Family Practice Grand Rounds

The Undiagnosed Patient

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DR. CHARLES E. DRISCOLL *(Assistant Professor, Department of Family Practice)*: I would like to introduce Dr. William Clements, who is serving a dual role as a discussant and as a patient without a diagnosis. I would also like to welcome our guest, Mr. Don Smith, who will share with us his perceptions of what it is like to be a hospitalized patient without a diagnosis. His family is seated in the audience.

Mr. Smith, who was healthy and productive, suddenly developed a serious and incapacitating illness. Before he could understand what was going on, his physician suggested hospitalization, and he found himself 30 miles from home, no longer able to control his own life.

The illness Mr. Smith experienced is a great imitator that can present with a variety of symptoms. We are not going to focus on the illness, lupus erythematosus, although I will tell you a little about it so that you can understand the clinical setting. Once the illness is defined, we lose the "excitement" of the mystery. Nevertheless, I will give you some basic information about systemic lupus and how it presented in this case so that you can understand the problem we had. Then we will discuss what it is like to cope with the stresses of being hospitalized for an undiagnosed illness—having many tests, and having a number of important but unresolvable things on your mind.

Table 1 compares Mr. Smith's findings in the right-hand column with figures on the left from a large series of patients.[1] He entered the hospital with stiff and swollen wrists, his left knee and right elbow were swollen, and he had pain and stiffness in his back. He had chills, and his admission temperature was 38.9° C. Skin eruptions were also present on admission. A violet-colored plaque was found on the flexor surfaces of both wrists, and there were splinter hemorrhages under most nails. The characteristic malar "butterfly rash" of lupus was never observed, but Mr. Smith did experience the abrupt onset of a bright violaceous rash that covered his entire back and is still present two months later. Lymphadenopathy observed in Mr. Smith involved nodes in his neck, primarily a single large rubbery node in the posterior auricular chain. Biopsy, culture, and tissue studies on the node were unremarkable. There were no abnormalities in the blood urea nitrogen, creatinine, or urine analysis.

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Table 1. Clinical Findings of Systemic Lupus Erythematosus

Manifestation	Cumulative Percentage*	This Patient
Arthritis/arthralgia	92	+ Wrists, knee, back, elbow
Fever	84	+ Chills, temperature 38.9°C
Skin eruptions	72	+ Wrists, black, hands
Lymphadenopathy	59	+ Posterior cervical
Renal involvement	53	− Normal uric acid, blood urea nitrogen, creatinine
Anorexia	53	+ Weight loss, anorexia
Raynaud's phenomenon	50	+ Witnessed in hospital
Cardiopulmonary	50	+ Pericarditis, endocarditis, rales
Central nervous system involvement	26	+ Foot "went to sleep"
Hepatomegaly	25	+ 4-cm enlargement

*Adapted from Mannik and Gilliland[1]

However, Mr. Smith was experiencing anorexia, nausea, vomiting, and was "generally feeling bad" when he came into the hospital. He experienced an episode of Raynaud's phenomenon in the hospital.

Mr. Smith, would you share what you told me just a few minutes ago about your fishing trip?

MR. DON SMITH: Normally, I can take cold real well. The temperature has to be about 10 below zero before I put gloves on. I was out fishing the other day when the temperature was 50° F, and I got so cold that my hands turned pure white and got to tingling. I had to quit.

DR. DRISCOLL: You correctly recognized that as being another occurrence of Raynaud's phenomenon.

Cardiopulmonary involvement in this case included pericarditis and pericardial effusion. The patient had a changing heart murmur that puzzled us the entire time he was in the hospital. He had endocarditis with a murmur that was definitely valvular in origin, and he had bilateral rales in his chest with small pleural effusions.

You can see from Table 1 that central nervous system involvement occurs in 26 percent of the cases, but the literature reports that it is rare to have peripheral neural involvement. The day after Mr. Smith went home from the hospital, still without a definite diagnosis, his foot "went to sleep." A week or two ago it was unchanged. Is it better yet?

MR. SMITH: Just the toes are still asleep.

DR. DRISCOLL: So, we were able to identify all of these clinical findings very clearly, including an enlarged liver. Retrospectively, the findings fit lupus very well. We were not treating Mr. Smith for lupus, however; we were treating him for bacterial endocarditis. Nine out of 10 of his findings can also be present in that disease. We were most concerned about the changing heart murmur and the pericardial effusion, so we began penicillin therapy as a lifesaving measure before all the data needed to make a solid diagnosis were available.

