FDA Queries Alzheimer's Trial Results

The Food and Drug Administration has notified California physician William Summers that it is considering barring him from conducting clinical trials of new drugs. The agency took this action because of questions it has about a previous study in which Summers and his colleagues tested the effects of the experimental drug THA in patients with Alzheimer's disease. The results, which were published in the high-profile *New England Journal of Medicine* in November 1986, indicated that the THA treatment could alleviate the patients' symptoms to a degree not seen with other experimental Alzheimer's therapies.

The study generated a firestorm of interest. It was a major stimulus to the initiation of a multi-center clinical trial under the joint sponsorship of the National Institute of Aging, the Warner-Lambert Company of Morris Plains, New Jersey, and the Alzheimer's Disease and Related Disorders Association. That trial began in September 1987, but was halted by the FDA in November when 20% of the first patients showed signs of liver damage.

Meanwhile, doubts about the methodology used by Summers in his earlier THA study had surfaced in several letters-to-the-editor that the *New England Journal* published in May. In addition, the FDA had begun its own investigation at least partly because agency officials were concerned that the physician was commercializing an as yet unproven therapy. He had formed a for-profit corporation and was charging patients up to $12,000 for a full year of THA therapy. Summers maintains that the fees covered only the cost of the research.

The FDA conducted an audit of the Summers data from the THA study in the summer of 1987. As a result, the agency presented the physician with an FDA-483 form that lists a large number of patient records and data that the FDA inspectors said that they could not locate. The 483 form also raised questions about whether the THA trial was truly double-blinded, as the *New England Journal* report claimed. To avoid compromising the integrity of drug trials, they are usually conducted in a double-blind fashion, with neither the patients nor the individuals who assess their conditions knowing when a patient is receiving the test drug and when a placebo.

An investigator who is issued a 483 form is entitled to reply, and if he can supply the missing information to the FDA's satisfaction, the matter can end. However, according to a report by Gina Kolata in the *New York Times*, Frances Kelsey of the FDA's Office of Scientific Investigations has now sent Summers a letter that lists 14 findings that she says cast doubt on conclusions of the study he conducted. If all the problems cannot be cleared up, the investigator may be barred from conducting new drug trials.

Kelsey declined to discuss the Summers investigation, saying, "It's still an open file and I have no comment." Summers confirmed that he had received the letter, but he, too, declined to discuss the situation at this time. He had, however, previously sent *Science* a copy of a letter that he wrote in November to a *Wall Street Journal* editor.

Summers states in this letter that some 55% of the items of information—out of a total of 355 by Summers' count—listed in the 483 form were already provided in the material examined by the FDA inspectors. Summers could supply corroborative material for another 29%, leaving 16% still outstanding.

While all this has been going on, the FDA has given permission for the resumption of the multi-center THA trial, in which Summers is not participating. There are theoretical reasons for thinking that the drug might be of some use in treating Alzheimer's disease. It bolsters the concentration of a brain chemical that is deficient in the patients. The FDA is requiring that lower doses of the drug be used in the resumed trial and that the patients are to be monitored very closely for signs of liver damage or other side effects. ■ JEAN L. MARX

Second Chance for Rice Research Center

The West Africa Rice Development Association (WARDA) has a new headquarters near Bouaké in Côte d'Ivoire. Besides moving to a new location, the problem-ridden organization has put into effect a number of reforms aimed at giving it a fresh start.

WARDA has been regarded as the least effective of the international agricultural research centers operating under the CGIAR* organization. Founded in the early 1970s to foster self-sufficiency in rice production in West Africa, it earned scathing evaluations for both its research performance and management. A variety of proposals were considered for WARDA including outright abolition or merger with other organizations. A decision was finally made to restructure WARDA and revise its strategy (*Science*, 5 Dec. 1986, p. 1190).

The problems with WARDA's scientific program started with its original strategy which was pitched to improving rice production in West Africa by adapting high-yielding varieties of rice developed elsewhere, mostly in Asia. As it turned out, these varieties did poorly under African environmental conditions. They also proved ill-suited economically, because the exotic varieties required water, fertilizer, and pesticides in amounts usually not available in African agriculture.

*The Consultative Group on International Agricultural Research is sponsored by the World Bank and other United Nations agencies and funded mainly by the United States and and other industrial countries.

Eugene Terry. *New director general of the West Africa Rice Development Association.*

Where the emphasis formerly was on testing rice varieties brought in from outside, WARDA's new strategy is to emphasize research to generate technologies that fit African conditions. WARDA plans to concentrate on developing rice varieties suitable for cultivation under three systems of rice production—upland rice grown under rainfed conditions, mangrove swamp rice, and irrigated rice. The aim will be to give farmers in those agroclimatic zones options in rice varieties that will meet the stresses of growing conditions, increase yields, and suit African tastes.

