The Reflex Sympathetic Dystrophy Syndrome (RSDS)

III. Scintigraphic Studies, Further Evidence for the Therapeutic Efficacy of Systemic Corticosteroids, and Proposed Diagnostic Criteria

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Sixty-four patients were evaluated prospectively for a reflex sympathetic dystrophy syndrome (RSDS), using quantitative clinical measurements, high-resolution roentgenography and scintigraphy. Five separate groups were identified by their clinical features, allowing us to distinguish patients with definite or incomplete forms of the RSDS as well as 16 patients with other disorders. Scintigraphy was found to be a useful diagnostic study that may also provide a method of predicting therapeutic response. Systemic corticosteroid therapy proved to be a highly effective mode of treatment for up to 90 percent of the patients with the RSDS.

The reflex sympathetic dystrophy syndrome (RSDS) was first recognized over a century ago [1]. Subsequent reports have described a number of clinical variants, differing primarily in their associated features and predisposing factors [2]. Unfortunately, a clear concept of this disorder has been frustrated by the lack of clear diagnostic criteria, the myriad of terms applied to the syndrome [2], the absence of proved therapeutic modalities and our poor understanding of its pathophysiology.

The classic features of the RSDS were vividly recorded by Mitchell, Moorehouse and Keen [1] and have been reiterated more recently by DeTakats [3] and Steinbrocker and Argyros [4]. These consist of pain and tenderness, usually in a distal extremity, associated with signs or symptoms of vasomotor instability, trophic skin changes and swelling. A suspected predisposing event can be identified in up to 65 percent of the cases [2]. Roentgenographic evidence of acute, patchy, bony demineralization in the affected extremity is characteristic [4–7]. Scintigraphy, performed systematically in a small number of patients, revealed increased periarticular radionuclide activity [7], suggesting that this technique may prove useful in patients suspected of a RSDS.

The therapeutic modalities available in the RSDS have been reviewed recently [2]. Sympathetic blockade or systemic corticosteroid therapy appear to offer the greatest hope of success, especially when employed early [8]. Our results with systemic corticosteroid treatment in a small group of patients was encouraging [9], and this observation is confirmed and extended here.

In the present prospective study, 64 patients were assessed for possible RSDS, using clinical measurements, scintigraphy and high resolution roentgenography. Diagnostic criteria that may help in further defining this complex disorder were evaluated, and the therapeutic

