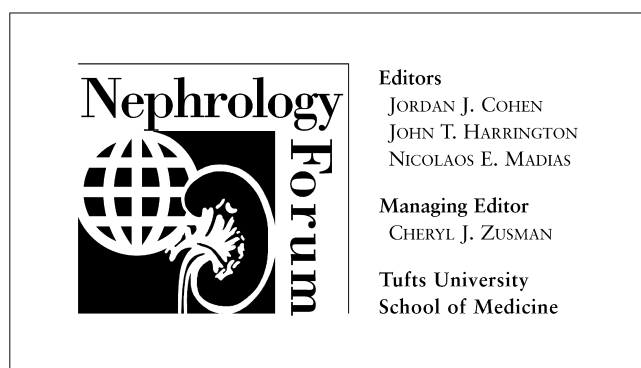


Psychosocial factors in dialysis patients

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CASE PRESENTATION

A 57-year-old African American woman with end-stage renal disease (ESRD) due to diabetic nephropathy was admitted to the hospital for marked anorexia, weight loss, and fatigue. These symptoms coincided with a depressed mood for a prolonged period. Four years prior to admission, hemodialysis for ESRD was started. After treatment with dialysis had commenced, she noted that her earlier feelings of sadness, anorexia, and fatigue improved. She became a candidate for renal transplantation. Continuous ambulatory peritoneal dialysis (CAPD) was started 30 months prior to admission. Her weight and height at that time were 64 kg and 5 feet 2 inches, respectively. Citing “stress” in her life, the patient intermittently complained of forgetfulness, mild confusion, and anorexia during the first 12 months she was treated with CAPD. She maintained her weight at 64 kg, and her serum albumin concentration remained in the range of 3.5 to 4.0 g/dL. Several episodes of peritonitis during the beginning of her second year of CAPD aggravated her feelings of sadness, frustration, and anxiety. By 12 months prior to admission, her weight had fallen to 55 kg and her serum albumin concentration had dropped to 2.9 g/dL.

Six months prior to this admission, the patient stated that her depressed mood and energy level were improving. She blamed personal and financial problems for her feelings of

sadness and fatigue. She began to look for part-time work but was hampered by low back pain. Complaints of financial problems as well as anorexia and low energy re-emerged four months prior to admission. She refused offers of psychological counseling as well as free nutritional supplements.

Three months before this admission, her weight was 46 kg and the serum albumin concentration was 2.6 g/dL. She was referred to a psychiatrist who prescribed fluoxetine (Prozac). A family conference was held the next month to address her poor emotional and nutritional status. She was openly depressed at the meeting.

Four weeks prior to this admission, she was admitted to the hospital because of extreme fatigue. Her inpatient care included enteral nutrition via a nasogastric feeding tube. She was discharged after three weeks to a skilled nursing facility, where she remained for one week before being readmitted to the hospital with severe depression and failure to thrive.

Her medical history was significant for hypertension for more than 14 years, type 2 diabetes mellitus, and hypercholesterolemia. A total abdominal hysterectomy was performed 17 years prior to admission. She had worked as a clerk for the U.S. Navy, and had been divorced several years prior to initiation of dialysis. Her medications were erythropoietin, calcium carbonate, insulin, multivitamins, iron supplements, docusate sodium, calcitriol, sorbitol, lovastatin, lorazepam, famotidine, cisapride, and fluoxetine.

On admission to the hospital, her blood pressure was 115/85 mm Hg, her heart rate was 112 beats/min, and she weighed 45 kg. Physical examination revealed an emaciated but alert woman in no apparent distress. She had mild peripheral neuropathy, but no other significant abnormalities were detected.

Laboratory data on admission included a white blood cell count of 5300/ μ L; hematocrit, 25%; sodium, 131 mEq/L; potassium, 4.0 mEq/L; chloride, 105 mEq/L; bicarbonate, 21 mEq/L; BUN, 22 mg/dL; serum creatinine, 3.8 mg/dL; calcium, 3.7 mg/dL; phosphorus, 2.0 mg/dL; cholesterol, 153 mg/dL; protein, 3.6 g/dL; and albumin, 1.5 g/dL.

Upon admission she refused enteral feeding and any medical therapy, including dialysis. A consulting psychiatrist found her depressed yet able to make decisions regarding her medical care. Several conferences among the medical, psychiatric, and renal teams along with the patient and her family took place during the first week of admission. A joint decision was made to uphold the patient’s original wishes to forgo any active treatment of her physical condition. Supportive care to improve the patient’s comfort was provided. She died on hospital day 19.

Key words: end-stage renal disease, stress, depression, social support, illness effects, marriage, family.

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DISCUSSION

DR. PAUL KIMMEL (*Professor of Medicine, Division of Renal Diseases and Hypertension, George Washington University Medical Center, Washington, D.C.; and Director, Diabetic Nephropathy and HIV Programs, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA*): We recently celebrated the 20th anniversary of the *Kidney International* "Nephrology Forum." Another 20th anniversary should be observed, however: that of the March 1980 Forum, "Emotional dehiscence after renal transplantation," in which Dr. Samuel H. Basch focused on a woman who had trouble adjusting to the stresses of end-stage renal disease (ESRD). At the time, the literature on the topic comprised only 18 references. To date, most outcome data in ESRD patients have related to demographic and treatment correlates of survival, which are largely unmodifiable, but recently individual investigators and the United States Renal Data System (USRDS) have considered the effects of patients' social situation, perceptions and responses to the illness, physicians and dialysis unit staff, spouses and families, and socioeconomic status on outcomes. I will focus on patients treated with center hemodialysis, because they comprise the preponderance of patients with ESRD in the United States, and the vast majority of the ESRD patients over 65 years of age who seem most at risk for developing complications from depression [1, 2]. In contrast to the earlier Forum, I will not focus on individual clinical issues in this review, but rather will discuss whether psychosocial factors affect outcomes, and assess the nature of their biologic mediators.

Today's patient started renal replacement therapy with hemodialysis and later switched to continuous ambulatory peritoneal dialysis (CAPD). While treated with a plethora of medications, including tranquilizers and antidepressants, she exhibited symptoms of uremia, depression, and malnutrition. No medical cause was evident for her downhill course. After a multidisciplinary evaluation found her to be depressed but capable of formulating her own health care plans, a joint patient/family/medical team consensus led to the decision to discontinue dialysis and provide only supportive care. She died soon thereafter. Fundamental to understanding this case are the constructs of stress and coping.

