

Correspondence



Oral Contraceptives and the Risk of Breast Cancer

To the Editor: In the Women's Contraceptive and Reproductive Experiences (Women's CARE) Study, Marchbanks et al. (June 27 issue)¹ carefully verified previous investigations showing that there is no association between combination oral contraceptives and the risk of breast cancer among women older than 45 years of age.² However, when data from women 35 to 44 years old are combined for analysis, the risk of breast cancer associated with recent use of oral contraceptives may not be fully apparent among the youngest women. The investigators report that they found a higher risk of breast cancer among the women 35 to 39 years old than among the older women. However, because the risk of breast cancer associated with recent oral-contraceptive use is greatest among very young women,² and may be twice that among nonusers in some subgroups,^{2,3} closer examination of the women 35 to 39 years old in this study is warranted.

Although oral-contraceptive use does not appear to increase the risk of breast cancer among older women, the findings need to be interpreted within the context of risk over the course of a lifetime. For example, oral contraceptives may cause nascent tumors to become clinically evident earlier in women who use contraceptives than in those who do not. Consequently, oral-contraceptive users in whom cancer does not develop at a young age (e.g., before the age of 40 years) may be less susceptible at older ages to the promotional effects of oral contraceptives. The results of the Women's CARE Study sparked media reports that oral contraceptives should no longer be considered a risk factor for breast can-

cer, when in fact there may be some evidence that recent use increases risk in very young women.

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To the Editor: The case-control study by Marchbanks et al. of oral-contraceptive use and breast cancer among women 35 to 64 years of age is not reassuring because of a fundamental mistake. The authors failed to study women who had never taken any hormones, either oral contraceptives or hormone-replacement therapy, as their base line.

Seventy-six percent of the case subjects and 78 percent of the controls had used oral contraceptives, and 38 percent and 41 percent, respectively, had used hormone-replacement therapy. How many of the 4575 case subjects and 4682 controls had never taken hormones? It is impossible to know the effects of hormones without comparing women who have used them with women who have never used them.

The United Kingdom National Case-Control Study Group's report on women younger than 36 may be more reliable, since few younger women use hormone-replacement therapy.¹ There was a significantly increasing trend in the risk of breast cancer with longer use of combined-formulation pills. The risk in nulliparous women with longer use was 2.3 times the risk in women with no use. However, when women who had used progestin-only pills were compared with those who had never used combined-formulation pills, the former group was found to have a 60 percent greater risk of breast cancer after as little as 1 to 12 months of use, mostly during lactation. This increase in a very short time is wor-

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risome, especially since intermittent, large doses of progestins are being promoted for emergency contraception.

Similar muddling has confounded studies of progestins and estrogens and the risks of endometrial and ovarian cancers.² The incidence of hormone-dependent cancers has increased in countries where hormones are taken. The exception was in the mid-1970s, when hormone use and the incidence of breast cancer fell, until both increased again beginning in the mid-1980s.³

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1. Chilvers C, McPherson K, Peto J, Pike MC, Vessey MP. Oral contraceptive use and breast cancer risk in young women. *Lancet* 1989;1:973-82.
2. Grant ECG, Price EH, Steel CM. Risks of hormone replacement therapy. *Lancet* 1999;354:1302-3.
3. Grant ECG, Antony HM, Myhill S, Price EH, Steel CM. Breast cancer and hormone exposure. *Lancet* 1996;348:682.

To the Editor: Marchbanks et al. add to epidemiologic studies that are almost equally divided on the question of whether the Pill amplifies the risk of breast cancer in women with a family history. However, since combined-formulation oral contraceptives may stimulate breast-cell division and are contraindicated in women who currently have cancer, those with a strong family history of breast cancer should be cautious about using oral contraceptives.