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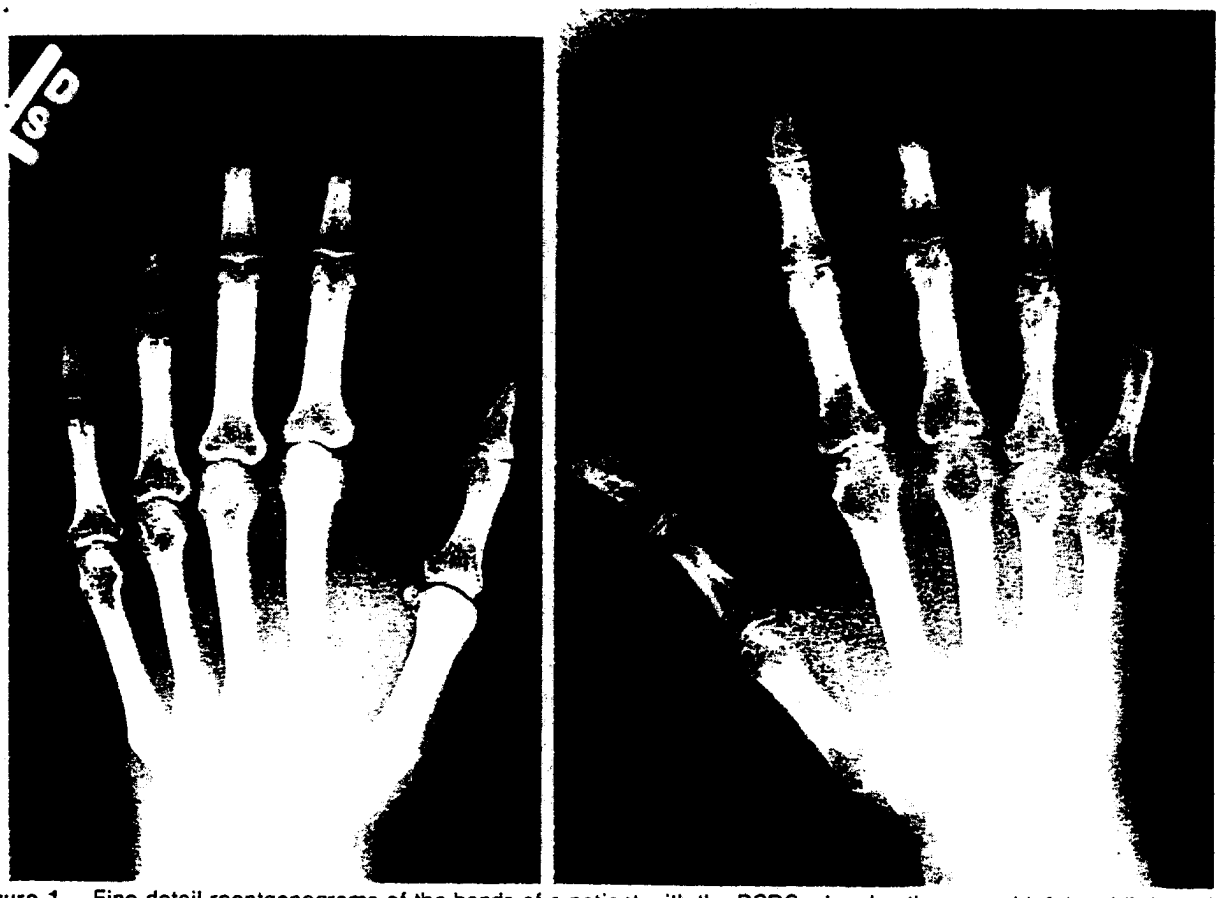

Figure 1. Fine-detail roentgenograms of the hands of a patient with the RSDS, showing the normal left hand (**left**) and the characteristic patchy demineralization in the affected right hand (**right**).

efficacy of stellate ganglion blockade and systemic corticosteroid administration was compared.

METHODS

Patients. All patients referred to the Rheumatology Clinic or Consultation Service, The Milwaukee County Medical Center, in whom a diagnosis of RSDS was seriously considered were included in the study. Their clinical findings were recorded, and the most likely precipitating event was identified whenever possible. Prior treatment and subjective responses were noted. Patients with *isolated* proximal sites of involvement (e.g., knee, hip, shoulder) as the sole site of involvement were excluded because of the uncertainty that RSDS affects such areas [2].

Clinical Criteria. Patients were divided into five groups, based upon their clinical findings. Group I consisted of patients with pain and tenderness in an extremity associated with symptoms or signs of vasomotor instability (particularly temperature or color changes), *and* generalized swelling in the same extremity (definite RSDS). Group II consisted of patients with pain and tenderness associated with vasomotor instability or swelling in an extremity (probable RSDS). Patients in group III (possible RSDS) had only pain and (usually) tenderness in an extremity which could not be attributed to recent trauma or to a specific nerve injury. Group IV (possible RSDS) consisted of patients who had vasomotor instability and swelling but no pain and (usually) no tenderness. In group V the patients had other disorders identified or did not fulfill the criteria for inclusion in other groups.

Trophic skin changes, although characteristic of the RSDS, were not used as a criterion since these changes may be associated with chronic swelling of another etiology, chronic disease alone or other disorders such as scleroderma.

Clinical Measurements. Objective, semiquantitative measurements were performed, as previously described [9], in patients with upper extremity involvement before treatment, at various intervals during treatment and after treatment.

In all cases, a subjective estimate was made of the patient's pain response during treatment. Patients who experienced pain relief of over 75 percent were regarded as having an excellent response; of 50 to 75 percent, a good response; of 25 to 50 percent, a fair response; and less than 25 percent, a poor response.

