

# Update

Vol. 10 No.1  
January 1992

## Difficult Diagnosis

One of the thorniest and most troubling problems in medical practice is the questionable diagnosis. In some instances, the initial history, physical examination, and tests present a puzzling array of symptoms, signs, findings and other information. A literature search, consultation, or referral to a specialist ensues, and often the mystery is solved. In other instances, the mystery persists or a diagnosis is made but comes into doubt when the patient does not improve or otherwise respond as expected with treatment.

Such cases can bring tremendous pressure to bear upon the resources of the clinician. When the challenge involves pulmonary, allergic, or immunologic disease, the National Jewish Center for Immunology and Respiratory Medicine is available to provide assistance. The nation's only referral center whose singular and overall focus is the study of such conditions, National Jewish places at the disposal of referring physicians a unique range of

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specialized facilities and capabilities for diagnosis and treatment.

Because a large number of patients are encountered every year at the Center, members of the medical staff often possess knowledge of rare diseases or rare patterns of relatively common processes which lead them to fruitful diagnostic and therapeutic paths. Research-oriented physicians have the time as well as the tools to conduct the kind of in-depth studies that particularly difficult cases demand.

Typically, a patient is referred to the Center because he or she is responding poorly to therapy. A diagnostic evaluation is conducted, forming the basis for a treatment plan tailored to the individual's needs.

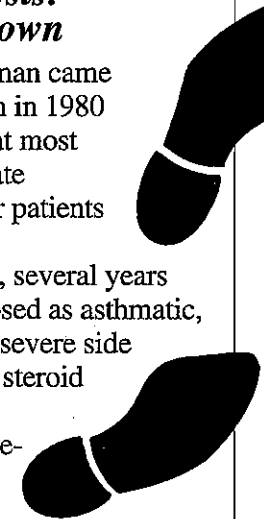
Usually, in the process, the initial diagnosis is confirmed. But sometimes refinements are made which intrigue, instruct and surprise. The following are a few such cases from the National Jewish files.

***A good reason to  
miss a diagnosis:  
It isn't yet known***

The young woman came to National Jewish in 1980 for the reasons that most commonly motivate physicians to refer patients here.

At 29 years old, several years after being diagnosed as asthmatic, she was suffering severe side effects from daily steroid therapy. She was Cushingoid, severely depressed, and plagued by seizures and bleeding ulcers, among other problems.

Despite aggressive management, her symptoms were poorly controlled. Trips to the emergency

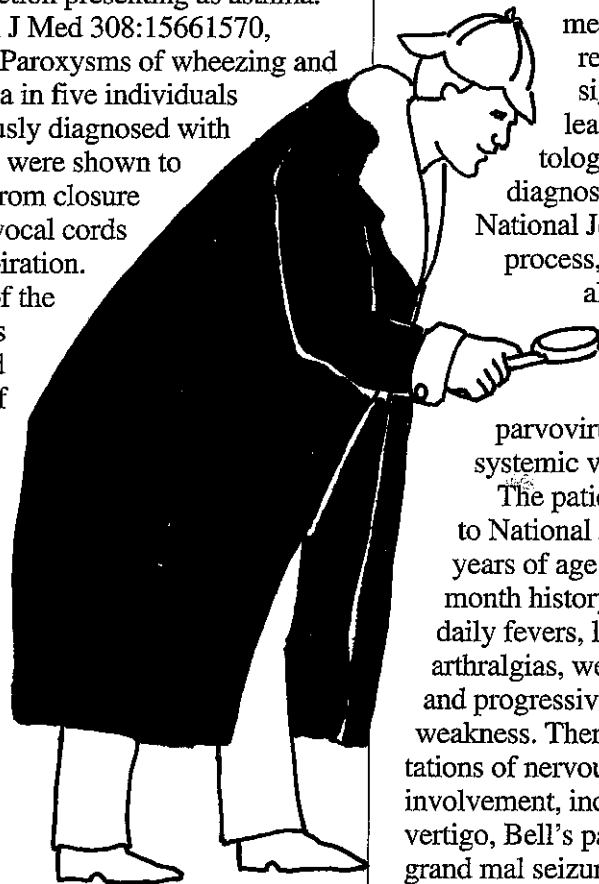


room had become a regular part of her life. Her throat bore the scars of eight tracheostomies!

