The AED (Antiepileptic Drug) Pregnancy Registry

A 6-Year Experience

Lewis B. Holmes, MD; Diego F. Wyszynski, MD, MHS, PhD; Ellice Lieberman, MD, DrPH; for the AED Pregnancy Registry

Background: Pregnancy registries are a new method for assessing the fetal risks from exposures in pregnancy. We present the findings of the North American AED (anti-epileptic drug) Pregnancy Registry for phenobarbital sodium–exposed pregnancies.

Objective: To determine whether exposure during pregnancy to anticonvulsant drugs as monotherapy, and phenobarbital in particular, is associated with an increased risk of major malformations in comparison with unexposed controls.

Design: Evaluation of registry data.

Setting: The North American AED Pregnancy Registry.

Patients: Pregnant women throughout the United States and Canada who were taking an anticonvulsant drug and who called a toll-free telephone number to enroll.

Interventions: Each woman was interviewed by telephone at enrollment, at 7 months’ gestation, and post partum. With the mother’s written permission, her medical records and those of her infant were obtained.

Main Outcome Measures: Major malformations identified by 5 days of age. Criteria for the release of findings were established by the independent Scientific Advisory Committee on the basis of malformations identified in infants of women who had enrolled prospectively before having had any prenatal screening (“pure” enrollees).

Results: Five (6.5%) of 77 pure pregnancies with exposure to phenobarbital monotherapy were associated with major malformations (95% confidence interval, 2.1%-14.5%). When compared with the background rate (1.62%), there was a significantly increased risk (relative risk, 4.2; 95% confidence interval, 1.5-9.4).

Conclusions: A hospital-based pregnancy registry can establish the fetal risk of major malformations for a commonly used drug. Prenatal exposure to phenobarbital is associated with a significantly increased risk of fetal abnormalities.

Arch Neurol. 2004;61:673-678

Pregnancy registries have been developed to provide an early signal of an increased frequency of major malformations associated with prenatal exposure to the products monitored by the registry. The first such registry, developed by Andrews and her associates at Burroughs Wellcome in 1984, enrolled pregnant women who had taken the antiviral drug acyclovir. Subsequent company-based registries have focused on drugs and vaccines.

Hospital-based pregnancy registries have been established for specific diseases, eg, neonatal lupus, as well as for women with epilepsy. The hospital-based registry collects information from the enrolled pregnant woman herself, whereas the company-based registry receives information only from the referring physician.

The protocol for the AED Pregnancy Registry was developed during several biannual meetings by a committee of neurologists-epileptologists, epidemiologists, birth defect specialists, and teratologists, with financial support from several companies that manufacture and market antiepileptic drugs (AEDs). We present herein the refinements and developments during 6 years (1997-2002) in enrolling the first 3002 pregnant women and in releasing the first significant findings, which were in phenobarbital-exposed pregnancies.

Methods

Structure of the AED Pregnancy Registry

The staff of the registry includes individuals experienced in clinical teratology, epidemiol-
ogy, neurology, and genetics (the current staff is listed in the acknowledgment at the end of the article). The major policy decisions of the AED Pregnancy Registry, such as establishing release criteria and decisions to release findings, were made in separate meetings by the nonindustry Scientific Advisory Committee (see acknowledgment), which is blind to the identity of the drug until the findings are released. Representatives from each sponsoring company constitute the Steering Committee (see acknowledgment), which meets semiannually with the Scientific Advisory Committee. The Steering Committee is informed about the decisions of the Scientific Advisory Committee and is invited to comment, but cannot change the decisions.

AWARENESS METHODS

The function and activities of the AED Pregnancy Registry have been publicized in regular mailings in the United States and Canada to neurologists, epilepsy nurses, obstetricians, teratogen counselors, and lay groups with an interest in epilepsy, such as the 59 chapters of the Epilepsy Foundation. An exhibit has been presented at several regional, national, and international scientific meetings. Additional advertising efforts include letters and e-mail messages to neurologists and obstetricians, articles in women’s magazines, newspapers, and specialty-based periodicals for practicing physicians.

INFORMED CONSENT

The informed consent document signed by each enrolled woman is reviewed and approved annually by the Human Studies Committee of the Massachusetts General Hospital in Boston. The information obtained is maintained in a database with limited access to the Registry Advisory Committee and is invited to comment, but cannot change the decisions.

