HELPING HANDS

Collagen injections could soon treat Dupuytren's disease

With their research spanning nearly 20 years and results showing promise for a new method to treat Dupuytren's disease, **Lawrence C. Hurst, M.D.**, **Marie Badalamente, Ph.D.**, and **Edward D. Wang, M.D.** received the 2009 OREF Clinical Award.

Photo Courtesy of AAOS

(l-r): Thomas A. Einhorn, M.D. presents the 2009 OREF Clinical Award to Lawrence C. Hurst, M.D., Marie Badalamente, Ph.D., and Edward D. Wang, M.D. ▶

NAVIGATING OPTIONS TO TREAT DUPUYTREN'S DISEASE

Their work on "Injectable Clostridial Collagenase: Striving toward non-operative treatment for fibroproliferative disorders" has led to a new minimally invasive method for treating Dupuytren's disease, which may soon be approved by the Food and Drug Administration (FDA). The OREF Clinical Award recognizes this achievement.

"I spent my career as an academic surgeon, so it's nice to have people say, 'you've done a good job and we respect what you've accomplished,'" said Dr. Hurst, professor and chairman of the Department of Orthopaedics, and chief, Division of Hand Surgery at Stony Brook University Medical Center, Stony Brook, NY.

The OREF Clinical Award, administered by the American Academy of Orthopaedic Surgeons (AAOS), and supported by Kappa Delta Sorority, recognizes outstanding clinical research related to musculoskeletal disease or injury. Recipients, who must be members of the AAOS, the Orthopaedic Research Society (ORS), the Canadian Orthopaedic Association or the Canadian ORS, or sponsored by a member of one of these groups, submit original manuscripts to be considered for the award. Winners receive $20,000.

"Dupuytren's disease is not cancer. It's not polio. But most senior hand surgeons find that in badly afflicted patients, surgery is quite arduous and they're looking forward to having a simpler way to help their patients," said Dr. Hurst.

EARLY COLLAGENASE TESTING

Dr. Hurst began his research career in the early 1980s investigating nerves, but that was not to be his only focus. "My chair at Stony Brook at the time said, 'You're a hand surgeon. You have to do something on Dupuytren's disease. All hand surgeons research Dupuytren's surgery,'" he explained.

Dr. Hurst began collaborating with Dr. Badalamente, professor of research orthopaedics at Stony Brook University Medical Center, by analyzing specimens from Dupuytren's disease patients under a microscope. When they attended an instructional course lecture presented by the late **Robert M. McFarlane, M.D.**, a renowned Dupuytren's disease researcher and past president of the American Society for Surgery of the Hand, Drs. Hurst and Badalamente asked him to review their research. Encouraged by Dr. McFarlane's enthusiasm for their results, Drs. Hurst and Badalamente published several articles on Dupuytren's disease in *The Journal of Hand Surgery and Hand Clinics*, among other journals. In 1985, they received an OREF Research Grant for Dr. Hurst's project: "The Pathology of Dupuytren's Contracture: Effects of Prostaglandins on Myofibroblasts."

It was Dr. Hurst's nerve research, however, that first piqued the interest of a small start-up, Biospecfics Technologies Corp. (BTC), that was manufacturing a compound of the enzyme collagenase. **Mr. Thomas L. Wegman**, the CEO and part-owner of the company, hoped Dr. Hurst could use collagenase to help prevent scarring, which causes pinching when nerves are repaired.

"I said, 'But you need the scar to stick the nerve together,'" Dr. Hurst recalled. "'So if you use too much you're going to be in trouble. But I'm investigating another disease, Dupuytren's, where the collagenase could be helpful.'"

Drs. Hurst and Badalamente began researching Clostridial collagenase by injecting cords removed during complete fasciectomies, with a small amount — 500 units — of collagenase, and incubating them in a petri dish overnight. The next day the researchers placed the injected cord in an Instron — a tensile testing machine — to learn how much force it would take to break a cord.

"We showed very quickly that the cord would pull apart with almost no force at all. Sometimes you would hardly get it in the clamps and it would fall apart," Dr. Hurst explained.

