Original Communications

Enzyme Injection as Nonsurgical Treatment of Dupuytren's Disease

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Surgical fasciectomy is the currently accepted treatment of Dupuytren's disease. The goal of this study was to test the clinical safety and efficacy of clostridial collagenase injection as a nonsurgical treatment of Dupuytren's disease in a phase II open-label trial. Thirty-five Dupuytren's disease patients entered the study (32 men and 3 women). The mean age was 65 years. The first 6 patients were treated following a dose escalation protocol and received 300, 600, 1,200, 2,400, 4,800, and 9,600 U collagenase injected into the cord that was causing contracture of the metacarpophalangeal (MCP) joint. There were no beneficial clinical effects of these injections. The remaining 29 patients had collagenase injections at a dose level of 10,000 U, causing contractures of 34 MCP joints, 9 proximal interphalangeal (PIP) joints, and 1 thumb. Twenty-eight of the 34 MCP joint contractures corrected to normal extension (0°) and 2 of the 34 MCP joint contractures corrected to 5° of normal extension, with full range of motion, within 1 to 14 days of injection. In the patients with PIP joint contractures, 4 of the 9 joints corrected to normal (0°). One PIP joint corrected to within 10° of normal and 2 corrected to within 15° of normal. There were 2 failures; these patients will require surgery. The mean follow-up period was 20.0 ± 5.6 months for the MCP joints and 14.1 ± 6.6 months for the PIP joints. Clostridial collagenase injection of Dupuytren's cords causing MCP and PIP joint contractures appears to have merit as nonsurgical treatment of this disorder. Pending further placebo, double-blind studies, collagenase injection to treat Dupuytren's disease may be a safe and effective alternative to surgical fasciectomy. (J Hand Surg 2000;25A:629–636. Copyright © 2000 by the American Society for Surgery of the Hand.)

Key words: Collagenase, enzymatic fasciectomy, Dupuytren's disease.

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Since its first recognition in the early European medical literature by Plater in the 17th century,[1] only surgery has proven successful in the treatment of Dupuytren's disease. A number of nonsurgical interventions have been tested without clinical success.[2–11] Given the acceptance of surgical treatment, why should other therapeutic approaches be considered? First, surgery does not "cure" Dupuytren's disease. While it is true that patients with metacarpophalangeal (MCP) joint contractures are usually satisfied after surgery, those with proximal interphalangeal (PIP) joint contractures frequently find that surgery does not provide complete extension of the finger. Recurrence rates are also reported to be quite high, ranging from 26% to 80%.[12,13] Recurrence also can be associated with initial con-

tracture severity, Dupuytren's diathesis, advanced disease state, and presence of associated diseases, such as diabetes, epilepsy, or alcoholism.[14]

A second reason for pursuing nonsurgical treatment for Dupuytren's disease is patient satisfaction. Patients often express satisfaction in terms of surgical correction but are not always satisfied in terms of overall surgical process. Common patient complaints relate to time out of work, having to endure the surgery itself, being in pain after surgery, having limited use of the hand for activities of daily living, and sometimes prolonged and extensive postoperative therapy. These patients are clearly looking for a valid and simple treatment alternative.

Many nonsurgical treatments have been investigated but have proven ineffective. These have included such therapies as radiation, dimethyl sulfoxide, massaging with vitamin E cream, physical therapy, ultrasonic therapy, steroids, anti-gout medications, and interferon-γ.[2–11]

Enzyme fasciotomy was first used in an attempt to rupture Dupuytren's cords in 1969.[15] This study was repeated by Hueston[15] in 1971 using a mixture of trypsin, hyaluronidase, and lidocaine. This treatment was conducted during surgery and Hueston[15] reported full passive extension in all patients 15 minutes after injection. The study provided no long-term results, however. McCarthy[16] also reported the injection of Hueston's enzyme mixture in 14 patients with Dupuytren's disease and noted recurrence in the initial preoperative deformity in 75% of the study subjects at 2 to 3 years after injection. He concluded that there was a similar rate of recurrence with both surgery and the enzyme fasciotomy, but believed there was a greater morbidity in the enzymatic fasciotomy and abandoned it as offering no advantage over surgery. Enzyme fasciectomy using collagenase, whose specific substrate is collagen, may offer an advantage over less-specific enzymes in treating Dupuytren's cords.

