Understanding Pain and Improving Management of Sickle Cell Disease: the PiSCES Study

Wally R. Smith, MD; Viktor E. Bovbjerg, PhD, MPH; Lynne T. Penberthy, MD, MPH; Donna K. McClish, PhD; James L. Levenson, MD; John D. Roberts, MD; Karen Gil, PhD; Susan D. Roseff, MD; and Imoigele P. Aisiku, MD, MSCR

Richmond and Charlottesville, Virginia and Chapel Hill, North Carolina

Until recent decades, sickle cell disease (SCD) was associated with recurrent, disabling pain, organ failure and death in childhood or early adulthood. SCD treatment advances have now decreased pain and prolonged survival, but episodic or chronic pain may still require substantial analgesic use and frequent hospitalization for pain episodes. This pain is poorly characterized and often poorly treated. Adult patients may face barriers to comprehensive SCD care, stigmatization of their care-seeking behavior by providers and lack of family support, forcing them into maladaptive coping strategies.

The Pain in Sickle Cell Epidemiology Study (PiSCES) attempts to develop and validate a biopsychosocial model of SCD pain, pain response and healthcare utilization in a large, multisite adult cohort. PiSCES participants complete a baseline survey and six months of daily pain diaries in which they record levels of SCD-related pain and related disability and distress as well as responses to pain (e.g., medication use, hospital visits).

PiSCES will advance methods of measuring pain and pain response in SCD by better describing home-managed as well as provider-managed pain. PiSCES will assess the relative contributions of biological (disease-related), psychosocial and environmental (readiness to utilize) factors to overall pain and pain response in SCD, suggesting targets for biobehavioral interventions over time. Importantly, PiSCES will also identify "triggers" of SCD pain episodes and healthcare utilization in the moment of pain, suggesting targets for timely care that mutes pain episodes.

Key words: sickle cell disease ■ utilization ■ pain ■ epidemiology

 From the Division of Quality Health Care (Smith, chairman and associate professor; Penberthy, assistant professor), Department of Biostatistics (McClish, associate professor), Department of Psychiatry (Levenson, vice chairman, professor), Division of Hematology/Oncology (Roberts, associate director of clinical research/professor), Department of Pathology (Roseff, associate professor) and Department of Emergency Medicine (Aisiku, assistant professor), Virginia Commonwealth University, Richmond, VA; Department of Health Evaluation Sciences, University of Virginia, Charlottesville, VA (Bovbjerg, associate professor); and Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC (Gil, professor—clinical research/chairman). Send correspondence and reprint requests for *J Natl Med Assoc.* 2005;97:183–193 to: Wally R. Smith, MD, Virginia Commonwealth University, Division of Quality Health Care, Box 980306, Richmond, VA 23298; phone: (804) 828-6938; fax (804) 828-4862; e-mail: wrsmith@vcu.edu

INTRODUCTION

Sickle cell disease (SCD) is a genetic disease well-known to be manifested by sometimes profound hemolytic anemia. It may have protean, total-body manifestations. However, its primary symptomatic manifestation is acute to subacute paroxysmal episodes of ischemic pain, known as "painful crises," due to red blood cell vaso-occlusion. Crises may begin as soon as six months after birth and may continue throughout life. Because of the recurrent and chronic nature of crises, and patients' often numerous resultant encounters with the healthcare system due to crises, SCD presents a significant financial burden on patients, their families and the healthcare system.

Like many other chronic diseases, SCD is manifested by exacerbations and remissions, resulting ultimately in chronic organ failure and premature death. But unlike many other diseases, the etiology of SCD is a genetically mediated production of one or more aberrant hemoglobins. These aberrant hemoglobins, including sickle hemoglobin (Hb S), are inherited as an autosomal recessive trait. Thus, the most severe form of SCD, homozygous sickle cell anemia (Hb SS), occurs when Hb S is inherited from both parents. In the United States, this happens in about one in 375 African-American births.[1-3]

Since African Americans are on average poorer, have more limited access to healthcare services and die sooner than Caucasians,[4] understanding health services for SCD may yield unique insights into the relationship between symptoms and illness on one hand, and access, quality, healthcare utilization and costs for the poor and underserved on the other. Pain is the primary symptomatic manifestation of SCD and the most common reason for presentation to a medical provider.[5] However, pain, manifestations of pain and proper treatment of pain in adults with SCD, both acutely and over time, are all poorly understood.

A RESEARCH AGENDA FOR BIOBEHAVIORAL PAIN MANAGEMENT IN SICKLE CELL DISEASE

Understanding the New Epidemic of Sickle Cell Disease

An important reason for the poor understanding of pain in SCD is that adult SCD is a new "epidemic," poorly described epidemiologically. In 1970, the estimated median survival for patients with SCD was 20 years, so treating the pain of SCD was primarily left to those caring for children. Fortunately, with important advances, such as prophylactic penicillin for children, mortality rates in children have drastically decreased.[6] In one study between 1968 and 1992, rates decreased by 41% for one-to-four-year-olds, by 47% for five-to-nine-year-olds and by 53% for 10-to-14-year-olds.[7] By the 1980s, the federally funded Cooperative Study of SCD (CSSCD)[8] found median survival was into the fourth decade for homozygous patients; that patients with doubly heterozygous forms of SCD, such as Hb SC, fared even better; that higher hematocrit was associated with more pain; and that higher percentages of persistent fetal hemoglobin (Hb F) were associated with less severe disease and longevity.

Median SCD survival now stretches well into the fourth or fifth decade.[9] This improved survival has created the relatively new phenomenon of adults with chronic SCD. It has also resulted in adult medical professionals treating pain in a disease for which they have limited training and experience. A third of patients in one study reported inadequate pain relief in the hospital, and nearly half reported long delays in being treated.[10]

There is very little evidence-based data on which to base treatment for the growing population of adults with SCD. Available epidemiologic data focuses on the frequency of pain resulting in emergency department (ED) use and hospitalizations for crisis pain in SCD, and few investigations have characterized the manifestations of SCD outside of traditional healthcare facilities, or how patients respond to SCD pain other than by visiting their physician. It is unknown what percent of patients treat their crises at home versus what percent utilize various healthcare professionals.

