Post Traumatic Stress Disorder [letter]
Lindauer, R.J.L.

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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. 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. Trained interviewers collected data in the context of a personal telephone interview.

The main results — the scores on the summary scales for physical and mental health — are shown in Table 1. The mean overall score on the scale measuring physical health was 50.1 — that is, very close to the expected value. In contrast, the mean overall score on the scale measuring mental health was 48.2 — that is, about 20 percent of 1 SD below the expected value, with lower numbers indicating lower perceived mental health. Mean scores on both scales were higher among younger and more educated persons.

These results, indicating a slight depression in the mental health score, can be compared with historical data. In 2000, as part of a nationwide survey conducted by the Italian National Institute of Statistics, these surveys were administered to a sample of 140,000 citizens; the mean scores were 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.

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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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PHYSICAL HEALTH SUMMARY SCALE</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>921</td>
<td>51.0±7.3</td>
</tr>
<tr>
<td>Female</td>
<td>1007</td>
<td>49.3±9.2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 yr</td>
<td>1134</td>
<td>52.3±6.6</td>
</tr>
<tr>
<td>≥50 yr</td>
<td>794</td>
<td>47.0±9.7</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school only</td>
<td>983</td>
<td>48.0±9.5</td>
</tr>
<tr>
<td>High school or more</td>
<td>945</td>
<td>52.3±6.4</td>
</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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**INSTRUCTIONS FOR LETTERS TO THE EDITOR**

Letters to the editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: • Your letter must be typewritten and triple-spaced. • Its text, not including references, must not exceed 250 words if it is in reference to a recent Journal article and 400 words in all other cases (please provide a word count). • The letter must have no more than five references and one figure or table. • The letter must be signed by no more than three authors. • Letters referring to a recent Journal article must be received within four weeks of its publication. • Include your full mailing address, telephone number, fax number, and e-mail address. • Letters to the editor may be submitted over the Internet at http://secure.nejm.org/letters. You may also send us your letter by standard mail or fax.

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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.

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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 and when traumatic sexual experiences, which are more prevalent among women, are excluded and the rates of PTSD resulting from other traumatic events are compared.

In addition, Yehuda’s statement that the finding in one study that 50 percent of cases of PTSD in women (as compared with 15 percent of those in men) appear to result from sexual or physical assault is attributable to “the extremely high frequency of sexual and physical assault among women” is false. The cited article reports that the prevalence of exposure to assaultive violence was lower among women (traumatic sexual experiences occurred more frequently among women, but physical assaults in general occurred less frequently), and that the difference between the sexes in the proportions of cases of PTSD that were attributable to assaultive violence resulted primarily from the greater vulnerability of women to PTSD after such events.

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**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.

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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.

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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.

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Uniformed Services University School of Medicine
Bethesda, MD 20814-4799

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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.
patients will have only a marginal benefit in terms of sur-
dial survival figures, we would like to point out that most
patients whose outcome is not adequately reflected by me-
nosis, quality of life and control of symptoms are relevant
was 7.4 to 8.1 months. In a disease with such a poor prog-
cressive 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 prog-
agnosis, quality of life and control of symptoms are relevant
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 gem-
citabine, $6,689 for cisplatin and docetaxel, and $10,035
for carboplatin and paclitaxel.
Few studies have assessed the views of patients with ad-
non–small-cell lung cancer who are receiving pal-
lientive 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.² Although we accept that there is a small group
of patients whose outcome is not adequately reflected by me-
dian survival figures, we would like to point out that most
patients will have only a marginal benefit in terms of sur-
with these expensive and toxic regimens.

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

1. Schiller JH, Harrington D, Belani CP, et al. Comparison of four che-
motherapy regimens for advanced non–small-cell lung cancer. N Engl J
2. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in
patients with advanced non-small cell lung cancer: descriptive study based

The authors reply:

To the Editor: Schiller and colleagues (Jan. 10 issue)¹ re-
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1. Ursano RJ, Grieger TA, McCormack JE. Prevention of post-traumatic
stress: consultation, training and early treatment. In: van der Kolk BA,
McFarlane AC, Weissak H, eds. Traumatic stress: the effects of overwhelm-
ing experience on mind, body, and society. New York: Guilford Press,

Chemotherapy for Lung Cancer

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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 not 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.4 The 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.5 Five additional members indicated support for an indication of empirical antifungal therapy restricted to high-risk patients with neutropenia. The analyses presented in the article followed the prespecified plan.

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

To the Editor: Bell and Redelmeier (Aug. 30 issue) 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?

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To the Editor: Much has been written, including a recent editorial in the Journal, 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 might be more competent in physical diagnosis?

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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 criteria 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.

The authors’ Table 3 shows that for 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.

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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, 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. Moreover, some diseases that are difficult to diagnose did not show this pattern (e.g., ischemic colic...
tis). 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).

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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, 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. \(^2,3\) This method permits determination of the sex of the fetus with 100 percent accuracy when maternal serum is analyzed during the first trimester of pregnancy. \(^4\) This method allows an early diagnosis, but the miscarriage rate after 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. \(^2,3\) This method permits determination of the sex of the fetus with 100 percent accuracy when maternal serum is analyzed during the first trimester of pregnancy. \(^4\) As a consequence, a new strategy for the prenatal diagnosis of X-linked genetic disorders is now possible. With this strategy, the sex of the fetus is determined by analysis of maternal serum between 10 and 13 weeks of gestation, followed by chorionic villus sampling if the fetus is identified as male. If the fetus is identified as female, chorionic villus sampling is not performed, and fetal sex is confirmed later in the pregnancy by ultrasonography.

This new strategy has been carried out in 131 pregnant women at risk for a fetus with an X-linked genetic disease (Table 1), after they received genetic counseling and gave written informed consent. In two cases, the sex of the fetus 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 the safest procedure is desired, maternal serum analysis can be paired with ultrasonography; a recent study has shown that ultrasonographic identification of fetal sex is possible within the first 12 weeks of gestation. \(^5\) Our proposed strategy leads to a substantial decrease in the use of unnecessary diagnostic tests such as karyotyping and molecular analysis in the case of female fetuses and decreases the number of diagnostic tests such as karyotyping and molecular analysis in the case of female fetuses and decreases the number of time-consuming, costly, and risky chorionic villus-sampling procedures.


table

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases</th>
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<tbody>
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<td>Hemophilia</td>
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<td>Alport’s syndrome</td>
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<td>Other</td>
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