antidepressants including venlafaxine (Salin-Pascual, Galicia-Polo, and Drucker-Colin, 1997), and the selective serotonin reuptake inhibitors (SSRIs) like paroxetine (Saletu et al, 1989), and electroconvulsive therapy (Cohen and Dement, 1966). Psychostimulants that suppress REM sleep include methylphenidate (Chatoor et al, 1983) and dextroamphetamine (Saletu et al, 1989), exercise (Driver et al, 1988), and bright-light treatment used for SAD. One can predict the amount of clinical improvement that a depressed patient will eventually experience with tricyclic antidepressant treatment by measuring the amount of REM sleep suppression after the first dose (Höchli et al, 1986).

Figure
11.3

REM Sleep Propensity Over a 24-Hour Period



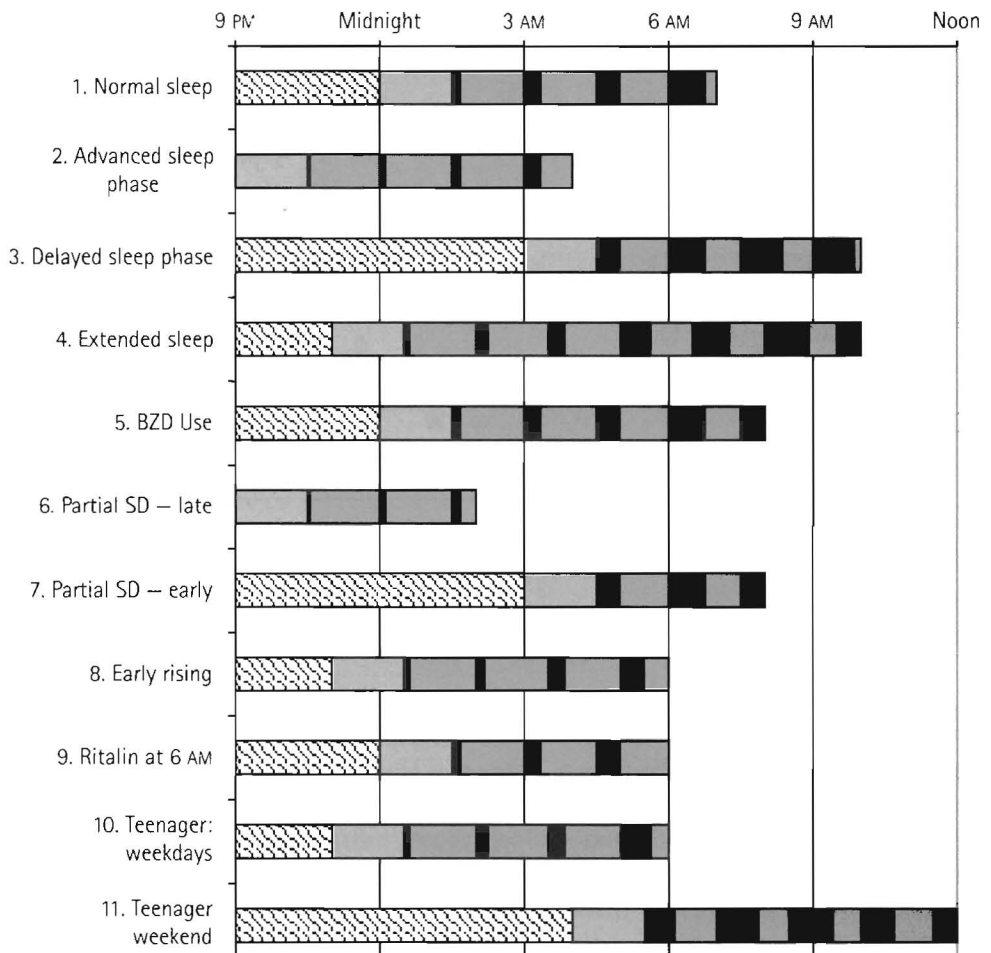
Conversely, the antihypertensive medication reserpine, which has depression as a side effect, is known to increase REM sleep (Faber and Havrdova, 1981). A depressed person who gets better with sleep deprivation will relapse if they have a nap, which includes REM sleep (Wiegand et al, 1987). Wiegand and colleagues (1987) proposed what they call “the depressiogenic sleep theory”; that is, *too much REM sleep may induce depression*. Given what I said earlier about the possibility that fatigue in cancer and other conditions is a mild form of depression, my proposal is to extend Wiegand’s theory to include fatigue as a consequence of excessive REM sleep.

People often ask, If sleep is good for you, isn’t it a good idea to get as much as you can? I ask them in turn, Is there anything that they can think of that we need, where some is good, for which excessive amounts do *not* lead to problems? Too much food causes obesity; too much sunlight causes skin cancer and cataracts; too much oxygen causes blindness in premature infants; too much water can result in seizures! And too much REM sleep may cause fatigue and depression.

Dr. Winningham: You’ve talked about REM sleep as a *stage* of sleep that possibly promotes depression and fatigue. How would cancer patients (or anyone else who becomes fatigued or depressed) get too much REM sleep? It sounds like sleep *patterns* are involved.

Figure 11.4

REM Sleep Distribution as a Function of Sleep Timing and Duration



Crosshatch represents time awake before falling asleep; black portions, REM sleep; and gray portions, non-REM sleep (i.e., stages 1 through 4). BZD = benzodiazepine; SD = sleep deprivation.

Dr. Olders: To answer this question, we need to consider how REM sleep is *distributed* during sleep (see Figure 11-2). Normally, the first REM period occurs about 90 minutes after sleep onset; subsequent REM periods recur with a cycle length of about 90 minutes, but each REM interval throughout the night is longer than the previous one. It appears that REM sleep propensity has a diurnal variation (Akerstedt et al, 1993): It increases through the night (Carskadon and Dement, 1985), peaking at about 8:30 AM (Taub, Hollingsworth and Bruce, 1983), and then decreases through the day (Webb and Agnew, 1968) to reach a

Table 11.1

REM Sleep as a Function of Timing Versus Duration

	Time of Sleep Onset	Awakening Time	Total Sleep (hr)	REM Sleep (hr)	REM (% of Total Sleep)	Change in REM (%) From Baseline
1. Normal sleep (baseline)	Midnight	7 AM	7	1.75	25%	0%
2. Advanced sleep phase	9 PM	4 AM	7	0.67	10%	-62%
3. Delayed sleep phase	3 AM	10 AM	7	2.96	42%	69%
4. Extended sleep	11 PM	10 AM	11	3.48	32%	99%
5. BZD use	Midnight	8 AM	8	2.25	28%	28%
6. Partial SD-late	9 PM	2 AM	5	0.33	7%	-81%
7. Partial SD-early	3 AM	8 AM	5	1.74	35%	-1%
8. Early rising	10:30 PM	5:30 AM	7	1.10	16%	-37%
9. Ritalin at 6 AM	Midnight	6 AM	6	0.99	17%	-43%
10. Teenager: weekdays	11 PM	6 AM	7	1.31	19%	-25%
11. Teenager: weekend	4 AM	Noon	8	3.58	45%	105%

BZD = benzodiazepine; SD = sleep deprivation.

minimum between 6:00 and 8:00 PM. A set of hypothetical values is plotted in Figure 11-3. Using these hypothetical values for REM sleep propensity, it is possible to demonstrate visually how REM sleep distribution varies as sleep timing and duration change in different situations (see Figure 11-4).

For each of the conditions shown in Figure 11-4, the total sleep time and the REM sleep time, based on the hypothetical values for REM sleep propensity, are calculated and shown in Table 11-1. In Table 11-1 and Figure 11-4, "normal sleep" is taken to consist of seven hours, from midnight to 7:00 AM. Advanced sleep phase, experienced to a greater or lesser degree by many elderly people, results in a 62% decrease in REM sleep for the conditions in our "thought experiment." Many people with advanced sleep phase offset the loss of REM sleep by returning to bed in the morning.

The delayed sleep phase syndrome (DSPS) experienced by some teenagers and young adults who find it next to impossible to get up early in the morning causes a 69% increase in REM sleep compared to normal sleep in our thought experiment, even though the total number of sleep hours is the same. DSPS, it should be noted, results in poor morning alertness, and in one study 75% of sufferers were or had been depressed (Regestein and Monk, 1995). Late sleeping, by itself, may aggravate or precipitate depression (Globus, 1969; Wehr et al, 1979), whereas delayed sleep can lead to feelings of depression, as well as decreased alertness, happiness, and energy (David et al, 1991). Could these effects be related to excessive REM sleep?

Staying in bed past the usual time of getting up results in longer sleep duration. Unfortunately, sleeping nine hours or longer is associated with poorer physical health (Belloc and Breslow, 1972) and with higher mortality (Wingard and Berkman, 1983). In nursing home residents, increasing impairment in activities of daily living correlates with longer sleep times (Meguro et al, 1990). The thought experiment demonstrates that extended sleep doubles REM sleep.

Continuing with this thought experiment, the amount of REM sleep varies more with the *timing* of sleep than with its *duration*. This may explain why late partial sleep deprivation, but not early partial sleep deprivation, can be an effective treatment against depression and premenstrual syndrome (Parry et al, 1995). The antidepressant response correlates with shorter REM duration (Sack, 1988). Even advancing the sleep phase by several hours without reducing sleep time has an antidepressant influence (Sack et al, 1985).

The sleep habits of some teenagers may also help explain their mood switches. For example, my daughter, who typically goes to bed at 11:00 PM on school nights and gets up before 6:00 AM, seems to have plenty of energy for the long commute, her classes, after-school sports and extracurricular activities, homework, and chatting with friends. On weekends, however, if she remains in bed until noon, she remains listless all afternoon, getting little accomplished, “comes alive” at 11:00 PM, and wants to party. It seems that the longer the time elapsed between the “depressiogenic” REM sleep of the morning, the better she feels.

Dr. Winningham: For years I’ve been concerned about the “get more rest” advice given to people with cancer. When I started my research back in 1981, that was common advice. I told cancer patients to take one or two short—20 to 30 minutes maximum—naps per day and to maintain regular sleep patterns. That advice was treated with so much incredulity that I reluctantly started saying 30 to 45 minutes maximum. I’m sorry I ever changed. One thing was certain: The people I observed who spent more time in bed went downhill quickly. I always wondered whether it was bed rest, the cancer, or treatments. The purpose of the exercise programs I developed was to counter the effects of the decreased activity. Can you elaborate on the application to cancer patients of what you just suggested?

