Letter from the Chief
Michael B. Brenner, MD, Chief, Division of Rheumatology, Immunology and Allergy, surveys the activities of the Division and its multidisciplinary Centers.

Collaborative Clinic Enhances Understanding of Interstitial Lung Disease and Tailors Treatment
The Interstitial Lung Disease (ILD) Clinic’s expert rheumatologists and pulmonologists provide multidisciplinary evaluation of patients with ILD, including their classification outcomes and options for treatment.

Active Clinical Trials and Innovative Research in Systemic Lupus Erythematosus
With a broad range of new trials, biomarker studies, and recent data for longitudinal studies, specialists in the Lupus Center provide new treatments for many forms of lupus.

Delivering Specialized Care and New Treatment Approaches for Adults with Juvenile Rheumatic Disease
The Center for Adults with Pediatric Rheumatic Illness (CAPRI) addresses the specific needs of adults with pediatric rheumatic disease and their complications, while facilitating the transition to adult care.

Specialists Offer Extensive Studies of Treatment and Risk Factors for Concomitant Systemic Rheumatic Disease and Skin Disease
Rheumatologists and dermatologists in the Center for Skin and Related Musculoskeletal Disease offer a novel approach to the diagnosis and management of patients with diseases with both musculoskeletal and cutaneous involvement.
The Interstitial Lung Disease (ILD) Clinic, co-directed by rheumatologist Paul F. Dellaripa, MD, and pulmonologist Hilary J. Goldberg, MD, MPH, aims to advance the management of patients with ILD – either associated with connective tissue disease, such as rheumatoid arthritis, scleroderma, or inflammatory myositis, or attributed to idiopathic pulmonary fibrosis (IPF) – through multidisciplinary evaluation, clinical trials, and outcomes research.

“Comprehensive evaluation of patients with interstitial lung disease involves looking beyond the symptoms,” noted Dr. Goldberg. “For example, lung manifestations in ILD often occur well before rheumatic indications.”

Caring for hundreds of patients each year, the ILD Clinic’s nine-member team, which consists of rheumatologists, pulmonologists, radiologists, and pathologists with expertise in interstitial lung disease, offers a unique approach to coordinated patient care.

**ILD Classification**

A recent study by ILD Clinic specialists demonstrates the impact of rheumatologic evaluation in the
management of patients with ILD (Rheumatology, doi:10.1093/rheumatology/keq233). Based on a retrospective review of patients referred to the ILD Clinic over a 12-month period, the study determined that differentiation between ILD attributable to connective tissue disease (CTD-ILD) versus IPF, was important in specifying diagnosis and planning treatment. In total, the study found that 54 percent of patients referred to the ILD Clinic had a change in diagnosis, and that changes in therapy were made in 80 percent of patients with CTD-ILD and 27 percent of patients with IPF (Figure 1).

“Determining the nature of the disease is critical in providing the most effective course of treatment,” said Dr. Dellaripa. “Many patients with ILD due to rheumatic or connective tissue disease may benefit from additional immunomodulatory therapy, while a diagnosis of IPF may lead to discontinuation of immunosuppressive therapy in order to prevent substantial treatment-related side effects.”

Patients in the ILD Clinic are concurrently evaluated and treated by a rheumatologist and a pulmonologist, who combine with specialized pathologists and radiologists to review each patient’s laboratory and imaging studies. For patients who require transplantation, the ILD Clinic streamlines referrals to the Lung Transplant Program at Brigham and Women’s Hospital – which has completed 369 single and bilateral lung transplants to date. Recently expanded donor criteria have increased organ availability and patient eligibility for lung transplantation.

**Current Studies**

The ILD Clinic participates in a range of studies designed to advance care for patients, including:

- **OMERACT (Outcomes Research in Rheumatology) Trial** – This international study seeks to identify factors – including biomarkers, radiographic studies, and other tests – that correlate with improved outcomes during treatment of ILD.

