Consider medicine’s progress over the past half-century. Millions today still recall the terror of polio, the spectre of the iron lung – and the miracle of the Salk vaccine. Others, too young to remember polio, remember lining up for the smallpox vaccine in school, the horribly scarred faces of Third World children infected with this virus – and the triumph of eradicating that disease from humanity. In many ways, the progress of medicine has been astonishing.

Vasculitis, too, has witnessed major breakthroughs. Many forms of this disease, once nearly always fatal, are now often controllable and – with good fortune – curable. But in treating vasculitis, we still grapple with a mighty, two-headed monster. One head of this monster represents complications from the disease itself. The other represents the potentially devastating complications of therapy. The story of Jean deRoulhac Moxley epitomizes most of the challenges and many of the bittersweet rewards experienced by doctors who care for patients with vasculitis. Her story illustrates that all too often, our successes are fragile and sometimes fleeting. It also underscores the need for ongoing research — and advances — in our understanding of these conditions.

I remember the winter’s day in early 1999 when we first met. Mrs. Moxley and her husband, Robert, were dressed elegantly: he in a handsome suit, tie, and hat; she in a navy blue suit with gold cording – and white gloves. They had planned on dinner in town following her appointment. I would soon learn that in their 50 years of marriage, the Moxleys seldom needed an excuse for a celebration. On this, day, even a doctor’s appointment was cause enough for a night on the town. But once she removed her gloves, I knew we were in big trouble.

Jean had already suffered from polymyositis (an inflammatory muscle disease) for four years.
Grappling With A Mighty Monster: Continued

(Continued from page 1)

She had been referred to the Vasculitis Center because the most serious complication of that disease – vasculitis – had recently landed her in the hospital with critically little blood flow to her fingers [see figure]. The vasculitis threatened not only the viability of her fingers but also, I realized, her life.

Her fingers, “cyanotic” (blue) and intensely painful, were the most obvious sign of her disease, in partial remission because of a thick blanket of prednisone. Thus, a woman already weakened by four long years of steroid treatment – and now two other toxic medications, methotrexate and azathioprine – confronted a new, more serious twist in of her disease. I examined her cool, mottled, tender fingertips and considered other options for treatment. A variety of options played through my mind: all of them risky. As her referring doctor had thought, “I’m afraid she’s going to get a bad infection one of these days and die”. There was no doubt: putting this already immunocompromised woman on an even more powerful medication might lead to cancer, bone marrow suppression, damage to her bladder, and, yes, an infection. But upping the ante was clearly the only chance we had to prevail. The current approach had failed: even after four years, the medicines had not controlled her disease, and their side-effects were slowly killing her. Following a long, frank discussion, the Moxleys and I agreed that there was really only one choice: cyclophosphamide.

For three years, the new strategy worked – beautifully. Knowing the risks, we watched her like hawks: Robert; the children, Karen and David; Judy, Chas, and I. Jean came to clinic every four weeks. We monitored her bloodwork closely. We carefully adjusted her cyclophosphamide dose, and walked the narrow line between holding her disease at bay and causing side-effects. As the new medicine took effect, her fingers hurt less and “pinked up”. We decreased her prednisone dose to its lowest level in years. Her face grew slimmer, her muscles stronger, her outlook brighter. Her smile became a familiar and welcome sight in clinic every month as she walked slowly toward the examining room, with Robert just a pace or two behind, invariably wearing a coat and tie and looking his best.

Over the next 12 months, we wrestled the mighty monster into remission. Jean stopped her cyclophosphamide after a year; I breathed a sigh of relief. Eventually, I noted, she became more limited by her arthritic knees than by vasculitis. She felt so well she began to think of having her knees replaced, so that she might return to the family’s hunting lodge deep in the Maine woods, the site of many happy occasions. Getting her back to Maine became our goal. She made it through one knee replacement and contemplated another. She planned a new addition to the Moxley home and began to travel again, back to Arizona, to the farm where she had grown up. I think she could have managed a trip to Maine, too, but the remoteness of the cabin and her potential need for medical attention made her nervous. By the fall of 2001, I think we had missed our chance.