Dr. Olders: Certainly. We can use our thought experiment to explain how cancer patients might be getting excessive REM sleep: sleeping too long, or simply sleeping late in the morning. For example, sleeping 11 hours, from 11:00 PM until 10:00 AM, doubles the amount of REM sleep, as does sleeping only 8 hours, from 4:00 AM until noon. Just adding one extra hour of sleep in the morning, which might result from using sleeping medication such as benzodiazepines, can increase REM sleep by 28%. Could this help to explain why taking sedative or hypnotic medication greatly increases the risk of becoming depressed (Patten, Williams, and Love, 1996)?

Dr. Winningham: And of course, the experience of cancer interferes with normal sleep patterns in so many ways. As I’ve pointed out for years, many people deal with fatigue by get-

ting more rest, which results in more fatigue! It's nice to run into someone else who can give concrete reasons why this is counterproductive. It's quite logical and there are so many reasons. It's quite destructive. I think one of the few benefits of managed care is that patients don't spend as much time in the hospital lying in bed and watching television at all hours.

Dr. Olders: That's right. Why would cancer patients sleep longer or later in the morning? One reason is increased opportunity. Cancer patients frequently stop working, particularly when in active treatment, when fatigue is most severe (Smets et al, 1998). Hospitalized patients may have little to do other than sleep. Some patients use sleep as a way to escape boredom or the psychological distress caused by receiving their diagnosis, or to find respite from physical pain or other symptoms such as nausea or dyspnea. In addition, interferons and interleukins produced by the illness or as a result of the acute inflammatory response during cancer treatment induce sleepiness (Darko et al, 1992; Modofsky, 1993). Finally, opioids, antidepressants, many antiemetics, and antiepileptic medications used for pain control cause drowsiness.

This becomes a trap: Sleeping longer is likely to lead to insomnia (Aserinsky, 1969). Insomniacs, believing that their sleep difficulty means they're not getting enough sleep, attempt to sleep longer by spending more time in bed and napping more (Spielman, Saskin, and Thorpy, 1987). They are also more likely to take hypnotic medications. All these strategies may worsen their insomnia.

Sleeping longer, and in particular, sleeping later or returning to bed after breakfast increases the amount of REM sleep. I would like to hypothesize that this excessive REM sleep causes fatigue, or increased fatigue and other depressive symptoms. In individuals who are predisposed to clinical depression (on a genetic basis, for example), too much REM sleep may trigger a full-blown depressive episode.

What evidence is there for this hypothesis? It is known that ill people sleep more (Guilleminault and Mondini, 1986) as do cancer patients receiving treatment (Greenberg et al, 1993; Jamar, 1989). As the number of hours of daytime rest increases, so does physical fatigue (Kobashi-Schoot et al, 1985), which may be promoted by the excessive rest (Graydon et al, 1995; Winningham, 1991). Fatigue leads patients to attempt to sleep even more (Dodd, 1984); excessive sleep leads to insomnia (Spielman, Saskin, and Thorpy, 1987), which frequently coexists with fatigue in cancer patients (Degner and Sloan, 1995; Graydon, 1994; Irvine et al, 1994; Knobf, 1986; McCorkle and Quint-Benoliel, 1983; Sarna, 1993).

While there is a large body of mostly indirect evidence that excessive REM sleep can cause depression, and lots of convincing data that REM sleep suppression is an effective antidepressant treatment, there is little research on the influence of REM sleep on fatigue. Students whose sleep was prolonged to ten hours or more developed a "worn out" syndrome, described by the terms "tired, lethargic, in an irritable mood, fuzzy thinking, difficulty getting started" (Globus, 1969). The impaired mood and performance caused by sleep prolongation are hypothesized to be due to augmentation of REM sleep (Taub, 1980). Long sleepers have poorer psychological adjustment compared to short sleepers (Mont-

plaisir, 1984). Melatonin, which increases sleep duration, also increases self-reported fatigue (Dollins et al, 1994).

Fatigue and hypersomnia are related in human immunodeficiency virus (HIV)-infected individuals (Darko et al, 1992), in chronic fatigue syndrome patients (Morris, Weardon, and Battersby, 1997), and in patients with infectious mononucleosis (Guilleminault and Mondini, 1986). In cancer patients receiving radiotherapy, fatigue correlated highly with number of hours of daytime rest (Kobashi-Schoot et al, 1985). A questionnaire study of cancer

Swiss Cheese Memory—Part One

About ten years ago, I enrolled at a major university to pursue a master's degree in political science with an emphasis on political economy. After several quarters, during which I worked in a paint factory and also taught, I had emergency surgery for cancer.

I had always been physically vigorous—never an illness—I was a really big guy and could work like a horse (with apologies to the horse). Not long after beginning chemotherapy, I began to experience physical symptoms. My little fingers and ring fingers, and the sides of my hands above those fingers and on up my forearm, began to tingle periodically, like they were asleep. Then similar symptoms began to show up in my feet and legs. As the nerves continued to deteriorate, the burning and tingling pain increased in intensity and became constant. Other physical symptoms began to manifest themselves: sleep apnea, loss of balance, and tremendous exhaustion—the word fatigue doesn't do it justice. It took great concentration just to keep from falling flat on my face if I just stepped on a pebble, or walked on an uneven surface. It was all I could do to get to school. I was sleeping 12 to 14 hours a day. I was taking elevators instead of stairs because to climb one flight of stairs (20 steps) at school required more energy than I had.

The worst part was the cognitive problems resulting from lack of energy. My brain just wasn't working right. I developed what my wife referred to as "Swiss cheese memory." I could read and retain the conceptual material in the philosophy of science and political science courses, but the high-level math in the graduate courses was impossible. It was so confusing.

Homework for Economics 666 went something like this: I attended the lectures and read the chapters. Sometimes I seemed to read the chapters again and again without remembering the material. Later, I would try to work the practice problems. For an hour or so I would practice the techniques involved in matrix math with total partial differential equations, "Jacobians," "transforms," whatever material was in the chapter. Satisfied that I could work the problems, I would take a nap before supper. When I woke up an hour later, I could remember having studied and successfully worked the problems an hour before, but when I went back, I had no memory of how to solve the problems. When I would go back through the chapter, the material was vaguely familiar, but I couldn't use the mathematical rules to manipulate the data.

After three or four painstaking reviews of each chapter, I would have a reasonably good grasp of what I was supposed to be able to do. I understood the relationship between the mathematical concepts and the questions they were supposed to answer. I still could not manage to keep in my memory the techniques, rules,

patients showed that the later patients got out of bed in the morning, the greater their fatigue (Olders, submitted for publication, 1999). High-fatigue patients were also more depressed, had more insomnia, used more sleeping medication, and spent more time in bed, compared to low-fatigue patients.

Dr. Winningham: You have presented a good argument for considering “sleep therapy” interventions in cancer. This is a brave new world in developing our CRFS arsenal. How-

and processes required to figure out the math. They just didn't stick. I had always done well in courses like this before; in fact, I tutored others. I was familiar with the background material. Yet now, I was putting in five or six times the effort and failing miserably. It was humiliating.

It was unthinkable to me: I was failing my economics class and there was nothing I could do about it. . . . Nobody understood, and no one could explain to me why all this was happening. Since no one seemed to be interested, they clearly had no suggestions about anything I might do to improve. I could not study any harder. Then I started becoming depressed. Piled on top of the physical problems, it only made the fatigue worse. For whatever reason—and I believe it was the terrible fatigue— that part or aspect of the memory I needed to permanently store those mathematical skills was simply inaccessible. After several tries at Economics 666, I dropped out of graduate school, one class and one thesis short of a degree.

For most of my adult life, I have had considerable self-confidence . . . a belief in my own abilities: I always felt like, come what may, I could overcome, persevere, tough it out, see it through. . . . I knew I was pretty smart. Now, in addition to my Swiss cheese memory, I had a Swiss cheese self-concept. I was flawed, defective, damaged goods . . . weak . . . vulnerable! It was very frightening. I felt victimized and I was too easily fatigued and mentally exhausted to do much about it.

I continued to have more surgeries. There were many complications. I had terrible reactions to the anesthetics. Grinding fatigue became so much a part of my life that it was hard to remember a time when I could do things without effort. Vague memories of vigor and effortless living taunted me.

That's been a number of years. All I can say is, if you haven't experienced it, you can't possibly understand what it's like. . . . I hear others talk about their cancer fatigue, and I can really identify with what they're saying. Then I look at the fatigue questionnaires. I must tell you folks: You just aren't getting it. Those questionnaires are make-believe. What we have experienced is actually much, much worse. And it doesn't always go away. Remember that.

Could I go back now and do the math and get the degree? I don't know. And frankly, the distasteful and depression-laced memories of having experienced several abject failures in those days were so demoralizing that I have been afraid to try. I am not sure whether my “math memory” has recovered; certainly it doesn't appear that the holes in my gradually recovering Swiss cheese self-confidence are entirely healed.

ever, I'm thinking about the bone marrow transplant patients or those on biological agents for whom an overwhelming fatigue seems to be an inherent part of the treatment. I suspect you are not talking about these patients. After all, some of them have trouble with even small amounts of exertion.

Dr. Olders: I think that the fatigue many of them experience is what I refer to as "acute fatigue," which all of us experience after physical exertion. But in their case, because of the result of anemia, dehydration, extreme deconditioning, interleukins, and interferons, it surpasses the fatigue experienced by healthy individuals and the recovery is much slower. In distinction, the fatigue that I am talking about I refer to as *chronic fatigue*, because it seems to be there even without any exertion.

Dr. Winningham: I agree with you, and this kind of deconditioning happens very rapidly—it starts within 24 hours of bed rest (note further comments on this in Chapters 2 and 18). I think a lot of what people feel when they first try ambulating is the acute effect of dehydration and cardiovascular deconditioning that contributes to orthostatic hypotension. To counter this effect in astronauts, National Aeronautics and Space Administration (NASA) researchers developed a fluid bolus drink they nicknamed "Astro-aid." Astronauts drink it shortly prior to reentry to help them adapt to gravitation effects. I think the idea of a fluid bolus—whether by intravenous line or by mouth—prior to ambulation would be worth investigating in very deconditioned patients. We would need to experiment with the timing required from bolus to ambulation, contraindications, and so forth.