ENROLLMENT AND INTERVIEWS

To enroll, the eligible woman herself must call the toll-free telephone number of the registry. She is interviewed 3 times: (1) at enrollment, (2) at 7 months’ gestation, and (3) post partum (up to 8 to 12 weeks after the expected date of delivery). The structured interviews include questions on dose, frequency, and medical indication of each medication; signs and symptoms of epilepsy (or mood disorders); the apparent cause of the epilepsy; demographic characteristics; habits, eg, alcohol intake, cigarette smoking, use of illicit drugs, and other prescribed and over-the-counter medications taken; and family history of epilepsy and birth defects.

Enrolled women are subdivided into 2 groups: “pure” prospective and “traditional” prospective. The pure prospective enrollees do not know, at the time of enrollment, whether the fetus has a malformation. The traditional prospective enrollees have some knowledge of the status of the fetus, typically after having prenatal screening by ultrasound. Women are not enrolled after the pregnancy has ended.

MEDICAL RECORDS OF MOTHERS AND INFANTS

Release forms are mailed to the mothers to be signed and returned to the registry. Initially, records were requested from 4 sources: the mother’s neurologist, her obstetrician, the birthing hospital, and the infant’s pediatrician. Because of time constraints, since 2000 the requests have been sent only to the woman’s neurologist (or other physician treating other medical conditions) and the infant’s physician. Other records are requested as indicated by the mother’s reports, such as the cardiologist or urologist of her infant.

The information from the interviews and the medical records is abstracted and entered into a database with the use of Access software, which creates analyzable files for the statistical software Stata, version 7.0 (Stata Corp, College Station, Tex).

MONOTHERAPY AND POLYThERAPY

For this study, an anticonvulsant drug was defined as a drug prescribed to suppress seizure activity; some of these drugs are also used to treat the symptoms of mood disorders and other conditions. The term monotherapy was used when only 1 anticonvulsant drug was taken at any time during pregnancy. The term polytherapy was used when more than 1 anticonvulsant was taken, either concurrently or consecutively.

INCLUSION AND EXCLUSION CRITERIA

A major malformation was defined as a structural abnormality with surgical, medical, or cosmetic importance. Exclusions were as follows: (1) minor anomalies; (2) deformations; (3) physiological features due to prematurity, such as undescended testes; (4) birthmarks; (5) genetic disorders and chromosomal abnormalities; and (6) any finding by prenatal sonography, such as absence of one kidney, or at surgery (or autopsy) that was not identified by an examining pediatrician.

The written descriptions in the pediatricians’ examinations were reviewed separately by 2 registry dysmorphologists (Joan M. Stoler, MD, and L.B.H.), blinded to exposure status, to determine inclusion or exclusion. Any disagreement was resolved by consensus.

RELEASE CRITERIA

Initially, the rates of malformations, relative risks, and 95% confidence intervals (CIs) among infants exposed to the most commonly used monotherapies were determined for the infants of both pure prospective and traditional prospective enrollees, as for phenobarbital-exposed pregnancies. Later, the Scientific Advisory Committee decided to use only the findings in the infants of pure prospective enrollees to reduce potential bias; this approach was used subsequently in the analysis of valproate sodium–exposed pregnancies. For an external comparison, “controls” were the malformed infants identified at birth among 69 277 newborns by the Active Malformations Surveillance Program at Brigham and Women’s Hospital, Boston. The baseline rate was 2.24%, which was reduced to 1.62% after exclusion of infants with genetic disorders and chromosome abnormalities. The criterion for release of results for a positive association (relative risk >1) was met when the lower of the 95% confidence limits was 2.0 or higher. The release criterion for no associated increase in the frequency of all major malformations was met when the upper of the 95% confidence limits did not exceed 2.0. Because the malformations identified by the Surveillance Program are those that occur between birth and 5 days of age, the malformations in anticonvulsant-exposed infants were restricted to those identified at birth.

