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Occupational Acroosteolysis

I. An Epidemiological Study

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An epidemiological study was performed covering 5,011 employees with 21,510 man-years experience in various phases of vinyl chloride (VC) and polyvinyl chloride (PVC) manufacturing in 32 plants throughout the United States and Canada. The total number of definitive cases of acroosteolysis (AOL) was 25; 16 other individuals were under suspicion. This condition is clearly associated with the hand cleaning of polymerizers. Workers engaged in oither phases of VC or PVC manufacturing do not appear to be at risk of developing AOL. The importance of Raynaud's phenomenon as a concomitant of AOL is emphasized. Several statistical approaches for rapid medical survey are suggested. Acroosteolysis appears to be a systemic rather than local disease. Presently, neither the etiological agent nor its portal of entry is known.

WITH THE emergence of a new clinical entity, occupational acroosteolysis (AOL),[1] it became a manifest responsibility of the polyvinyl chloride (PVC) industry to define more clearly the character, extent, and possible causes of this disorder. Though individual corporations might survey their employees, a statistically valid construction of the problem could not be developed without collation of the health experience of all PVC producers. To maintain the privacy of proprietary information associated with details of manufacture, some disinterested group was needed to evaluate operating processes, as these might relate to the causation of AOL. Accordingly, the Manufacturing Chemists' Association requested the Institute of Industrial Health (Institute of Environmental and Industrial Health as of Jan 1, 1970) to conduct an epidemiological survey of the PVC industry in the United States and Canada to meet their responsibility to the workers and the public.

The institute was requested to determine the extent of the problem among PVC workers. By establishing a specific job association with AOL, it was hoped to determine where the risk of incurring AOL arose within the PVC process. It was important to determine whether AOL was associated only with the synthesis stage or if those handling the finished polymer also might be affected.

The primacy of this consideration stems from the widespread use of the polymer in the fabrication of a multitude of manufactured goods that enter general commerce. While the number of workers engaged in the chemical synthesis of PVC is relatively small, there are thousands of small manufacturers engaged in the fabrication of products derived from this versatile plastic.

Further, it was hoped that the epidemiological and industrial hygiene[2] investigation might define more precisely how variations in manufacturing processes might relate to variations in the prevalence of AOL among PVC producers. Medical and industrial hygiene studies might furnish some clues to the precise etiological agent(s) as well as suggest preventive measures that might be applied in the industry.

In addition, it was planned that a small,

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NAME ______________ Soc. Sec. No. ______
(5-13)

RACE W N Other ______ AGE _____ SEX M F
(14) (15-16) (17)

DEPT. NO. ______________
(18-19)

COMPANY SERVICE DATE ______________
Month (20-21) Year (22-23)

ARE YOU (RIGHT) (LEFT) HANDED?
(24)

Do Not Write in This Box

Corp. ______________
(1-2)

Plnt. ______________
(3-4)

TO ANSWER THE FOLLOWING QUESTIONS, PUT A CIRCLE AROUND YOUR ANSWER. FOR EXAMPLE: MONDAY IS THE DAY AFTER SUNDAY (YES) (NO)

Have you noticed SUDDEN whiteness, blanching, or paleness of the fingers of your	RIGHT HAND	(YES)	(NO)	25
	LEFT HAND	(YES)	(NO)	
Have you noticed a sudden redness or blueness of the fingers of your	RIGHT HAND	(YES)	(NO)	26
	LEFT HAND	(YES)	(NO)	
IF YOU HAVE NOTICED ANY OF THE ABOVE, are these changes brought on by cold	(YES)	(NO)	(DON'T KNOW)	27
HAVE YOUR HANDS OR FINGERS BEEN BOTHERED WITH ANY OF THE FOLLOWING:				
Tingling or pins-and-needles feeling	RIGHT HAND	(YES)	(NO)	28
	LEFT HAND	(YES)	(NO)	
Warm feeling in hands or fingers	RIGHT HAND	(YES)	(NO)	29
	LEFT HAND	(YES)	(NO)	
Cold feeling in hands or fingers	RIGHT HAND	(YES)	(NO)	30
	LEFT HAND	(YES)	(NO)	
Numbness, fingers fall asleep	RIGHT HAND	(YES)	(NO)	31
	LEFT HAND	(YES)	(NO)	
Stiffness, fullness, or tightness of fingers	RIGHT HAND	(YES)	(NO)	32
	LEFT HAND	(YES)	(NO)	
Frequent tenderness, soreness, or pain at fingertips	RIGHT HAND	(YES)	(NO)	33
	LEFT HAND	(YES)	(NO)	