In the spring of 2002, she had developed a persistent cough. A CAT scan of her chest confirmed my worst fears: “ground glass” infiltrates in her lungs. The inflammation had returned, marking another crossroads in her care. Reluctantly, in view of her previous exposure to cyclophosphamide, we re-started that medication, though only at a low dose. One month later, that appeared to have been the right decision. The cough was gone, and a follow-up CAT scan confirmed that the lung infiltrates had disappeared.

One morning in April I got a call from Karen:
“Mom’s crashed”. Jean had developed a high fever and was disoriented. My immediate response: “I’ll meet you in the Emergency Room”. In the ER, things looked even worse than they had sounded on the telephone. At times, Jean was difficult to arouse. As I helped perform the spinal tap, the words of her referring doctor ran through my mind again: “I’m afraid she’s going to get a bad infection one of these days…”. At midnight, the radiologist paged me with the MRI results: inflammation in the temporal lobe of her brain. This could mean only one thing — viral encephalitis.

Despite the odds posed by her baseline frailty, her age, the severity of her infection, and her immunosuppressed state, at times during the next three weeks it looked as if Jean might make it. During this period, I had the privilege again of observing the power of a family’s love. One morning, on rounds very early by myself, I found her completely unresponsive. “This looks grim”, I thought, my heart sinking. At that moment, her son David arrived. As Jean lay with her eyes closed, we conferred for a few moments in hushed tones. David was sure his mother was just asleep. To my astonishment, she responded immediately to his greeting and kiss with a strong “Good morning, David!” What a relief those three words were! Such flickers throughout her weeks in the hospital raised our hopes that she might defy the overwhelming odds. Robert was at her bedside continuously, always dressed in his finest. He explained, “If she wakes up, I want her to see me at my best”.

In the end, the relentless two-headed monster encircled and overwhelmed us. The need to stop the cyclophosphamide because of the infection allowed the lung inflammation to advance unchecked. When it became clear that we could not stave off the inevitable any longer, I prescribed heavy doses of morphine to ensure her comfort. She died peacefully in a room full of flowers and family, with pictures of the Moxleys in happy times.

A medical practitioner more than two thousand years ago summarized the profession’s goals: “To cure sometimes; to relieve suffering often; to comfort always”. At the Johns Hopkins Vasculitis Center, our efforts in patient care and research are devoted to finding the answers that will permit cures as well as comfort, so that life’s celebrations may go on.

Would you like to hear from us?

We would like to continue to send you our Newsletter and to provide you with other vasculitis updates as they arise. New federal regulations going into affect on April 14 will place significant restrictions on our ability to contact you without your written permission. In the next two weeks, you will receive from us another mailing that contains an authorization form for future contact. We ask that you read, sign, and return the form to us as soon as you can.
Frequently Asked Questions: "Hemorrhagic cystitis"
Cyclophosphamide (CYTOXAN®) And The Bladder

Three months after starting cyclophosphamide (CYC) for Wegener’s granulomatosis, 17 year-old Bridget McCormick developed severe pain whenever she urinated. She thought it was the worst urinary tract infection (UTI) she had ever had. The pain was so bad that she had to be prescribed narcotics. Her family doctor was puzzled, because her urinalysis showed no white blood cells (usually found in UTIs), but rather “too numerous to count” red blood cells. Nevertheless, he put her on antibiotics, and told her that she would begin feeling better soon. What is wrong here?

The problem: Bridget has developed drug-induced cystitis, a potentially serious complication of CYC treatment. Below, we address several FAQs about CYC and the bladder.

How would I know that I have developed hemorrhagic cystitis?
Sometimes patients are severely symptomatic and believe, like Bridget, that they have a bad UTI. Their symptoms are characterized by frequent urination – perhaps every half hour – and burning or stinging on urination. In severe cases, patients urinate pieces of the bladder surface that have been seared off by the inflammation. This is, of course, very disturbing and extremely painful. Other patients have relatively few symptoms at the time the problem is diagnosed, and the only clue is the demonstration of small amounts of blood in the urine. Some patients have enough blood in their urine to notice it themselves, but most of the time a microscope is required to see it (hence the term “microscopic hematuria”). This emphasizes the importance of regular screening for early hemorrhagic cystitis.