Dr. Olders: That's interesting. Regarding the disease and deconditioning-related fatigue: Attempting to reverse the deconditioning to improve exercise tolerance is the key. When a person is not experiencing chronic fatigue, however, I wouldn't want to fiddle with his or her sleep. For people who both have chronic fatigue and suffer from acute fatigue due to deconditioning, anemia, etc., I would want to make sure the chronic fatigue is addressed first, so that the patient will have the motivation to exercise or work with physiotherapy. I feel that the kind of fatigue that worsens as the day wears on may be either sleepiness, acute fatigue, or both, probably superimposed on chronic fatigue.

By the way, regarding those patients who as a result of their treatment are unable to stand: When I say, "Get up," I really mean wake up and stay awake. I see palliative patients who are entirely bed bound and obviously are not going to get up out of bed. This is where Ritalin comes in handy, because it keeps people awake and more alert in the morning even when they stay lying down. Coffee can also be a great help!

Dr. Winningham: You mentioned a few criteria for sleep disturbances earlier. Could you please elaborate on how you would perform a differential diagnosis on a fatigued cancer patient?

Dr. Olders: When a cancer patient presents with complaints of fatigue, depression, or sleep disturbance, I include in my psychiatric history taking the patient's psychiatric history, fam-

ily psychiatric history, usage of alcohol or illicit or street drugs, medications, allergies, medical history, history of present illness, relationships, history of psychotrauma or severe stress (other than cancer), religious or spiritual values, and mental status. (Figure 11-5 presents a pocket guide abbreviating the interview questions that can be copied for personal, clinical use.) In addition, I address more specific issues or questions:

- *Fatigue/tiredness (differentiated from drowsiness/sleepiness)*—how often, what time of day or evening, how distressing, impact on life (work, play, relationships).
- *Are you depressed?* This single question has been shown to outperform the Beck Depression Inventory in correctly identifying persons with depression (Chochinov et al, 1997). If the answer is yes, rule out a history of depression, bipolar depression, or dysthymia using DSM-IV criteria.
- *Time of going to bed, time of waking in the morning. What does the person do after waking?* Stay in bed? Get up and have breakfast? Read the newspaper? Follow up with the question, “And what do you do after that?” It no longer surprises me to find individuals frequently going back to bed after breakfast, or after getting the kids off to school.
- *Time of getting out of bed for the day.* If the person tells you they wake up early, but further questioning reveals he or she remains in bed or goes back to bed, find out when the person gets up for good.
- *Daytime naps*—what time of day, how long, how often, how long before they fall asleep.
- *Sleep habits before the illness (when working and doing well).* This is usually a baseline for sleep duration and timing. For example, a patient who went to bed at 11:00 PM and was up at 5:00 AM when working will be spending too much time in bed and getting up too late if they start getting up at 6:30 AM while continuing to go to bed at 11:00 PM.
- *Quality of sleep.* If the person seems to have a sleep disturbance, I ask how long it takes to fall asleep, whether the patient wakes during the night, the reasons for waking, the number of times, and how long it takes to fall asleep again.
- *Daytime drowsiness/sleepiness*—how often, what time of day or evening, how distressing, occurrence of accidents or near-accidents due to drowsiness. This is very important. It is critical that patients know when medications can contribute to drowsiness. Failure to identify and appropriately refer people who subsequently have accidents can engender civil and possibly criminal liability for health care providers.
- *Use of sleeping aids*—prescribed medications (including using somebody else’s pills), over-the-counter (OTC) drugs, herbal and other “natural” products, alcohol, or other substances.
- *Frequency of sleep problems*—difficulty falling asleep, difficulty staying asleep, waking too early, inability to get up.

Figure
11.5

Olders Interview Guide for Fatigue, Depression, and Sleep Disturbances

Olders Fatigue, Depression, and Sleep Disturbance Screen

Pocket guide for interviewing patients with complaints of fatigue, depression, or sleep disturbances.

General Psychiatric History Taking

History of present illness

Past psychiatric history (Consider possibility of clinically significant but undiagnosed conditions.)

Family psychiatric history (Also ask about family history of violence or abuse.)

Use of alcohol and/or illicit/street drug use (also ask re "natural" or herbal products that may have psychotropic implications.)

Medications (prescribed, "borrowed," and over-the-counter [OTC])

Allergies (include environmental, prescription and OTC meds, and adverse reactions to dental or surgical anesthetics)

Past medical history

Relationships

History of psychotrauma, severe stress (separate from dx of cancer)

Religious/spiritual values

Mental status

Specific Questions

Fatigue/tiredness (differentiated from drowsiness/sleepiness)

How often? Time of day or evening? How distressing?

Impact on life (work, play, relationships, spiritual undertakings)?

Ask: "Are you depressed?"

Yes or No. If answer is Yes, question further for typical symptoms of depression, dysthymia, or bipolar disorder, using DSM-IV criteria as a guide.

Time going to bed?

Time waking in the morning?

What does the person do after waking?

Stay in bed? Get up and have breakfast? Read the newspaper?

Follow up question, "And what do you do after that?"

Watch for reports of going back to bed afterward.

Time getting out of bed for the day?

If the person says they wake up early, but further questions reveal they remain in bed or go back to bed, find out when they get up for good.

Daytime naps

What time of day? How long? How often? How long to fall asleep?

Where do they nap (bedroom, couch, recliner)?

Sleep habits before onset of illness (when working and doing well)

Use as baseline for sleep duration and timing. Ask about "shift" work.

Quality of sleep?

Restless? Agitated? Solid? Uninterrupted?

How does the person feel on awakening?

Groggy? Clear headed and rested? Disoriented? No energy? Weak? Headache?

If sleep disturbance is reported or suspected, ask . . .

Frequent difficulty falling asleep, staying asleep, or waking earlier than desired. How often, distress due to these symptoms, significant change in sleep patterns from when well, even if not distressed.

Daytime drowsiness/sleepiness

How often? What time of day or evening? How distressing?

Accidents/near accidents due to drowsiness

Failure to identify and appropriately refer cases who subsequently have accidents can engender civil and possibly criminal liability.

Use of sleeping aids

Prescribed meds (including "borrowed" from someone else), OTC meas, herbal/natural products, alcohol, or other substances

Frequency of sleep problems

How distressed by sleep problem

Use of stimulants (coffee, tea, caffeinated soft drinks)

What? How much? How often?

Attitudes toward sleep

If you feel sleepy, does that always mean you're not getting enough sleep?

If you feel fatigued, does that mean you need more sleep?

If you sleep poorly at night, do you make up for it by sleeping late or by taking a long nap?

If you've slept poorly, would you go into work late or call in sick?

Physical exam, lab tests, consultations

As indicated, based on the differential diagnosis

Thyroid stimulating hormone (TSH) and Vitamin B₁₂ levels should be routinely requested for depressed patients.

For patient with excessive daytime sleepiness not ascribable to medications such as hypnotics, sedatives, opioids, antidepressants, anticonvulsants, or other sedating drugs, and where the history or information obtained from a bed partner suggests sleep apnea, a referral to a sleep disorders specialist or sleep laboratory is indicated.

Consider psychiatric consultation where appropriate.

Collect 24-hour sleep/rest log for 14 continuous days.

- *Level of distress due to the sleep problem.*
- *Use of stimulants (coffee, tea, caffeinated soft drinks).*
- *Attitudes toward sleep.* For instance, if they feel sleepy, does that always mean they're not getting enough sleep? If they feel fatigued does that mean they need more sleep? If they sleep poorly at night, do they make up for it by sleeping late or by taking a long nap? If they've slept poorly, would they go in to work late or call in sick?
- *Sleep log or diary* (Figure 11-6 is a sleep log for patients). Ask patients to record daily, for a period of two weeks, the following: sleep medications taken, time into bed, time of "lights out," how long it takes to fall asleep, how many awakenings occur, how many minutes were they awake, time of morning waking (after which they couldn't sleep), time of arising, time returning to bed (if applicable), time arising for the day, daytime naps (when, how long), sleepiness during the day (rated on a scale from 1 to 5), fatigue during the day (rated on a scale from 1 to 5), coffee (number of cups), tea, caffeinated soft drinks.
- *Physical examination, laboratory tests, consultations.* As indicated, based on the differential diagnosis, thyroid-stimulating hormone (TSH) and vitamin B₁₂ levels are routinely measured in depressed patients in our clinic. For patients with excessive daytime sleepiness not ascribable to medications such as hypnotics, sedatives, opioids, antidepressants, anticonvulsants, or other sedating drugs, and where the history, obtained from a bed partner, suggests sleep apnea, a referral to a sleep disorders specialist or sleep laboratory is indicated.

Dr. Winningham: I doubt whether even a small fraction of people suffering from the CRFS are getting an evaluation like the one you just described. It doesn't even sound complicated. We could probably design a questionnaire patients could fill out at their leisure and bring into the clinic. Once again, it comes back to what we learned from the NASA bed rest studies during the past 40-plus years: If you take a healthy young athlete and put him to bed, he will deteriorate, physically, and start exhibiting signs of depression, cognitive impairment, nausea, lethargy, and a host of other symptoms. Figures 11-5 and 11-6 are provided to help readers gain experience in asking these questions. Given answers relating to the above questions or issues, how do you formulate a diagnosis?

Dr. Olders: When fatigue and other depressive symptoms are present in the context of people who spend more time in bed than they need (the presence of primary insomnia or hypersomnia is an indicator), especially when they are getting out of bed later than usual or returning to bed in the morning, it may be that excessive REM sleep is causing their symptoms.

Dr. Winningham: Excuse me . . . so those simple questions can help to discriminate between a behaviorally treatable fatigue or depression and one where the fatigue has other causes. What else?

