
Family Practice Grand Rounds

The Undiagnosed Patient

Charles E. Driscoll, MD, and William M. Clements, PhD
Iowa City, Iowa

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/arthritis	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 Gilliland¹

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/mm³ when he entered the hospital (his lowest white cell count was 10,000/mm³), 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/mm ³	61	11,500/mm ³
Positive latex fixation test	20	Negative × 2
Thrombocytopenia, platelet count, <100,000/mm ³	15	Adequate
False-positive VDRL	15	Negative × 2
Positive direct Coomb's test	14	Not done

*From Mannik and Gilliland¹

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.

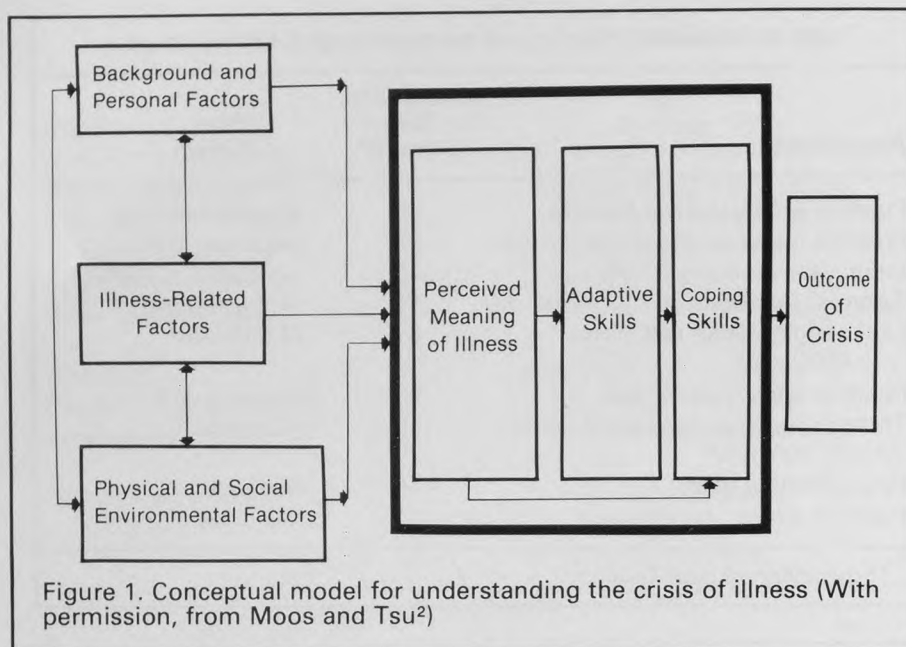
Incidentally, some of these tests are expensive. Mr. Smith's hospital bill was an impressive 4 feet 7 inches long! His hospital costs totaled \$5,050 for a 19-day hospitalization.

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



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

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ALDOMET® (Methyldopa|MSD)

Tablets, containing 125, 250, or 500 mg methyldopa; Oral Suspension, containing 250 mg methyldopa per 5 ml and alcohol 1%.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions. With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstated. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstated in such patients. Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, prolonged carotid sinus hypersensitivity, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatulence, diarrhea, colitis, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Bone marrow depression, leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Dermatologic:* Rash as in eczema or lichenoid eruption; toxic epidermal necrolysis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, hyperprolactinemia, amenorrhea, impotence, decreased libido, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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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

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Imodium[®] (loperamide HCl) Capsules

BRIEF SUMMARY

Before prescribing, please consult complete prescribing information, a summary of which follows:

INDICATIONS

IMODIUM is indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. IMODIUM is also indicated for reducing the volume of discharge from ileostomies.

CONTRAINDICATIONS

IMODIUM is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS

Antiperistaltic agents should not be used in acute diarrhea associated with organisms that penetrate the intestinal mucosa, e.g., enteroinvasive *E. coli*, *Salmonella*, *Shigella*, and in pseudomembranous colitis associated with broad-spectrum antibiotics.

Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy. In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. IMODIUM therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop in patients with acute ulcerative colitis.

PRECAUTIONS

In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of IMODIUM should be discontinued.

Abuse and Dependence: Physical dependence to IMODIUM in humans has not been observed. However, studies in monkeys demonstrated that loperamide hydrochloride at high doses produced symptoms of physical dependence of the morphine type.

Carcinogenesis: In an 18-month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis) there was no evidence of carcinogenesis.

Pregnancy: Safe use of IMODIUM during pregnancy has not been established. Reproduction studies performed in rats and rabbits with dosage levels up to 30 times the human therapeutic dose did not demonstrate evidence of impaired fertility or harm to the offspring due to IMODIUM. Higher doses impaired maternal and neonate survival, but no dose level up to 30 times the human dose demonstrated teratogenicity. Such experience cannot exclude the possibility of damage to the fetus. IMODIUM should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether IMODIUM is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children have not been established. Therefore, use of IMODIUM is not recommended in the pediatric age group (under the age of 12). In case of accidental ingestion of IMODIUM by children, see Overdosage Section for suggested treatment.

ADVERSE REACTIONS

The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The following patient complaints have been reported: Abdominal pain, distention or discomfort; Constipation; Drowsiness or dizziness; Dry mouth; Nausea and vomiting; Tiredness.

Hypersensitivity Reactions (including skin rash), however, have been reported with IMODIUM use.