RESULTS

PRELIMINARY RESULTS—PHENOBARBITAL

From February 1, 1997, through December 16, 2002, 3002 women were enrolled in the AED Pregnancy Registry. Of these 3002 enrolled women, 2230 (77.6%) reported taking an anticonvulsant as monotherapy and had either a live-born infant or a pregnancy terminated because of a
fetal abnormality. One hundred forty-six women (6.3%) (77 in the pure prospective group and 69 in the traditional prospective group) used phenobarbital as monotherapy during the first trimester of pregnancy, after exclusion of 19 because of attrition (7 withdrawals and 12 who were lost to follow-up). Five infants with major malformations were born to the 77 mothers in the pure prospective group (proportion, 6.5%; 95% CI, 2.1%-14.5%). The defects, occurring in 1 neonate each, were coarctation of the aorta with abnormal valves; cleft lip and palate; pulmonary atresia; ventricular septal defect, membranous type; and tetralogy of Fallot. Two of the 69 newborns in the traditional prospective group had a major malformation (cleft lip and palate) (proportion, 2.9%; 95% CI, 0.3%-10.1%).

Medical records from pediatricians were received for 45 (58%) of the 77 neonates in the pure prospective group and 49 (71%) of the 69 neonates in the traditional prospective group. The mothers of the other infants declined many requests for these signed release forms, citing most often the concern that this documentation could be harmful to her or her infant son or daughter in the future. The verbal reports of the mother and the written reports of her infant’s pediatrician were compared. There was 100% agreement for the 45 pure prospective cases and 98% agreement for the 49 traditional prospective cases concerning the presence of a major malformation: in 1 case in the latter group, a submucous cleft palate was reported by the pediatrician but not by the mother, who had been told that no treatment was necessary. (A subsequent otolaryngology consultation showed there was no submucous cleft palate.)

INTERNAL COMPARISON

The prevalence at birth of congenital anomalies among live offspring of the 77 women in the pure prospective group exposed to phenobarbital (5 [6.5%]) was compared with that of offspring of 796 women exposed to 3 other frequently used AED monotherapies who were pure prospective enrollees (23 [2.9%]) (95% CI, 1.8%-4.3%). (The identity of these 3 drugs cannot be provided, as the findings have not been released.) For the comparison, the relative risk was 2.0 (95% CI, 0.9-4.5). When infants of women in both the pure and traditional prospective groups were compared, the relative risk was reduced to 1.5 (95% CI, 0.7-3.2). These comparisons show that there was no significant difference in the rate of malformations among phenobarbital-exposed infants in comparison with those exposed to the other AEDs. The 2 groups were very similar in terms of their demographic characteristics and prenatal exposures (Table).

EXTERNAL COMPARISON

The number of newborns with major anomalies observed among women exposed to phenobarbital was compared with the number of cases expected on the basis of the rate (1.62%) from the Active Malformations Surveillance Program at Brigham and Women’s Hospital14 and other hypothetical rates ranging from 1% to 3%. The relative risk of having an affected offspring for phenobarbital-exposed women in the pure prospective group was 4.2 (95% CI, 1.5-9.4; 1-sided P = .001). The difference continued to be significant statistically if the population prevalence rate of birth defects was lower than 2%. When both pure and traditional prospective cases were combined, the relative risk was 3.0 (95% CI, 1.4-6.1; 1-sided P = .002).

Experience has shown that the US Food and Drug Administration’s pregnancy categories for drugs (A, B, C, D, and X) do not correlate well with information on teratogenicity from other sources.13,17 A written description of the information available has been proposed as an alternative to the pregnancy classification system. Pregnancy exposure registries are being encouraged as a way to obtain more complete information about potential fetal risks (or safety) from medications that are taken by pregnant women.17,18

The findings presented herein for 77 phenobarbital monotherapy–exposed pregnancies, enrolled before prenatal screening, are the most extensive information available to date on this drug’s risks to the exposed fetus. The speed with which this information was obtained is a significant justification for a pregnancy registry. The other advantages of this hospital-based registry are as follows: (1) many women enrolled before having any prenatal screening, which means they did not know the health status of their unborn infant; (2) the rate of loss to follow-up was a low 7.2% (the rate is 2.1% in the entire registry); (3) the ability to obtain information from the mothers, as this is likely to be more complete than information reported by the mother’s prescribing physician; (4) the use of inclusion and exclusion criteria that defined the potential outcomes of the exposure more precisely; and (5) the level of cooperation of pediatricians, family practitioners, and consultants in providing detailed information on the infant’s malformations.

There are limitations of this pregnancy registry. First, the information reviewed on the external controls from the Active Malformations Surveillance Program14 at Brigham and Women’s Hospital in Boston is more extensive than the information obtained by mail from the registry-enrolled infants’ physicians. It would be better to enroll controls through the AED Pregnancy Registry and obtain information in the same fashion as for anticonvulsant-exposed infants; this process is now under way. Second, the controls from the Active Malformations Surveillance Program will not include many women with epilepsy who are not being treated with anticonvulsant drugs. This is of theoretical concern if the woman’s disease makes her more likely to have a malformed infant, which some,19 but not all,20,21 studies suggest.

