

## THE TERATOGENICITY OF ANTICONVULSANT DRUGS

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**ABSTRACT**

**Background** The frequency of major malformations, growth retardation, and hypoplasia of the midface and fingers, known as anticonvulsant embryopathy, is increased in infants exposed to anticonvulsant drugs in utero. However, whether the abnormalities are caused by the maternal epilepsy itself or by exposure to anticonvulsant drugs is not known.

**Methods** We screened 128,049 pregnant women at delivery to identify three groups of infants: those exposed to anticonvulsant drugs, those unexposed to anticonvulsant drugs but with a maternal history of seizures, and those unexposed to anticonvulsant drugs with no maternal history of seizures (control group). The infants were examined systematically for the presence of the major malformations, signs of hypoplasia of the midface and fingers, microcephaly, and small body size.

**Results** The combined frequency of anticonvulsant embryopathy was higher in 223 infants exposed to one anticonvulsant drug than in 508 control infants (20.6 percent vs. 8.5 percent; odds ratio, 2.8; 95 percent confidence interval, 1.1 to 9.7). The frequency was also higher in 93 infants exposed to two or more anticonvulsant drugs than in the controls (28.0 percent vs. 8.5 percent; odds ratio, 4.2; 95 percent confidence interval, 1.1 to 5.1). The 98 infants whose mothers had a history of epilepsy but took no anticonvulsant drugs during the pregnancy did not have a higher frequency of those abnormalities than the control infants.

**Conclusions** A distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself. (N Engl J Med 2001;344:1132-8.)

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**A**NTICONVULSANT drugs<sup>1</sup> taken by pregnant women to prevent seizures are among the most common causes of potential harm to the fetus. In the 1970s and 1980s, the anticonvulsant drugs used most frequently to prevent seizures — phenobarbital, phenytoin, and carbamazepine — were found to cause major malformations, microcephaly, growth retardation, and distinctive minor abnormalities of the face and fingers in infants exposed to them during pregnancy.<sup>2-8</sup>

However, medical textbooks<sup>9-11</sup> have suggested that these defects are caused by other factors, such as genetic abnormalities that cause the mother's epilepsy and are inherited by the fetus.<sup>12</sup> To elucidate this issue, we conducted a cohort study of three groups of infants: those whose mothers took anticonvulsant drugs during the pregnancy, those whose mothers

had epilepsy but took no anticonvulsant drugs during the pregnancy, and those whose mothers had no history of epilepsy and took no anticonvulsant drugs during the pregnancy (the control group).

**METHODS****Study Design**

This study was conducted from 1986 to 1993 at five maternity hospitals in the Boston area: Brigham and Women's Hospital, Beth Israel Hospital, St. Margaret's Hospital, St. Elizabeth's Hospital, and Newton-Wellesley Hospital. Potential subjects were identified in the labor and delivery suites by nurses who asked the women if they had taken any medication for seizures during the pregnancy and if they had ever had a seizure.<sup>13</sup> Women who answered yes to either question were then interviewed, with the approval of their obstetricians and nurses, to inform them about the study and to determine whether they qualified for inclusion. Women were excluded if they did not speak English, had a multiple-gestation pregnancy, or had another potentially teratogenic factor, such as type 1 diabetes mellitus. If the women qualified, they were asked to enroll and to give written informed consent. The study protocol was reviewed and approved annually by the institutional review board at each participating hospital. If a mother chose not to enroll, the results of the pediatrician's examination of her infant were reviewed to obtain birth weight, length, head circumference, and the presence or absence of any major malformations; these infants were not examined by a study physician.