Understanding Measures of Pain in Sickle Cell Disease

Another important reason for the poor understanding of pain in SCD is that, other than healthcare utilization, measures of pain in SCD are poorly developed. Because there is not a trusted, widely accepted pain measure in SCD that allows communication between physicians and patients, adults in particular sense distrust when, during a crisis, they describe to caregivers the presence, intensity, lack of relief or recurrence of their pain. Unlike ischemia due to myocardial infarction or peripheral vascular disease, to date, ischemic pain due to red blood cell vaso-occlusion has no observable clinical correlates. Physicians cannot depend on physical exam or laboratory means to validate subjective descriptions of painful crises. This may often lead to physician frustration and skepticism of patient reports of pain as well as both physician and patient dissatisfaction, particularly when urgent care is provided by a physician who has never met the patient.

For this reason, we believe the research agenda will only be advanced by measuring the variability in *pain* in SCD on one hand, and *response to pain* on the other, simultaneously and independently. This has not been done in previous large-scale studies, which have defined and quantified pain crises as episodes of healthcare.

Healthcare utilization as a proxy measure of pain in SCD is insufficient in several ways. First, bias could result, because counts of utilization may underestimate the true crisis frequency, by excluding crises that last only a few hours and may be self-treated. Anecdotally, many patients tell clinicians they loathe, and therefore avoid, coming to busy EDs for a painful crisis and treat even severe pain crises at home. Second, bias could result because counts of utilization may overestimate the true crisis frequency. Multiple visits (e.g., to the ED) may occur during a single painful crisis, or utilization not due to crisis pain may occur. In the CSSCD, utilization episodes that occurred within a two-week period were counted as one episode. Seventy-four patients were excluded from the analyses, because they had "more than 10 closely spaced episodes," making it difficult to determine an accurate pain rate. Further, nearly 40% of individuals did not utilize healthcare for a crisis during a three-year period.[11]

Third, distortion and bias could result because other factors besides pain may independently influence healthcare utilization due to crises, distorting the response to an underlying crisis. For example, managed care cost- and utilization-containment pressures are driving down utilization. This has muddied the relationship between utilization rates and need for care.

Thus, to better understand pain and the response to pain in SCD, studies that measure pain and utilization using independent measures are needed. These studies should compare pain-based crisis measures with utilization-based crisis measures. They should demonstrate the percentage of home-managed crises. They should offer a method of discounting or adjusting for background, chronic pain

when counting acute crises. Last, they should propose and refine a biologically based, reproducible means of comparing SCD pain across studies and between patients that could be used to determine the relative effectiveness of SCD pain interventions.

Understanding Variables that Explain Pain in Sickle Cell Disease

To date, only biological and demographic variables have been well-shown to explain pain variation

Table 1. Variables Measured in PiSCES

Category	Variables	Definition(s)	Measurement Instrument(s)
Disease-Related Variables	Demographic	Age, gender	Self-report
	Genotype	SS, SC, Sß$^+$thal, Sß^{0}thal, Other, % Hb F	Hemoglobin electrophoresis
	Hematologic variables	Hemoglobin, reticulocyte count, white cell count, platelet count	Coulter counter, peripheral smear
	Pain and pain response	Pain intensity (0–9), pain-related distress (0–9), pain-related interference (0–9), pain relief (0–9), subjective report in crisis" (yes/no), pain location (front/back body locator charts), analgesic use (names of drugs, number of pills), various healthcare utilization (yes/no)	Daily pain diary
	Hydroxyurea use	Dose, length of therapy, benefit	Self-report from survey
	Treatment	Usual opiate and opiate dose, other medications including antidepressants	Self-report from survey
	Renal failure	Creatinine >1.4 mg/dL	Serum chemistries
	Proteinuria	4+, or >300 mg/dL	Urine dipstick analysis, protein content
Psychosocial Variables	Stress	Sickle cell disease-specific stressors	Sickle Cell Disease Stress Questionnaire
	Mental health status	Score signifying anxiety and/or depression	Prime-MD Patient Health Questionnaire
	Coping behaviors	Positive coping attempts, negative coping styles	Coping Strategies Questionnaire, Chronic Pain Coping Inventory
	Social interactions	Low support from significant others and friends, negative social interactions	Multidimensional Scale of Perceived Social Support, Test of Negative Social Exchange
	Cognitive dysfunction	Cognitive score <27 (excludes from diary collection)	Mini-Mental status exam
	Functional status	Fair or poor scale scores	Medical Outcomes Study SF-36
	Socioeconomic status	Lower Index scores, income <$20,000	Hollingshead's two factor index, self-report from survey
Readiness (to utilize) Variables	Access	Low insurance class, no primary care provider, in managed care, poor transportation, long distance to care	Self-report from survey
	Perceived threat from disease	High scale score	RAND Health Outlook questionnaire
	Perceived benefits/ barriers to care	Scale score high benefit, low barriers	RAND Medical Care opinion questionnaire