Third, pregnancy registries evaluate the frequency of all malformations, not specific malformations, such as spina bifida, a postulated effect of prenatal exposure to the anticonvulsants carbamazepine22 and valproate sodium.23 To establish correlations, such as a 3-fold increase in the occurrence of a malformation with a frequency of 1 in 1000 (like spina bifida or cleft lip), 2915 infants in the pure prospective, monotherapy-exposed group would have to have been enrolled. Since only 35%
of the women enrolled, to date, have been exposed to monotherapy and are pure prospective enrollees, 8329 enrollees would be needed to establish this correlation with 80% power.

The women who have enrolled (Table) are better educated and more likely to take vitamin supplements than a random sample of eligible women would be. If vitamin supplementation decreased the rate of major malformations in the infants of women who take anticonvulsant drugs, this characteristic could affect the findings in the registry. However, in one previous study and in the analysis of the findings in the registry, there was no evidence of prevention by vitamin supplementation.

It is remarkable that phenobarbital has been marketed in the United States since 1912, but only recently has there been information published on the teratogenicity of phenobarbital as monotherapy. Early reports by Melchior et al in 1967 and Jones et al in 1992 raised a question as to its teratogenicity, but they included infants exposed to both monotherapy and polytherapy. Seip in 1976 described a pattern of dysmorphic features in 26 newborns with 80% power. If vitamin supplementation decreased the rate of major malformations in the infants of women who take anticonvulsant drugs, this characteristic could affect the findings in the registry. However, in one previous study and in the analysis of the findings in the registry, there was no evidence of prevention by vitamin supplementation.

It is remarkable that phenobarbital has been marketed in the United States since 1912, but only recently has there been information published on the teratogenicity of phenobarbital as monotherapy. Early reports by Melchior et al in 1967 and Jones et al in 1992 raised a question as to its teratogenicity, but they included infants exposed to both monotherapy and polytherapy. Seip in 1976 described a pattern of dysmorphic features in 26 newborns exposed to high levels of phenobarbital. The findings in the first cohort study of children exposed to phenobarbital as monotherapy were published in 2001. Sixty-four phenobarbital-exposed newborns were identified by interviewing 128049 pregnant women admitted to labor at 5 hospitals in the Boston area. The examinations, by masked examiners, included measurements of many physical features and a systematic search for many more subjective physical features, such as the presence of the features of the “fetal anticonvulsant face” (or midface hypoplasia) and distal digital hypoplasia. The frequencies of the potential phenotypic effects in the 64 phenobarbital-exposed infants were as follows: microcephaly (4.8%), growth restriction (1.6%), major malformations (4.7%), midface hypoplasia (15.2%), and digit hypoplasia (9.6%) as separate outcomes, or a total of 26.6% in comparison with a total of 8.5% for the same 5 outcomes in 508 unexposed controls examined blindly in the same fashion (odds ratio, 3.9; 95% CI, 1.4-10.9).

Having established the significant fetal risks, ie, a 4-fold increase in the frequency of major malformations such as cleft lip and palate and heart defects, it is unfortunate that the low cost of phenobarbital makes it likely to be used in developing countries. In 1990, the World Health Organization noted that, on average, phenobarbital as monotherapy was used in developing countries. In 1990, the World Health Organization noted that, on average, phenobarbital was used in developing countries. It is remarkable that phenobarbital has been marketed in the United States since 1912, but only recently has there been information published on the teratogenicity of phenobarbital as monotherapy. Early reports by Melchior et al in 1967 and Jones et al in 1992 raised a question as to its teratogenicity, but they included infants exposed to both monotherapy and polytherapy. Seip in 1976 described a pattern of dysmorphic features in 26 newborns exposed to high levels of phenobarbital. The findings in the first cohort study of children exposed to phenobarbital as monotherapy were published in 2001. Sixty-four phenobarbital-exposed newborns were identified by interviewing 128049 pregnant women admitted to labor at 5 hospitals in the Boston area. The examinations, by masked examiners, included measurements of many physical features and a systematic search for many more subjective physical features, such as the presence of the features of the “fetal anticonvulsant face” (or midface hypoplasia) and distal digital hypoplasia. The frequencies of the potential phenotypic effects in the 64 phenobarbital-exposed infants were as follows: microcephaly (4.8%), growth restriction (1.6%), major malformations (4.7%), midface hypoplasia (15.2%), and digit hypoplasia (9.6%) as separate outcomes, or a total of 26.6% in comparison with a total of 8.5% for the same 5 outcomes in 508 unexposed controls examined blindly in the same fashion (odds ratio, 3.9; 95% CI, 1.4-10.9).