The women enrolled in the study were asked to provide demographic data and to complete questionnaires administered by a research assistant to determine why they were taking anticonvulsant drugs (e.g., epilepsy or bipolar disorder); the dosage of each anticonvulsant drug; the characteristics of the seizures, their frequency during the pregnancy, and whether the women lost consciousness during seizures; and the family history with respect to epilepsy. With the written authorization of each woman, the results of all diagnostic tests (e.g., magnetic resonance images, electroencephalograms, and skull radiographs) and the dosages and serum concentrations of any anticonvulsant drugs were obtained. The responses to the questions and the results of the diagnostic evaluations of the women were reviewed by the study epileptologist to determine the type of epilepsy and its apparent cause with the use of an international classification of epilepsy.<sup>14</sup>

For each of the infants born to the enrolled women (i.e., either an infant exposed to anticonvulsant drugs or an infant not exposed to anticonvulsant drugs whose mother reported having had epilepsy), a control was recruited from the 10 infants born closest in time to him or her. Selecting randomly from this group of infants, we approached each mother until one was enrolled for each index infant. The same questionnaire was administered to the mothers of the control infants, with a separate consent form.

**Examination of the Infants**

The infants in all three groups were examined by a study physician; this physician was unaware of the exposure status of the

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infant during 93 percent of the examinations. The protocol for the physical examination listed 53 minor physical features to be recorded as present or absent. The dermal-ridge patterns (i.e., loops, whorls, and arches) on all fingers were recorded with magnification by otoscope, and 29 measurements were made, including the circumference and bitemporal width of the head, the inner canthal distance, and the length of the nose and upper lip (measured with a plastic ruler, a tape measure scored in millimeters, or sliding calipers; Seritex, Carlstadt, N.J.). The nose was measured from the lowest point in the depression of the bridge of the nose to the level of the alae nasi. The upper lip was measured from the base of the nasal septum to the upper edge of the vermilion border.

The outcomes of interest were major malformations, microcephaly, growth retardation, and hypoplasia of the midface and fingers. Major malformations were defined as structural abnormalities with surgical, medical, or cosmetic importance (identified during the first five days of life). Features that were not classified as major malformations are listed in Table 1.

The analysis included only singleton infants, because multiple births are associated with an increased risk of malformations. Microcephaly and growth retardation were defined respectively as head circumference and length or weight more than 2 SD below the mean value for infants of the same race, sex, and gestational age.<sup>16</sup> Normal values for black infants were adjusted to those of the previous week of gestation for white infants.<sup>17</sup> Hypoplasia of the midface (in singleton infants born at 37 weeks of gestation or later) was defined as the presence of at least two of the following three features: a short nose, a long upper lip, and either telecanthus or a broad bridge of the nose. These features were considered to be present if the measurements were more than 1 SD above or below the mean values for the control infants. Hypoplasia of the fingers was defined as marked stiffness of the distal interphalangeal joint in 1 or more fingers or 6 or more arch patterns among the 10 dermal-ridge patterns. In a previous study,<sup>18</sup> 5 percent of the dermal-ridge patterns were arches among children who were not exposed to anticonvulsant drugs.

### Statistical Analysis

Individual logistic-regression analyses were conducted for each of the main outcomes. The correlation between outcome and each category of exposure (no maternal history of seizure or exposure to drugs, maternal history of seizures without exposure to drugs, exposure to one drug, exposure to more than one drug, and exposure to all drugs) was adjusted for maternal cigarette smoking (half a pack or more per day); ingestion of alcohol (14.8 ml [0.5 oz] on two or more occasions per week); self-reported use of cocaine or other illicit drugs; loss of consciousness during a seizure, presence of a febrile illness with a temperature above 39°C (102°F) for 48 hours, or presence of an important medical illness (e.g., multiple sclerosis); maternal or paternal head size or height more than 2 SD below the mean; or the presence of a major malformation in a first-degree relative.