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**Figure 1**

**Characteristics of patients with a final diagnosis of CTD-ILD**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-ILD clinic diagnosis</th>
<th>Post-ILD clinic diagnosis</th>
<th>Serologies</th>
<th>Imaging pattern</th>
<th>Change in treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>54 F</td>
<td>IPF</td>
<td>Anti-synthetase syndrome</td>
<td>+ANA, +PL-12</td>
<td>UIP</td>
<td>CS, MMF initiated</td>
</tr>
<tr>
<td>47 F</td>
<td>ILD/seronegative RA</td>
<td>Anti-synthetase syndrome</td>
<td>+ANA, +Jo-1</td>
<td>NSIP</td>
<td>MTX added for arthritis</td>
</tr>
<tr>
<td>46 F</td>
<td>ILD/rheumatic disease</td>
<td>Anti-synthetase syndrome</td>
<td>+ANA, +PL-12</td>
<td>NSIP</td>
<td>CS, MMF changed to CYC</td>
</tr>
<tr>
<td>44 M</td>
<td>ILD/seronegative RA</td>
<td>DM</td>
<td>+ANA, +Jo-1</td>
<td>NSIP</td>
<td>CS, MMF initiated</td>
</tr>
<tr>
<td>43 M</td>
<td>ILD/rheumatic disease</td>
<td>DM</td>
<td>+ANA, +Jo-1</td>
<td>Other</td>
<td>CS, MMF initiated</td>
</tr>
<tr>
<td>42 F</td>
<td>IPF</td>
<td>UCTD</td>
<td>+ANA, +Ro</td>
<td>Other</td>
<td>Increased CS</td>
</tr>
<tr>
<td>61 F</td>
<td>IPF</td>
<td>UCTD</td>
<td>+ANA</td>
<td>Other</td>
<td>CS, MMF initiated</td>
</tr>
<tr>
<td>57 F</td>
<td>IPF</td>
<td>UCTD</td>
<td>+ANA, +Sm</td>
<td>Other</td>
<td>CS initiated</td>
</tr>
<tr>
<td>56 M</td>
<td>IPF</td>
<td>UCTD</td>
<td>+ANA</td>
<td>NSIP</td>
<td>CS initiated</td>
</tr>
<tr>
<td>55 M</td>
<td>ILD/SLE</td>
<td>UCTD</td>
<td>+ANA</td>
<td>Other</td>
<td>MMF initiated</td>
</tr>
<tr>
<td>54 M</td>
<td>IPF</td>
<td>SS</td>
<td>+ANA, +Scl-70</td>
<td>NSIP</td>
<td>CS, MMF initiated</td>
</tr>
<tr>
<td>53 F</td>
<td>ILD/RA</td>
<td>SS</td>
<td>+ANA, +Scl-70</td>
<td>Other</td>
<td>MTX discontinued, CS tapered, MMF initiated</td>
</tr>
<tr>
<td>52 F</td>
<td>ILD/SLE</td>
<td>Limited SS</td>
<td>+ANA, nucleolar</td>
<td>Other</td>
<td>Discontinued hydroxychloroquine</td>
</tr>
<tr>
<td>51 F</td>
<td>ILD NOS</td>
<td>SS</td>
<td>+ANA</td>
<td>LIP</td>
<td>Rituximab initiated</td>
</tr>
<tr>
<td>50 F</td>
<td>ILD NOS</td>
<td>SS</td>
<td>+ANA, +La</td>
<td>LIP</td>
<td>Rituximab initiated</td>
</tr>
<tr>
<td>59 F</td>
<td>ILD NOS</td>
<td>WG</td>
<td>c-ANCA, pr3 staining</td>
<td>Other</td>
<td>CS, Rituximab initiated</td>
</tr>
<tr>
<td>60 M</td>
<td>ILD/UCTD</td>
<td>SLE</td>
<td>+ANA, dSNA, La</td>
<td>Other</td>
<td>CS, MMF initiated</td>
</tr>
<tr>
<td>61 M</td>
<td>ILD/RA</td>
<td>RA</td>
<td>+RF, +anti-CCP</td>
<td>UIP</td>
<td>CS tapered</td>
</tr>
<tr>
<td>59 F</td>
<td>ILD/RA</td>
<td>RA</td>
<td>+RF</td>
<td>UIP</td>
<td>No change</td>
</tr>
<tr>
<td>58 F</td>
<td>ILD/RA</td>
<td>RA</td>
<td>+RF</td>
<td>NSIP</td>
<td>No change</td>
</tr>
<tr>
<td>57 F</td>
<td>ILD/RA</td>
<td>RA</td>
<td>+RF</td>
<td>UIP</td>
<td>No change</td>
</tr>
<tr>
<td>56 F</td>
<td>ILD/RA</td>
<td>RA</td>
<td>+RF</td>
<td>NSIP</td>
<td>No change</td>
</tr>
<tr>
<td>55 F</td>
<td>ILD/rheumatic disease</td>
<td>MCTD</td>
<td>+ANA, +RNP</td>
<td>Other</td>
<td>No change</td>
</tr>
<tr>
<td>54 F</td>
<td>Possible ILD</td>
<td>MCTD</td>
<td>+ANA, +RNP</td>
<td>NSIP</td>
<td>CS taper, MMF added</td>
</tr>
</tbody>
</table>