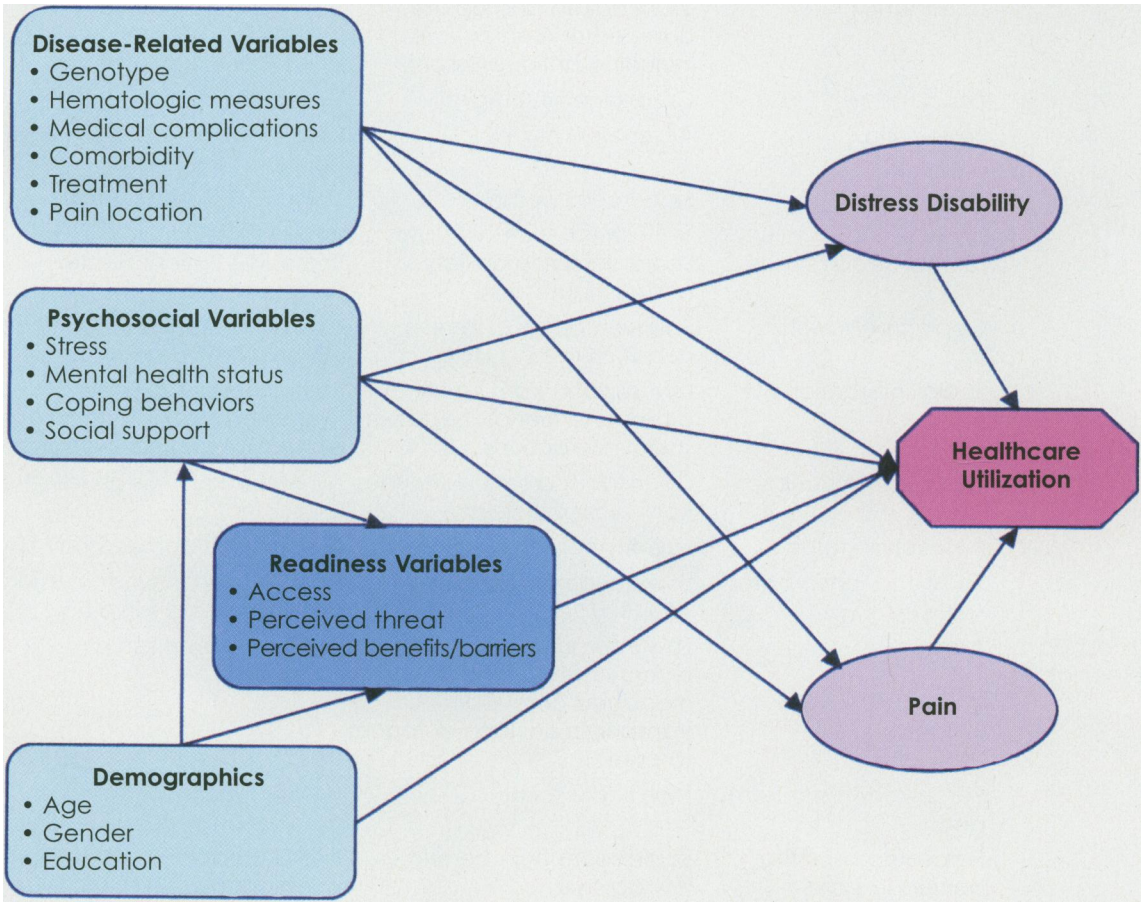
in SCD. These variables explain only part of the observed variance in crisis frequency.[12] Only now is knowledge emerging about how other variables may influence differences in pain responses. It would be reasonable to test whether SCD, like many other chronic diseases, conforms to Andersen's healthcare utilization model[13] or the biopsychosocial model of illness popularized by Engel[14] and others. Measures of factors from the psychosocial and environmental domain may help predict patient pain and response to pain. Were important predictor variables found, it would then be reasonable to test interventions that attempt to alter these predictors.

While a number of studies have explored psychosocial determinants of utilization in SCD,[15-18] only a few biobehavioral interventions have attempted to alter pain and utilization in SCD. Vichinsky and others tested a multifaceted, intense intervention to improve pain management of sickle cell patients through counseling and carefully monitored opiate prescribing. This program reduced ED visits for the 10 patients who suffered chronic pain from 386 to 164, and reduced admissions from 41 to 23 during sequential six-month periods. It is unclear which element(s) of this intervention was critical or how opiate dose influenced utilization.[19]

Gil showed that, at three-month follow-up of a randomized trial, a pain-coping skills intervention in African-American adults with SCD lowered pain perceptions from a laboratory-induced pain stimulus and significantly increased coping attempts. Using prospective daily pain diaries, this study found that on pain days when subjects used coping strategies, they had less major healthcare contacts than on pain days when they did not use coping strategies.[20]

Other interventions have met with limited success. Gil showed earlier that a brief training in cognitive coping skills resulted in increased coping attempts, decreased negative thinking and lower tendency to report pain during laboratory-induced noxious stimulation.[21] Kaslow reported a family intervention in children with some success.[22] Dinges used self-hypnosis as an adjunct to traditional modes of treatment. Self-hypnosis significantly reduced pain days. Both the proportion of "bad sleep" nights and the use of pain medications also decreased significantly during the self-hypnosis treatment phase.[23]

Figure 1. Draft conceptual explanatory model of pain and utilization over time in sickle cell disease.

