

Systemic Sclerosis Secondary to Occupational Exposure

GREGORY R. OWENS, M.D., THOMAS A. MEDSGER, M.D. Pittsburgh, Pennsylvania

RECEIVED

12 1988

Systemic sclerosis is a multisystem disease characterized by widespread fibrotic and degenerative changes in the skin, vasculature, and internal organs [1]. Pulmonary involvement, including either pulmonary fibrosis [2] or pulmonary arterial hypertension due to vascular obliteration [3], is commonly seen in patients with this disorder. The etiology of systemic sclerosis is unknown. A number of occupational and other exposures have been implicated as potential causes of systemic sclerosis or closely related conditions, including silica dust [4], epoxy resins [5], rapeseed oil [6], carbidopa [7], bleomycin [8], and benzene [9]. We report herein the case histories of two chemical workers exposed to meta-phenylenediamine in the same building in whom systemic sclerosis subsequently developed.

CASE REPORTS

Patient 1

This 39-year-old man worked in a restaurant and in the shipping department of a rayon manufacturing company. Since 1981, he had been employed as a chemical operator in Building 156 in a large chemical company in the Charleston, West Virginia, area where he unloaded and transferred chemicals. During August 1981, he had worked primarily with meta-phenylenediamine and had been involved in three accidental spills with this chemical. In October 1983, Raynaud's phenomenon, swelling of the hands, and hyperpigmentation of his hands and forearms developed. Following another chemical accident in January 1984, in which he was exposed to fumes of meta-phenylenediamine, he experienced the sudden onset of a productive cough, fatigue, and shortness of breath. He was unsuccessfully treated with bronchodilators and antibiotics and was referred to our institution. Physical examination revealed normal vital signs, with the exception of a respiratory rate of 22/minute. Results of examination of the ears, nose, and throat were normal. Evaluation of the lungs showed a few bibasilar rales. Results of cardiac and abdominal examinations were normal. Periungual erythema and puffy fingers bilaterally were present, as were mild skin thickening and hyperpigmentation of the fingers and dorsum of the forearms.

Laboratory evaluation revealed a normal blood cell count, and the erythrocyte sedimentation rate was 7 mm/hour. Levels of electrolytes and creatinine were normal, as were the results of liver function tests. An antinuclear antibody was positive at 1:100 with a homogeneous pattern, but all scleroderma-selective

autoantibodies were absent (anti-centromeres, anti-SCL-70, and anti-PM-SCL). The results of other serologic studies, including anti-SM, anti-RNP, and rheumatoid factor, were negative. A chest radiograph revealed interstitial changes in all lung fields consistent with pulmonary fibrosis. Pulmonary function tests showed a forced vital capacity of 3.09 liters (61 percent of predicted), a total lung capacity of 4.36 liters (64 percent of predicted), and a single-breath diffusing capacity for carbon monoxide of 4.0 ml/minute/mm Hg (14 percent of predicted). Arterial desaturation from 92 to 78 percent occurred with minimal exercise. An open lung biopsy procedure revealed pulmonary fibrosis with minimal inflammation. No abnormality of the pulmonary vasculature was noted.

Therapy with prednisone 60 mg/day, D-penicillamine 250 mg/day, and nasal oxygen at 2 liters/minute was started. The patient noted an improvement in respiratory symptoms, but two months later as the corticosteroid dose was decreased to 35 mg/day, shortness of breath worsened and the partial pressure of oxygen at this time was 48 mm Hg. High-dose prednisone therapy was re-instituted with symptomatic improvement.

Patient 2

This 58-year-old man had worked his entire adult life for the same large chemical corporation in the Charleston, West Virginia, area as did Patient 1. From 1944 to 1948, he worked as a laborer, primarily cleaning pipes containing vinyl chloride. From 1948 to 1977, he worked as a chemical operator. During this time, he was exposed to a variety of chemical compounds, primarily of the amine class, and specifically meta-phenylenediamine. He worked as a supervisor in Building 156 from 1977 to 1981, where he was exposed to the same amines and, in addition, silicon tetrachloride. He retired in 1981 because of health problems.

In January 1980, reflux esophagitis with heartburn developed, followed one month later by diffuse swelling and redness of both hands. In August 1980, he noted the onset of Raynaud's phenomenon, shortness of breath, and pedal edema and was treated with furosemide. Bradycardia was detected, and an electrocardiogram revealed complete heart block. A pacemaker was inserted.

His condition remained clinically stable until 1983, when shortness of breath worsened such that he could walk only one block without stopping. In addition, he reported the development of a chronic cough productive of scanty amounts of white sputum. He was hospitalized twice in 1983 for pneumonia. In 1984, he was treated with prednisone and a theophylline compound. He denied chest pain or paroxysmal nocturnal dyspnea.

Physical examination in 1984 revealed normal vital signs. Examination of the head, eyes, ears, nose, and throat was significant only for telangiectasia of the left cheek and bridge of the nose. The lungs revealed biba-

From the Divisions of Pulmonary Medicine and Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania. Requests for reprints should be addressed to Dr. Gregory R. Owens, University of Pittsburgh, School of Medicine, Division of Pulmonary Medicine, 440 Scaife Hall, 3550 Terrace Street, Pittsburgh, Pennsylvania 15261. Manuscript submitted January 15, 1988, and accepted in revised form April 1, 1988.

silar dry rales. Results of examination of the heart and abdomen were normal. The extremities showed sclerodactyly, telangiectasia over the fingers, and diffuse hyperpigmentation.