Roentgenographic Studies. Fine-detail roentgenography of the hands or feet was performed in all but one case. Roentgenograms were examined blindly by three observers and scored as "positive" if diffuse or patchy osteopenia (**Figure 1**) was present in the clinically affected extremity.

Scintigraphic Studies. Scintigraphy was performed in a majority of patients, using technetium-99m (^{99m}Tc) methylene diphosphonate (MDP), or occasionally ^{99m}Tc-ethane-1-hydroxy-1-1-diphosphonate (EHDP). After the injection of 15 mCi

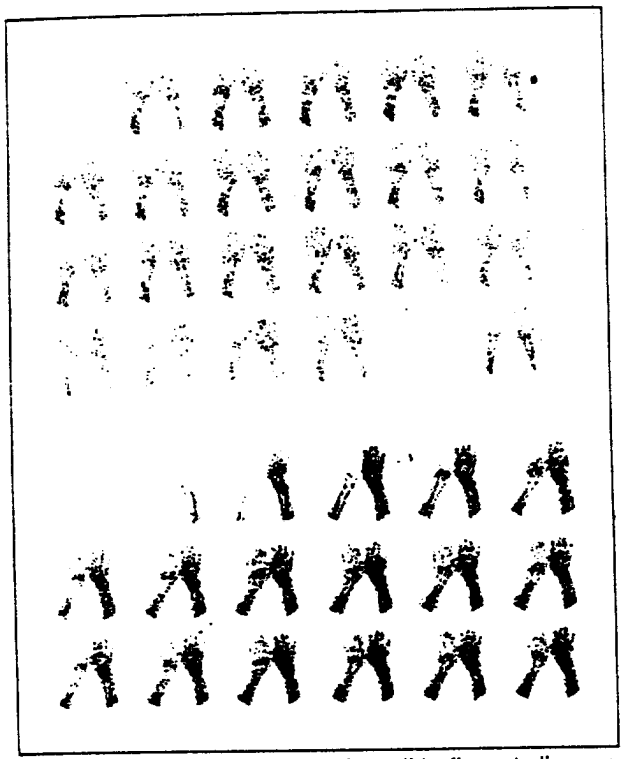

Figure 2. Rapid-sequence radionuclide flow studies are illustrated. A normal, symmetrical flow pattern (top) is readily distinguished from the asymmetrical flow (bottom) in a patient with the RSDS.

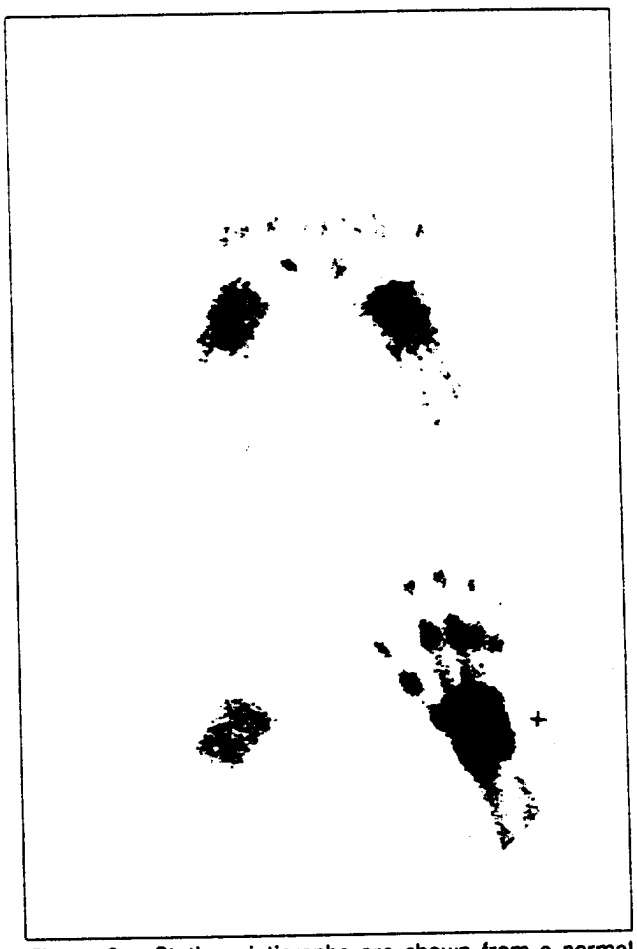

Figure 3. Static scintigraphs are shown from a normal subject (top) and a patient with RSDS (bottom). The increased activity in periarticular tissues of the affected hand is evident.