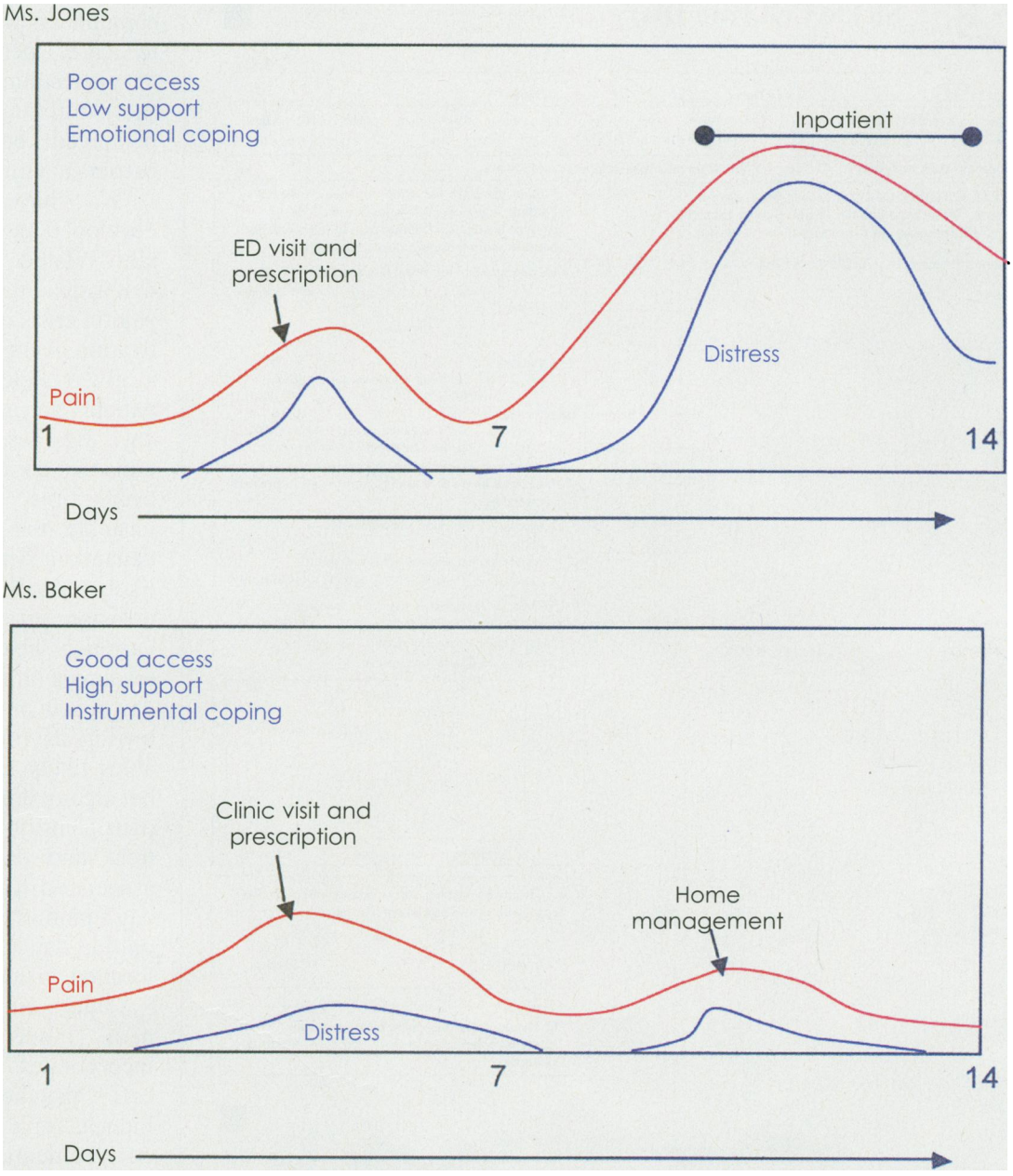


A Conceptual Model of Pain and Response to Pain in Sickle Cell Disease

Our emerging SCD research program seeks to approach SCD and its treatment at the genetic, biological, clinical, personal and healthcare system levels. We have developed a model of pain and response to pain in SCD (Figure 1) to serve as a framework on which to study SCD pain, the most common clinical manifestation of SCD in adults. The model is informed by a combination of Andersen's and Engel's above models, by the Health Belief Model[24,25] and by empirical research to date on pain and response to pain in SCD.

Engel's model suggests that biological, psychological and social factors all interact to produce health and/or illness. Andersen's healthcare utilization model suggests that all of these factors interact to produce variability in healthcare utilization. The Health Belief Model proposes that attitudes reflecting readiness to act determine healthcare behaviors

Figure 2. Draft conceptual explanatory model of daily pain, distress, and pain response in sickle cell disease in two patients.



when cues to take action are present (e.g., pain). We have used the framework of the Health Belief Model to review studies relating SCD utilization to psychosocial variables.[26]