Figure 11.6

Sleep Log for Fatigue, Depression, and Sleep Disturbances

Name _____														Sleep Journal for 12 Noon to 12 Noon Starting Date ____/____/____													
12N	1p	2p	3p	4p	5p	6p	7p	8p	9p	10p	11p	12a	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12N			
<p>Codes:</p> <p>B = Mark time lying in bed with solid line</p> <p>C = Mark time lying on couch or recliner with solid line</p> <p>N = Nap (daytime sleep)</p> <p>Mark times at beginning and end with slash marks</p> <p>Mark time actually napping/sleeping at beginning and end on above solid or wavy line (depending on where you were) with an "X"</p> <p style="text-align: center;">B = —————X~~~~~X————— </p> <p style="text-align: center;">Ex NB = 3:00 PM through 5:00 PM, x from 4:00 through 4:50 PM</p> <p>Sleepy = SL <————> Fatigued = F <————> for the duration of the event</p> <p>Mark any other symptom like Pain as Pain <————> Nausea = <————></p>																											
SM = Sleep Medications Taken (Specify how much of <u>what</u> & <u>when</u>). Number each amount taken																											
ST = Stimulants (coffee, tea, caffeinated soft drinks, pills - how much and when). Number each specific intake throughout the day. Ex. ST1 = 1 12 oz Coke, St2 = 1 cup coffee																											
Comments:																											
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Dr. Olders: Benzodiazepines, particularly when taken during the day, or long-acting benzodiazepines such as clonazepam taken anytime, may contribute directly to feelings of fatigue and lacking energy. Because these medications promote sleep, they may cause patients to sleep later than usual. Daytime drowsiness due to medication may also result in napping. Extra sleep, particularly when close to the REM sleep peak at about 8:30 AM, will result in excessive REM sleep and thus lead to more fatigue.

Dr. Wunningham: You've presented a convincing argument. What kinds of treatments or interventions do you recommend?

Dr. Olders: The first is early rising to reduce REM sleep. As demonstrated earlier, timing of sleep has a very powerful influence on the amount of REM sleep obtained. Getting up early is an effective technique to reduce REM sleep. REM sleep deprivation has an antidepressant effect, and to the extent that fatigue is a depressive symptom, an antifatigue effect. I counsel patients to get up at 6:00 AM, or simply to go back to the sleeping pattern they followed when well.

Dr. Wunningham: That is important. Often, hospitalized patients get in the habit of watching late night television, a habit they continue when they go home. I often wish we could pull the plug on telephones and televisions at 10:00 PM. What else do you recommend?

Dr. Olders: Hypnotic medications are a critical issue. Getting up early may be extremely difficult for people taking benzodiazepines. It is important to convince patients of the necessity to taper and eventually discontinue these medications, not only because they perpetuate the fatigue, but also because they can be dangerous of their own accord. This is especially true of elderly patients. The risk of falls, automobile accidents, cognitive impairment, disinhibition, depression, and dependence are all increased. Unfortunately, most people, including physicians, are unaware that benzodiazepines quadruple the risk of becoming depressed for hospitalized patients (Patten, Williams, and Love, 1996). For individuals taking benzodiazepines for insomnia, therapeutic alternatives include sleep hygiene, sleep restriction (described below), and trazodone. Trazodone, being an antidepressant, will not increase the risk of depression as benzodiazepines do, and in doses of 25 or 50 mg at bedtime it will promote sleep. If benzodiazepines are being used for anxiety, one can propose antidepressants, exercise, or relaxation training instead. Again, trazodone in low doses may help control agitation.

Dr. Wunningham: What sleep recommendations do you present?

Dr. Olders: If insomnia is a problem, the following can be helpful:

- Arise at the same time each day, whether you have slept well or not, or even if you have not slept at all.

- Limit daily in-bed time to a “normal” amount. This depends on age, and on what worked for the individual when well. I usually recommend seven hours for middle-aged adults, six hours for people in their 60s or early 70s, and five to six hours for elderly clients.
- Limit or discontinue use of drugs that act on the central nervous system (e.g., caffeine, nicotine, alcohol, and stimulants).
- Cut out daytime naps, if they exceed 15 or 20 minutes.
- Establish physical fitness with a routine of exercise early in the day, followed by other activity.
- Avoid evening stimulation; substitute either listening to the radio or leisure reading for watching television.
- Try a warm 20-minute body bath or soak near bedtime.
- Eat on a regular schedule; avoid large meals near bedtime.
- Practice an evening relaxation routine.
- Maintain comfortable sleeping conditions.
- Spend no longer than 20 minutes awake in the bed.
- Adjust your sleep hours and routine to optimize your daily schedule and living situation.
- Use the bedroom only for sleeping or making love, so as to train yourself not to be in bed while awake.

By far the most effective and long-lasting treatment for insomnia is sleep restriction (Morin et al, 1999), also called *sleep compression*. The way you do it is you take patients’ estimates of how many hours of actual sleep they get in 24 hours. They should then spend only that many hours in bed each night. Once they have been sleeping well for a week at a given stage, increase the time in bed by a half hour.

Dr. Winningham: Naps are often a source of confusion. You just said to eliminate naps longer than 20 minutes in duration. People take extended daily naps of several hours. I have had people tell me they need daytime naps of several hours, but I see no miraculous improvement. I am convinced it makes things worse and impairs nighttime sleep. I have told people to use an inexpensive watch with an alarm or a kitchen timer to keep naps short. Could you elaborate?

Dr. Olders: Timing is critical. Short naps are refreshing, relieve drowsiness (Harrison and Horne, 1996), and increase alertness and feelings of well-being. Longer naps induce sluggishness and torpor, referred to as *sleep inertia*, and may also impair nighttime sleep. This is how I handle it: When patients feel drowsy or sleepy, they should take a *brief nap*; that is, lie down for not more than 15 or 20 minutes. A kitchen timer may indeed be useful for waking up. If they have not fallen asleep after 15 minutes, they do not need a nap. Period. If they fall asleep after 5 or 10 minutes and sleep for only a few minutes, they will be able to get going again easily.

Dr. Winningham: Dr. Olders, some professionals are now using psychostimulants to enhance cognitive awareness. You mentioned the use of psychostimulants to treat fatigue and depression in patients with cancer.

Dr. Olders: Psychostimulants, particularly methylphenidate (Ritalin), are widely used to treat attention deficit disorder, but they may also be helpful in treating fatigue and depression in patients with cancer or other illnesses. It has been used for years to treat apathy and withdrawal in poststroke and dementia patients (Galynker et al, 1997; Watanabe et al, 1995).

A retrospective study of elderly depressed stroke patients showed that 53% of patients treated with methylphenidate had complete remission of symptoms, with an average peak response time of 2.4 days. In comparison, 43% of nortriptyline-treated patients required an average of 27 days to remission (Lazarus et al, 1994). Of depressed, hospitalized oncology patients at the Massachusetts General Hospital, 73% showed marked or moderate depressive symptom improvement with dextroamphetamine or methylphenidate, usually within 2 days (Olin and Masand, 1996). In patients with malignant glioma, methylphenidate, 10 mg given twice daily, led to improved gait, increased stamina, and motivation to perform activities (Meyers et al, 1998).

Dr. Winningham: How does methylphenidate work to reduce depression and fatigue? I have heard it interferes with onset of sleep. Doesn't that create a problem?

Dr. Olders: Besides its direct REM-suppressant effects, methylphenidate also helps keep people awake (Bishop et al, 1997), which further reduces REM sleep, particularly if it is administered early in the morning so it doesn't interfere with sleep onset in the evening. I have obtained excellent results in treating fatigue in both inpatients and outpatients by administering 5 to 20 mg at 6:00 AM.

Dr. Winningham: Another drug being used for cancer patients is pemoline (Cylert). In the United States, pemoline is a schedule IV drug while methylphenidate is a schedule II drug. Pemoline requires monitoring of hepatic enzymes. There are few data on the use of these drugs in cancer patients. Recent work supported by the National Institute on Drug Abuse at the National Institutes of Health indicates that the abuse risk for methylphenidate in patients for whom it is appropriate is very low despite its similarity to other stimulants like cocaine and amphetamines. The oral form of methylphenidate does not reach peak concentrations in the brain until 60 minutes after ingestion, compared to 9 minutes for the intravenous form and 5 minutes for cocaine (Volkow et al, 1998).

To be honest, when I first heard about using methylphenidate and pemoline in this way, I was not enthusiastic. I could not find clinical trials on the use of these medications in the cancer patients who were demanding them. I am particularly concerned about the potential for interactions with other drugs they may be taking. In addition, psychostimulants are appetite suppressants and may contribute to weight loss if misused. Treatment for breast cancer is associated with weight gain. When I first heard of breast cancer

patients on the West Coast demanding methylphenidate, I wondered if they were also considering weight control. This could potentially be associated with psychostimulant abuse even after treatment. However, after I thought about it, I asked myself, "How is fatigue different from pain?" We do not hesitate to treat pain or nausea with appropriate pharmacological interventions. If fatigue is indeed viewed as a syndrome, there is room for many interventions. Considering the seriousness and universality of the CRFS, I now think the appropriate use of psychostimulants warrants investigation. What other interventions do you think may help?

Dr. Olders: There is no doubt that light is the most important cue for adjusting our circadian biological clocks. Individuals who are insufficiently exposed to light, especially morning light, may develop DSPS. This can occur if people keep their bedrooms dark, if windows are small, or views are obstructed with trees, fences, walls, etc. Encourage patients to keep their drapes or blinds open at night while they're asleep. Natural light wakes them up in the morning. As a matter of good hygiene, when buying or renting housing, look for bedrooms that receive plenty of natural light.

Dr. Winningham: How about foods or OTC interventions? What should we be looking for?

Dr. Olders: Caffeine is important because it may induce its own metabolism. In fact, individuals who use small amounts, or who use it irregularly, may have more severe and longer-lasting insomnia or anxiety than those who consume larger quantities on a daily basis. Caffeine acts as a mood elevator. In the ongoing Nurses' Health Study involving about 86,000 nurses in the United States, those who drank no coffee committed suicide at 2.9 times the rate of those who drank two or more cups daily (Kawachi et al, 1996). I encourage *consistent* caffeine consumption (e.g., two cups of coffee daily).

I also encourage people to engage in cardiovascular (i.e., aerobic) exercise. Exercise has been associated as a useful treatment for depression and fatigue. Exercise has also been associated with improved sleep if patients do not exercise too near to bedtime. The exercise I recommend is at an intensity that raises your heart rate and causes you to breathe harder—but not enough to become out of breath. For someone who is ambulatory but deconditioned, walking with one's arms swinging is vigorous enough, thank you! I also work with elderly people, many of whom are in exercise programs where they sit and lift their arms or legs. Even for people with joint or muscle injuries, aqua fitness programs can provide sufficiently vigorous exercise.