We used two logistic-regression techniques to evaluate the interrelated outcomes: collapsed logistic-regression analyses relating the probability of at least one of the outcomes to the category of exposure, and generalized estimating equations assessing a global effect of anticonvulsant drugs on each set of outcomes after adjustment for confounders and for correlation among outcomes measured in the same subject.<sup>19</sup>

## RESULTS

By screening 128,049 women in labor and delivery suites, we identified 509 who had taken one or more anticonvulsant drugs during pregnancy, 386 of whom had taken one drug and 123 of whom had taken two or more drugs (30 women who had switched from one drug to another were included in the latter group) (Table 2). Among the 386 women who had

**TABLE 1. PHYSICAL ABNORMALITIES NOT CONSIDERED TO BE MAJOR MALFORMATIONS.**

| ABNORMALITY   | EXAMPLE  |
|---|--|
| Minor physical features   | Transverse crease on the palm  |
| Positional deformity or deformation <sup>15</sup>                                 | Hip dislocation in infant after breech delivery                                  |
| Physical features at birth that are normally present before 37 weeks of gestation | Patent ductus arteriosus, undescended testicle                                   |
| Findings on prenatal ultrasonography but not on physical examination              | Mild hydronephrosis, absence of one kidney                                       |
| Genetic disorders   | Chromosomal abnormalities, disorders due to single mutant genes (e.g., albinism) |

taken only one anticonvulsant drug, 35 had taken the drug for medical conditions other than epilepsy. A total of 606 other women reported a history of seizures but had not taken an anticonvulsant drug during the pregnancy. We identified 1186 women who had not been exposed to anticonvulsant drugs during pregnancy and had no history of seizures.

The number of subjects in each group was reduced by application of the exclusion criteria, refusals to participate, and missed examinations (Table 2). Fewer women who had taken an anticonvulsant drug declined to participate (17.0 percent [73 of 430]) than did the women with a history of seizures who had not taken an anticonvulsant drug (34.1 percent [119 of 349]) and the women in the control group (48.4 percent). The history of seizures in the 98 remaining women in the group who had a history of epilepsy but who had not taken an anticonvulsant drug during pregnancy was confirmed by a review of the medical records or electroencephalograms for 90 percent (records for 84 percent, electroencephalograms for 81 percent). Ninety-four percent of these women had taken an anticonvulsant drug at some time in their lives (73 percent for two or more years) before becoming pregnant with the infant in this study. The causes and types of seizures in the two groups are shown in Table 3.

### Outcomes in Enrolled Infants

We examined singleton infants born to 223 of the 386 women who had taken one anticonvulsant drug, 93 of the 123 women who had taken two or more anticonvulsant drugs, 98 of the 98 women with a history of seizures who had not taken anticonvulsant drugs, and 508 of the 1186 women in the control group (Table 4). Among the women who had taken one anticonvulsant drug, 87 had taken phenytoin, 64 phenobarbital, 58 carbamazepine, 6 valproic acid, 6 clonazepam, 1 diazepam, and 1 lorazepam.

There were no significant differences between the infants of mothers with a history of seizures who had

**TABLE 2.** ENROLLMENT OF INFANTS BORN TO WOMEN WHO HAD TAKEN ANTICONVULSANT DRUGS DURING PREGNANCY, INFANTS BORN TO WOMEN WHO HAD A HISTORY OF SEIZURES BUT HAD NOT TAKEN ANTICONVULSANT DRUGS, AND CONTROL INFANTS.

| CATEGORY  | INFANTS EXPOSED TO ANTICONVULSANT DRUGS | INFANTS WITH A MATERNAL HISTORY OF SEIZURES NOT EXPOSED TO ANTICONVULSANT DRUGS | CONTROL INFANTS |
|---|---|---|-----------------|
|   | number of infants                       |   |                 |
| Identified  | 509                                     | 606   | 1186            |
| Excluded because maternal history of epilepsy involved childhood febrile seizures only      | 0                                       | 183   | 0               |
| Ineligible for participation  |   |   |                 |
| Death of infant   | 7                                       | 5   | 8               |
| Non-English-speaking mother   | 14                                      | 24  | 54              |
| Multiple birth  | 28                                      | 12  | 53              |
| Sibling of a previously enrolled infant   | 23                                      | 29  | 0               |
| Exposure to other teratogens  | 7                                       | 4   | 27              |
| Eligible for participation  | 430                                     | 349   | 1044            |
| Not examined  |   |   |                 |
| Obstetrician or nurse refused*  | 11                                      | 13  | 67              |
| Mother refused  | 73                                      | 119   | 438             |
| Mother was discharged sooner than expected  | 30                                      | 50  | 31              |
| Potential enrollees   | 316                                     | 167   | 508             |
| Excluded because maternal condition was not epilepsy or the episodes were not true seizures | 0                                       | 69  | 0               |
| Singleton infants examined  | 316                                     | 98†   | 508             |

\*When the obstetrician or the nurse was asked by the research assistant if she could approach the mother to describe the study, either the obstetrician or the nurse said that the mother should not be approached.

