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III. A Clinical Study

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Four subjects with acroosteolysis were studied clinically. All had osteolytic lesions, especially in the distal phalanges of the hands, and Raynaud's phenomenon. All had worked as polyvinyl chloride reactor-vessel cleaners, with hand scraping being the common mode of operation. Raynaud's phenomenon antedated osteolytic lesions. One of the subjects was in negative calcium and phosphorus balance. Plethysmographic abnormalities were present in three. Esophageal motility was normal. Scintiscans of the hands using sodium fluoride labelled with radioactive fluorine (^{18}F) revealed variable uptakes in the fingers which correlated with the radiographic lesions. A wide variety of clinical laboratory parameters were normal.

OCCUPATIONAL acroosteolysis (AOL) consists primarily of Raynaud's phenomenon and osteolysis of the distal phalanges in the hands. Suciu et al first described Raynaud's phenomenon in polyvinyl workers in 1963.¹ Osteolytic lesions were reported in other cases.²⁻⁷ Other associated clinical features such as hepatomegaly, the cutaneous stigmata of scleroderma, hypothyroid parameters, and numerous abnormal laboratory tests have been reported.¹⁻⁷ Epidemiologically, patients with AOL are associated with the manufacture of vinyl chloride polymers, more specifically with the hand cleaning of the polymerization reactors.

This paper reports the results of intensive clinical investigation of four patients with AOL. These four patients were selected from those employees of 32 plants engaged in the manufacture of vinyl chloride polymers throughout the United States.

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Methods

Each patient was admitted to the Clinical Research Unit, University of Michigan Hospital, for a two-week period where detailed medical histories were investigated and physical examinations performed. Details of the work histories and environmental exposures were derived from in-plant epidemiological studies carried out jointly by the Institute of Environmental and Industrial Health of the University of Michigan and the Manufacturing Chemists' Association. Table 1 lists the laboratory parameters applied. In addition, calcium and phosphorus balance studies were carried out, using a dietary history to establish a constant calcium-phosphorus intake to which each patient was accustomed. Daily 24-hour urine specimens were collected, and stool specimens were pooled every three days for calcium and phosphorus determinations. Appropriate correctional computations for unabsorbed foods were made. Catecholamines and 5-hydroxyindole acetic acid were determined on 24-hour urine collections, often partitioned by six-hour units and usually collected on days of provocative cold stresses during plethysmographic determinations.

Numerous roentgenographic techniques were introduced, ranging from skeletal survey films to barium swallow radiographs and bone xerography. Scans of the hands and sacral region, using sodium fluoride labelled with radioactive fluorine (^{18}F), were undertaken in two of the patients. Plethysmography of the forearms and hands, using the method of Zweifler et al, was employed.⁸ Esophageal motility studies were made, using Saladin et al's technique.⁹

Results

History.—Blanching of the hands was the first sign of AOL. In two of the men, the onset was gradual over a few weeks, and in two it was abrupt, as shown in Table 2. Cold was the inciting factor in all cases. The blanching was associated with either tingling of the hands or tenderness of the fingertips. The polyvinyl work exposure to first blanching ranged from one to 23

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Fig 1.—Note transverse defects in distal phalanges of fingers one to four on left hand and fingers one to three on right hand. Marginal defect is present in distal portion of distal phalanx of right fifth finger (case 1).

Table 1.—Laboratory Investigation of AOL Patients

Biochemistry		Serum Enzymes	
Sodium	Calcium	Alkaline phosphatase	Threonine aldolase
Potassium	Phosphorus	Acid phosphatase	Malic dehydrogenase
Carbon dioxide	Cholesterol	Serum glutamic oxaloacetic transaminase	Glutamic dehydrogenase
Chloride	Glucose (fasting)	Serum glutamic pyruvic transaminase	Leucine aminopeptidase
Bilirubin direct/total	Magnesium	Lactic de hydrogenase isogram	Aldolase
Urea nitrogen	Lipids	5' Nucleotidase	Creatine phosphokinase
Creatinine	Phospholipids	Serine dehydrotase	Isocitrate dehydrogenase
Total serum protein	Triglycerides		
Electrophoresis serum	Catecholamines	Immunological Tests	
Albumin	Norepinephrine	Venereal Disease Research Laboratory	Antinuclear factor
α -1	Epinephrine	LE cell	Cryoglobulins
α -2		Direct Coomb's	Immunophoresis
β		Latex-rheumatoid factor	IgA
γ		Cold agglutinins	IgM
			IgG