FINDING THE RIGHT DOSE

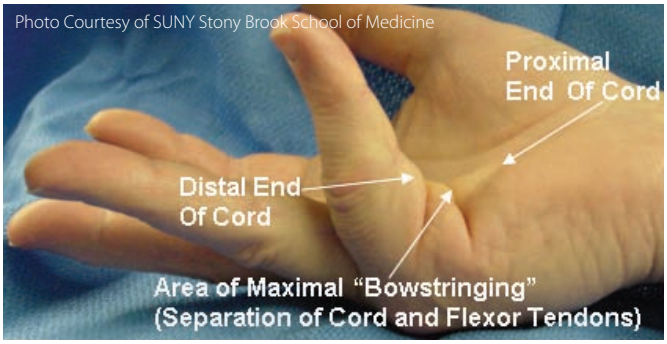
Based on these laboratory findings, Dr. Hurst applied for an Investigational New Drug (IND) number from the FDA, and received approval to test the collagenase compound on humans. Drs. Hurst and Badalamente developed an open-label study and started by injecting 500 units — the same amount that had worked in the lab — into Dupuytren's disease patients' hands. Nothing happened.

"Dr. Badalamente kept saying, 'we need to increase the dose,' but I kept thinking, if we do that we're going to watch the hand melt. But we became convinced that we could raise the dose safely because 12,000 units of the same compound had been injected once a day for three days to treat another disease."

To change the dosage, Dr. Badalamente applied to the FDA to receive permission for a dose escalation curve. Dr. Hurst would begin by injecting 400 units, then double to 800, then again to 1,600, and continue doubling until he found the effective amount without causing harm.

"In one of those early cases, I injected the patient and when he returned the next day, I'd planned to manipulate the fingers to try to break the cord," said Dr. Hurst. "I went to just shake his hand and the cord popped. He said it hurt, but he could straighten his fingers and he was as happy as a clam."

Dr. Hurst explained that the smaller dose didn't work because the living tissue contained some inhibitors to the drug that were not present in the dead tissue they'd tested in the lab. The higher dose overcame these inhibitors.



After finding 10,000 units of collagenase to be a successful dose, Dr. Hurst tested patients by injecting them on Mondays and pulling on their fingers on Tuesdays, watching for the cord to break under the skin.

> "...COLLAGENASE INJECTIONS WORK TO TREAT DUPUYTREN'S DISEASE WITH FEW COMPLICATIONS."

COLLAGENASE SUCCEEDS

Once they'd established the dose, Drs. Hurst and Badalamente continued to test patients and showed good results at 10,000 units. Dr. Hurst would inject the patients on Mondays, and on Tuesdays he would pull on their fingers and watch the cord break under the skin. To ensure he wasn't breaking anything that should remain intact, Dr. Hurst did not give patients anesthetics, allowing their pain to be a guide to the amount of force applied during manipulation. According to Dr. Hurst, the cords usually broke just before the threshold where he felt he should stop, although there were some cases in which cords broke before patients even returned for the second part of the treatment.

Based on the promising results, Drs. Hurst and Badalamente wrote a double-blind, prospective, randomized study for which they received funding and approval from the FDA in the 1990s. They injected patients and continued testing the collagenase at Stony Brook University Medical Center, and **Vincent R. Hentz, M.D.**, professor of orthopaedic surgery at Stanford Hospitals and Clinics, Stanford, Calif., applied the treatment to his patients as well. The Clostridial collagenase continued to succeed, and in the 2000s, the researchers wrote a Phase III clinical trial protocol for the FDA, but their research was delayed.

TWO STEPS FORWARD...

For Drs. Hurst, Badalamente, and Wang, the OREF Clinical Award came after overcoming a plethora of obstacles. A large turnover at the FDA meant their proposal was given to a new group that wasn't satisfied with the protocol, requiring the research team to revise it and resubmit it for review.