The purpose of this study was to test the clinical safety and efficacy of clostridial collagenase injection as a nonsurgical therapy to rupture Dupuytren's cords in a phase II open-label trial.

Materials and Methods

Thirty-five Dupuytren's patients entered the study, 32 men and 3 women with a mean age of 64.8 $\pm$ 11.0 years. One patient was lost to follow-up due to unrelated medical reasons. Our prior laboratory studies using both cord tissue obtained at surgery and an *in vivo* animal model indicated that a dose of 300 U collagenase might be safe and sufficient to cause cord rupture.[17,18] Therefore, the first study patient received a 300-U collagenase injection into the cord, that was causing MCP joint contracture. This failed to cause cord rupture and a dose escalation protocol was then used. The next 5 patients received 600, 1,200, 2,400, 4,800, and 9,600 U collagenase, respectively, injected into the cord that was causing contracture of the MCP joints. One patient who had no benefit in the dose escalation study entered the following phase of the study.

The remaining 29 patients, including 34 MCP joints, 9 PIP joints, and 1 thumb cord, had collagenase injections (Figs. 1, 2) at a dose level of 10,000 U followed by a 10- to 12-hour period of hand immobilization in a soft bulky gauze dressing. After this period there was no further immobilization. The 10,000 U collagenase was delivered in 0.25 mL for MCP joints and 0.20 mL for PIP joints using a sodium/calcium diluent and an insulin syringe. Eighteen right hands and 16 left hands were treated. For MCP joints, 10 little fingers, 20 ring fingers, 4 long fingers, and 1 thumb were involved. For PIP joints, 6 little fingers, 1 ring finger, and 2 long fingers were involved. Thirteen patients had multiple finger/joint involvement. Each joint was treated separately.

Before each injection ultrasound was used to visualize the underlying flexor tendon of the affected finger and to measure the depth from the skin to the surface of the flexor tendon sheath (Fig. 3). This was done to identify a safe zone between the skin and flexor tendon sheath to avoid inappropriate injection of the tendon. Ultrasound was not used to guide injections but it was used to ensure that only the cord was injected, even though the cord is easily visualized and palpated. There were no tendon injections in any patient.

Patients were seen the following day, when passive extension, within the patient's pain tolerance, was applied to rupture the cord. No local anesthetic was used when attempting cord rupture; the patients tolerated this well. If cord rupture did not occur on the day after the injection, the patients were instructed to apply extension force themselves. On the day after the injection the patients were fitted with a night extension splint that was worn for 4 months. All patients were instructed to do extension exercises at home. Daily vitamin E massage for 4 months was suggested to keep the treatment area soft and pliable. Serial follow-up examinations occurred on days 7 and 14 and at months 1, 2, 3, 6, 9, and 12. Patients are examined annually for 2 to 5 years after injection.