Laboratory evaluation revealed a normal complete blood cell count, and the erythrocyte sedimentation rate was 6 mm/hour. Electrolyte and serum creatinine levels were normal. Serologic studies, including anti-nuclear antibody, extractable nuclear antigen, rheumatoid factor, anti-centromere, anti-SCI-70, anti-SM, and anti-RNP, were all negative. The chest radiograph showed bibasilar interstitial markings consistent with pulmonary fibrosis, and an esophagram revealed a mild dilation of the esophagus with gastroesophageal reflux. The electrocardiogram showed complete heart block with a paced rhythm of 70 beats/minute. Pulmonary function tests revealed a forced vital capacity of 4.37 liters (86 percent of predicted) and a single-breath carbon monoxide diffusing capacity of 10.7 ml/minute/mm Hg (40 percent of predicted). Arterial blood gases showed a pH of 7.46, a partial carbon dioxide pressure of 37 mm Hg, and a partial pressure of oxygen of 75 mm Hg. He was treated with D-penicillamine 500 mg and prednisone 10 mg daily. The patient was seen in follow-up two years later, at which time there was no change in his symptoms, pulmonary function, or arterial blood gases.

COMMENTS

Systemic sclerosis is a disease of multiple organ systems that occurs primarily in women and that has an incidence of up to 12 cases per million population per year [10]. Although there is no clear reason for the development of the disease in the majority of patients, exposure to certain chemical agents may be associated with its occurrence.

Workers who are exposed to siliceous dusts are predisposed to the development of systemic sclerosis. A variety of reports have documented an unusually high prevalence of systemic sclerosis in underground gold miners [11], sand blasters [12], and workers in potteries and foundries [13]. The risk of the development of systemic sclerosis was estimated to be increased 17-fold in gold miners from South Africa [11] and increased 110-fold among German underground coal miners [14]. Systemic sclerosis most commonly developed in motormen in the mines who were exposed to the highest concentrations of respirable silica [4].

Another circumstance followed by the development of scleroderma after a delay of five to more than 20 years is the injection of foreign substances, usually silicone or paraffin, almost exclusively for breast augmentation [15]. This association has been noted almost exclusively from Japan.

Other evidence for an association between chemical agents and scleroderma comes from the epidemic of "toxic oil syndrome" in Spain in 1981 [6]. This epidemic occurred after the ingestion of adulterated cooking oil, rape seed oil. After an acute illness, the victims experienced the development of skin changes reminiscent of scleroderma and sometimes more typical of eosinophilic fasciitis, as well as neuropathies, the sicca syndrome, and pulmonary and esophageal dysfunction.

Exposure to vinyl chloride by inhalation or transcutaneously has also been documented to produce a scleroderma-like disease. In one study, skin changes indis-

tinguishable from scleroderma developed in 10 of 200 workers who produced vinyl chloride [16]. However, a number of clinical features suggested that the resulting condition was not typical systemic sclerosis. The skin lesions that were noted tended to be nodular. Clubbing and radiographic evidence of lysis of the distal phalanx and erosive sacroiliitis occurred, and hepatic fibrosis was evident. A genetic susceptibility to this condition has been suspected [18].

Yamakage *et al* [5] described a scleroderma-like disorder occurring in men engaged in the polymerization of epoxy resins. This disease occurred after only short-term exposure and with a relatively high incidence (six of 233 workers). The authors suggested that a biogenic amine, bis(4 amino-3-methyl-cyclohexyl) methane, was the causative agent. Neither of the two workers whose case histories were provided had evidence of pulmonary involvement. The same authors also described an association between the development of generalized morphea and exposure to organic solvents [19]. Although these subjects were not studied prospectively for internal organ involvement, the majority of the patients had either esophageal dysfunction or pulmonary fibrosis, suggesting a systemic rather than an isolated cutaneous process.

The development of other pseudo-sclerodermatous states has been described in persons with elevated levels of the amine serotonin (L-5-hydroxytryptophan). Both endogenous increases, as seen in the carcinoid syndrome [20], and treatment with exogenous serotonin for intention myoclonus [7] have been associated with the development of a scleroderma-like syndrome.

The most pertinent case reports in the literature relate to the development of scleroderma in persons exposed to aliphatic and aromatic hydrocarbon solvents [19,21-26]. Numerous instances of systemic sclerosis following occupational exposure to trichlorethylene [21-23] or perchlorethylene [24] have been described. Exposure to benzene, an aromatic hydrocarbon, may be followed by disease that tends to be limited to the hands and feet rather than becoming a multisystem disorder [9,25]. Methylene chloride, present in many paint removers, may cause acute pneumonitis [26], a circumstance similar to the disease present in our patients.

There are several reasons to believe that the development of systemic sclerosis in the two workers reported in this study is more than coincidental. First, only 20 other men were employed during the time spent in Building 156 by the two workers. Likewise, the onset and explosive progression of disease shortly after several documented chemical accidents in Patient 1 reinforces the likelihood of a relationship of disease to the workplace. An epidemiologic survey of the facility would provide a definitive answer to the association of the workplace and the onset of disease. However, it has not been possible to carry out such an evaluation.

Elucidating a specific causative exposure in these two patients is more difficult. One patient had been exposed to vinyl chloride, a known cause of a scleroderma-like syndrome, in the past. Because of the prolonged delay between the vinyl chloride exposure and the onset of scleroderma, we believe this agent was not a causative one. Likewise, both patients were intermittently exposed to silicon tetrachloride, which yields hydrochloric acid and free silica upon chemical break-

down. It is possible that the disease described herein was precipitated by an unusual type of exposure to silica, but this seems unlikely. The most attractive potential causative agent is meta-phenylenediamine. In the company facilities, this agent was used most commonly in Building 156. Second, Patient 1 was subjected to heavy exposure several times shortly before the development of an explosive syndrome, which included lung involvement. Finally, as detailed earlier, other biogenic amines have been implicated in the development of scleroderma-like illnesses.