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The authors reply:

To the Editor: Althuis and Brinton express concern regarding oral-contraceptive use and the risk of breast cancer among women who receive a diagnosis of breast cancer at a young age. Our data are not fully informative on this topic; we restricted our study to relatively older women (35 to 64 years old) because we were primarily interested in resolving the long-standing question of whether former use of oral contraceptives during the reproductive years would increase the risk of breast cancer later in life, when the incidence of breast cancer is higher. When we examined the data from our youngest subgroup of women, those who were 35 to 39 years old, the relative risks of breast cancer associated with any, current, and former use of combination oral contraceptives were 1.3 (95 percent confidence interval, 0.9 to 1.8), 1.2 (95 percent confidence interval, 0.8 to 1.8), and 1.3 (95 percent confidence interval, 0.9 to 1.8), respectively.

Use of combination oral contraceptives was the exposure of interest in most of our analyses; we selected a reference group comprising women who had never taken any type of oral contraceptive. To address Grant's concern, we repeated selected analyses with a new reference group, consisting of women who had never used oral contraceptives, hormone-replacement therapy, or contraceptive shots or implants; the relative risks of breast cancer associated with any, current,

and former use of combination oral contraceptives among women 35 to 64 years old were 1.0 (95 percent confidence interval, 0.8 to 1.1), 1.0 (95 percent confidence interval, 0.8 to 1.3), and 0.9 (95 percent confidence interval, 0.8 to 1.0), respectively.

Although many have shared Friedenson's concern, we found that oral-contraceptive use among women with a family history of breast cancer was not associated with an increased relative risk of breast cancer. Our findings are similar to those of a large pooled analysis of 54 studies.¹

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Major Birth Defects after Assisted Reproduction

To the Editor: We agree with Hansen et al. (March 7 issue)¹ that many studies of birth defects after in vitro fertilization suffer from methodologic problems, but we believe that their study has similar limitations. The authors compared the outcomes of roughly 1000 children conceived with in vitro fertilization with those of control infants born to mothers who were significantly younger than the women who conceived with in vitro fertilization, were more likely to be parous, and were more ethnically diverse. In addition, they made no attempt to control for a history of infertility or the age of the father — factors that have previously been reported to be prognostic of adverse outcomes of pregnancy.^{2,3}

Each year, the Society for Assisted Reproductive Technology collects data on the outcomes of in vitro fertilization from its members, whose clinics perform more than 90 percent of all such procedures in the United States. Among 134,985 children conceived as a result of assisted reproductive technology between 1996 and 2000, 2597 infants (1.9 percent) were reported to have a major birth defect. This rate is similar to the incidence of major abnormalities reported in general populations in both Europe and North America.^{4,5} Although we acknowledge that infertility treatment is not without risks, we believe that our data should be reassuring to both practitioners who perform in vitro fertilization procedures and their patients.

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1. Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *N Engl J Med* 2002;346:725-30.
2. Draper ES, Kurinczuk JJ, Abrams KR, Clarke M. Assessment of separate contributions to perinatal mortality of infertility history and treatment: a case-control analysis. *Lancet* 1999;353:1746-9.

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To the Editor: Classification of neonatal abnormalities is often problematic in reports on the condition of children conceived with in vitro fertilization or intracytoplasmic sperm injection. Hansen et al. put hypoplastic left heart syndrome and tetralogy of Fallot in the same category as tricuspid aortic valve and ventricular septal defect, although the latter two are minor or equivocal defects that do not usually require surgical correction. The authors do not report which specific defects occurred in which group (in vitro fertilization vs. intracytoplasmic sperm injection vs. control), nor do they report which couples had profound male-factor infertility necessitating the use of intracytoplasmic sperm injection. Since gonadal failure in men has been linked to a higher incidence of abnormalities of the sex chromosomes in offspring conceived with intracytoplasmic sperm injection,¹ observed defects in children conceived with assisted reproductive technology could derive from intrinsic paternal factors, rather than from the procedures used.

Moreover, Hansen et al. do not consider the potential effect of the experience of the clinician with in vitro fertilization or intracytoplasmic sperm injection. Data from clinical pregnancies or delivery rates per embryo transferred might give some indication of this effect, but these data were not reported. As others have observed,² putative causal relations between assisted reproduction and reproductive outcomes may be affected by the standards according to which procedures are performed. In the context of different findings from other large studies,^{3,4} the data of Hansen et al. appear to suggest only that infants conceived with intracytoplasmic sperm injection or in vitro fertilization at the three Australian clinics they studied may have a different risk of some birth defects than do infants who are conceived naturally.