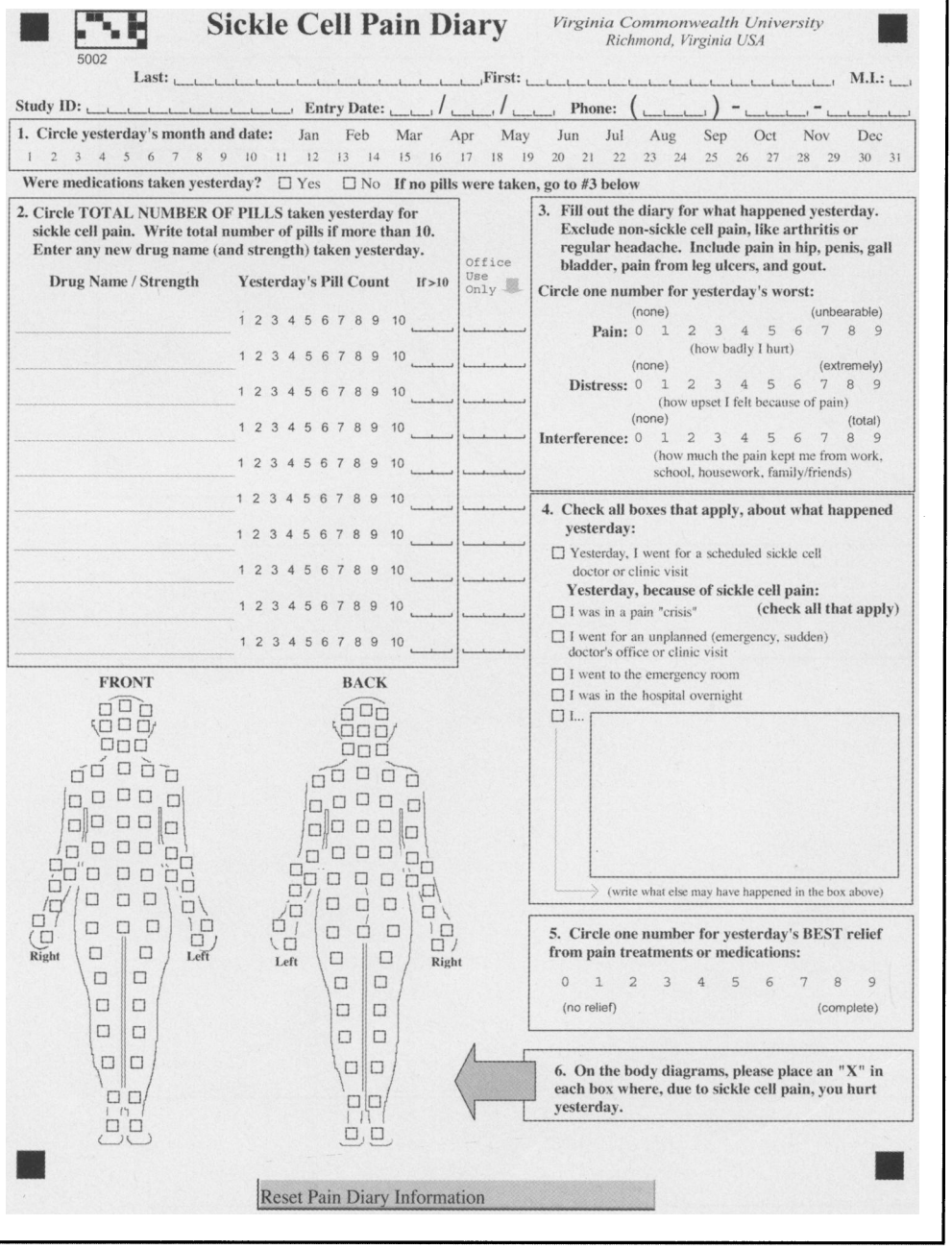
Our model hypothesizes that several classes of variables act in concert over time to explain pain and response to pain (the physical response of disability, the emotional response of distress and the coping response of healthcare utilization) in SCD. These predictor variables may cause or relieve pain, which in turn may provoke disability, distress and/or increases or decreases in utilization. These predictor variables may also directly cause utilization. Alternatively or additionally, these predictor variables may influence the relationship between pain and utilization, as may disability and distress.

Figure 1 shows that psychosocial variables in our model include stress, mental health status, coping behaviors and social support. Demographic variables include age and gender. Disease-related variables include sickle genotype, hematocrit, percent hemoglobin F, pain location, sickle complications and comorbidities. Treatment variables include hydroxyurea, which not only reduces the frequency of painful crises[27] but also lowers sickle cell mortality;[28] usual opiate and opiate dose; and other medications, including antidepressants. Readiness (to utilize care) variables include various components of access to care, perceived threats resulting from (not) utilizing, and perceived benefits/barriers to utilization.

We have also developed an important related model that instead models a painful crisis or a utilization event within a given sickle cell patient on a given day. Besides static traits that do not vary over time, many unstable, temporally dependent variables likely influence the decision to utilize various healthcare resources on a given day of pain or the following day(s). Variables likely include, but are not limited to, pain intensity, the distress and disability associated with that day's pain, treatment on that day and pain location on that day.

Thus, our daily pain model also incorporates biological, psychosocial, interpersonal and environmental variables to predict pain

Figure 3



and pain response. In general, we expect pain to be associated with distress but for the relationship and the response to be modified by other variables. For instance, equivalent pain in persons with effective coping strategies, high levels of family social support and adequate healthcare access may result in less distress and lower likelihood of ED or inpatient care, compared to those with ineffective coping, low support and poor access to regular care. Similarly, we expect that early, rapid and effective coping with pain (e.g., use of nonprescription analgesia, scheduling an urgent clinic visit, obtaining prescription analgesia) will blunt increases in pain and also reduce distress, both through pain reduction and through enhanced mental well-being resulting from effective coping and pain response.

Figure 2 illustrates, through two hypothetical examples, some of the expected temporal relationships among pain, distress due to pain, medication use and healthcare utilization within the context of personal, interpersonal and environmental factors. Ms. Jones, for instance, experiences two pain episodes within the illustrated 14 days. She has poor access to healthcare (e.g., no insurance, no primary care provider), little support from friends and family (e.g., for transportation), and a history of coping with pain that focuses on emotions rather than on action. On about day three, her pain increases steadily, followed by increased distress. Without effective support, coping or access to primary care, her pain and distress lead to the ED, to which she is transported by a cousin who happens to be visiting. Her pain subsides after a prescription analgesic, but Ms. Jones does not keep a follow-up outpatient clinic appointment, since she cannot afford to pay out of pocket. On day seven, her pain increases again. With no way to get to the hospital, her pain and distress escalate rapidly, until she is compelled to seek care, at which time she is admitted in a severe pain episode.

Another patient, Ms. Baker, also experiences two periods of elevated SCD pain during the two weeks. However, during the initial episode, Ms. Baker initiates a round of nonprescription pain relief as soon as the pain begins and makes a clinic appointment, to which she is taken by her spouse, as the pain increases. At the visit, analgesia is prescribed, which successfully stems the pain. Although her pain is similar to that of Ms. Jones's initial episode, her more effective coping and support reduces her distress. During the second episode, Ms. Baker again recognizes the pain increase. Because she has been prescribed analgesia to take as her pain warrants, she is able to stem the pain without a clinic visit. Though her distress increases initially, the combination of effective analgesia, support and coping quickly reduces distress.

Summary of Research Agenda

In summary, the research agenda for better understanding and managing pain in SCD can be served best first by gaining a better understanding of the prevalence of disease and the frequency of pain in adults with SCD. Second, it is critical to distinguish pain in SCD from healthcare utilization and other responses to pain in SCD. Patients, physicians, researchers, planners and policy makers would all benefit from this distinction. Third, a measure of pain that is acceptable, available and useful to patients and physicians would, in particular, enhance communication between physicians and patients. Enhanced communication would be a first important step to a group of underserved patients receiving better pain relief. Fourth, it is critical to determine various kinds of predictors of pain and of response to pain in SCD. Treatment could be improved if new, potentially mutable variables were found that explained pain variability or variability in response to pain.