Although chemically induced systemic sclerosis may account for only a small fraction of scleroderma cases, the recognition of specific causative agents may ultimately lead to an improved understanding of the mechanism of disease induction, including vascular, immunologic, and fibroproliferative events, and possibly to the development of rational therapy.

REFERENCES

1. Medsger T: Systemic sclerosis (scleroderma), eosinophilic fasciitis and calcinosis. In: McCarty DJ Jr, ed. *Arthritis and allied conditions*, 9th ed. Philadelphia: Lea and Febiger, 1985; 996-1034.
2. Owens G, Fino G, Herbert D, et al: Pulmonary function in progressive systemic sclerosis: comparison of CREST syndrome variant with diffuse scleroderma. *Chest* 1983; 84: 546-550.
3. Stupi A, Steen V, Owens G, Barnes L, Rodnan G, Medsger T: Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986; 29: 515-524.
4. Rodnan G, Benedek T, Medsger T, Cammarata R: The association of progressive systemic sclerosis (scleroderma) with coal miners' pneumoconiosis and other forms of silicosis. *Ann Intern Med* 1967; 66: 323-334.
5. Yamakage A, Ishikawa H, Saito Y, Matori A: Occupational scleroderma-like disorder occurring in men engaged in the polymerization of epoxy resins. *Dermatologica* 1980; 161: 33-40.
6. Alonzo-Ruiz A, Zea-Mendoza A, Salazar-Vallinas J, Rocamora-Ripoll A: Toxic oil syndrome: a syndrome with features overlapping those of various forms of scleroderma. *Semin Arthritis Rheum* 1986; 15: 200-212.
7. Sternberg E, Van Woert M, Young S, et al: Development of a scleroderma-like illness during therapy with L-5-hydroxytryptophan and carbidopa. *N Engl J Med* 1980; 303: 782-787.
8. Finch W, Rodnan G, Buckingham R, Prince R, Winkelstein A: Bleomycin induced scleroderma. *J Rheumatol* 1980; 7: 651-659.
9. Corjak L, Szegedi G: Benzene exposure and systemic sclerosis (letter). *Ann Intern Med* 1987; 107: 118.
10. Medsger T: Epidemiology of progressive systemic sclerosis. *Clin Rheum Dis* 1979; 5: 15-25.
11. Erasmus L: Scleroderma in gold miners in the Witwatersrand with particular reference to pulmonary manifestations. *S Afr J Lab Clin Med* 1957; 3: 209-231.
12. Ziskind M, Weil H, Anderson A, Samari B, Nelson A, Waggenpack C: Silicosis in shipyard sandblasters. *Environ Res* 1976; 2: 237-243.
13. Parkes WR: *Occupational lung disorders*, 2nd ed. London: Butterworths, 1982; 157.
14. Hausteil U, Ziegler V, Zschunke E, Munzberger H, Kopping H: Progressive systemic sclerosis with silicosis in the German Democratic Republic. In: Black C, Myers A, eds. *Systemic sclerosis (scleroderma)*. New York: Gower Medical Publishing, 1985; 138-141.
15. Kurnagai Y, Shiokawa Y, Medsger T, Rodnan G: Clinical spectrum of connective tissue disease after cosmetic surgery. Observations on 18 patients and a review of the Japanese literature. *Arthritis Rheum* 1984; 27: 1-12.
16. Langauer-Lewewicka H, Kurzbaue H, Byczkowska Z, Wocka-Marek T: Vinyl chloride disease: neurological disturbances. *Int Arch Occup Environ Health* 1983; 52: 151-157.
17. Veltman G, Lange C, Juhe S, Stein G, Bachner V: Clinical manifestations and course of vinyl chloride disease. *Ann NY Acad Sci* 1975; 246: 6-17.
18. Black C, Pereira S, McWhirter A, Welsh K, Laurant R: Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. *J Rheumatol* 1986; 13: 1059-1062.
19. Yamakage A, Ishikawa H: Generalized morphea-like scleroderma occurring in people exposed to organic solvents. *Dermatologica* 1982; 165: 186-193.
20. Fries J, Lindgren J, Bull J: Scleroderma-like lesions and the carcinoid syndrome. *Arch Intern Med* 1973; 131: 550-553.
21. Sahian E, Burton J, Keaton K: A new syndrome with pigmentation, scleroderma, gynecomastia, Raynaud's phenomenon, and peripheral neuropathy. *Br J Dermatol* 1978; 99: 437-440.
22. Flindt-Hansen H, Isager H: Scleroderma after occupational exposure to trichlorethylene and trichloroethane. *Acta Derm Venereol (Stockh)* 1987; 67: 263-264.
23. Lockey J, Kelly C, Cannon G, Colby T, Aldrich V, Livingston G: Progressive systemic sclerosis associated with exposure to trichloroethylene. *J Occup Med* 1987; 29: 493-496.
24. Sparrow G: A connective tissue disorder similar to vinyl chloride disease in a patient exposed to perchlorethylene. *Clin Derm* 1977; 2: 17-22.
25. Walder B: Do solvents cause scleroderma? *Int J Dermatol* 1983; 22: 157-158.
26. Buie S, Pratt D, May J: Diffuse pulmonary injury following paint remover exposure. *Am J Med* 1986; 81: 702-704.



ARTHRITIS CARE ASSOCIATES, P.C.