†The history of seizures in the mothers of these infants was confirmed by a review of the medical records or electroencephalograms for 90 percent (records for 84 percent and electroencephalograms for 81 percent).

not taken anticonvulsant drugs and the control infants, either in terms of individual outcomes or overall. The groups of infants exposed to either one anticonvulsant drug or two or more drugs had a higher frequency of all of the features of the embryopathy associated with exposure to anticonvulsants (i.e., major malformations, microcephaly, growth retardation, and hypoplasia of the midface and fingers) than did the other infants (20.6 percent of infants exposed to one drug and 28.0 percent of infants exposed to two or more anticonvulsant drugs had one or more of these abnormalities, as compared with 8.5 percent of control infants) (Table 4). The frequency of most outcomes was increased in the 87 infants exposed to phenytoin alone and the 64 infants exposed to phenobarbital alone, as compared with control infants. The frequency of major malformations, microcephaly, and growth retardation, but not hypoplasia of the midface and fingers, was higher in the 58 infants exposed to carbamazepine than in the 508 control infants.

**TABLE 3.** APPARENT CAUSE AND TYPE OF SEIZURES IN ALL ENROLLED WOMEN WITH EPILEPSY WHOSE SINGLETON INFANTS WERE EXAMINED.\*

| VARIABLE                                      | ANTICONVULSANT DRUGS DURING PREGNANCY (N=316) | No ANTICONVULSANT DRUGS DURING PREGNANCY (N=98) |
|---|---|---|
|   | no. (%)                                       |   |
| <b>Apparent cause or category†</b>            |   |   |
| Familial                                      | 62 (20.3)                                     | 27 (27.6)                                       |
| Cryptogenic                                   | 146 (47.7)                                    | 45 (45.9)                                       |
| Trauma  | 56 (18.3)                                     | 21 (21.4)                                       |
| Brain tumor                                   | 8 (2.6)                                       | 0   |
| Infection                                     | 11 (3.6)                                      | 4 (4.1)   |
| Vascular event, including lupus erythematosus | 7 (2.3)                                       | 0   |
| Congenital abnormality                        | 14 (4.6)                                      | 3 (3.1)   |
| Lead poisoning                                | 2 (0.6)                                       | 0   |
| Total   | 306   | 100   |
| <b>Types of epilepsy‡</b>                     |   |   |
| Simple partial                                | 40 (13.9)                                     | 17 (17.3)                                       |
| Complex partial                               | 204 (70.8)                                    | 62 (63.3)                                       |
| Absence                                       | 0   | 1 (1.0)   |
| Generalized                                   | 40 (13.9)                                     | 16 (16.3)                                       |
| Juvenile myoclonic                            | 4 (1.4)                                       | 2 (2.0)   |
| Total   | 288   | 98  |

\*Twenty women were classified as having episodes that were not true seizures, and eight women could not be interviewed. Because of rounding, not all percentages total 100.

†More than one possible cause was present for several women; apparent causes were established for 306 of the 316 women who received anticonvulsant drugs during pregnancy.

‡The type of epilepsy was established for 288 of the 316 women.

