FDA Draws Criticism on Prenatal Test

Despite protests by two medical groups, FDA signals its approval for kits that help detect neural tube defects

Despite objections by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and others, the Food and Drug Administration (FDA) on 17 June essentially approved wider use of a laboratory test that detects neural tube defects in a fetus. The doctors argue that without restrictions, there will be much more room for error in testing, which may ultimately lead to unnecessary abortions. Their position however, fell into conflict with the Reagan Administration's commitment to deregulation, which prevailed.

At issue are diagnostic kits, manufactured by several companies, that detect neural tube defects such as spina bifida or anencephaly. The tests, which are potentially a multimillion-dollar business, measure the level of alpha-fetoprotein in a serum sample taken from an expectant mother. Elevated levels of the protein indicate that the fetus may have a neural tube defect, but a positive result must be confirmed by several more procedures including ultrasonography and amniocentesis. If additional tests are not performed, a mother runs the risk of aborting a healthy fetus by mistake. Under ideal conditions, the tests would help pinpoint the one or two children in 1000 born in the United States who have the defect.

Reliable laboratory results and meticulous attention to follow-up tests are crucial in determining whether the fetus does have an actual defect. But because the tests have not yet been approved for general use, doctors and laboratories are generally unfamiliar with the entire procedure. For this reason, the obstetricians' and pediatricians' groups have urged FDA to impose temporary restrictions on the tests until doctors are sufficiently knowledgeable about their use and laboratories become more proficient at analyzing the serum. They suggest that, after 2 years, the need for restrictions could be reevaluated.

FDA took this advice to heart in 1980 and proposed a set of fairly stiff regulations on the test. According to the proposals, the serum test could only be conducted in a highly organized program. A coordinator, most likely employed at a community hospital, would make sure that qualified laboratories were available, that positive serum results were followed by more sophisticated techniques, and that detailed records were kept by doctors, labs, and manufacturers.

Last month, however, FDA commissioner Arthur Hayes, Jr., withdrew the proposed restrictions, saying that they "are not needed to ensure the safe and effective use" of the kits. The FDA will now simply require companies to submit quarterly reports about the test and place labeling on the product for patients and physicians. It will also monitor the progress of 1000 patients at each of five different medical centers on an alpha-fetoprotein testing program.

Hayes' decision was as bold as it was controversial. Ever since the restrictions were circulated in 1980, the issue of whether to approve the kits has been enmeshed in scientific and political debate. The matter became so touchy that two FDA commissioners put it on the back burner during their tenure.

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The medical community, for example, has been divided over the issue. Although the organizations representing the obstetricians and pediatricians have supported the restrictions, the American Medical Association has opposed them, charging that the FDA would be dictating the practice of medicine. Manufacturers of the kits, not surprisingly, fought the proposed limitations too. The issue became particularly sensitive when antiabortionists voiced opposition to the use of the kits altogether.

So the Reagan Administration found itself caught between two principles it espouses—opposition to more regulation and opposition to abortion. In this case, deregulation won out. FDA withdrew the restrictions because they were too burdensome, says an agency spokesman, Christopher Smith. They would have "done nothing except raise the cost of the test." He remarked that a majority of comments received by the agency objected to the proposals. He also noted that FDA evaluated the tests on their own merits. "If you argue that women may abort a fetus more often, that's not our concern," he says. "What the physician and a woman do with the data is their business."

Ervin Nichols, a top official at the American College of Obstetricians and Gynecologists, says, "We are extremely disappointed with FDA's actions." The proposed restrictions "were most appropriate and we still feel that way."

Nichols and others still want to find a way to ensure quality control over the whole process of determining a neural tube defect. Their concern focuses on three areas: providing adequate genetic counseling to the parents, educating the physician, and ensuring reliable laboratory results.