PAUL D. SAVILE, M.D., F.A.C.P.
Rheumatology
Metabolic Bone Disease

400A South Ruffner Road
CHARLESTON, WV 25304
(304) 340-0333

July 7, 1986

John L. McClaugherty, Attorney at Law
Jackson, Kelly, Holt & O'Farrell
1600 Laidley Tower
P. O. Box 553
Charleston, West Virginia 25322

Re: Sherman L. Handley
Claim No. 84-49760

Dear Mr. McClaugherty:

I saw this patient on 3-6-84 at the request of his pulmonary disease specialist, Dr. Patel. He gave a history that in October of 1983 he had developed swelling of his hands quite suddenly and he also noticed that his fingers became purple in the cold. He said he had been working at low temperatures of minus 5 degrees Fahrenheit and caught a cold and cough. On January 23rd he became dyspneic on exertion and could not climb a flight of stairs. He was seen by physicians and given antibiotics, then he was admitted to the hospital and was seen by Dr. Patel who found a pulmonary infiltrate and suspected scleroderma with pulmonary involvement.

At this time he was very breathless even on walking into the living room; the skin of his hands had become tight; weight had decreased 7 pounds in the hospital; and he had developed indigestion on medications and severe heartburn. While he denied dysphagia, he said he was now unable to drink quickly. He said he was told he had a hiatus hernia. His fingertips were numb. He said he was a chemical operator at Carbide emptying out tanks and that he believed that silicon tetrachloride releasing hydrochloric acid fumes was the cause of all his problems.

UCC
060794

John L. McLaugherty, Attorney at Law
Re: Sherman L. Handley
July 7, 1986
Page 2

When I examined him I found his blood pressure to be 130/90. He weighed 176 pounds and was 5'10". There were telangiectases over his chest and he said they had been present 10 years. The lung sounds were normal. The only other finding was of scleroderma of the forearms and hands and left cheek of his face.

On 5-3-85 I found harsh breath sounds and fine crackling rales over the right mid zone bilaterally but less on the left. The patient was already taking prednisone, 40 mg daily at breakfast. Other lab tests performed by Dr. Patel had shown a strongly positive antinuclear antibody test at a titer of 1:640. I did not repeat this. A blood count showed an elevated white count of 13,800 with 76% polymorphs which I interpreted as being due to the high dose prednisone. His serum cholesterol was 435 also high, again which I interpreted as being caused or aggravated by prednisone. At this point it was clear that the patient was suffering from the disease scleroderma with pulmonary involvement and his pulmonary involvement was his main problem.

I told Mr. Handley that there was no treatment known to be safe and effective for this disease but some physicians use a drug called D-penicillamine. I told him that I do not use this drug for that purpose but that the physicians at the University of Pittsburgh see a lot of cases of scleroderma and do use th drug. If he wished I would refer him there.

As it turned out, the patient went to Pittsburgh with one disease scleroderma and returned with four diseases, three of them iatrogenic. When he came back he had not only scleroderma but also cushing syndrome secondary to high dose prednisone: recurrent pneumothorax requiring emergency admission to the Charleston Area Medical Center and resulting from open lung biopsy; and the nephrotic syndrome resulting from D-penicillamine medication. I attempted to reduce the prednisone dosage but it was increased again by the Pittsburgh physicians. I also stopped the Penicillamine and the nephrotic syndrome cleared only to return again on restarting a very small dose. (It is also possible that while I was prescribing a very small dose, the patient may have been taking a larger dose since he believed it would save his life).

UCC
060795

John L. McClaugherty, Attorney at Law
Re: Sherman L. Handley
July 7, 1986
Page 3

Beeson and McDermott Textbook of Medicine, 14th Edition, states that there is a 3 to 1 ratio of females to males in this disease. In a 1985 article entitled Pulmonary Involvement in Systemic Sclerosis, Dr. Owens and his colleagues in Pittsburgh fail to mention the percentage of patients who are female. However, in an article entitled Pulmonary Function in Progressive Systemic Sclerosis published in Chest 84-5 1983, they had 83 women and 5 men with CREST syndrome and 67 women and 10 men with diffuse scleroderma. In their article "Interstitial Lung Disease in Scleroderma" Silver and Associates, Arthritis and Rheumatism, 271, 254, 1984 studied 20 patients with interstitial lung disease due to scleroderma. Of these, 9 were females and 11 were males, (30% males). In another paper by the Pittsburgh group, American Journal of Medicine 77, 489 1984 they reported 69% of 26 patients with diffuse scleroderma were females and 86% of 22 patients with the CREST syndrome were females. However, they go on to say that in their 'methods' that the 22 patients with the CREST syndrome had been selected from 51 patients in their research unit over an 18 month interval from June of 1981 through December of 1982. While scleroderma is more often seen in women, it certainly occurs in men too.

The true prevalence of any disease in a community is hard to estimate. There have been many attempts to estimate the prevalence of rheumatoid arthritis in various countries and the figures suggest that somewhere between .5% and 2% of the adult population suffers from the common disease rheumatoid arthritis. During the period when I saw 77 patients with scleroderma, I saw 1860 patients with rheumatoid arthritis. Thus, scleroderma is 1/20 as common as the common disease rheumatoid arthritis. It is uncommon but it is not rare.

When Dr. Owens learned that Sherman Handley had worked for Carbide, he formed a belief that breathing chemicals must have caused scleroderma in this particular case. When he heard of another patient who had attended the Cleveland Clinic, this solidified his belief.