Can it happen with either oral or intravenous CYC?
Yes – hemorrhagic cystitis can occur with either oral or intravenous administration of CYC. With intravenous CYC, a medication called MESNA can be administered simultaneously to lessen the likelihood of this complication. MESNA binds to acrolein and decreases the risk of bladder damage. Unfortunately, for many forms of vasculitis, oral CYC is preferred because it is more effective in establishing long-term disease control. There is no oral form of MESNA available in the United States.

How is it treated?
Unfortunately, only supportive care is available. The medication must be stopped immediately. Patients are encouraged to continue to drink plenty of fluids. (Keeping fluids in the bladder helps lessen the pain). Narcotics are administered if patients need them; many do. The symptoms of hemorrhagic cystitis usually subside over three to four weeks. The lack of any satisfactory treatment for hemorrhagic cystitis (except for time) underscores further the importance of prevention.

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**Contributions to Research**

Johns Hopkins is an active center for research. Much of our work in vasculitis is funded through grants. Other research support is made possible through private donations, large and small. If you would like to make a contribution to vasculitis research, please send your tax-deductible gift, payable to The Johns Hopkins Vasculitis Center. Our address is: 5501 Hopkins Bayview Circle, JHAAC Room 1B.1A, Baltimore, MD 21224. Questions about philanthropic giving may be directed to Anita Durel (410) 516-6606.

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**Preventing Hemorrhagic Cystitis**

*Following these guidelines helps avoid this complication of cyclophosphamide (CYC).*

- Take CYC first thing in the morning (so that it will not remain in the bladder overnight).
- Drink at least eight 8-ounce glasses of liquid a day (to maintain a brisk urine output).
- Keep in mind the goal of discontinuing CYC as soon as possible. We try to keep patients on CYC for no more than 6 months. Some patients, unfortunately, require longer courses, or second courses if the disease flares.
- If your CYC is administered intravenously, make sure that you are given MESNA at the same time.
- Have a urinalysis performed every two weeks while on CYC, to screen for “microscopic hematuria” - small amounts of blood in the urine that may herald the development of hemorrhagic cystitis.

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**Dr. Stone Receives K24 Award**

Dr. John Stone was recently named a recipient of a K24 Award from the National Institutes of Health. The purpose of the award is twofold. First, the K24 supports Dr. Stone’s work in “translational” research in vasculitis; that is, his efforts to bring laboratory breakthroughs to the bedside. Examples of this are the clinical trials of new therapies conducted by the Center; projects related to genetic discoveries in these diseases; and the proteomics initiative discussed in the Spring 2002 edition of the newsletter. Second, the award also supports Dr. Stone’s mentoring of junior investigators in the field of vasculitis research, to help insure a continuing supply of talented young researchers in this area.

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Are there long-term complications of hemorrhagic cystitis?

There can be. We know that patients treated with long-term courses of CYC – i.e., a year or more – have much greater risks of developing bladder cancer than those who have never received this medication. The risk may be as much as thirty-two times higher. (We believe that the shorter courses of CYC now endorsed will lead to lower rates of this cancer). Patients who have experienced hemorrhagic cystitis should be evaluated by annual urinalyses and periodic cystoscopies, to ensure that long-term bladder problems are not developing.

Bridget’s symptoms resolved after 3 or 4 very uncomfortable weeks. Her disease is no under good control with methotrexate.
From Kussmaul to Kawasaki
Thumbnail sketches in the history of vasculitis
Part Two: Wegener’s granulomatosis to Behçet’s disease

Forms of vasculitis have plagued human beings for thousands of years. Writings from antiquity, including those of Hippocrates, speak of patients with symptoms and maladies that strongly recall the diseases we now recognize as vasculitis (See Behçet’s disease, below). As described in the Fall Issue of the Newsletter, the “modern” era of vasculitis began in 1866. In that year, the German physicians Kussmaul and Maier described the case of a tailor who developed “periarteritis nodosa”, known to us as polyarteritis nodosa (PAN). Their observations formed the basis of vasculitis classifications that continue to this day: most forms of vasculitis are grouped by their similarities to or contrasts with PAN. In this edition of the Newsletter, we conclude our two-part series on the history of vasculitis.