Have you noticed any of the following changes of the skin of your hands, wrists, or arms:

Thickening of the skin	*(YES) (NO)	34
*If yes, is it on (HANDS) (WRISTS) (ARMS)		
White, raised patches of skin	*(YES) (NO)	35
*If yes, is it on (HANDS) (WRISTS) (ARMS)		
Whitish pimples	*(YES) (NO)	36
*If yes, is it on (HANDS) (WRISTS) (ARMS)		
Shiny skin patches	*(YES) (NO)	37
*If yes, is it on (HANDS) (WRISTS) (ARMS)		
Small, raised areas, or lumps less than 1/2 inch around (NOT including warts)	*(YES) (NO)	38
*If yes, is it on (HANDS) (WRISTS) (ARMS)		

Have you been bothered by these fingernail troubles:

Pits or scars of the fingernails	(YES) (NO)	39
Ridges or cracking of the fingernails	(YES) (NO)	40

Have you used hand-held power tools or air-driven tools at work in the past six years:

(DAILY) (ONCE A WEEK) (LESS THAN ONCE A WEEK) (NEVER) 41

Have you ever broken, fractured, or crushed a finger? (YES) (NO) 42

If yes, was it the	(RIGHT)	or	(LEFT) hand?	
Which finger was injured	(Thumb)		(Thumb)	
	(Index)		(Index)	
	(Middle)		(Middle)	43
	(Ring)		(Ring)	
	(Little)		(Little)	

selected sample of workers affected with AOL be studied in the clinical research unit of the University of Michigan Medical Center.[3] Previously, Rousch and co-workers[4] performed an extensive clinical evaluation of a group of such workers. Subsequent examinations here were designed to determine whether any new clinical features had developed since those prior studies.

Polyvinyl Chloride Manufacturing: A Brief Review

A more definitive description of the process whereby PVC is synthesized, finished, and compounded is reported elsewhere in this issue.[2] A brief review of the operation is appropriate to the premises underlying the epidemiological considerations.

Vinyl chloride (VC), together with water, peroxide catalysts, and other additives, are placed in a reactor where polymerization is completed after ten to 16 hours. Unreacted VC is exhausted from the reaction vessel and the suspension or emulsion of the plastic transferred to equipment for dewatering and drying. Following ventilation of the reactor, one or two workers enter the vessel to remove the residue from its surfaces, using putty knives or chisels.

Sixteen plants, in addition to synthesizing, also compound PVC while five plants are engaged only in compounding the resin.

Methods

Survey Techniques.—Nineteen corporations known to be engaged in the polymerization of VC were assessed. The workers who served as the study populations were employed in 32 plants in the United States and Canada. All employees who worked at the time of the survey, or in the past, in any capacity in plants manufacturing VC, PVC, or in compounding such resin were surveyed. In multiple-product plants, all workers having any possible exposure to the PVC process were studied. This population underwent medical survey, work history questionnaires, and hand x-ray filming.

The self-completion medical questionnaire was designed to probe for signs of Raynaud's phenomenon or symptoms associated with peripheral vascular insufficiency. In addition, questions were posed to disclose skin or dermal appendage abnormalities, use of power tools, and hand-injury history.

X-ray films of both hands were requested from the cooperating plants; specific directions concerning film type, exposure factors, technique, and identification were sent to each plant. The x-ray films, when forwarded to the institute, were coded and transmitted without identification to two radiologists for independent interpretation. The findings were recorded on a specifically designed checklist which was then returned for statistical collation. Hand x-ray films that served as controls were drawn from 2,407 men over age 18; this represented the entire male population of the town of Tecumseh, Mich.

Work history questionnaires were completed by each individual employee or by the personnel department at each plant or both. These forms recorded work assignments between Jan 1, 1961, through Dec 31, 1966; each worker noted the first and last month of assignment for each specific assignment during that period. At each plant, a team of investigators converted local job designations to standard job titles. These are listed in the paper on the industrial hygiene aspects.[2]

Pilot Run

In order to determine the reliability of survey techniques and recording methodological patterns, a pilot run was carried out at one large plant. Following this, minor modification of procedures and forms was accomplished.

