Post Traumatic Stress Disorder [letter]

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Post-Traumatic Stress Disorder

To the Editor: After the September 11 terrorist attacks, many people in the United States had substantial symptoms of stress.1,2 However, little information is available from other countries.

Between October 6 and October 13, 2001, we conducted a survey measuring subjective health status by means of a standardized instrument—the 12-item Short-Form Health Survey—in a sample of 1928 persons who were representative of the population of Italy. This instrument had been calibrated to provide an expected mean value of 50.3 for physical health and 50.0 on the mental health summary scale. We conclude that the September terrorist attacks negatively influenced mental health summary scores outside the United States.

GIOVANNI APOLONE, M.D.
PAOLA MOSCONI, B.I.O.L.S.C.D.
Istituto di Ricerche Farmacologiche Mario Negri
20157 Milan, Italy

CARLO LA VECCIA, M.D.
Università degli Studi di Milano
20133 Milan, Italy
lavecchia@marionegri.it

4. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item se-

### Table 1. Subjective Health Status in a Representative Sample of the Italian Population, October 2001.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NO. OF SUBJECTS</th>
<th>SCORE ON THE 12-ITEM SHORT-FORM HEALTH SURVEY</th>
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<td>PHYSICAL HEALTH SUMMARY SCALE</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>921</td>
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<td>1007</td>
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<td>945</td>
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</tr>
<tr>
<td>All subjects</td>
<td>1928</td>
<td>50.1±8.4</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD.

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To the Editor: In his editorial, in discussing the relation between the traumatic events of September 11 and post-traumatic stress disorder (PTSD) in patients, Ursano (Jan. 10 issue) remarks that “cases of bioterrorism-related anthrax that have occurred since September 11 have highlighted the need for changes in the health care system. Substantial funds and effort are needed to render the system capable of handling a serious attack...whether it involves biologic, chemical, or radiologic weapons.” Although there is much truth in this advice, it should not completely distract us from the more effective approaches of primary prevention.

Recent history provides a good example. During the early 1980s, hospitals in the United States were asked to prepare for an influx of casualties from a “limited nuclear war” that might occur in Europe. Members of the International Physicians for the Prevention of Nuclear War and Physicians for Social Responsibility, among others, thoughtfully responded that the health care system cannot save large numbers of casualties of nuclear disaster and emphasized instead international cooperation for the reduction of nuclear arsenals. This proved to be a successful approach.

WILLIAM S. BECKETT, M.D.
University of Rochester School of Medicine and Dentistry
Rochester, NY 14642
bill.beckett@urmc.rochester.edu


To the Editor: In her review of PTSD (Jan. 10 issue), Yehuda confounds the vulnerability to traumatic events with the vulnerability to PTSD after such events and draws a mistaken conclusion — namely, that the data argue against an increased vulnerability to PTSD among women. One of the most consistent findings in epidemiologic research involving samples of civilians is the higher vulnerability of women than men to PTSD. Although women are less likely to have the type of traumatic experiences that lead to PTSD, they are more likely to succumb to PTSD after such experiences. This is the case even when the type of traumatic event is controlled for. In addition, Yehuda’s statement that the finding in one study of major depression among women and 48.5 percent among men is false. The cited article reports that the prevalence of exposure to assaultive violence resulted primarily from the greater vulnerability of women to PTSD after such events.

NAOMI BRESLAU, PH.D.
Henry Ford Health System
Detroit, MI 48202
nbresla1@hfhs.org


To the Editor: In the section on epidemiologic aspects of PTSD, Yehuda does not mention coexisting conditions such as major depression. The rate of coexisting major depression among patients with PTSD is high — 47.9 percent among women and 48.5 percent among men. In Figure 1 in the section on the biologic aspects of PTSD, Yehuda concludes that in patients with PTSD, there is an increased sensitivity of the negative-feedback system of the hypothalamic–pituitary–adrenal axis, whereas the opposite is found in patients with major depression. How can we understand the high rate of major depression coexisting with PTSD in the light of these contrasting hormone profiles?