Wegener’s Granulomatosis (1936)

In 1936, a young German pathologist at the University of Kiel, Friedrich Wegener, described three patients in their 30s whose illnesses began in a seemingly innocuous fashion: symptoms of an upper respiratory infection. Soon, however, the patients’ illnesses developed into overwhelming systemic diseases, leading to death from kidney failure within 6 months of the first onset of symptoms. Wegener recognized that the upper respiratory tract inflammation associated with this curious, terrible condition represented a new disease distinct from PAN. Wegener continued to study and write about the disease for the rest of his own life, publishing his last paper on the disease in 1990, the year he died.

Ironically, it was actually Wegener’s former college roommate, Heinz Klinger, who reported the first cases of this disease – five years before Wegener did! As part of his medical school thesis, Klinger reported two patients, one a physician and the other a carpenter. Both patients, like those of Wegener, died of overwhelming systemic disease. Klinger postulated that an infection of some kind was the cause of his patients’ disease – a theory that prevails in many circles today. Failing to recognize the novel disease features of the patients he wrote of, Klinger entitled his thesis: “Variants of Periarteritis Nodosa”. Klinger eventually opted for a career in surgery but remained lifelong friends with Wegener, who apparently truly had never read his former roommate’s thesis before encountering Wegener’s granulomatosis (WG) patients of his own!

For decades after the original work of Klinger and Wegener, the course of WG usually followed that described in those first reports: an inexorable progression to death. With advances in therapy beginning in the 1970s, particularly the use of cyclophosphamide, physicians’ ability to control WG began to improve remarkably. If diagnosed quickly enough now, nearly all patients improve with treatment. More than 80% of patients achieve disease remissions (although, with time, a substantial proportion suffer disease flares). Doctors’ two biggest challenges today with WG are diagnosing the disease before serious damage occurs, and keeping patients in remission while avoiding the toxic side effects of standard therapy (see the Jean

(Continued on page 7)
Churg-Strauss Syndrome (1951)
In 1951, Jacob Churg and Lotte Strauss identified another branch on the Periarteritis nodosa family tree. They described a series of 13 patients with asthma, fever, elevated numbers of eosinophils in the blood and tissues, and inflammation within blood vessels. All of the patients had developed asthma well before the onset of full-blown vasculitis. Churg and Strauss recognized immediately that the striking number of eosinophils associated with this condition distinguished their patients from those with PAN.

We now recognize that the Churg-Strauss syndrome (CSS) proceeds through three stages. First, there is the development of asthma or allergies (this phase may last for months or years). Second, large numbers of eosinophils infiltrate the lungs, gastrointestinal tract, and other tissues. Finally, inflammation develops within the walls of blood vessels, leading potentially to such complications as the crippling involvement of peripheral nerves. Early diagnosis is the key to preventing damage from this disease. Most patients respond very quickly to steroid treatments (such as prednisone). In the future, therapies directed specifically against the eosinophil may lead to treatment advances in CSS.

Microscopic Polyarteritis (Microscopic Polyangitis; 1948)
As implied by the similarities in name of microscopic polyarteritis and polyarteritis nodosa, microscopic polyarteritis (known more properly now as microscopic polyangitis [MPA]) was thought to be a form of PAN that involved smaller sizes of blood vessels – ones requiring a microscope to see. In 1948, English physician Charles Davson and colleagues distinguished MPA from classic PAN by its tendency to involve the smallest blood vessels within the kidney. These tiny vessels, known as glomeruli [“glō mair’ yoo lie”], are the blood-filtering portion of the kidneys. Damage to the glomeruli from vasculitis can lead to kidney failure and dialysis.