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2. Tucker M, Graham J, Han T, Stillman R, Levy M. Conventional insemination versus intracytoplasmic sperm injection. *Lancet* 2001;358:1645-6.
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To the Editor: The results reported by Hansen et al. are somewhat at variance with other published data, including those from a large Belgian series¹ and a Danish national study,² both of which included larger numbers of children conceived with intracytoplasmic sperm injection. Possible reasons for the discrepancies include the use by Hansen et al. of criteria derived from the *International Classification of Diseases, 9th Revision*,³ which do not allow one to draw distinctions easily between major and minor birth defects, and the investigators' attempt to avoid observational bias by using one pediatrician to determine whether the observed congenital anomalies were more likely to occur in a population of infants conceived with intracytoplasmic sperm injection. No evidence is given to support the validity of this method, but the results depend fundamentally on its use.

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1. Bonduelle M, Liebaers I, Deketelaere V, et al. Neonatal data on a cohort of 2889 infants born after ICSI (1991-1999) and of 2995 infants born after IVF (1983-1999). *Hum Reprod* 2002;17:671-94.
2. Loft A, Petersen K, Erb K, et al. A Danish national cohort of 730 infants born after intracytoplasmic sperm injection (ICSI) 1994-1997. *Hum Reprod* 1999;14:2143-8.
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The authors reply:

To the Editor: Drs. Steinkampf and Grifo question our failure to adjust for paternal age, ethnic group, and type of infertility. Questions are also raised about the size of our study. However, our study was powered to be large enough to demonstrate statistically significant results with adjustment for maternal age, parity, the sex of the infant, and correlations between siblings. Although the Aboriginal population has a higher rate of birth defects, this population was underrepresented in the groups that used assisted reproductive technology and cannot therefore account for the excess risk. Stratification according to type of infertility, although potentially informative, would inevitably have led to small, underpowered analyses that would have been susceptible to misinterpretation.¹ We did adjust for maternal age; maternal and paternal ages are highly correlated, and it is therefore unlikely that any residual effects of paternal age could account for our findings.

Drs. Steinkampf and Grifo suggest that data from the Society for Assisted Reproductive Technology and population-based data from other parts of the world are more reassuring than our results, and Drs. Silles and Palermo express reservations about the classifications of birth defects we

used. We used registry data and so were not reliant, as the Society for Assisted Reproductive Technology is, on practitioners' reports of birth defects that are present at delivery.² We agree that the classification of major birth defects is problematic and that there is no consensus on this matter.³ However, we had the advantage that our data on birth defects for all three groups of infants were identified through the same reporting mechanism, which extends beyond birth, and were classified according to the same system, thus ensuring comparability among groups.⁴

Drs. Sills and Palermo argue that excess defects in infants conceived with intracytoplasmic sperm injection may be due to paternal factors rather than to the technology itself and that the performance standards in Western Australia may explain our findings. We agree that it is impossible to disentangle the intrinsic conditions underlying the need for intracytoplasmic sperm injection from risks associated with the technology itself. There are no data, however, to substantiate the latter concern. Western Australian clinics use protocols that are similar to those used by others, and their success rates mirror those found elsewhere, including the United States.^{2,5}

Dr. Sutcliffe and colleagues question our decision to have a single independent pediatrician who was blinded to the mode of conception assess which defects might have been diagnosed earlier because of closer surveillance during the first year of life. This secondary analysis was intended specifically to minimize the possibility of differential diagnostic vigilance among groups and confirmed the results of our primary analyses, which did not depend "fundamentally" on it.

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5. Western Australian Reproductive Technology Council. Annual report, 1 July 1999–30 June 2000. Perth, Western Australia: Health Department of Western Australia, 2000.