Pain in Sickle Cell Epidemiology Study (PiSCES)

As a step in advancing this research agenda, we designed and implemented the Pain in Sickle Cell Epidemiology Study (PiSCES). PiSCES is a longitudinal, etiologic study of pain in SCD, with particular emphasis on potentially mutable etiologic, nonbiological variables. It is also a methodological study of the relationship between pain and the response to pain in SCD. Using the biopsychosocial model of Figure 1, PiSCES investigators seek to understand correlates of pain and healthcare resource utilization in adult sickle cell patients and to look for targets for interventions to improve pain and optimize that utilization. We aim to:

- Measure the temporal patterns of pain and response to pain in SCD, including home management.
- Examine the relative importance of biological, psychological and socioenvironmental variables in explaining the course of pain, pain dysfunction and response to treatment for pain in SCD.
- Elucidate emotions and emotional disturbances, in addition to depression, (e.g., anger, fear, anxiety) which are associated with SCD, and determine how these emotions modify the experience of pain and the response to pain.

To accomplish these aims, we are building multivariate models to explain both within-patient and between-patient differences in pain and response to pain. Table 1 lists the outcome and predictor variables for PiSCES. Outcomes variables are operationalized using self-reported pain diaries (described below), collected daily over six months. Predictor variables are

operationalized using individual variables and summary scores of scales, obtained from primary data collection using validated instruments. Predictor variables are organized into the three classes discussed in our conceptual model: demographic and disease-related (biological) variables, psychosocial variables and readiness-to-utilize (environmental) variables.

METHODS OF PiSCES

Design, Inclusion Criteria

The study is a prospective cohort of primarily adults in Virginia with SCD. We are assembling the cohort from various sources. We are studying each patient's pain and response to pain for six months. Patients aged 16 or older with SCD living in any cities or counties in Virginia are eligible to enroll. The majority of the patients have come from the Richmond and Tidewater areas, as these areas have the highest population of African Americans. Pediatric patients less than 16 years of age are excluded, because they are suspected to differ substantially from adults in both their clinical course and healthcare utilization patterns. Patients on chronic exchange transfusion are excluded because of effects on hematologic factors and pain. Patients not oriented to person, place and time (mini-mental status score <27); or unable to answer questions by telephone are excluded, because of inability to comply with diary completion.

Recruitment, Enrollment and Compensation

The first of several sources of recruitment is a network of community sites that are members of the Statewide Sickle Cell Chapters of Virginia Inc. The second source is the network of clinics, hospitals and EDs—including our own—around Virginia. The third source is referrals from patients, health departments, social services offices and home management care providers. The fourth source is direct recruiting via health fairs, universities, targeted mailings (including physician offices), and radio public service announcements. Of an estimated 1,000 SCD patients in the state of Virginia, over 300 eligible participants have been recruited, with enrollment scheduled to close during the fall of 2004.

Patients identified as potentially eligible for the study are invited and scheduled for an enrollment visit, at which informed consent and baseline data are obtained. The enrollment visit is conducted at one of two community sites, or one of three geographically dispersed sickle cell clinics at two academic medical centers—whichever is most convenient for the patient.

Patients are compensated for their participation as follows: $10 for entry and exit visits; $1 for each completed diary during months one to four of the patient's enrollment; and $1.50 per day for diaries completed during months five and six. Compensation only occurs if the diaries are postmarked or received within three business days.

Data Collection and Management, Retention

We collect an entry survey, perform one venipuncture for blood analysis and collect urine for urinalysis at entry. Urine and serum collection are performed by a central, CLIA-certified laboratory. We repeat this process at exit, save the mini-mental status exam. We collect a pain diary every day for six months, inpatient healthcare utilization data from the state hospital discharge file, and if applicable, cause of death data from the Virginia Health Department.

The entry survey consists of baseline identifying and demographic data, and measurement of explanatory and predictor variables (Table 1). It takes approximately 40–50 minutes to complete.

After patients complete the entry survey, they are trained to complete an initial pain diary. They then enter a period of training and monitoring for up to two weeks. Consistency of receipt of mailed daily diaries is recorded daily on a grid in a tracking database. Returned pain diaries are reviewed closely by research assistants for completeness and face validity. Patients who fail to complete diaries consistently or appropriately by visual inspection are retrained. Patients are contacted if their diaries are three or more days late or for any information missing on the diaries. When necessary, data have been collected in person by study staff during participant inpatient hospital stays.

Records of all contacts made are maintained in a tracking log in the database. In addition, we mail monthly postcards to encourage all patients to continue sending diaries on a daily basis. Every month, patients are compensated based on the number of diaries sent. Along with their check, a month's supply of diaries and envelopes with reminder instructions for completing and mailing diaries are sent to active patients.

No patient is dropped from the study for failure to complete diaries appropriately. We are retaining in the sample all enrolled patients who complete a baseline survey. We also accept and record all patients' diary data, regardless of its timeliness and the patient's compliance status. We, however, mark all late diaries as such and are conducting comparative analysis of late vs. timely diaries to determine the effect of timeliness on diary reporting.

However, patients are classified by compliance with diary submission. Specifically, patients whose timely diary submission rate is satisfactory during each of the six months of the study are referred to as compliant

patients. In contrast, we refer to recruited, noncompliant patients as those who complete only a baseline survey and one month (30) or fewer diaries, and to patients who complete greater than 30 daily diaries but are not fully compliant as partially compliant patients. We define attrition not to mean that we cannot use a given patient in any of the planned outcome analyses, but rather that we lack data to use a given patient in some of the planned outcome analyses.