The need for close monitoring rests on the fact that the test is only a gross technique to screen for neural tube defects. Of 1000 pregnant women, 50 will show a high reading. A second serum sample must be taken to check the earlier results. This step will eliminate 10 to 20 false positives. But a second positive result must be further confirmed by ultrasonography and amniocentesis.

Furthermore, the test can only be administered between the 16th and 18th week of pregnancy to achieve accurate results. If the gestational age is miscalculated and the test is conducted beyond the 18th week, the sample may give a false positive reading. Women carrying more than one fetus will also have a high level of alpha-fetoprotein.

Nichols stresses the need for genetic counseling at every step of the way. He fears that, without proper guidance, a woman may decide to abort her child on the basis of only a preliminary result of one positive test. She may become so distressed, he says, that she will not complete the series of follow-up tests that may take up to 1 month. Right now, there are not enough genetic counselors, Nichols says. But temporary restrictions imposed by FDA on the test would allow some time to train more counselors.

Part of the key to quality control obviously rests with the physician but apparently it will require a major educational

effort by the medical societies or the FDA. Findings of a study recently submitted for publication by a Johns Hopkins researcher, however, are not very encouraging. Neil Holtzman, an associate professor of pediatrics and a key researcher in alpha-fetoprotein testing, conducted an experiment in 1980 that evaluated obstetricians' knowledge about the test procedures after they were taught about the technique. Holtzman looked at three groups: one set of about 25 doctors were given oral and written instruction about the test and then used the test to screen patients with the help of a coordinator; other doctors were instructed about the test but did not do any screening; the control group comprised physicians who were not formally taught about the test.

Holtzman found that, even after instruction and practice in screening, physicians demonstrated no better knowledge of the test than the controls or the other group. He says that many physicians in the screening program "did not know when the tests should be administered and did not know how to follow up" when quizzed about the procedures. One surprising finding of the study is that no unnecessary abortions were performed among the 1500 participating women. Holtzman suggests that the physicians relied heavily on the coordinator to guide them through the process.

Supporters of federal restrictions emphasize the need to evaluate a laboratory's ability to analyze the serum samples, as highlighted by a 1982 study by the Centers for Disease Control (CDC). The agency sent various samples to 16 labs which were known for their dependability. Vincent Przybyszewski, one of the researchers, says that the labs showed wide variation in their results on the same samples. They achieved only 80 percent agreement on specimens that had either very high or very low levels of alpha-fetoprotein. No agreement was reached with samples that were borderline cases.

In the opinion of James Macri, director of the neural tube defect laboratory at the State University of New York at Stony Brook, the CDC results "were chaotic." Macri says that based on his experience, accumulated from the Stony Brook program which has screened some 60,000 women for fetuses with neural tube defects, a lab should do a minimum of 400 assays a week to ensure proficiency. The large sampling would also help the lab more accurately calculate normal values for alpha-fetoprotein levels, which vary from one community to another. Macri's recommendation is

Fetal Surgery for Neural Defects?

Pregnant women who learn that they are carrying a fetus with a neural tube defect are faced with a difficult choice. They can have an abortion or they can carry the fetus to term, realizing that the chances are high that the child will be handicapped. Although some children with neural tube defects have no or only minimal handicaps, most are paralyzed below the waist and have no bowel or bladder control. Most are also mentally retarded.

In the future, however, fetal surgery to correct neural tube defects may provide an option between abortion and a handicapped child. Gary Hodgen of the National Institute of Child Health and Human Development (NICHD) and Maria Michejda of Georgetown University School of Medicine are developing methods for treating fetuses with encephaloceles and spina bifida. So far, they have had some surprising results with monkey fetuses, but much more work is required before their technique could be applied to humans.

Techniques developed by Hodgen and his associates have already led to the use of fetal surgery to correct hydrocephaly. This condition—in which fluid builds up in the ventricles of the brain, causing such pressure that the brain may be irreversibly damaged—is the major cause of mental retardation in children with spina bifida. Most babies with hydrocephaly are treated after birth, but by then much of the damage is already done.