National Jewish was able to help the patient in some important ways. Her steroid intake was reduced. Intensive training in self-care and psychosocial counseling were beneficial. She returned home to California feeling much better.

Two years later, her local physician received a call from Denver asking if the patient could return to the Center for further evaluation. Researchers at National Jewish had discovered a previously unrecognized vocal cord dysfunction which staff members who had treated her believed might be affecting her.

The findings were later reported in the *New England Journal of Medicine* (Christopher KL, Wood RP, Eckert RC, Blager FB, Raney RA, Souhadra JF. Vocal cord dysfunction presenting as asthma. *N Engl J Med* 308:1566-1570, 1983). Paroxysms of wheezing and dyspnea in five individuals previously diagnosed with asthma were shown to result from closure of the vocal cords on inspiration. None of the patients showed signs of



bronchial hyperreactivity in response to methacholine challenge or other tests.

Motion pictures taken through a fiberoptic laryngoscope revealed the pattern now considered classic for the disorder — adduction of the anterior two-thirds of the vocal cords, leaving only a tiny diamond-shape chink at the back of the throat for passage of air.

This disorder can mimic asthma or accompany it. In the case of the young California woman, her asthma was so mild that after receiving what is now standard therapy for the vocal cord condition (speech therapy and psychological counseling), she was able to discontinue all medications and live symptom-free.

### *A researcher pursues a solution*

A remembered journal article and a clue from the family medical history recently played a significant role in leading a rheumatologist to refine a diagnosis initially made at National Jewish. In the process, the researcher also made the first identification of a case of chronic parvovirus B19-associated systemic vasculitis.

The patient initially came to National Jewish at five years of age with an eight-month history of unexplained daily fevers, livedo reticularis, arthralgias, weight loss, fatigue and progressive muscle weakness. There were manifestations of nervous system involvement, including ataxia, vertigo, Bell's palsy and grand mal seizures. An

EMG was positive for spotty myopathy and a muscle biopsy revealed leukocytoclastic vasculitis. Polyarteritis nodosa was diagnosed. Prednisone treatment was begun.

Recurrent CNS involvement was only transiently responsive to pulse Solumedrol. Immuran therapy and cyclophosphamide therapy were initiated. Despite the escalation in therapy, the child's fevers continued intermittently, inflammatory markers remained elevated, and reduction of oral steroid doses below 1 mg/kg/day provoked a clinical flare.

Immunologic studies revealed multiple abnormalities indicating dysfunction of T and B cells. Phenotypic analysis of peripheral blood showed lymphopenia involving CD4 cells, CD8 cells and B cells. The patient had no reaction to skin testing with tuberculin, candida, trichophyton, tetanus, or diphtheria antigens. In vitro, his peripheral blood mononuclear cells showed poor proliferative responses to PHA, candida, tetanus and PPD and an increased response to concanavalin A and pokeweed mitogen. Serum concentrations of immunoglobulin of all classes was low. There were no detectable IgG antibodies to the human immunodeficiency virus, to leptospiral antigen or to tetanus toxoid, and the titers of antibodies to the polio and herpes simplex viruses were low. The patient's serum was also negative for Hepatitis B surface antigen, for immune complexes, and for complement split products.

Searching for a possible infectious etiology of the patient's vasculitis, Terri H. Finkel, M.D., Ph.D., recalled a 1989 *New England Journal of Medicine* article

(Kurtzman, et. al., Vol. 321, p. 519) describing symptoms suggestive of immune-complex deposition in acute and chronic parvovirus infection. Dr. Finkel also remembered that the patient's older brother had suffered a syndrome consistent with acute parvovirus infection several years before, when the patient was only six months old.