Fifteen patients required repeat injections: 6 pa-

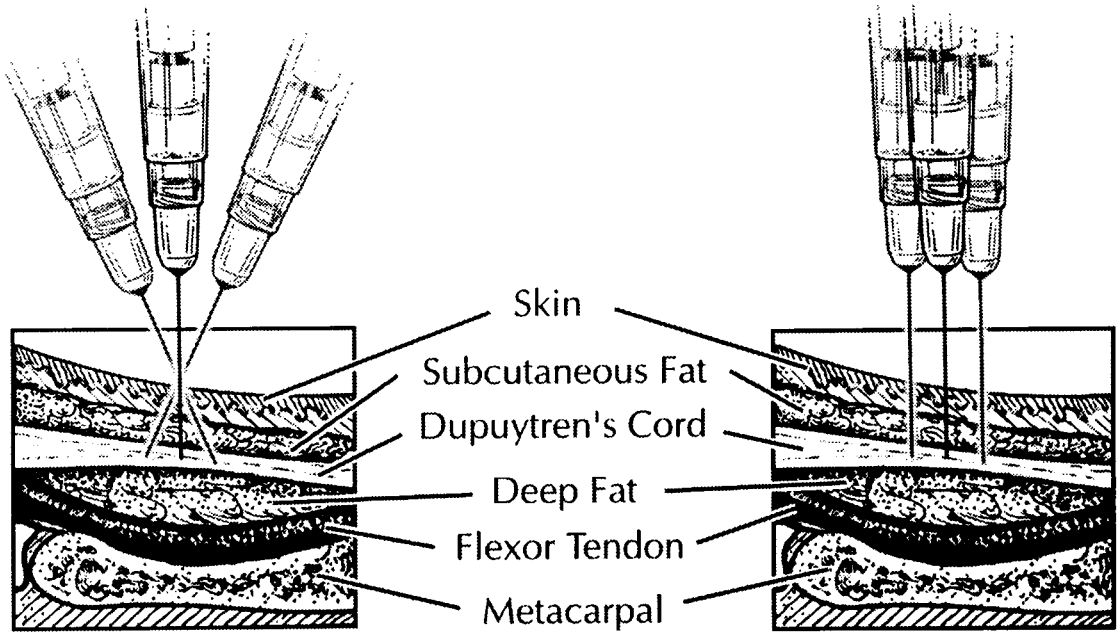

Figure 1. Cord injection using an insulin syringe. Injection of the flexor tendon must be avoided. With the needle in the cord, injection is gentle and slow. Part of the volume (0.25 mL for MCP joints and 0.20 mL for PIP joints) is put in 3 different, but closely adjacent, positions to avoid forcing liquid through the cord and into the deep fat over the flexor tendons. (Reprinted with permission.[19])

tients received 2 injections, 5 received 3 injections, 2 received 4 injections, 1 received 5 injections, and 1 received 6 injections. Repeat injections were scheduled if the joint angle did not correct to 0° to 5°. Repeat injections were given 4 to 6 weeks apart. Finally, to assess possible allergic effects to collagenase injection(s), serial immune titers of serum immunoglobulin E were performed at all follow-up intervals, excluding days 1 and 14. As a safety measure, before repeat injections, patients who showed a serum immunoglobulin E titer between 1 and 15 ng/mL were given an allergy scratch test using a Dermapik (Greer Labs Inc, Lenoir, NC) and 1:100 and 1:1,000 of 10,000 U collagenase. The presence of a red wheal indicated a positive scratch test. Fourteen patients had a scratch test; none had a positive result.

Before treatment all patients signed written, informed consent. This project was reviewed and approved by the SUNY Stony Brook Institutional Review Board and was conducted under an investigational new drug number from the US Food and Drug Administration, Center for Biologics Evaluation and Research.

Results

In the first 6 patients treated under the dose escalation protocol, the mean degree of initial MCP joint contracture was 49° ± 11°. Collagenase injection had no effect in reducing the degree of MCP joint contracture and failed to rupture the cords in these patients.

In the remaining 29 patients the mean degree of initial MCP joint contracture was 42° ± 13° (range, 20° to 79°). The mean degree of initial PIP joint contracture in the 9 patients treated was 52° ± 16° (range, 30° to 79°). Table 1 details the spectrum of contractures in all patients.

Twenty-eight of the 34 MCP joints treated with 10,000 U collagenase (82% of the patients) achieved full extension to 0° with full range of motion (Figs. 4, 5). One patient had correction of both the left long and ring MCP joints to within 5° of normal extension. There were 2 failures. One patient with a ring finger MCP joint contracture of 30°, despite receiving 6 injections, needed to undergo surgical fasciectomy. The other patient, who had little and ring finger MCP joint contractures of 95° and 65°, respectively, achieved a correction to only 40° in each of these joints. The patient with the thumb cord achieved correction from 45° to 10°. There were recurrences in 3 fingers at 2 years after injection. One patient had an initial 40° ring finger MCP joint contracture. The recurrence was to 25° at 2 years. The other patient had initial contractures of 55° of the right long finger MCP joint and 30° of the left ring MCP