Several years ago, Hodgen and his associates at the NICHD developed a shunt to treat hydrocephalus in utero. They tested the shunt, which drains excess fluid from the brain, in monkey fetuses and found that the treated monkeys seemed to have normal brain functions. Untreated hydrocephalic monkeys had serious brain damage, often dying within a few days of birth because they could not nurse or suck from a bottle. The technique proved so successful in monkeys that some physicians recently decided to try treating unborn babies. So far, too few human fetuses have been treated to assess the results.

Now Hodgen and Michejda are developing a way to treat encephaloceles—a neural tube defect in which a portion of the brain protrudes through the skull—by fetal surgery. The standard treatment, after birth, is to surgically remove the protruding brain tissue and close the skull. Because the part of the brain pushed out includes the visual cortex, babies born with encephaloceles usually are blind and often are mentally retarded.

Hodgen and Michejda can produce encephaloceles in monkey fetuses by giving the mother a synthetic corticosteriod. During the second trimester they open the uterus, partially pull out the fetus, and cut off the protruding brain. They then seal the skull with bone paste—a mixture made of ground fetal bones and culture medium—and return the fetus to the womb, preventing spontaneous abortions by using drugs to relax the uterus. Surprisingly, the brains of the monkey fetuses regenerate in utero and the monkeys are born fully able to see.

"We have studies under way to correct spina bifida," says Hodgen, "and we are trying to develop an adequate model." It has proved difficult to produce spina bifida in monkeys by giving them teratogens, so Hodgen is producing the defect surgically. He cuts into the fetus' back, allowing the nerve bundle to hemorrhage. Then he uses bone paste to close the opening in the spine in order to allow the spinal nerves to regenerate.

Surgical treatment of neural tube defects in human fetuses is still a long way off, however, and use of the technique would raise difficult ethical problems. For example, it will be necessary to have sources of fetal bones. Hodgen believes that once the need is known, parents would donate the bones of spontaneously aborted fetuses, just as they now sometimes donate the organs of young children who are brain-dead.

Hodgen says that his goal in trying to correct neural tube defects is to give these babies a chance for a normal life if their disease is detected in utero by alfa-fetoprotein tests. "We have an obligation, given the value we put on the quality of human life, to try to offer women other alternatives," than abortion, he says.—**GINA KOLATA**

buttressed by a 1979 report written by a blue-ribbon panel in Britain, which also advised a minimum of 400 samples. The proposed FDA restrictions would have required a lab to conduct only 50 tests weekly. The agency position now is that there is "no established relationship between volume of tests and proficiency." CDC is, however, developing some guidelines on quality control.

Macri is also concerned that, unless laboratory results are reliable, women will undergo amniocentesis unnecessarily. If too many women elect to have amniocentesis based on faulty data, the invasive procedure may do more harm to the mother and fetus than if the test were not performed, Macri argues.

FDA could learn from the experience with alpha-fetoprotein testing in Britain, he says. In that country, neural tube defects have caused considerable concern because the abnormalities occur in five out of 1000 children, a rate five times higher than in the United States. The 1979 study, headed by Sir Douglas Black, then president of the Royal College of Physicians, emphasized the need "to ensure that there were sufficient health professionals and facilities to perform followup testing and analysis" and called for extensive reporting to judge the program's effectiveness.

Some states, such as California and Maryland, are already establishing their own monitoring programs. Some observers predict that other states will follow suit, but to Macri and others a federal effort is needed.

FDA plans to issue formal approval of the alpha-fetoprotein tests in the near future and to announce exactly what kind of information it will require from doctors, manufacturers, and labs. Nichols of the obstetrics society and others seem pretty much resigned to the FDA's withdrawal of the proposed restrictions. When the official approval notice does appear, the Washington-based Health Research Group plans to file a petition for a hearing before Commissioner Hayes. If granted, supporters of the restrictions might get one more crack at persuading FDA to limit use of the tests.