Although the patient himself had never exhibited a classical syndrome of parvovirus infection and at no point in his course had been anemic, as would have been expected if this organism were the culprit in his disease, tests for the virus were carried out. The results were stunning. His serum was positive for both IgG and IgM parvovirus antibodies. Parvovirus B19 DNA was detected through several sophisticated laboratory procedures conducted in National Jewish's Ruskin Clinical Immunology Diagnostic Lab and at the Centers for Disease Control. Because previous studies had shown that serum containing anti-parvovirus B19 antibodies can neutralize this viral infection, the patient was treated for three months with a commercial immunoglobulin preparation. After two months of therapy, his fevers, muscle weakness, rash and malaise had resolved. His inflammatory parameters had returned to normal. Steroid dosage was successfully tapered and steroid and cyclophosphamide therapy discontinued with no exacerbation of the disease.

The patient is currently in excellent health and has been off all medications for one year.

### *The mystery of the missing pressures*

The coincidental appearance of two unrelated medical conditions can produce confusion in diagnosis.

A 68-year-old white male with

a 40-year smoking history and a diagnosis of progressive interstitial lung disease (ILD) was referred to the pulmonary disease clinic at National Jewish for a second opinion. Physical exam and arterial blood gas measurement produced several findings commonly associated with interstitial processes — rales, high respiratory rate, finger clubbing, hypoxemia. The chest film revealed an elevation of the right hemidiaphragm as well as subpleural honeycombing characteristic of severe ILD.

Pulmonary function tests were performed, and the results are shown in Table 1 and Figures 1 and 2 below:

The results of the pulmonary function tests were most compatible with a primary restrictive process. The reduction in total lung capacity (TLC), thoracic gas

volume (TGV) and vital capacity (FVC) with little or no reduction in expiratory flow rates were characteristic of a restrictive ventilatory process. Exercise testing probably would have shown further desaturation, but the patient's hypoxemia at rest obviated the need for such testing.

Bronchoscopy revealed no lesions, and minimal endobronchial secretions were noted. The lavage data showed a normal total cell count and a normal percentage of lymphocytes. The numbers of neutrophils and eosinophils were elevated. These findings are most consistent with advanced and progressive ILD.

The low elastic-recoil pressure at TLC was unexpected. Characteristically, patients with interstitial processes have high recoil pressures when compared to reference

Table 1. Pulmonary Function Values before and after Bronchodilator

	Before Bronchodilator	After Bronchodilator
FVC (L)	2.02 (47)*	2.25 (51)
FEV <sub>1</sub> (L)	1.83 (62)	2.03 (69)
FEV <sub>1</sub> FVC(%)	87	90
FEF <sub>25-75%</sub> (L/s)	2.42 (71)	3.12 (91)
TLC (L)	4.01 (64)	4.28 (68)
TGV (L)	2.77 (74)	2.54 (68)
RV (L)	1.71 (91)	1.56 (83)
D <sub>LCO</sub> (mL • torr • min <sup>-1</sup> )	12.50 (41)	
D <sub>LCO</sub> /V <sub>A</sub>	3.83 (80)	

\*Values in parentheses are % of predicted.

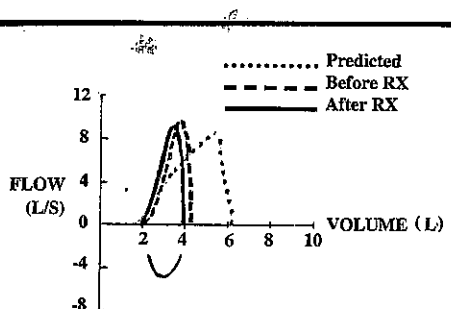


Fig. 1. Forced expiratory flow-volume curves, showing predicted values and values obtained before and after bronchodilator.