UCC
060796

John L. McClaugherty, Attorney at Law
Re: Sherman L. Handley
July 7, 1986
Page 1

I like to distinguish in my own mind between my beliefs and knowledge. Many people used to believe that the world was flat, today very few believe that. We now have knowledge that it is round. Thus, people's beliefs can sometimes be confirmed as knowledge accumulates but other times beliefs can be demonstrated to be false by acquiring new knowledge. Therefore, we have to question Dr. Owens beliefs and look at his stated reasons for coming to the belief.

Dr. Owens states that it is unusual for men to get scleroderma in the first place. He also says that it is very unusual for the disease to have a very rapid onset of symptoms. So unusual was this combination that Dr. Owens thought that a lung biopsy was needed. The question then is: How common is scleroderma lung in men and can it have a sudden onset and progression?

Silver and Associates, Arthritis and Rheumatism, 271, 254, 1984 state that lung disease has a slow gradual deterioration or a rapid downhill course and this is unpredictable by any testing method used at the present time. Barnett and Coventry, The Medical Journal of Australia, 1040, 1969, report on treatment of 61 personally observed patients with systemic scleroderma seen in Melbourne. They state "these cases presented a very diverse picture, varying from patients with ischemia and sclerotic changes of the fingers only, who lived in good health to old age, to patients rapidly developing skin changes over the whole body who died within a few months or years." Most of us who treat numbers of patients with scleroderma are aware of this peculiar variation in the clinical course of the disease. The first patient I saw in Morgantown in 1974 was an 18 year old girl who died of her disease in less than 12 months. I diagnosed a 75 year old man as suffering from scleroderma of recent onset in November of 1985 and after assuring him that his disease was mild and it was safe for him to take a vacation in Buffalo, New York, I was called by a physician from New York to say that he had been admitted in a crisis and was in pulmonary failure. That patient has returned

UCC
060797

John L. McClaugherty, Attorney at Law
Re: Sherman L. Handley
July 7, 1986
Page 5

to the Charleston Area Medical Center where he is now on permanent kidney dialysis and who will clearly die in the near future. Last month I saw a middle aged man, a dispatcher working for a food company, whose onset of disease was explosively sudden in 1983 and in May 1986 he was in the Charleston Area Medical Center having lost 80 pounds weight, unable to swallow food or to digest it or to stand up by himself. These things happen. Scleroderma frequently has an explosive onset in men and in women.

A majority of patients with scleroderma are housewives. In Table I, I list the occupations of men with scleroderma; 100 men with rheumatoid arthritis; and 89 men with osteoarthritis. There were 2 men who worked for Carbide, one was Mr. Handley and the other was a man sent over by the Medical Department because of a positive antinuclear antibody test and Raynaud's phenomenon. While this does not conform to the ARA criteria for scleroderma, I include this as a possible case. Since so many patients with osteoarthritis have retired, I have examined those employed and expressed in parenthesis the percentage of the total employed under occupation.

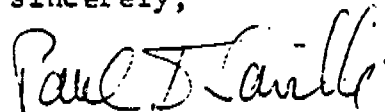
Thus, we find that of 100 men with rheumatoid arthritis seen in my office between 1984 and 1986 5% worked for Union Carbide. Of 89 men with osteoarthritis seen in the same time period, 49 were still employed and 4% worked for Carbide. The question may now be asked: Is the presence of two Carbide employees among 24 men with scleroderma an unusual event in my practice? The answer is no. In my practice only the presence of four or more patients with scleroderma who were employed by Union Carbide would have been an unusual or unexpected event. The disease remains a condition seen mostly in housewives and those that occur in males are distributed among the many occupations of the workers of the Kanawha Valley according to the laws of chance. Based upon my examination of Mr. Handley, my review of the literature, and my review of the occupations of men with scleroderma, rheumatoid arthritis or

UCC
060798

John L. McClaugherty, Attorney at Law
Re: Sherman L. Handley
July 7, 1986
Page 6

osteoarthritis seen by me in my office around the time that Mr. Handley was seen, I conclude that there is no causal relationship between Mr. Handley's scleroderma and his occupation.

Yours sincerely,



Paul D. Saville, M.D., F.A.C.P.

FDS/lw
Enclosure

UCC
060799

TABLE I

UCC
060800

RHEUMATOID ARTHRITIS

<u>OCCUPATION</u>	<u># MALE</u>
UMW	45
Office	25
Carpentry	9
Driver	
Bus, Truck Equip.	6
Carbide*	5
DuPont*	2
Allied Chemical*	1
Columbia Gas	1
Mechanic	3
Dept. Nat. Res.	1

100 Random Male Patients

Total Rheumatoid Arthritis
1975 - 1986 is 1860

PROGRESSIVE
SYSTEMIC SCLEROSIS

<u>OCCUPATION</u>	<u># MALE</u>
UMW	8
Office	5
Carbide*	2
Libbey Owens	1
(Engineering, Boat)	
Construction	4
Retired	2
Dept. Voc. Rehab.	1
Child	1

Total Scleroderma Patients
from 1975 - March 1,
1986 is 77 - 24 Male
53 Female

OSTEOARTHRITIS

<u>OCCUPATION</u>	<u># MALE</u>
UMW	13 (27%)
Office	12 (25%)
Postal	3 (6%)
Plumbing	3 (6%)
Carpentry	2 (4%)
Mechanic	3 (6%)
Sales	2 (4%)
Janitor	2 (4%)
Bus Driver	1 (2%)
Barber	1 (2%)
Dentist	1 (2%)
Unemployed	1 (2%)
Carbide*	2 (4%)
Monsanto*	1 (2%)
Alloy*	1 (2%)
Elk Metals	1 (2%)