of radionuclide, scintigraphs of the affected and contralateral regions were obtained as rapid-sequence blood flow studies at 2 sec/frame for 2 minutes and as a 3-hour delayed static image. In a number of cases, the total counts over the affected and contralateral extremity were determined immediately after the flow study to assess the relative rates of uptake (or blood pooling).

Scintigraphs were reviewed by all of us. Flow studies were Considered "positive" when there was asymmetric appearance of radionuclide in the affected and contralateral extremities (**Figure 2**). Static images were "positive" when there was a general increase in periarticular activity on the affected side relative to the contralateral side (**Figure 3**), as previously described [6,7,10]. Increased radionuclide activity at the site of prior trauma or fracture was excluded from analysis.

TREATMENT

Twenty patients were treated with stellate ganglion blockade. Several had received this prior to referral, and their subjective responses were recorded. Other patients were given stellate ganglion blockade during the course of the study so that objective measurements were available. The majority of patients were given corticosteroids. Initial therapy in most instances consisted of prednisone, 60 to 80 mg for two to four days, 40 to 60 mg for two to four days and 30 to 40 mg for two to four days in four equally divided doses; subsequently, the dose was rapidly tapered as a single morning dose of 40, 30, 20, 10 and 5 mg for two or three days each. Occasionally, higher doses were given for up to two weeks, but patients rarely received more than three or four weeks of systemic corticosteroid therapy. Several patients required retreatment because of a poor or incomplete initial response, or because of a recurrence of symptoms weeks or months later.

RESULTS

Patients. The characteristics and demographic data of our patients are shown in **Table I.** Twenty-one patients fulfilled criteria for RSDS, as they exhibited each of the features of the complete syndrome (group I); their condition was classified as "definite RSDS." There were 11 patients with probable (group II) and 16 patients with possible (groups III and IV) RSDS. The associated disorders which clinically and temporally appeared to represent a "precipitating event" are listed for groups I through IV in **Table II,** using the categories previously suggested [2].

Sixteen patients (25 percent) did not satisfy criteria for an RSDS (group V). Another diagnosis was established in 14 (88 percent) of these patients, including infectious arthritis (two patients), rheumatoid arthritis (one patient), Reiter's syndrome (one patient), systemic lupus er-

TABLE I Characteristics of Patients in Each of Five Groups

Group	Patients (no.)	Female (no.)	Age (yr)*	Duration (wk)*	Involved Site†	
					UE	LE
I	21	14	52.4 ± 13.7	25.1 ± 23.2	14	7
II	11	5	48.5 ± 17.9	84.2 ± 155.0	7	4
III	9	5	43.3 ± 17.4	152.7 ± 148.2	7	2
IV	7	3	55.3 ± 17.2	38.6 ± 34.5	4	3
V	16	9	43.7 ± 14.4	34.5 ± 36.3	14	2
Total	64	36	48.3 ± 15.2	75.9 ± 67.9	46	18

* Values given indicate the mean ± standard deviation.
† UE = upper extremity (hand); LE = lower extremity (foot).

TABLE II Frequency of Associated Conditions in Patients with Possible RSDS (Groups I through IV)

Group	Patients (no.)	Possible Etiologic Factors (no.)							
		Trauma	Peripheral Nerve Injury	Fracture	Myocardial Ischemia	Cerebral Disease or Hemiplegia	Spinal Cord Injury	Idiopathic or Miscellaneous	Total
I	21	3	2*	10*	0	3	1	4	23*
II	11	1	1	2	0	3	1	3	11
III	9	5	1	0	1	1	0	1	9
IV	7	1	0	3	0	0	0	3	7
Total	48	10	4	15	1	7	2	11†	50
Percent	—	20	8	30	2	14	4	22	100

* Two patients had peripheral nerve injuries as a result of fractures.
† Three patients had carcinomas (two breast, one lung) but this appeared to be clinically implicated in the RSDS in only one patient with a shoulder (? brachial plexus) metastasis.

