Prenatal Diagnosis of Neural Tube Defects

But questions about abortion, access to testing, and the quality of life of affected children stand in the way of a screening program

Slowly, deliberately, and agonizing all the way, this country is moving toward offering pregnant women tests for the prenatal diagnosis of neural tube defects—the most common birth defects in the United States. Pregnant women found to be carrying affected fetuses would be offered abortions.

Many, if not most, obstetricians and pediatricians who know of the tests view the proposed screening program as a blessing. "Neural tube defects are among the worst of all birth defects and the birth of an affected child is a tragedy," says Joseph Schulman of the National Institute of Child Health and Human Development. About 2 of every 1000 babies born in this country have neural tube defects, and women who have already had one affected child have a 5 percent chance of giving birth to another. But approximately 95 percent of the time there is nothing in a woman's family or medical background to hint that she is carrying an affected child. No one knows why neural tube defects occur or how to prevent the birth of children with these defects, short of detecting them prenatally and aborting them.

The defects occur when the neural tube, which forms the brain, spinal cord, and spinal column of the embryo, does not completely close during early development. About half the time, the tube is open at the top and the baby is born with no brain, or only a rudimentary one. This condition, called anencephaly, is always fatal. Most anencephalic babies are either stillborn or die within a day or so after birth, although a few have lived for as long as a month.

In the remaining neural tube defects the tube fails to close along the spine. The babies then are born with spina bifida, a condition in which a portion of the nerve column of the spine is exposed. Twenty percent of the time, the open spine is covered by skin, in which case the children generally have normal intelligence and, with surgery, have no physical handicaps or only minor ones. The rest of the time, however, the open spine is not covered and the spinal cord and nerve bundles protrude at the site of the defect, sometimes looking like a red lump on the baby's back. Often, these children with "open" spina bifida have an accompanying birth defect that prevents fluid from draining from their heads, a condition called hydrocephaly. This condition can be surgically ameliorated, but often irreversible damage to a child's brain is done before and just after birth by the increased fluid pressure.

Children with open spina bifida usually survive, but many are mentally retarded, many have no bowel or bladder control, nearly all require extensive medical and surgical treatments, and most have some degree of paralysis, usually from the waist down.

Despite this bleak picture of life with neural tube defects, not everyone concerned with the proposed screening program is anxious to get on with it. At a recent conference,* participants debated, often emotionally, the ethical and procedural difficulties they envision when screening begins. For example, there are questions of informed consent and counseling and, especially, the question of just how bad spina bifida is and how readily women should be given the opportunity to abort affected fetuses. There are also more technical questions related to how the program would be set up. The present health care system cannot handle the screening of most of this country's 3 million pregnant women. Health care planners worry about how, and whether, to monitor the quality of the laboratories and testing centers that will certainly spring up once a program begins. Then there is the question of whether all pregnant women should be assured equal access to the screening tests, and if so, how.

The Food and Drug Administration (FDA) is drafting regulations that would allow the sale of screening test kits to be used by commercial laboratories. After a public comment period, final regulations will be written and the kits should appear on the market. Already, several major drug companies have kits and are waiting for FDA approval to market them.

The screening test for neural tube defects was developed in 1972 by David J. H. Brock of Western General Hospital in Edinburgh. Brock discovered that there are large amounts of alpha-fetoprotein (AFP), a serum protein that is normally produced only during fetal life, in the amniotic fluid of women carrying fetuses with neural tube defects. He reasoned that the AFP pours out of the open spine or skull of an affected fetus and enters the amniotic fluid. He then guessed that some of this excess AFP should pass through the membranes of the amniotic sac and into the mother's blood.

Normally, some AFP is always present in the amniotic fluid and therefore in the mother's blood because AFP is excreted in the fetus's urine. In addition, some AFP enters the maternal circulation by passing through the umbilical cord and the placenta. What Brock demonstrated is that there is significantly more AFP in the blood of women bearing fetuses with neural tube defects than of women bearing normal fetuses.

The amount of AFP normally found in the blood varies considerably during pregnancy, Brock found. He determined that the optimum time for testing is between 16 and 19 weeks of pregnancy. At that time, the difference between the normal amount of AFP in the blood and the amount present when a fetus has a neural tube defect is great enough to make a blood test for AFP feasible.