At the end of six months of participation in the study, patients are contacted via telephone or mail to set up an appointment to complete the exit survey and lab studies.

Pain Diary

We developed the pain diary for PiSCES to reflect multiple descriptive aspects of pain; response to pain; and the multiple, temporally variable factors that affect pain in SCD. The pain diary (Figure 3) asks participants to recall the past 24 hours, reflecting on their worst pain intensity, their response to pain (i.e., distress, disability, healthcare utilization and type of utilization), their use of opiate and nonopiate analgesics, and their bodily sites of pain. Participants record their pain, distress and disability on a 0–9 ordinal scale. Separate boxes record whether participants made a call for a prescription refill, used nonopiate analgesics, opiate analgesics, made a scheduled or unscheduled visit to a physician's office or clinic, or visited an ED or hospital. Open-ended questions allow patients to write in other methods of pain relief and behavior modification techniques. Front and back body locator charts allow a detailed notation of pain sites beyond central or peripheral categorization. Pain sites are indicated using an "X" on as many site blocks as apply, on a diagram of the front and back drawing of a body.

Analyses

All PiSCES analyses will be hypothesis driven, based on our conceptual model of SCD, previous exploratory work and other scientifically plausible underpinnings. Major analyses will consist of both between-patient and within-patient predictive models using multivariable regression. Both the within-patient and between-patient regression models will predict pain and various types of utilization episodes, including nonopiate analgesic use, opiate use, office visits, ED visits and hospitalization. Within-patient models will determine within-patient "triggers" of painful episodes, hospitalizations, ED visits and other utilization events.

The between-patient models will predict mean or median pain, distress and disability, the number of painful episodes and the percentage of each patient's crises that result in various types of utilization. We will enter the classes of predictor variables in Table 1 simultaneously rather than progressively.

One series of models will predict mean daily pain during the approximately 188 days of observation. The second series of models will predict the number of crises each patient experiences during six months. Pain intensity ratings and diary data will be transformed into pain episode counts. We will explore several definitions of an episode (crisis). The first and foremost definition will be one or more consecutive days that the box, "I was in a crisis," is checked on a daily diary. The number of painful crises will be defined as the number of groups of consecutive days that box is checked. The length of a given painful crisis will be the number of consecutive days the box is checked.

For the second definition of a crisis, we will use a mathematical formula to obtain individualized pain thresholds that define a painful episode for each patient based on their daily pain intensity ratings. Each patient's threshold will be defined as $M+\sqrt{}$ IQR, or their median pain intensity for the six months, plus the square root of the interquartile range of their pain for the six months. The threshold definition takes into account differences in pain tolerance and sensitivity as well as differences in pain stimuli. Several pain location patterns may also emerge from descriptive analyses, and though they are outcomes themselves, may also be predictive of pain response. We will explore whether locational patterns can define a "crisis."

To predict response to pain, we will first build a series of predictive models to explain the outcome variable "number of utilization episodes." A utilization episode will be defined as a period of consecutive days in which each daily diary has indicated that an unplanned visit to an MD, ED visit or hospitalization has occurred. (An alternative utilization episode might possible be more narrowly defined to only include ED visit or hospitalization, or expanded to include days when opiates have been used.) Next, we will predict the utilization percentage, or the percentage of each patient's painful crises that result in a given type of utilization. (100% x [number of patient's painful crises with associated utilization/total number of patient's painful crises]). To measure effects of pain location on models of these outcomes, we will enter as predictor variables any discovered patterns of location from the body locator chart.

To conduct within-patient analyses, we will determine within-patient "triggers" of painful episodes, hospitalizations, ED visits and other utilization events by treating each event as an outcome, using a nested case-crossover design.[29] Analysis will consist of conditional logistic regression to relate potential triggers to the event. Separate analyses will be performed for each dependent variable, including painful episodes,

ED use, hospital use and other pain-related utilization. Independent, "trigger" variables will include (change in) pain intensity, pain location, number of pain sites, disability, distress, treatment and adjunctive relief measures 1–3 days prior to the index event or control day. One important clinical application of the result will be the ability to predict crises in ambulatory patients and perhaps intervene to abort them.

Importance and Impact: Advancing the Research Agenda

Results of PiSCES will very likely stimulate additional etiologic questions regarding pain in SCD that require further study. For example, if results of our within-patient, case-crossover study suggest that pain and subjective pain crises are inherently predictable using diary data from the days preceding the crisis, questions may arise regarding subjective circumstances preceding each patient's crisis.

Other interesting questions arising from clinical anecdotes include: Were patients aware hours or days ahead of time that they were going to have a crisis, similar to the "aura" preceding a grand mal seizure? If not, might they have become aware by more detailed self-observation or by attending to their pain diary scores? If patients were aware of an impending crisis, did they take measures to abort or prevent the crisis, such as calling their physician for pre-emptive intravenous fluids or pain relief, or did they pursue a complementary and alternative medicine intervention, such as a heating pad, warm baths or massage, or other strategies to alleviate their pain, in addition to their home medication?

Further, if results of our case-crossover studies suggest, as we hypothesize, that medication, ED and hospital utilization occur for reasons other than severity of that or the preceding days' pain, distress or disability, then further case-crossover studies or qualitative reason-for-visit information could be illuminating. For example, why did patients choose to go to the ED rather than stay home and manage their pain? Applying our conceptual model in Figure 1 suggests that linking such qualitative data to our already planned quantitative diary data might be more informative than the quantitative data alone. In fact, patients may utilize different particular instrumental coping strategies on a given day. Further, acutely changing access issues, such as availability of childcare, job flexibility and transportation to care, may influence whether utilization occurs on a given day. Daily diaries may need to be further augmented to allow reporting of daily changes in these potential predictors.