Epidemiological Design.—Acroosteolysis appeared to consist of characteristic x-ray film abnormalities and Raynaud's phenomenon. Since the latter would be expected to occur only infrequently in a population not at risk of developing AOL, it could be used as a prime indicator of the existence of AOL. Thus, we hoped to establish an initial distinction between two populations, ie, one having AOL and the other not having it.

Comparison of prevalence of defects with the Tecumseh control population of 2,407 men suggested that all defects occurred in the PVC population with a greater frequency than in the control population (Table 1). However, the significance of this finding was clouded by an unavoidable bias which minimized the value of the Tecumseh population as a control group, ie, identification marks which could not be readily obliterated were present on these control films.

Furthermore, as is apparent from previous discussions of the x-ray film abnormalities, linear radiolucent defects could be confused with old trauma, the absence of a tuft might

Table 1.—*Prevalence of X-Ray Film Defects in Control and PVC Populations*

		Control, N = 2,407		PVC Population, N = 5,011	
	Defect No.	No.	%	No.	%
Marginal defect	1	44	1.83	321	6.41
Marginal defect, with residual fragment	2	5	0.21	35	0.70
Transverse defect	3	6	0.25	40	0.80
Transverse defect, with distal fragmentation	4	0	...	21	0.42
Total resorption of distal portion phalanx	5	2	0.08	9	0.18
Sclerosis, with recalcification	6	1	0.004	15	0.30
Shortening	7	11	0.46	63	1.26
Widening of tuft	8	4	0.17	43	0.86
Widening of shaft	9	1	0.004	7	0.14
Soft-tissue clubbing	10	2	0.08	40	0.80
Total	55	76	3.16	594	11.87

follow amputation, or shortened phalanges could be consistent with a congenital defect. Defects such as sclerosis of the shafts, widening of the tufts, and soft-tissue clubbing were each susceptible to subjective reader error. Furthermore, each of these defects could arise from other bony disease or injury. Even multiple finger involvement could be consistent with these etiological possibilities. Because these problems did exist, significant divergencies in x-ray film interpretations were found (Table 2).

Because of these complexities, for the purposes of first appraisal, marginal defects of the phalangeal tuft (defect 1) were not considered as indicative of AOL unless both roentgenologists independently concurred as to the presence of this abnormality. The existence of marginal defects with residual fragment(s) (defect 2), transverse defects (defect 3), transverse defect with distal fragmentation (defect 4), and total resorption of distal portion of phalanx (defect 5) were considered as possibly diagnostic of the bony defect of AOL if found by only one radiologist and if other causes for these defects could not be eliminated. Every man with any of these five abberations was followed up subsequent to the field survey. If there was a history of trauma involving the involved finger or if the appearance of these x-ray film lesions was clearly consistent with trauma, these individuals were eliminated from suspicion.

Other x-ray film defects of an even less specific nature are known to be associated with the later stages of AOL but are not in themselves considered diagnostic. These x-ray film findings included sclerosis of the phalanges (defect 7), widening of the tuft (defect 8) or of the shaft (defect 9), and soft-tissue clubbing (defect 10). Finally, we looked with suspicion upon any bony defects involving multiple fingers regardless of whether they were AOL-specific (ie, defects 2 to 5).

In addition to those defects previously reported to occur in conjunction with AOL, those x-ray film abnormalities unrelated to AOL were grouped as defect 11.

Combining the x-ray film findings and Raynaud's, several diagnostic criteria were set up (Table 3). The diagnostic criteria for category 0 consisted of essentially normal workers while category 1 included individuals having x-ray film abnormalities which by history or radiographic evaluation or both were found to be consistent with old trauma, disease other than AOL, congenital or familial defects, etc. The history of persons in diagnostic category 3 disclosed cold-induced finger blanching unassociated with x-ray film abnormalities, clearly meeting our criteria for AOL. Category 4 consisted of persons without Raynaud's phenomenon and suggestive, though not diagnostic, x-ray films for AOL. Category 5 included those with classical AOL x-ray film defects (2 to 5 and 1, 6, and 7 without and with concurrence, respectively) and Raynaud's phenomenon. Category 6 had typical AOL bone abnormalities (as diagnosed in category 5) but without Raynaud-positive replies to the medical questionnaire.

Computational and Statistical Analysis. —Medical and work questionnaires and x-ray film reports were checked for completeness. They were then coded, verified, punched, and stored in an electronic computer. Quality control checking of the punch cards, using a 25% sample, revealed an error of 0.1% among these cards.