But even then, the blood test has many false positives. Women carrying twins or triplets or women further along in pregnancy than they think will appear to have anomalously high concentrations of AFP in their blood. Some congenital defects such as nephrosis, in which the fetus's kidneys allow too much AFP to be excreted in the urine, and malformations in which the stomach, liver, or other organs are outside the body result in positive AFP blood tests. Women whose fetuses have died have high blood AFP concentrations because the fetus starts to deteriorate and loses AFP. Finally, some women with normal fetuses have positive AFP blood tests for unknown reasons. These women, however, seem to be at an increased risk of having spontaneous abortions, stillbirths, and premature births.

*National Conference on Maternal Serum Alpha-Fetoprotein: Issues in the Prenatal Screening and Diagnosis of Neutral Tube Defects, held on 28 to 30 July 1980 in Washington, D.C., and sponsored by the National Center for Health Care Technology and the Food and Drug Administration.

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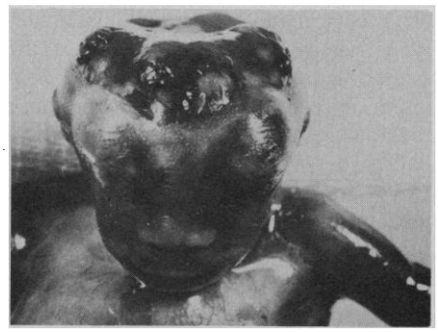
To eliminate the false positives as much as possible, Brock devised a precise sequence of screening tests. First, women are given a blood test in the 16th week of pregnancy. At this time approximately 50 of 1000 pregnant women will have very high AFP concentrations—above the 95th percentile of the normal range. The test is repeated on these women, and 30 will have a second high reading. These 30 are then given ultrasound scans to check for twins or triplets, for fetal death, or for incorrect gestational dates. The ultrasound will eliminate approximately 15 of the women from consideration. The remaining 15 are given amniocentesis to check for AFP in the amniotic fluid and also to check for acetylcholinesterase, a nerve enzyme that often is present in the fluid when the fetus has a neural tube defect.

In 1 or 2 of these 15 women, all indications will be that they are carrying a child with a neural tube defect. It is fairly straightforward to decide whether the fetus has anencephaly or spina bifida, since anencephaly is readily apparent in ultrasound scans. A few radiologists are so proficient that they can even see some cases of spina bifida, but most cannot. The women who have positive results in all the tests are advised of the status of their fetuses and are offered abortions.

Brock finds that this sequence of tests detects virtually all cases of anencephaly and four out of five cases of spina bifida. The number of cases detected depends on the definition of how high AFP concentrations in the blood must be for a positive test. "There is an unavoidable trade-off," Brock says. "As you move the cutoff point up, the detection efficiency goes down." But a lower cutoff point means that more women will be needlessly sent on for sonograms and amniocentesis. Not only are these procedures expensive—an ultrasound scan costs at least $50 and amniocentesis costs more than $60—but most researchers estimate that up to 0.5 percent of fetuses die as a result of the extraction of amniotic fluid for amniocentesis.

With a minimum of debate, the United Kingdom began offering the screening tests to pregnant women in 1974, just 2 years after Brock developed the tests. By now, 700,000 pregnant women have been screened, including Princess Anne and the Duchess of Gloucester. About 50 percent of all pregnant women in the United Kingdom are tested and the tests have been 88 percent successful in detecting fetuses with anencephaly and open spina bifida. Now that laboratories in the United Kingdom are screening for acetylcholinesterase as well as AFP in amniotic fluid, says Brock, "the level of false positives will be brought down so low that you cannot measure it."

Two years ago, the FDA was set to give marketing approval for AFP test kits in this country. But, largely through the efforts of Carol Buchholz, who chairs the board of the Spina Bifida Association of America, the FDA was persuaded to hold off. Buchholz says she was concerned that there would be no quality control over the laboratories offering the tests, that there would be no assurance that sonograms, amniocentesis, and good counseling services would be available, and that women might not have equal access to the tests. The FDA decided to hold off issuing proposals for marketing until this fall. Its new proposals, reportedly, will require that testing be done only through centralized programs that could assure that the women give informed consent, that follow-up tests are available after the initial blood tests, and that specially trained counselors would be available.