Most of the major malformations identified were types of abnormalities that also occur in infants whose mothers have not taken an anticonvulsant drug (Table 5). However, two of the major malformations are known to be more common in infants exposed to anticonvulsant drugs: marked hypoplasia of the nails plus stiff joints, which is much more common in infants exposed to phenytoin with or without phenobarbital than in unexposed infants,<sup>21,22</sup> and lumbosacral spina bifida, which is most common in infants exposed to either carbamazepine or valproic acid.<sup>23</sup>

Among the infants exposed to one drug, there was no difference in the frequency of the five outcomes between those whose mothers had cryptogenic or familial epilepsy and those whose mothers had epilepsy due to trauma, infection, a tumor, a vascular event, or a congenital anomaly. The frequency of the major outcomes among the 35 infants whose mothers had taken an anticonvulsant drug to treat other conditions, such as manic-depressive disease, was also increased (9.3 percent had major malformations and 25.3 percent had growth retardation or microcephaly). Fifty-three of the 316 women who had taken any anticonvulsant drug reported having had convulsive seizures

TABLE 4. FREQUENCY OF SELECTED OUTCOMES IN EXAMINED SINGLETON INFANTS.\*

| OUTCOMES   | INFANTS EXPOSED TO A SINGLE ANTICONVULSANT DRUG |                |                 |                | ALL INFANTS EXPOSED TO ANY ANTICONVULSANT DRUG | INFANTS EXPOSED TO TWO OR MORE ANTI-CONVULSANT DRUGS | UNEXPOSED INFANTS BORN TO WOMEN WITH A HISTORY OF SEIZURE | UNEXPOSED INFANTS BORN TO WOMEN WITH NO HISTORY OF SEIZURE (CONTROLS) |
|--|---|----------------|-----------------|----------------|--|--|---|---|
|  | PHENYTOIN                                       | CARBAMAZEPINE  | PHENOBARBITAL   | TOTAL          |  |  |   |   |
| <b>Major malformations†</b>  |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 3/87 (3.4)                                      | 3/58 (5.2)     | 3/64 (4.7)      | 10/223 (4.5)   | 18/316 (5.7)                                   | 8/93 (8.6)   | 0/98 (0.0)  | 9/508 (1.8)   |
| Odds ratio (95% CI)‡   | 1.9 (0.3-9.2)                                   | 3.0 (0.6-16)   | 2.7 (0.6-16.4)  | 2.6 (0.8-8.3)  | 3.3 (0.9-8.3)                                  | 5.1 (1.0-21.1)§                                      |   | 1.0   |
| <b>Microcephaly¶</b>   |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 1/87 (1.1)                                      | 2/56 (3.6)     | 3/62 (4.8)      | 8/219 (3.7)    | 11/309 (3.6)                                   | 3/90 (3.3)   | 2/96 (2.1)  | 8/508 (1.6)   |
| <b>Growth retardation¶¶</b>  |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 2/87 (2.3)                                      | 3/57 (5.3)     | 1/63 (1.6)      | 8/221 (3.6)    | 15/313 (4.8)                                   | 7/92 (7.6)   | 2/97 (2.1)  | 6/508 (1.2)   |