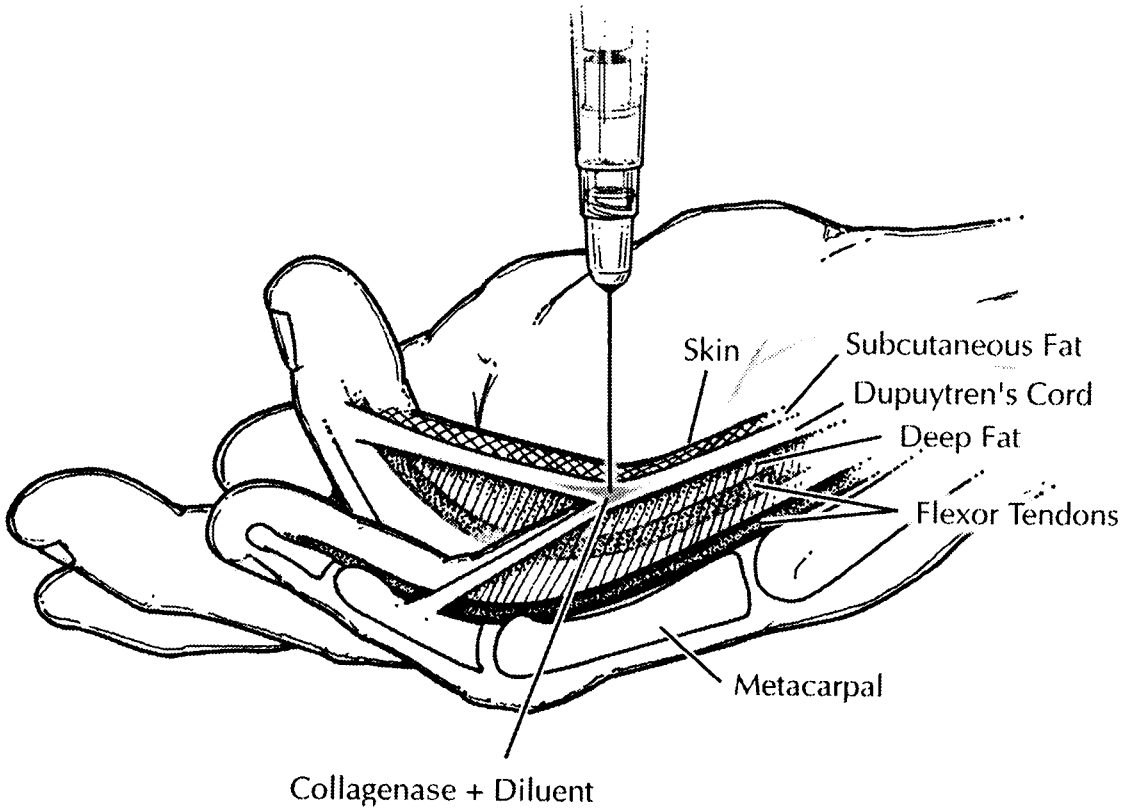

Figure 2. Cord injection. If a patient has a Y-shaped cord, created by a combination of a central and natatory cord, the point of the Y should be injected. Injection of this site may result in simultaneous correction of adjacent finger MCP joint contractures. (Reprinted with permission.[19])

joint. His left ring MCP joint recurred to 20° and the right long MCP joint recurred to 10°. The mean follow-up period in the 29 patients who received 10,000 U collagenase injections was 20.0 ± 5.6 months.

In the 9 patients who received injections into the cord causing PIP joint contractures, 4 (44%) achieved full extension to 0° with full range of motion (Fig. 6). One patient corrected to 10° of full extension and 2 patients corrected to 15° of full extension. Two patients failed and required surgery. The mean follow-up period in these 9 patients was 14.1 ± 6.6 months.

Metacarpophalangeal cord rupture was achieved at day 1 in 15 cases, at day 7 in 13 cases, and at day 14 in 6 cases. Correction of PIP joints occurred within the first 2 weeks of injection. Two joint corrections were also achieved simultaneously in 11 fingers. These consisted of MCP/PIP joint contractures of the same finger in 7 fingers and MCP/MCP joint involvement of adjacent fingers in 4 fingers. In the case of MCP/MCP joint corrections of adjacent fingers, the initial Y-shaped cord consisted of a pretendinous and natatory cord.

There were no major adverse reactions in any patient. Minor local adverse reactions included tenderness to pressure at the injection site with minimal palmar, and sometimes dorsal, edema and minimal hematoma. Six patients with only PIP joint contractures experienced ulnar border forearm tenderness with elbow and axilla lymphadenopathy after injection. All symptoms resolved within 1 to 2 weeks of injection. In subsequent ongoing studies, some patients with MCP contractures also had this effect; therefore, it does not appear to be confined to patients with PIP joint contractures. There were no skin ulcerations or tendon ruptures. Thirteen of 15 patients who had multiple injections showed serum titers of immunoglobulin E without adverse clinical effects. These titers decreased over time.