TABLE III Roentgenologic Findings in the Five Groups

Group	Total Patients (no.)	Changes in Roentgenogram		Changes on Scintigraph			
				Static Images		Flow Study	
		No.	% Positive	No.	% Positive	No.	% Positive
I = "Definite" RSDS	21	21	81	18	83	16	69
II = "Probable" RSDS	11	11	45	10	40	10	40
III = "Possible" RSDS	9	9	22	8	13	3	0
IV = "Possible" RSDS	7	7	57	7	28	7	43
V = Other diagnoses	16	15	29	7	0	4	0
Total	64	63	49	50	44	40	46

ythematosus (one patient), uncharacterized arthritides (two patients), rotator cuff tears demonstrated arthrographically (two patients), peripheral neuropathy (four patients), and hysterical conversion reaction (one patient). Thus, almost half of these patients had an inflammatory arthritis (based upon synovial fluid findings [11]) and considerable generalized edema (often pitting) of their involved extremity. Careful examination always disclosed a localized site of tenderness (and pain) despite diffuse edema. Absence of pain and tenderness in the hand or foot when there is extreme wrist or ankle pain is strong evidence against an RSDS [2].

Clinical Measurements. Initial measurements were available for 63 percent of the patients with upper extremity involvement (86 percent of those in groups I and II) and confirmed our previous observations [9]. The grip strength in the affected hand was reduced 136.2 ± 16.8 mm Hg (mean ± SEM, n = 18) when compared with the contralateral hand. Similarly, the tenderness score was 95.5 ± 8.5 U (n = 10) greater in the affected hand, and all but one patient, who had essentially equal tenderness bilaterally, had greater scores on the affected side. Finally, ring sizes were 12.9 ± 2.0 mm (17 patients) greater in the proximal interphalangeal joints of the

TABLE IV Responses of Patients to Stellate Ganglion Blockade or Systemic Corticosteroid Therapy*.

Group	Patients Treated (no.)	Response			
		Poor (%)	Fair (%)	Good (%)	Excellent (%)
		Stellate Ganglion Blockade			
I	7	71	28	0	0
II	4	100	0	0	0
III	4	100	0	0	0
IV	2	100	0	0	0
V	3	67	33	0	0
Total	20	85	15	0	0
		Systemic Oral Corticosteroid Therapy			
I	17	6	11	29	53
II	9	22	11	22	44
III	5	100	0	0	0
IV	3	33	0	33	33
V	1	100	0	0	0
Total	35	29	9	23	40

* Subjective responses of pain relief were graded as discussed in text.

affected hand. Only two patients had increased proximal interphalangeal joint sizes on the contralateral hand (7 ± 2 mm).

Roentgenographic Studies. Many roentgenograms exhibited the characteristic patchy demineralization of bone usually associated with the RSDS (Figure 1). However, the presence of unilateral diffuse osteopenia was considered sufficient for roentgenograms to be read as "positive," as this may be observed in patients with RSDS of greater than six to 12 weeks duration [4–6]. Roentgenograms were positive in approximately half the patients in the study (**Table III**). Osteopenia was found in 81 percent of the patients with definite RSDS (group I), 45 percent with probable (group II) and 57 percent with possible RSDS (group III).

Osteopenia was not related to duration of symptoms, as only 25 percent of the patients with complaints exceeding one year had this finding. In contrast, 28 percent of the patients with complaints of 12 or fewer weeks had osteopenia. Most of these subjects (12 of 18, 67 percent) had definite or probable RSDS. Osteopenia was found as early as five to eight weeks in four patients.

All five patients in group V with osteopenia had inflammatory (three patients) or infectious (two patients) arthritis, which may have contributed to the initial diagnostic confusion.