months. The length of the interval bore relationship to the mode of onset or the severity of the symptoms.

A summary of the habits and dietary history of these patients is detailed in Table 3. Three of the four men were cigarette smokers with smoking histories of nine

(case 1), 15 (case 4), and 25 (case 2) pack-years. Half drank coffee (three or nine cups per day). All were casual tea drinkers. Three drank between three and 18 bottles of beer each month. One (case 4) drank 120 cans of beer per month but no whiskey while the others consumed less than four

Fig 2.—Hands show further resorption of bone, resulting in shortening of terminal phalanges of all fingers except left fifth and right fourth, latter having developed transverse defect. Right fifth finger has shown additional resorption of distal phalangeal tip. Soft-tissue clubbing is related to shortened phalanges (case 1).



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Table 5.—Physical Findings on Patients With AOL

Physical Findings	Case 1	Case 2	Case 3	Case 4
Skin				
Dorsal-thickening hands	+	+*	+	—
Blanching				
Without cold	—	—	†	+
With cold	+	+	+	+
Joints				
Synorial thickening	PIPI MP† Knees	PIPI	—	—
Incidental	Dupuytren's contracture Finger R 2 and 3 L 3 and 4	Thickening of wrist extensors	Shortening of finger tips	

* Also fingers.

† Proximal interphalangeal.

‡ Metacarpophalangeal.



Fig 3.—Erosive and sclerotic changes in sacro-iliac joints bilaterally (case 1).

Fig 4.—Erosive lesions of os calcis posterior to bony spur (case 1).



imens which were sometimes partitioned in six-hour increments (Table 6). One patient's third-period value of 2.8 occurred during a cold stress while plethysmography was being done (case 1). Another patient's third value of 1.6 did not increase under similar cold stress (case 2).

Plethysmographic studies revealed normal pulse volumes in all but one patient (case 2). All patients except one (case 3) showed diminished pulse volumes with cold stress typical of the

Raynaud's phenomenon observed in other diseases. Esophageal motor activity was normal in all subjects as shown by barium fluoroscopy and Saladin's et al motility technique.⁹

Radiological Findings.—The radiographic findings of the four patients analyzed are summarized in the case report.

Report of Cases

CASE 1.—X-ray films made elsewhere prior to the patient's hospitalization at the University of Michigan exhibited normal hands on Oct 20, 1968, and, in 1967, showed marginal bone defects of the right third and left second, third, and fourth distal phalanges and distal fragmentation of the distal phalanx of the left first digit. On Aug 8, 1967, transverse defects were noted on the distal phalanges of the left fingers one to four and right one to three, with resorption of the distal portion of the distal phalanx of the right fifth finger. The appearance of the hands on Oct 12, 1967, when the patient was first seen, is shown in Fig 1. Some reparative changes were noted in comparison with the previous films, with persistent transverse defects in fingers one to four on the left and one to three on the right with a marginal defect in the distal portion of the distal phalanx of the right fifth finger. Further check-up examination was obtained on Jan 9, 1969, and Oct 24, 1969, the latter being shown in Fig 2.