Discussion

The results of this study have shown that clostridial collagenase injection of Dupuytren's cords causing MCP and PIP joint contractures has merit as a nonsurgical treatment of this disorder. In a pilot dose escalation phase of this study, we determined that 10,000 U collagenase was a clinically safe and effective dose for inducing cord rupture in both MCP

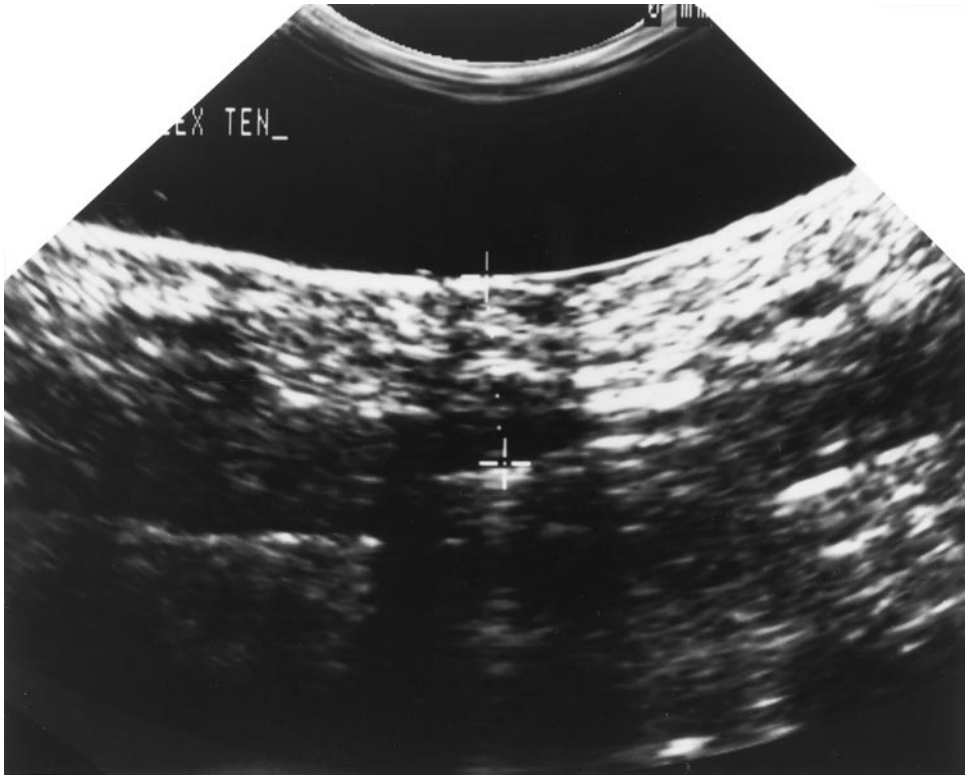

Figure 3. Ultrasound of the MCP joint. The actual structures are not well delineated. The flexor tendons are located deep to the lower cross hairs. Tendon motion is easily seen in real time. The cord is located between the cross hairs. (Reprinted with permission.[19])

and PIP joints. Twenty-eight of the 34 MCP joint contractures corrected to 0° with full range of motion and 2 of the 34 MCP joint contractures to 5° of normal extension. This constitutes a success rate of 88%. An additional unexpected, but encouraging, finding in this study was that 8 patients had multiple finger corrections after collagenase injection, 4 having MCP/PIP correction of the same finger and 4 having MCP/MCP correction of adjacent fingers. In the case of MCP/PIP joint contractures, it appears that release of the pretendinous cord was sufficient to induce this result. In the MCP/MCP cases involving adjacent fingers, the injection was placed at the Y intersection point of the pretendinous and natatory cords.