Scintigraphic Studies. Scintigraphs were obtained in 78 percent of the patients and were positive in 44 percent (Table III and Figures 2 and 3). Although the frequency of positive flow studies was less than that of positive static scans, this difference was not statistically significant. Only one patient (group IV) with asymmetrical flow had a normal static scan.

Half of the patients in groups I through IV (18 of 36) showed asymmetrical radionuclide activity on the flow studies. In 15 of the 18 patients, flow was increased on the affected side, suggesting enhanced perfusion on that side.

Forty-nine percent (21 of 43) of the patients in groups I through IV had both positive roentgenograms and scintigraphs, whereas in 33 percent both studies were negative. Scintigraphs were positive in two patients whose roentgenograms showed no abnormalities (one each in groups II and IV).

Assuming that patients in groups I and II indeed had a RSDS whereas those in groups III and IV did not, the scintigraph proved to be a more specific study than the roentgenogram (86 percent versus 71 percent), whereas the sensitivities were virtually identical (68 percent versus 39 percent)* [12].

Treatment. None of the 20 patients receiving stellate ganglion blockade had a good response (**Table IV**). Ten were referred *after* failure of stellate ganglion blockade and, therefore, represented a selected group; the remaining 10 received stellate ganglion blockade while under our care either because of personal preference (two patients), prior failure of corticosteroid therapy (five patients) or presence of medical disorders contraindicating high-dose systemic steroid therapy; such as diabetes mellitus (three patients). One such case is illustrated in **Figure 4**; this patient had both subjective and objective improvement during a series of stellate ganglion blockade followed by a worsening of her condition. She had a rapid and sustained improvement with systemic corticosteroid therapy.

In contrast to the data with stellate ganglion blockade, 63 percent of the patients had a good to excellent response to systemic corticosteroid therapy, and this figure was increased to 82 percent and 66 percent in the subsets with definite and probable RSDS respectively

* Other combinations actually enhance this difference. It is likely that the sensitivity and specificity of the roentgenograms are overestimated in this study because of the careful selection of patients and their referral for possible RSDS, thereby eliminating patients with simple disuse osteoporosis (see [6] and [13]).

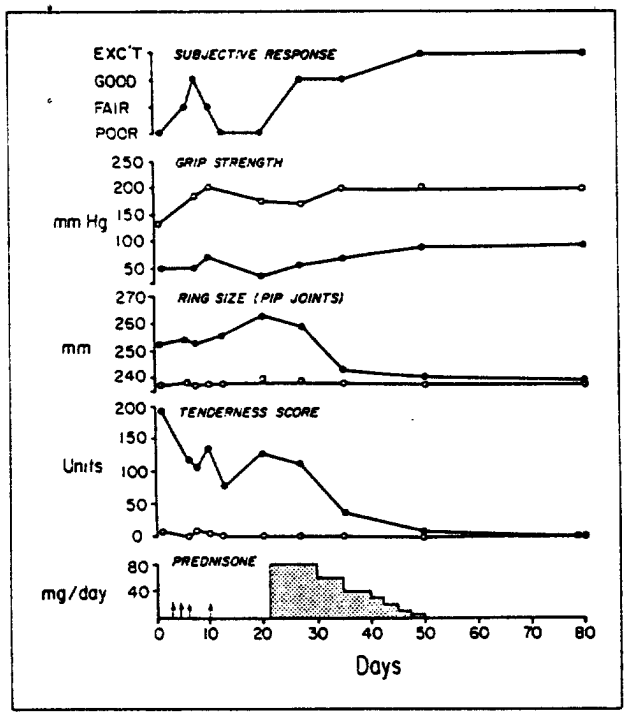

Figure 4. The clinical measurements and subjective responses of a patient with the RSDS are shown for the affected hand (●) and contralateral hand (O). The patient was treated initially with four stellate ganglion blocks (arrows) which provided a mild, transient improvement. Administration of systemic corticosteroids subsequently resulted in an excellent, sustained response.