The notion of stress has resisted definition since it was introduced in the 1930s by Hans Selye. Stress connotes a change in the physical condition, environment, or psychosocial setting of an organism [3]. "Stress mediators," typically neurohumoral effectors of the central nervous system or hypothalamic-pituitary-adrenal (HPA) axis, are thought to have both protective and maladaptive consequences, depending on the peak intensity and timing of the response. Stress has been operationalized as

"allostasis," the ability to achieve stability through change [3]. "Allostatic load" refers to "the wear and tear that the body experiences due to repeated cycles of allostasis as well as the inefficient turning-on and shutting-off of these responses [3]." Failure of levels of a stress mediator to return to normal after a challenge also constitutes an abnormality of the allostatic system of stress responses [3]. Allostatic load (the physical effect of stress) has been quantified in human studies by an algorithm composed of various hemodynamic, biochemical and anthropometric measurements that can predict a patient's risk of developing cardiovascular disease, a decline in physical and cognitive function, and earlier-than-expected mortality [3]. There can be variable end-organ responses to increased allostatic load. The ability of stress mediators to return to baseline is also a salient issue for patients with renal dysfunction. The manner in which the response to changes in perception occurs in different people is critical, as outcomes can be quite variable in patients with similar allostatic loads. Age, gender, presence of comorbid illness, developmental history, and genetic heterogeneity can contribute to different outcomes, but personality, mood, and habits and behaviors (such as diet; level of exercise; use of tobacco, alcohol, and regulated substances; and spiritual observance) can alter the allostatic load as well. These responses can be thought of as "coping factors." In addition, relationships among patients, physicians, and dialysis staff; integration within a social network; education; occupation and financial status; and place of residence all might influence medical outcomes. Studies of stress have indicated that the two most important determinants of outcome are the perceptions accompanying the stressor and the functional status of the subject [3].

Stressors in the life of a dialysis patient can include dietary and time constraints, functional limitations, loss of employment, changes in self-perception, alterations in sexual function, general and perceived effects of illness, medications used to treat the illness, and fear of death. The demands of ESRD treated with hemodialysis include potential changes in a patient's status in marital, familial, occupational, and societal contexts; the expenses and worries associated with the treatment and the illness, and the uncertainty, anxiety, and costs entailed while waiting for a transplant. In addition, treatment within a unit implies a complex relationship with dialysis personnel: physicians, nurses, technicians, and other staff. Adaptive coping can produce desired outcomes—full employment and successful function within a dyad and family. In the absence of such coping, disability and marital and family dysfunction can occur, as well as depression, anxiety, loss of one's role and identity, and development or worsening of alcohol and substance abuse.

"Psychosocial parameters" include the vast number of

psychologic variables and aspects of the social environment that affect all of us and are central to the patient's perception of quality of life [4]. The biopsychosocial model posits many intersecting levels of variables that might determine overall health status, and which are available for analysis. These parameters include individual demographic data (age, ethnicity, gender), physiologic measures (body mass index; cardiovascular, immunologic, and conditioning status), psychologic and behavioral parameters (distress, personality factors, health-promoting or -damaging habits), and social or environmental factors (for example, occupational imperatives, level of social support, access to health care, residential characteristics, and socioeconomic status). Patient-level psychosocial parameters include personality factors, affect, and perceptions of distress, well-being, or illness; patient/spouse indices include marital satisfaction; and patient/physician/dialysis staff measures include satisfaction with health care, compliance with the dialysis regimen, and level, number, and quality of interactions with personnel and staff.

Much of the information regarding psychosocial parameters in patients with renal disease is at the descriptive level, although some studies have correlated psychosocial indices with physiologic or demographic measures. Psychosocial factors might affect mortality outcomes through at least four mechanisms: access to health care, compliance with the dialysis prescription or medication regimen [5, 6], nutritional status, and neuroendocrine or immunologic function [6, 7]. Today I will consider seven factors that inform the lives of hemodialysis patients and the medical outcomes associated with those factors. Specifically, I will look at depression, perception of the burden of illness and social support, as well as marital, familial, therapeutic, and residential and socioeconomic circumstances.

Depression

The World Health Organization forecasts that within the next 20 years, depression will be the second most common debilitating and economically costly illness worldwide [8]. Compound depression, which occurs when depression co-exists with another psychiatric or medical illness [6, 9, 10], is characterized by a greater magnitude of depressive affect and is usually more resistant to treatment. Depression is associated with increased mortality in patients with acute myocardial infarction and in general medical inpatients [6, 10].

One should not confuse the diagnosis of depression with depressive effect or the symptoms of depression. A variety of syndromes associated with depressive affect have been described, including major depression and dysthymia [9]. With few exceptions [11, 12], these disorders have not been well studied in patients with renal disease. According to the criteria of the American Psy-

chiatric Association outlined in the Diagnostic and Statistical Manual IV, major depressive disorder is diagnosed when a change from baseline occurs, lasting at least two weeks, during which the patient experiences either depressed mood or loss of interest in usual activities or anhedonia (the inability to experience pleasure) and at least five other symptoms of depression from a group of nine, including depressed mood most of the day, nearly every day; markedly diminished interest or pleasure in most activities for most of the day; significant weight loss or gain, or appetite disturbance; insomnia or hypersomnia; fatigue or loss of energy nearly every day; psychomotor agitation or retardation; feelings of worthlessness, or excessive or inappropriate guilt; diminished ability to think, concentrate, or be decisive; or recurring thoughts of death, including suicidal ideation [9]. Dysthymia is a chronic but milder depressive disorder, defined by depressed mood present on more days than not for a period of two years and at least two of the symptoms of depression, but not thoughts of death or suicide.

Severe depression is characterized by disability, such as an inability to function at work or do household chores. The lifetime risk for major depressive disorder in the general population is from 10% to 25% in women and 5% to 12% in men; the point prevalence is from 5% to 9% in women and 2% to 3% in men [9]. The prevalence of depression is lowest in community samples, and progressively higher in outpatient and inpatient settings [9]. Screening tools to assess depressive affect include the Hamilton Rating Scale for Depression and the Beck Depression Inventory (BDI) [9]. In subjects without chronic illness, a BDI score < 9 suggests no or minimal depression, 10 to 18 represents mild to moderate depressive affect, 19 to 29 is moderate to severe, and ≥ 30 indicates severe levels of depression [6], although other rating systems have been employed.

Although documentation from well-designed, large, epidemiologic studies is absent, depression is thought to be the most common psychiatric abnormality in patients with ESRD treated with hemodialysis [6, 7, 13]. Depression can be a response to a loss [6], and ESRD patients have sustained multiple losses, including loss of role within the family and workplace, renal function and mobility, physical skills, cognitive abilities, and sexual function. But a 1985 literature review noted that the prevalence of depression varied between zero and 100% in studies of dialysis patients over the previous two decades [14], suggesting that its true prevalence was unknown and that the diagnosis of depression is highly dependent on the assessment tool used.

The prevalence of depression in outpatients with ESRD treated with hemodialysis is unknown. In a review of hospitalization data from ESRD patients treated with dialysis in the U.S. in 1993, 8.9% were hospitalized with a psychiatric diagnosis [15]. In 25% of these patients,

the psychiatric diagnosis was the primary reason for the admission. The most common psychiatric disorders in the population were depression and affective disorders (26%), organic brain syndromes and dementia (26%), schizophrenia and other psychoses (22%), and drug and alcohol abuse (15%). Dialysis patients were more likely than non-ESRD patients with ischemic heart disease or cerebrovascular disease to be hospitalized with a diagnosis of depression, but they had a risk of hospitalization with depression equal to that of non-ESRD patients with diabetes mellitus. Also, dialysis patients were more likely to be hospitalized with a psychiatric illness later in the course of their ESRD. These findings suggest that these psychiatric complications are not simply a consequence of a short-term adjustment reaction to the regimen, but a long-term concomitant of coping with the chronic illness and its treatment. These data, however, identified patients with the most severe psychologic and/or psychiatric disorders.