I think traumatic stress influences not only the norepinephrine system and the hypothalamic–pituitary–adrenal axis, but also systems such as the dopaminergic, serotonergic, endogenous opiate, and γ-aminobutyric acid–benzodiazepine systems. Moreover, since there are two types of steroid receptors (type I [mineralocorticoid] and type II [glucocorticoid]), the balance between the two types has an important role in developing psychopathology.

Yehuda also describes brain areas involved in fear responses, such as the amygdala, the anterior paralimbic region, and the anterior cingulate and orbitofrontal areas, but she does not discuss in detail the interaction between the limbic system (amygdala and hippocampus) and the prefrontal cortex. One of the important functions of the prefrontal cortex, however, is extinction — the inhibition of fear responses caused by the amygdala.

R.J.L. LINDAUER, M.D.
Academic Medical Center
1105 BC Amsterdam, the Netherlands
rjlindauer@amc.uva.nl

To the Editor: I was disappointed that the review by Yehuda did not address the question of the legitimacy of the diagnosis of PTSD as it has been elucidated by others. It appears that some authorities think that this diagnosis is overused.

T. Mark Meyer, M.D.
Aiken Internal Medicine
Aiken, SC 29801

Dr. Yehuda replies:

To the Editor: The greater probability that PTSD will occur after rape than after an accident is best attributed to differences in the ability of these events to engender fear or feelings of helplessness, not to preexisting vulnerabilities of those who have the two types of experiences. Similarly, it is arguable that being assaulted by a man who weighs 200 lb is a different experience for a woman who weighs 110 lb than for a man who weighs 190 lb. Accordingly, the increased likelihood of PTSD in women may reflect more severe traumatic experiences, rather than an inherent vulnerability to illness. This explanation is bolstered by the fact that the prevalence of PTSD after events such as an accident, a natural disaster, or the death of a loved one is not significantly higher among women than among men. It cannot be assumed that controlling for the type of traumatic event sufficiently accounts for the manner in which differences between the sexes alter the character of an event within a broadly conceived category.

The coexistence of depression with PTSD may simply reflect an overlap of symptoms (e.g., insomnia, impaired concentration, irritability, loss of interest, and restricted emotion). Most studies have found little or no contribution of depression to the neuroendocrine alterations associated with PTSD. Conversely, women with depression who have been abused early in life have reduced cortisol levels and increased responsiveness of the hypothalamic–pituitary–adrenal axis, as do patients with PTSD, raising the possibility that biologic subtypes of PTSD and depression may be categorized according to whether traumatization occurred early or later in life, rather than according to the nature, severity, and coexistence of symptoms.

The objective of the review was to report findings associated specifically with PTSD, not fear or stress in general, and to highlight the fact that such findings are in some ways distinct from those related to the physiology of fear or stress. PTSD is worthy of study precisely because its understanding will require more than the repackaging of current ideas about “stress” as explanations for its occurrence and pathophysiology. Increased recognition of the unique and circumscribed biologic profile associated with PTSD warrants the development of new pharmacologic approaches that might take into account the specific biologic underpinnings of this disorder.

It has historically been convenient to question the legitimacy of the diagnosis of PTSD for a number of social and political reasons, including the potential culpability of those who inflict traumatic stress on others. That the diagnosis may sometimes be overused does not speak to its legitimacy but to the lack of widespread understanding about what PTSD is, who is at risk, and how the disorder can best be diagnosed. As our understanding of these matters increases, the confusion, debate, and misuse that surround the diagnosis will abate.