| Major malformations, microcephaly, and growth retardation (one or more)  |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 4/87 (4.6)                                      | 6/58 (10.3)    | 7/64 (10.9)     | 20/223 (9.0)   | 34/316 (10.8)                                  | 14/93 (15.1)   | 3/98 (3.1)  | 21/508 (4.1)  |
| Odds ratio (95% CI)‡   | 1.1 (0.2-7.1)                                   | 2.7 (0.9-13.4) | 2.9 (0.8-13.4)  | 2.3 (1.0-6.9)  | 2.9 (1.2-7.1)§                                 | 4.1 (1.3-17.5)§                                      | 0.8 (0.1-4.5)   | 1.0   |
| 95% CI of the generalized estimating equation  | 0.3-5.9   | 0.9-14.1       | 0.8-11.2        | 1.1-7.1§       | 1.4-7.5§                                       | 1.9-19.3§  | 0.1-3.7   |   |
| <b>Midface hypoplasia**</b>  |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 7/53 (13.2)                                     | 2/38 (5.3)     | 7/46 (15.2)     | 16/148 (10.8)  | 23/203 (11.3)                                  | 7/55 (12.7)  | 2/70 (2.9)  | 13/339 (3.8)  |
| Major malformations, microcephaly, growth retardation, and midface hypoplasia (one or more)                            |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 11/87 (12.6)                                    | 8/58 (13.8)    | 14/64 (21.9)    | 36/223 (16.1)  | 57/316 (18.0)                                  | 21/93 (22.6)   | 5/98 (5.1)  | 32/508 (6.3)  |
| Odds ratio (95% CI)‡   | 2.1 (0.9-9.3)                                   | 2.4 (0.8-9.1)  | 4.2 (1.7-16.4)§ | 2.9 (1.4-7.2)§ | 3.3 (1.6-7.2)§                                 | 4.3 (1.4-15.6)§                                      | 0.8 (0.2-3.4)   | 1.0   |
| 95% CI of the generalized estimating equation  | 0.9-6.8   | 1.0-7.7        | 1.5-10.1§       | 1.4-6.0§       | 1.6-6.1§                                       | 1.8-11.9§  | 0.3-3.0   |   |
| <b>Hypoplasia of the fingers†††</b>  |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 9/74 (12.2)                                     | 0/46 (0.0)     | 5/52 (9.6)      | 14/184 (7.6)   | 20/260 (7.7)                                   | 6/76 (7.9)   | 2/83 (2.4)  | 11/471 (2.3)  |
| Major malformations, microcephaly, growth retardation, midface hypoplasia, and hypoplasia of the fingers (one or more) |   |                |                 |                |  |  |   |   |
| No./total no. (%)  | 18/87 (20.7)                                    | 8/58 (13.8)    | 17/64 (26.6)    | 46/223 (20.6)  | 72/316 (22.8)                                  | 26/93 (28.0)   | 6/98 (6.1)  | 43/508 (8.5)  |
| Odds ratio (95% CI)‡   | 2.8 (1.1-8.8)§                                  | 1.7 (0.4-4.6)  | 3.9 (1.4-10.9)§ | 2.8 (1.1-9.7)§ | 3.2 (1.3-5.0)§                                 | 4.2 (1.1-5.1)§                                       | 0.7 (0.2-2.4)   | 1.0   |
| 95% CI of the generalized estimating equation  | 1.3-7.2§  | 0.6-5.0        | 1.7-7.6§        | 1.4-4.9§       | 1.5-4.8§                                       | 1.5-7.6§   | 0.3-2.7   |   |