In subsequent years, additional contrasts between MPA and PAN became clear. For example, whereas PAN does not involve the lungs (an observation made in 1866), severe cases of MPA may be complicated by life-threatening pulmonary hemorrhage. In addition, MPA is often associated with a type of antibody known as ANCA: anti-neutrophil cytoplasmic antibody. Patients with WG and CSS [see above] also have ANCA in many cases. We will highlight these antibodies and their roles in these diseases in an upcoming edition of the Newsletter.

For decades after Davson et al. described the differences between MPA and PAN, medical science frequently failed to distinguish between these diseases. The 20th Century medical literature is replete with reports that jumble together cases of MPA and PAN. The current treatment for MPA, a combination of prednisone and cyclophosphamide, is very similar to that of other severe forms of vasculitis. New approaches, however, are clearly on the way (watch this space for news about a new clinical trial under development at the Vasculitis Center).
Cogan’s Syndrome (1945)
In 1945, Daniel Cogan of the Massachusetts Eye and Ear Infirmary in Boston reported four patients between the ages of 20 and 35 who presented with either eye problems, ear dysfunction, or both. The eye problems consisted of pain, redness, and sensitivity to light. The ear dysfunction was characterized by disabling vertigo (caused by an inner ear malady) and progressive deafness. Cogan noted that the eye and ear involvement could occur either simultaneously or be separated in onset by a number of months. Compared to the ear disease, the eye inflammation in Cogan’s syndrome is usually easy to control with steroid eyedrops. The hearing dysfunction, however, may require treatment with intensive immunosuppression. A substantial portion of patients lose their hearing, and following repeated disease flares some become completely deaf. In 10-15% of cases, a large-vessel vasculitis resembling Takayasu’s arteritis develops (see Newsletter, Fall 2002).

Henoch-Schönlein Purpura (1801)
Dr. William Heberden, a London physician, described the first cases of Henoch-Schönlein [Hee’ nock - Shirm’ lin’] purpura (HSP) in 1801. Heberden, one of the most accomplished physicians of all time, also became known for his descriptions of “Heberden’s nodes”, which occur on the first knuckle in degenerative arthritis; and “angina”, the chest pain that results from coronary artery insufficiency. In describing HSP, Heberden wrote of a 5-year old boy who “…was seized with pains and swellings in various parts…He sometimes had pains in his belly with vomiting…and the urine was tinged with blood. Presently, the skin of his leg was all over full of bloody points”. The young boy suffered all four disease hallmarks of HSP: arthritis, gastrointestinal involvement, kidney inflammation, and purpura (see figure). Fortunately, the puzzling affliction resolved on its own after several weeks and never returned. This pattern of self-resolution is often observed in HSP, particularly in children.

Johann Schönlein (1837) and Eduard Henoch (1874) reported additional cases decades after Heberden. They recognized that the disorder often followed upper respiratory tract infections and was not always self-limited, sometimes progressing to serious kidney involvement. Sir William Osler, the first Physician-in-Chief at Johns Hopkins Hospital, commented on the similarities between HSP and “serum sickness”. (“Serum sickness” is an allergic reaction usually caused in Osler’s day by the administration of horse serum as a “remedy” for a variety of human ailments. This remedy, gratefully, has fallen by the wayside).

Cryoglobulinemia (1933)
In 1933, the Bulletin of the Johns Hopkins Hospital included a report of a new disease. Maxwell Wintrobe, then a second-year resident at Hopkins, evaluated a patient with “symptoms of coldness, blanching, and a peculiar mottling of the extremities, as well as other signs of disturbed circulation”. Upon drawing the patient’s blood...
himself, Wintrobe noted an odd thing: the immediate precipitation of a “dense, yellowish gray layer of material”. Slipping the tube of blood into the pocket of his lab coat, he went to show the unusual finding to his colleagues. When he retrieved the tube only minutes later, however, the yellowish gray material, warmed sufficiently by residing in his pocket, had dissolved again into the blood.