Dr. Winningham: There is little doubt that there are multiple positive emotional as well as physiological consequences of safe aerobic activity. Pinto and Maruyama (1998) wrote a concise review article about exercise in breast cancer survivors. What do you consider the most important, practical intervention?

Dr. Olders: Of all the above interventions, the one that is most crucial for the successful treatment of cancer fatigue, in my clinical experience, is having the patient get up early. Many can-

Table

11.2

Sleep: Popular Myths and the Facts

Myths	Facts
I won't have enough energy to function if I haven't had a good night's sleep.	Partial sleep does not impair exercise performance (Meney et al, 1998).
If I've slept poorly, I should make up for it by sleeping late.	Sleeping late may aggravate or precipitate depression (Globus, 1969; Wehr et al, 1979).
If some sleep is good for you, more sleep is better.	Longer sleep is associated with poorer physical health and increased mortality (Belloc and Breslow, 1972; Wingard and Berkman, 1983), and causes insomnia (Aserinsky, 1969).
After a poor sleep, the fatigue I experience is from lack of sleep.	Insomniacs have less daytime sleepiness (Middelkoop et al, 1996) and better reaction times at night (Bonnet and Rosa, 1987), indicating sufficient sleep.
I haven't slept a wink all night! No wonder I'm tired!	People with insomnia underestimate the amount they sleep (Frankel et al, 1976), in some cases to extremes (McCall and Edinger, 1992).
I'm too depressed to get out of bed.	Total sleep deprivation takes away depression (Gill et al, 1993) as does late partial sleep deprivation (Sack et al, 1988).
You can't convince me that my getting up late has anything to do with feeling tired.	A study in cancer outpatients showed that the later people got up, the more fatigue they experienced (Olders, personal conversation 1999).

cer patients are quite willing to try any approach that will relieve their lack of energy and motivation. They may be skeptical, initially, about any possible benefits from getting up early, but they frequently become enthusiastic supporters of the principle when they experience a rapid improvement (often the same day) when they get out of bed at 6:00 AM. Unfortunately, there are significant numbers of cancer patients who hold dear to a number of false beliefs and attitudes. Table 11-2 lists several popular myths and the facts. When an empathetic presentation of the facts still fails to convince, it may be necessary to involve family members who will undertake to get the patient up and keep them up each morning.

Dr. Winningham: It all sounds rather like “tough love,” and it’s so different from conventional attitudes. It reminds me of the resistance I first encountered in proposing exercise programs for cancer patients! I found encouragement from the patients’ physicians to be a strong influencing factor in converting patients and families. I just reviewed a series of fatigue inventories and in no place did I find questions that asked about specific sleep patterns, or whether patients tried a sleep hygiene plan.

Dr. Olders: Figure 11-1 contains a collection of time-honored sayings on how people have viewed sleep throughout the ages. It is clear that sleep has been a controversial topic for a long time.

As for patients who insist they cannot get up early, or when a trial of early waking fails, an alternative is methylphenidate. I get more consistent results when the medication is taken at 6:00 AM, instead of the more usual 8:00 or 9:00 AM. A second dose at noon, recommended by some, seems to make little difference in my experience. Starting at 5 mg, the single daily dose can be increased to 10 mg after two or three days, with further increases depending on clinical response.

It's rare to find inpatient settings that are sufficiently staffed to provide the one-on-one intervention often required to wake a hospitalized patient at 6:00 AM and keep them awake during the morning. Accordingly, for hospitalized or bed-bound patients, I start with methylphenidate as a first intervention.

When depressive symptoms are prominent, or when methylphenidate even at larger doses fails to improve patients' fatigue, I will start with or add to the methylphenidate an antidepressant, such as paroxetine, which I also give at 6:00 AM. Consider a tricyclic antidepressant such as desipramine for patients with anorexia or nausea, which may be worsened with SSRIs.

Check TSH levels; even mildly abnormal levels should be treated when fatigue or depression is present. We also use intramuscular vitamin B₁₂ when blood levels are even marginally low. Vitamin B₁₂ supplementation may play a role in treating DSPS (Ohta et al, 1991; Okawa et al, 1990).

While my clinical experience certainly suggests that the hypothesized link between excessive REM sleep and cancer fatigue is well founded, further research is essential to confirm that a link exists. Only randomized controlled trials can adequately determine whether getting up early or early-morning psychostimulant treatment, or both, is a useful intervention. Clearly, if excessive REM sleep can be shown to cause cancer fatigue, it strongly suggests that the fatigue (as distinct from sleepiness) that plagues sufferers from many other illnesses has a similar origin, and should respond to the same treatments and preventive approaches. This is an important public health issue, given the lost productivity due to illness-related fatigue as well as costs for its medical treatment.

Dr. Winningham: From a syndrome perspective, it is reasonable that sleep interventions be considered in all fatigued cancer patients. There is no doubt that some patients are affected by profound chemical changes in their bodies. As you share this, I find myself reflecting on all the patients I remember talking with—and I ask, Could they have handled the restrictions you are suggesting they place on their sleep? On the other hand, people were equally incredulous when I suggested exercise to improve functioning and well-being in cancer patients in the early 1980s. What you are saying is going to take a real adjustment in attitude.

Since syndromes are, by definition, multifactorial, it would be logical that there are also several possibilities for interventions. It is unlikely that there is one cure for some fatigued cancer patients. Our best approach should be to find several strategies, each of which help somewhat. I think this could become one of the most powerful tools in our arsenal. Like exercise, it may not be magical for everyone, but it may be useful for many patients in controlling some of the most devastating side effects, and, like exercise, it has a powerful physiological as well as emotional effect. Can you explain how light exposure and times influence the mechanisms you outlined above?

Dr. Olders: Well, a condition in which fatigue and lack of energy figure prominently is seasonal affective disorder (SAD). That morning treatment with bright light if effective implies a connection between SAD and circadian rhythms. It is often assumed that the farther north one lives, the higher the risk of SAD because the amount of daylight in winter decreases as one goes north. However, Iceland has little SAD even though it is quite far north, at 64 degrees latitude. Iceland has two peculiarities that might explain its low incidence of SAD. First, Icelanders stay on Standard Time all year-round. Second, even though this island by its longitude should be in a time zone two hours earlier than Greenwich Mean Time (GMT), the residents actually adhere to GMT. In early November, the sun rises for Icelanders after 9:00 AM, almost three hours later than for Montrealers at the same time of year.

What is the possibility that the switch from Daylight Savings Time to Standard Time may be the trigger for SAD in North America? Consider the facts: The time switch takes place on the last weekend of October each year, and results in everyone getting up an hour later with respect to the time of sunrise, thereby acutely increasing their REM sleep. Would we all feel better, more energetic, if we stay on Daylight Savings Time all year-round? What about going to double Daylight Savings Time, so we all get up an hour earlier in relation to sunrise?

Dr. Wunningham: What about the use of antidepressants?

Dr. Olders: Tricyclic antidepressants should be avoided in the elderly. The anticholinergic effects impair memory, increase risk of orthostatic hypotension, and can have untoward effects on the heart. SSRIs may be sedating in some individuals. They are the preferred treatment for panic disorders and phobic disorders. If these disorders interfere with sleep, they may help insomnia.

Dr. Wunningham: Recommendations about drugs and dosages change with regularity. The National Cancer Institute's PDQ (Physician's Data Query) Web site provides a continual update on topics specific to mental health and related pharmacological interventions. Rather than making recommendations or listing values here, clinicians and researchers are encouraged to refer to this site on a regular basis: <<http://cancernet.nci.nih.gov/clinpdq/supportive.html>>. Since depression is reported to be the most common DSM-IV diagnosis in cancer patients, DSM IV diagnostic criteria are presented in Table 11-3 with specific implications for cancer patients.

Table 11.3

Diagnostic Criteria for Depression: Implications for Fatigue and Cancer

Criterion A

5 or more of the following symptoms during same 2-week period and a change from prior functioning:
At least (1) depressed mood or (2) loss of pleasure or interest in life must be present.

Characteristics

1. Daily depressed or irritable mood, most of the day, by subjective report
2. Notably diminished interest in most activities (can be objective or subjective report)
3. Significant nondieting weight gain or loss (5% change in body weight in a month); can also be reflected in marked increase or decrease in daily appetite
4. Daily insomnia or hypersomnia
5. Daily psychomotor slowing or agitation (objective, not just subjective feelings)
6. Daily fatigue or loss of energy
7. Feelings of worthlessness or inappropriate guilt (not just over illness)
8. Daily decreased ability to focus or concentrate, indecisiveness (subjective or objective report)
9. Recurrent thoughts of death, suicidal ideation with or without a specific plan; not just fear of death

Implications for Fatigue and Cancer

1. Fatigue can appear as a depressive feeling as well as irritability. Keeping a sleep diary as well as noting the time of day the patient feels best may help in making the diagnosis as well as developing priorities.
2. Diminished activities may become evident to family members before the patient becomes aware of them.
3. It is important to note the source of the weight loss. Gastrointestinal problems (nausea, vomiting, and diarrhea), increased bed rest, glycogen depletion, and fatigue (decreased fluid intake) can result in several pounds of water loss secondary to dehydration. In addition, many medications can dull the sense of thirst. Medications can also contribute to weight gain. Source of weight gain or loss should be investigated and corrected.
4. Precancer sleep patterns should be maintained. Naps should be limited to 1 or 2 for a limited period of 15–20 minutes each per day to minimize disturbance to nighttime sleep cycles. Change in sleep patterns may become obvious to family members before the patient notices them.
5. Ask a trusted family member or friend to observe and help with activity. If the person responds to a strenuous day, such as a treatment day, or a surgical procedure by sleeping late or sleeping longer, 2 or even 3 days of aggravated exhaustion may ensue. These cyclic changes are physiologically based and will be delayed (i.e., after the stressful event is over). It is essential to return to regular sleep hours as soon as possible.
6. Watch for changes in activity based on nadirs, anemia, and stressors.
7. It is common for patients, especially women, to express guilt about not fulfilling their social roles as a parent or spouse. In addition, relatives may lay guilt trips on the patient, accusing them of malingering or using their cancer for secondary gain.
8. The impaired ability to concentrate or focus is one of the common characteristics of cancer-related fatigue. This may particularly show itself in the inability to keep track of money (e.g., balancing a checkbook, paying bills, keeping track of bank accounts, paying taxes), appointments, and time. Studies show that this cognitive impairment may be long lasting and may be associated with specific cancer treatments.
9. Be aware of the patient's prior experience with cancer, knowledge of pain control, fear of the course of the disease, fear of loss of independence, and other issues that may be related to fear of death but appear as suicidal/death ideation. Also be aware of possible retraumatization experiences related to prior intense life experiences that may contribute to feelings of hopelessness.