Table 2.—Agreement and Number of Fingers Showing X-Ray Film Defects in 1,302* PVC Workers

	Defect No.		No. of Fingers Involved 1	2	3	4	5	6	7	8	9	10	Total	Negative for Specific Defect	% Agree
Marginal defect	1	Agree	30	3	0	1	0	0	0	—	—	—	34		
		Disagree	237	30	11	4	3	1	1	—	—	—	287	981	10.6
		Total	267	33	11	5	3	1	1	—	—	—	321		
Marginal defect, with residual fragment	2	Agree	6	1	—	—	—	—	—	—	—	—	7		
		Disagree	27	1	—	—	—	—	—	—	—	—	28	1,267	20.0
		Total	33	2	—	—	—	—	—	—	—	—	35		
Transverse defect	3	Agree	9	0	—	2	0	0	—	—	—	1	12		
		Disagree	25	1	—	0	1	1	—	—	—	0	28	1,262	30.0
		Total	34	1	—	2	1	1	—	—	—	1	40		
Transverse defect, with distal fragmentation	4	Agree	1	—	1	—	—	—	—	—	—	—	2		
		Disagree	17	—	1	—	—	—	—	—	—	—	18	1,281	9.5
		Total	18	—	1	—	—	—	—	—	—	—	20		
Total resportion of distal portion phalanx	5	Agree	2	1	—	—	—	—	—	—	—	—	3		
		Disagree	5	1	—	—	—	—	—	—	—	—	6	1,293	33.3
		Total	7	2	—	—	—	—	—	—	—	—	9		
Sclerosis, with recalcification	6	Agree	0	1	0	1	—	0	—	—	—	—	2		
		Disagree	9	1	2	0	—	1	—	—	—	—	18	1,287	13.3
		Total	9	2	2	1	—	1	—	—	—	—	20		
Shortening	7	Agree	6	2	1	0	—	1	—	1	1	0	12		
		Disagree	39	6	1	1	—	1	—	2	1	1	52	1,238	18.9
		Total	45	8	2	1	—	2	—	3	2	1	64		
Shortening	7	Agree	6	2	1	0	—	1	—	1	1	0	12		
		Disagree	39	6	1	1	—	1	—	2	1	1	52	1,238	18.9
		Total	45	8	2	1	—	2	—	3	2	1	64		
Widening of tuft	8	Agree	0	1	—	—	—	0	—	0	—	—	1		
		Disagree	35	3	—	—	—	2	—	2	—	—	42	1,259	2.3
		Total	35	4	—	—	—	2	—	2	—	—	43		
Widening of shaft	9	Agree	0	0	—	0	0	0	—	—	—	—	0		
		Disagree	3	1	—	1	1	1	—	—	—	—	7	1,259	2.3
		Total	3	1	—	1	1	1	—	—	—	—	7		
Soft-tissue clubbing	10	Agree	3	0	—	0	0	0	0	—	1	—	5		
		Disagree	26	1	—	2	2	1	2	—	1	—	35	1,295	...
		Total	29	1	—	2	2	1	2	—	2	—	40		
Totals		Agree	57	9	2	4	0	2	0	1	2	1	78		
		Disagree	423	45	15	8	7	9	3	4	2	1	517		
		Total	480	54	17	12	7	11	3	5	4	2	595*		

* The difference between these two figures and those in the defect 11 category, ie, other defects, is not shown here.

Frequently, workers performed several different duties during a period spent on one assignment. Where this existed, an estimate was made at each plant of the fraction of time spent in each segment of the job assignment. Since the fraction 1/12 was used for each month a worker spent full time in various jobs during the year, it was convenient to use this fraction of 12ths where his daily or weekly work was divided between two or more jobs. Thus, if a worker spent one half his time performing one specific component of his assignment, the value of 6/12 was assigned to our standard job title for that time period on assignment. The remaining 50%, or 6/12, of his time was distributed over one or more applicable job components during the period of assignment. By this method, job experience on each of the standard jobs could be computed in terms of months or fractions thereof.

The computer was utilized to perform collation and statistical manipulations of data.