\*The controls (the unexposed infants born to women with no history of seizure) formed the comparison group in the calculation of the odds ratios. CI denotes confidence interval.

†Major malformations did not include genetic disorders, positional deformities or deformations, and minor anomalies and features found on prenatal ultrasonography but not on physical examination.

‡Values were adjusted for cigarette and alcohol use, substance abuse, and severity of seizures.

§P≤0.05 after adjustment for multiple comparisons with a control with use of Dunnett's multiple-comparison procedure.<sup>20</sup>

¶These values were based on data from infants born in Halifax, Nova Scotia.<sup>17</sup>

¶¶Values were adjusted for cigarette and alcohol use, substance abuse, severity of seizures, and head circumference and height of the mother.

\*\*These values were based on the length of the upper lip, the length of the nose, and the inner canthal distance; if two out of three measurements were more than 1 SD from the mean, midface hypoplasia was considered to be present.

††Values were based on the presence of arch patterns on at least six fingers, stiff interphalangeal joints, or both.

**TABLE 5.** MAJOR MALFORMATIONS IDENTIFIED IN SINGLETON INFANTS ENROLLED AND EXAMINED BY STUDY PHYSICIANS.

| ANTICONVULSANT-DRUG EXPOSURE                | MALFORMATIONS*   |
|---|--|
| Phenytoin                                   | Ventricular septal defect and inguinal hernia<br>Penile hypospadias  |
| Phenobarbital                               | Calcaneovalgus deformity of the foot<br>Tetralogy of Fallot<br>Unilateral cleft lip  |
| Carbamazepine                               | Hypoplasia of the mitral valve<br>Tetralogy of Fallot, esophageal atresia, vertebral anomalies, and multiple terminal transverse limb defects<br>Multiple ventricular septal defects<br>Large cavernous hemangioma on leg (5 cm by 4 cm) |
| Phenytoin and phenobarbital                 | Imperforate anus<br>Postaxial polydactyly, postminimi (type B)   |
| Phenytoin and mysoline                      | Severe hypoplasia of fingernails and toenails, with decreased flexion of interphalangeal joints  |
| Phenytoin and carbamazepine                 | Ventricular septal defect  |
| Phenytoin and valproic acid                 | Coarctation of the aorta   |
| Carbamazepine, phenytoin, and valproic acid | Membranous ventricular septal defect   |
| Carbamazepine, valproic acid                | Lumbosacral spina bifida   |
| Phenytoin, phenobarbital, carbamazepine     | Aortic-valve stenosis<br>Congenital dysplasia of the hip   |
| None  | Cleft palate<br>Membranous ventricular septal defect<br>Penile hypospadias<br>Undescended testicle on right side (in two infants)<br>Postaxial polydactyly, postminimi (type B), left hand<br>Talipes equinovarus                        |

\*Unless otherwise noted, each set of one or more malformations occurred in one infant.

with whole-body shaking during the pregnancy. Twenty-seven of the 53 women had the convulsive seizures in the first trimester. Two of the 27 infants whose mothers had convulsive seizures in the first trimester had a major malformation (7.4 percent), as compared with 22 of the 281 infants of women who reported other types of seizures (7.8 percent).

#### Outcomes in Unenrolled Infants

Since not all of the mothers who were approached about enrolling in this study chose to participate, the medical records (i.e., the results of the pediatricians' examinations) of the infants who were eligible but not enrolled were reviewed to determine whether they had a major malformation or growth retardation. This analysis showed that there were no significant differences between infants who were enrolled and examined by the study investigators and infants who were eligible but were not enrolled and examined by study personnel. The 114 eligible, unexamined infants who were exposed to anticonvulsant drugs were somewhat less likely to have a major malformation than the 316 examined infants who were exposed to anticonvulsant drugs (1.8 percent vs. 5.7 percent,  $P=0.10$ ) and slightly but not significantly more likely to have microcephaly (6.1 percent vs. 3.6 percent,  $P=0.30$ ) or growth retardation (5.3 percent vs. 4.8 percent,  $P=0.90$ ). Among the eligible control infants, there were no significant differences between the 508 infants who were

enrolled and examined as part of the study and 536 infants who were not enrolled in the frequency of major malformations (1.8 percent vs. 1.7 percent,  $P=0.90$ ), microcephaly (1.6 percent vs. 2.6 percent,  $P=0.30$ ), or growth retardation (1.2 percent vs. 1.7 percent,  $P=5.00$ ). Data were not analyzed for unenrolled infants born to mothers with a history of epilepsy who had not taken an anticonvulsant drug during pregnancy, because we could not confirm the maternal history of epilepsy.

#### DISCUSSION

We found that infants exposed to a single anticonvulsant drug taken by the mother during pregnancy had a significantly higher frequency of associated abnormalities than control infants, and that infants whose mothers had a history of epilepsy but took no anticonvulsant drugs during pregnancy did not have an increased rate of these abnormalities. This study had several strengths: the examiner, who was almost always unaware of the infants' status regarding exposure to drugs, looked systematically for all of the features of the embryopathy associated with exposure to anticonvulsant drugs in the three groups of infants; the findings were objective<sup>12,24-27</sup>; and explicit criteria for the inclusion and exclusion of major malformations were used. Since teratogens cause distinctive patterns of abnormalities, the statistical analysis took into account the interrelation of several outcomes.