(Table IV). Of the 11 patients who were treated with stellate ganglion blockade first, one had an excellent (Figure 4); four, a good; one, a fair; and five, a poor response to the administration of systemic corticosteroids. Conversely, none of five patients who were given stellate ganglion blockade after corticosteroid therapy improved. The duration of symptoms prior to the administration of corticosteroids did not seem to affect the response.

Objective measurements compared favorably with patients' subjective responses (**Table V**). Interestingly, objective improvement was present in all but one patient who received corticosteroid therapy, particularly in the tenderness scores.

Patient responses to corticosteroid therapy also were compared to results of their scintigraphic studies. Ninety percent of the patients with positive scintigraphs showed good or excellent improvement. Conversely, 64 percent of the patients with negative scintigraphs showed a poor to fair response to corticosteroid therapy. Thus, presence of a positive scintigraph is significantly correlated with good to excellent therapeutic response, $P < 0.001$, χ^2.

COMMENTS

The present study has defined several aspects of the RSDS that previously have created diagnostic and therapeutic confusion.

Diagnosis and Differential Diagnosis. Patients were divided into five groups, based upon strict clinical criteria. In 25 percent of the patients initially suspected of having a RSDS, insufficient evidence was found to support this diagnosis (group V). An alternative diagnosis was established in 14 (88 percent), providing some insight into which disorders may be confused with the RSDS.

Pain, tenderness, swelling and warmth (vasomotor instability ?) were present in the distal extremity of seven patients with arthritis. Although these findings were unilateral, careful examination revealed local tenderness, isolated to the involved joint(s), rather than the diffuse tenderness so characteristically found in the RSDS [1,2]. Two cases of unsuspected septic arthritis were found. Four additional patients had specific peripheral nerve injuries with sensory and/or motor changes in the expected distribution but with none of the other features of RSDS.

Steinbrocker and Argyros [4] have suggested that "circumscribed" forms of the RSDS exist, such as isolated Dupuytren's contractures. We found no evidence to support this concept either in this study or in a number

TABLE V **A Comparison of Serial Objective Measurements and Subjective Responses of Patients with the RSDS Treated with Systemic Corticosteroids***

Subjective Response	Objective Response: Δ Grip Strength (mm Hg) A	Δ Grip Strength (mm Hg) B	Δ Tenderness (U) A	Δ Tenderness (U) B	Δ Ring Size (mm) A	Δ Ring Size (mm) B
Excellent	+46.4 ± 7.2†	+24.0 ± 5.0	−84.9 ± 7.7	+2.9 ± 4.6	−13.2 ± 2.1	−4.7 ± 2.1
Good	+98.0 ± 83	+32.7 ± 33.3	−58.0 ± 24.9	−21.5 ± 17.2	−7.3 ± 2.2	−4.5 ± 2.5
Fair	+30.0 ± 17.6	+1.7 ± 19.6	−24.7 ± 23.1	−4.0 ± 10.8	−3.0 ± 1.6	−2.7 ± 1.8
Poor	+60	+20	−16 ± 11.4	−14 ± 10	−3.5 ± 2.5	−4.0
Combined	+46.3 ± 14.8	+21.0 ± 7.5	−61.2 ± 0.7	−7.4 ± 5.0	−9.1 ± 1.6	−4.2 ± 1.3

* A = Predominantly affected hand; B = contralateral hand. Changes represent differences in measurements from before to at least one week after corticosteroid therapy.
† Mean ± SEM.

TABLE VI Proposed Clinical Diagnostic Criteria for RSDS

Definite RSDS
Pain and tenderness in the distal extremity
Signs and/or symptoms of vasomotor instability
Swelling in the extremity—often with periarticular prominence
(Dystrophic skin changes usually present)
Probable RSDS
Pain and tenderness
AND
Vasomotor instability
OR
Swelling
(Dystrophic skin changes often present)
Possible RSDS
Vasomotor instability
OR/AND
Swelling
No pain, but mild-moderate tenderness may be present
(Dystrophic skin changes occasionally present)
Doubtful RSDS
Unexplained pain and tenderness in an extremity

of patients observed previously. Nonetheless, patients in groups II through IV may indeed have "partial" or "incomplete" forms of the syndrome.

