hinges on two facts. First, blue supergiants are smaller than red supergiants, even if the masses are the same. Second, a supernova's ejecta shell has to reach a certain size before its outer layers become tenuous enough to let the heat radiate efficiently. This means that a shell produced by a blue precursor star will have to travel much further before it can radiate than the shell from a red precursor, which means in turn that the gas deep inside will be at a much lower temperature when the radiation begins. In technical terms, the gas will have cooled by adiabatic expansion. The result is less thermal radiation and a dimmer supernova.

In short, the two mysteries are actually one mystery: if the supernova was dim because the Sanduleak star was blue, then *why* was it blue?

In retrospect, say the modelers, it might have been better to ask the question the other way around: why should supernova precursors only be red? Although it is true that virtually all the supernovas seen in other galaxies had red precursors, those were also the brightest supernovas. Perhaps we just never noticed the dimmer ones. Furthermore, it turns out that the people who model supergiant evolution on the computer have known all along that the star's color is very sensitive to such details as its precise composition, or the extent of thermal convection in its envelope. "It's very delicately balanced," says Chicago's Arnett. "Relatively minor changes can make it tip from one one side to the other."

Not only do the theorists find it very easy to get supernovas out of blue supergiants, but they have divided into two contending camps over just how it happened. Arnett's calculations, for example, suggest that the Sanduleak star may have always been blue, that it blew up without ever going into a red supergiant phase. But Woosley and others suggest that the star did go through a red phase before it contracted again and moved back to the blue. Their models show that it could have done this by internal evolution, by shedding some of its distended envelope, or by some combination of both.

For the moment, at least, the evidence seems to favor the latter hypothesis. Red supergiants are known to shed material in much the same way that the sun emits the solar wind, only more vigorously. Moreover, there is spectroscopic evidence from the International Ultraviolet Explorer satellite that 1987A is surrounded by a tenuous shell of material, about 1 light-year in radius, that was shed about 30,000 years ago. On the other hand, the final word is not yet in—which is why the astronomers keep watching, and waiting, and wondering. ■

M. MITCHELL WALDROP

Alzheimer's Drug Trial Put on Hold

Signs of liver damage in test patients brings controversial drug study to temporary halt

WHAT goes up, must come down. And for now, THA, a drug that was widely touted as a treatment for Alzheimer's disease, is down, although perhaps not out. On 23 October, a multicenter clinical trial to test THA (tetrahydroaminoacridine) in patients with the neurological disease was brought to a halt because 8 of the first 41 patients who received the drug showed signs of liver damage. The development is the latest in a year of controversy about THA and its proposed role in treating Alzheimer's disease.

The drug first burst into the public consciousness last November as the result of an article and an accompanying editorial in the 13 November issue of *The New England Journal of Medicine*. William Summers, a physician in private practice in Arcadia, California, and his colleagues reported that THA could alleviate the symptoms of Alzheimer's disease. Their article said, for example, that "One subject was able to resume most of her homemaking tasks, one was able to resume employment on a part-time basis, and one retired subject was able to resume playing golf daily."

For Alzheimer's victims, these were amazing accomplishments, indicating a much greater degree of patient improvement than those produced by previous experimental Alzheimer's treatments. Not surprisingly, Summers' results, which received a great deal of attention in the press, generated in biomedical circles what could be called a firestorm of interest in THA.

Alzheimer's disease now afflicts as many as 3 million people, most of them elderly, and is characterized by a relentlessly progressive neurological degeneration that robs its victims first of their memories and reasoning powers and then of their lives. When Alzheimer's family members heard the news about the Summers article they besieged physicians and the government for access to THA. Summers recollects that his office alone received 1800 telephone inquiries about the drug in the 10 days following the publication of his paper.

The public interest in THA ultimately led to the initiation of the now interrupted clinical trial, which started in September of this year under the sponsorship of the National Institute of Aging (NIA), the Warner-Lambert Company of Morris Plains, New Jersey, and the Alzheimer's Disease and Related Disorders Association. Meanwhile, however, scientific doubts about Summers' results emerged in the 18 June issue of the *New England Journal*, which included five letters that criticized the research on several grounds.