Rachel Yehuda, Ph.D.
Mount Sinai School of Medicine
New York, NY 10029
rachel.yehuda@med.va.gov

The editorialist replies:

To the Editor: In discussing the prevention of terrorist attacks, Dr. Beckett highlights the value of the primary prevention of PTSD and other trauma-related psychiatric disorders such as depression. Primary prevention of post-traumatic psychiatric disorders is particularly important, since 34 to 44 percent of those in whom PTSD or depression develops after a traumatic event have no previous predisposing psychiatric illness. In our complex sociopolitical world, of which terrorism and war are a part, the prevention of these human-made disasters is important work for all, including physicians and health care providers. As in the case with seat belts and car accidents or smoking and lung cancer, event-related psychiatric disorders offer the opportunity for primary prevention by changing the types of behavior that trigger the disease process.

One of the most successful prevention programs was initiated in Australia to prevent malignant melanoma, a disease that is expected to affect more than 53,000 new patients and cause 7400 deaths in the United States this year. The campaign was built on a community-wide effort to “slip, slap, slop” — that is, slip on a T-shirt, slap on a hat, and slop on sunscreen lotion. Community action was the mechanism of primary disease prevention — a “vaccination” that resulted in a change in behavior.

Primary prevention often leads to collaboration with communities, educators, journalists, the media, and most important, community leaders. Prevention of the human-made disaster of war and terrorism will require similar but more complex psychosocial interventions. It is a worthy goal.

Robert J. Ursano, M.D.
Uniformed Services University School of Medicine
Bethesda, MD 20814-4799
rursano@usuhs.mil


Chemotherapy for Lung Cancer

To the Editor: Schiller and colleagues (Jan. 10 issue) report equivalent overall survival and response rates for four third-generation chemotherapy regimens in advanced non–small-cell lung cancer. The median survival in the four groups was 7.4 to 8.1 months. In a disease with such a poor prognosis, quality of life and control of symptoms are relevant end points, but neither of these end points was mentioned, nor were hospitalization rates or costs reported. Assuming that four cycles of the regimen are given during a three-to-four-month period, that the body-surface area is 1.7 m², and that the glomerular-filtration rate is 75 ml per minute, we estimate that the cost per patient for the chemotherapy alone in the United Kingdom would be as follows: $4,678 for cisplatin and paclitaxel, $5,545 for cisplatin and gemcitabine, $6,689 for cisplatin and docetaxel, and $10,035 for carboplatin and paclitaxel.

Few studies have assessed the views of patients with advanced non–small-cell lung cancer who are receiving palliative chemotherapy. Silvestri et al. found that many would not choose chemotherapy to obtain a survival benefit of three months or less but would choose it if it improved their quality of life. Although we accept that there is a small group of patients whose outcome is not adequately reflected by median survival figures, we would like to point out that most patients will have only a marginal benefit in terms of survival with these expensive and toxic regimens.

IMOGEN LOCKE, M.R.C.P.
CHARLES M. GILLHAM, F.R.C.R.
Middlesex Hospital
London W1T 3AA, United Kingdom


The authors reply:

To the Editor: We agree with Locke and Gillham that survival in advanced lung cancer is poor, even with chemothera-
pathy; that chemotherapy is expensive; and that side effects and quality of life are important considerations. However, it is also important to note that the one-year survival rate of 35 percent in our study is an improvement over the one-year survival rate of 10 percent reported in studies that examined the use of the best supportive care. Although we recognize the dangers inherent in comparisons with historical controls, additional evidence suggesting that chemotherapy affects survival comes from randomized studies showing the ben-
et of chemotherapy with two agents, as compared with sin-
gle-agent therapy with cisplatin. We submit that these slight improvements in survival represent a clinically significant difference and that, given the option, many if not most patients with good performance status would elect chemotherapy. Furthermore, many studies have shown that chemotherapy can result in improvement in symptoms or improvement in the quality of life. Lastly, although chemotherapy certainly has substantial side effects, the incidence of clinically significant, moderate-to-fatal (grade 3, 4, or 5) toxic effects was 15 percent or less in the carboplatin-plus-paclitaxel group.