Criterion B

Not part of a mixed episode.

Characteristics

1. Both manic and major depressive episode for 1 week or more
2. Severe enough to impair functioning, characteristics of harm, or psychotic features
3. Symptoms not due to the physiological effect of a substance or general medical condition (e.g., hyperthyroidism)

Implications for Fatigue and Cancer

Family as well as personal history should be carefully screened for a history of DSM-IV diagnoses. Note that patients and their families may not admit to mental illness in the family because of the stigma; indeed, they may accept such behaviors as "normal." Ask about violence, substance use and abuse, and estranged family relationships as a round-about way to get at this issue. Where there is special concern, based on clinical symptoms, a genogram may be a subtle and less threatening way of identifying family histories with suicides, depression, and substance abuse. History is critical because use of corticosteroids or antidepressants in an individual with a history of or potential for mania can contribute to a full-blown psychotic manic episode. In addition, a rapid decrease in such medications may precipitate a profound and unexpected depression.

Criterion C

Symptoms cause significant impairment in functioning.

Implications for Fatigue and Cancer

Regardless of whether the impairment is caused by fatigue or whether it is caused by depression, any symptoms that contribute to functional impairment can often lead to increased fatigability and depression and should be treated aggressively.

Criterion D

Symptoms are not due to direct physiological effects of substance or medical condition (e.g., hypothyroidism).

Implications for Fatigue and Cancer

1. After corticosteroid treatment, patients often talk about "crashing," a profound exhaustion, possibly accompanied by depression.
2. In cancer, it is common for other, less life-threatening conditions to be minimized as "just part of the cancer." These conditions, however, may have a significant effect on mood and functioning. Hypothyroidism can present with many minor subjective, and apparently unrelated symptoms including fatigue, paresthesias, difficulty focusing, clinical presentation of asthma, repeated infections, and sensory changes. This may lead to patients' complaints not being taken seriously or being categorized as depressed, anxious, or malingering.

Criterion E

Symptoms cannot be accounted for by a more obvious or significant cause (e.g., grief), last 2 months or more, or result in functional impairment, suicidal thoughts, psychosis, or decreased psychomotor activity.

Implications for Fatigue and Cancer

When the symptoms are unresolved or become severe, the patient should be referred to a psychiatrist for treatment and should be given the opportunity for psychotherapy as appropriate. Unresolved past experiences can be a source of retraumatization and hopelessness that should be identified and promptly treated. Do not wait for such conditions to spontaneously improve.

Note: The DSM-IV specifies that these criteria do not include symptoms that are clearly due to a general medical condition or mood incongruent delusions or hallucinations.

Source: Adapted by Maryl L. Winningham (1999) from *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed., American Psychiatric Association (Copyright, 1994), Washington, DC. Used with permission.

I'd like to change the topic, if I may. Research as well as clinical observation has validated the high incidence of nightmares in individuals who have been traumatized. However, over the past few years, I've run into an interesting phenomenon you may be able to help explain: people who have gone through a period of enormous trauma—prolonged stress in their lives—who say they never dream. They describe their sleep, usually five to six hours per night, as “one unbroken darkness.” Given their background, it would be expected they would have nightmares, but they don't. They say if they do dream, it is in the form of brief, realistic little “dreamlets” on the fringes of awakening. I have no doubt psychoanalysts would be quite frustrated by this. (The poet Elias Canetti wrote, “All the things one has forgotten scream for help in dreams.”) But these people claim to have no nightmares. In fact, some have told me they do not think they even turn or move at night (a feature of REM sleep), because they wake up with numbness on the side of the body on which they slept. What is interesting is that, as a whole, they seem to be busy, creative, and dynamic. There seems to be no cloud over them. However, I have noticed when they get cancer or some chronic illness that is emotionally and physically very draining, they can decompensate quite quickly. I am concerned about these people, particularly in view of the reported higher suicide rate among Holocaust and other major trauma survivors. The literature talks about a higher risk of depression, especially in women, in homes where there was violence and sexual abuse. We have refugees and former victims of human rights violations among us. Although these people can look pretty normal in everyday life, they have been tortured and scarred. They spend a good deal of their energy trying to adapt to a new setting, to a new country, while ignoring or overcoming their past. It's almost as if they are trying to outrun the past while desperately holding on to the here and now. But then the past comes nipping at their heels. As I talked with others about this, I realized this is a population we seem to have overlooked.

There is a great deal about cancer and its treatment milieu that can retraumatize someone who has hidden wounds. In countries where there is repression and persecution, physicians and nurses are often the assistants in the white coats who assist in torture. The health care system is full of authority figures—but then, so was their former life. Procedures we put patients through are humiliating (but so are abuse and torture), painful, freedom limiting (NPO means “no water, no food”), and include invasions of privacy and dignity. They may have been raped, both men and women. But how is that different, to a tired, elderly, or confused mind, from vaginal, prostate, or rectal examinations? Cancer is a life-threatening experience, but they've been there before, often asking, “Why me?” with no clear answer.

As a group, they are unlikely to talk about their former experiences. As someone once suggested, “Paranoia is a normal response to a paranoid society.” They may lack insight into their reaction to past experience, although they may be otherwise intelligent and alert. They may do well for as long as 30 or 40 years, then crash. During the process of diagnosis and treatment for cancer, they may become incredibly depressed, or be confronted by post-traumatic stress disorder (PTSD)-like responses.

How do you reach out to them? I have been able to find little in the literature about this phenomenon. Could it be that the worst, the unimaginable, the most inhumane things had already happened? Had the stuff of nightmares come true already? When they were willing to talk with me about it, in every case, they suddenly appeared to be dissociative, with flat affect. Is it possible that by staying so busy, they have erected a mental barrier to the horrors of their past that not even the weakness of sleep can breach? Could there really be people who do not dream? What about the lack of nightmares? How do they survive and carry on normally for so long? Even as thought experiments are used to explore scientific issues, I use poetry to explore issues of deep human significance. I used the poem "Repression" to gain insight into this problem (see page xii). What are your thoughts?

Dr. Olders: I was touched by the poem. I think it has more to do with not remembering dreams than with not dreaming at all. I don't profess to have any sort of expertise when it comes to dreams, but my take on this goes as follows: For most people, most dreams, including nightmares, occur during REM sleep. REM sleep tends to occur more during the later part of the night, peaking (see Figures 11-3 and 11-4 and Table 11-1) around 8:30 AM. If you get up early, you will have less REM sleep, hence less dreaming. With the deconditioning and physical exhaustion of illness, they may spend more time in bed, sleep more, and have more time for REM sleep than previously.

Dr. Winningham: That sounds reasonable. Also, people who are very active usually don't sit around after they wake up trying to remember dreams. They usually get right into the activities of their day.

Dr. Olders: To remember a dream consciously seems to require waking up during the dream or perhaps shortly afterwards. If you are sleeping seven or eight hours, chances are excellent that you will wake up briefly several times during the night, particularly toward the end of your sleep, when there is less deep sleep. The busy, creative people you have known who don't seem to dream are sleeping only five or six hours, if I remember correctly. If they are a little sleep deprived, they will be sleeping deeply (i.e., more slow wave sleep for a larger proportion of their sleep), less likely to wake up, and therefore less likely to remember their dreams. They are probably also getting up early.

Dr. Winningham: Perhaps in response to debilitating illness, they start sleeping more, or change their sleep patterns, thus opening themselves up for breakthrough nightmares and memories. I have a friend whose mother lived through some unspeakable experiences during World War II. Several years ago, she suffered anoxic damage to her brain. Since then, she seems to be trapped in an in-again, out-again twilight of reliving the horrors. I wonder if the strange behavior of elderly, confused patients finds a basis in earlier, traumatic experiences. One of my former students, now a hospice nurse, suggested this might be the basis for the "sundown syndrome."

Lawrence Langer, the Holocaust scholar, has written about this existential confusion and isolation in his book *Admitting the Holocaust: Collected Essays* (1995). Cancer also has a

Table 11.4	Posttraumatic Stress Disorder (PTSD): Issues Relevant to Cancer and Fatigue
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Criterion A

Exposure to a traumatic event with 2 characteristics.

Characteristics

1. Person experienced or was involved in event(s) characterized by actual or threatened serious harm or death to physical integrity of self or others.
2. Response included intense fear, helplessness, or horror. This may be manifested by agitated or disorganized behavior.

Issues Relevant to Cancer and Fatigue

1. Threat of disfigurement, loss of life, independence, and social roles can profoundly influence cancer survivors. Much depends on their past experiences and vulnerability. Keep in mind that vulnerability is not always obvious. Individuals who appear to be carefree, independent, or insensitive may be at greatest risk. Most significantly, the threat is relative, not absolute, depending on background and the perceived current type and degree of threat.
2. Response may not be obvious, nor may it be immediate. The need to focus on immediate lower survival needs (on Maslow's hierarchy) may force the person to postpone or suppress dealing with feelings and emotional response. Since disorganized or agitated behavior is also characteristic of cognitive fatigue in cancer, this may be misinterpreted or misunderstood by both patients and professionals. Such behavior should be carefully examined as to cause.

Criterion B

This traumatic event is reexperienced as 1 or more of the characteristics.

Characteristics

1. Recurrent, intrusive, and threatening recollections of the event(s).
2. Recurrent nightmares.^b
3. Feeling as if the traumatic experiences were recurring (may include sense of reliving the experience, hallucinations, or dissociative "flashback" episodes).
4. Intense emotional distress upon reexposure to internal or external cues that recall some aspect of the traumatic place or event.
5. Physiological reactivity on exposure to those cues.

