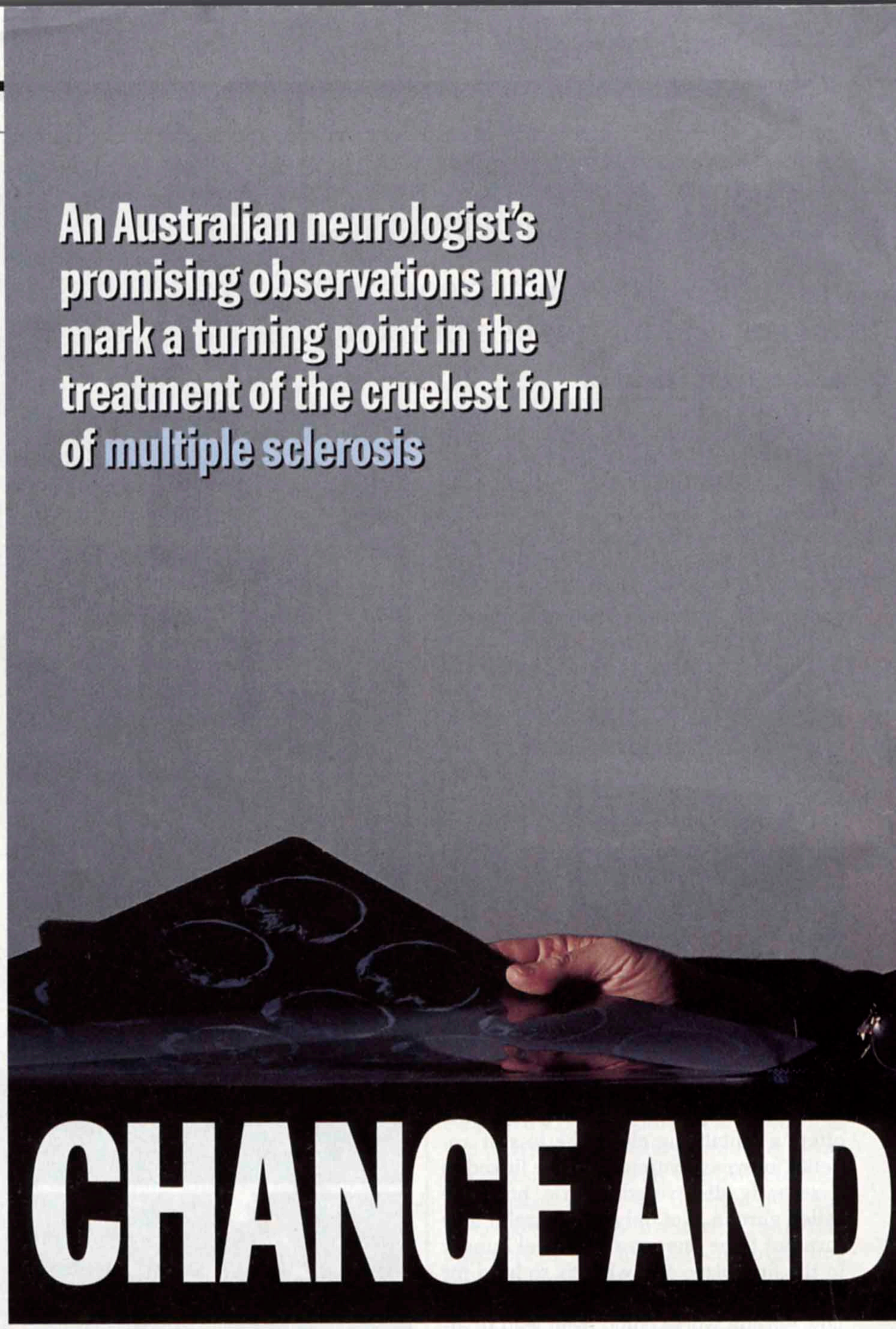
CHANCE AND

An Australian neurologist's promising observations may mark a turning point in the treatment of the cruelest form of multiple sclerosis



By **DANIEL WILLIAMS**

LATE LAST YEAR, SYDNEY NEUROLOGIST Dan Milder was running out of ideas on how to treat one of his multiple sclerosis patients. Diagnosed less than two years ago, "Samantha" was going down fast. Her vision was blurred and she was unable to see color; she was incontinent and incoherent, and her balance was so poor she was confined to a wheelchair. Milder had already advised her parents that Samantha, 28, might have to spend the rest of her life in a nursing home.

With no other goal than slowing her rate of decline—the best medicine could hope to do for Samantha's type of MS—Milder adjusted her drug regimen, combining a new MS drug with an older one. Her response stunned him. Within weeks, she was mentally sharper and her vision had improved. Within months, she was able to jog. Incredulous, Milder put another patient onto a similar program. Again the results were impressive. He tried it on a third, also with success. Last weekend, he presented his observations at a myology conference in Corfu, Greece. "Because of the dramatic and unexpected improvement in Milder's patients," says Byron Kakulas, Professor of Neuropathology at the University of Western Australia and one of the country's most distinguished medical researchers, "I support his recommendation that a controlled trial of the treatment be undertaken."