Despite these potential benefits, many physicians have approached the treatment of lung cancer in a somewhat nihil-

istic fashion, even though the results with chemotherapy in most other adult solid tumors are roughly of the same magni-

tude and even though the benefit of adjuvant chemotherapy in less advanced cancer is also moderate. (For example, the absolute improvement in overall survival is only 3 to 5 percent at five years in patients with node-positive breast cancer.) Why is this? We think that patients with lung cancer tend to arouse less sympathy than patients with other diseases, even though many of them started smoking in the period from the 1940s to the 1960s, before the health hazards of smoking were widely appreciated. Others started smoking in their adolescence in response to peer pressure or the enticements of advertisements or have tried unsuccessfully to quit. Even those who have managed to “kick the habit” are not immune to lung cancer; it is estimated that approximately half of all cases of lung cancer occur in former smokers. We believe that patients with lung cancer should have the same access to treatment as patients with other types of cancer.

JOAN H. SCHILLER, M.D.
University of Wisconsin
Madison, WI 53792

DAVID HARRINGTON, PH.D.
Dana–Farber Cancer Institute
Boston, MA 02115

DAVID H. JOHNSON, M.D.
Vanderbilt University
Nashville, TN 37232

1. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on indi-

dividual patients from 52 randomised clinical trials. BMJ 1995;311:899-

909.
3. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfa-
4. Early Breast Cancer Trials’ Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 ran-
Decisions about Voriconazole versus Liposomal Amphotericin B

To the Editor: The letter from Powers et al. (Jan. 24 issue)1 challenged our use of the unstratified analysis in evaluating the overall response to empirical antifungal therapy and stated that a Bonferroni correction for multiple testing is required for the comparison of treatment groups with respect to the frequency of breakthrough fungal infections. The basis for our analyses2 is the protocol document that was approved before the study by the data safety and monitoring board of the National Institute of Allergy and Infectious Diseases Mycoses Study Group. The plan in the protocol is for an unstratified analysis of the primary end point, which was the overall response to empirical therapy. Among the elements of the composite end point, only the difference between treatment groups in the frequency of breakthrough fungal infections was specified in the protocol. Consequently, a Bonferroni correction for multiple comparisons was not necessary. The analyses presented in the article followed the prespecified plan.

The vote by the Antiviral Drug Products Advisory Committee of the Food and Drug Administration was unanimous against the broad approval of voriconazole for the indication of empirical antifungal therapy in patients with neutropenia. Two members voted yes, two were equivocal, and six voted no for the broad indication.3 This vote then prompted further discussion concerning voriconazole for empirical antifungal therapy in high-risk patients with neutropenia. Goldberger also requested that the committee provide guidance in developing language for this possible indication of empirical antifungal therapy with voriconazole. One advisory committee members affirmed support for an indication of empirical antifungal therapy with voriconazole, particularly in high-risk patients with neutropenia.

THOMAS J. WALSH, M.D.
National Cancer Institute
Bethesda, MD 20892
walsh@mail.nih.gov

JEANNETTE LEE, PH.D.
WILLIAM E. DISMUKES, M.D.
University of Alabama at Birmingham
Birmingham, AL 35294-0111

The authors reply:

To the Editor: Voriconazole fails to meet the statistical definition of noninferiority in both the stratified and unstratified analyses of the overall response in the clinical trial that compared voriconazole with liposomal amphotericin B as empirical antifungal therapy in febrile patients with neutropenia.1 In certain disease states, failing to meet the noninferiority margin in a clinical trial could mean that the drug not only may not be equivalent to the control regimen but also may have no efficacy as compared with no treatment.2

As Marr states in the accompanying editorial,3 the previous trials of empirical antifungal therapy in patients with neutropenia that compared amphotericin B deoxycholate with no treatment had insufficient power to determine a difference in the rate of breakthrough fungal infections. Although this does not mean that empirical antifungal therapy is not beneficial in febrile patients with neutropenia, these trials do not give a clear estimate of the magnitude of such a benefit. Given these uncertainties, one could view failing to meet the noninferiority margin of ~10 percent as demonstrating that voriconazole may not be equivalent to the control regimen, and, in the worst case, may not have a benefit over no treatment.