Issues Relevant to Cancer and Fatigue

1. The need for recurrent follow-up examinations and diagnostic tests, and the fear of associated recurrence, extend the risk of the traumatic events.
2. See note.^c
3. Patients describe a literal "flashback" experience while on the way to the clinic, entering the building, smelling certain clinic-associated odors, undergoing CT scans, preparing for bone marrow biopsies, or thinking of follow-up treatments. Be aware of patients describing their experience of cancer and cancer treatment with such terms as *rape*.
4. These flashback or associated reliving experiences may occur without warning; they may be self-reinforcing, producing a feedback loop of avoidance behavior (see criterion C below).
5. The link between the stimulus and the response may not be evident. Patients who are identified as suffering from this problem should be referred for professional therapy and possible treatment with appropriate psychotropic medications.

Criterion C

Persistent avoidance of anything associated with the trauma and numbing of responsiveness (not present prior to the trauma) with 3 or more of the characteristics.

Characteristics

1. Avoidance of thoughts, feelings, or conversations about anything associated with the trauma.
2. Avoidance of places, events, or people that may arouse memories.
3. Selective inability to recall a significant aspect of the trauma.

4. Diminished interest or participation in related activities or events.
5. Feeling of detachment or estrangement from others.
6. Limited affect (may be perceived by other than patients).
7. Sense of doom or shortened life span.

Issues Relevant to Cancer and Fatigue

1. & 4. Patients may also avoid support groups, association with former clinical employees, or any literature or information sources, or show disinterest in follow-up monitoring.
2. & 3. Indicators of this problem may include avoidance of follow-up appointments, repeated "forgotten" clinic visits, or inability to remember significant aspects of treatment, allergies, or prior medical conditions. (Patients who are potential candidates for this problem may actually be identified by themselves, family or clinical personnel as "tough," "coping well," "a real survivor," "responsible," or "nothing gets me/her/him down.")
5. & 7. The feeling of detachment, estrangement, or sense of doom may be interpreted by the person as "destiny" or "karma." It is critical to be sensitive to cultural background in evaluating potential risk among patients.
- 5., 6., & 7. These characteristics have been described in Holocaust survivors and those who have survived incredibly traumatizing experiences. Be alert for body marks, comments, cultural affiliation, or any other identifiers that may hint of someone at high risk. Referral for specialized therapy is critical since there may be a higher risk of suicide.

Criterion D

Persistent evidence of posttraumatic arousal (2 or more characteristics)

Characteristics

1. Insomnia.
2. Irritability or unpredictable explosive anger.
3. Trouble focusing or concentrating.
4. Hypervigilance.
5. Exaggerated startle reaction.

Issues Relevant to Cancer and Fatigue

Notice the presence of irritability and trouble concentrating on this list as well as the criteria for depression. These appear to be frequent long-term characteristics of fatigue.

Criterion E

Duration of the disturbance (B, C, and D) 1 month or more.

Issues Relevant to Cancer and Fatigue

The disturbance may manifest for the first time even several years after cancer treatment. Some patients may interpret this as a sign of cancer recurrence or of impending doom.

Criterion F

Disturbance results in significant clinical distress or impairment related to some significant aspect of life.

Issues Relevant to Cancer and Fatigue

The effects of PTSD can be summarized as functional impairment, impaired ability to pursue self-care activities, increased time spent sleeping, and continued emotional distress. This should be recognized as a reason for referral for treatment as soon as the condition is suspected.

^a less than 3 months (acute) or more than 3 months (chronic). "With delayed onset" means onset of symptoms is at least 6 months after the stressor.

^b Some patients with extremely traumatic backgrounds have been reported to have suppressed dream recall. See discussion in this chapter.

Source: Adapted from the DSM-IV criteria for posttraumatic stress disorder (American Psychiatric Association, 1994). Copyright 1998 by Maryl L. Winningham. All rights reserved. Used with permission of the author.

“why me” stage where many people try to find meaning in their experience. Flint (1995) found that women who participated in support groups attended to their grieving process more, and were willing to look for meaning as part of their adjustment process. But what about those who were more closed (i.e., those who did not participate)? She observed that it seemed to reflect their mother’s values of closedness. They were less likely to attend to grieving and did not look for meaning. What if they were afraid to look? What if their past experiences had already told them there was no meaning, that they could expect only loneliness, isolation, and bewilderment?

Countless studies indicated that people who develop PTSD were more likely to have suffered abuse and trauma when they were young. Although this phenomenon has been studied most commonly in Vietnam veterans and Holocaust survivors, it also applies to survivors of childhood violence and physical, verbal, and sexual abuse. Table 11-4 presents the DSM-IV characteristics of PTSD with special implications for people with cancer.

Several years ago, Oppenheim (1996), a practicing physician, published an article entitled, “7 Ways Doctors Torture Their Patients.” He was serious about the title. He had taken an honest look at the health care system and realized there are many ways we torment our patients. We don’t mean to; we just don’t think about it. We don’t realize how the everyday part of our work looks to “outsiders,” especially those who are our “victims.” Patients do not come into the clinic with labels tattooed on their foreheads (although some still have tattooed numbers on their arms). It is important to pay special attention to individuals with backgrounds of childhood violence and abuse, imprisonment, psychiatric hospitalization (in some countries that was how political dissidents were dealt with), refugee status, and experiences as political prisoners. Be cautious whenever people show signs of aggression, or passivity, watching for signs of dissociation. Watch for small scars on the body that may present evidence of cigarette burns and other forms of torture. It is also important to remember that a practiced torturer does not have to leave physical scars in order to break someone. Torture scars are either the result of a sloppy interrogation or to make the person a living lesson to others. Sleep deprivation over a few days, especially when the victim is deprived of normal light-dark, day-night signals, is sufficient to break anyone.

For health care personnel who may wish to learn more about this, the American Association for the Advancement of Science has prepared material on how best to provide health care to meet these patients’ special needs. I would like to recommend *Serving Survivors of Torture* by Randall and Lutz (1991). Medications may be prescribed to keep persons from violent decompensation. Antidepressants, medications for bipolar disorder, anxiolytics, and others may help persons during cancer treatment. They often need psychotherapy to help them through this period. Of people who have experienced great trauma in the past, I have heard it said, “Men become violent, women become depressed.” Unfortunately, our society is more threatened by the violence and ignores the depression. There is also tremendous stigma in our culture, as well as others, associated with being the

victim of dehumanizing trauma as well as obtaining psychiatric help. For many immigrants, English is not their native language, making communication even more difficult.

There is another barrier to helping people with these experiences: Most Americans cannot begin to conceptualize the inhumane experiences others may have survived. Years ago, when I lived in Europe, I met people who had lived under both the Nazi and Communist regimes. The mass rape and pillage they experienced by both armies was beyond comprehension. Can you imagine how the experiences of cancer can retraumatize someone like that? Veterans of war also frequently have had overwhelming, unimaginable experiences. Often, these are the patients who don't seem to care, who appear hostile, the patients who don't communicate or cooperate, the people with walls. They may even be afraid to report symptoms, especially pain. As the population ages, we can expect to encounter more patients with this kind of background. They are already vulnerable, and the fatigability associated with cancer may be life-threatening to them.

There is another area I would like to address. It is mentioned in several other chapters of this book (especially Chapters 17 and 23). The problem of acute as well as chronic *cognitive impairment* is being increasingly recognized as a short-term phenomenon as well as among long-term survivors. In some cases, it may be part of the "fuzzy thinking" associated with depression and hypersomnia. However, it is clear there are other influences, often related to treatments, that leave people impaired for years afterwards, sometimes for life. There are several reasons for this:

1. People are having to work throughout their treatments. High-functioning individuals seem to be especially sensitive to cognitive losses. They may have increasing difficulty with planning, functioning independently, following through on projects, forgetting meetings and appointments, and short-term memory. Sometimes people even lose their jobs because of this. The cognitive effects of fatigue in cancer, especially as a long-term issue, have not been addressed adequately. Superficially, they do not seem to qualify for Americans with Disabilities Act protection, nor are they able to access the disability system.
2. Psychometric tests are becoming increasingly sensitive. This is critical since these deficits may not correlate with any objective imaging or chemistry diagnostic techniques. Even now, the tests still don't pick up on difficulties with everyday living that may develop, including handling money and paying bills. Organizational abilities like money management and keeping track of dates are central to independent, adult living. While compiling this book, I heard many times, "I didn't realize I hadn't paid the bills until the gas/electricity were shut off. People think I'm being irresponsible, but I'm trying harder than ever before in my life."
3. Patients may be aware something is wrong, but they may not even be aware they are suffering through a comparative deficit, particularly if people do not explain the characteristics and how their lives may be affected.

4. There has been scant research on developing means of helping cancer patients adapt to these deficits so they can remain productive following the termination of their treatment. The use of psychostimulants, used with other disorders, may help support developments in behavioral training.
5. More cancer patients are surviving longer; however, the therapies exact their toll on the body. In all the other major chronic illnesses, medications work with the body. In cancer, the treatments usually work *against the body*, exerting a toxic effect on normal as well as malignant cells. The therapies can have a long-term effect on the nervous system that impairs general physical functioning as well as cognitive functioning. Hence, the ability to prolong life must be supported by the rehabilitative therapies (Meyers et al, 1998).

There are several established sources from which we can draw as we develop interventions to help people cope effectively. As pointed out in Chapters 17 and 23, select techniques used for people who have suffered mild traumatic brain injury (MTBI) may be helpful. Certainly there are common characteristics in some of the limitations. In a recent study using methylphenidate (Ritalin) therapy, brain tumor patients showed improved moods, cognition, and function (Meyers et al, 1998). In another study of patients with primary malignant brain tumors, postacute traumatic brain injury rehabilitation seemed to offer a cost-effective means of optimizing functioning (Sherer, Meyers, and Bergloff, 1997).

Dr. Olders: I'd like to interject something here. The fact that cognitive impairment seems to respond to methylphenidate suggests that it may also have something to do with depression, just as fatigue does. We know that in elderly patients, depression can produce a pseudodementia, which at times is indistinguishable from a true dementia like Alzheimer's disease. Total sleep deprivation has been used as a diagnostic test for this kind of cognitive impairment, in cases where there had been no response to other antidepressants (Williams, Yeomans, and Coughlan, 1994). It sounds possible to me that in some cancer patients, getting too much REM sleep might produce cognitive dysfunction more so than fatigue or frank depression. Getting up early might be a useful intervention for these people also.