*Treatment changes are also noted. NOS: not otherwise specified; F: female; M: male. LIP = lymphocytic interstitial pneumonia    NSIP = nonspecific interstitial pneumonia   UIP = usual interstitial pneumonia  UCTD = undifferentiated connective tissue disease*
Staffed by seven board-certified rheumatologists with extensive expertise in the evaluation and treatment of all forms of lupus, the Lupus Center provides skilled care for patients with all forms of lupus erythematosus. Co-directed by Bonnie L. Bemmas, MD, and Karen Costenbader, MD, MPH, the Lupus Center sees approximately 700 patients per year – while coordinating care with specialists in the Brigham and Women's Hospital Departments of Neurology, Nephrology, Dermatology, Obstetrics and Gynecology.

The Lupus Center includes an active clinical trials program led by Elena M. Massarotti, MD, Director of Clinical Trials, and a vigorous area of clinical research.

Current studies at the Center include:

- **APRIL** – A randomized, double-blind, placebo-controlled, multicenter, prospective dose-finding Phase II/III study with atacicept given subcutaneously to subjects having recently experienced a non-renal flare of systemic lupus erythematosus (SLE). *(Please contact Principal Investigator Elena M. Massarotti, MD, at emassarotti@partners.org for more information.);

- **NIH Centers of Excellence Study** – The Lupus Center is one of the few centers nationwide to participate in an NIH Autoimmunity Centers of Excellence study examining the role of Vitamin D supplementation on the interferon alpha (IFN) signature in patients with stable SLE. *(Please contact Project Principal Investigator Elena M. Massarotti, MD, at emassarotti@partners.org for more information.)

**Assessing Biomarkers for SLE Disease Activity**

Dr. Costenbader and other rheumatologists at the Lupus Center completed a study with Beth Israel Deaconess Medical Center *(Arthritis Rheum. 2010 May; 62(5):1431-7.) that investigated variants in T cell CD44 cell surface markers as potential markers of SLE disease activity and kidney involvement. Clinical information and blood samples were obtained from 72 patients with SLE and 32 healthy individuals. Expression of CD44 variants v3 and v6 on T cell subsets was determined by flow cytometry. The results indicated that expression levels of CD44 variants v3 and v6 T cells are potentially useful biomarkers of SLE activity and are highly correlated with kidney disease and the presence of certain autoantibodies in lupus patients. Results of these studies suggest promising new ways to enable earlier detection of disease and estimation of disease progression.