Having established the significant fetal risks, ie, a 4-fold increase in the frequency of major malformations such as cleft lip and palate and heart defects, it is unfortunate that the low cost of phenobarbital makes it likely to be used in developing countries. In 1990, the World Health Organization noted that, on average, phenobarbital as monotherapy was used in developing countries. It is remarkable that phenobarbital has been marketed in the United States since 1912, but only recently has there been information published on the teratogenicity of phenobarbital as monotherapy. Early reports by Melchior et al in 1967 and Jones et al in 1992 raised a question as to its teratogenicity, but they included infants exposed to both monotherapy and polytherapy. Seip in 1976 described a pattern of dysmorphic features in 26 newborns exposed to high levels of phenobarbital. The findings in the first cohort study of children exposed to phenobarbital as monotherapy were published in 2001. Sixty-four phenobarbital-exposed newborns were identified by interviewing 128049 pregnant women admitted to labor at 5 hospitals in the Boston area. The examinations, by masked examiners, included measurements of many physical features and a systematic search for many more subjective physical features, such as the presence of the features of the “fetal anticonvulsant face” (or midface hypoplasia) and distal digital hypoplasia. The frequencies of the potential phenotypic effects in the 64 phenobarbital-exposed infants were as follows: microcephaly (4.8%), growth restriction (1.6%), major malformations (4.7%), midface hypoplasia (15.2%), and digit hypoplasia (9.6%) as separate outcomes, or a total of 26.6% in comparison with a total of 8.5% for the same 5 outcomes in 508 unexposed controls examined blindly in the same fashion (odds ratio, 3.9; 95% CI, 1.4-10.9).
bitone (phenobarbital), which is on the World Health Organization list of essential drugs, could cost as little as US $5 per person per year.\textsuperscript{29} In addition to its risk of causing major malformations, exposure to phenobarbital in utero has been shown to cause effects on intelligence,\textsuperscript{30} especially on language.\textsuperscript{31} However, in reports of its use in rural Mali, a poor underdeveloped country, for example, the emphasis was on low cost and effectiveness in controlling seizures without any acknowledgment of its potential teratogenicity.\textsuperscript{32}

Accepted for publication December 22, 2003.

From the Genetics and Teratology Unit, Pediatric Service, Massachusetts General Hospital, Boston (Dr Holmes); Department of Pediatrics, Harvard Medical School, Boston (Dr Holmes); Genetics Program, Department of Medicine, Boston University School of Medicine (Dr Wyszynski); and Department of Obstetrics and Gynecology, Brigham and Women's Hospital and Harvard Medical School, Boston (Dr Lieberman). A listing of the AED Pregnancy Registry staff and its Scientific Advisory Committee appears below.

This article is dedicated to the late J. Fred Annegers, PhD, who was a member of the Scientific Advisory Committee for several years and made many very significant contributions to the development of this registry.

Author contributions: Study concept and design (Drs Holmes, Wyszynski, and Lieberman); acquisition of data (Drs Wyszynski and Lieberman); analysis and interpretation of data (Drs Holmes, Wyszynski, and Lieberman); drafting of the manuscript (Dr Holmes); critical revision of the manuscript for important intellectual content (Drs Holmes, Wyszynski, and Lieberman); statistical expertise (Dr Wyszynski); obtained funding (Dr Holmes); administrative, technical, and material support (Drs Holmes and Wyszynski).