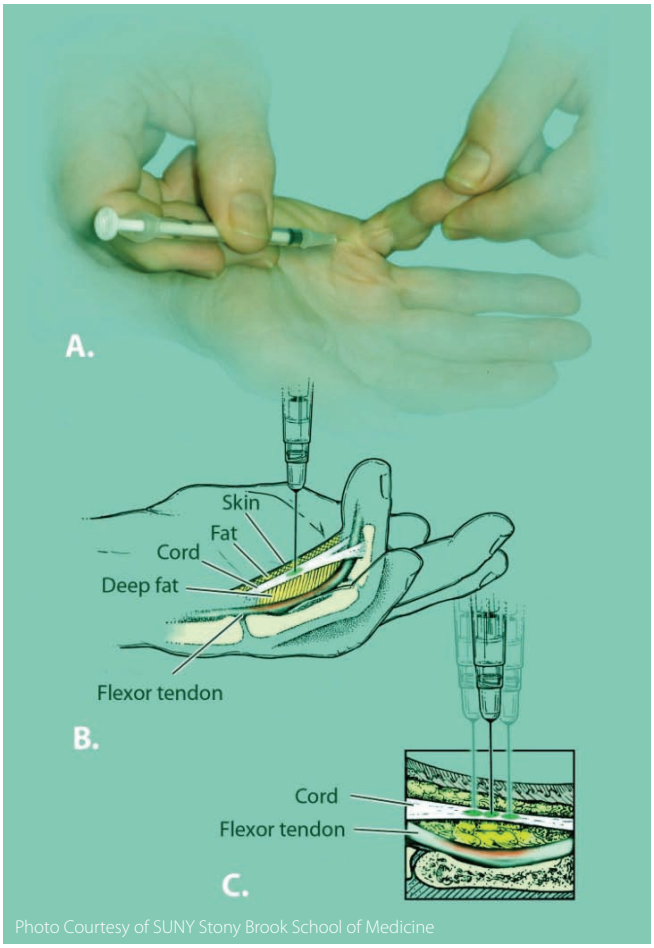


Photo Courtesy of SUNY Stony Brook School of Medicine

▲ **Non-operative treatment for Dupuytren's disease:** Dr. Hurst and Dr. Badalamente's research on injectable Clostridial collagenase shows promise for a non-operative method to manage Dupuytren's disease. This new minimally invasive treatment may soon be approved by the FDA.