Children with attention deficit and hyperactivity disorder (ADHD) may sleep more than normal children (Tirosh et al, 1993). This may help to explain the therapeutic effectiveness of methylphenidate in ADHD. To the extent that cancer patients sleep excessively, they might experience some of the same symptoms as ADHD patients, and respond to the same sort of interventions. It would also be worthwhile, I think, to see what effect getting up early has on people with ADHD.

Dr. Winningham: Thank you! Ideally, every oncology clinic should have a consulting board-certified neuropsychologist with experience in working with cancer patients and their families. However, this is not an ideal world. In areas where such consultation and rehabilitation are not available, primary health care providers can encourage patients to

work on organizational skills and MTBI-type rehabilitation tasks. Two books that are excellent resources are *The Rehabilitation of Brain Functions: Principles, Procedures, and Techniques of Neurotraining* by Craine and Gudeman (1981) and *The Thinking Skills Workbook: A Cognitive Skills Remediation Manual for Adults* by Carter, Caruso, and Languirand (1984). Patients who have undergone procedures like bone marrow transplantation or who have received some kind of high-dose chemotherapy find themselves physically and mentally impaired afterward (Ganz, 1998; Schagen et al, 1999; van Dam et al, 1998). Family members might even be taught to work with patients to redevelop or sharpen cognitive skills.

Other rehabilitation techniques are those used in people who have ADHD. Although it seems quite remote to suggest that someone with long-term cognitive fatigue has anything in common with ADHD, there are some important similarities. For example, trouble initiating and following through on tasks, irritability, trouble with memory, and trouble prioritizing are common to MTBI and ADHD. Organizational techniques used with them may be especially helpful for cancer survivors who still suffer from the cognitive “blahs.”

Sleep hygiene, a structured lifestyle, good nutritional intake, and regular moderate exercise can help minimize deficits while promoting functioning and feelings of well-being in all three groups of patients. Organizational and management training may also facilitate more successful on-the-job performance. Use of medications to help with cognitive clarity may also help. In short, the fatigue experience of cancer represents a significant challenge for employees (Mock, 1998).

During the time I was working on this book, I was considering what could be done to help cognitively impaired patients organize. Missed appointments, confused times and dates, and difficulty keeping track of seemingly simple things make cancer survivors with cognitive impairment look careless or immature. Although identifying and carrying out priorities were identified as big problems, the use of commercial planners and personal information managers usually did not work in the long run; neither did making lists of priorities. Not only did *others* around them not understand, but also *they* did not understand themselves. There is a special planner/organizer for adults and children with ADHD that incorporates a conceptually different approach than anything I have seen before. The psychologist Janice Goldstein, who is the codeveloper of this product, is a breast cancer survivor! She said she found some of the techniques she taught her patients to be useful when she was going through cancer treatment. The SpectraPlanner is organized in a way that uses appealing color coding and a unique spatial orientation that facilitates an overview of activities. For research or clinical application, information about how and where to order the SpectraPlanner is located at the end of this chapter. This is what Goldstein had to say about how the planner was developed:

The SpectraPlanner was conceived by myself and a colleague, Kate Goldfield, in our work with individuals who have attentional and organizational problems. I am a psychologist who has spent a great deal of my career trying to understand the relationship between

Figure
11.7
Proposed ICD-10 Criteria for Cancer-Related Fatigue (1998 Draft)

- A. Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is (1) significant fatigue.
 1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level;
 2. Complaints of generalized weakness or limb heaviness;
 3. Diminished concentration or attention;
 4. Decreased motivation or interest to engage in usual activities;
 5. Insomnia or hypersomnia;
 6. Experience of sleep as unrefreshing or nonrestorative;
 7. Perceived need to struggle to overcome inactivity;
 8. Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued;
 9. Difficulty completing daily tasks attributed to feeling fatigued;
 10. Perceived problems with short-term memory;
 11. Post-exertional malaise lasting several hours;
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.
- D. The symptoms are not primarily a consequence of co-morbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

Source: From Cella, D., Peterman, A., Passik, S., Jacobson, P., and Breitbart, W. (1988). Progress toward guidelines for the management of fatigue. *Oncology*, 12 (11A), 373. Used with permission.

how people learn and how they organize their time. I noticed the substantial impact that attention and concentration had on an individual's success in careers and in relationships with others. My understanding of the impact of attention and concentration became even clearer during my own treatment for breast cancer. During that time I realized even further how much more difficult it is to maintain a sense of organization when one is struggling with the lethargy and exhaustion created by chemotherapy and radiation. With both these professional and personal experiences in hand, my colleague and I tried to come up with a hands-on tool.

Thus evolved the SpectraPlanner. Spectra uses a unique color-coded format and logical top-to-bottom design to facilitate personal organization for teens as well as adults. It has stickers that help individuals to actively plan their time and think ahead about what may be coming up. The "week to do" stays in view all week long and the "month to do" stays in view for the month. This helps with the "out of sight, out of mind" problem of short-term memory impairment.

This is an example of what we need to prevent impairments from becoming disabilities, and disabilities from becoming handicaps. This is more than just a quality of life issue,

Figure
11.8

Diagnostic Interview Guide for Cancer-Related Fatigue (1998 Draft)

Note: Capitalized text represents instructions to the interviewer. Text in quotations represents statements to be read verbatim to the respondent.

1. "Over the past month, has there been at least a 2-week period when you had significant fatigue a lack of energy, or an increased need to rest every day or nearly every day?" CIRCLE ONE: YES NO
IF NO STOP HERE, IF YES, CONTINUE.
- "For each of the following questions, focus on the worst 2 weeks in the past month (or else the past 2 weeks if you felt equally fatigued for the entire month)."
2. "Did you feel weak all over or heavy all over? (every day or nearly every day?)" CIRCLE ONE: YES NO
3. "Did you have trouble concentrating or paying attention? (every day or nearly every day?)" CIRCLE ONE: YES NO
4. "What about losing your interest or desire to do the things you usually do? (every day or nearly every day?)" CIRCLE ONE: YES NO
5. "How are you sleeping? Did you have trouble falling asleep, staying asleep, or waking too early? Or did you find yourself sleeping too much compared to what you usually sleep? (every night or nearly every night?)" CIRCLE ONE: YES NO
6. "Have you found that you usually don't feel rested or refreshed after you have slept (every day or nearly every day?)" CIRCLE ONE: YES NO
7. "Did you have to struggle or push yourself to do anything? (every day or nearly every day?)" CIRCLE ONE: YES NO
8. "Did you find yourself feeling sad, frustrated, or irritable because you felt fatigued? (every day or nearly every day?)" CIRCLE ONE: YES NO
9. "Did you have difficulty finishing something you had started to do because of feeling fatigued? (every day or nearly every day?)" CIRCLE ONE: YES NO
10. "Did you have trouble remembering things? For example, did you have trouble remembering where your keys were or what someone had told you a little while ago? (every day or nearly every day?)" CIRCLE ONE: YES NO
11. "Did you find yourself feeling sick or unwell for several hours after you had done something that took some effort? (every day or nearly every day?)" CIRCLE ONE: YES NO
IF LESS THAN SIX ITEMS INCLUDING #1 ARE MARKED YES, STOP HERE.
12. "Has fatigue made it hard for you to do your work, take care of things at home, or get along with other people?" CIRCLE ONE: YES NO
IF #12 IS NO, STOP HERE.
13. IS THERE EVIDENCE FROM THE HISTORY, PHYSICAL EXAMINATION, OR LABORATORY FINDINGS THAT THE SYMPTOMS ARE A CONSEQUENCE OF CANCER OR CANCER THERAPY? CIRCLE ONE: YES NO
IF #13 IS NO, STOP HERE.
14. ARE THE SYMPTOMS PRIMARILY A CONSEQUENCE OF COMORBID PSYCHIATRIC DISORDERS SUCH AS MAJOR DEPRESSION, SOMATIZATION DISORDER, SOMATOFORM DISORDER, OR DELIRUM? CIRCLE ONE: YES NO
IF #14 IS YES, PATIENT DOES NOT MEET CRITERIA FOR CANCER-RELATED FATIGUE.
IF #14 IS NO, PATIENT MEETS CRITERIA FOR CANCER-RELATED FATIGUE.

Source: From Cella, D., Peterman, A., Passik, S., Jacobson, P., and Breitbart, W. (1988). Progress toward guidelines for the management of fatigue. *Oncology*, 12 (11A), 375. Used with permission.

it is an economic exigency in our current health care environment, and interventions like this may prove to be quite cost-effective.

Diagnostic Interview Guide for Cancer Fatigue (1998 Draft)

One development that may be especially helpful is the use of established, recognized diagnostic criteria and a diagnostic interview guide for cancer fatigue. Recently Cella and colleagues (1998) proposed draft criteria for an International Diagnostic Classification (ICD-10) diagnosis of cancer fatigue (see Figure 11-7). The medicolegal ramifications of this development are significant because it would allow cancer fatigue to be recognized by the medical and disability system (see Chapter 14 for further discussion about this). In the same publication, this team published a one-page diagnostic interview guide for fatigue that could be used both in clinical practice and for screening in research (see Figure 11-8). They emphasized this guide is a draft. It could be a critical unifying factor in research and clinical practice.

Where Do We Go From Here

This chapter has examined a number of unusual topics with reference to the CRFS. Yet, all of them can be part of the weary effects of the CRFS. Sleep disturbances, fatigue, depression, PTSD, retraumatization, and cognitive impairments suggest still other dimensions related to the CRFS and hold the possibility of innovative interventions. The implications of this discussion should challenge researchers and clinicians in new directions; this in turn should place new instruments in the hands of clinicians to address the CRFS in an inexpensive and practical manner. In patients who appear to be suffering from any of these problems, screening instruments included in this chapter as well as a good psychiatric history are of vital importance.

Cognitive fatigue, also discussed in other chapters in this book, is being increasingly recognized as a long-term source of distress. Without reinventing the wheel, techniques developed for treating other patient populations may be applicable to cancer survivors. A few recent studies point to the urgent need for additional research on risks and interventions related to this problem.

Endnote

1. The historical precedence for using “thought experiments” as a technique for presenting logical links in science originated with Galileo Galilei (ca. 1600) and is presented in Chapter 2. Rogers, E. M. (1960) *Physics for the Inquiring Mind: The Methods, Nature, and Philosophy of Physical Science*. Princeton, NJ: Princeton University Press, 8–9.

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