In addition to spurring further etiologic studies, results may prove useful to develop multifactorial intervention studies. Intervention studies would be warranted if results suggested that several of the collected mutable variables are important predictors in our multivariate predictive models of pain and utilization. An intervention study could, for example, compare multifactorial case management conducted only at healthcare sites to home health-case management similar to that of current geriatric home healthcare programs.

In summary, we believe PiSCES will advance knowledge of the etiology and influences on pain and pain response in SCD. By revealing potentially mutable explanatory variables, the study's results may identify targets of biobehavioral treatment interventions. The study will also advance methods of measuring pain and pain response in SCD. By measuring pain directly, simultaneously with utilization, our results may validate or invalidate prior studies. Results of this study can be used to improve diagnosis and treatment of sickle cell pain, to dispel myths about sickle cell pain and those who endure it, and to improve the quality of life for patients with SCD.

REFERENCES

1. Motulsky AG. Frequency of sickling disorders in U.S. blacks. *N Engl J Med.* 1973;288:31.

2. Meany FJ, Riggle SM. Newborn screening report, 1990. Austin, TX: Council of Regional Networks for Genetic Services; 1992.

3. SCD Guideline Panel. SCD: Screening, Diagnosis, Management and Counseling in Newborns and Infants. Clinical Practice Guideline no. 6. AHCPR Pub. No. 93-0562. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. April 1993.

4. Smedley BD, Stith AY, Nelson AR, eds. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Institute of Medicine, Board on Health Science Policy. 2002; National Academy Press, Washington, DC.

5. Gallaway S.et al. Sickle cell anemia—a review. *J Emerg Med.* 1988;6:213-226.

6. Scott RB. Health care priority and sickle cell anemia: special communication. *JAMA.* 1970;214:731-734.

7. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: a randomized trial. *N Engl J Med.* 1986; 314:1593-1599.

8. Lee A, Thomas P, Cupidore L, et al. Improved survival in homozygous sickle cell disease: lessons from a cohort study. Brit Med J 1995;311:1600-1602.

9. Davis H, Schoendorf KC, Gergen PJ, et al. National trends in the mortality of children with sickle cell disease, 1968 through 1992. *Am J Public Health.* 1997;87:1317-1322.

10. Gaston MH, Rosse W. The cooperative study of sickle cell disease: review of study design and objectives. *Am J Pediatr Hematol Oncol.* 1982;4:197-200.

11. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in SCD. Life expectancy and risk factors for early death. *N Engl J Med.* 1994;330:1639-1644.

12. Wierenga KJJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. *Lancet.* 2001;357:680-683.

13. Murray N, May A. Painful crises in sickle cell disease—patients' perspectives. *BMJ.* 1988;297:452-454.

14. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in SCD. Rates and risk factors. *N Engl J Med.* 1991;325:11-16.

15. Baum K, Dunn DT, Maude GH, et al. The painful crisis of homozygous sickle cell disease: a study of risk factors. *Arch Intern Med.* 1987;147:1231-1234.

16. Andersen R. A behavioral model of families' use of health services: HSA studies, University of Chicago Research Series No. 25, 1968.

17. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science.* 1977;196:129-136.

18. Wison Schaeffer JJ, Gil KM, Burchinal M, et al. Depression, disease severity and sickle cell disease. *J Behav Med.* 1999;22:115-126.

19. Grant MM, Gil KM, Floyd MY, et al. Depression and functioning in relation to health care use in sickle cell disease. *Ann Behav Med.* 2000;22:149-57.

20. Gil KM, Carson JW, Porter LS, et al. Daily stress and mood and their association with pain, healthcare use, and school activity in adolescents with sickle cell disease. *J Pediatr Psychol.* 2003;28:363-373.

21. Gil KM, Carson JW, Porter LS, et al. Daily mood and stress predict pain, health care use and work activity in African-American adults with sickle-cell disease. *Health Psychol.* 2004;23:267-274.

22. Vichinsky E, Johnson CS, Lubin BH. Multidisciplinary approach to pain management in SCD. *Pediatrics.* 1989;84:500-508.

23. Gil KM, Carson JW, Sedway JA, et al. Follow-up of coping skills training in adults with sickle cell disease: analysis of daily pain and coping practice diaries. *Health Psychol.* 2000;19:85-90.

24. Gil K, Wilson J, Edens J, et al. Effects of cognitive coping skills training on coping strategies and experimental pain sensitivity in African-American adults with SCD. *Health Psychol.* 1996;15:3-10.

25. Kaslow NJ, Collins MH, Loundy MR, et al. Empirically validated family interventions for pediatric psychology: SCD as an exemplar. *J Pediatric Psychol.* 1997;22:213-227.

26. Dinges DF, Whitehouse WG, Orne EC, et al. Self-hypnosis training as an adjunctive treatment in the management of pain associated with SCD. *Int J Clin Exp Hypn.* 1997;45:417-432.

27. Becker MH. The Health Belief Model and personal health behavior. *Health Education Monographs.* 1974;2:409-419.

28. Chen M, Land K. Testing the health belief model: LISREL analysis of alternative models of causal relationships between health beliefs and preventive dental behavior. *Soc Psych Quarterly.* 1986;49:45-60.

29. Reese FL, Smith WR. Psychosocial determinants of health care utilization in SCD patients. *Ann Behav Med.* 1997;19:171-178.

30. Charache S, Terrin ML, Moore RD, et al. Investigators of the Multicenter Study of Hydroxyurea and Bonds DR. Effect of hydroxyurea on frequency of painful crises in sickle cell anemia. *N Engl J Med.* 1995;332:1317-1322.

31. Steinberg MH, Barton F, Castro O, et al. Effect of Hydroxyurea on Mortality and Morbidity in Adult Sickle Cell Anemia: Risks and Benefits Up to Nine Years of Treatment. *JAMA.* 2003;289:1645-1651.

32. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol.* 1991;133:144-153. ■