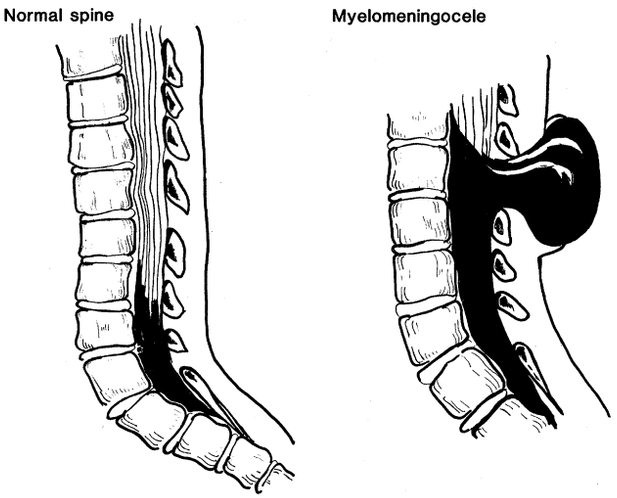
How bad are neural tube defects? Above is a spina bifida child with braces. [Source: Spina Bifida Association of America] Below is an anencephalic fetus. [Source: James Macri, State University of New York at Stony Brook]

In the meantime, several U.S. researchers have begun pilot screening programs. James E. Haddow of the Foundation for Blood Research in Scarborough, Maine, is screening women in that state and plans to begin a program elsewhere in New England. James N. Macri of the State University of New York in Stony Brook screens women in Long Island. And Neil A. Holtzman of Johns Hopkins University is starting a program in Baltimore County, Maryland.

Brock is amazed that the United States is moving so slowly to start screening for neural tube defects. "Listen to Macri and Haddow. They have an enormous amount of experience," he said at the meeting, pointing out that the Long Island and Maine programs have run smoothly. As for worries about the capabilities of commercial laboratories, he said he learned from experience that "It's a remarkable arrogance to think that a specialist in research can run a service better than a specialist in service." Urging the United States to get on with it, Brock said, "Do not overcomplicate measures that are inherently simple. If I had to encapsulate the British experience I would say, 'It works. It works much better than you anticipate.' " Brock said later that the American hesitation about instituting the test is foreign to him. "We lack your capacity for agonizing over issues. A conference of this nature would be unthinkable in the U.K."

A number of U.S. scientists and clinicians agree with Brock that this country is moving far too slowly. Schulman, for example, asks, "Do we have to reinvent the wheel just because it wasn't invented in this country?" He and Mark I. Evans of the University of Chicago argue that the methods of AFP screening are not new—they are routine. The blood tests and tests of amniotic fluid involve radioimmunoassays, which are part of any commercial laboratory's stock-in-trade. Obstetrical sonograms are commonplace. "Taps" to extract amniotic fluid are simple. "Any obstetrician can learn to do a tap in a short time," says Evans.

As for the current unavailability of medical resources for mass screening, Schulman remarks that he has never seen a medical technology for which there are paying customers where facilities did not spring up to meet the demand. Paying customers for screens for neural tube defects should be no problem. Susan Gleeson, director of professional and provider policy of Blue Cross/Blue Shield Associations, says that Blue



Spina bifida. Normal spine is shown on the left. On the right, the neural tube has failed to close, and the spinal cord and nerve bundles protrude through the baby's back. [Drawing by Jane Walsh]

Cross will pay for the tests when the FDA approves them. Apparently there also is no legal reason why Medicare cannot pay.

Macri, on the other hand, favors the gradual spread of pilot test programs, such as his own, rather than a rush to offer the tests to all who want them. He agrees that facilities will spring up once the testing begins, but says, "What worries me is what will happen before the services spring up." He envisions women who have two positive blood tests but no access to follow-up tests deciding to terminate their pregnancies.