During this period of time, there has been further resorption of bone, resulting in shortening of the terminal phalanges of all fingers except the left fifth, which has remained uninvolved, and the right fourth, which has maintained its length but has developed a transverse

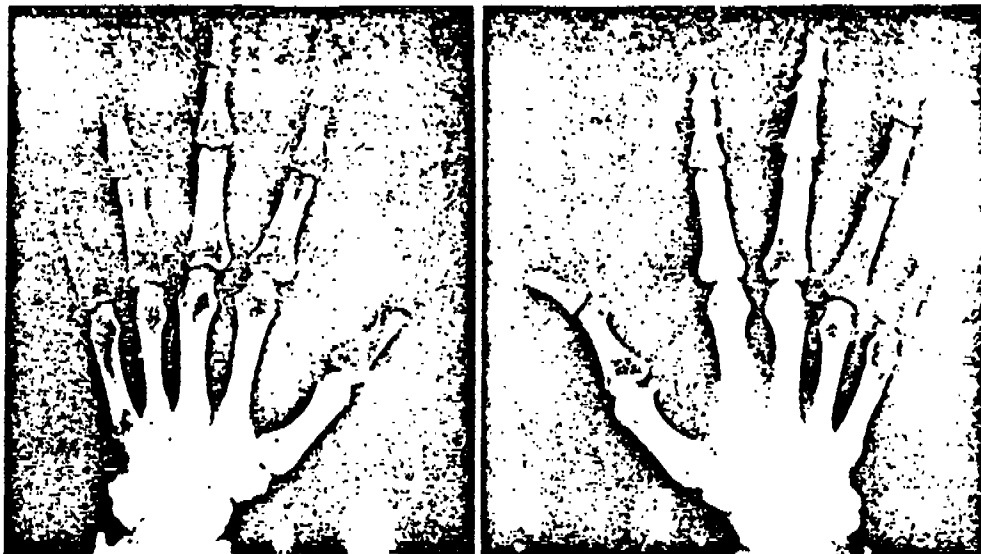


Fig 5.—Left hand shows marginal defect at tip of distal phalanx of second finger, with transverse defect in distal phalanx of third finger. Right hand shows transverse defects in distal phalanges of second and third fingers and an additional distal marginal defect of second finger (top [case 2]). Scintigram shows uptake of sodium fluoride ^{22}F (bottom).



Fig 6.—Sacro-iliac joints show erosive and sclerotic changes, more marked on left (case 2).



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Table 8.—Five-hydroxyindole Acetic Acid and Catecholamine Studies in Patients With AOL

Urinary Excretion	Case 1			Case 2			Case 3			Case 4		
	Mg	Urine Volume	Creatinine	Mg	Urine Volume	Creatinine	Mg	Urine Volume	Creatinine	Mg	Urine Volume	Creatinine
Five-hydroxyindole acetic acid												
8am-2pm	0.78	390	0.36	2.0	265	0.59				390		0.30
2pm-8pm	0.92	460	0.42	2.2	240	0.54				1,208		0.97
8pm-2am	2.80	730	0.62	1.2	300	0.69				416		0.33
2am-8am	0.89	140	0.12	1.6	210	0.48				430		0.34
Total (1)	5.39	1,720	1.52	7.0	1,015	2.30				2,444		1.94
Total (2)	5.8	2,170	1.47	...	...	...				...		...
Total (3)	4.0	1,720	1.46	...	...	...				...		...
Catecholamine	7.6											
Epinephrine							23.6					
Norepinephrine							6.1					

defect. The right fifth finger has shown additional resorption of the phalangeal tip. Soft-tissue clubbing is noted in the shortened phalanges. Some sclerosis is noted along the margins adjacent to the transverse defects. This patient also showed extensive erosive and sclerotic changes in the sacro-iliac joints, as seen in Fig 3. An erosive lesion was also found in the plantar surface of the os calcis, as depicted in Fig 4.

CASE 2.—This patient had an extensive skeletal survey on Feb 8, 1968, with positive findings limited to the hands and pelvis.

As shown in Fig 5, the left hand revealed a marginal defect at the tip of the distal phalanx of the second finger while the third finger showed a transverse defect in the distal phalanx. At the same time, the right hand present-

ed transverse lytic defects in the distal phalanges of the second and third fingers and an additional distal marginal defect of the second finger.