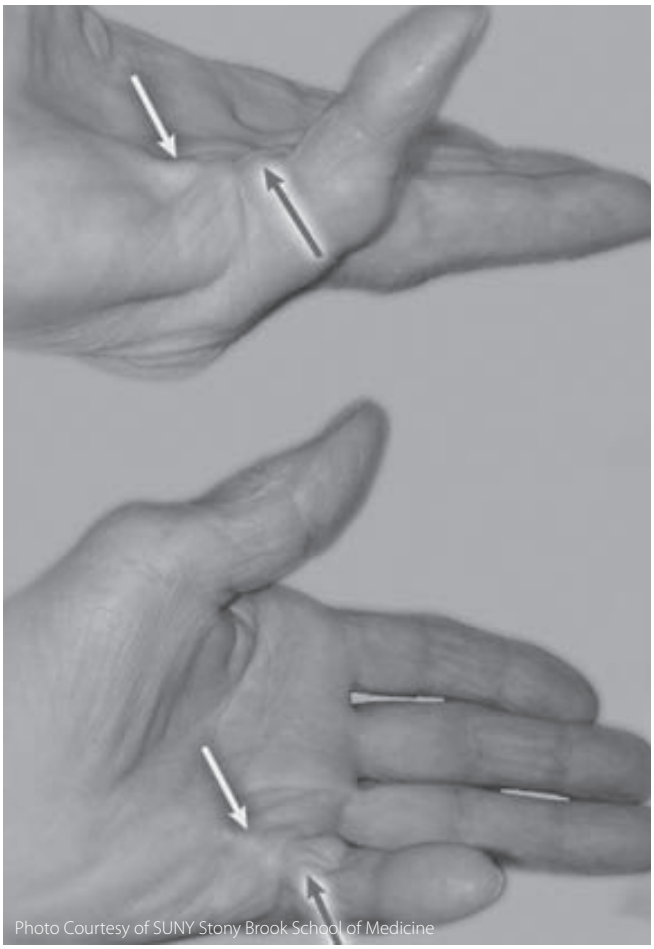


Photo Courtesy of SUNY Stony Brook School of Medicine

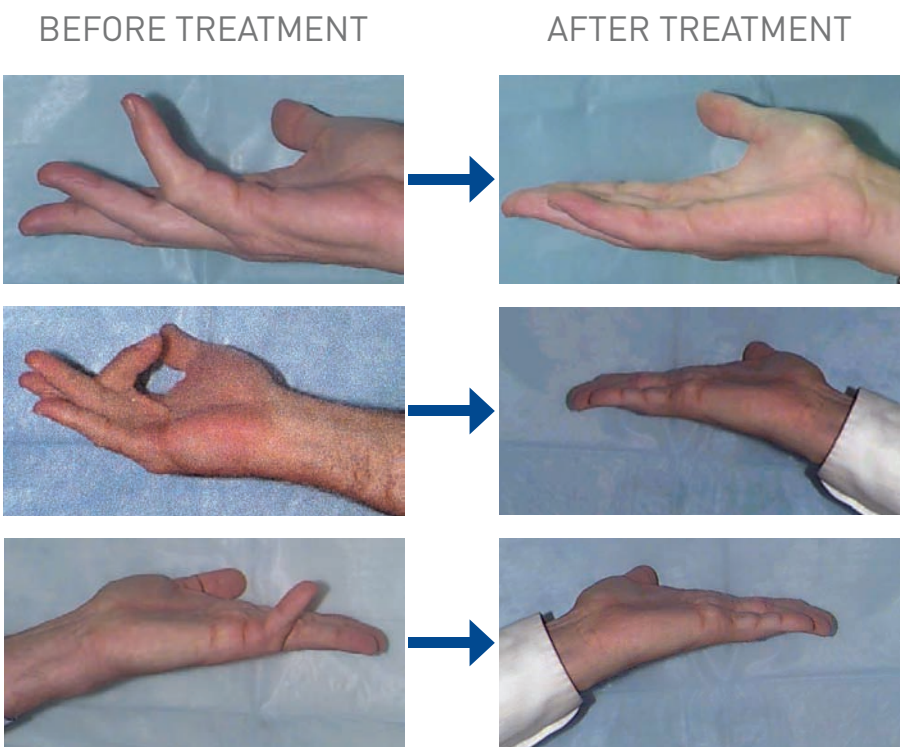
▲ Dupuytren's disease clinical appearance and pathoanatomy: Dupuytren's Disease occurs when the connective tissue in the hand contracts, thickens and shortens, developing into cords that prevent its sufferers from straightening their fingers. It begins as a sometimes painful lump (Dupuytren's nodule), and as the disease progresses, the tissue continues to contract the fingers.

The slow approval of the Phase III protocol wasn't the only obstacle. BTC, the company producing the collagenase compound, wasn't able to keep up with demand and sold its rights to another company, Auxilium, while the University of New York at Stony Brook retained the IND. Because a new company was manufacturing the compound, the researchers had to prove to the FDA that Auxilium's compound was exactly the same as BTC's.

WHEN IT RAINS...

After establishing the manufacturing process, Dr. Hurst and his research team ran into yet another roadblock. They received the collagenase compound as a lyophilized cake, similar in appearance to Styrofoam. They would add dilutin, essentially saline according to Dr. Hurst, and use the resulting solution for the injections. Some of the vials they received, however, appeared to have half the amount of the compound, though once diluted it acted exactly the same as the "full" vials. Auxilium decided that the cause should be determined and fixed before proceeding. Upon investigation, Drs. Hurst and Badalmente learned that moisture was seeping into the vials and diluting the compound, making it look like less, although the vials still contained the same dosage. Once this problem was resolved, the FDA and Institutional Review Board (IRB) finally approved the Phase III clinical trial.

Within the United States, 16 sites participated in the double-blind, randomized controlled study — termed the



Photos Courtesy of SUNY Stony Brook School of Medicine

Before and after: The Cord I Collagenase Study, double-blind, randomized, controlled investigation showed that collagenase injections work to treat Dupuytren's disease with few complications. Currently a Cords II Collagenase Study is taking place in Australia, where five sites are testing the drug. Within the IRB-approved study, more than 2,700 patients have been injected with good results, prompting the collagenase production company, Auxilium, to submit a Biological Licensing Application to the FDA.

Cord I Collagenase Study — which had a placebo ratio of two to one, meaning out of 300 patients, 200 would receive the drug rather than a placebo. Patients entering the study received a consent form and education to explain the treatment and the possibility that they would receive the placebo instead of the real drug. If they did not respond to treatment, they were allowed to enter the open-label study after some time had passed.