Of all the thousand natural shocks, MS is among the most dreadful. Most commonly striking women aged between 20 and 40, it stems from a betrayal by the victim's immune system, which attacks myelin, the protective sheath around nerve fibers. The myelin is replaced by plaques of hardened tissue which disrupt the transmission of signals to and from the brain and cause symptoms such as impaired vision, loss of balance and coordination, slurred speech, memory loss and, in severe cases, paralysis.

Most patients start out with a type of MS called relapsing-remitting: after an attack they recover, either spontaneously or with the help of drugs—until the next attack. But about half of these patients go on, like Samantha, to develop progressive MS, in which remissions have never been demonstrated. Indeed, many doctors consider them impossible, because they believe these patients have suffered not only myelin destruction but irreparable damage to the nerve fibers. Milder's observations challenge that view and may offer hope to many thousands of MS victims throughout the world. But experts have learned to be skeptical. "MS has had many false dawns," warns Professor George Ebers, head of clinical neurology at Oxford University.

If Milder has made a momentous discovery, it happened largely by chance. When Samantha was in bad shape last November, Milder had her on a powerful MS drug—a new immunomodulator called interferon beta-1b—and steroids. But the program wasn't working. He considered prescribing an anti-cancer drug called mitozantrone, but this can damage the heart and Samantha's family said no.

He had to withdraw the steroids because they made Samantha psychotic. For a substitute, he settled on an immunosuppressant called azathioprine, which had been superseded a few years before as the top-shelf MS drug. Azathioprine can slightly increase the risk of cancer, so Milder prescribed a low dose. He also started Samantha on a different immunomodulator, glatiramer acetate—though in hindsight he regards that switch as unimportant.

Nearly two months later, Samantha visited Milder in his surgery. She was walking and seeing colors again. Her mother reported that the improvement had begun within days of starting the new treatment. "I was very surprised," recalls Milder, who immediately began researching whether these drugs had been used together before on people with progressive MS. He could

ROB YOUNG FOR TIME

NSPIRATION

HELP AT HAND? "MS is a nasty disease that robs people of a lot of their dignity," says Milder

find no record of it. "When she came to see me in April and I was told she was able to run half a kilometer, the significance of the whole thing began to dawn on me," Milder says. "I'm not aware of any [progressive MS] patient being able to run after a period—not of months, but years—in which they have been significantly unsteady."

Milder resolved to try the drugs on "Amy," 50. Her vision was poor and she needed a stick to walk. Sometimes her legs would "freeze," she says, and she'd stand on the spot until they came back to life. She was also, says Milder, "floridly disinhibited": brain disturbances had made her uncharacteristically effusive and tactless. Milder put her on azathioprine and interferon beta-1b.

Three weeks later he visited Amy at home. In the garden, he tested her vision with cards on which numbers are indistinct against a patterned background. Her score was higher than she'd achieved for years. Later, in her lounge room, she stood unsupported on one leg. "I'd never seen her do that in the eight years I'd been treating her," Milder says. He has also observed remarkable—and rapid—improvements in balance and mobility in a third patient, a 27-year-old woman.

The events spun Milder into turmoil. It seemed incredible that two drugs—routinely used together in relapsing-remitting MS—had apparently not been tried on patients with the progressive form of the disease. More incredible to him was their apparent effect: they had "reversed deficit." The three women are not cured, he says, but they are better than he'd ever imagined they could be. "Everyone who knows her says they can't believe the improvement," says Samantha's mother. "She's our little miracle." Meanwhile, Amy's walking stick is folded up in a plastic bag in her bedroom, and she says she feels confident enough on her feet to cross the road between traffic.

Milder asked himself the necessary questions. Might these patients not have progressive MS? Had they previously been exaggerating their symptoms? Might their improvement be unrelated to the drugs? Was he seeing a placebo effect? Based on research, the patients' histories and his knowledge of the disease—built up over 20 years as a consultant neurologist—he confidently answered no to all of them. Exactly why these drugs seem to work, Milder isn't sure. But he theorizes that the onset of progressive MS, rather than being an endpoint for worthwhile treatment, may in fact be a window for a more effective drug assault that gives myelin a chance to regenerate. Perhaps, he speculates, the immune attack taking place in progressive MS is less ferocious than that in the relapsing-remitting form—and therefore easier to subdue.

Milder stresses that the treatment seems to do no more than suppress MS. (Samantha's improvement appeared to plateau after four months of treatment.) And where paralysis results from plaques on the spinal cord rather than the brain, the drugs almost certainly won't help. But if a clinical trial validates his discovery, the implications could be far-reaching. "It may be possible," Milder says, "by modifying doses and by various other permutations and combinations, to suppress the disease further."

Oxford's Ebers is open-minded. "I am of the view that everyone should be listened to in these matters, especially when there is no effective treatment for a disease. [Milder's] observations ... could form the basis for further exploration." But Ebers' reference to false dawns is hard to ignore. "Usually," he says, "these are because of overenthusiastic interpretation of small numbers of patients in uncontrolled studies of short follow-up." UWA's Kakulas is equally cautious, but believes "there is a sound neuropathological basis for recovery in Dr. Milder's patients in the form of remyelination." A saving grace of MS is that it's not a fatal disease. Sufferers can wait and see whether Milder's dawn is a real one. ■