Figure 5 compares a typical sodium fluoride ^{18}F scintiscan of the hands and the corresponding roentgenograms. A slight increase in sodium fluoride ^{18}F uptake is seen in the distal phalanges of the left third and right second and third fingers while the uptake is diminished over the distal phalanges of the left fifth and right fourth and fifth fingers. Generally, uptakes over the remaining bones of the hands are uniform.

The sacro-iliac joints also displayed extensive erosive and sclerotic change, more marked on the left, as shown in Fig 6.

CASE 3.—Extensive skeletal survey on this

Fig 7.—Hands show shortening and widening of distal phalanges of all fingers, with resultant clubbing of soft tissues (case 3).



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patient on March 18, 1968, showed shortening and widening of the distal phalanges of all fingers (Fig 7), with resultant clubbing of the soft tissues. These changes were interpreted as the end stages of healing of AOL. The sacro-iliac joints showed erosive and sclerotic changes, more marked on the right (Fig 8).

Review of previous x-ray films made elsewhere indicated that some sacro-iliac joint changes were present on April 8, 1959, and that the hands had not changed in appearance since October 1966.

CASE 4.—Review of previous x-ray films made of this patient indicated that no abnormality of the hands was present on Feb 20, 1967, or Jan 23, 1968. On July 15, 1968, films of the sacro-iliac joints exhibited erosive and sclerotic changes, and the hands revealed marginal defect of the distal phalanges of the left third and the right fourth fingers, slight irregularity of distal phalanx of the right fifth finger, and transverse defects of the distal phalanges of the thumbs bilaterally.

Skeletal survey on Oct 20, 1968, noted separation of the tip of the styloid process of the right ulna, marked resorptive and sclerotic changes of the sacro-iliac joints (Fig 9), and some progression of the hand involvement, with transverse defects now involving the distal phalanges of the left digits one to three and

Fig 10.—Hands show transverse defects in distal phalanges of left fingers one to three and right fingers one and four, with an additional marginal defect of left second finger (case 4).

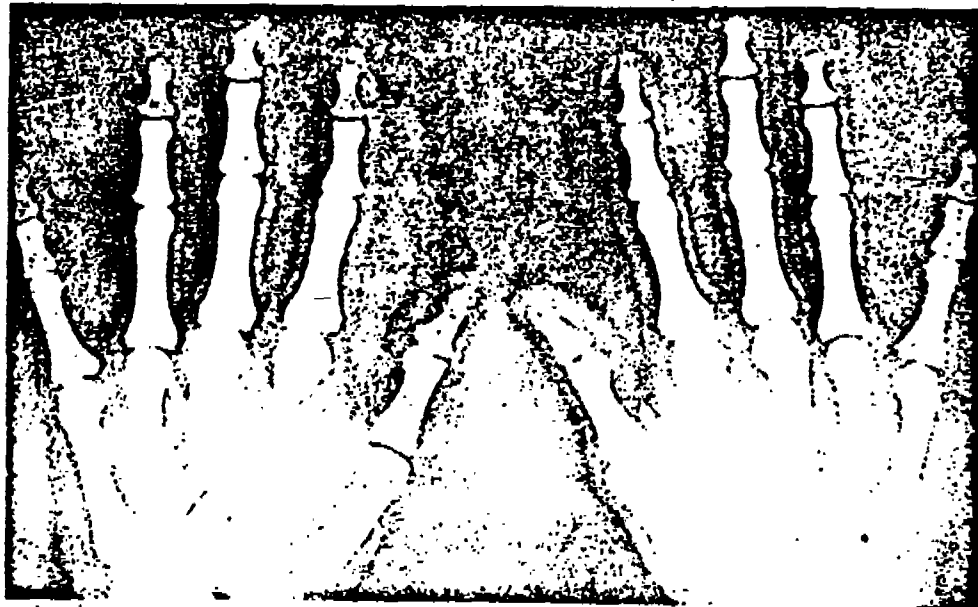


Fig 2.—Sacro-iliac joints show erosive and sclerotic changes, more marked on right (case 3).