Total Male Osteoarthritis
in Current Files 1983,
1984, 1985, 1986 - 89

Employed 49
Over 65 40

% Represents Employed Only

* Chemical Plants

6-6-86

Systemic Sclerosis Secondary to Occupational Exposure

GREGORY R. OWENS, MD, THOMAS A. WEDSGER, MD, Pittsburgh, Pennsylvania

Systemic sclerosis is a multisystem disease characterized by widespread fibrotic and degenerative changes in the skin, vasculature, and internal organs [1]. Pulmonary involvement, including either pulmonary fibrosis [2] or pulmonary arterial hypertension due to vascular obliteration [3], is commonly seen in patients with this disorder. The etiology of systemic sclerosis is unknown. A number of occupational and other exposures have been implicated as potential causes of systemic sclerosis or closely related conditions, including silica dust [4], epoxy resins [5], rapeseed oil [6], carbidopa [7], bleomycin [8], and benzene [9]. We report herein the case histories of two chemical workers exposed to meta-phenylenediamine in the same building in whom systemic sclerosis subsequently developed.

CASE REPORTS

Patient 1

This 49-year-old man worked in a restaurant and in the shipping department of a rayon manufacturing company. Since 1981, he had been employed as a chemical operator in Building 156 in a large chemical company in the Charleston, West Virginia, area where he unloaded and transferred chemicals. During August 1981, he had worked primarily with meta-phenylenediamine and had been involved in three accidental spills with this chemical. In October 1983, Raynaud's phenomenon, swelling of the hands, and hyperpigmentation of his hands and forearms developed. Following another chemical accident in January 1984, in which he was exposed to fumes of meta-phenylenediamine, he experienced the sudden onset of a productive cough, fatigue, and shortness of breath. He was unsuccessfully treated with bronchodilators and antibiotics and was referred to our institution. Physical examination revealed normal vital signs, with the exception of a respiratory rate of 22/minute. Results of examination of the ears, nose, and throat were normal. Evaluation of the lungs showed a few bibasilar rales. Results of cardiac and abdominal examinations were normal. Periungual erythema and puffy fingers bilaterally were present, as were mild skin thickening and hyperpigmentation of the fingers and dorsum of the forearms.

Laboratory evaluation revealed a normal blood cell count, and the erythrocyte sedimentation rate was 7 mm/hour. Levels of electrolytes and creatinine were normal, as were the results of liver function tests. An antinuclear antibody was positive at 1:100 with a homogeneous pattern, but all scleroderma-selective

autoantibodies were absent (anti-centromere, anti-SCL-70, and anti-PM-SCL). The results of other serologic studies, including anti-SM, anti-RNP, and rheumatoid factor, were negative. A chest radiograph revealed interstitial changes in all lung fields consistent with pulmonary fibrosis. Pulmonary function tests showed a forced vital capacity of 3,009 liters (61 percent of predicted), a total lung capacity of 4,036 liters (64 percent of predicted), and a single-breath diffusing capacity for carbon monoxide of 4.0 ml/minute/mm Hg (14 percent of predicted). Arterial desaturation from 92 to 78 percent occurred with minimal exercise. An open lung biopsy procedure revealed pulmonary fibrosis with minimal inflammation. No abnormality of the pulmonary vasculature was noted.

Therapy with prednisone 60 mg/day, D-penicillamine 250 mg/day, and nasal oxygen at 2 liters/minute was started. The patient noted an improvement in respiratory symptoms, but two months later as the corticosteroid dose was decreased to 35 mg/day, shortness of breath worsened and the partial pressure of oxygen at this time was 48 mm Hg. High-dose prednisone therapy was re-instituted with symptomatic improvement.

Patient 2

This 58-year-old man had worked his entire adult life for the same large chemical corporation in the Charleston, West Virginia, area as did Patient 1. From 1944 to 1948, he worked as a laborer, primarily cleaning pipes containing vinyl chloride. From 1948 to 1977, he worked as a chemical operator. During this time, he was exposed to a variety of chemical compounds, primarily of the amine class, and specifically meta-phenylenediamine. He worked as a supervisor in Building 156 from 1977 to 1981, where he was exposed to the same amines and, in addition, silicon tetrachloride. He retired in 1981 because of health problems.

In January 1980, reflux esophagitis with heartburn developed, followed one month later by diffuse swelling and redness of both hands. In August 1980, he noted the onset of Raynaud's phenomenon, shortness of breath, and pedal edema and was treated with furosemide. Bradycardia was detected, and an electrocardiogram revealed complete heart block. A pacemaker was inserted.

His condition remained clinically stable until 1983, when shortness of breath worsened such that he could walk only one block without stopping. In addition, he reported the development of a chronic cough productive of scanty amounts of white sputum. He was hospitalized twice in 1983 for pneumonia. In 1984, he was treated with prednisone and a theophylline compound. He denied chest pain or paroxysmal nocturnal dyspnea.

Physical examination in 1984 revealed normal vital signs. Examination of the head, eyes, ears, nose, and throat was significant only for telangiectasia of the left cheek and bridge of the nose. The lungs revealed biba-

From the Divisions of Pulmonary Medicine and Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania. Requests for reprints should be addressed to Dr. Gregory R. Owens, University of Pittsburgh, School of Medicine, Division of Pulmonary Medicine, 440 Scarfe Hall, 3550 Terrace Street, Pittsburgh, Pennsylvania 15261. Manuscript submitted January 15, 1988, and accepted in revised form April 1, 1988.

lar dry scales. Results of examination of the heart and lungs were normal. The extremities showed sclerodactyls, telangiectasia over the fingers, and diffuse hyperpigmentation.