Summers had also taken what would prove to be a controversial action when in June 1986 he formed a for-profit corporation, Solo Research, Inc., to make THA therapy available to Alzheimer's patients at a cost of up to $12,000 for the first full year of treatment. According to Summers, he formed the corporation to obtain the funds necessary to continue his studies of THA.

He had been unsuccessful at getting a research grant, despite several applications, and he was using money generated by his private medical practice to support the Alzheimer's research. "If I hadn't gone to that mode [the corporation] the work would have never been completed," he recently told *Science*. He also says that the money went to pay only expenses for the THA research, including the cost of the drug and of technicians' salaries, but, "None of it ever came to me."

Nevertheless, officials of the Food and Drug Administration (FDA) were concerned that Summers was commercializing an as yet unproven therapy. According to the FDA's Paul Leber, they also did not want to see additional patients exposed to THA until it could be studied more thoroughly. The *New England Journal* paper describes the results of treating only 17 patients, a small number on which to conclude that a drug that might be used by millions of people is safe and effective.

Early this year Leber told Summers that he could take up to a total of 45 patients, including those that had already begun receiving the drug. However, Summers was not to charge for the experimental therapy beyond the "usual and customary" fees for his services. Summers says that he has since put another $18,000 from his private practice into the research.

Whatever the merits of that research, it was instrumental in the move to a more comprehensive clinical trial for THA. "The trial was stimulated by the public's expectations that were stimulated by Summers' patients," says Andrew Monjan of NIA, which is providing $1.9 million in funds for the trial. Kenneth Davis of Mount Sinai Medical Center in New York, the principal investigator for the study, also recruited Warner-Lambert's help, with the company agreeing to contribute $3 million to the project. The Alzheimer's association is putting up another $250,000.

The clinical trial, as it was eventually set up, was to include a total of 300 patients at 17 medical centers. Summers was invited to participate, but declined, citing the costs, among other things. To limit the availability of THA, the FDA turned down the applications of investigators who wanted to conduct their own independent THA research.

The first patients began entering the multicenter trial in September of this year. Because of the relatively limited experience with THA, especially for long-term use, the trial was designed to test the drug's safety, as well as its efficacy. "We are dealing with a substance that did not undergo the usual scrutiny of a phase I trial," Monjan says. "This is a combination of a phase I and phase II trial." (Phase I trials evaluate maximum tolerated doses and side effects of drugs; Phase II trials evaluate efficacy.)

One of the concerns about Summers' results with THA is the discrepancy between the patient improvements he finds and the more modest results of previous studies that were based on a similar therapeutic strategy. "This was a much larger response than anyone else had previously obtained," says Davis, who stresses that there is nonetheless a rational reason for thinking that the drug might help alleviate the symptoms of Alzheimer's disease. THA is an inhibitor of the enzyme acetylcholinesterase, which breaks down the neurotransmitter acetylcholine.

About 10 years ago, researchers learned that the brain of an Alzheimer patient shows major losses of acetylcholine-producing neurons in the learning centers. This finding raised hopes that the patients' symptoms could be alleviated by bolstering acetylcholine concentrations in the brain much as the symptoms of Parkinson's disease are alleviated by L-dopa.

In the past few years, investigators, including Davis, have shown that other inhibitors of acetylcholinesterase, principally the drug physostigmine, produce modest memory improvements in some Alzheimer's patients, presumably because inhibiting the enzyme potentiates the activity of whatever acetylcholine the brain is capable of producing. Walter Kaye and his colleagues at the National Institute of Mental Health obtained similar results when they gave Alzheimer's patients THA plus lecithin, which provides a source of choline for acetylcholine synthesis. Summers also asks his patients to take lecithin with the THA, although they may not always do it.

Some researchers question whether acetylcholine-bolstering strategies can possibly have the potential for causing more than mild improvements in Alzheimer's symptoms. They note that the brains of the patients show extensive losses—70% and higher—of the nerve cells that produce acetylcholine. Moreover, neurons producing other neurotransmitters are also affected.