OVERDOSAGE

Animal pharmacological and toxicological data indicate that overdosage in man may result in constipation, CNS depression, and gastrointestinal irritation. Clinical trials have demonstrated that a slurry of activated charcoal administered promptly after ingestion of loperamide hydrochloride can reduce the amount of drug which is absorbed into the systemic circulation by as much as ninefold. If vomiting occurs spontaneously upon ingestion, a slurry of 100 gms of activated charcoal should be administered orally as soon as fluids can be retained.

If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 gms of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone.

In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Based on the fact that relatively little drug is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

In clinical trials an adult who took three 20 mg doses within a 24-hour period was nauseated after the second dose and vomited after the third dose. In studies designed to examine the potential for side effects, intentional ingestion of up to 60 mg of loperamide hydrochloride in a single dose to healthy subjects resulted in no significant adverse effects.

HOW SUPPLIED

IMODIUM is available as 2 mg capsules of loperamide hydrochloride. The capsules have a light green body and a dark green cap, with "JANSSEN" imprinted on one segment and "IMODIUM" on the other segment. IMODIUM capsules are supplied in bottles of 100 and 500 and in blister packs of 10 x 10 capsules.

IMODIUM (loperamide hydrochloride) is an original product of Janssen Pharmaceutica, Belgium and is manufactured by Ortho Pharmaceutical Corporation, Raritan, New Jersey. February 1983. U.S. Patent 3,714,159.

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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

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SINEQUAN® (doxepin HCl)

Reference: 1. Barranco SF, Thrash ML, Hackett E, Frey J, et al (Pfizer Pharmaceuticals, Pfizer Inc., New York, N.Y.): Early onset of response to doxepin treatment. *J Clin Psychiatry* 40:265-269, 1979.

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intermittent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdose. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred. **Hematologic:** Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdose consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdose due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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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-

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VERMOX[®] CHEWABLE TABLETS

(mebendazole)

THE UNDIAGNOSED PATIENT

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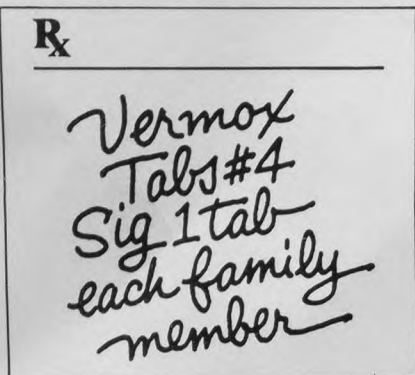
image, preserve relationships with family and friends, and prepare for an uncertain future. The importance of each task varies widely, depending on the coping skills that each patient carries into the encounter with illness.

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

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DESCRIPTION VERMOX (mebendazole) is methyl 5-benzoylbenzimidazole-2-carbamate.

ACTIONS VERMOX exerts its anthelmintic effect by blocking glucose uptake by the susceptible helminths, thereby depleting the energy level until it becomes inadequate for survival. In man, approximately 2% of administered mebendazole is excreted in urine as unchanged drug or a primary metabolite. Following administration of 100 mg of mebendazole twice daily for three consecutive days, plasma levels of mebendazole and its primary metabolite, the 2-amine, never exceeded 0.03 µg/ml and 0.09 µg/ml, respectively.

INDICATIONS VERMOX is indicated for the treatment of *Trichuris trichiura* (whipworm), *Enterobius vermicularis* (pinworm), *Ascaris lumbricoides* (common roundworm), *Ancylostoma duodenale* (common hookworm), *Necator americanus* (American hookworm) in single or mixed infections. Efficacy varies as a function of such factors as pre-existing diarrhea and gastrointestinal transit time, degree of infection and helminth strains. Efficacy rates derived from various studies are shown in the table below:

	Whipworm	Common Roundworm	Hookworm	Pinworm
cure rates				
mean	68%	98%	96%	95%
(range)	(61-75%)	(91-100%)	—	(90-100%)
egg reduction				
mean	93%	99.7%	99.9%	—
(range)	(70-99%)	(99.5-100%)	—	—

CONTRAINDICATIONS VERMOX is contraindicated in pregnant women (see Pregnancy Precautions) and in persons who have shown hypersensitivity to the drug.

PRECAUTIONS PREGNANCY: VERMOX has shown embryotoxic and teratogenic activity in pregnant rats at single oral doses as low as 10 mg/kg. Since VERMOX may have a risk of producing fetal damage if administered during pregnancy, it is contraindicated in pregnant women.

PEDIATRIC USE: The drug has not been extensively studied in children under two years; therefore, in the treatment of children under two years the relative benefit/risk should be considered.

ADVERSE REACTIONS Transient symptoms of abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms.

DOSAGE AND ADMINISTRATION The same dosage schedule applies to children and adults. The tablet may be chewed, swallowed or crushed and mixed with food. For the control of pinworm (enterobiasis), a single tablet is administered orally, one time. For the control of common roundworm (ascariasis), whipworm (trichuriasis), and hookworm infection, one tablet of VERMOX is administered, orally, morning and evening, on three consecutive days. If the patient is not cured three weeks after treatment, a second course of treatment is advised. No special procedures, such as fasting or purging, are required.

HOW SUPPLIED VERMOX is available as chewable tablets, each containing 100 mg of mebendazole, and is supplied in boxes of twelve tablets. VERMOX (mebendazole) is an original product of Janssen Pharmaceutica, Belgium.

US Patent 3,657,267
December 1979

Committed to research...
because so much remains to be done.

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