Table 1. Joint Involvement

Contracture (°)	*No. of Joints*
MCP joint	
20–29	3
30–39	12
40–49	6
50–59	7
60–69	5
70–79	1
PIP joint	
30–39	2
40–49	3
50–59	1
60–69	1
70–79	2

There were 3 recurrences of MCP joint contractures at 2 years after injection and 1 recurrence of PIP joint contracture at 3 months after injection. It is reasonable to anticipate that some patients with MCP and PIP joint contractures will recur with the passage of time. In the development of this nonsurgical injection therapy and many discussions with our patients, however, it is apparent that the prospect of reinjection for a recurrence is much less troublesome to patients than the prospect of having to undergo additional surgery.

Of the 9 PIP joint contractures treated with collagenase injection, 4 corrected to 0°, 1 corrected to 10° of normal extension, and 2 corrected to 15° of normal extension. These patients were very pleased with

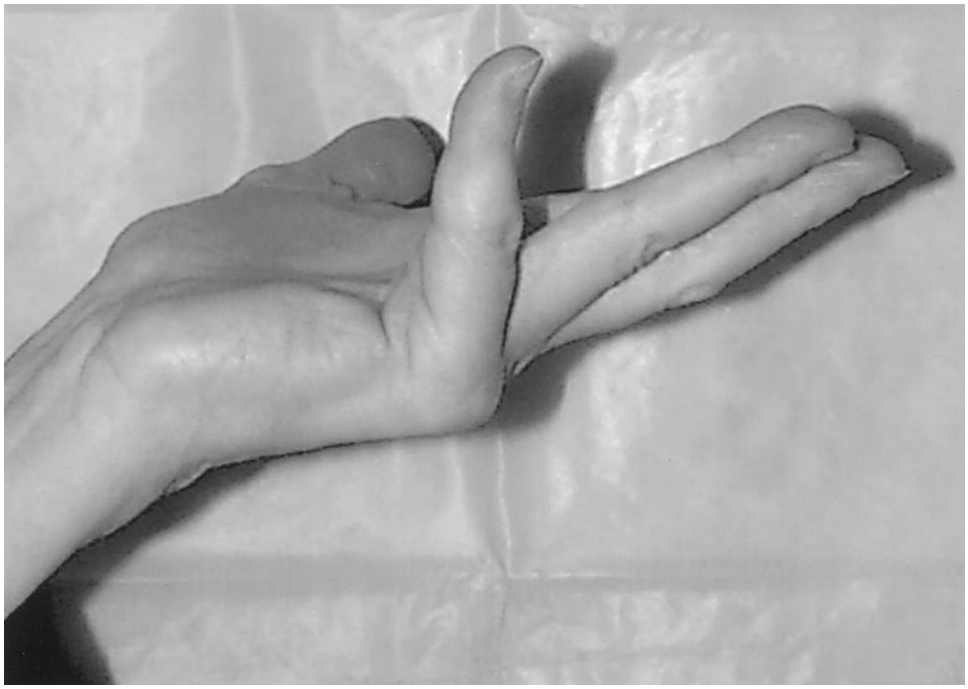

Figure 4. A patient with a left little finger MCP joint contracture of 75° before injection.

their results. Minor adverse reactions experienced by all patients included injection site tenderness, mild hand swelling, and minimal hematoma or forearm tenderness, but all these effects resolved without event within 1 to 2 weeks of the injection and were extremely well tolerated by all patients. Inappropriate injection of tendons, nerves, or vessels will likely result in damaging lysis of the collagen contained in these structures. Therefore, careful palpation and injection of the Dupuytren's cord is necessary. Insertion of the insulin needle also can be an indicator of inappropriate insertion into a nerve, such as one displaced by a spiral cord, as no local anesthesia is used. Additionally, and most importantly, collagenase injection did not induce an adverse immune reaction, even after multiple injections, as shown by

