scientists who have already been subject to the audit say zealous and inexperienced auditors may not be painting a fair portrait. At the University of Wisconsin at Madison, one indignant scientist said the audit team seemed preoccupied with equipment such as minicomputers and kept asking naïve questions about why they were needed. There were no scientists on the team, and answers provided seemed to go over the heads of the auditors. The scientist also complained that audits seemed to be held when the principal investigator was absent, a situation in which the person responsible for the equipment is not in a position to defend or explain apparent discrepancies.—WILLIAM J. BROAD

FDA to Reexamine Bendectin Data

The Food and Drug Administration (FDA) has decided to take another look at all studies to date that might bear on the question of whether Bendectin causes birth defects. Bendectin is the only drug specifically approved for nausea and vomiting of pregnancy and it is taken by about 25 percent of all pregnant women in this country.

The FDA last looked at Bendectin studies in September of 1980 at which time its panel of experts examined data from animal studies and 13 epidemiological studies and concluded that there is no demonstrated relation between the drug and birth defects. However, it is impossible to prove that any drug is harmless. The panel recognized a "residual uncertainty" about Bendectin's safety during pregnancy (*Science*, 31 October 1980, p. 518).

Despite the FDA's conclusions, a growing number of parents are convinced that Bendectin caused birth defects in their children. More than 100 lawsuits have been filed against Merrell-Dow, Bendectin's manufacturer, although the plaintiffs lost in the one case that did go to trial. Recently, public attention has been focused again on Bendectin as a result of newspaper stories indicating that there is new evidence which shows a strong link between Bendectin and birth defects.

The FDA's decision to reexamine all the Bendectin data was prompted by a meeting on 8 April between FDA commissioner Arthur Hull Hayes, Surgeon General C. Everett Koop, Representative Doug Walgren (D–Pa.), and Harry Meyer, director of the National Center for Drugs and Biologics.

Susan McFalls, a member of Walgren's staff, says the congressman is concerned by some new data that he believes may implicate Bendectin in birth defects. There is a rat study showing that Bendectin may cause diaphragmatic hernias, a potentially fatal defect in which the stomach and other organs get into the lung cavity through a hole in the diaphragm. There is a monkey study showing that Bendectin may cause ventricular septal defect, a hole between the chambers of the heart. And there is evidence from a new in vitro test for teratogens that Bendectin may cause birth defects. "We have been concerned for some time because we have seen both these defects [diaphragmatic hernias and ventricular septal defects] in reports from physicians and patients," McFalls says.

Ann Wilk, a reviewing pharmacologist at the FDA, notes the very preliminary nature of the new Bendectin studies. The rat study, done by Reimer Roll of Bundesgesundheitsamt in West Berlin, is still unpublished and the FDA has only a summary statement and reams of raw data which the agency is now having translated into English. Roll apparently sees a slight incidence of diaphragmatic hernias at very high doses of Bendectin with no dose-response effect. But, says Wilk, the FDA cannot yet say anything about his methods. In the meantime, Roll is repeating his study and the FDA is repeating it "with some modifications," according to Wilk.

The monkey study, conducted by Andrew Hendrickx of the Primate Research Center at the University of California at Davis, also is unpublished except in abstract form. Hendrickx, however, notified the FDA of his results in May of 1981. He gave 12 cynomolgus monkeys 10 to 20 times the normal human dose of Bendectin throughout the major period when organs are developing. Two of the monkeys aborted their fetuses. He then examined seven of the remaining fetuses about 2 months prior to term. In four of the seven, he saw an intraventricular septal defect, but it is not clear what this finding means because fetal monkeys normally have a hole in the septum earlier during development. When Hendrickx examined the three monkey babies that were carried to full-term, he found that they were completely normal. Wilk asks of the septal holes that Hendrickx found in the four fetuses, "Was this a delay in development or would it persist until birth?"

Merrell-Dow is now funding Hendrickx in a much larger study, which will take 2½ years and will be double-blind. There will be four groups of monkeys, 20 pregnancies in each group, and three doses of Bendectin.

In the meantime, another small-scale monkey study, involving nine animals and conducted by Harold McClure of Yerkes Primate Research Center, showed no effect of Bendectin on rhesus monkey fetuses.

After hearing of these animal studies, the FDA requested that researchers conducting epidemiological studies, including Boston University's Drug Epidemiology Unit and the Centers for Disease Control, look for an association between Bendectin and heart defects or diaphragmatic hernias. In these studies none has been found as yet.

The in vitro study that McFalls referred to was conducted by John Hassell of the National Institute of Dental Research. He added Bendectin to cultured cells that normally would develop into cells resembling cartilage. The added Bendectin prevented this development. Hassell and Wilk concur that it is difficult to evaluate this study because no in vitro test has yet been validated—it has not been shown that these tests can reliably distinguish known teratogens from substances known not to harm fetuses.

At the present time, the FDA is considering a labeling change for Bendectin to reflect the possibility that the recent animal studies may turn out to demonstrate teratogenicity. Bendectin's label now says there is no evidence of teratogenicity in animal tests. But the agency scientists feel that, in the final analysis, their best data will be from continued epidemiological monitoring of Bendectin. And, as yet, there is no persuasive evidence from human studies that the drug causes birth defects.—GINA KOLATA

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