"We've treated this problem much too simplistically," says Francis Pirozzolo of Baylor College of Medicine in Houston, who coauthored one of the critical letters in the *New England Journal*. "It's not like Parkinson's disease. Multiple transmitter systems are involved. The best we can hope for [from THA] is some symptomatic relief."

Davis disputes this contention, however. He notes that other neurotransmitter systems are also involved in Parkinson's disease. Yet L-dopa can reverse the symptoms at least until the brain damage becomes too extensive to be overcome.

According to Davis, a critical aspect of the THA regimen used by Summers, and one that might possibly explain the better results he obtained, is an initial phase of study that is aimed at finding the best dose for each patient. "It is absolutely critical to find the best dose. Patients vary in their responsiveness," he explains.

It was during the dose-finding phase of the multicenter trial that the evidence of liver toxicity began turning up. Eight patients, who were in the fourth or fifth week of a gradual buildup of the THA doses, developed elevated levels of liver enzymes in their blood, which is an indication that liver cells are dying, but no other symptoms of liver damage. Toxicity studies of THA in experimental animals, which are being conducted at Warner-Lambert, have not produced signs of liver damage, according to the company's Elkan Gamzu.

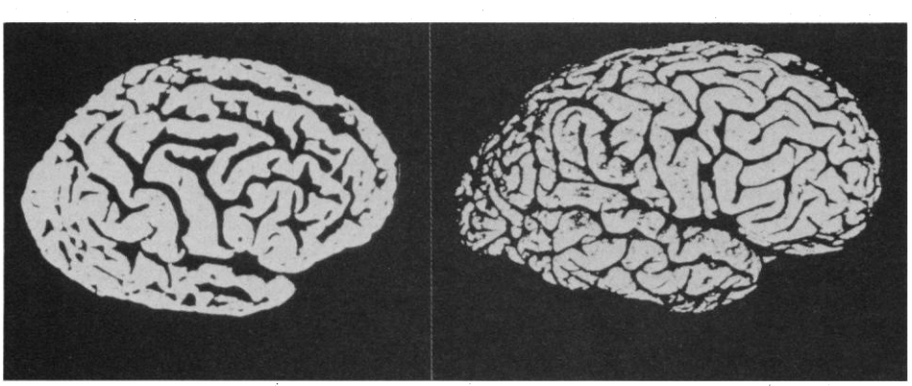
In any event, the trial has now been stopped, and the patients are being watched to see whether the liver damage is reversible. "We wanted to pause to see what happens to the patients," Leber says. "If they all get better, consideration will be given to restarting the trial." The concentrations of the liver enzymes are decreasing, Davis says, and a proposal for modifying the drug regimen will be submitted to the FDA soon.

During the dose-finding phase of the trial, "best doses" that seemed to improve the patients' conditions were found for about half of the 41 individuals who entered the study. Their conditions were assessed by means of the "Alzheimer's Disease Assessment Scale."

Summers' THA research has been severely criticized because of the assessment methods he has used. "The outcome variables were inappropriate. We don't know anything about the properties of these particular tests," Pirozzolo says. According to Pirozzolo, the tests have not been validated to show that the results correlate with the pathological condition of the patients. He suggests the Mini Mental State test as a more appropriate measure.

Summers counters that there are no easy-to-administer tests that are suitable for assessing the mental conditions of Alzheimer's patients. He finds the Mini Mental State test unacceptable because its contents can be too easily learned, even by Alzheimer's patients, when given repeatedly.

According to Davis, the Alzheimer's Disease Assessment Scale "has been shown to be valid, reliable, and sensitive to pharmacologically induced changes. We saw enough to be encouraged to continue with the study." Whether that happens will be up to the FDA. ■ JEAN L. MARX



Stanley Rapoport, NIA

Comparison of normal and Alzheimer's brains. *An Alzheimer's brain (left) shows extensive degeneration. It is smaller and has much less folding of the cortex than a normal brain. Will THA help restore some of the lost functions?*