Lowry and Atcherson reported an 18% prevalence of major depression, using American Psychiatric Association criteria, in a group comprised mostly of white patients beginning home hemodialysis in Iowa [16]. Hinrichsen et al found that 17.7% of prevalent center hemodialysis patients satisfied criteria for minor depressive disorder, and 6.5% met criteria for a diagnosis of major depression according to the Schedule for Affective Disorders and Schizophrenia [11]. Suicidal ideation and depressed mood were the best discriminators among patients with major depression, minor depression, and those without depression.

Craven et al showed that a BDI score ≥ 15 had a 92% diagnostic sensitivity and 80% specificity in making the diagnosis of depressive disorder in patients with ESRD treated with hemodialysis or peritoneal dialysis [12]. Although the positive predictive value (39%) was much lower than the negative predictive value (99%), diagnostic accuracy was high. Therefore, the investigators were able to separate depressive symptoms from the psychiatric disorder [12]. The cutoff score used in patients without renal disease (≥ 10) was associated with more false negatives and a lower positive predictive value. They showed that 45.4% of patients had depression as assessed by the BDI [12]. They also found that 8.1% of dialysis patients (all of whom had been treated for more than three months) had a major depressive disorder, and 6.1% had a dysthymic disorder. In our studies of almost 300 African American patients with ESRD treated with hemodialysis in the Washington, D.C. area, 46.4% of patients had a BDI score > 10 , 41.4% > 11 , 34.6% > 13 , 24.7% > 15 , 15.6% > 19 , and 3.7% > 30 . Approximately 5% were diagnosed with major depression, or were referred for psychiatric care (unpublished data). The mean BDI score in our population was 11.4 ± 8.1 .

Smith, Hong, and Robson pointed out the dramatic

overlap between the symptoms of depression and those of uremia [14]; this finding has been noted in other chronic illnesses as well. The potential confounding between uremic and depressive symptoms makes research in this chronically ill population difficult. But no overlap exists between the symptoms of uremia and the thoughts or cognitions accompanying depression: feelings of guilt and worthlessness, preoccupation with thoughts of death, and ideas and plans regarding suicide. Depressive symptoms thus can be characterized as either somatic or cognitive. To address the issue of whether the cognitive or somatic aspects of depression are more important in patients with renal disease, we devised the "Cognitive Depression Index" (CDI) [17] by excluding those items dealing with somatic symptoms from the BDI. Although the CDI correlates highly with the BDI in our hemodialysis patient population, except for early studies [17], the CDI has not provided discriminative power in predicting outcomes [18, 19].

Few studies have assessed psychosocial factors in a longitudinal manner or in relation to the stage of ESRD or the course of the life cycle of an ESRD patient, an important analytic control. In a 1987 longitudinal study, Husebye et al showed that 42% of hemodialysis and peritoneal dialysis patients over the age of 70 had an unchanged level of depression when reassessed after three years [20]. More than 25% of patients were less depressed on re-evaluation, but almost 33% exhibited a higher level of depressive symptoms. In our cross-sectional studies, we found no relationship between the amount of time that the patient had been treated for ESRD and the level of depressive affect [19, 21]. Our longitudinal studies, however, revealed a tendency for levels of depression to decrease over time [18]. This tendency reflects successful patient adjustment to the stresses of ESRD but also a potential consequence of survivor bias. Although mean levels of depression tended to remain stable over time, there was variation in individuals [18, 19].

The possible interrelationships between depressive affect and extent of compliance in patients with ESRD have not received much attention, and links between these two parameters have been difficult to establish [5]. Depression and other psychologic factors could influence compliance and patient perceptions, including assessment of quality of life [4, 5, 7], and these perceptions could possibly shorten patient survival. Everett and colleagues showed that stress was directly correlated with increased interdialytic weight gain in hemodialysis patients but noted that an increased patient perception of depression was associated with less interdialytic weight gain for unknown reasons [22]. However, other studies have been unable to delineate an association between depressive symptoms and compliance with fluid restriction [5].

In our studies, increased depression was associated

with increased serum phosphate concentration and with poor compliance with the dialysis prescription (unpublished data) [5, 21]. The magnitude of depressive affect did not correlate with laboratory measures of compliance in patients beginning hemodialysis [23]. Incident patients with higher levels of depressive affect, however, tended to have poorer attendance at hemodialysis sessions (unpublished data). Depressive affect also correlated with perception of the illness' effects and inversely with perceptions of satisfaction with life and social support. Depression scores did not correlate with functional scores or severity of illness scores in patients beginning hemodialysis [23]. In prevalent patients, however, increased disability (but not severity of illness) correlated with increased depressive affect (unpublished data).

An extensive literature has linked depressive affect and disorders with immune dysfunction [reviewed in 6]. Careful studies have shown that decreased cellular immunity is present in unmedicated patients with depression in the absence of chronic medical illness [24]. Depressed patients have higher circulating levels of interleukin-1 (IL-1) [25] and other acute-phase reactants [26] compared to control subjects; the same findings were obtained in patients with ESRD [27]. Cytokines also might be markers for depression [reviewed in 28]. It is also noteworthy that infusion of IL-1 produces side effects similar to the symptoms of the uremic syndrome [reviewed in 28].

Friend and colleagues showed that increased levels of depression predicted the onset of diminution in serum albumin levels in hemodialysis and peritoneal dialysis patients with ESRD [29]. The reverse did not occur, implicating a primary role of depression in mediating medical outcomes. In our population, a higher level of depressive affect also correlated with lower serum albumin concentrations in prevalent patients (unpublished data). In preliminary studies of 295 maintenance hemodialysis patients, increased BDI and CDI scores (signifying increased levels of depressive affect) correlated with levels of the immune markers, total hemolytic complement and T-cell function. Also, BDI scores correlated with levels of circulating IL-1 (unpublished data). These mediators are associated with mortality in hemodialysis patients [27, 28].

We recently demonstrated an association between increased levels of depressive affect and higher β -endorphin levels in female African American hemodialysis patients [28]. Depression can be a particularly potent stressor in female hemodialysis patients, causing physiologic stimulation of the autonomic nervous system. These data suggest different relationships between depression and medical mediators, depending on duration of dialysis and on gender. Such differences might provide clues regarding adaptation and coping, or they could represent

specific relationships in subgroups or in cohorts of patients who survive on dialysis for long periods.