Chest roentgenogram revealed a normal cardiac silhouette and the erythrocyte sedimentation rate was 8 mm/hour. Electrolyte and serum creatinine levels were normal. Serologic studies, including antinuclear antibody, extractable nuclear antigen, rheumatoid factor, anti-centromere, anti-SCL-70, anti-SM, and anti-RNP, were all negative. The chest radiograph showed bilateral interstitial markings consistent with pulmonary fibrosis, and an esophagram revealed a mild dilation of the esophagus with gastroesophageal reflux. The electrocardiogram showed complete heart block with a paced rhythm of 70 beats/minute. Pulmonary function tests revealed a forced vital capacity of 1.07 liters (36 percent of predicted) and a single-breath carbon monoxide diffusing capacity of 10.7 ml/minute/mm Hg (40 percent of predicted). Arterial blood gases showed a pH of 7.46, a partial carbon dioxide pressure of 37 mm Hg, and a partial pressure of oxygen of 75 mm Hg. He was treated with D-penicillamine 500 mg and prednisone 10 mg daily. The patient was seen in follow-up two years later, at which time there was no change in his symptoms, pulmonary function, or arterial blood gases.

COMMENTS

Systemic sclerosis is a disease of multiple organ systems that occurs primarily in women and that has an incidence of up to 12 cases per million population per year [10]. Although there is no clear reason for the development of the disease in the majority of patients, exposure to certain chemical agents may be associated with its occurrence.

Workers who are exposed to siliceous dusts are predisposed to the development of systemic sclerosis. A variety of reports have documented an unusually high prevalence of systemic sclerosis in underground gold miners [11], sand blasters [12], and workers in potteries and foundries [13]. The risk of the development of systemic sclerosis was estimated to be increased 17-fold in gold miners from South Africa [11] and increased 110-fold among German underground coal miners [14]. Systemic sclerosis most commonly developed in motormen in the mines who were exposed to the highest concentrations of respirable silica [4].

Another circumstance followed by the development of scleroderma after a delay of five to more than 20 years is the injection of foreign substances, usually silicone or paraffin, almost exclusively for breast augmentation [15]. This association has been noted almost exclusively from Japan.

Other evidence for an association between chemical agents and scleroderma comes from the epidemic of "toxic oil syndrome" in Spain in 1981 [6]. This epidemic occurred after the ingestion of adulterated cooking oil, rape seed oil. After an acute illness, the victims experienced the development of skin changes reminiscent of scleroderma and sometimes more typical of eosinophilic fasciitis, as well as neuropathies, the sicca syndrome, and pulmonary and esophageal dysfunction.

Exposure to vinyl chloride by inhalation or transcutaneously has also been documented to produce a scleroderma-like disease. In one study, skin changes indis-

tinguishable from scleroderma developed in 10 of 200 workers who produced vinyl chloride [16]. However, a number of clinical features suggested that the resulting condition was not typical systemic sclerosis. The skin lesions that were noted tended to be acral, the lung and radiographic changes were minimal, telangiectasia and erosive dermatitis occurred, and hepatic fibrosis was evident. A definite susceptibility to this condition has been suspected [16].

Namawake *et al* [5] described a scleroderma-like disorder occurring in men engaged in the polymerization of epoxy resins. This disease occurred after only short-term exposure and with a relatively high incidence (six of 200 workers). The authors suggested that a biogenic amine, bis(4- amino-3-methyl-phenyl)hexyne methane, was the causative agent. Neither of the two workers whose case histories were provided had evidence of pulmonary involvement. The same authors also described an association between the development of generalized morphea and exposure to organic solvents [19]. Although these subjects were not studied prospectively for internal organ involvement, the majority of the patients had either esophageal dysfunction or pulmonary fibrosis, suggesting a systemic rather than an isolated cutaneous process.

The development of other pseudo-sclerodermatous states has been described in persons with elevated levels of the amine serotonin (L-5-hydroxytryptophan). Both endogenous increases, as seen in the carcinoid syndrome [20], and treatment with exogenous serotonin for intention myoclonus [21] have been associated with the development of a scleroderma-like syndrome.

The most pertinent case reports in the literature relate to the development of scleroderma in persons exposed to aliphatic and aromatic hydrocarbon solvents [19,21-26]. Numerous instances of systemic sclerosis following occupational exposure to trichloroethylene [21-23] or perchloroethylene [24] have been described. Exposure to benzene, an aromatic hydrocarbon, may be followed by disease that tends to be limited to the hands and feet rather than becoming a multisystem disorder [9,25]. Methylene chloride, present in many paint removers, may cause acute pneumonitis [26], a circumstance similar to the disease present in our patients.

There are several reasons to believe that the development of systemic sclerosis in the two workers reported in this study is more than coincidental. First, only 20 other men were employed during the time spent in Building 156 by the two workers. Likewise, the onset and explosive progression of disease shortly after several documented chemical accidents in Patient 1 reinforces the likelihood of a relationship of disease to the workplace. An epidemiologic survey of the facility would provide a definitive answer to the association of the workplace and the onset of disease. However, it has not been possible to carry out such an evaluation.

Elucidating a specific causative exposure in these two patients is more difficult. One patient had been exposed to vinyl chloride, a known cause of a scleroderma-like syndrome, in the past. Because of the prolonged delay between the vinyl chloride exposure and the onset of scleroderma, we believe this agent was not a causative one. Likewise, both patients were intermittently exposed to silicon tetrachloride, which yields hydrochloric acid and free silica upon chemical break-

down. It is possible that the disease described herein was precipitated by an unusual type of exposure to silica, but this seems unlikely. The most attractive potential causative agent is meta-phenylenediamine. In the company facilities, this agent was used most commonly in Building 186. Second, Patient 1 was subjected to heavy exposure several times shortly before the development of an epidemic syndrome, which included lung involvement. Finally, as detailed earlier, other biogenic amines have been implicated in the development of scleroderma-like illnesses.