WARDA's new headquarters site at Mbe/foro-foro in central Côte d'Ivoire is situated in the transition zone between tropical forest and savannah. The center headquarters was previously located in Monrovia, Liberia. A major criticism in the past was that the headquarters was an administrative center with no crop research facilities so that the organization's professionals were isolated from fieldwork. The new site will serve WARDA as both headquarters and main research base. Major research activities will also take place at stations in Senegal and Sierra Leone and fieldwork will continue in Liberia.

Presiding over the rebuilding of WARDA is a new director general, Eugene Terry. A Sierra Leone national, he joined WARDA last September after 15 years at the International Institute of Tropical Agriculture (IITA), another CGIAR center. Terry holds a Ph.D. in plant pathology from the University of Illinois.

WARDA differed organizationally from the other CGIAR centers in being an intergovernmental entity with its West African member countries sharing authority. Other CGIAR centers are governed by boards whose members represent the international agricultural research community. Under the new constitution for WARDA, its governance more closely resembles the CGIAR model with equal numbers of members of the new board appointed by the CGIAR and by the 15 member countries.

The key agreement on restructuring was reached at the end of 1986 with the ministers of agriculture of the member countries approving the new WARDA constitution. The process of carrying out the planned changes in organization and program is expected to be completed by 1990. In a deck-clearing move, the new board last year presided over a reduction of staff by about 40%. Terry says that the reconstituted WARDA is expected to have an internationally recruited professional staff of 32, some 25 of them active full time in research. Terry says recruiting for key staff jobs is going well.

The reforms appear to have reassured the major donor countries, which were wavering in their willingness to fund WARDA. At a meeting of CGIAR directors general last autumn WARDA got a financial vote of confidence from eight donors that should ensure funding through a 2-year transition period until 1990 when a reorganized WARDA is scheduled to be fully operational. The Center's annual operating budget then is projected at about $6 million.

The old WARDA was plagued by deficits, caused in part by a neglect of dues paying by West African member countries with crippled economies. Late last year, one CGIAR official noted that the former delinquents were paying up, a sign, he suggested, they had decided that the new WARDA had a future. ■ JOHN WALSH

Part of AIDS Virus Is Patented

Harvard University has been granted an American patent on a key component of the AIDS virus. Many reseachers believe that the component, a protein known as GP120, is the key to developing better diagnostic tests and new vaccines for AIDS, so the patent could be potentially lucrative.

While other scientists in the early 1980s were studying smaller glycoproteins on the surface of the AIDS virus, Myron Essex and Tun-Hou Lee of Harvard University focused their attention on one of the big ones, GP120. It looks like "a pin stuck through a golfball," Essex says. In 1984, Essex and Lee discovered that GP120 provoked the biggest immune response of any of the surface antigens from the AIDS virus. They passed this news on to representatives from the university's patent office during one of their routine visits to Harvard scientists, who in turn suggested filing a patent application on the protein.

Myron Essex. *Found that GP120 provokes largest immune response.*

The product patent, issued on 16 February, covers GP120 and proteins that cross-react with it, according to Joyce Brinton, director of Harvard's Office of Patents, Trademarks, and Licensing. The claims do not name a specific amino acid sequence describing GP120, which, Essex has said, can vary 1 to 20%. In general, claims involving natural substances that describe the function, rather then chemical composition, of the substance can result in a broader, stronger patent, according to Charles Van Horn, director of the organic chemistry and biotechnology examining group of the U.S. Patent and Trademark Office.

Some companies are using fragments of GP120 to develop vaccines, but, Brinton said, "I don't know whether fragments would be subject to royalties. It would seem like [they] would." The most common AIDS tests on the market now are based on a mix of surface proteins, including GP120, but again it is not clear whether these products would be subject to royalties.

Harvard awarded an exclusive license to use the patent to Cambridge Bioscience Corp. of Worcester, Massachusetts. So far the company has contributed about $350,000 to Harvard to support Essex and Lee's AIDS research. The firm's financial support for their research has been an "unusual arrangement," Brinton says, because Essex is a member of the company's science board and holds a small amount of equity in the firm. Harvard administrators were worried about a potential conflict of interest between Essex and the company, but at the time, Cambridge Bioscience was the only party willing to support the research. University officials approved the arrangement after an agreement was struck on certain controls to minimize any possible conflict of interest.

It is not uncommon for universities, including Harvard and Massachusetts Institute of Technology, to award exclusive licenses to companies in which a university scientist has a vested interest. Essex says he has not paid much attention to the financial potential of his research. Since progress in AIDS vaccine development so far has been limited, "I don't have real high hopes [of royalties] the way things are going," he remarks. The university says it will use its portion of any royalties to fund fellowships for AIDS researchers in developing countries. ■ MARJORIE SUN