We previously highlighted the similarity of symptoms of depression and abnormal cytokine regulation such as fatigue, cognitive defects, and appetite and sleep disturbances to those of uremia [reviewed in 28]. Cytokine dysregulation might be similar in patients with depression and ESRD, and possibly provides a link between the pathogenesis of symptoms in these two conditions. The end organ effects of circulating stress compounds, as mediators of allostasis, which cannot return to physiologic levels because of failure of renal or dialytic clearance, are largely unknown in patients with renal disease.

Over the last 20 years, several studies assessed the relationship between depression and mortality in hemodialysis patients but reached contradictory conclusions. Ziarnik and colleagues evaluated 47 center hemodialysis patients before they commenced renal replacement therapy. Because patients who died within one year had higher baseline depression scores than did the survivors, they concluded that depression was an early mortality marker [30]. Wai and coworkers used discriminant analytic techniques to study 241 home hemodialysis patients, and concluded that age, level of serum albumin, stress, and extent of depressive affect were different between survivors and non-survivors at baseline [31]. A study of 167 home hemodialysis patients demonstrated that personality factors, in addition to age and depression, differentiated survivors and non-survivors [32]. In a population of 64 non-diabetic center and home hemodialysis patients, those with BDI scores > 14 had significantly poorer survival rates [33]. Our own study of hemodialysis and peritoneal dialysis patients revealed an association between CDI scores and mortality [17].

These and other early studies, however, often failed to use appropriate sophisticated statistical techniques to account for variation in potential confounding variables and mortality risk factors such as age, race, gender, comorbid conditions, nutritional markers and status, and dose of dialysis. In addition, studies were typically performed on small cross-sections of hemodialysis groups without control for the time since patients had started renal replacement therapy for ESRD and in the absence of longitudinal follow-up. Finally, most studies reported level of depressive affect assessed at the convenience of the interviewer, and not at the time of a signal event in the patient's emotional life or medical course, or at the time of diagnosis of depression.

In contrast to these earlier studies, several more recent and better-designed studies have failed to demonstrate an association between depression and survival in hemodialysis patients. Devins et al studied 97 hemodialysis, peritoneal dialysis, and transplant patients and could not discern an association between depressive affect and mortality over approximately four years [34]. Husebye

Table 1. Therapeutic options for patients with depression

Antidepressant drugs
Older agents
First-generation tricyclic antidepressants
Second-generation tricyclic antidepressants
Heterocyclic antidepressants
Monoamine oxidase inhibitors
Newer agents
Selective serotonin release inhibitors (SSRIs)
Serotonin reuptake inhibitors
Noradrenaline reuptake inhibitors
Selective norepinephrine reuptake inhibitors
Reverse inhibitors of monoamine oxidase
5-hydroxy-tryptophan ₂ receptor antagonists
5-hydroxy-tryptophan _{1a} receptor agonists
Dopamine reuptake inhibitors
Dopamine antagonists
Herbal and alternative remedies (such as St. John's wort)
Psychotherapy
Electroconvulsive therapy

and colleagues studied 78 hemodialysis and CAPD patients more than 70 years of age but could not show a relationship between depressive affect and mortality [20]. Christensen and colleagues also were unable to show an association of level of depressive affect and survival in 78 primarily white hemodialysis patients followed for 7 to 60 months, although age and BUN predicted early mortality [35]. We also did not discern an association between depression and mortality using Cox regression techniques in a population of 295 mostly African American, urban hemodialysis patients, when variations in age, medical comorbidity, dialyzer type, and level of albumin were controlled [19].

In the longitudinal phase of our study, as many as six sequential assessments of depressive affect were made [18]. After a median follow-up period of a little more than three years, we were, however, able to demonstrate that a one standard deviation increase in depression score evaluated over time was associated with an 18% to 32% increased risk of mortality when variations in other risk factors were controlled.

Options for treating depression consist of pharmacotherapy, psychotherapy, and electroconvulsive therapy, alone or in combination (Table 1) [9]. First- and second-generation tricyclic antidepressants, selective serotonin release inhibitors, serotonin and noradrenaline reuptake inhibitors, monoamine oxidase inhibitors and reverse inhibitors of monoamine oxidase, 5-hydroxy tryptophan₂ receptor antagonists, and herbal and alternative remedies (such as St. John's wort) have all been used and evaluated in the treatment of depression in patients without coexistent medical illness [9]. There is no evidence that the serotonin release inhibitors confer an advantage over the tricyclic antidepressants for treatment of major depression in patients without concurrent serious medical illness [9]. Therefore the side effect profiles associated

with an individual class of drugs are of paramount importance in choosing therapy; this relates both to the potential of discontinuation due to unpleasant symptoms and the problems associated with specific physiologic complications in medically ill patients, such as orthostatic hypotension and cardiac arrhythmias with therapy using the tricyclic antidepressants in dialysis patients. Sertraline (Zoloft), a selective serotonin release inhibitor, and fluoxetine (Prozac), a serotonin reuptake inhibitor, improve orthostatic hypotension in hemodialysis patients, perhaps by direct effects on autonomic tone mediated by serotonin [36, 37]. The dose of tricyclic antidepressants must be carefully titrated during therapy. The therapeutic dose for selective serotonin release inhibitors is usually the starting dose. Both classes of drugs are cleared by the liver, and therefore usually no dose adjustment is necessary for decreased renal function in the absence of hepatic disease. Patients should be treated for at least six weeks before an evaluation is made regarding the outcome of therapy. Concurrent supportive psychotherapy can be useful, as this approach can increase efficacy and decrease the relapse rate [9].

Few studies have evaluated therapy for depression in patients with chronic renal failure. Steltzer treated five hemodialysis patients who had major depressive episodes with tricyclic antidepressants. Three had an excellent response but two did not respond [38]. Kennedy, Craven and Roin treated 8 of 10 hemodialysis and peritoneal dialysis patients who had major depressive episodes with desipramine or, in one case, mianserin [39]. Six patients completed the trial, and five recovered from their depressive syndrome. Blumenfeld and colleagues performed a randomized, double-blind, placebo-controlled study of fluoxetine in 14 patients with major depression and ESRD treated with hemodialysis [40]. No patient discontinued treatment because of side effects. Patients treated with fluoxetine had improvement in depression scores after four weeks, but differences could not be demonstrated from baseline values after eight weeks of therapy [40].

In an innovative study, Friend and colleagues demonstrated that participation in a group therapy session in the dialysis unit was associated with significantly improved survival in urban patients [41]. Although this was not a randomized controlled study, and it potentially suffers from selection biases, it provides important theoretical and practical bases for further studies. Institution of an exercise program at a Greek hemodialysis center was associated with a dramatic improvement of affect of patients, with the most severely depressed patients benefiting most from the intervention [42]. Although changes might have been in the somatic rather than cognitive aspects of depression, exercise might still be a worthwhile supplemental therapy that has few, if any, deleterious side effects in selected patients.