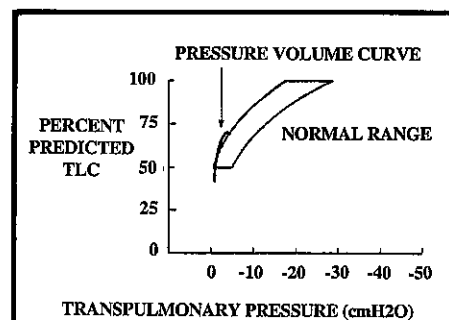


Fig. 2. Pressure-volume relationship obtained with esophageal balloon, showing the pressure-volume curve before bronchodilator, and a reference envelope.

values. This provides a "gold standard" for the physiologic assessment of ILD.

The pressure-volume characteristics of the lung normally are evaluated through introduction of a balloon catheter into the lower esophagus. To obtain reproducible and valid measurements, the staff of the Pulmonary Physiology Unit at National Jewish has developed methods to carefully control the procedure eliminating such technical problems as incorrect positioning, kinking or leaking of the balloon.

When low elastic-recoil pressures were obtained on a second test, experience told the Pulmonary Physiology Unit staff where to look next. Further investigation of the patient's history resulted in reported symptoms of an unrepaired hiatal hernia, which also was suggested by the elevated hemidiaphragm on the radiograph. Although the problem is not generally recognized, hiatal hernias dampen esophageal pressures. The real "pressure-volume indicator" probably would have shown increased elastic recoil.

This case was reported by Jack Wanger, R.R.T., and Charles Irvin, Ph.D., in *Respiratory Care*, 34:1069, 1989.

### ***When the fundamental problem isn't medical***

Because psychosocial consultation is an important component of the clinical program at National Jewish, cases of Munchausen's syndrome and other psychological disorders with significant medical impact sometimes come to light. The following case history involves factitious pulmonary illness, which is especially rare.

The patient was a 19-year-old woman who came to the Center for evaluation and treatment of

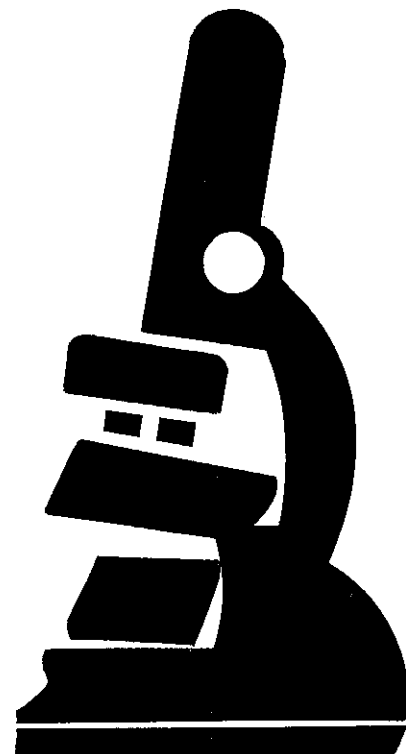
intractable bronchorrhea. She reported a history of frequent bouts of bronchitis from infancy, which had resulted in multiple emergency room visits and antibiotic therapy throughout childhood. Since age 17, she'd had nine hospital admissions for status asthmaticus, required prednisone chronically and suffered from Cushingoid habitus.

An outpatient evaluation at National Jewish included a normal immunologic workup and pulmonary function tests, negative methacholine and histamine challenges, and a negative exercise study.

The patient was discharged and encouraged to return should her symptoms exacerbate. She was re-hospitalized within two weeks, treated with steroids and released. Eleven days later she was brought to National Jewish by air ambulance.

Upon arrival, the patient exhibited laryngeal stridor and diffuse, loud, wet rhonchi. Throughout her hospitalization, she displayed coarse rhonchi, nonproductive cough, and the inability to clear secretions, even after saline induction. A mucociliary clearance scan was within normal limits. A curious laboratory test result led to the suspicion that the patient might have been inducing her symptoms: A sputum culture grew *Proteus mirabilis*, an organism normally found in the genitourinary and gastrointestinal systems but not in the lungs. It appeared that the young woman was making herself ill by aspirating her own urine.