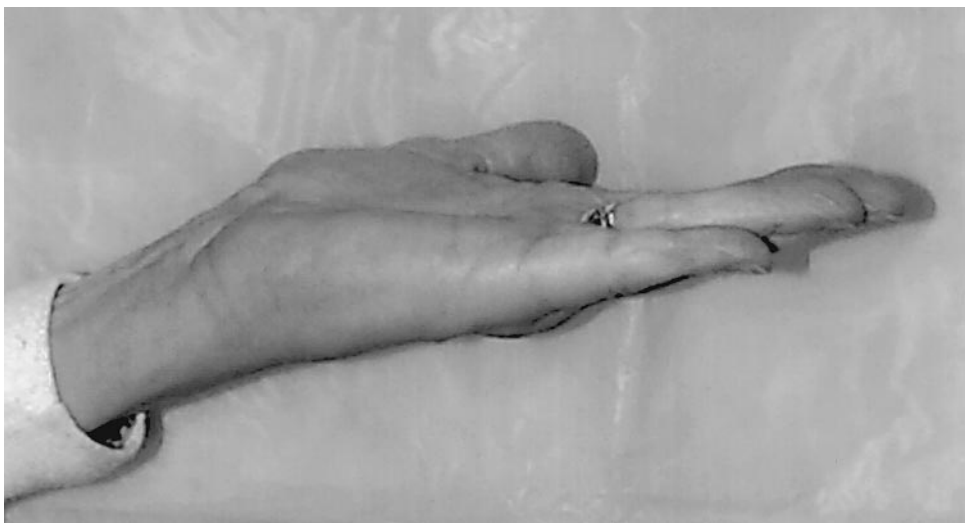

Figure 5. The same patient shown in Figure 4 after 1 collagenase injection.

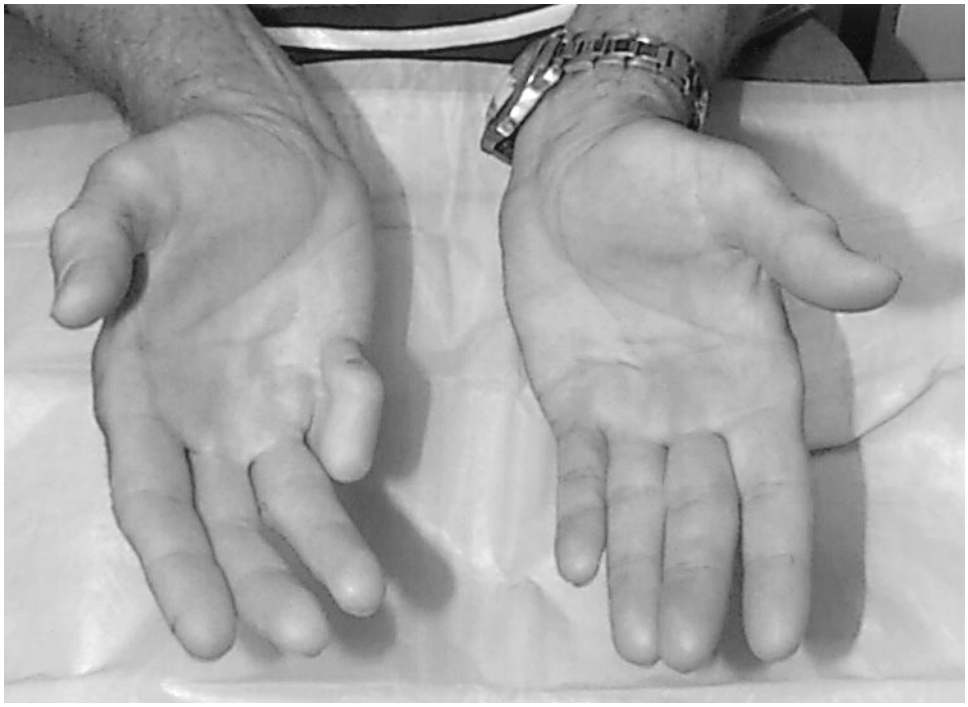

Figure 6. A patient presented with bilateral little finger contractures of the MCP, PIP, and distal interphalangeal joints. The left little finger had the appearance of the right little finger. After 3 injections the patient's left little finger corrected to normal with full range of motion.

our serial results relating immunoglobulin E serum titers to adverse immune events.

This study was conducted under an investigational new drug number with the US Food and Drug Administration. The results of this phase II open-label clinical trial indicate that clostridial collagenase injection of Dupuytren's cords causing MCP and PIP joint contractures has merit as a nonoperative treatment of this disorder. At present, random, placebo, double-blind studies are ongoing. Pending the results of that investigation and multicenter random, placebo, double-blind studies, we believe that collagenase injection for Dupuytren's disease will be shown to be a safe and effective alternative to surgical fasciectomy. As with any new therapeutic modality, the treatment will need to stand the test of time with regard to long-term follow-up results with special attention to recurrence and extension of the disease.

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