

## Witness to a Miracle: The Initial Cortisone Trial: An Interview With Richard Freyberg, MD

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In February 1949, Philip S. Hench, MD, assembled in Rochester, Minn, a team of 5 of the most renowned clinicians in the United States to observe the effects of compound E, subsequently known as cortisone, on 2 Mayo Clinic patients with rheumatoid arthritis. Their confirmation of Dr Hench's report of the drug's astounding clinical success at the Seventh International Congress on Rheumatologists in New York City in June provided instant validation of compound E and other corticosteroid compounds. The medical miracle of the discovery and clinical trials of cortisone later resulted in the award of the 1950 Nobel Prize in physiology or medicine to Dr Hench and Dr Edward C. Kendall. Dr Tadeus Reichstein of Switzerland shared in this award.

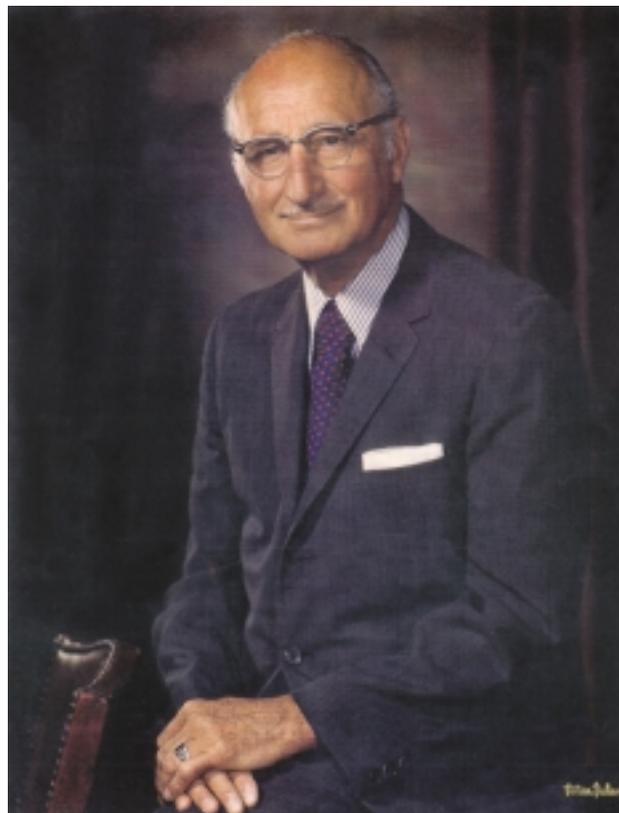
Richard H. Freyberg, MD, the last surviving visiting clinician of the initial compound E study, recalled the famous Rochester cortisone trial in an interview with Mary Ellen Warner, MD, shortly before his death in 1999.

**Mary Ellen Warner (MEW):** Richard H. Freyberg, professor emeritus at Cornell University Medical College, was born and raised in Goshen, Ind. He attended the University of Michigan, receiving his undergraduate degree in 1926, medical degree in 1930, and his postgraduate training in internal medicine and biochemistry from 1930 to 1936. More than just an ardent student, he won the 1926 Big Ten Athlete of the Year Award for his success in track and field events and also was an outstanding saxophonist. Shortly after completing his postgraduate training, Dr Freyberg was chosen to establish the Rackham Arthritis Research Unit at the University of Michigan and directed its research program until 1944. That year he moved to New York City to become director of the newly established Division of Rheumatic Disease at the Hospital for Special Surgery, chief of the Arthritis Clinic at New York Hospital, and clinical professor of medicine at Cornell University Medical College.

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Dr Freyberg

Throughout his career Dr Freyberg was actively engaged in the investigation of rheumatism. He served as president of the American Rheumatism Association in 1948 and 1949. He was a founder of the Arthritis Foundation and one of its directors for 22 years. In 1962 he received the Arthritis Foundation's prestigious Floyd B. Odlum Award. He was a Master of the American College of Physicians and honorary member of 11 international societies for rheumatic diseases.

