these three points. First, in the EPaNIC trial, early parenteral nutrition failed to improve the outcome in the preplanned subgroup of 863 patients with a very high nutritional risk.[3] Second, the assumption that more severely ill patients would benefit from early enhanced feeding was proven wrong; when subgroups were defined according to severity of illness on admission, it was clear that early parenteral nutrition caused the most harm in the most severely ill subgroup, whereas the intervention did not alter the outcome in the least severely ill patients.[3] In addition, the administration of early parenteral nutrition aggravated rather than reduced muscle weakness in the sickest patients requiring prolonged intensive care.[4] Third, a retrospective analysis showed that it was the dose of amino acids, not the amount of glucose, that explained the harm evoked by early parenteral nutrition, an observation that is completely in line with the results from a study of experimentally induced critical illness in rabbits.[3,5]

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Since publication of their article, the authors report no further potential conflict of interest.

1. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506-17.
2. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013;309:2130-8.
3. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187:247-55.
4. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 2013;1:621-9.
5. Derde S, Vanhorebeek I, Güiza F, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology 2012;153:2267-76.

DOI: 10.1056/NEJMc1404896

Global Biomedical R&D Expenditures

TO THE EDITOR: In their Perspective article, Chakma et al. (Jan. 2 issue)[1] report estimates for global trends in expenditures on health research and development (R&D). Their analysis is questionable. First, expenditure data should be deflated in the national currency and then compared with the use of an appropriate exchange rate for one base year. The authors' approach overestimates growth in countries with relative currency appreciation. Second, the standard approach is to deflate expenditure data with the use of the implicit gross domestic product (GDP) price index, not the National Institutes of Health R&D price index, which flatters countries with high inflation. Third, it is better to compare R&D expenditures with the use of GDP purchasing power parities (PPPs) than with current exchange rates, which underestimate the contribution of countries in which exchange rates overstate the cost of domestic activities and thus of R&D.

When we recalculate the data using 2012 PPP exchange rates and 2012 GDP prices, China (up $8.7 billion between 2007 and 2012) shows the largest increase in R&D expenditures, instead of Japan (up $2.8 billion). India (up $1.6 billion) and South Korea (up $4.3 billion) show larger increases than originally estimated; Australia's increase is smaller (up $0.4 billion). The decline in the United States is not so marked (down $4.0 billion).

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No potential conflict of interest relevant to this letter was reported.

1. Chakma J, Sun GH, Steinberg JD, Sammut SM, Jagsi R. Asia's ascent — global trends in biomedical R&D expenditures. N Engl J Med 2014;370:3-6.

DOI: 10.1056/NEJMc1405176

THE AUTHORS REPLY: We disagree with the unreferenced assertion that the approaches suggested by Young et al. are "standard" or "better." Most important, their suggestion to use the implicit GDP price index is problematic because it reflects economy-wide inflation, not biomedical R&D inflation, which diverges significantly from GDP.[1,2] In particular, Young et al. are incorrect to conclude that there has been a "not so marked" U.S. decline on the basis of economy-wide inflation, when U.S. biomedical R&D inflation is known.[3,4] Similarly, their suggestion to use GDP PPP is flawed, because costs of domestic biomedical R&D activities and corresponding PPP are unknown. Decade-long analyses of R&D-specific prices show that "at the industry level, use of GDP PPP as a proxy for R&D PPP is inappropriate."[5] Finally, we do agree that currency appreciation may overstate domestic growth, but on this point, our approach and their approach do not produce meaningfully dissimilar results. Adjusting historical nominal R&D expenditures at an exchange rate from a single time point shows similar annual growth rates, except for those in Japan and India. Our analysis supporting the relative and absolute decline of U.S. spending remains valid.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Grabowski H, Vernon J, DiMasi JA. Returns on research and development for 1990s new drug introductions. Pharmacoeconomics 2002;20:Suppl 3:11-29.
2. Messinis G. Patent quality and R&D productivity in pharmaceuticals: the role of inflation and international collaboration. Working paper no. 27. Melbourne, VIC, Australia: Centre for Strategic Economic Studies, Victoria University of Technology, 2005 (http://www.cfses.com/documents/pharma/27-Patent_Quality_and_R&D_Productivity.pdf).
3. Research and development in the pharmaceutical industry. Washington, DC: Congressional Budget Office, October 2006.
4. Dorsey ER, de Roulet J, Thompson JP, et al. Funding of US biomedical research, 2003-2008. JAMA 2010;303:137-43.
5. Dougherty SM, Inklaar R, McGuckin RH, van Ark B. International comparisons of R&D expenditure: does an R&D PPP make a difference? Cambridge, MA: National Bureau of Economics, 2007 (http://www.nber.org/papers/w12829).

DOI: 10.1056/NEJMc1405176

Emphysematous Aortitis after Endovascular Graft

TO THE EDITOR: Huang and Wu (Jan. 9 issue)[1] report a case of death after endovascular aortic repair of a thoracic aortic aneurysm. I was surprised that the authors did not consider the diagnosis of aortoesophageal fistula, a rare but well-known and well-described complication of this surgery.[2-5] Persistent mechanical pressure from the enlarged aneurysm sac causes an erosive communication with the adjacent esophagus, leading to sac infection and hematemesis. The described findings of endoleak (persistent pressurization of the aneurysm sac), fever, air in the aneurysm adjacent to the esophagus, and death due to massive hematemesis strongly suggest a diagnosis of aortoesophageal fistula rather than poor oral hygiene, as was presumed.

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No potential conflict of interest relevant to this letter was reported.

1. Huang YL, Wu MT. Images in clinical medicine: emphysematous aortitis after endovascular graft. N Engl J Med 2014;370:158.
2. Chiesa R, Tshomba Y, Kahlberg A, et al. Management of thoracic endograft infection. J Cardiovasc Surg (Torino) 2010;51:15-31.
3. Eggebrecht H, Mehta RH, Dechene A, et al. Aortoesophageal fistula after thoracic aortic stent-graft placement: a rare but catastrophic complication of a novel emerging technique. JACC Cardiovasc Interv 2009;2:570-6.
4. Yavuz S, Kanko M, Ciftci E, Parlar H, Agirbas H, Berki T. Aortoesophageal fistula secondary to thoracic endovascular aortic repair of a descending aortic aneurysm rupture. Heart Surg Forum 2011;14(4):E249-E251.
5. Chiba D, Hanabata N, Araki Y, et al. Aortoesophageal fistula after thoracic endovascular aortic repair diagnosed and followed with endoscopy. Intern Med 2013;52:451-5.

DOI: 10.1056/NEJMc1403841

THE AUTHORS REPLY: Johnston points out that our diagnosis should have been aortoesophageal fistula. We agree that aortoesophageal fistula may have been the cause of massive hemateme-