

if they respond to placebo, given proper informed consent? What exactly is the participant told before the trial and after being dropped? Does the informed consent in such trials include all "procedures to be followed" including the fact that there is a "deceptive" elimination period? Does the consent form describe the exact circumstances by which patients can be terminated without their consent? It is possible (or perhaps even likely) that some trials have informed consents that may not quite adhere to the *Federal Register*,<sup>2</sup> not to mention the Nuremberg Code and the Declaration of Helsinki.

In addition, the history of the run-in period to increase the efficiency of the randomized controlled trial is much older than the authors of this article apparently realize. The attempt to eliminate placebo responders goes back to some of the earliest double-blind randomized controlled trials. For example, Gold and colleagues<sup>3</sup> attempted a placebo run-in phase in their famous trial that began in 1932. The issue of detecting placebo responders<sup>4</sup> was an active research agenda in the early 1950s, and large adherence run-in periods were used as early as the late 1960s.<sup>5,6</sup>

Ted J. Kaptchuk, OMD  
Beth Israel Deaconess Medical Center  
Boston, Mass

1. Pablos-Méndez A, Barr G, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. *JAMA*. 1998;279:222-225.
2. *Protection of Human Subjects: Informed Consent*, 46. *Federal Register*, 1788 (1981).
3. Gold H, Kwit NT, Otto H. The xanthines (theobromine and aminophylline) in the treatment of cardiac pain. *JAMA*. 1937;108:2173-2179.
4. Beecher HK, Keat AS, Mosteller F, Lasagna L. The effectiveness of oral analgesics (morphine, codeine, acetylsalicylic acid) and the problem of the placebo "reactors" and "non-reactors." *J Pharm Exp Ther*. 1953;109:393-400.
5. National Diet-Heart Study Research Group. The National Diet-Heart Study Final Report. *Circulation*. 1968;37(suppl 3):1-428.
6. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. *JAMA*. 1970;213:1144-1152.

*In Reply.*—Dr Glynn and colleagues point out that including nonadherers in a clinical trial may compromise the validity of an efficacy study; we would not take issue with this point of view. Our article was meant to call attention to the complexities of applying estimates of treatment effects derived from such studies directly to clinical practice, difficulties that are compounded when considering alternative interventions tested in trials without a run-in period. We agree that it is difficult to know whether using a placebo drug run-in period to exclude nonadherers will lead to underestimation or overestimation of the adverse effects of a drug in the randomized phase of a trial. However, the use of an active drug run-in period to exclude nonadherers will selectively exclude those who are nonadherent because of adverse effects. The result will be underestimation of the rate of adverse effects in the randomized phase compared with the unselected population expected in clinical practice.

We also agree with Glynn and colleagues that predicting adherence in clinical practice is difficult, and that clinical trials may not be helpful in this regard. Adherence during a clinical trial may be lower than in practice because of uncertain benefit, or may be higher because of measures such as reminders and monetary incentives. We do not propose the use of adherence-adjusted estimates. We offered an example to illustrate, first, that differences may be of clinical, not just theoretical, significance, and second, that the assumptions required are highly artificial, as noted by Dr Riley.

The interesting ethical issues raised by Dr Kaptchuk are beyond the scope of our article. We recognize that other variations of run-in periods occur as a design feature in clinical trials and hope for further consideration of the subject.

The widespread acceptance of run-in periods in clinical trials to exclude nonadherers, nonresponders, subjects with adverse effects, or placebo responders will add complexity to the secondary, comparative analyses of the results and their ap-

plication in clinical practice. Many clinicians may not fully understand the distinction between an efficacy and an effectiveness study and how this distinction may influence the interpretation of clinical trial results. Clinicians also may not fully understand how the use of a run-in period may need to be taken into account in applying the trial's results to a patient. A major point of our article is that investigators who report such trials should address these issues explicitly in the publication of their results.

Ariel Pablos-Méndez, MD, MPH  
R. Graham Barr, MD  
Steven Shea, MD  
Columbia University  
New York, NY

### SV40-Contaminated Poliovirus Vaccine and Childhood Cancer Risk

*To the Editor.*—In examining the carcinogenic effects of exposure to simian virus 40 (SV40)—contaminated poliovirus vaccine, Strickler et al<sup>1</sup> concluded that such exposure "was not associated with significantly increased rates of ependymomas and other brain cancers, osteosarcomas, or mesotheliomas." The expectation that the available data provided reliable incidence rates for a comparative analysis using Poisson regression techniques deserves reconsideration.