“Our hope is that, through advances in early disease detection, we can help minimize damage and long-term effects of lupus and many other rheumatic diseases,” said Dr. Costenbader.

**Developing New Tools for Expansion of Longitudinal Studies**

Dr. Costenbader and other specialists in the Lupus Center recently led a multi-center study to develop and evaluate a new way to enable earlier detection of disease and estimation of disease progression.
Dedicated to providing a continuum of care for adults with juvenile rheumatic illness, including juvenile idiopathic arthritis (JIA), lupus, and vasculitis, the Center for Adults with Pediatric Rheumatic Illness (CAPRI) offers specialized treatment approaches and facilitates the transition from pediatric to adult care. A unique collaboration with Children’s Hospital Boston, CAPRI incorporates a variety of specialists at Brigham and Women’s Hospital to meet the specific needs of patients with juvenile-onset rheumatic disease in adulthood.

**Differences between juvenile-onset and Adult-onset Disease**

“Since inflammation strikes during key developmental years, juvenile idiopathic arthritis can lead to a range of long-lasting complications, including significant musculoskeletal and orthopedic issues,” said Peter A. Nigrovic, MD, director of CAPRI. “This inflammation can persist into adulthood, so we promote aggressive treatment of inflammation using newer medications to prevent long-term damage and disability.”

Center specialists use approaches that may vary from those typically applied to adult-onset disease. For example, Dr. Nigrovic and colleagues have accumulated evidence that early use of the IL-1 antagonist anakinra can yield substantial long-term benefit in the care of patients with a form of arthritis termed systemic JIA, as presented at the recent meeting of the American College of Rheumatology.

Complications of JIA often involve musculoskeletal and orthopedic issues – such as erosive joint disease, early osteoarthritis, growth deformity, cervical spine ankylosis and instability, temporomandibular joint arthritis, mandibular deformities, and complicated joint replacements in growth-deformed bone. Among other potential medical issues are eye disease, cardiovascular risk, amyloidosis, reproductive issues and associated autoimmune conditions – including type I diabetes, thyroid disease, celiac disease, gonadal failure, and immunodeficiencies, such as IgA deficiency and common variable immunodeficiency.

CAPRI addresses these complications in conjunction with orthopedic surgeons, cardiologists, neurologists, and ophthalmologists at Brigham and Women’s Hospital. Additional CAPRI services, such as those provided by social work, are designed to help patients in the development of self care skills and independence in medical, vocational, and social areas.

Dr. Nigrovic and Patience H. White, MD, from the Arthritis Foundation, have published an article outlining important aspects of the care and differences between juvenile-onset and adult-onset arthritis (Arthritis Rheum. 2006 Apr 15;55(2):208-16.). In addition to the many medical conditions affected by JRA, the article outlines psychosocial considerations in JRA.

“The onset of disease during childhood affects patients socially and emotionally, as well as physically,” said Dr. Nigrovic. “Personalities and life interests develop during the early teen years, and we find that children and their parents tend to be more focused on their disease, rather than social and vocational interests. It is very important to address these challenges well before the age of transition to adult care.”

Long-term psychosocial effects of JIA include issues with body image, delay in marriage, increase in unemployment, and reduced quality-of-life. In addition, patients in their teens or early twenties with JIA often alter their activities and goals to accommodate limits, fatigue, and pain brought on by their disease. CAPRI specialists encourage these patients to take an active role in disease management and to develop and maintain age-appropriate interests.

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 specialty to rheumatologist Elinor Mody, MD, and dermatologist Abrar Qureshi, MD, MPH, the Center for Skin and Related Musculoskeletal Diseases offers an innovative approach to the diagnosis and management of patients with diseases with both musculoskeletal and cutaneous involvement.

“Together, we are able to tackle many of the diagnostic and treatment challenges that these conditions present, while looking at the larger picture in order to determine the extent of the patient’s disease burden,” said Dr. Mody.

