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For the Editors
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A little more than a year ago, we published an editorial calling for papers describing research on human subjects (1). Research on human subjects is becoming more feasible because of advances in methodology, and investigations on human subjects are needed to advance the areas of human physiology and disease covered by the Journal. Patient-oriented research in particular is often perceived as being applied rather than basic research, but we reasoned that these demanding investigations can provide essential new biological insights and have an important place in our Journal, even though the depth of mechanistic analysis is of necessity more limited than in research on simpler systems. To encourage submissions of papers that involved human studies, we made a commitment to judge them on their capacity to advance the field within the context of human research.

During the ensuing year, there has been a striking increase in the number of submissions involving human subjects. In parallel, the number of accepted papers that required human subjects increased more than threefold in 2004 compared with 2003, with ~10% of papers published in 2004 involving human subjects. We also are pleased to have witnessed an increased number of papers in which human pathogens were studied but with human papers relative to papers involving human subjects. In 2004 the number of accepted papers in this sphere was ~5%, a twofold increase over 2003. These changes bring some balance to experimental medicine in the Journal, which clearly retains its focus on “basic” research and disease models in which deeper mechanistic studies are possible. We hope that future studies in these more tractable experimental systems will be inspired by findings in patients.

Editorial challenges
The increase in human subject papers has placed new demands on our peer review process, especially as the increase was superimposed on a high submission rate in other areas. We are still in the process of adjusting to these new needs. Glenn Heller (Memorial Sloan-Kettering Cancer Center, New York, NY) and Madhu Mazumdar (Weill Cornell Medical College, New York, NY) have essential roles as Consulting Biostatistics Editors. We also are benefiting from the expert advice of a number of referees who are familiar with human research, several of whom have joined our Advisory Editorial Board. Most recently, we welcomed David Hafler (Harvard Medical School, Boston, MA), Kevin Tracey (North Shore University Hospital, Manhasset, NY), and Jean-Laurent Casanova (Necker Medical School, Paris, France), who bring broad expertise in autoimmunity, inflammation, and infectious disease biology, respectively.

Evaluating human research
What are the Editors looking for when they screen papers involving human subjects? Three of the criteria are the same as for all other papers: conceptual novelty, state of the art approaches, and the highest biological or therapeutic importance. But there is one difference with human papers relative to papers with simpler experimental systems. Although new mechanistic insight is essential, we do not necessarily expect the depth of the mechanistic workup to be comparable. Some of the human studies we have published involve a detailed analysis of a very small number of patients, whereas others involve a larger number of subjects. Typically, the investigators were not able to pursue and firmly establish mechanism in one paper in a way that is expected of research with mice. Nonetheless, the Editors and most referees appreciate the constraints imposed by protocols that must protect human subjects and, in each case, the potential impact of the study was judged to be high, in spite of these limitations.

Experimental medicine in patients
The human subject papers that we have published reflect a diversity of topics and approaches. All are careful, systematic studies that provide new biological insight, but very few have involved actual experiments in patients using experimental or approved interventions to understand human physiology. This is where our research enterprise needs to grow and this will require much more support than it is currently receiving. As scientists, we are accustomed to dissecting and analyzing a system in a reductionist way, often in genetically altered animals, to understand what is going on and in many cases to inspire future treatments. But in human subjects there is often a need to take a more integra-
tive and interventional approach and try to direct physiology in order to understand disease processes and initiate new therapies. In this issue, Pascual and colleagues investigate the role of specific cytokines in the pathogenesis of a form of childhood arthritis. They obtained clues that interleukin-1 may be involved, and show that blockade of interleukin-1 results in marked amelioration of this disease (2). Also in this issue, Chang and colleagues, having found earlier indications that NKT cells might be providing protection against cancer, assessed the capacity of mature dendritic cells, charged with a synthetic glycolipid, to expand NKT cells in patients with advanced cancer. They discovered that the levels of NKT cells in blood undergo prolonged expansion and that this can be associated with increased adaptive immunity to a third party cytomegalovirus antigen (3). The systematic study of a problem by intervention in patients is a powerful form of research, but it is currently a small and relatively neglected part of our profession. For research on patients to grow we need to overcome many of the obstacles and omissions that are currently apparent in terms of training, funding, and access to clinical-grade reagents (4).

A barrier to publishing in basic scientific journals with broad readerships is an additional obstacle to the development of careers in patient-based research. Surely the increase in submitted and accepted papers that we have seen reflects that investigators who study human subjects want to see their work published in these journals. The problem has been that most basic science journals simply are not prepared to get excited about the best findings that can be made in human subjects. We are excited by the new insights into human disease and physiology that we have published over the past 18 months. Nevertheless, the JEM and other journals may not get to publish more experimental medicine in patients unless the research community more broadly overcomes the difficulties encountered by investigators who study human subjects.

REFERENCES