Fig 9.—Sacro-iliac joints show erosive and sclerotic changes bilaterally (case 4).

right digits one and four and an additional marginal defect of the left second digit (Fig 10). Irregularity of the lower pole of the right patella was also noted.

Comments

Raynaud's phenomenon was the first manifestation noted by these subjects and in the majority of the cases reported. Harris and Adams³ reported one case in which distal digit shortening occurred first, while Wilson et al⁴ noted this in five of his 31 cases. This suggests that the vascular lesion tends to antecede the bone changes in most individuals. None of these patients exhibited Raynaud's phenomenon of the feet, which confirms Wilson et al's experience. All of these individuals had been "reactor cleaners" i.e., they spent some hours each week cleaning the polyvinyl chloride polymerization kettles shortly prior to or at the time of the onset of their disease. No consistent relationship was found between the occurrence of severity of either Raynaud's phenomenon or the osteolytic lesions and those habit patterns which have been shown to influence vascular responses, eg, cigarette smoking and the ingestion of alcohol, coffee, or tea. Likewise, neither the bone lesions nor Raynaud's phenomenon seemed to correlate with the daily consumption of milk or dietary calcium. Dallas and Nordin¹⁰ have shown that while dietary deficiencies or calcium may or may not potentiate osteoporosis of various types, an adequate calcium intake of 15 mg/kg is protective. Only one patient (case 2) had less than this amount (5.8 mg/kg). Since such dietary histories have been shown to be quite reliable,¹¹ their habitual calcium intakes do not appear to be a consistent causative factor in their cases. Likewise, the calcium-phosphorus balance studies on these men reveal no clear-cut abnormality or pattern. This result might be anticipated since these men have been away from reactor cleaning for several months, and the mass of involved bone is slight compared to the entire skeleton. However, it should be pointed out that a two-week balance period is a short observation period though they were placed on calcium and phosphorus intakes comparable to their usual eating habits to obviate disruption of their "steady state."

At first glance, it appeared that there was a rich history of heart disease or hypertension or both in the parents of these men. Comparison of them with healthy male chemical workers not involved in polyvinyl chloride manufacture and matched in age suggests a significant correlation by the χ^2 test, using Yate's correction. Whether such an observation suggests a hereditary frailty to explain the susceptibility of those individuals developing AOL is speculative. The number of observations is too small to support seriously such a contention at this time.

The extent and character of other muscular skeletal findings such as tendon and synovial thickening confirm the findings of others.

We are able to offer no suitable explanation for the frequent episodes of intermittent orthostatic tinnitus described by three of these men.

Suciu et al described liver enlargement, various vague asthenic symptoms, and manifestations of hypothyroidism. Such findings were not present in these men or had they been in the past.

The radiological findings in occupational AOL have been reviewed recently on the basis of the epidemiological investigation of the polyvinyl chloride industry. Workers in other countries have described lytic lesions in the distal phalanges of the hands, styloid processes of the ulna and radius, and the sacro-iliac joints.^{1,2,4}

These four patients demonstrate the entire spectrum of radiographic hand changes in occupational AOL from the earliest marginal erosion of the distal phalanx through the extensive transverse defect, with ultimate healing resulting in a short and wide phalanx. The fact that all four showed sacro-iliac involvement suggests that the incidence of involvement at this site is probably higher than previously suspected.

The additional smaller abnormalities found in the ulnar styloid, on calcia, and lower pole of the patella suggest that these areas might well be evaluated in other cases as they appear in order to get a more accurate estimate of their incidence.

The sodium fluoride ²⁴F scintiscan data suggests that the more advanced osteolytic changes with transverse defects at this time were picking up more fluorine and probably