Now let's move to the laboratory studies that were done to try to come up with a diagnosis. Table 2 compares the laboratory findings with a cumulative percentage of patients. Notice that for five of the nine tests the percentages include a majority of lupus patients. You can see that Mr. Smith did not meet diagnostic criteria for lupus. His hemoglobin was 14.2 g/100 mL, his white cell count was 11,500/mm^3 when he entered the hospital (his lowest white cell count was 10,000/mm^3), and his platelets were reported as adequate. Mr. Smith did not have a positive latex fixation test or a positive VDRL, both of which are sometimes falsely positive.

Table 2. Laboratory Findings of Systemic Lupus Erythematosus

Abnormality	Cumulative Percentage*	This Patient
Positive antinuclear antibodies	99	Negative at 1:20 × 2
Positive lupus erythematosus cells	80	Negative × 2
Increase γ-globulin >1.5%	75	γ-globulin = 1.4%
Anemia, hemoglobin <11 g/100 mL	72	14.2 g/100 mL
Leukopenia, white cell count <4500/mm³	61	11,500/mm³
Positive latex fixation test	20	Negative × 2
Thrombocytopenia, platelet count, <100,000/mm³	15	Adequate
False-positive VDRL	15	Negative × 2
Positive direct Coomb's test	14	Not done

*From Mannik and Gilliland[1]

It has been said that a positive antinuclear antibody titer is the "sine qua non for a positive diagnosis" of lupus.[1] Mr. Smith had *two negative* antinuclear antibody titers during his hospital stay. Other negative laboratory studies included anti-DNA antibodies, 2 chemistry profiles, and 13 cultures (9 blood, 1 bone marrow, 1 lymph node, urine, and throat). Tuberculosis test, electrocardiogram, and three chest roentgenograms with tomograms were also negative, as was an upper gastrointestinal series and a small bowel examination.

Pleural and pericardial effusions were diagnosed by abdominal computed tomographic scan, which included the lower chest. The indication for this test was the possibility of lymphoma.

Incidentally, some of these tests are expensive. Mr. Smith's hospital bill was an impressive 4 feet 7 inches long! His hospital costs totaled $5,050 for a 19-day hospitalization.

So, how did we finally determine it was lupus? We never gave up. Positive findings included a sedimentation rate of 43 mm/h, indicating some sort of extraordinary process. An arthrocentesis of his swollen knee yielded cloudy fluid with a white cell count of 50,000/mm³, of which 91 percent were segmented cells; it was a sterile effusion. A purple-red rash on Mr. Smith's back appeared on the 12th hospital day, and skin biopsy revealed the presence of immunofluorescent antigens in an epidermal position consistent with the diagnosis of lupus. The biopsy, however, was not reported until one week after the patient had left the hospital. The biopsy findings led us finally to the correct diagnosis.

Lupus occurs at a frequency of 2 or 3 per 100,000, and 9 out of 10 cases occur in women. When a man presents with symptoms of a disorder that occurs 90 percent of the time in women, that disorder is not usually the first thing suspected. Lupus remained in the differential diagnosis, but it was low on our list. I do not think we were in error to treat with a presumptive diagnosis of endocarditis. I am thankful, though, that we were persistent enough to eventually get to make the correct diagnosis.

Now, let's put aside these fascinating medical aspects and consider the stress Mr. Smith experienced. I will present a model that helps explain how Mr. Smith felt about what was happening to him. If physicians understand the model, we may be able to be more successful in helping both patients and family cope with the stresses of an undiagnosed illness. Drawn from *Coping With Physical Illness*[2] by Moos and Tsu, the model illustrates what happens during the crisis of acute illness (Figure 1). Important background and personal factors include age (or the timing of the illness in the life cycle), intelligence, emotional