The Food and Drug Administration has approved liposomal amphotericin B and voriconazole for empirical antifungal therapy in febrile patients with neutropenia on the basis of trials with a design similar to that of the voriconazole trial. Although there were important differences in patient demographics and end-point definitions between these trials, both drugs were within a ~10 percent margin of noninferiority as compared with the control regimen.4

We still believe that one should use caution in interpreting the results of subgroup analyses when there is no statistically significant evidence of efficacy in the primary end point of the trial. The demonstrated efficacy of voriconazole in invasive aspergillosis4 and the subgroup analysis in high-risk patients from the empirical-therapy trial generate hypotheses that voriconazole may have a benefit in empirical therapy of febrile patients with neutropenia, but it is not possible to determine this conclusively from the study by Walsh et al. We hope there will be interest in conducting further studies of voriconazole and other antifungal drugs as empirical antifungal therapy in febrile patients with neutropenia, including the high-risk subgroup of patients, in order to answer these important questions.

JOHN H. POWERS, M.D.
CHERYL A. DIXON, PH.D.
MARK GOLDBERGER, M.D., M.P.H.
Food and Drug Administration
Rockville, MD 20850
powersjoh@cdrf.fda.gov

Mortality among Patients Admitted to Hospitals on Weekends as Compared with Weekdays

To the Editor: Bell and Redelmeier (Aug. 30 issue)\(^1\) have quantified something that clinicians have long suspected: it gets tough in hospitals over the weekend. Their study has enormous implications for hospital staffing and therefore deserves careful scrutiny. The authors suggest that the higher mortality observed on weekends as compared with weekdays is not explained by greater severity of illness in patients presenting on the weekends. However, the Charlson comorbidity index may not be sensitive enough to discern important differences in the severity of disease.

If weekend staffing were the problem, admission at 6 p.m. on Friday would be the point of highest risk. Is the mortality rate among patients admitted on Friday evening higher than that among patients admitted on Sunday or other weekdays?

HOWARD K. GOGEL, M.D.
Southwest Gastroenterology Associates
Albuquerque, NM 87106
hkgogel@aol.com


To the Editor: Much has been written, including a recent editorial in the Journal,\(^1\) about the decreased attention given to physical diagnosis in medical education and the poor skills of new graduates. Is it possible that the diagnosis of an aneurysm is more likely to be delayed on a weekend because of the time it takes for the patient to be presented to a senior physician who may be more competent in physical diagnosis?

MEIR LIRON, M.D.
Yakum 60972, Israel
mliron@yakum.co.il


To the Editor: To avoid problems of multiple statistical tests, Bell and Redelmeier used seven a priori criteria to select three diseases for analysis. However, ruptured aortic aneurysm does not meet the criterion that “patients with the condition typically receive a substantial amount of care in clinical settings other than a critical care unit or emergency department.” Ruptured aortic aneurysm is treated in the emergency room, the operating room, and the surgical intensive care unit. The authors used hip fracture as a control disease because it is treated primarily in the operating room. Similarly, acute epiglottitis meets neither their criterion of high frequency nor that of a high in-hospital mortality rate: fewer than 10 patients died of this disease over the course of the study. In contrast, conditions such as pneumonia and heart failure accounted for thousands of deaths and met the authors’ other criteria but were not selected for the main analysis.