Clinical Evaluation of Positive Cases.—Four employees with active disease were admitted to the Clinical Research Unit of the University of Michigan Medical Center. Extensive clinical, laboratory, and physiological tests and radiographic, isotopic, nutritional, and metabolic balance studies were performed. The findings are reported in detail.[4]

Results

General Population Statistics.—The study population consisted of 5,011 workers, of which 96.4% were men; 95.7% were white, 4.1% Negro, and 0.2% other. The mean age was 35.8 years, with the median and modal range being 35 to 39 years. These workers were employed by 19 corporations at 32 plants in the United States and Canada; of the 32 plants, all but six were engaged in PVC synthesis. This number of plants represented 92% of the PVC synthesis industry in this country. The population at risk represented a total of 21,510 man years.

Population Analysis.—In order to construct several population groups for attribute comparisons, we applied our diagnostic criteria for AOL (ie, x-ray film defects 2 to 5 plus Raynaud's phenomenon). Using this approach, we found that the clearly defined cases of AOL were limited to seven plants. Using these same diagnostic criteria (Table 3), we detected another group of 21 plants which had all employees in category 0 and 1, or less than a total of two individuals in diagnostic category 3 (Raynaud's without bone change) or diagnostic category 4 ("AOL questionable" x-ray film without Raynaud's) or both. To determine whether there was a risk of developing AOL among those working with the finished polymer, we extracted for further analysis a third population group, constituted by the five plants whose employees worked exclusively with the finished PVC-producing consumer products. These three groupings left three individual plants in which there remained a question of AOL's existence. The distribution of diagnostic categories among these four populations appears in Table 4.

The reason for requiring the coexistence of x-ray film abnormality and Raynaud's phenomenon to establish the diagnosis of AOL becomes apparent upon consideration of the three individuals in diagnostic category 5 (ie, x-ray films characteristic of AOL but without Raynaud's phenomenon at time of survey). We determined by follow-up that of these three workers, two had manifested Raynaud's phenomenon during the 1950's prior to survey period. The third subject was re-x-rayed subsequent to the survey and demonstrated progressive changes characteristic of AOL; however, he has never noted Raynaud's disorder. In view of this finding that 24 of 25 workers with severe AOL-type x-ray film defects had associated Raynaud's phenomenon, we believe it is appropriate to link these two abberations in order definitively to diagnose AOL. Thus, using as our criteria Raynaud's phenomenon or finger defects qualified as above or both, 25 men were found to have clearly established cases of AOL.

Table 3.— *Roentgenographic and Symptomatic Criteria for Diagnostic Categories 0 to 6*

Diagnostic Category	Raynaud's Phenomenon	Hand X-Ray: Abnormal, Consistent With AOL	Specific X-Ray Defect, Consistent With AOL									
			1	2	3	4	5	6	7	8	9	10
0	–	–	–	–	–	–	–	–	–	–	–	–
1	–	±*	–	–	–	–	–	–	–	–	–	–
3	+	±		–	–	–	–	–	–	±	±	±†
4	–	±		–	–	–	–	±	±	±	±	±‡
5	+	+	+	+	+	+	+	+	+	+	+	+
6	–	+	+	+	+	+	+	+	+	+	+	+

* Indicates only those lesions that may be seen in AOL (defects 8 to 11 though not diagnostic of AOL.
† Single finger involved, no concurrence between readers.
‡ No concurrence between readers.

Table 4.—*Distribution of Diagnostic Categories Among Four Subpopulations With PVC Study Group*

	Total Population	Diagnostic Categories				
		0-1	3*	4†	5‡	6§
7 plants with cases of AOL	1,673	1,598	41	9	22	3
3 plants with questionable AOL	910	893	14	3	0	0
17 plants without AOL	1,873	1,851	17	3	0	0
5 plants compounding only	557	554	2	1	0	0
Totals	5,013	4,896	74	16	22	3

* Raynaud's phenomenon only.
† Questionable x-ray, no Raynaud's phenomenon.
‡ X-rays characteristic of AOL, with Raynaud's phenomenon.
§ X-rays characteristic of AOL, without Raynaud's phenomenon at time of survey.

Intrapopulation Differences

Signs and Symptoms.—We determined the number of workers in each of the four

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Table 5.—*Intergroup Prevalence of Raynaud's Phenomenon Not Associated With AOL (Corrected for Male Populations Only)*

	Diagnostic Category 3 Alone		Diagnostic Categories	
	No.	% Male Population	1-2	Total
Plants with cases of AOL	41	2.50	1,582	1,623
Plants without cases of AOL	19	0.82	2,294	2,313
Plants with questionable cases of AOL	14	1.70	817	831
Plants compounding only	1	0.23	438	439

Table 6.—*Abnormal Number of Cases of Raynaud's Phenomenon Occurring in Various Size PVC-Plant Populations**

Population Range	Abnormal No. of Raynaud's Phenomenon
25-44	3 or more†
45-82	4 or more
83-120	5 or more
121-180	6 or more
181-220	7 or more
221-280	8 or more
281-340	9 or more
341-400	10 or more
401-460	11 or more
461-500	12 or more

* $P = 0.01$.