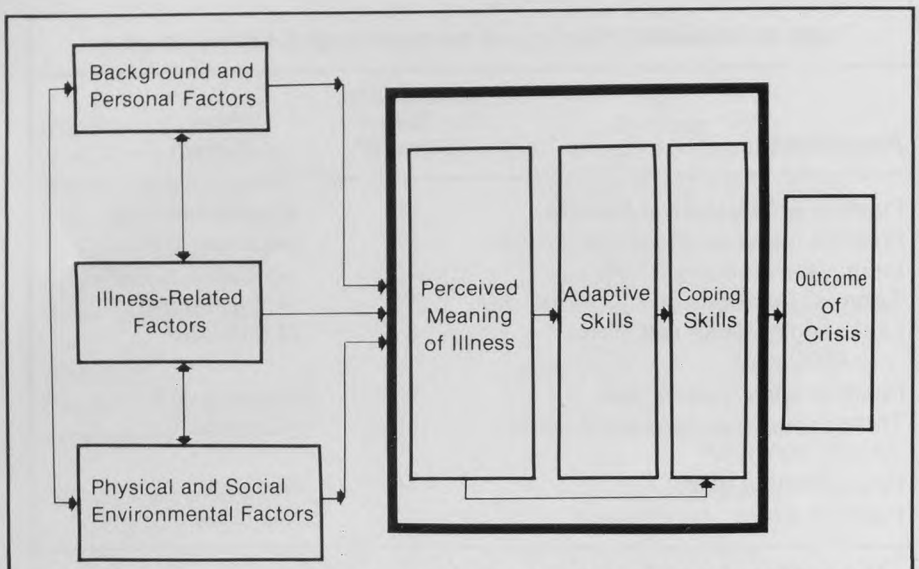

Figure 1. Conceptual model for understanding the crisis of illness (With permission, from Moos and Tsu[2])

development, philosophical and religious beliefs, inner coping experiences (not only the patient's own prior experiences but also the experiences of people he has known who have dealt with a serious illness), and general strength and self-esteem. Illness-related factors are the type, intensity, and location of symptoms (for example, head pain elicits a more significant emotional response than arm pain), and the rate, onset, progression, and intensity of the illness. Is pain involved? Is disfigurement involved? Is there a body region that has a special meaning, such as the breast in a pubescent female? Physical and social-environmental factors include the hospital setting, interactions between patients and patients, patients and nurses, and patients and physicians, and the environment of special care units. Also consider what is going on in the patient's life at home or at work when he or she comes into the hospital. The patient is influenced by the personal meaning of the illness and equipped with a set of skills that can be mobilized to cope with the illness.

DR. WILLIAM M. CLEMENTS *(Associate Professor and Pastoral Counselor, Department of Family Practice)*: Don, will you please tell us about the work you do and the sorts of things you were doing about the time you became sick?

MR. SMITH: I am a farmer, and I also run a tavern with a partner. I had just finished putting Chempost (fertilizer) on 400 acres of crop ground, so I thought that I was possibly reacting to the chemicals. First my feet started hurting. I thought maybe my shoes weren't very good, so I bought a new pair. Then my knees started to ache a little bit. My neck got a little stiff. Then I thought that maybe I was coming down with the flu. I ached all over. I went to Williamsburg (to the Family Practice Model Office) and saw the doctor there. He took some blood and gave me some pills. I went back a couple days later, when I was really starting to hurt. That's when the doctor sent me to Mercy Hospital in Iowa City.

DR. CLEMENTS: Didn't you mention that you have an audit going on in your business?

MR. SMITH: Yes. The business just went through a two-year audit with the Internal Revenue Service, which doesn't really please me, since we didn't come out too good. Stupidly, you know, I was doing these things I thought I had to do just to make a living. I worked in the fields about 12 to 14 hours, then went down and worked in the tavern another 5 to 6 hours. I got about 3 or 4 hours of sleep at night. Later on I read that lupus is caused by a lot of stress, overtiredness, and things like

Continued on page 694

Continued from page 690

that. Nobody changes their life style until something happens to them. I have.

DR. CLEMENTS: What were some of the other possibilities you were thinking of in addition to the chemicals?

MR. SMITH: After I got into the hospital and they kept listening to my heart, I thought, "Oh no, what's going on?" Every time they came in they were always checking my chest. I thought, "Maybe I have a heart problem." I thought, "Maybe I have some kind of cancer or something. I don't know what's going on. You're doing an awful lot of tests and nothing is coming out."

DR. CLEMENTS: So you were keeping a list—the chemical problem, the heart problem, cancer. Anything else?

MR. SMITH: I can't remember that first two weeks very well. People came to visit me, and I have completely forgotten it. My family told me that I was sicker than I thought I was.

DR. CLEMENTS: Do you recall anybody asking you what you had?

MR. SMITH: Everybody. They still ask me, and I tell them I still don't know. Who has ever heard of lupus?

DR. CLEMENTS: How about your physicians? Did any of them ask you what illnesses you were concerned about?

MR. SMITH: Not really. I thought that when I started on the penicillin, it would cure me.

DR. CLEMENTS: I have a personal interjection here. When I have been a patient, rarely has a physician ever asked me what *my* diagnosis was. What was on *my* list. That might be a helpful question to ask sometimes, because the patient always has only partial information. Sometimes a patient's suspicions can be a lot worse than any differential diagnosis you physicians may have.

DR. ROBERT E. RAKEL *(Professor and Head, Department of Family Practice)*: Even if patients don't say that cancer is in their minds, I usually assume that it is. It often is there, and they are afraid to mention it.