The discovery and clinical trials of cortisone by Philip S. Hench, MD, and Edward C. Kendall, PhD, are events integral to the history of Mayo Clinic. Dr Freyberg is the last surviving member of a very close-knit team of visiting physicians who braved the cold of a Rochester winter in

1949 to participate in a unique clinical demonstration of compound E, subsequently known as cortisone. His account of this demonstration, the development and clinical introduction of cortisone, and the camaraderie among Dr Hench and his colleagues that led to the rapid acceptance of cortisone into practice provides fascinating commentary on this momentous event.

**Richard H. Freyberg (RHF):** In 1929, Dr Hench observed remarkable remission in a man with rheumatoid arthritis who developed jaundice. He speculated that an antirheumatic substance (he called it substance X) developed with jaundice, a finding he confirmed in other Mayo Clinic patients that year. One year later he noticed similar remissions in arthritic women who became pregnant. Could substance X be responsible for both? Dr Hench sought the assistance of Edward C. Kendall, PhD, chief of the Division of Biochemistry at the Mayo Clinic. Dr Kendall had found various compounds isolated from the adrenal cortex to be present in both pregnant women and patients with jaundice. He was able to produce only minute amounts of several of these compounds. Dr Hench and his associate, Charles H. Slocumb, MD, subsequently administered several of these compounds to volunteers with arthritis. Unfortunately, none produced any clinical benefit. It was unclear if the compounds didn't have clinical effects or if insufficient amounts were given to produce these effects.

That same year, Tadeus Reichstein, PhD, of Switzerland and other biochemists who were interested in compounds of the adrenal gland determined that their extraction from bile as opposed to adrenal cortex produced quantities large enough to study in multiple patients. With this information, Dr Kendall and biochemists from Merck & Company laboratories combined efforts to produce a few grams of 17-hydroxy-11-dehydrocorticosterone, a substance named compound E by Dr Kendall. These precious grams were sent to Dr Hench for clinical study.

In September 1948, Dr Hench, Dr Slocumb, and Howard F. Polley, MD, administered this compound to a volunteer Mayo Clinic patient who had rheumatoid arthritis. The resulting improvement was amazing. They administered the compound to several other patients and had similar results.

Drs Hench and Kendall and Merck & Company realized that they were witnessing a medical miracle but agreed that it had to be verified before it was reported to the public. Dr Hench agreed to arrange for a team of well-known physicians who had an interest in the study of rheumatic disease to observe the results of a clinical demonstration in Rochester. He immediately went to work organizing an event that, if successful, would result in the timely reporting of

the clinical effects of compound E at the Seventh International Congress on Rheumatologists in June 1949.

Who could he choose? I was president of the American Rheumatism Association (later the American College of Rheumatology) in 1948 and 1949 and in that position would organize the scientific program for the Seventh International Congress. It was an especially important meeting in 1949 since the congresses had been interrupted during World War II, and this meeting would be the first in a decade. Therefore, I was a logical choice to be included in Dr Hench's Rochester demonstration. He also selected Walter Bauer, MD, a pioneer in the study of rheumatic diseases from Harvard; Edward Rosenberg, MD, and Paul Holbrook, MD, respected clinicians from Chicago and Tucson, respectively; and Edward Boland, MD, a prolific investigator in rheumatic diseases from Los Angeles.

Arranging the weeklong meeting on short notice to bring together 5 busy academicians and clinicians was difficult. Fortunately Dr Hench was a close friend to each. I recall that he phoned me at the 1948 meeting of the Canadian Medical and Chirurgical Society in Montreal and so sincerely requested that I come to the phone that the meeting host came to the podium, interrupted my presentation, and urged that I speak with Dr Hench. I said, "But I'm in the middle of this presentation." He replied, "That's all right, I'll just tell them that you've been called away temporarily for an emergency call. I've got a few jokes that should hold them for a while." How could any of us argue with Dr Hench when he was so persuasive?