The Surveillance, Epidemiology, and End Results (SEER) database captures only tumors occurring during ages 26 to 41 years, 17 to 31 years, and 9 to 24 years in the childhood-exposed, infant-exposed, and unexposed cohorts, respectively, as defined by Strickler et al. Clearly, the ages for which tumor incidence is known for the entire childhood-exposed and unexposed cohort are incongruent. Poisson regression is a powerful statistical tool; however, negative conclusions drawn from a comparison of 2 or more regression models mathematically generated from incidence rates of very different age groups may represent a misuse of the method and, perhaps, an error in judgment. Since these cancers are highly correlated with age, statistical and clinical conclusions are best limited to age groups adequately represented in all comparison groups.

Acknowledging the small numbers of ependymomas in SEER, the authors conclude no increase in these rates related to exposure. The ependymoma rates were 0.17 of 100 000 and 0.11 of 100 000 for the childhood-exposed and unexposed cohorts, respectively. Ependymoma incidence peaks in the first decade of life; therefore, higher rates of these tumors were likely to have occurred in the exposed cohort during childhood and would not be captured in SEER.

Both SV40 exposure and cancer rates in the small, homogeneous state of Connecticut may not represent those of the entire United States. Other investigators<sup>2</sup> have reported the incidence of ependymal neoplasms in Connecticut children younger than 20 years increased after the mid-1950s. Given the evidence<sup>3</sup> suggesting potential perinatal transmission of SV40, cohorts born after 1963 could also be infected with SV40 and may have similar cancer risks. Increased cancer reporting over time could contribute to higher tumor rates in the unexposed cohort.

With 71 mesotheliomas, the authors report negative results, mentioning that the small case number and young age of the cohorts limits this analysis. In fact, only 2 mesotheliomas occurred in the unexposed cohort compared with 45 and 23 in the childhood-exposed and infancy-exposed groups. Mesothelioma in the youngest cohort (unexposed) would be unlikely, so the accurate study conclusion is that no conclusions can be drawn, rather than there was "no significant cohort effect."

Ignoring that poliovirus vaccines contained different amounts of SV40 further complicates the interpretation of these data, because SV40 carcinogenesis is dose related. The

SEER data indicate that SV40 should not directly lead to cancer; however, it is unlikely that SV40 per se causes cancer, because most, if not all, human carcinogens require additional factors for tumor development. Just as SV40 may render infected persons more susceptible to asbestos carcinogenicity,<sup>4,5</sup> SV40 infection may play a similar role in the development of disease among individuals exposed to other carcinogens.

The analysis by Strickler et al<sup>1</sup> provides no reliable evidence regarding the presence or absence of an increased cancer risk relative to SV40 exposure. The role of SV40 as a potential cofactor in carcinogenesis deserves to be investigated more carefully.

Susan Gross Fisher, PhD  
Loyola University Medical Center  
Maywood, Ill

1. Strickler HD, Rosenberg PS, Devesa SS, Hortal J, Fraumeni JF, Goedert JJ. Contamination of poliovirus vaccines with simian virus 40 (1955-1963) and subsequent cancer rates. *JAMA*. 1998;279:292-295.
2. Dohrmann GJ, Farwell JR, Flannery JT. Ependymomas and ependymoblastomas in children. *J Neurosurg*. 1976;45:273-283.
3. Heinonen OP, Shapiro S, Monson R, et al. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol*. 1973;2:229-235.
4. Carbone M, Rizzo P, Grimley PM, et al. Simian virus-40 large-T antigen binds p53 in human mesothelioma. *Nat Med*. 1997;3:908-912.
5. Wiman KG, Klein G. An old acquaintance resurfaces in human mesothelioma. *Nat Med*. 1997;3:839-840.

**In Reply.**—Our study examined essentially all available information on cancer rates in the United States relevant to the periods before, during, and after the widespread exposure of infants and children to SV40 through contaminated poliovirus vaccine (1955-1963). Incidence data were obtained from the SEER program, the principal source of cancer statistics for the nation, which began in 1973. Thus, for the birth cohorts injected with contaminated vaccine, surveillance had not started until these individuals were at least 10 years of age. To examine rates of cancer at younger ages, we studied national mortality statistics as well as incidence data from the Connecticut Tumor Registry, the only population-based cancer registry in the country that was well established at the time of the event.

In trying to determine the age intervals addressed by SEER, Dr Fisher appears to have made an error in subtraction. The infant-exposed cohort was covered by SEER from ages 10 through 37 years, the childhood-exposed cohort from ages 20 through 46 years, and the unexposed cohort from ages 3 through 29 years. Thus, the cohort exposed in infancy, the critical period of exposure in animal models, overlapped with the unexposed cohort for ages 10 through 29 years in SEER.

This age overlap was ideal for the evaluation of osteosarcomas, a tumor reported by Fisher's colleagues<sup>1</sup> at Loyola University to contain SV40 DNA. Although the incidence of osteosarcoma is highest during the teenage and young adult years, we found that risk was unrelated to birth cohort in our data. The suitability of our statistical analysis was demonstrated by the closeness of observed and modeled cancer rates, as shown in Figure 1 of our article. Incidence data from Connecticut confirmed there were no changes in osteosarcoma incidence related to the period of vaccine contamination in any age group.