Formally established seven years ago, the Center is one of the few in the nation to deliver simultaneous rheumatologic and dermatologic evaluation of these patients. In addition to care for patients with psoriasis and psoriatic arthritis, the Center treats a wide range of diseases that can affect both the skin and the joints, such as discoid and systemic lupus, Sweet’s syndrome and other neutrophilic dermatoses, dermatomyositis, pyoderma gangrenosum, sarcoidosis, scleroderma, and vasculitis, among others. Residents and fellows from the Division of Rheumatology, Immunology, and Allergy and from the Department of Dermatology rotate simultaneously through the Center and thus reap extraordinary educational benefits from this collective enterprise. The Center often excels in the diagnosis and management of difficult clinical problems, as illustrated by the following vignette:

A 47-year-old woman with longstanding rheumatoid arthritis and rash was referred to the Center. Her RA had responded well to etanercept, but she now presented with a slightly pruritic, nonpainful rash on the forearms. On examination, she was found to have a maculopapular rash (at right), forming annular lesions on the arms and legs. Diascopy was positive, showing brownish discoloration after erythema had blanched out. As there was concern for a vasculopathic or vasculitic versus granulomatous eruption, a biopsy was performed. The biopsy demonstrated dermal multifocal non-necrotizing granulomas. Cultures were negative. Consideration was given to stopping etanercept, but rheumatologic evaluation suggested the importance of continuing TNF alpha blockade for continued control of RA. Instead, high potency topical steroids were used for successful management of the eruption.

Current Studies in Psoriasis and Psoriatic Arthritis

The Center has promoted the early detection and treatment for psoriasis and psoriatic arthritis through a number of publications over the last seven years, and is currently examining the long-term safety of current medications for psoriasis and psoriatic arthritis, as well participating in further studies to assess new agents:

- **PSOLAR (Psoriasis Longitudinal Assessment and Registry)** – Principal Investigator Abrar Qureshi, MD, MPH is leading this national registry to further evaluate the safety of infliximab (Remicade) and ustekinumab (Stelara) in patients with plaque psoriasis and other overlapping forms of psoriasis. The registry also will evaluate clinical outcomes, quality of life, and potential risks for patients who may receive standard therapies for psoriasis. (Please contact Abrar Qureshi, MD, MPH, for more information at aqureshi@bics.bwh.harvard.edu);

- **ESPRIT (Post-marketing, Observational Study of Humira in Patients with Chronic Plaque Psoriasis)** – Led by Principal Investigator Abrar Qureshi, MD, MPH, ESPRIT is a 10-year observational study of patients taking adalimumab (Humira) for chronic plaque psoriasis. (Please contact Abrar Qureshi, MD, MPH, for more information at aqureshi@bics.bwh.harvard.edu.)

- **New Trials for Chronic Plaque Psoriasis** – New trials for patients with moderate to severe chronic plaque psoriasis include a phase II, randomized, placebo-controlled, dose-range finding study of subcutaneous SCH 900222 and a phase III, randomized, placebo-controlled study of oral CP-690,550. (Please contact Abrar Qureshi, MD, MPH, for more information at aqureshi@bics.bwh.harvard.edu);

“Approximately 20 to 30 percent of patients with psoriasis will develop psoriatic arthritis,” said Dr. Qureshi. “Using a novel approach, we are striving to improve screening of
patients with psoriasis for symptoms of inflammatory arthritis through simple tools that can be used during a clinic visit, as well as studies to help us better understand the development and risk factors for psoriatic arthritis.”

Other tools developed by the Center for the study of psoriasis and psoriatic arthritis include:

- **Psoriatic Arthritis and Psoriasis Follow-up Study (PAFS)**
  - The Center has compiled clinical data, including responses to medications, on more than 900 patients with psoriasis and psoriatic arthritis. Plans are underway to expand the use of this registry for the inclusion of imaging modalities to determine whether patients may have evidence of psoriatic arthritis prior to the onset of symptoms, as well as studies on such co-morbidities as obesity and cardiovascular disease.