Low and Very Low Birth Weight after Use of Assisted Reproductive Technology

To the Editor: Schieve et al. (March 7 issue)¹ suggest that the observed increase in the risk of low birth weight among singleton infants conceived with assisted reproductive tech-

nology is more likely to be due to the treatment than to an underlying condition in infertile women. They report that a subgroup analysis of couples with male-factor infertility supports this contention. However, the use of this group to represent women who are free of infertility-related conditions may be inaccurate, since this diagnosis does not exclude the presence of other causal factors. Indeed, according to 1999 data from the Society for Assisted Reproductive Technology, 17.5 percent of couples had multiple factors that included both female and male factors.² Moreover, the diagnosis of male-factor infertility has been used loosely and may be nonspecific, as demonstrated by Guzick et al., who showed that the traditional criteria used in the evaluation of semen are not diagnostic of male infertility.³ Analysis of the data with the use of more specific diagnoses of maternal conditions, such as tubal-factor infertility, could also help in the evaluation of the authors' conclusions.

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To the Editor: Schieve et al. observed an increased rate of multiple births in pregnancies that resulted from in vitro fertilization, attributable to the transfer of multiple embryos, but they did not find a greater risk of low birth weight in multiples conceived with in vitro fertilization than in multiples conceived spontaneously. In contrast, for singletons, in vitro fertilization was associated with a higher risk of low birth weight than was spontaneous conception. Hence, although it seems counterintuitive, twinning appeared to provide some relative protection from the effect of in vitro fertilization on the risk of low birth weight.

An alternative explanation, however, is that the transfer of multiple embryos during in vitro fertilization results in a high ratio of dizygotic twins to monozygotic twins.¹ Hence, after controlling for the confounding effect of zygosity, we should expect to observe that the relative risk of low birth weight in twins conceived with in vitro fertilization is higher than that in twins conceived spontaneously—in accordance with the findings among singletons. Such a finding would be consistent with recent work showing that dizygotic twins conceived with in vitro fertilization had shorter gestations, lower birth weights, and lower Apgar scores than dizygotic twins conceived spontaneously.² Thus, there is a continued need to identify and classify sources of risk associated with in vitro fertilization.

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2. Lambalk CB, van Hooff M. Natural versus induced twinning and pregnancy outcome: a Dutch nationwide survey of primiparous dizygotic twin deliveries. *Fertil Steril* 2001;75:731-6.

The authors reply:

To the Editor: Drs. Kovalevsky and Coutifaris are concerned that a diagnosis of male-factor infertility does not exclude the presence of other causal factors. For the years covered in our study, infertility diagnoses were ascertained through the abstraction of clinic records. Each infertility clinic was asked to list the primary infertility diagnosis and was given the option of listing a secondary diagnosis. We agree that this system has limitations. Diagnostic protocols most likely varied among the more than 300 clinics included in the registry, and underreporting of additional diagnoses may have occurred. We limited our analyses of infants born to couples with male-factor infertility to those born to couples with a primary diagnosis of male-factor infertility and no reported secondary diagnosis (a total of 2759 couples, or 66.6 percent of the couples with a primary diagnosis of male-factor infertility). Thus, our findings for this subgroup suggest that the risk of low birth weight is higher than would be expected for infants conceived with assisted reproductive technology whose mothers were unlikely to have an underlying infertility-related disease.

In the interest of brevity, we did not present separate findings according to maternal diagnosis (such as tubal-factor infertility), but we have analyzed our data to examine this issue. The rate of low birth weight among singletons conceived by couples with tubal-factor infertility was 13.5 percent, as compared with 5.7 percent in the general population.

Dr. Davies suggests that our results for twins may have been biased toward the null hypothesis because we were unable to classify either the twins conceived with assisted reproductive technology or the twins in the general population according to zygosity. We agree. It is likely that a larger proportion of twins in the general population was monozygotic and that these twins may have been at higher risk for fetal growth restriction. For this reason, as well as for those outlined in our article, we do not believe that the lack of association between assisted reproductive technology and low birth weight in twins is inconsistent with a possible treatment effect.

In sum, our findings among singletons are suggestive of an effect of assisted reproduction technology on the risk of low birth weight. However, because our data were collected retrospectively from a large, population-based registry, we had only limited information on patients' medical conditions. A study that prospectively follows pregnancies that result from the use of assisted reproductive technology is needed in order to address this important issue more definitively.