Suicide, the gravest complication of depression, disproportionately affects older white men in the U.S. Patients with ESRD can display suicidal behavior differently, and perhaps attempt and commit suicide more easily than non-medically ill populations, by noncompliance with the dialysis regimen or by manipulation of their hemoaccesses [6, 43]. In a landmark paper, Neu and Kjellstrand reported a 9% incidence of withdrawal from dialysis, which accounted for 22% of deaths of the presumably primarily white ESRD patients in their study [44]. Of 1,766 patients over 13.5 years old, 3 clearly committed suicide; the investigators suggested that this rate was approximately 15 times greater than that in the general population. The prevalence of suicide varies among ethnic groups, with African Americans having a relatively low suicide rate [45]. Most patients who withdraw from dialysis are elderly or have diabetes [1, 44]. Death from suicide occurred at a rate of approximately 0.2% per 1,000 dialysis patient years [1]. Medical complications and failure to thrive are the most common causes for withdrawal [1]. Withdrawal rates were two to three times greater in white compared to Asian, Native American, or black patients in any age category [1]. The relationship of antecedent depression to withdrawal and suicide has been poorly delineated.

Perception of the burden of illness

Perception of the burden of illness is defined as patients' assessment of how the disease interferes with their lives in personal, social, familial, and occupational contexts [4, 7, 46]. Patients with the same medical diagnoses can have divergent views regarding the intrusive effects of their illness, depending on age, gender, ethnic and cultural background, personality, and extent of social support or marital satisfaction. The existence of other medical problems, for example, congestive heart failure, angina, recent surgery, or infection, also can modify patients' perceptions of illness. Perception of illness is likely an important aspect of coping with or adjustment to chronic illness.

Patients' perception of their well-being, an important component of quality of life, is easily assessed and forms an important part of the medical evaluation [4, 46, 47]. Perception of effects of illness can differ at different stages of the hemodialysis patient's course and is not necessarily linked with objective medical indicators, such as measures of functional status. Appraisal of burden of illness is associated with measurements of general well-being, happiness, depression, and social support, and with levels of neuroendocrine and immune mediators.

Assessment of the burdensome nature of an illness also can be related to patient expectations and cultural factors, and can vary among patients of different ages. Elderly African American dialysis patients experienced fewer symptoms, lesser perception of effects of illness,

and greater satisfaction with their health and more satisfaction with their lives than did elderly white dialysis patients [48]. These findings are important if perception of illness is associated with clinical outcomes, because cognition might be amenable to modification through counseling or psychotherapy. Perception of fewer effects of illness correlated with better attitudes towards compliance, greater perceived family support, and lower levels of stress [5, 7, 21].

Medical and demographic factors such as age, severity of co-morbid medical illness, and anthropometric measures did not correlate with perception of illness effects in our patient population, yet feelings that their illness interfered with their lives were associated with lower levels of circulating total hemolytic complement and with increased levels of circulating IL-1 in our group of 295 hemodialysis patients (unpublished data).

Perception of illness intrusiveness was not associated with behavioral compliance measures in our studies [5]. We also have been unable to show that more severe medical illness leads to lower levels of perceived social support or to a decreased perception of well-being [19]. Patients' perceptions of increased illness intrusiveness were associated with poorer survival in our patient population [19]. Shulman et al also found a higher mortality rate in patients with perception of greater illness [33]. Self-rated health status and satisfaction with life indices were associated with survival in univariate analyses in older hemodialysis patients, but were not associated with survival when controlled for the level of functional status [49].

Social support

Social support is the perception that an individual is a member of a complex network in which one can give and receive affection, aid, and obligation [50]. Social support can be received from family members, friends, pastors, acquaintances in the workplace, and medical personnel, and is well recognized as an important factor in the patient's adjustment to chronic and acute illness [35, 50, 51]. Social support has been consistently linked to improved health outcomes in numerous studies from the U.S. and abroad as well as in populations with varying chronic illnesses characterized by different geographic settings, socioeconomic status, and ethnic backgrounds [50]. In fact, differences in social support among groups have been suggested as accounting for differences in the mortality rate of dialysis patients among units [52] or among national populations [19], and possibly are responsible for differences in compliance [5, 53]. Although the relationships are consistent and robust, the mechanisms underlying the connection between social support and illness have not been clearly delineated [50, 54]. Candidates for mediators between social support and improved health include better access to and utilization

of health care; better compliance; and better psychologic, neuroendocrine, or immunologic function [19, 50, 54].

Several studies have shown an association between survival and perception of social support in ESRD patients of different ethnic backgrounds [19, 20, 35, 55, 56]. In one prospective study, a quality-of-life measure that included social support predicted survival of hemodialysis patients [55]. In another study, family cohesion as a measure of social support predicted survival [35]. The effects of medical and treatment parameters such as nutritional status, delivery and intensity of dialysis, and patient compliance were not controlled in these studies, however. Further, patients' assessment of giving social support predicted improved survival in hemodialysis patients [56]. We showed that increased perception of social support predicted survival when variation in age, severity of comorbid illness, level of serum albumin, dialysis membrane type, and study site were controlled [19].

High levels of social support have been associated with increased utilization of medical services [50]. Social support has been associated with compliance of ESRD patients treated with hemodialysis [5, 7, 19, 23], although the findings have been variable and partly depend on the parameters assessed in different populations. Hemodialysis patients who perceived substantial family support had lower levels of interdialytic weight gain and better biochemical compliance measures [51]. A large study using USRDS data found that patients who did not live alone were less likely to shorten their hemodialysis treatments [57]. However, the study noted no association between household composition and attendance at hemodialysis sessions, interdialytic weight gain, or serum phosphate level. Indirect indices of social support and measures of social adjustment were associated with greater interdialytic weight gain in studies in Israel and the United Kingdom [5]. Moreover, other studies either could not establish relationships between measures of social support from family and friends and compliance in hemodialysis patients [5] or found a correlation of greater perception of social support with worsened compliance [5]. We found no correlation of social support measures and standard laboratory compliance measures. In contrast, perception of total social support and social support received from friends was correlated with improved attendance at scheduled dialysis sessions (unpublished data) [5]. Indices of social support correlated with level of depressive symptoms, perception of illness effects, and satisfaction with life in our studies [19].

We noted an interesting correlation between levels of circulating β -endorphin and total perceived social support from friends, but not from other individual sources of social support in incident patients (unpublished data). Levels of circulating IL-12 were inversely related to the level of perceived total support and support received from friends in 75 such patients. In prevalent patients,

support received from friends correlated inversely with neuroendocrine mediators associated with mortality, and positively with mediators associated with survival (unpublished data). These findings suggest that patients' friends play a unique role during the course of dialysis.

Marital issues

Relations with an intimate partner can either have positive aspects, such as associations with greater perceived social support, or negative ones, associated with hostility. Marital stability, satisfaction and perceptions of hostility have been associated with differential health outcomes in the general population [reviewed in 28]. Unhappily married individuals report poorer health than do happily married or divorced people with similar demographic characteristics. Marital conflict can affect perceptions of illness and interfere with the ability of a patient to comply with the complex dialysis regimen. Declines in reported marital satisfaction have been associated with subsequent poorer health evaluations.