- **Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire** – Developed by specialists at the Center, this published self-administered patient questionnaire has been requested by dermatologists worldwide to help identify patients with psoriasis who should be referred to a rheumatologist for evaluation for psoriatic arthritis. PASE has been translated into 18 languages and used in more than 21 countries for clinical and research purposes. The benefits of this questionnaire and other screening tools were outlined in the *Journal of Rheumatology* (J Rheumatol, 2008. 35(7): p. 1423-5).

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**Collaborative Clinic Enhances Understanding of Interstitial Lung Disease and Tailors Treatment... continued from page 3**

Findings from this group are expected to aid in the development of future clinical trials for ILD:

- **Rituxamab and ILD** – The ILD Clinic is one of only two centers nationally to engage in an ongoing trial of rituxamab for the treatment of ILD;

- **IPF Studies** – The ILD Clinic also is part of the ARTEMIS-IPF trial, a Phase III, randomized, multi-center study to evaluate the efficacy and safety of ambrisentan in patients with early IPF.

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**ILD and Dermatomyositis**

A 59 year-old-male patient with new onset rash, muscle weakness and dyspnea, and desaturation with exercise was referred to the Interstitial Lung Disease Clinic. A chest CT scan showed diffuse bilateral ground glass opacities (Picture 1). Skin findings led to a diagnosis of ILD associated with dermatomyositis, for which treatment with intravenous cyclophosphamide and corticosteroids was initiated. Six months later, the patient was transitioned to azathioprine therapy. Follow up CT scan (Picture 2) showed resolution of ground glass opacities. The patient no longer requires immunosuppression and no longer has dyspnea. Pulmonary function tests have improved to near normal.
new questionnaire that enables patient self-assessment of organ damage specifically caused by lupus (Arthritis Care Res 2010 Apr;62(4):559-68.). The Lupus Damage Index Questionnaire (LDIQ) was modeled on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Results of the study, which involved 569 lupus subjects and 14 lupus rheumatologists from 11 international lupus centers, as well as 605 lupus participants in the community-based National Data Bank for Rheumatic Diseases (NDB), demonstrated that the LDIQ could be valuable in the expansion of lupus research, particularly to longitudinal, community-based studies. The metric properties of the LDIQ compared well with SDI and included assessment of correlations with outcome and disability measures, sensitivity, specificity, Spearman’s correlations, and agreement, using the SDI as the gold standard.

In the development of the new Lupus Damage Index Questionnaire (LDIQ), many questions about potential damage in different organ systems were asked of lupus patient participants. The proportion to which each of the individual organ system questions (domains) contributes to the total LDIQ score is represented above.

Delivering Specialized Care and New Treatment Approaches for Adults with Juvenile Rheumatic Disease... continued from page 5

Research Advances in Arthritis

In the laboratory, Dr. Nigrovic is investigating the role of mechanisms of inflammation in arthritis, focusing on the role of mast cells and neutrophils in the earliest phase of inflammatory response. He also collaborated on a study of the role of platelets and their microparticles in RA (Science. 2010 Jan 29;327(5965):528-9.). The study identified platelet fragments called microparticles in joint fluid from patients with RA and other forms of inflammatory arthritis, including juvenile idiopathic arthritis, but not in joint fluid from patients with osteoarthritis. These microparticles were proinflammatory, eliciting cytokine responses from synovial fibroblasts via interleukin-1. Using both pharmacologic and genetic approaches, investigators in the study identified the collagen receptor glycoprotein VI as a key trigger for platelet microparticle generation in the inflamed joint. This study has raised the intriguing possibility that interference with platelets and their microparticles may be a promising new avenue of anti-inflammatory therapy.