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Male Circumcision, Penile Human Papillomavirus Infection, and Cervical Cancer

To the Editor: Castellsagué et al. (April 11 issue)¹ did not correct for several of the major known risk factors for cervical cancer: race or ethnic group, smoking, human immunodeficiency virus (HIV) infection, poor diet, long-term use of oral contraceptives, and low socioeconomic status.² Samples for testing for human papillomavirus (HPV) were obtained by intraurethral swabbing and swabbing of the external surface of the glans and coronal sulcus. This surface is dry on circumcised penises but moist on intact penises, increasing the likelihood of detection of HPV regardless of the actual rate of infection.

In other work involving the same participants, the HPV genotypes in the men did not match those in their partners. This finding strongly suggests that the relation between HPV in men and that in their partners was not one of simple transmission.³

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1. Castellsagué X, Bosch FX, Muñoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med* 2002;346:1105-12.
2. What are the risk factors for cervical cancer? Atlanta: American Cancer Society, 2002. (Accessed October 10, 2002, at http://www.cancer.org/eprise/main/docroot/CRI/content/CRI_2_4_2X_What_are_the_risk_factors_for_cervical_cancer_8?sitearea=CRI.)
3. Franceschi S, Castellsagué X, Dal Maso L, et al. Prevalence and determinants of human papillomavirus genital infection in men. *Br J Cancer* 2002;86:705-11.

To the Editor: Castellsagué et al. present evidence that male circumcision is associated with reduced risks of penile HPV infection and cervical cancer in female partners. They theorize that removal of the foreskin "markedly decreases" both the surface area susceptible to HPV infection and the likelihood of mucosal trauma during intercourse. However, the mucosal surface of the foreskin has been described as a "specific erogenous zone"¹ and an "important component of the overall sensory mechanism of the human penis."² Prudence dictates that before promoting circumcision as preventive treatment against disease, researchers should confirm that the procedure is ethically appropriate and has no adverse long-term effects on sexual sensation or function.

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1. Winkelmann RK. The erogenous zones: their nerve supply and its significance. *Proc Mayo Clin* 1959;34:39-47.
2. Taylor JR, Lockwood AP, Taylor AJ. The prepuce: specialized mucosa of the penis and its loss to circumcision. *Br J Urol* 1996;77:291-5.

The authors reply:

To the Editor: Travis raises the issue that potential confounding could explain the inverse association between

male circumcision and the risk of cervical cancer in female partners. In fact, the addition to our final logistic-regression model of the race or ethnic background of monogamous female partners and their smoking status, use of oral contraceptives, and level of education lowered the odds ratio for cervical cancer from 0.75 to 0.64 (95 percent confidence interval, 0.39 to 1.04), thus showing an even stronger inverse association. Information on HIV status and diet was not collected in this study, but for these variables to be considered true confounders, they must be related both to circumcision status (which is very unlikely in the case of diet) and to cervical cancer. Although HIV status and circumcision status might be associated with one another, HIV infection alone is not considered a cause of cervical cancer. Furthermore, estimates of the prevalence of HIV infection in the populations we studied were too low to explain the associations we found.

Travis also suggests that the association might be explained by potential HPV-DNA-detection bias introduced by circumcision. Although it is plausible that circumcision compromises cellular yield, the quality and sensitivity of our polymerase chain reaction overcome this potential limitation. We used amplification of a fragment of the β -globin gene as an internal quality control for each specimen, thus ensuring both the high quality of the DNA and the presence of cells. Samples from which the β -globin and HPV L1 genes could not be amplified were excluded from the analyses, and no differences were found between the subjects with such samples and those with valid samples. Finally, we admit that the lack of correlation of HPV genotypes between the two partners¹ is puzzling, but it should not call into question our findings regarding circumcision, since the study involving couples provided information only on the HPV status of each partner at the time of the sampling.