† Raynaud's, as defined, is cold, white fingers brought on by hand or body chilling or both.

plant groups having one, two, three, etc, through 26 positive responses to questions concerning signs and symptoms. A graphical representation of the frequency with which respondents noted bilateral hand symptoms in those plants where AOL was believed to occur and in those free of AOL is provided in the Figure.

The one-tailed Kolmogorov-Smirnov (K-S) two-sample test[5] was applied to the two distributions. The same analysis was directed to the compounding plant population AOL-free plant group (see above). The distribution of positive signs and symptoms were found similar in both groups. Accordingly, for the "AOL-free" population in the Figure, we have included the employees of the compounding plants. On the basis of affirmative responses concerning the presence of any symptoms, this test indicated that these two distributions did not stem from a common population pool ($P < 0.001$).

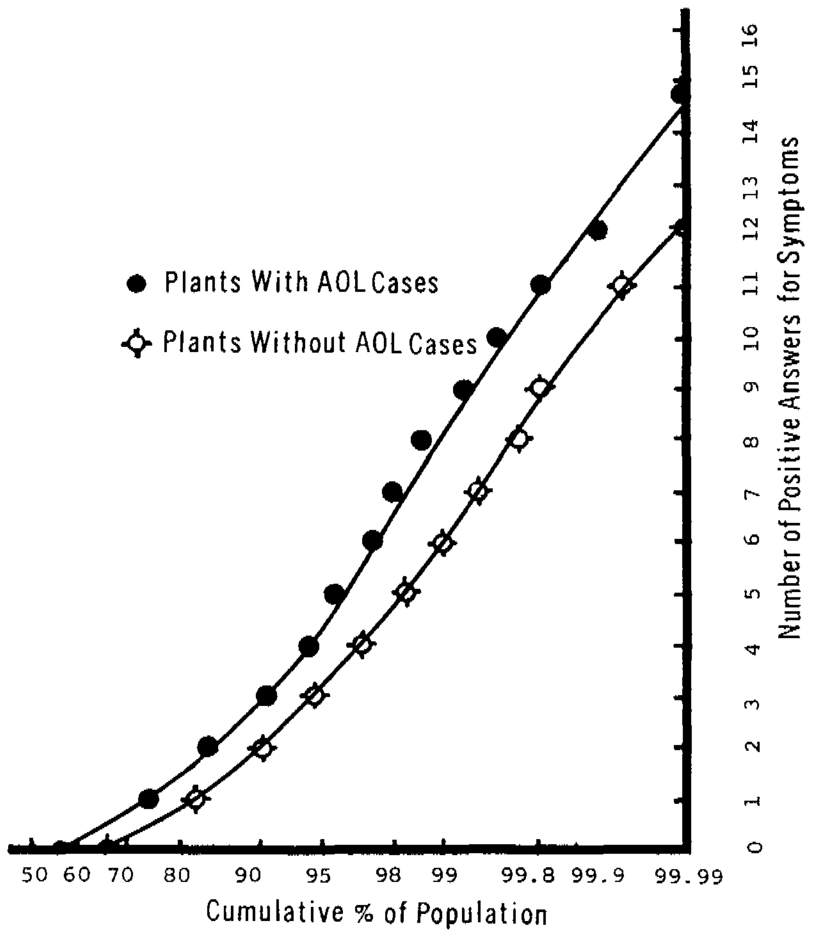
This K-S test indicates that the frequency of occurrence of the asymptomatic state (ie, zero symptoms, the Figure) was different in populations believed to be free of AOL as contrasted with those probably having cases of AOL (see above). This observation could be used to screen a group of workers at unknown risk of AOL development by simply determining how many individuals reported only a single symptom. In order to determine whether more intensive scrutiny of a group of 25 or more workers at unknown risk of developing AOL is warranted, one can use a test based upon the normal approximation of the binomial, with $p = \frac{2}{3}$:

$$\frac{\frac{2}{3} - p}{\sqrt{\frac{1}{3} \cdot \frac{2}{3} \cdot \frac{1}{n}}}$$

where n is the number of employees questioned, where n is 24 and p is the fraction of population free of symptoms. Should the value obtained exceed 1.65, further investigation of the population in question should be considered.