DR. CLEMENTS: Now, let's take a look at the major adaptive tasks involved in coping with an illness. Patients generally have to cope with these illness-related tasks in an unfamiliar environment

Continued on page 696

Continued from page 694

while they are feeling rotten. Lots of strange people come into the room; many of them look alike and dress alike. The patient can have a hard time remembering who is who. Sometimes the patient never really knows what someone's role is if he or she doesn't identify himself or herself.

There are other general sorts of adaptive tasks. Imagine the questions spinning in a patient's head—Is this a chemical reaction? Cancer? Heart problem? It takes considerable work just to maintain an emotional balance, to maintain the perspective that the disease may not be one of those things, that it could be something else. And there are always the questions: "What does this mean in terms of my future? How is my life going to change?" Don, did those particular issues bother you?

MR. SMITH: At one point I think a doctor came in and told me I might have lupus, but they weren't sure. It gave me an answer to tell my family and friends who asked me what I had. It was getting into the third week, and I was lying around there thinking, "There's work to do out there." If I hadn't had my partner, I don't know where I'd be.

DR. CLEMENTS: Did you wonder what lupus meant to you?

MR. SMITH: A lot of questions keep coming up all the time. I met a couple of women in our area who have lupus. Everything I read pertains to women. I have never found an article that deals with men. I don't know what to expect about the rest of my life. I don't know what to look forward to. What will it feel like if I have a relapse?

DR. CLEMENTS: One coping skill is seeking out all of the information. I know that you have been reading a lot.

MR. SMITH: My daughter brought some nursing publications home. They tend to put the disease in a bad light by bringing out the worst cases. The best publication I found was from the National Lupus Foundation in St. Louis; it is in layman's language I could understand—plain words.

DR. CLEMENTS: I suspect you have had to learn new ways of going about life. You've had to change some things, for instance the hours you work. What sort of goal do you have for yourself in terms of working?

MR. SMITH: I don't work nights at the tavern anymore—I get eight hours of sleep at night. My

plans are still in the building stage. I don't know if I'm in remission or not. When I talk to other patients with lupus, they say they just go about their lives as usual. I sure don't feel normal yet. I don't look normal, especially my back.

DR. DRISCOLL: So, when you compare yourself with other people you have met with lupus, you think you are not where you should be? These are the questions you are asking, and nobody is answering?

MR. SMITH: Yes, and nobody knows the answers.

DR. DRISCOLL: You were dealing with a lot of uncertainty when we were making the diagnosis, and now that you have a name for it, you still have a lot of questions. Dr. Clements, what are some other coping skills?

DR. CLEMENTS: Even in a crisis such as acute physical illness, we depend on whatever psychological skills we normally use to cope with life. However, these pre-existing coping skills probably are accentuated at a time of stress like this.

One skill we all rely on is a psychological defense called denial, in which we say to ourselves that whatever it is we are experiencing could be attributed to something benevolent. We try to minimize the gravity of the situation.

We also mentally rehearse alternative outcomes—"What if my illness goes in a particular direction? What will my life be like?" It is very common to go through a rehearsal of various sorts of outcomes. This is a very private and personal thing that we all do when we face serious health problems. Unfortunately, Don has read some of the worst outcomes because medical literature does not put much emphasis on people who have adapted quite well and live a relatively normal life.

People frequently encounter significant stresses in a hospital. For instance, Don had a roommate who was seriously ill and couldn't talk with him. How did you feel about that?

MR. SMITH: My first roommate went home after a day or two, but the next roommate I had was pretty sick. I finally asked to be transferred because he would get up out of bed and fall down and I would have to ring the nurse to get help. They tried to restrict him. I heard he died the day after I moved.

Then they put me in another room for a couple of days with a man who was seriously ill with cancer. He would talk all night. I kept listening to him, waiting for him to take his last breath because I knew he wasn't going to last too much longer. I moved out of that room before he died. It is uncomfortable to be in a room with someone you know is dying. I thought, "Maybe they think I am dying, and that's why they put me with him." I don't know what the hospital can do about this—they can't always put compatible people together.

DR. CLEMENTS: It was definitely interfering with your rest and certainly with your relaxation. You did complain?

MR. SMITH: Not with the first patient, but I did with the next one.

DR. CLEMENTS: Looking back, how much of the strain you experienced was due to not knowing what you had?

MR. SMITH: I am not sure how much it bothered me. I always thought that someone would discover what I had. But I really can't remember what happened early in my hospitalization.

DR. DRISCOLL: I think what Don is saying is very important for physicians to realize, too. We may have spent a half-hour going over a specific test, talking about what it was and what the results were, and that particular day you may have been off in another place in your mind.

