

4, 5, and 6) resulting in hyper-IgD, hyper-IgE, or both. This effect has not been reported in humans, and at this time, this observation pertains to data collected in studies of our and Hoffmann's murine model³ of mevalonate kinase deficiency that were not cited in the Perspective.

Elizabeth J. Hager, Ph.D.

K. Michael Gibson, Ph.D.

University of Pittsburgh School of Medicine
Pittsburgh, PA 15261
elizabeth.cothren@chp.edu

1. Haas D, Hoffmann G. Mevalonate kinase deficiency and autoinflammatory disorders. *N Engl J Med* 2007;356:2671-3.
2. Neven B, Valayannopoulos V, Quartier P, et al. Allogeneic bone marrow transplantation in mevalonic aciduria. *N Engl J Med* 2007;356:2700-3.
3. Gibson KM, Tse T, Pappu A, Steiner R, Hoffmann G, Hager E. Chronic inflammation and hyper-IgD/IgE in mice with targeted deletion of the mevalonate kinase gene. *J Inherit Metab Dis* 2007;30:Suppl 1:45. abstract.

More on Severe Cutaneous Reaction with Radiotherapy and Cetuximab

TO THE EDITOR: In their letter to the editor, Budach et al. (Aug. 2 issue)¹ report on two patients with squamous-cell carcinoma of the head and neck who had severe radiation dermatitis while receiving a combination of radiotherapy and cetuximab, a regimen found to be superior to radiotherapy alone in our proof-of-concept phase 3 trial.² Severe radiation dermatitis can occur after irradiation alone, but grade 4 dermatitis is rarely observed. In reviewing the case histories of the patients, Budach et al. note that Patient 1 had previously received etoposide-based therapy and Patient 2 had previously received a full course of radiotherapy to the head and neck. Furthermore, both patients had cirrhosis, and one had renal insufficiency. Whether these coexisting conditions altered the pharmacodynamics of cetuximab and, when confounded by the preexisting occult chemotherapy- or radiotherapy-induced dermal injury, predisposed the patients to the development of more severe radiation dermatitis is difficult to assess. The absence of a cetuximab-induced maculopapular rash in Patient 1 might argue against any critical role of cetuximab in exacerbating radiation dermatitis in this patient.

James A. Bonner, M.D.

University of Alabama at Birmingham
Birmingham, AL 35233

Kian Ang, M.D., Ph.D.

M.D. Anderson Cancer Center
Houston, TX 77030

Dr. Bonner reports serving as a consultant for Bristol-Myers Squibb and Imclone Systems. Dr. Ang reports serving as a consultant for Merck KGaA and ImClone Systems and having received grant support from ImClone Systems. No other potential conflict of interest relevant to this letter was reported.

1. Budach W, Bölke E, Homey B. Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med* 2007;357:514-5.

2. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567-78.

THE AUTHORS REPLY: We agree with Bonner and Ang that severe radiation dermatitis may occur after irradiation alone but that grade 4 lesions are rarely observed. Previous chemotherapy is unlikely to explain the severe reaction in our patients, since Patient 1 had received her radiotherapy for breast cancer after induction chemotherapy without an enhanced skin reaction, and Patient 2 had not received chemotherapy at all. Both patients had Child–Pugh class A cirrhosis. Pharmacokinetic studies of cetuximab have shown that Child–Pugh class A cirrhosis does not modify serum levels of the drug or enhance cutaneous side effects.^{1,2} In the absence of marked proteinuria, negligible renal elimination of antibodies occurs. However, glomerular or tubular damage may markedly increase renal protein loss, which may include loss of immunoglobulins.^{3,4} Hence, renal insufficiency with polyuria and proteinuria, as observed in Patient 1, would be more likely to result in a loss of antibodies than in antibody retention. We believe these findings argue for a causal relationship between this treatment protocol and the observed cutaneous side effects, but more data are needed to help determine how often and in what clinical situations this complication may occur.

Wilfried Budach, M.D.

Edwin Bölke, M.D.

Bernhard Homey, M.D.

University of Düsseldorf
D-40225 Düsseldorf, Germany
wilfried.budach@uni-duesseldorf.de

Since publication of the letter, Dr. Homey reports receiving research funding from Roche. No other potential conflict of interest relevant to this letter was reported.

1. Fracasso PM, Burris H III, Arquette MA, et al. A phase 1 escalating single-dose and weekly fixed-dose study of cetuximab: pharmacokinetic and pharmacodynamic rationale for dosing. *Clin Cancer Res* 2007;13:986-93.
2. Zhu AX, Stuart K, Blaszkowsky LS, et al. Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. *Cancer* 2007;110:581-9.

3. Bakoush O, Torffvit O, Rippe B, Tencer J. High proteinuria selectivity index based upon IgM is a strong predictor of poor renal survival in glomerular diseases. *Nephrol Dial Transplant* 2001;16:1357-63.

4. Branten AJ, du Buf-Vereijken PW, Klasen IS, et al. Urinary excretion of beta2-microglobulin and IgG predict prognosis in idiopathic membranous nephropathy: a validation study. *J Am Soc Nephrol* 2005;16:169-74.

Myocardial Infarction Induced by Appetite Suppressants in Malaysia

TO THE EDITOR: During the past 10 years, there has been a precipitous rise in the number of reports of adverse drug reactions in Malaysia.¹ Of these reports, 20 have involved antiobesity medications, of which only phentermine and orlistat are legally available. Sibutramine, whose approv-