This study addressed the conflicting interpretations of two previous analyses of the same 104 infants exposed to anticonvulsant drugs.<sup>5,28</sup> In those studies, epidemiologists concluded that the mother's epilepsy, not the anticonvulsant drug, was the teratogen.<sup>28</sup> By contrast, the clinicians concluded that these infants had the physical features of embryopathy associated with exposure to anticonvulsant drugs.<sup>5</sup> The authors of both reports recommended that future studies enroll a group of infants whose mothers had previously had epilepsy but who had taken no anticonvulsant drugs during pregnancy and that these infants be examined for the features of this embryopathy.<sup>5,28,29</sup>

The identification and recruitment of mothers with a history of epilepsy who had taken no anticonvulsant drugs during the pregnancy was another strength of our study. Such women were recruited in two other recent studies,<sup>27,30</sup> which also found no increase in the risk of embryopathy in infants whose mothers had epilepsy but took no anticonvulsant drugs during pregnancy. Other studies<sup>12,28,31,32</sup> have reached different conclusions, but there was a risk of misclassification, because the process of classifying the mother's reported epilepsy did not include a personal interview or a review of her medical records.

There is also concern that the mother's seizures themselves could have a harmful effect on the fetus, as suggested in case reports.<sup>33</sup> This issue was addressed to a limited extent in our study. The frequency of major malformations was the same in the infants of women taking anticonvulsant drugs who had loss of consciousness during seizures in the first trimester of pregnancy and in infants of women taking anticonvulsant drugs who had other types of seizures. We also found that infants of women who had taken anticonvulsant drugs as treatment for mood disorders, migraine, or pain had an increase in the frequency of embryopathy that was similar to that among infants of women with epilepsy. A limitation of our study is that we did not include pregnancies that were terminated electively after fetal abnormalities associated with anticonvulsant drugs were diagnosed by prenatal screening. We identified additional cases in which the fetus was exposed to anticonvulsant drugs among pregnancies terminated electively at the largest participating hospital, through a separate surveillance program for malformations,<sup>34</sup> but we did not include these pregnancies because we could not enroll a comparison group of unexposed fetuses among the other elective terminations.

In previous studies,<sup>7,26,27</sup> infants exposed to carbamazepine were considered by clinical inspection to have an increased frequency of hypoplasia of the face and fingers characteristic of the embryopathy associated with exposure to anticonvulsant drugs. This feature was not found in the infants exposed to carbamazepine whom we examined. The difference in the findings can be addressed with more objective meth-

ods, such as cephalometric radiography<sup>35,36</sup> and dermatoglyphy and radiography of the hands.<sup>22</sup> This difference is important, because the hypoplasia of the midface<sup>35,36</sup> associated with hypoplasia of the facial bones could be a marker for cognitive dysfunction.<sup>37</sup>

One would predict that some infants exposed to anticonvulsant drugs have a greater risk of harmful effects than others because of an underlying genetic susceptibility. Such an interrelation between genetic factors and environmental exposure has been suggested in studies of the teratogenicity of maternal cigarette smoking<sup>38</sup> and alcohol use.<sup>39</sup> In the case of anticonvulsant drugs, a deficiency of the detoxifying enzyme epoxide hydrolase<sup>40,41</sup> and an increase in free radicals formed by the anticonvulsant drug<sup>42</sup> are two theories of the reason for increased susceptibility. We predict that the correlations identified in this study will be much stronger in the more susceptible subgroup of children exposed to anticonvulsant drugs. Phenytoin, phenobarbital, and carbamazepine are folic acid antagonists, and one postulated mechanism for their teratogenicity has been the induction of folic acid deficiency.<sup>43</sup> However, Hernández-Díaz and her associates<sup>44</sup> recently reported that when pregnant women taking these anticonvulsant drugs also took a multivitamin supplement that included folic acid, it did not reduce the incidence of cardiovascular or urinary tract abnormalities or oral clefts in their infants.

We conclude that exposure in utero to anticonvulsant drugs is associated with a distinctive pattern of physical abnormalities in infants that are best identified by objective examination. The physical features of infants exposed to various anticonvulsant drugs are not the same. We found no evidence that infants born to women with a history of epilepsy who took no anticonvulsant drugs during pregnancy have an increased risk of the pattern of physical abnormalities associated with exposure to anticonvulsant drugs. The occurrence of such embryopathy was correlated with exposure to anticonvulsant drugs, regardless of the underlying maternal illness being treated.

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