ing further careful investigation of the risk–benefit ratio of therapeutic complement blockade in this toxin-mediated vasculopathy.

Anne-Laure Lapeyraque, M.D.
Hôpital Sainte-Justine
Montreal, QC, Canada

Michal Malina, M.D.
Center for Pediatrics and Adolescent Medicine
Heidelberg, Germany

Véronique Fremeaux-Bacchi, M.D., Ph.D.
Hôpital Européen Georges-Pompidou
Paris, France

Tobias Boppel, M.D.
Neurology Center
Heidelberg, Germany

Michael Kirschfink, M.D., Ph.D.
Institute of Immunology
Heidelberg, Germany

Mehdi Oualha, M.D.
Hôpital Necker–Enfants Malades
Paris, France

François Proulx, M.D.
Marie-José Clermont, M.D.
Françoise Le Deist, M.D.
Hôpital Sainte-Justine
Montreal, QC, Canada

Patrick Niaudet, M.D.
Hôpital Necker–Enfants Malades
Paris, France

Franz Schaefer, M.D.
Center for Pediatrics and Adolescent Medicine
Heidelberg, Germany
franz.schaefer@med.uni-heidelberg.de

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter (10.1056/NEJMc1100859) was published on May 25, 2011, and updated on June 30, 2011, at NEJM.org.

1. Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic–uremic syndrome. N Engl J Med 2009;360:544-6.
2. Nathanson S, Kwon T, Elmaleh M, et al. Acute neurological involvement in diarrhea-associated hemolytic uremic syndrome. Clin J Am Soc Nephrol 2010;5:1218-28.
3. Orth D, Khan AB, Naim A, et al. Shiga toxin activates complement and binds factor H: evidence for an active role of complement in hemolytic uremic syndrome. J Immunol 2009;182:6394-400.
4. Thurman JM, Marians R, Emlen W, et al. Alternative pathway of complement in children with diarrhea-associated hemolytic uremic syndrome. Clin J Am Soc Nephrol 2009;4:1920-4.
5. Fang CJ, Fremeaux-Bacchi V, Liszewski MK, et al. Membrane cofactor protein mutations in atypical hemolytic uremic syndrome (aHUS), fatal Stx-HUS, C3 glomerulonephritis, and the HELLP syndrome. Blood 2008;111:624-32.

Investigation of a Researcher's Death Due to Septicemic Plague

TO THE EDITOR: Infection with virulent *Yersinia pestis* is associated with rapid dissemination and a high risk of death. Attenuated vaccine strains exist that lack a chromosomal fragment comprising the high-pathogenicity island involved in iron uptake and the pigmentation segment associated with the microbe's heme-staining phenotype and its survival in arthropods.[1] Attenuated strains, such as *Y. pestis* KIM D27, are routinely manipulated in many laboratories with the use of biosafety level 2 precautions; to our knowledge plague infection caused by a nonpigmented *Y. pestis* strain has not been reported in the United States.[2]

We report a case of lethal septicemic plague caused by an attenuated, nonpigmented *Y. pestis* isolate (designated UC91309). A 60-year-old researcher with a history of insulin-dependent diabetes, hypertension, and hyperlipidemia presented to the emergency department with a 1-week history of worsening shortness of breath and associated dry cough, fevers, chills, and weakness. His condition rapidly deteriorated, and despite resuscitation efforts the patient died after 13 hours.

Blood cultures grew *Y. pestis*, and an autopsy revealed abnormally high levels of iron deposition in the noncirrhotic liver (Fig. 1A). Testing of antemortem serum samples revealed markedly elevated levels of ferritin, iron, total iron-binding capacity, and iron saturation. The iron level in the liver tissue was consistent with hereditary hemochromatosis,[3] and genetic testing confirmed the presence of a C282Y mutation. Analysis of the UC91309 genome sequence revealed the insertion of an antibiotic-resistance cassette that had been engineered by the patient as a research activity, indicating that the patient isolate was the laboratory-manipulated strain and not a naturally occurring U.S. strain.