We thank Bhimji and Harrison for reminding us that circumcision may have other consequences, since the procedure removes an important erogenous zone; this and other “noninfectious” considerations should also be taken into account before any recommendations are made. Since we received numerous letters (and even a targeted, data-damaging cyberattack) from pro- and anti-circumcision groups, we would like to emphasize that our study was not intended to provide global evidence against or in favor of recommending circumcision. Nevertheless, we still think that there is a need for a comprehensive multidisciplinary review that considers all aspects of male circumcision and identifies which kinds of studies are still required in order to elaborate evidence-based recommendations regarding this controversial issue.

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Changes in the Transmission of Tuberculosis in New York

To the Editor: According to the article by Geng et al. (May 9 issue),¹ the majority of cases of active tuberculosis in the New York City area are now reactivation cases in recently arrived immigrants. However, current guidelines advise chemoprophylaxis only in people 35 years of age or younger.² How should we use the current information³ in advising therapy for immigrants older than 35 who have a positive skin test with purified protein derivative, chest radiographs that show no abnormalities, and no evidence of underlying immune compromise?

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1. Geng E, Kreiswirth B, Driver C, et al. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. *N Engl J Med* 2002; 346:1453-8.
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To the Editor: Geng and colleagues use their finding of a strain of *Mycobacterium tuberculosis* in one or several patients (unique or part of a cluster) to distinguish reactivation from cross-infection. Initially, any cluster must have had a single member. Left long enough, a unique carrier would infect others and become part of a cluster. The number of unique patients and patients in a cluster will therefore vary with the intensity of surveillance, which may be greater for immigrants than for U.S.-born persons. If a major source of infection is immigration, we might expect to find an immigrant in most clusters. In clusters without an immigrant, it is arguable that there was reactivation in a home-born member. It would be interesting to know how many clusters there were of each kind.

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To the Editor: An important population in which the problem of “poor acceptance and completion rates for treatment of latent [tuberculosis] infection” is evident is the growing population of foreign-born or foreign-trained health care professionals. Many have a history of bacille Calmette-Guérin (BCG) vaccination in infancy, and a blind faith in their vaccination seems to prevent them from availing themselves of treatment for latent tuberculosis infection to prevent active tuberculosis.¹

Since the 1920s, BCG has been given to children in developing countries, including most on the current World Health Organization (WHO) list of tuberculosis “hot spots.” Approximately 100 million children receive BCG annually,

and most experts agree that it is highly variable in protecting adults against tuberculosis.² Furthermore, tuberculin reactions from BCG given in infancy invariably wane within five years.³

According to the recent American Thoracic Society–Centers for Disease Control and Prevention statement, endorsed by the Infectious Diseases Society of America and the American Academy of Pediatrics, “No method can reliably distinguish tuberculin reactions caused by BCG from those caused by natural mycobacterial infections. Therefore a positive reaction to tuberculin in BCG vaccinated persons indicates infection with *M. tuberculosis* when the person tested is at increased risk for recent infection.”⁴ If this simple fact were accepted by foreign-trained physicians and their employers (as a condition of employment), such physicians could become true role models, both in accepting indicated treatment for themselves and in educating their patients.

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To the Editor: Geng and colleagues showed, using DNA fingerprinting, that bacillary tuberculosis in foreign-born persons in New York is largely due to reactivation of latent infection with *M. tuberculosis*. Even in the tuberculosis-endemic Chingleput district of southern India, epidemiologic studies have shown that tuberculosis in adults is predominantly reactivation disease.^{1,2} In the Perspective accompanying the report by Geng et al., Bloom³ highlights the imperative of tuberculosis control in developing countries and echoes the WHO approach — namely, detection of at least 70 percent of cases and cure in at least 85 percent of them. This approach will result in cure in only 60 percent of cases. Even persons receiving treatment would already have infected others before diagnosis and treatment.⁴

Most new infections are in children. Thus, even with detection and treatment, children will continue to become infected and, years later, to have reactivation disease. If we do not control the progression to reactivation in the pool of infected children, we lose a window of opportunity to reduce future disease and consequent transmission.² Originally, BCG inoculation was intended to reduce childhood infection with *M. tuberculosis*.¹ The Chingleput vaccine trial and other studies have clearly shown that BCG vaccination does not prevent infection.^{1,2,4} Therefore, the global tuberculosis-control strategy must include screening of children for infection. If children who are in contact with infected adults are found to be infected, they should be given preventive

chemotherapy to reduce the future risk of reactivation disease; all children should be screened at periodic intervals (for example at 5, 10, and 15 years of age); and recently infected children should also be given preventive chemotherapy. Such an approach would not only be good clinical pediatrics; it would also be good public health.

