

Figure. A: Biopsy specimen of the lymph node showing diffuse infiltration of lymphocytes with mild nuclear irregularity and scattered giant cells resembling Reed-Sternberg cells (hematoxylin-eosin, original magnification $\times 400$). B: In situ hybridization showing giant cells positive for Epstein-Barr virus–encoded ribonucleic acid (EBER) (methyl green, original magnification $\times 200$). C: Histology of the resected gastric tissue showing moderately differentiated adenocarcinoma (hematoxylin-eosin, original magnification $\times 100$). D: In situ hybridization showing that the cancer cells were positive for EBER (methyl green, original magnification $\times 100$).

GEOGRAPHY OF RANDOMIZED CONTROLLED TRIALS IN GENERAL INTERNAL MEDICINE: IS THE UNITED STATES' SHARE DECLINING?

To the Editor:

Contributions by the United States to highly reputed basic science, general medicine, nuclear medicine, and ophthalmology journals have decreased in the last decade (1–3). Several factors may be responsible for this unexpected downward trend. A decline in research funding may be the main reason. Increased high-quality research by researchers from other countries may also have a role. For this purpose, we sought to identify randomized controlled trials by country, which were published in the top seven general internal medicine journals during the last decade, as well as the publication trend over time.

We selected the following journals from the category “General, and General Internal Medicine” established by the Institute for Scientific Information (4): *The New England Journal of Medicine*, *The Journal of the American Medical Association*, *The Lancet*, *Annals of Internal Medicine*, *Archives of Internal Medicine*, *British Medical Journal*, and *The American Journal of*

Medicine. We searched MEDLINE in November 2002 to obtain the country affiliation of the randomized controlled trials published from 1991 to 2000 in these journals. We manually searched hard copies of articles if the affiliation data were not available on MEDLINE. Nonparametric tests for trend were performed using STATA statistical software, version 7 (STATA

Table. Publication of Randomized Controlled Trials in the Top Seven General Internal Medicine Journals (1991 to 2000) For the Top Ten Countries

Country	1991	2000	1991–2000
	(n = 351)	(n = 395)	(n = 3500)
	Number (%)		
United States	175 (50)	186 (47)	1604 (46)
United Kingdom	50 (14)	72 (18)	634 (18)
Canada	15 (4)	25 (6)	171 (5)
Netherlands	16 (5)	17 (4)	156 (4)
France	8 (2)	12 (3)	109 (3)
Italy	9 (3)	6 (2)	102 (3)
Australia	10 (3)	11 (3)	83 (2)
Germany	7 (2)	9 (2)	76 (2)
Denmark	9 (3)	4 (1)	64 (2)
Sweden	6 (2)	6 (2)	60 (2)

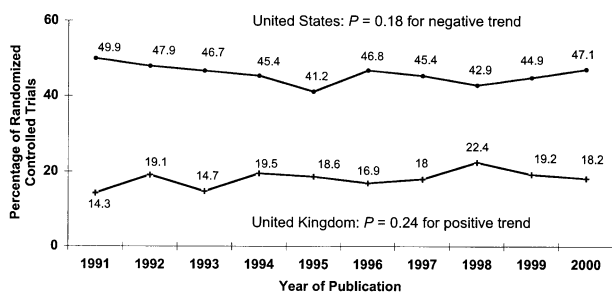


Figure. Publication of randomized controlled trials (percentage of total) from the United States and the United Kingdom (1991 to 2000).

Corporation, College Station, Texas), to determine any changes in the contributions of different countries over time.

From 1991 to 2000, 3500 randomized controlled trials were published in the selected journals. The United States had the most publications ($n = 1604$ articles [46%]), followed by the United Kingdom ($n = 634$ articles [18%]) (Table). However, the United States showed a negative trend during this period (Figure), whereas the United Kingdom showed a positive trend, although these trends were not significant. Other countries did not have any significant publication trends over time. Our findings suggest that although research funding in the United States may have decreased somewhat during the last decade, as suggested by the negative trend observed with respect to the United States' contribution of articles to different journal categories (1–3), support for conducting randomized controlled trials has remained fairly constant.

Our findings should be interpreted in the context of the following limitations. Although we selected journals with the highest impact factors, we studied only a small subgroup of general and general internal medicine journals. However, in a study in which all the randomized controlled trials that were published during 1995 to 1999 and were included in the MEDLINE database were searched, the United States' share was 45% (5), which is similar to our recent estimates. In addition, some studies in-

volved a multinational collaboration, and MEDLINE only identifies the affiliation of the corresponding author.

In conclusion, the proportion of U.S. randomized controlled trials published in top general internal medicine journals has decreased somewhat during the past decade, although this decline is not statistically significant.

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GRAPEFRUIT AND TONIC: A DEADLY COMBINATION IN A PATIENT WITH THE LONG QT SYNDROME

To the Editor:

We report a 31-year-old woman who was admitted with polydipsia a

few weeks after she had received the diagnosis of diabetes based on the presence of hyperglycemia. She had a known asymptomatic long QT syndrome, for which she was taking low-dose atenolol. At age 19 years, she had undergone implantation of a pacemaker because of asymptomatic second-degree atrioventricular block. Her older brother and sister had died of sudden death when they were about 30 years old.

Shortly after admission, she developed frequent convulsive syncopes due to torsade de pointes. Electrolyte level, thyroid function, and glycemia were normal. The QTc interval was 0.58 seconds. Treatment with intravenous magnesium sulfate and metoprolol had no effect on the duration and incidence of torsade de pointes. Overdrive ventricular pacing was not tolerated. Further investigation revealed that she had been drinking excessive amounts of grapefruit juice and quinine-containing tonic water because of her polydipsia. Forty-eight hours after the discontinuation of these drinks, the torsade de pointes disappeared. The QTc interval was 0.45 seconds after 2 days. No arrhythmias were induced with programmed electrical stimulation. However, a cardiac defibrillator was implanted because of her family history of the long QT syndrome. The patient was discharged. She was instructed to take metoprolol (100 mg) once a day, as well as about maintaining an appropriate diabetic diet. She also received a list of products that may prolong the QT interval or induce torsade de pointes.

Torsade de pointes in this patient may have been brought about by the concomitant excessive intake of grapefruit juice containing naringin and tonic water containing quinine. Quinidine, the optical isomer to quinine, prolongs the QT interval (1). It may also trigger torsade de pointes during, for example, astemizole therapy (2). The inhibitory effect of the flavonoid naringin on the liver cytochrome P450 3A4, which is involved