PATIENTS FLOCK TO PARTICIPATE

"We've been at this so long that patients Google the research and ask to be part of the study. I've had patients who've had perfect surgical results on one hand, but have contracture on the other and I ask, 'Why are you here; why don't you just have the surgeon operate on the other hand?' They say, 'I know somebody who was in one of your research studies and I want it because it's simpler,'" Dr. Hurst explained.

There may be a good reason Dupuytren's disease patients hope to participate in the research study.

"The trial showed quite conclusively that collagenase injections work to treat Dupuytren's disease with few complications," Dr. Hurst said. "We had two tendon ruptures, which were scary, but we modified the protocol to instruct doctors where exactly to place the injection. If you put it in the wrong place, you can harm the tendon. Since we changed the protocol, we haven't had any more problems."

Currently, a Cords II Collagenase Study is taking place in Australia, where five sites are testing the drug. According to Dr. Hurst, within the IRB-approved study, they have now injected more than 2,700 patients, and continue to show good results for patients who receive the real drug rather than the placebo. Auxilium, the company now producing the collagenase, has submitted a Biological Licensing Application to the FDA, which has 6 to 18 months to approve, reject, or request modification and further testing. If approved, Clostridial collagenase will be available to treat Dupuytren's disease.

Said Dr. Hurst, "Our FDA is extremely good at making sure drugs work and that they're safe. What they do is important, but the process is arduous."

RESEARCH HELPS EVERYONE

Despite the long process, Dr. Hurst said that being an educator, researcher, and clinician is rewarding. He enjoys teaching doctors because he helps them help their patients.

"Research is rewarding because it allows us to take something from the bench to the clinical laboratory, to the General Clinical Research Center [at Stony Brook University

Medical Center], use it, and then produce a product that will hopefully go on for years helping patients after I'm no longer practicing," he said.

In fact, Dr. Wang, associate professor of hand and general orthopaedic surgery at Stony Brook University Medical Center, and Dr. Badalamente have investigated whether collagenase may be useful in another clinical application: treating frozen shoulder.

And research, as Dr. Hurst indicated, is important for all clinicians to support.

"If you're a clinician, practicing and caring for patients, and making a living doing so, you're using tools — whether it's an implant or a drug — that wouldn't be there if research hadn't been done, and research couldn't be done if seed money weren't available."

Providing seed money, Dr. Hurst said, is OREF's strength. According to Dr. Hurst, it encourages young investigators to continue with their research and allows them to gather data that lead to substantial support from larger funding bodies such as the National Institutes of Health (NIH) and the FDA.

"As competitive as the NIH is, you cannot apply for funding with one research credit on your CV and a really great idea," Dr. Hurst explained. "You have to request funding with a very strong application based on strong preliminary data, and you can't get data without initial funding, whether it's from your university or from OREF." ■

ABOUT
DUPUYTREN'S DISEASE

Dupuytren's, believed to be a hereditary disease, occurs when the connective tissue in the hand contracts, thickens, and shortens, developing into cords that prevent its sufferers from straightening their fingers. It begins as a lump (Dupuytren's nodule), which is sometimes painful, and often, according to Dr. Hurst, patients seek treatment because they suspect cancer. As the disease progresses, the tissue continues to contract the fingers, making everyday tasks such as grasping a glass, placing the hand in a pocket, or shaking hands difficult or even impossible.

Patients suffering from Dupuytren's disease have several treatment options. For those in the early stages, steroid injections can soften the lumps and reduce tenderness, but additional injections may become necessary if the disease progresses. Radiation, which has been used in Europe but not the United States, can slow the disease process, but long-term effects are unknown. A minimally invasive procedure, called a needle fasciotomy, employs a needle to break the cord that's preventing the patient from straightening his or her fingers, but this may cause nerve complications and recurrence is also a problem.

Surgical treatments include: subcutaneous fasciotomy, where the cord is broken with a scalpel rather than a needle; partial fasciectomy, which removes enough tissue to correct the contracture but does not remove all pathological tissue; or complete fasciectomy which is the complete removal of the palm tissue, and possibly skin grafting. These methods may not prevent recurrence, and could lead to further complications, especially complete fasciectomy, which has the highest risk for stiffness and could permanently prevent the fingers from bending. For patients who suffer from severe recurrences of the disease after several surgeries, amputation — usually of the little finger — may be needed but is rare.