**MEW:** Please describe your recollections of the Rochester demonstration.

**RHF:** We all arrived at Dr Hench's home on the last Sunday in February 1949, with plans to stay for 5 days. It was an experience like no other. Dr Hench had the week's events and study materials arranged like a professor would prepare grand rounds. He turned his home into a clinic, complete with x-rays, microscopes, movie pictures of earlier treatments, and posters of his studies. After we arrived at his home on Sunday afternoon, we left only to review his volunteer patients at the Saint Marys Arthritis Clinic. A few of us ventured to the Kahler Hotel to sleep, but most stayed with Dr Hench and his wonderful family. It was a week of miraculous discovery, exchange of information, and collegiality.

The plan was for us to examine 2 volunteer Mayo Clinic arthritis patients on Monday morning and record our findings. These patients would receive injections of compound E on Monday afternoon. We'd then examine them daily until Friday. During the remainder of the time, we'd gather

at the Hench home to hear presentations on earlier studies of compound E. Between the time that Dr Hench had arranged the demonstration and our meeting, he and his colleagues had demonstrated compound E's antiarthritic effects in patients with different rheumatic or inflammatory diseases, including lupus erythematosus, rheumatic fever, and rheumatoid spondylitis (now known as ankylosing spondylitis).

That Monday we went to the Saint Marys Arthritis Clinic, at that time the only clinic in the country dedicated as a separate academic entity. We made our own examinations of the 2 patients before Dr Hench injected them with what later turned out to be huge amounts (approximately 300 mg) of compound E. It was quite a sight: 5 physicians pounding on these patients' backs, prodding their joints, and testing their extremities at the same time. Despite this near assault, the patients cooperated beautifully. They were wonderful volunteers who loved Dr Hench. During the course of 2 days, we watched them miraculously improve. Within 24 hours, we saw a generalized effect from the compound that led one to say, "I never felt so well during the time that I've had arthritis as I do now." Although we didn't see anti-inflammatory changes in the joints in that first 24 hours, the patients were able to function better. One patient had been unable to sit down into a chair without assistance. He would flop, a move later called the "Hench flop" by diagnosticians. He could sit and rise unassisted on the second day. The other patient was an old sea captain who had been unable to shave, so he'd grown a beard. On the second day, he shaved.

By the third day, we saw improvement in the inflammation of the patients' joints. Their laboratory studies improved, with profound effects such as the sedimentation rates dropping from over 100 [mm/1 h] to the 20s. However, by the fourth and fifth days, these improvements disappeared, as did the patients' general feeling of well-being. In one short week, we had seen the complete cycle of treatment response and realized that the positive impact of compound E would require prolonged treatment.

Merck & Company provided each of us with enough compound E to return to our practices and try it on our own volunteers. We were assigned to treat different forms of arthritis. For instance, I was responsible to study patients with rheumatoid spondylitis. We were asked to summarize our results in independent presentations at the Seventh International Congress and also to comment on our Mayo Clinic observations. Fortunately, all of our studies verified our observations in Rochester. Our presentations emphasized these astounding results. In his prepared discussion at the Congress, the very conservative Dr Bauer exclaimed, "Gentlemen, this is no humbug." Coming from him, that in itself was astounding.

**MEW:** What was it like living in the Hench home?

**RHF:** We were treated like family. It was a very intimate group of people. We felt right at home in the Hench house. All meals were prepared at the Kahler Hotel and sent over, or Mary Hench would have sandwiches put together while our meetings continued. It was a very exciting time; we never took time to stop and eat. Instead, we ate as we continued to talk about the demonstration, compound E, rheumatic disease, and advances in medicine in general. One after another, Dr Hench and his associates presented their findings, generating more lively discussion. The only time we weren't together was when several had to go to the Kahler Hotel to sleep because of a lack of beds in the Hench home for all of us. It was no mean feat in those days to get a room at the Kahler. However, Mary Hench was a Kahler, the daughter of the man who built the hotel. While this association earned a bed, it didn't earn single rooms. To show how close we grew during that week, I can still remember watching Dr Hench's son half walking, half crawling up the stairs to bed late one evening, his bare tail hanging out of his pajamas with his posterior flap down and his mother in hot pursuit. We really were a part of the Hench home life during our stay.