In their second analysis, the authors identified the 100 most frequent causes of death (categorized according to the diagnostic code in the International Classification of Diseases) and found 23 for which the odds ratios for mortality associated with weekend admission were significantly greater than 1.00. However, of these 23 categories, 13 were some kind of cancer and should have been excluded from any analysis of outcomes of acute care that was based on mortality data. Patients with terminal cancer may have been admitted preferentially on weekends, when their oncologists were not available to refer them for alternative end-of-life care.\(^2\)

The authors’ Table 3 shows that for 2 of the remaining 10 categories, the confidence interval for the adjusted odds ratio includes 1.00. In addition, the category they refer to as “renal failure,” which reflects “unspecified” renal failure and for which mortality was significantly increased among patients admitted on the weekend, does not include the larger number of cases of “acute” and “chronic” renal failure; for those categories, the odds ratios were not significantly increased. Other categories (such as “cardiac dysrhythmia” and “cardiac-conduction disorder”) should have been aggregated, and still others (such as “general cardiovascular symptoms”) overlap with categories for which there was not an increased risk of mortality associated with weekend admission. We do not believe that the authors’ data support their conclusion that there are significant differences in mortality between patients admitted on weekdays and those admitted on weekends.

MITCHELL P. LAKS, M.D., PH.D.
MICHELLE ROTBLAT
Albert Einstein College of Medicine
Bronx, NY 10467
mlaks2000@yahoo.com


The authors reply:

To the Editor: Gogel wonders whether differences in mortality rates are observable in comparisons between patients who arrive near the start of the weekend and those who arrive near the end of the weekend. Our study had limited power to compare the mortality rates associated with individual diseases between patients admitted on Friday night and those admitted on Sunday night. We found that aggregate mortality rates (including all admissions) were similar for the two periods. However, because conditions leading to admission on Friday night are quite different from those on Sunday night, with many more admissions on Friday night related to lifestyle,\(^1\) these rates are difficult to interpret.

Liron asks whether the increases in mortality with weekend care are attributable to a decline in the skills needed for physical diagnosis. We agree that failures of diagnosis might contribute to the increased mortality; however, some diseases whose diagnosis is straightforward (e.g., renal failure) were also associated with higher mortality with weekend admission.\(^2\) Moreover, some diseases that are difficult to diagnose did not show this pattern (e.g., ischemic col-

Furthermore, the increase in mortality with weekend admission was similar in community hospitals and teaching hospitals. Hence, we do not attribute the entire problem to physicians who are less experienced in physical diagnosis. Laks and Rotblat recognize that our first analyses addressed only a few selected diseases. We therefore provided the second analysis, in which we examined all of the 100 most common causes of death (including pneumonia and heart failure). Ruptured aortic aneurysm satisfied our initial criteria because its management requires complex radiologic investigations, substantial operating-room resources, and efforts to coordinate this acute care. Acute epiglottitis satisfied our criteria since it was 1 of the 100 most common causes of death in children. Pneumonia and heart failure did not satisfy our criteria because critically ill patients are usually transferred to the intensive care unit rather than to the wards.

Laks and Rotblat speculate that the increased mortality in our second analysis might reflect deaths of patients with cancer who were admitted for end-of-life care. Yet cancer was also common among the diagnoses that were not associated with increased weekend mortality (12 of 77 diagnoses). Also, most of the excess deaths with weekend admission occurred within 48 hours after arrival, which is not what would be expected with palliative terminal care. Contrary to their speculation, aggregate analyses of patients with any type of renal failure showed an increase in mortality with weekend admission (26 percent, vs. 23 percent with weekday admission; P=0.007), as did analyses of patients with any type of cardiac disorder (8.7 percent, vs. 8.2 percent with weekday admission; P<0.001).

Donald A. Redelmeier, M.D.
Chaim M. Bell, M.D.
University of Toronto
Toronto, ON M4N 3M5, Canada
dar@ices.on.ca

3. Alapati SV, Mihas AA. When to suspect ischemic colitis: why is this condition so often missed or misdiagnosed? Postgrad Med 1999;105:177-80, 183-4, 187.