It is not at all clear what the program will cost, but most analysts think that either it will save money or, at worst, it will nearly break even. Godfrey Oakley of the Center for Disease Control in Atlanta says the CDC estimates that a screening program will pay for itself two to one. Assuming that half of the pregnant women in this country are screened, the CDC estimates that the annual cost will be $30 million, in 1977 dollars. The screening will avert costs of $60 million to $72 million each year, Oakley says, which includes the cost of medical care for children with spina bifida and the money lost when mothers cannot work because they must care for their affected children.

Still, there are objections to the program, a major one involving the politically touchy issue of abortions. At the conference, there seemed to be an irreconcilable difference of opinion between some parents of spina bifida children and some obstetricians over just how bad this birth defect really is.

Buchholz, who is herself the mother of a child with spina bifida, says she speaks for many parents when she tells of the positive side of spina bifida. She showed slides of happy, smiling children in braces or wheelchairs, playing together and engaging in normal activities. She said, "I do not think the birth of my child was a tragedy. These children think of themselves as having a future." Yet doctors, Buchholz remarked, are often extremely negative about the prognosis for children with spina bifida. "I don't think physicians think of the children as going to school, playing, having a normal life. They only see them as sick children," she said.

Stephen B. Parrish of Loyola University Medical Center, who also has a child with spina bifida, made an impassioned plea for the lives of such children. He said that he knows of many families who have raised children with spina bifida and feel so strongly about the value of these children's lives that they are eager to adopt others. He urged couples to think about giving up spina bifida children for adoption rather than aborting them.

The physicians at the conference seemed to have less optimistic views. Evans, for example, says, "In my opinion, many prospective parents would rather abort a normal fetus than miss detecting one with spina bifida. Most obstetricians would agree with me but would not say it publicly." He explains that if a normal fetus is aborted, the couple can always try again, but the birth of a spina bifida child is a lifelong tragedy. Brock says that, in the United Kingdom, "the screening programs only got off the ground because the feeling is that the prognosis for a child with spina bifida is pretty gloomy."

A source of difficulty in discussing the value of life for spina bifida children was the wide variance between the prognoses given by the conference participants. Barbara Crandall of the Center for Health Statistics at the University of California, Los Angeles, for example, was quite pessimistic, stating that 90 percent of children with spina bifida are handicapped, 70 percent die by age 2, and 25 percent of those who survive beyond 2 years are mentally retarded. The Spina Bifida Association of America, in contrast, states in its pamphlet that "we can expect children born with spina bifida to have normal intelligence, normal lifespans, and to become contributing members of society."

Yet, says LeRoy Walters, who is director of the Kennedy Center for Bioethics of Georgetown University, "with all deference to the good intentions of the Spina Bifida Association, I don't think it is conveying accurate information for parents." In reviewing the literature he found that 33 to 63 percent of spina bifida children had IQ's above 80. If the children did not have hydrocephaly, 83 to 90 percent had IQ's above 80. But twice as many spina bifida children have hydrocephaly as do not, Walters says.

Of great concern to a number of conference participants is the possibility that women who are tested and found to be carrying fetuses with spina bifida will be coerced, explicitly or implicitly, to have abortions. The Spina Bifida Association wants to be sure that women hear the "positive side" of the disorder, in as simple, nontechnical language as possible. Walters worries that even if both sides of the issue are clearly presented, there may be subtle pressure to abort. "What if some women decided not to be screened or, if screened, not to terminate their pregnancies? What obligations would taxpayers have toward such [spina bifida] children? It's a very tough problem," he remarks.

Walters explains that possibly all society owes parents is information about whether their unborn child has spina bifida. He says it is not clear to him whether couples who decide to bear spina bifida children have a right to financial help. If they do not have this right, then the lack of financial support for these handicapped children "would certainly exert some pressure on people to terminate pregnancies." At present, much of the monetary burden of raising these children falls on the parents.

Perhaps Brock is correct in his belief that this country is spending an inordinate amount of time agonizing over these issues. "The ethical issues tend to wither away once a screening program begins. The problems are largely in the mind, not in the field," he says. But John C. Fletcher, who is assistant for bioethics at the National Institutes of Health, feels that "The fact that we are spending 2 years debating this screening program is a comment on the complex, delicate role of technology in our society."

—GINA BARI KOLATA