To study ependymoma, a brain cancer that mainly affects children younger than 5 years, we examined data from Connecticut. Contrary to Fisher's assertion, the incidence of ependymoma showed no rise during or immediately following the period of vaccine contamination in children 0 to 4 years, 5 to 9 years, or 10 to 14 years of age (Figure 2 in our article). Fisher cites an earlier study of childhood brain cancer in Connecticut conducted in the 1970s, which did not properly control for age.<sup>2</sup> That study broadly defined *children* as individuals younger than 20 years and used the raw number of cancer cases without reference to the increasing infant population during the years of the baby boom.

Our findings are consistent with studies in other countries. In Germany, Geissler<sup>3</sup> found that ependymoma incidence was somewhat lower among 885 783 persons treated in the first year of life with SV40-contaminated vaccine, as compared with 891 321 individuals born shortly thereafter, based on 22 years of follow-up. In Sweden, Olin and Giesecke<sup>4</sup> observed no increase of ependymoma among children given contaminated vaccine. Olin and Giesecke<sup>4</sup> also confirmed our null results regarding osteosarcoma and mesothelioma. The Swedish data, like our own, are sparse for the investigation of mesothelioma, since the birth cohorts exposed to SV40-contaminated vaccine did not yet reach the peak age for this asbestos-related neoplasm. Mesothelioma incidence rates around the world have increased markedly over the past several decades, but predominantly among older individuals unlikely to have received SV40-contaminated vaccine. In Sweden, mesothelioma rates have shown increases similar to those observed in the United States, although adults in that country did not receive SV40-contaminated vaccine (Patrick Olin, MD, PhD, written communication, September 16, 1997).

The findings to date are unremarkable, but it is clear that further surveillance of exposed cohorts in the United States and other nations is needed to clarify the potential risks from SV40-contaminated poliovirus vaccine.

Howard D. Strickler, MD, MPH  
Philip S. Rosenberg, PhD  
Susan S. Devesa, PhD  
Joseph F. Fraumeni, Jr, MD  
James J. Goedert, MD  
National Cancer Institute  
National Institutes of Health  
Bethesda, Md

1. Carbone M, Rizzo P, Procopio A, et al. SV40-like sequences in human bone tumors. *Oncogene*. 1996;13:527-535.
2. Dohrmann GJ, Farwell JR, Flannery JT. Ependymomas and ependymoblastomas in children. *J Neurosurg*. 1976;45:273-283.
3. Geissler E. SV40 and human brain tumors. *Prog Med Virol*. 1990;37:211-222.
4. Olin P, Giesecke J. Potential exposure to SV40 in polio vaccines used in Sweden during 1957—no impact on cancer incidence rates 1960 to 1993. Presented at: International SV40 Workshop; January 1997; Bethesda, Md.

## CORRECTIONS

**Incorrect Data.**—In the Original Contribution entitled "Effect of Vitamin E and Beta Carotene on the Incidence of Angina Pectoris: A Randomized, Double-blind, Controlled Trial," published in the March 6, 1996, issue of THE JOURNAL (1996;275:693-698), the authors recently discovered a computing error that affects the size of the study population and has a slight effect on the relative risk (RR) estimates of the 29 133 participants in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study: 23 862 were free of coronary heart disease at baseline, and during follow-up 1920 new cases of angina pectoris were observed. Of these, 930 occurred among  $\alpha$ -tocopherol-supplemented subjects and 990 among the non- $\alpha$ -tocopherol-supplemented subjects, with an RR for incident angina pectoris of 0.94 (95% confidence interval [CI], 0.86-1.02;  $P=.15$ ); 980 among the beta carotene-supplemented subjects and 940 among non-beta carotene-supplemented subjects, RR, 1.04 (95% CI, 0.96-1.14;  $P=.34$ ). Compared to those who received placebo, the RR for the incidence of angina was 0.98 (95% CI, 0.86-1.11;  $P=.70$ ) for the  $\alpha$ -tocopherol group; 1.09 (95% CI, 0.96-1.23;  $P=.19$ ) for the beta carotene group; and 0.98 (95% CI, 0.86-1.11;  $P=.73$ ) for the group that received  $\alpha$ -tocopherol and beta carotene combined. The original conclusions remain unchanged.

**Incorrect Table Footnote.**—In chapter 17 of the Primer on Allergic and Immunologic Diseases entitled "Immunopathogenesis of Gastrointestinal and Hepatobiliary Diseases," published in the December 10, 1997, issue of THE JOURNAL (1997;278:1946-1955), an error occurred in Table 17-2 on page 1952. In the footnotes to the table, the expansion for the abbreviation AIH should have been autoimmune hepatitis.