In the remaining 48 patients, clinical findings were associated with the RSDS and they could be divided into four groups. Only group II appeared distinctive, differing in the frequency of associated conditions (Table II), in the roentgenographic and scintigraphic data (Table III), and in response to corticosteroid therapy (Table IV). Differences in the roentgenographic, scintigraphic and therapeutic findings were statistically significant, $P < 0.001$, Chi-square analysis, when compared with those in group I. Therapeutic responses were also significantly better in groups II and IV, $P < 0.05$. Based upon these data, as well as the presence of objective clinical changes of vasomotor instability and/or swelling, we propose the diagnostic criteria outlined in **Table VI.**

Roentgenographic and Scintigraphic Studies. Roentgenographic evidence of bony demineralization was most frequent in patients with "definite" RSDS, but it was not uncommon in the other groups (Table III). The characteristic roentgenographic appearance of acute, patchy osteoporosis in the RSDS has been extensively described [4-7,14]. It cannot be differentiated from disuse osteopenia [6,12,15-17], except possibly by documenting its early development [5]. For these reasons, osteopenia must not be considered a reliable "diagnostic" criterion.

As already stated, scintigraphy proved to be far more specific than roentgenography (86 percent versus 71 percent), with no sacrifice in sensitivity (68 percent versus 69 percent). Furthermore, scintigraphs appeared to be a useful guide to therapy. Ninety percent of the patients with positive scintigraphs experienced a good or excellent response to corticosteroid therapy compared with 34 percent of the patients with negative scintigraphs, $P < 0.001$. These results indicate that scintigraphy may be useful both as a diagnostic aid and as a predictor of therapeutic responses. As the numbers of patients are relatively small, this observation must be viewed cautiously until confirmed.

The presence of asymmetric radionuclide flow studies in half the patients was also interesting (Table III, Figure 2). It appears to be an indication of asymmetric blood flow and, if so, would be consistent with previous physiologic studies showing enhanced local blood flow in the affected extremity of patients with the RSDS [3,18-20].

In several patients, scintigraphs were positive initially but within normal limits following corticosteroid therapy, suggesting that scintigraphy may demonstrate an active, potentially reversible, process in certain subjects. These data are the subject of a separate report.

Treatment. The present study confirms our prior observations regarding the efficacy of corticosteroid therapy in the RSDS and extends them to patients with "incomplete" varieties of the syndrome (groups II and IV). Seventy-six percent of the patients with definite (group I, 14 of 17), probable (group II, six of nine) and possible (group IV, two of three) RSDS experienced a good or excellent subjective response. Interestingly, when the clinical measurements are included in this assessment of therapeutic response (data not shown), 90 percent of the patients given systemic corticosteroids had a good to excellent therapeutic response (improvement in both tenderness and swelling). These responses were not affected by the duration of symptoms prior to corticosteroid administration.

Stellate ganglion blockade may be effective in the RSDS [14,21,22]. However, sustained responses are not as frequent as commonly believed [2,8,22-25]. Our experience here was discouraging. But it must be appreciated that this study was not designed to compare stellate ganglion blockade with corticosteroids, since all patients who failed corticosteroid therapy were given stellate ganglion blockade, whereas the converse was not true. Appropriate studies are needed in this area.

In summary, the present study has provided some insight into the differential diagnosis of the RSDS. Arthritis of the wrist, carpal, ankle or subtalar joints may mimic the syndrome in the hand or foot. Careful attention to localizing symptoms and signs as well as to the proposed criteria may help in diagnosis. Changes on the roentgenogram are not a helpful diagnostic finding since involutional, disuse or inflammatory osteoporosis may be present in a number of patients suspected of an RSDS. Scintigraphy proved to be a valuable examination both in diagnosis and in predicting which patients would respond to corticosteroid therapy. Finally, this study firmly establishes the efficacy of systemic corticosteroid therapy in patients with the RSDS.

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