Although chemically induced systemic sclerosis may account for only a small fraction of scleroderma cases, the recognition of specific causative agents may ultimately lead to an improved understanding of the mechanism of disease induction, including vascular, immunologic, and fibroproliferative events, and possibly to the development of rational therapy.

REFERENCES

1. Medsger T: Systemic sclerosis (scleroderma), esophageal dysmotility and calcinosis. In McGarity CL, ed. *Arthritis and allied conditions*. 9th ed. Philadelphia: Lea and Febiger, 1985: 996-1034.
2. Owens G, Fink G, Herdort D, et al: Pulmonary function in progressive systemic sclerosis: comparison of CREST syndrome variant with diffuse scleroderma. *Chest* 1983; 84: 546-550.
3. Stupi A, Steen V, Owens G, Barnes L, Rodnan G, Medsger T: Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986; 29: 515-524.
4. Rodnan G, Benedek T, Medsger T, Cammarata R: The association of progressive systemic sclerosis (scleroderma) with coal miners' pneumoconiosis and other forms of silicosis. *Ann Intern Med* 1967; 66: 323-334.
5. Yamakage A, Ishikawa M, Saito Y, Hattori A: Occupational scleroderma-like disorder occurring in men engaged in the polymerization of acrylonitrile. *Dermatologica* 1980; 161: 11-19.
6. Wenzel-Fuld A, Dea-fenholz A, Eulzer-Volpels J, Podmore-Ripoll A: Toxic oil syndrome: a syndrome with features overlapping those of various forms of scleroderma. *Dermatol Immunol Rheum* 1986; 12: 100-110.
7. Garbino E, Van Veen M, Chung S, et al: Development of a scleroderma-like illness during therapy with 5-fluorouracil, cytoposin and carboplatin. *N Engl J Med* 1980; 303: 730-731.
8. Singer W, Rodnan G, Buchanan R, et al: Scleroderma-like illness after chemotherapy. *J Rheumatol* 1980; 7: 651-653.
9. Barnes L, Steen V, Owens G, et al: Scleroderma-like illness after chemotherapy. *Ann Intern Med* 1987; 107: 113.
10. Medsger T: Epidemiology of progressive systemic sclerosis. *Arthritis Rheum* 1979; 22: 15-25.
11. Grossman L: Scleroderma: a complex disorder. *Ann Intern Med* 1977; 86: 1-11.
12. Lawrence J, Lawrence J, Lawrence J, et al: Scleroderma-like illness after chemotherapy. *Ann Intern Med* 1987; 107: 113.
13. Barnes L, Steen V, Owens G, et al: Scleroderma-like illness after chemotherapy. *Ann Intern Med* 1987; 107: 113.
14. Barnes L, Steen V, Owens G, et al: Scleroderma-like illness after chemotherapy. *Ann Intern Med* 1987; 107: 113.
15. Haustein U, Jeger H, Schunke E, Muntzner H, Kopp H: Progression of systemic sclerosis with calcinosis in the German Democratic Republic. In S. J. Myers A, ed. *Systemic sclerosis (scleroderma)*. New York: Raven Press, 1985: 138-141.
16. Yamakage A, Ishikawa M, Medsger T, Rodnan G: Occupational scleroderma-like disease after coalminers' pneumoconiosis. Observations on Japanese patients and the Japanese literature. *Arthritis Rheum* 1984; 27: 141-142.
17. Longauer-Lewandowska M, Kurzbaue M, Byczkowska Z, Wocka Marek T: Scleroderma-like disease, neurological disturbances. *Int Arch Occup Environ Health* 1983; 52: 151-157.
18. Veitman G, Lange D, June S, Stein G, Bachner V: Clinical manifestations and course of vinyl chloride disease. *Ann NY Acad Sci* 1975; 246: 6-17.
19. Black C, Pereira S, Macmillan A, Nelson K, Laurent P: Genetic studies of the scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. *J Rheumatol* 1986; 13: 1059-1063.
20. Yamakage A, Ishikawa M: Generalized morphea-like scleroderma occurring in people exposed to organic solvents. *Dermatologica* 1982; 165: 186-193.
21. Fries J, Lindgren U, Bur J: Scleroderma-like lesions and the CREST syndrome. *Arch Intern Med* 1973; 131: 550-553.
22. Sainan E, Burton J, Keaton K: A new syndrome with pigmentation, scleroderma, gynecomastia, Raynaud's phenomenon, and peripheral neuropathy. *Br J Dermatol* 1973; 89: 437-440.
23. Pinot-Hansen H, Jager H: Scleroderma after occupational exposure to methylene chloride and trichloroethylene. *Acta Derm Venereol (Stockh)* 1977; 57: 160-164.
24. Lockey J, Kelly C, Dunlop J, et al: Scleroderma-like illness after exposure to systemic sclerosis associated with exposure to methylene chloride. *J Clin Invest* 1987; 79: 165-166.
25. Spornow G: A connective tissue disorder similar to scleroderma in a patient exposed to perchlorethylene. *Br J Dermatol* 1977; 57: 17-20.
26. Vaider B: Do solvents cause scleroderma-like illness. *Dermatol* 1980; 162: 1374-1375.
27. Eide G, Pratt C, Marx J: Diffuse pulmonary injury following perchlorethylene exposure. *Am J Med* 1986; 81: 702-704.