The AED Pregnancy Registry is supported by funds provided by Abbott Laboratories, Abbott Park, Ill; Eli Lilly Pharmaceuticals, San Diego, Calif; GlaxoSmithKline, Harlow, England; Novartis, Barcelona, Spain; Ortho-McNeil, Raritan, NJ; and Pfizer Pharmaceuticals, New York, NY. The current representatives of the sponsoring companies are as follows: Charles Schwanlein, MD, MPH, and Kenneth Sommerville, MD (Abbott Laboratories); Adrienne M. Rothstein, PharmD, MD, and Robert Leong, MD (Eli Lilly Pharmaceuticals); John Weil, MD (GlaxoSmithKline); Javier Cid-Ruizofa, MD, MPH, DrPH (Novartis); Daniel Fife, MD, PhD (Johnson and Johnson Pharmaceutical Research and Development LLC, Titusville, NJ); Joseph Hulihan, MD (Ortho-McNeil); and Cathy Sigler, DVM, PhD (Pfizer Pharmaceuticals). Also, Hochst-Marion-Roussel (Kansas City, Mo) was a sponsor for the first 2 years and UCB Pharma (Smyrna, Calif) made contributions during 2 years of the study.

The staff of the registry includes a director and teratologist (Dr Holmes), an epidemiologist (Dr Wyszynski; previously Dr Lieberman), a geneticist-dysmorphologist (Joan M. Stoler, MD), 3 neurologists-epileptologists (Edward Bronfield, MD; Daniel Hoch, PhD, MD; and Shahram Khoshbin, MD), a study coordinator (Maya Nambisan, MPH), a research assistant and interviewer (Ivelisse Santos-Rodriguez), an abstractor and data analyst (Helen Ahn), a pharmacist (Lois Parker, RPh), and a consultant in database programming (John Farrell). In addition, we thank especially the staff who helped to develop the registry since it began: Kelly Huntington, Elizabeth Harvey, PhD, Triptaa Surve, MPH, Bridget Riley, Sharon Ng Ok, Lorrie Walker, Marian Simpson, Fred Sheehan, Amy Cohen, Jonathan Raub, MPH, Kristin Morales, Barbara Jennings, MSW, Sabrina Petersen, Amanda Wilson, Adam and Jordan Cusner, and Dena Freedman.

Members of the Scientific Advisory Committee are Mark Yerby, MD (chair), Portland, Ore; Joseph Bruni, MD, Toronto, Ontario; Allen Hauser, MD, New York, NY; Margaret Jacobs, Bethesda, Md; Robert Mittendorf, MD, DrPH, Chicago, Ill; Janet Cragan, MD, Atlanta, Ga; Lewis B. Holmes, MD (director of the registry), Boston, Mass.

Corresponding author and reprints: Lewis B. Holmes, MD, Genetics and Teratology Unit, Pediatrics Service, Massachusetts General Hospital, Warren 801, 55 Fruit St, Boston, MA 02114-2696 (e-mail: holmes.lewis@mgh.harvard.edu).

REFERENCES


19. Olafsson E, Hallgrimsson JT, Hauser WA, Ludvigsson P, Gudmundsson G. Preg-
21. Nulman I, Scolnik D, Chitayat D, Farkas LD, Koren G. Findings in children ex-
posed in utero to phenytoin and carbamazepine monotherapy: independent ef-
23. Omtzigt JGC, Los FJ, Gobbee DE, et al. The risk of spina bifida aperta after first-
25. Nambisan M, Wyszynski DF, Holmes LB. No evidence of a protective effect due
to periconceptional folic acid (PCFA) intake on risk for congenital anomalies in
26. Melchior JC, Svensmark O, Trolle D. Placental transfer of phenobarbione in epi-
27. Jones KL, Johnson KA, Chambers CC. Pregnancy outcome in women treated with
28. Seip M. Growth retardation, dysmorphic facies and minor malformations fol-
65:817-821.
30. Reinsch JM, Sanders SA, Mortenson EL, Rubin DB. In utero exposure to phe-
31. Adams J, Harvey EA, Holmes LB. Cognitive deficits following gestational monotherapy
32. Nimaga K, Desplats D, Douno M, Farnarier G. Treatment with phenobarbital
and monitoring of epileptic patients in rural Mali. Bull World Health Organ. 2002;
80:532-537.

Call for Papers

ARCHIVES Express

The ARCHIVES launched a new ARCHIVES Express section in the September 2000 issue. This section will enable the editors to publish highly selected papers within approximately 2 months of acceptance. We will consider only the most significant research, the top 1% of accepted pa-
ners, on new important insights into the pathogenesis of disease, brain function, and therapy. We encourage authors to send their most exceptional clinical or basic
research, designating in the cover letter a request for ex-
pedited ARCHIVES Express review. We look forward to pub-
lishing your important new research in this accelerated manner.

Roger N. Rosenberg, MD
Editor