Chronic illness in a member of a dyad can radically change marital roles. Spouses can become caregivers and, regardless of role, can experience depression, hostility, or both. In addition, the spouse can be the object of the patient's negative emotions. Finally, sexual dysfunction can alter the dynamics of the relationship. Few studies exist on spousal or family relations in ESRD patients, and almost none focus on outcomes [58–61]. In one early study, more than 50% of couples that included a patient with ESRD experienced marital disruption [58]. Another study highlighted a correlation between patients' and spouses' BDI scores [61]. A study of 68 Israeli prevalent hemodialysis patients and their spouses revealed high levels of distress compared with normative groups, and high correlations between distress scores of spouses [59]. Although a high prevalence of sexual dysfunction affected home dialysis patients, their marital and social adjustment scores were comparable to those of the general population [62].

Dyadic conflict has been associated with endocrinologic and immunologic responses in women, but not men, in subjects without renal disease [63]. Strong negative emotion, such as perception of dyadic conflict, can be a particularly important stressor in women ESRD patients, activating physiologic and neuroendocrine pathways. Negative effect within a marital dyad sometimes is a stronger predictor of long-term marital satisfaction and stability than is positive emotional exchange. The giving and receiving of social support within a marriage also can change during the course of ESRD. In Canadian couples with one ESRD patient, women patients perceived that family support declined after the onset of illness. No change in perceived support was noted by male ESRD patients [60].

We studied the interrelationships among medical fac-

tors, neuroendocrine and immunologic factors, and outcome in 174 male and female hemodialysis patients in dyadic relationships [28]. Higher levels of depressive affect and increased perception of the burden of illness correlated with increased severity of illness and with higher circulating levels of IL-1 and β -endorphin, but these effects were only evident in women in the study. Marital satisfaction and conflict scores correlated with medical risk factors, psychosocial parameters, and circulating IL-1 and β -endorphin levels, but again, only in women. Neuroendocrine, immunologic, and marital indices predicted differential survival in the study group, but the dyadic indices were associated with outcome only in the women.

Family issues

Few data exist regarding family structure, relationships, and function in dialysis patients, or assessing outcome in patients within compared with those outside a family unit. Although some studies have evaluated family responses to home hemodialysis, the findings are often in groups too small to control for multiple demographic, socioeconomic, medical, and treatment variables. Almost no data link these factors with physiologic measures or ESRD patient outcomes. Families may be a source of social support or of stress. Fathers of pediatric patients with ESRD reported higher stress, depression, and anxiety than did the mothers [64]. These findings were more pronounced in parents of older children. Using a procedure for coding family interaction, Steidel et al demonstrated that family cohesion was associated with better patient compliance with dialysis regimens [65]. Poor compliance in pediatric ESRD patients was associated with poor adjustment of their parents [66]. Family structure and socioeconomic status also were associated with patient compliance. In a study of 74 urban African American hemodialysis patients and their families, we noted that better family coordination predicted better patient compliance with the dialysis prescription (unpublished data) [5]. Reiss and coworkers conducted a pilot study of 23 urban hemodialysis patients in families and found paradoxical relationships between factors usually considered strengths and hemodialysis patients' survival [67]. Surprisingly, patients who were more compliant in families functioning as integrated groups had higher mortality rates. The authors concluded that ESRD in a patient was a greater stress for organized families. They speculated that patients in vulnerable families bonded to the dialysis unit by exhibiting increasing compliance with the medical regimen.

We recruited almost 500 families of African American hemodialysis patients in Washington and Philadelphia for studies of family function and outcome. Families were categorized according to size and structure. A simple household was defined as one in which the patient lived

alone, or only with a spouse or partner. Complex households were defined as patients living with various combinations of relatives and non-relatives, often in multigenerational groups. After a three-year observation period, Cox regression analyses revealed that only age of the patient and household structure were associated with survival rates. Patients who lived in complex families had a significantly increased relative risk of mortality, but again, the differences among women were largely responsible for the overall findings [68]. These data suggest that African American women with ESRD treated with hemodialysis and living in complex households or in difficult marital situations are at particular risk for early death. This risk likely relates to the patient's expectations of and coping with family duties; many of these patients have limited economic resources and/or diminished social support. Previous studies have indicated that stress, inflammatory responses, and depressive symptoms are more common and more intense in women than in men; perhaps these responses are mediated by estradiol and differential activation of components of the HPA system [reviewed in 3, 28, 63].

Few studies have addressed the association of psychosocial and socioeconomic parameters, such as family closeness, income and education of the family, and relationships with the dialysis unit staff, with outcome. In a prospective, multicenter study of African American hemodialysis patients and their families, we used a family problem-solving task, measures of family closeness, family composition, and income to assess family function. We also evaluated patient "closeness" to the dialysis unit personnel. In contrast to what we expected to find, patient closeness to family, closeness to the dialysis unit staff, and greater family resources predicted earlier mortality. Patient closeness to family was a stronger predictor of patient mortality in families with better problem-solving skills, higher incomes, and more complex compositions (abstract; Leidner et al, *J Am Soc Nephrol*, 11: 1244A, 2000). The mechanisms underlying these associations are unclear, but the stress of hemodialysis might play a more destructive role in close knit, accomplished families, or in treatment settings that place high time or emotional demands on patients.

Relationships with dialysis personnel

The dialysis unit and staff might play an important role in determining outcomes, but few studies have addressed this issue. McClellan and colleagues showed that unmeasured dialysis unit characteristics predicted survival better than traits delineated by differences in the case mix [52]. We found that groups of dialysis unit staff exhibit specific characteristics over time despite a high turnover rate of individual employees; this stability suggests that a "culture" typifies each particular dialysis unit [69]. Few studies have evaluated the relationship

between patients' feelings about the dialysis staff and outcomes. In a subset of our population, we asked patients about their level of satisfaction with their nurses, technicians, and nephrologists. Patients' increased satisfaction with staff and their perception that staff cared about them correlated with higher serum albumin levels. Patients' increased satisfaction with physicians, but not nursing or technical personnel, correlated with improved attendance and greater total time compliance with the dialysis prescription (abstract; Kimmel et al, *J Am Soc Nephrol* 9:1092A, 1998). Dialysis unit staff characteristics also were associated with varying patient compliance, as assessed by biochemical indices [5]. Patients' interactions with staff as well as dialysis unit characteristics likely are important factors in mediating outcomes in dialysis programs with similar patient populations. In addition, the role of physicians and dialysis corporations responsible for the organization of dialysis units should be explored further.