Psychosocial consultation was conducted throughout the patient's outpatient and inpatient stays. Tests suggested that she was a passive, ineffectual, and immature person who experienced herself as unable to cope with the real or imagined stressors of everyday



life. In response, she strove desperately to embrace powerful others in hopes of assistance. Her multiple somatic complaints enabled her to associate with idealized, omnipotent physicians.

In an article in *Psychosomatics* (32:457-459, 1991), Karen Schmalzing, Ph.D., and other members of the National Jewish psychosocial team reported that in therapy sessions the patient was not directly confronted with concerns about intentional production of symptoms, as such a stance would likely sever abruptly her tenuous relationship with her idealized physicians, possibly exacerbating self-destructive behavior, somatic complaints and psychological regression. Face-saving and other special techniques are necessary in the treatment of somatizing patients, especially those with factitious disorders, who are widely known to be poor candidates for psychotherapy.

# Annual Update on Allergy and Clinical Immunology Keystone, Colorado February 12-16, 1992



The annual "UPDATE on Allergy & Clinical Immunology" is sponsored by National Jewish Center for Immunology and Respiratory Medicine. The conference is designed to give participants a better understanding of current trends in diagnosis and clinical management of patients with respiratory, allergic and immune system disorders. The focus of this conference is on the mechanisms and new therapeutic strategies for treatment of allergen immunotherapy, inflammation in asthma immune deficiencies, allergic skin disease and environmental insults.

National Jewish designates this CME activity for 14.25 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

## Program Topics and Faculty:

### Macrophages & Lymphocytes

Lanny Rosenwasser, M.D.

### Inflammatory Mediators

Peter Barnes, D.M.

### Eosinophils

William Busse, M.D.

### Role of Immunomodulatory Drugs in Asthma

Lanny Rosenwasser, M.D.

### Anti-inflammatory Therapy of Asthma

Stanley Szefer, M.D.

### Nocturnal Asthma

Richard Martin, M.D.

### Vocal Cord Dysfunction

Gary Cott, M.D.

### United Kingdom Approach to the

### Treatment of Asthma

Peter Barnes, D.M.

### Pathogenesis & Treatment of Allergic Rhinitis

Larry Borish, M.D.

### Viral Infections as Precipitants of Asthma

William Busse, M.D.

### Regulation & Modulation of the IgE Response

Donald Leung, M.D., Ph.D.

### Intravenous Gammaglobulin: A form of Passive Immunotherapy

Erwin Gelfand, M.D.

### Current Status of Active Immunotherapy

Harold Nelson, M.D.

### Mechanisms & Management of Anaphylaxis

Timothy Sullivan, M.D.

### Contact Dermatitis

William Weston, M.D.

### Sick Building Syndrome

Joseph Jarvis, M.D.

### Hypersensitivity Pneumonitis: New Approaches to Recognition and Management

Cecile Rose, M.D.

## Q & A Forum

Each day, from 4:30 - 5:00 p.m., morning speakers will be available to talk one-on-one with participants.

## Workshops

Pre-Registration is required to attend these workshops. There is no charge to attend with paid registration.

## Topics include:

- The Difficult Patient or Family: What to Do When Teaching Is Not Enough
- Evaluation of Immunodeficiency in Children
- Evaluation of Immunodeficiency in Adults
- Speech Therapy for Vocal Cord Dysfunction and Chronic Cough
- Eczematoid Eruptions in Allergy
- Practice of Immunotherapy

## Tuition:

Physicians: **\$400.00**

Allied Health Care & Physicians in Training: **\$300.00**

Fee includes: Workshops, course materials, continental breakfasts, break refreshments and special evening events.

For Complete Detailed Information, call or write:

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303-398-1828 or FAX 303-398-1125

Keystone, Colorado is located in the Rocky Mountains, 75 miles west of Denver CO.

The meeting is held at the luxurious mountain resort's conference center.