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The authors reply:

To the Editor: John points out the limited success of BCG vaccination in reducing cases of tuberculosis in highly endemic areas and urges that in such areas, widespread screening for and treatment of latent tuberculosis infection be instituted to reduce the risk of reactivation and thus progression to active disease. We agree that treatment of latent infection has been overlooked as a control strategy in countries with a high prevalence of tuberculosis. However, current approaches to the treatment of latent infection are far from ideal, since they rely mainly on prolonged self-administration of isoniazid in a schedule of 270 daily doses. Shorter-duration regimens, which can be delivered by directly observed therapy (such as a 12-dose regimen of once-weekly isoniazid and rifapentine) are needed and are being studied in large, controlled trials.

Much confusion persists regarding interpretation of the results of tuberculin skin tests in persons who have received the BCG vaccine — a problem that can lead to missed opportunities for tuberculosis prevention, as Reichman ably points out in his letter. There is no question that a positive skin test in an adult who was vaccinated with BCG at birth almost certainly represents true latent tuberculosis infection.¹ Health care personnel with latent tuberculosis infection should in general receive high priority for treatment of latent infection, since they can easily spread disease to vulnerable patients.²

Hughes-Davies addresses methodologic issues inherent in all molecular epidemiologic studies of tuberculosis (and epidemiologic studies in general). These caveats are well recognized.^{3,4} Hughes-Davies also raises the possibility that in our study, clusters may have often been started by non-U.S.-born persons, therefore implying that non-U.S.-born persons contributed more to ongoing transmission than we recognized. We believe this an unlikely possibility. Twenty of 51 clusters consisted solely of U.S.-born persons, and only 7 were made up solely of foreign-born persons. Of the 24 clusters containing both U.S.- and foreign-born persons, the index cases (defined as those with the earliest date of diag-

nosis relative to others in the cluster) were U.S.-born in 17, and the mean size of those clusters was 9.1 persons. In contrast, clusters containing only non-U.S.-born persons contained a mean of 2.8 persons. The long period over which cases were collected, as well as the high capture rate in our area (77 percent of isolates), makes our results robust.

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AIDS Orphans

To the Editor: Dr. Foster (June 13 issue)¹ highlights the epic tragedy of AIDS orphans in Africa and the absolute necessity of providing highly active antiretroviral therapy to adults in Africa. Current initiatives of the United Nations Program on HIV/AIDS that focus on preventing mother-to-child transmission of the human immunodeficiency virus (HIV)² serve only to exacerbate the orphan crisis. In Africa, where a major determinant of childhood survival is the presence of a healthy mother,³ it seems illogical to allow 28 million adults to die of HIV and then focus on "salvaging" the orphans.

Highly active antiretroviral therapy is the most effective strategy of chemoprophylaxis against mother-to-child transmission.⁴ It has been argued that Africa lacks the infrastructure and personnel required to provide highly active antiretroviral therapy safely. But many African countries have experience in treating tuberculosis, which involves multidrug therapy and surveillance for resistance. This experience could be built on and rapidly adapted for the provision and management of highly active antiretroviral therapy. The most rational first step would be to treat HIV-infected pregnant women with long-term highly active antiretroviral therapy, thereby ensuring that most mothers survive to look after their own children. Many African countries have vibrant medical schools with the necessary expertise on which to build partnerships with experienced institutions in the United States and other countries in order to make this goal attainable.

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To the Editor: My organization, the Society for Hospital and Resources Exchange, is a nongovernmental organization that has been working in a rural district in western Kenya for more than 12 years. We have been concentrating our efforts on the orphan problem for the past five years and now support 250 orphans directly and many more indirectly through our work with women's groups and other community groups.