Residential and socioeconomic issues

Residence, a key factor of socioeconomic status, as well as the location of the dialysis unit might contribute to outcome of patients with ESRD. Not enough study has been devoted to the notion that varying quality of physician care likely characterizes programs in different neighborhoods. Two studies have linked lower socioeconomic status to an increased incidence of ESRD [70, 71]. Although few groups have investigated the relationship between survival and socioeconomic status in the ESRD population, Port et al demonstrated that higher socioeconomic status was associated with improved survival in ESRD patients from Michigan [72]. But in preliminary investigations using a larger database, we found a paradoxical association (abstract; Kimmel et al, *J Am Soc Nephrol*, 11:1236A, 2000). Patients living in areas with higher socioeconomic status in the U.S. had poorer outcomes, but these effects were limited to minority populations. The reasons for this finding are unclear but possibly reflect different allocation of resources among groups in the same residential area, different access to health care and services, discordance between viewpoints of physicians and patients, or subtle effects of discrimination [45]. Minority populations in the ESRD program appear to be at risk from inequitable distribution of resources. To differing extents, psychosocial function might be related to socioeconomic status, in part as a result of perception of stress [73].

Conclusions

Few studies have tracked psychosocial responses longitudinally in patients treated for ESRD and linked these responses with outcome. Almost no data exist regarding examining psychosocial factors in patients with chronic renal insufficiency which predict subsequent outcome

during ESRD. Differences between outcomes of ESRD patients in different countries should be assessed; these studies should account for variations in family structure, social structure, and extent of perceived social support. Stress mediators should be evaluated at baseline and longitudinally in studies of patients with ESRD in which morbidity and mortality are outcomes.

Patients with ESRD treated with hemodialysis deal with the multiple stressors of their illness and attempt to cope with the demands of their spouses, families, occupations, and communities. A tremendous amount has been learned about the physiologic reactions of dialysis patients. The field of stress has just begun to make plausible connections between emotions and their biologic mediators. End-stage renal disease represents the paradigmatic chronic disease. Our patients are available for study on a consistent basis, and standard biochemical markers that are related to outcome are easily obtained and measurable. Nephrologists and their patients can contribute to a broader understanding of stress by elucidating the connections between psychosocial variables on the one hand and physiologic, endocrinologic, and neuroimmunologic variables on the other.

We should ask for our patients' own assessments of how they are doing, what their relationships are like in their marriages and families, and what life is like in their neighborhoods. Then we should carefully listen to their answers. Our patients' stories might be telling us as much about their mortality risk as their serum albumin concentration does. The time is ripe for interventions in the field of depression, social support, and patients' perceptions regarding their illnesses. I am sure that we can provide data by performing such studies that will be crucial in improving the quality and length of our patients' lives.

QUESTIONS AND ANSWERS

DR. NORMAN LEVY (*Adjunct Professor of Medicine and Clinical Professor of Psychiatry, SUNY Health Sciences Center at Brooklyn, New York*): Do you see any connection between anemia and depression? Is having 40% fewer red blood cells a factor that augments or precipitates depression? My second question is, although we know that the patient was given fluoxetine, we don't know whether she took it or what its effects were. Antidepressants are effective in 60% of all patients, so one often tries another antidepressant if the first doesn't work. I assume another drug wasn't used. Finally, did you consider whether this patient's refusal to accept dialysis was an outcome of a suicidal intent, which was a result of depression?

DR. KIMMEL: Few data have associated level of depression and hematocrit in cross-sectional studies of dialysis patients. We have analyzed data from 300 patients and found no relationship between level of depressive affect

and hematocrit. Data suggest that if anemia is corrected at the beginning of dialysis, quality-of-life indicators improve as the hematocrit increases over time [74]. But no one has determined that once the hematocrit has increased to approximately 35%, further increases are associated with improvement in quality-of-life indicators.

I think this patient gave up in the middle of her treatment. I don't know whether her course represented a vicious cycle of medical illness, which increased the intensity and morbidity of depression and in turn exacerbated the medical illness (which is what I think occurred), or whether another event supervened. Perhaps this patient didn't take the antidepressant drugs that we prescribed, just as she might not have taken many of the drugs that would have improved her laboratory values. We had a fairly dramatic family meeting, where the psychiatric team decided that the patient was rational and capable of making decisions, although she was severely depressed. The psychiatric and medical teams, the family, and the patient believed that her medical status was so poor that the attempt to gain weight and recover physical function was either useless or not worth the effort, since her perceived quality of life had declined to the point where a rational person might decide to stop living. We tried to manage the discontinuation of dialysis in the hospital, where the patient was given supportive and comfort care. This approach, termed providing a "good death," can be achieved in hemodialysis patients [75].

But you raise an extremely important issue. Early data suggested that the suicide rate in dialysis patients was 100 to 400 times greater than that in the general population, and that dialysis noncompliance gave patients an easy mechanism for committing suicide [43]. I think we are more aware of the problem now. The current suicide rate in patients with ESRD is much lower than it was 20 years ago [1]. But it is possible that although the suicide rate has decreased, the withdrawal rate might be higher. Whether withdrawal is a form of suicide is a hotly debated issue. Dr. Cohen at Baystate Medical Center believes that it is not [75], but many nephrologists do perceive withdrawal as a treatment failure and suicide.

DR. JOSEPH VASSALOTTI (*Associate Professor, Mount Sinai School of Medicine, New York, New York*): Administration of α -interferon, used in the treatment of chronic viral infections and certain cancers, has been associated with depression [76]. Could you comment on the relationship between depression and immune function in dialysis patients?

DR. KIMMEL: The relationship between depression and β -endorphins and IL-1 in married African American women is compelling. The original hypothesis of our study of 300 hemodialysis patients was that relationships between psychosocial factors and physiologic markers, including levels of cortisol and selected cytokines, and

extent of T-cell function and number, would be evident. We ended up not being able to demonstrate many such relationships. The timing of analyses might be crucial in demonstrating such relationships, however.

DR. ALAN CHRISTENSEN: (*Associate Professor of Psychology and Internal Medicine, University of Iowa, Iowa City, Iowa*): If we want to understand the association of some of these psychosocial factors and outcomes, we must understand the underlying causal mechanisms. We know from some of your work and others' that dialysis patients are immunocompromised and that immune deficiency is related to earlier mortality. Depressed patients are immunocompromised, as are patients with low social support. No one has determined whether the differences we see in mortality rate as a function of depression are due to immunologic differences. How might we understand better the causal relationships that link changes in psychosocial factors with outcomes?

DR. KIMMEL: We need to perform longitudinal studies to establish causal and temporal relationships. Dr. Friend has addressed this issue, relating a decline in albumin concentration to subsequent development of depression [29]. Our own studies taught us that multiple longitudinal evaluations are important in establishing causal relationships [18]. If we could measure the stress mediators and psychosocial variables concurrently, repeatedly over time, we could begin to determine temporal relationships as well. Finally, the best way to establish causal relationships is to perform an interventional trial.

DR. RONALD FRIEND (*Professor of Psychology, State University of New York, Stony Brook, New York*): We performed a correlational observation study, not an intervention [29]. At time one, we measured serum albumin and depression using the BDI, and then we measured these parameters a second time. We therefore determined that increased depressive affect at time one predicted decreases in serum albumin concentrations across time. The reverse did not occur.