**MEW:** Did you meet Dr Kendall during your stay in Rochester?

**RHF:** Yes, on several occasions. He had been to a medical meeting and was not back in Rochester until Thursday. He was a delightful man, perhaps one of the most modest men I've ever met. Despite his many accomplishments, he took little credit for any of them. Mayo Clinic was so fortunate to have both Drs Hench and Kendall. I don't know of any 2 men who worked as closely together as they did.

**MEW:** Clearly your time in Rochester was remarkable. How did the cortisone story continue?

**RHF:** The problem of producing sufficient amounts of compound E passed soon after studies demonstrated that the starting materials for the compound's synthesis found in bile were also found in yams and other vegetables grown in subtropical areas. This finding quickly resulted in an increased supply of compound E. The Food and Drug Administration approved the compound for use in 1950. Widened use quickly led to the discovery of its toxicity.

I can best describe the toxic effects of compound E by telling a story about Dr Hench. He was a very dedicated physician. Just prior to his presentation at the Seventh International Congress, he and I were sitting in his hotel

room when he received a call from a woman who had rheumatoid arthritis and was one of the first who had received compound E. She was crying on the phone. Between sobs she told how miserable she was, feeling persecuted, suffering delusions, and unable to sleep. This phone call had a profound effect on Dr Hench. Before I knew it, he was crying, "What have I done to this patient?" I am convinced that this phone call influenced the tone of his presentation that day. He cautioned the listeners to be alert for toxic effects, calling for careful scrutiny of patients and their complaints after they had received the drug.

The toxic effects of cortisone are now well known, but back then we were just about to discover the problems of accumulation of fat on the neck and face, double and triple chins, facial hair in women, and hair loss. It wasn't too much later that we began to prescribe wigs for women at the same time that we started treatment with cortisone. These problems were uncomfortable but tolerable. Several severe effects required stopping the medication altogether. Gastrointestinal ulcers and severe osteoporosis were sometimes life threatening. It became clear that complete remission of rheumatoid disease with cortisone rarely would be possible. Instead, cortisone would need to be used for partial remission, balanced against major toxic effects.

This problem with toxicity led to a huge effort to develop improved corticosteroids. Chemical substitutions on cortisone, such as the addition of fluorides, greatly increased the potency of the drugs and reduced toxicity. Nevertheless, side effects continue to limit our ability to treat rheumatoid disease with cortisone derivatives. The search for the ideal corticosteroid continues today.

**MEW:** You and Dr Hench obviously were close colleagues. Did you know many of the other Mayo Clinic physicians who were interested in rheumatic diseases?

**RHF:** Dr Hench and I were very close friends. His encouragement was the most stimulating mentorship in my professional life, and I will always be very grateful to him for it.

Mayo Clinic had many outstanding physicians who chose rheumatic diseases as their specialty. As I recall, residents at Mayo Clinic were given the opportunity to choose elective rotations in some specialties in internal medicine during their training, and many chose rheumatic diseases. This exposure and the high quality of their interactions with Drs Hench, Slocumb, Polley, and others was responsible for a large number entering the specialty. Often the best and brightest stayed on at Mayo Clinic. Other outstanding physicians were chosen to chair rheumatic disease divisions in medical schools across the country. Mayo Clinic obviously had a major impact on the specialty. All the Mayo Clinic physicians involved in this cortisone story later became presidents of the American Rheumatism Association. They were very highly respected. I valued each as a close colleague and outstanding physician.

**MEW Addendum:** Ten months after this interview, Dr Richard Freyberg died on January 23, 1999, at 94 years of age. He was an extremely gracious, talented man who served medicine and humankind well during his 48 years of caring for patients. He was a staunch supporter of academic medicine and a true friend of Mayo Clinic.

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