Transplacental Transfer of Small-Cell Carcinoma of the Lung

To the Editor: Although the estimated rate of cancer during pregnancy is 1 case per 1000 live births,1 and placental metastases are not uncommon, transplacental transmission of maternal tumors is rare. We report a case of small-cell carcinoma of the lung transmitted from a 37-year-old mother to her infant. At the time of delivery, the mother presented with a history of six weeks of increasing dyspnea, a nonproductive cough, and weight loss. She had a 40-pack-year history of cigarette smoking. Radiographs showed a central lesion in the left lung, a mass in the chest wall, and liver nodules. Biopsies of the chest wall and bone marrow showed metastatic small-cell carcinoma; the findings were consistent with a pulmonary origin. Despite aggressive therapy, she died five months later.

A preterm, 33-week-old boy was delivered by cesarean section. The placenta was infiltrated with small-cell carcinoma (Fig. 1). Laboratory and radiographic studies were unremarkable at birth, at three weeks, and at three months. At five months, computed tomographic scans showed nodules in the liver and right lung. A liver biopsy showed metastatic small-cell carcinoma similar to that seen in the placenta. Analysis of the liver-biopsy specimen with the use of fluorescence in situ hybridization showed a subpopulation of cells with a female XX pattern, a finding consistent with a tumor of maternal origin.

Figure 1. Photomicrographs of the Placenta.

The placenta weighed 497 g and measured 16 by 15 by 2 cm. Numerous tumor emboli of various sizes were present within the intervillous spaces (Panel A; hematoxylin and eosin, ×100). The tumor was characterized by cohesive small, blue cells with round or oval nuclei, delicate chromatin, small nucleoli, and eosinophilic cytoplasm (Panel B; hematoxylin and eosin, ×400). The tumor cells were positive for cytokeratin and were negative for CD45, CD99, chromogranin, synaptophysin, desmin, neuron-specific enolase, muscle-specific actin, vimentin, and thyroid transcription factor 1.
New Strategy for Prenatal Diagnosis of X-Linked Disorders

To the Editor: An invasive approach is still the gold standard for prenatal diagnosis of genetic disorders. Chorionic-villus sampling, the current procedure of choice, allows an early diagnosis, but the miscarriage rate after chorionic-villus sampling is as high as 6.8 percent, and the sampling-failure rate is at least three times the rate with amniocentesis.1 Cell-free DNA circulating in maternal plasma offers the possibility of a noninvasive approach to prenatal diagnosis.2 This method permits determination of the sex of the fetus with 100 percent accuracy when maternal serum analysis is performed only for male fetuses, averting an unnecessary risk of fetal loss in the case of females.2

In all other cases, the identification of fetal sex could not be ascertained because of spontaneous miscarriage. In all other cases, the identification of fetal sex based on the analysis of maternal serum was in complete agreement with the actual fetal sex. The identification of all 70 male fetuses was confirmed by karyotyping of chorionic villi, and ultrasonography confirmed the identification of all 59 female fetuses. Thus, invasive prenatal diagnosis was performed only for male fetuses, averting an unnecessary risk of fetal loss in the case of females.

If ultrasonography reveals a misdiagnosis, prenatal diagnosis is still feasible through amniocentesis. Furthermore, if

Table 1. X-Linked Genetic Diseases for Which the New Approach to Prenatal Diagnosis Has Been Used.

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
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<td>Hemophilia</td>
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<tr>
<td>Muscular dystrophy</td>
<td>31</td>
</tr>
<tr>
<td>X-linked mental retardation</td>
<td>8</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>7</td>
</tr>
<tr>
<td>Alport’s syndrome</td>
<td>7</td>
</tr>
<tr>
<td>X-linked severe immunodeficiency</td>
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</tr>
<tr>
<td>Retinitis pigmentosa</td>
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<tr>
<td>X-linked hydrocephalus</td>
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<td>Anhidrotic ectodermal dysplasia</td>
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<td>Lesch–Nyhan syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
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