DR. CLEMENTS: Let's have a period of general discussion at this point. I have one question for you: How does it affect you physicians to work with a patient for whom you don't have a diagnosis? I would think that not knowing the diagnosis makes it difficult to offer credible reassurance.

DR. REID HOLKESVICK *(Second-year family practice resident)*: Yes. I tried to get Mr. Smith to ventilate, but it wasn't very effective.

DR. CLEMENTS: I am sure there was a lot of frustration—probably mutual frustration.

MR. SMITH: Yes, there was. I could see that I was losing a lot of weight. My roommate at the hospital had cancer, and he was down to 73 pounds; I normally weigh 160 pounds and I was down to 142 pounds.

DR. CLEMENTS: So, you are comparing yourself with someone who has cancer. That is pretty powerful.

DR. KATHERINE COLE *(First-year family practice resident)*: When I do not know the diagnosis, I feel insecure, especially in a specialty

Continued on page 700

Continued from page 697

where I'm not the final authority. I am a family physician and a generalist, and the patient is probably wondering if I know what I'm doing. "Am I well trained?" I may start to wonder myself. I think insecurity is magnified by wondering what the patient is thinking.

DR. REUBEN WIDMER *(Professor, Department of Family Practice)*: The best thing about being the family physician is that we have good consultants. I wouldn't practice medicine as a family physician if I didn't have the good consultants we have. In Winfield, Iowa, where I was all by myself, it was threatening, but I knew I could reach out and get some help. Certainly it was comforting for the patients, too.

I once had a male patient with lupus, and it was just as hard to diagnose. The diagnosis was made clinically; we didn't have the modern laboratory tests 30 years ago. He's still alive and doing fine.

MR. SMITH: That's good to know!

DR. CLEMENTS: As a patient, my experience was different than Don's in that I was not feeling so rotten during the period of hospitalization. Also, I felt surrounded by friends; you were my colleagues *and* my physicians, and I felt comfort and care in that. The diagnostic issue for me became focused at a later date. Then I was unable to reconcile how I was feeling with what *I* thought I had. I felt a lot worse than I thought I should.

DR. WIDMER: Physicians don't often experience an undiagnosed disease, and it is difficult to completely understand how the patient is feeling. We need to ask, "What do *you* think you have?" Then we can help diffuse the stress a little bit.

DR. CLEMENTS: That can be very reassuring.

DR. DRISCOLL: It's time to summarize what we have said about the stresses and discomforts of being a patient with an undiagnosed medical condition. Adaptive responses, or coping skills, are used by most people to deal with any physical illness of a serious nature. Adaptive tasks include the management of discomfort and incapacitation, getting used to the hospital environment and diagnostic and treatment procedures, and developing adequate relationships with the professional hospital staff. The patient attempts to maintain a reasonable emotional balance and a satisfactory self-

Continued on page 702

Continued from page 700

image, preserve relationships with family and friends, and prepare for an uncertain future. The importance of each task varies widely, depending on the coping skills that each patient carries into the encounter with illness.

Denial, or minimization of the seriousness of the disease, is one such common coping skill. The patient seeks as much relevant information as can be obtained to decrease fear and anxiety. When the outcome of illness is uncertain, especially when the diagnosis is difficult, the patient rehearses alternative outcomes resulting in behavior change that can be observed by the health care team. Both the patient and the family expect reassurance and emotional support from physicians and hospital staff, who must be open to hearing these expressions of feeling. When the illness seems overwhelming, they can help the patient set limited goals and break the major problems into manageable bits.

The outcome of the illness event, beyond clinical factors, depends largely on the patient's background and other personal factors and on the physician's skill in shaping the psychosocial and environmental factors of the illness setting. Successful outcomes depend on understanding illness behavior in its context, equipping the patient with new coping skills, and promoting a team approach by the family, patient, and medical care team. The patient's "agenda," capacity for understanding, fears, and beliefs must be understood by each member of the team. Anticipatory guidance can then be given, and when the patient needs to express anger or denial, those expressions can be seen as normal coping mechanisms. Physicians must also understand their own reactions to the crisis of an undiagnosed serious medical illness and respond in a supportive way to each other as well as to the patient. In short, one statement characterizes the essence of managing the undiagnosed seriously ill patient: Teamwork is the key to successful outcome.

References

1. Mannik M, Gilliland BC: Systemic lupus erythematosus. In Isselbacher KJ, Adams RD, Braunwald E, et al (eds): Harrison's Principles of Internal Medicine, ed 9, New York, McGraw-Hill, 1980, pp 355-359
2. Moos RH, Tsu VD (eds): Coping With Physical Illness. New York, Plenum, 1977