I concur with Foster's statement that it is only through local groups with a long-term commitment who know and work with their communities that community groups will be organized effectively. We have had a difficult time trying to expand our efforts, because external aid is almost always given to large international organizations; we have been told more than once that even though the communities want to work with us, we are too small for these large organizations to fund. The track record of such organizations in our area is very poor; they come for a year or two and then disappear, having spent a great deal of money on administration but having accomplished little. Our communities are aware of these problems and have become very knowing and cynical about such large organizations.

It will be difficult to get the large donors to change their ways. Administering a large number of small projects is much more complicated than administering a small number of large projects. But it would be a great thing if publicity and pressure could be brought to bear to effect such a change.

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To the Editor: In response to Dr. Foster's article regarding the orphan problem in Africa, we would like to describe our experience in caring for orphans with HIV or AIDS in Thailand. Our organization, the Children's Rights Foundation, is a nongovernmental organization for children funded principally from Germany. One of the foundation's projects, Baan Gerda, provides family-style living arrangements and antiretroviral treatment to orphans with HIV infection. Baan Gerda is situated 200 km outside Bangkok on 5 acres of land donated to the foundation by the Prabatnampu temple, a well-known hospice for HIV-infected persons in Thailand. The complex contains five clean and well-ventilated homes, a central kitchen, a playground, and a health center. In each home, there are nine children and two HIV-infected caretakers. The caretakers function as parents to provide love and care to the children in their home. The homes are run independently of one another. There are four staff members

on site; all are trained in pediatric nutrition and HIV-related issues. The children generally come to us in bad health, malnourished, and with skin infections. Children undergo thorough medical examinations by a local physician and have their CD4 counts checked. A pediatric HIV specialist handles antiretroviral treatment using (for the most part) generic stavudine, lamivudine, and nevirapine. All children except one have had excellent clinical and immunologic outcomes. The cost of medical care for one child is \$100 per month.

Our long-term goal is to prepare our children for adulthood. Our highest priority is to provide them with love and care.

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Fulminant Hepatitis E in Japan

To the Editor: Hepatitis E virus (HEV) is the leading cause of water-borne epidemics of hepatitis in many developing countries in Asia and Africa, where high mortality has been reported among infected pregnant women.¹ Recently, it has become clear that sporadic hepatitis E occurs in persons in industrialized countries who have no evidence of exposure to HEV strains from countries where the infection is endemic.¹⁻³ However, the contribution of HEV to the development of fulminant hepatitis in industrialized nations is unclear.

To investigate whether HEV might be a cause of fulminant hepatitis in Japan, we conducted a study involving 18 patients (6 men and 12 women; mean [\pm SD] age, 55 \pm 17 years) who had received a diagnosis of non-A, non-B, non-C fulminant hepatitis between 1992 and 2001. They had no history of traveling abroad. Three (17 percent) of them had positive tests for anti-HEV IgM by enzyme immunoassay and for HEV RNA by reverse-transcription polymerase chain reaction.⁴ The HEV viremia in the three infected patients persisted for 11 to 15 days after the onset of disease, and they died 16 to 54 days after its onset. The HEV isolates from the three infected patients differed from each other by 10 to 21 percent in the 412-nucleotide sequence

(GenBank accession numbers, AB079762, AB079763, and AB079764). Two of the three isolates were most homologous to the known genotype IV isolate (T1) from China,⁵ with a nucleotide identity of 86 to 89 percent. The one remaining isolate had the highest identity (90 to 95 percent) with human and swine HEV isolates of genotype III (JRA1 and swJ570), which are considered indigenous to Japan.^{3,4}

Our results indicate that HEV may play an important part in inducing fulminant hepatitis in patients in industrialized countries. All three of the infected patients were men and were older than 60 years; in contrast, rates of fulminant hepatitis in developing countries, where HEV generally affects young adults, are high among pregnant women. The origin of our variants of HEV is unclear. Our patients with fulminant hepatitis E did not report contact with pigs or rats, although zoonosis has been suggested as a source of HEV infection. We conclude that HEV should be considered a potential cause of non-A, non-B, non-C fulminant hepatitis in industrialized countries.

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