Given the arguments and concerns of researchers and professional societies about quality control, it seems that Hayes had a reasonable basis to support temporary restrictions. If he had done so, he might have coincidentally allayed concerns by some antiabortionists. Instead, he has taken a very narrow view of FDA's role in judging safety and effectiveness of the tests. "I see lots of problems ahead," Macri says.

—**MARJORIE SUN**

Pesticide Office Demands New Safety Studies

Edwin Johnson, director of the Office of Pesticide Programs at the Environmental Protection Agency, called a news conference on 11 July to let reporters know that the gaps in health and safety data created by the Industrial Bio-Test (IBT) scandal are almost fully repaired. Earlier, his agency reported that IBT was responsible for submitting over 1200 invalid studies that were used to approve more than 200 pesticides. The laboratory's officials are now on trial in Chicago for committing wire and mail fraud (*Science*, 10 June, p. 1130). But Johnson said at the press conference that the "IBT situation has not proven to be the hidden public health disaster that some had feared."

Johnson released a summary of the IBT-related problems, announcing that the agency's review begun in 1977 is now complete. He also revealed a couple of new regulatory actions, the most important being that manufacturers of 35 compounds will be given 90 days to replace the IBT studies they relied on, commit themselves to filing new studies, or face suspension from the market.

Johnson emphasized that the actual number of problem chemicals is smaller than the early estimates suggested. He reported that there are only 140 compounds still in use which are supported in part by IBT data, and only five are supported wholly by IBT studies. Of these five, two are "major use" chemicals: prometon and dinoseb. The former is used for nonagricultural purposes and the latter is a food-related pesticide. Johnson's report notes that "A large majority (93 percent) of the pesticides tested by IBT also have non-IBT data available" to serve as a secondary assurance of safety.

However, at least one government expert told *Science* this report glosses over the problems that remain to be cleared up. For example, it does not indicate how many of the 140 compounds—some of which may be widely used—still depend heavily on IBT studies in the especially critical areas of carcinogenicity and chronic toxicity analysis. These are important for setting allowable human exposure levels. An aide to Johnson says, "There are many ways to cut the data; we didn't do it that way." Nor is it clear when the invalid studies needing replacement will be fixed. Because it can take 4 years to run a carcinogenicity study, it is fair to assume that for some chemicals now in use, it will take until 1987—10 years after the IBT scandal broke—to learn whether or not they pose a health hazard.

Meanwhile, in Chicago, the judge hearing the IBT case granted a mistrial on 11 July to Joseph Calandra, the founder and former president of IBT. He was allowed to drop out to undergo open heart surgery. (The operation was a success.) Calandra is now separated from his three colleagues, whose trial for fraud is expected to continue until September. He will be tried later.—**ELIOT MARSHALL**

NRC Delays Pipe Inspections

The staff of the Nuclear Regulatory Commission (NRC) has been urging the temporary shutdown of five boiling water reactors so they could be inspected for cracks in the cooling pipes. However, after a meeting between the reactor owners and NRC commissioners on 15 July, the NRC agreed to postpone the order until the Electric Power Research Institute (EPRI) comes out with the results of ultrasonic studies on cooling pipes. Those are expected by 4 August.

Owners of the five plants had planned to inspect pipes in the fall or winter. The NRC staff wanted to accelerate this schedule so as to minimize the risk of an accident. But the industry argued successfully that the seriousness of the cracks could be overstated, a possibility that the EPRI tests could verify.

General Electric reactors manufactured in the late 1960's and early 1970's have been plagued by cracks in pipes. They have been detected in 13 reactors around the country and 7 are currently shut down because of the problem. Replacement of pipes with ones made of higher grade steel could cost between $10 million and $100 million per reactor, according to industry sources.

—**CONSTANCE HOLDEN**