The route of entry of the organism was not determined despite a thorough autopsy and an investigation by the university and by local, regional, and national public health departments. It is possible that inadvertent exposure to a sub-

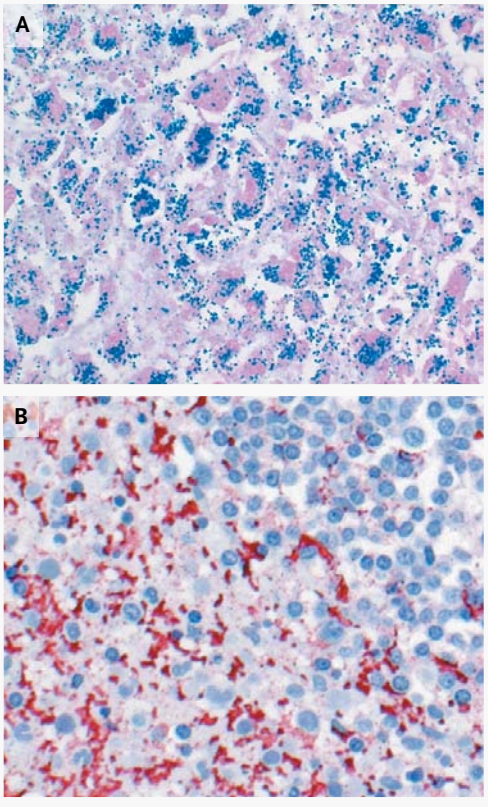

Figure 1. Histologic Studies of Tissues Obtained at Autopsy.

An iron stain confirms the presence of iron (blue) in individual hepatocytes (Panel A). The results of an immunohistochemical assay with a mouse anti–*Yersinia pestis* monoclonal antibody show numerous bacteria (red) in the spleen (Panel B). Image in Panel A courtesy of Dr. Ilyssa Gordon.

cutaneous or mucous membrane had occurred. Previous work showed that vaccine strains are attenuated for virulence but can cause lethal plague infections in animals pretreated with iron salts.[4] Studies in mice showed that UC91309 is attenuated and does not display a significant difference in virulence from the parent strain. Preloading animals with iron dextran enabled increased growth and dissemination of the UC91309 strain. In this case, clinically unrecognized hemochromatosis appears to have been a risk factor for severe infection with this attenuated, nonpigmented *Y. pestis* strain.

This report emphasizes the need for strict attention to protocols for laboratory safety. When illness does occur, all potential sources of microbial exposure should be considered and the nature of the ill person's employment determined. A plan for early, rapid assessment and treatment should be in place. Given the probable role of undiagnosed hemochromatosis in this fatal case, researchers working with yersinia species may choose to determine whether or not they have the hemochromatosis mutation.

Karen M. Frank, M.D., Ph.D.
Olaf Schneewind, M.D., Ph.D.
University of Chicago
Chicago, IL
kfrank@uchicago.edu

Wun-Ju Shieh, M.D., Ph.D.
Centers for Disease Control and Prevention
Atlanta, GA

Supported by the University of Chicago and the Great Lakes Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Consortium through an award from the National Institutes of Health (1-U54-AI057153).

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Buchrieser C, Rusniok C, Frangeul L, et al. The 102-kilobase pgm locus of Yersinia pestis: sequence analysis and comparison of selected regions among different Yersinia pestis and Yersinia pseudotuberculosis strains. Infect Immun 1999;67:4851-61.
2. Brubaker RR. Mutation rate to nonpigmentation in Pasteurella pestis. J Bacteriol 1969;98:1404-6.
3. Feder JN, Gnirke A, Thomas W, et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. Nat Genet 1996;13:399-408.
4. Hallett AF, Isaäcson M, Meyer KF. Pathogenicity and immunogenic efficacy of a live attenuated plaque vaccine in vervet monkeys. Infect Immun 1973;8:876-81.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

- Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article.
- Letters not related to a *Journal* article must not exceed 400 words.
- A letter can have no more than five references and one figure or table.
- A letter can be signed by no more than three authors.
- Financial associations or other possible conflicts of interest must be disclosed. Disclosures will be published with the letters. (For authors of *Journal* articles who are responding to letters, we will only publish new relevant relationships that have developed since publication of the article.)
- Include your full mailing address, telephone number, fax number, and e-mail address with your letter.
- All letters must be submitted at authors.NEJM.org.