DR. JUDITH VEIS (*Attending Physician, Washington Hospital Center, Washington, D.C.*): I am concerned about the ability of social workers to focus on the psychosocial aspects of care and to improve our patients' social support and satisfaction with life. Our social workers should focus more on these aspects, rather than insurance and transportation issues, which consume a lot of their time. Have any social support interventions been successful in other chronic illnesses?

DR. KIMMEL: Although not designed for dialysis patients, some social support interventions have focused on lower socioeconomic groups [77]. Educational groups meet once each week for six weeks and deal with concrete issues such as "How one accesses health care systems," or "How one assesses employment opportunities." Although those are models for rehabilitation or employment, they provide social support and enhance

coping skills, and are therefore worth considering in patients with ESRD.

DR. ROLF PETERSON (*Professor, Department of Psychology, George Washington University, Washington, D.C.*): I think probably the best model that we have at the moment is the effect of a social support intervention in patients with breast cancer [78, 79]. Provision of social support definitely affects not only quality of life, but length of life.

DR. CHRISTENSEN: Spiegel et al performed a randomized study of provision of social support in breast cancer patients [78]. The support was provided by the group itself and was coupled with hypnosis and other kinds of activities. Those who received the social support intervention survived for about three years on average, while in the control group, patients survived a little more than half as long.

DR. GERALD DEVINS (*Professor of Psychiatry and Psychology, University of Toronto, Toronto, Ontario*): You said that you believe the patient had given up, and that her health deteriorated after that. There has been a lot of interest lately in pre-dialysis interventions. Would you speculate about these options in this patient and for renal failure patients generally?

DR. KIMMEL: This patient had progressed far beyond the stage of chronic renal insufficiency. She had survived for a long time with end-stage renal disease. Actually she had been excited about starting dialysis while staying employed at her job. But disincentives made her continued employment difficult.

In studies performed with Dr. Peterson, we compared patients with chronic renal insufficiency and patients with ESRD [80]. The level of depressive affect in a small group of patients with chronic renal insufficiency was higher than that in a group of CAPD and hemodialysis patients. The patients with chronic renal insufficiency were evaluated when they were about to have their vascular access procedures, so I think it was a time fraught with anxiety for them. Further studies must be performed on individual patients through the course of their chronic renal insufficiency and ESRD to establish patterns of adjustment. If we could ameliorate the morbidity of chronic renal insufficiency, we could lower costs and perhaps improve the outcomes of ESRD. Dr. Devins, you used an educational intervention in patients with chronic renal insufficiency and dramatically improved outcomes. Can you tell us about the study?

DR. DEVINS: We identified people at the point of transition from chronic renal insufficiency to progressive renal failure, when the serum creatinine concentration was $\sim 350 \mu\text{m/L}$ (3.9 mg/dL). We gathered 204 patients from several hospitals in Montreal and Calgary and randomized them to standard education or enhanced-education interventions. The latter was a presentation delivered one on one by a psychologist. The patients were followed

until they started dialysis. The two groups had equivalent levels of serum creatinine at baseline. The nephrologists were unaware of the enhanced-intervention class. We measured how much patients knew about renal failure and its treatment before and after our educational interventions to make sure that the intervention produced a change in knowledge. Patients in the control group who received the standard education started dialysis a median of six months after randomization. Patients in the experimental group who received enhanced education started dialysis a median of 12 months after randomization [81]. Not only did gains in knowledge correlate with extension of the pre-dialysis interval, but patients in our experimental group continued to know much more about the disease and its treatment four and one-half years after starting dialysis.

DR. KIMMEL: Can you speculate on the mediators of this extraordinarily dramatic biologic effect?

DR. DEVINS: We are concluding a second study, of 300 patients, in which we hope to replicate this phenomenon and to test some mechanisms that might account for it. One mechanism might be that increased knowledge lessens the unpredictability of the patient's illness and thus helps control distress and anxiety. This mechanism even might improve blood pressure, an important factor in mediating the progression of renal failure.

We also have been evaluating nutritional intake. Do patients alter their diets after educational intervention? The patients in our experimental group commented that they were going to change their dietary behavior as a result of the educational intervention. We also speculate that social support might be an element of the educational intervention.

DR. SUSIE Q. LEW (*Professor of Medicine, George Washington University Medical Center*): You mentioned that depressed patients can be helped with intervention. Did any patients in your study receive medication or other therapy [18]? Did their biochemical or psychosocial factors change in any way?

DR. KIMMEL: We had a stop point in this study at which patients who had very high BDI levels were evaluated by a psychiatrist for suicidal tendencies. Those patients comprised a very small number, about 15 in 300. We haven't analyzed them separately.

DR. ROBERT STAR (*National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland*): I have noticed that a community of patients forms within the dialysis unit itself. I think this is particularly true in units where the chairs are very close together. Are there variations in the prevalence of depression or other psychosocial dysfunction in different dialysis units? Could group therapy take place during dialysis? Patients are dialyzed for perhaps 15 hours a week, and that time could be used constructively.

DR. KIMMEL: I'll answer the second question first. Yes,

and again I agree with Dr. Veis, social workers should perform interventions and provide social support rather than pursue administrative chores. Dr. Friend conducted a group therapeutic intervention that was associated with a dramatic improvement in outcome [41]. There are very few data about differences in psychologic characteristics between units. Even the few studies that address differences between patients treated with peritoneal dialysis and hemodialysis show few differences and are subject to selection biases.

But we did find that unit characteristics differed according to staff in five urban dialysis units [69]. Such findings suggest that a “culture” typifies each unit. When questions regarding unit and work characteristics are submitted to staff in different units, even with very high turnover rates within three years, the results in each unit are the same. That is, results are consistent within units and between units. McClellan and colleagues have shown that differences in dialysis unit outcomes are not completely accounted for by case mix or by measured unit characteristics such as staffing or profit status [52]. So to the extent that there are interactions between patients and units, I think it is likely that we will see different outcomes based on psychosocial differences among units.

DR. DAVID REISS (*Professor of Psychiatry and Behavioral Sciences, George Washington University Medical Center*): It is important to avoid letting patients get into a subgroup and talk about their illness. That seems to interrupt a positive therapeutic flow in these groups. The goal is to help the patient and family de-emphasize the illness, to keep the illness from becoming even more disruptive of their own and their family’s lives. I do not want to give the impression that the illness should be ignored, but the illness should not always be the central focus. It is best for staff, patients, and families to avoid labels such as “diabetic family” or “renal family.” That is a bad approach in family work. In preliminary studies, we found that the more that patients can keep their psychologic distance from the dialysis unit, the better their survival (abstract; Leidner et al, *J Am Soc Nephrol*, 11:1244A, 2000). These findings, noted when other factors such as disease severity were controlled, suggest that psychosocial factors constitute an independent effect. In a chronic illness, the more that patients can be involved in a set of circumstances that maintains their active engagement in a broad span of activities, the better their adjustment to chronic illness might be. So if you intervene with patients in adjoining chairs, I think you have to be careful not to emphasize their supporting each other’s complaints about their illness. An intervention must be designed to allow patients to use each other’s strengths to promote engagement with the world outside of illness.

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