Still curious, Wintrobe discovered that greater quantities of the yellowish gray substance could be precipitated by refrigeration, and ultimately determined that the yellowish gray substance was a protein. Because of their property of precipitating out of blood in cool temperatures, proteins of this nature became known as cryoglobulins (cryo = cold; globulin = protein). We now know that there are several different types of cryoglobulins: some associated with infections; others associated with autoimmune diseases; and still others associated with some forms of cancer. In the 1990s, investigators linked the great majority of cases of cryoglobulinemia to infections with hepatitis C.

Following his training at Hopkins, Wintrobe remained fascinated by blood problems throughout his career. In subsequent years, he became the Chief of Medicine at the University of Utah and developed a method for measuring the erythrocyte sedimentation rate, a standard test that remains vital to the practice of rheumatology.

**Behçet’s Disease (1937)**

Behçet’s [Buh shettes ’] Disease (BD) is a form of vasculitis characterized by ulcers in the mouth and on the genitals, inflammatory eye disease, central nervous system involvement, and a host of other manifestations. Although BD did not enter the medical lexicon until the 20th century, it is quite possible that the disease was first described in antiquity by none other than Hippocrates himself. In his **Third Book of Endemic Diseases**, Hippocrates wrote of patients with oral and genital ulcers and ocular disease – sensitivity of the eyes to light and, in some cases, loss of vision.

A Turkish physician, Dr. Hulusi Behçet, was a Professor of Dermatology at the University of Istanbul when he reported this disease. In 1937, he described two patients, a 40-year old man and a 34-year old woman with all of the major hallmarks of this disease. Behçet cared for these patients for two decades, even sending one to Vienna, a medical Mecca of the day. Treatment there with injections of gold and trivalent arsenic – two other wayside therapies – were unhelpful.

The fact that a Turkish physician was the first to describe BD in modern times follows logically from the geographical distribution of this disease. Rare in the United States, BD is 300 times more common along parts of the Old Silk Route, which extends from the Far East (China, Korea, and Japan) to the Middle East. In these regions, BD is a leading cause of blindness. The prevalence is perhaps highest in the region once known as Asia Minor: Turkey. The concentration of BD cases in this part of the world suggests the possibility of a genetic contribution to the disease. Indeed, BD is strongly associated with a gene known as HLA-B51.

*People who develop thorough understandings of their illnesses are more likely to form effective partnerships with their doctors. A full understanding of an illness includes some knowledge of the ailment’s history. We have attempted to provide that here. As this series of thumbnail sketches on the history of vasculitis indicates, the histories of these disorders are as varied as the diseases themselves.*

The Fall 2002 issue of the Newsletter featured thumbnail sketches on PAN, giant cell arteritis, polymyalgia rheumatica, Takayasu’s arteritis, Buerger’s disease, and Kawasaki’s disease. If you missed it or would like to see it again, the Newsletter can be downloaded in pdf format from the Johns Hopkins Vasculitis Center Website: 
[http://vasculitis.med.jhu.edu](http://vasculitis.med.jhu.edu)
Clinic Corner: Getting to the JHVC

Well, the hard part is done—you’ve incorporated a follow-up appointment into your busy schedule. But now, a new concern… how are you getting to the Vasculitis Center? Whether your travel plans include trains, planes, or automobiles, our Hopkins network can assist. Hopkins has two major programs that help travelers make Baltimore their temporary home.

The first program, the Travel Center (800-225-2201), assists patients with finding nearby lodging. Discounts apply for Hopkins patients. The Travel Center can also provide information about tourist sites and other attractions near your hotel. Many hotels offer free shuttle service from the hotel to the Hopkins campus.

For those of you traveling by plane, World Travel Partners (800-492-5916), can assist with flight arrangements. Since these coordinators are contracted, shorter wait times and no automation eliminates most of the pre-travel anxiety.

Driving? Park in the mid-campus lot on Hopkins Bayview Drive. Easy to get to off either I-895 or I-95. See the website for driving directions (www.jhbmc.jhu.edu). We look forward to seeing you at your next scheduled appointment!