The foregoing analyses do not relate to any individual symptom sought by our medical questionnaire. These statistical approaches only considered the absence or presence of any one symptom. While these findings suggest the possibility of asking a single question to screen a population at risk of developing AOL, is there any one question that might be used as a more pertinent screening device?

Focusing once more upon Raynaud's phenomenon, we found, by the use of factor analysis,[6] that this peripheral vascular disorder was significantly related to AOL. That is, those questions which appear to be consistently answered positively as a group constitute a cluster of symptoms or a factor. In addition, each symptom is associated with factors by scores called "loadings," which weigh the associational strength of the factor to the question at hand, ie, the occur-



Cumulative frequency with which workers reported bilateral hand symptoms in plants with and without cases of AOL.

rence of AOL. The most significant of these clusterings of symptoms was found to be, by factor analysis, questions 25, 26, and 27 (questionnaire form), ie, indicators of Raynaud's phenomenon. Accordingly, this constitutes one reason for examining the prevalence of this particular symptom complex among any group at risk of AOL development.

This logically leads to an examination of the relative prevalence of Raynaud's phenomenon in our various plant-population subgroupings. However, because Raynaud's phenomenon is more frequently associated with women and since that sex represented a relatively small part of the total study population, we first removed the female respondents from our data pool. Applying χ^2 analysis, we found that the prevalence of Raynaud's phenomenon was significantly different in the plants believed to be free of AOL ($P < 0.01$) vs those known to have AOL cases, while no difference was found between the "AOL-free" plants and the compounding locations (Table 5). If indeed the "AOL-free" plants represent a population at no significant risk of developing this disorder, one might infer that Raynaud's phenomenon may occur

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Table 7.—*Intergroup Differences Between Four Groups of PVC Plants*

Question No.	7 Plants With Cases of AOL, n = 1,673 vs 17 Plants Without Cases of AOL, n = 1,873	7 Plants With Cases of AOL, n = 1,673 vs 5 Plants Compounding, n = 557	17 Plants Without Cases of AOL, n = 1,873 vs 5 Plants Compounding, n = 557	3 Plants With Cases of ? AOL, n = 910 vs 17 Plants With Cases of AOL, n = 1,673	3 Plants With Cases of ? AOL, n = 910 vs 17 Plants Without Cases of AOL, n = 1,873
25	+*	+	−†	−	−
26	+	−	−	−	−
28	+	−	−	+	−
29	+	−	−	−	−
30	+	−	−	+	−
31	+	−	+	+	−
32	−	+	−	+	+
33	+	−	−	−	−
34	+	+	−	+	−
35	−	−	−	−	−
36	+	+	−	+	−
37	+	+	−	−	−
38	−	−	−	−	−
39	−	−	−	−	−
40	−	+	−	+	−

* Significant difference, $P < 0.01$, χ^2 analysis.
† No significant difference, $P > 0.01$, χ^2 analysis.

among the general population in eight of 1,000 men. We are unaware of any epidemiological data confirming this impression.

Extending our screening approach, could one predict the number of cases of Raynaud's phenomenon which might indicate the need for further investigation? Since it appears that the general male population incidence of this circulatory disorder is less than 1% (Table 5), by application of the cumulative probability distribution of the binomial with $P = 0.01$, one can determine, for various sizes of plant population, the minimum number of positive responses indicative of a possible AOL problem. Table 6 indicates the number of cases of Raynaud's phenomenon which would only rarely occur by chance ($P < 0.01$) in various size populations.

All signs and symptoms believed to be associated with AOL were compared as to their intergroup prevalences (Table 7). There were considerable differences in the prevalence of most signs and symptoms between the plants with and without AOL while the compounding plants appeared not to be dissimilar from the population believed to be free of AOL. By contrast, the group about which doubt existed as to the occurrence of AOL appeared to be somewhat more like the AOL-free group than the AOL-affected population.

Work History Analysis

A detailed review of the 25 clearly established cases of AOL revealed that 18 persons had worked in reactor cleaning at some time during the study; additionally, six others, by follow-up, were found to have worked at this task prior to the study. The one man who had no history of production-line polycleaning was a laboratory technician. However, detailed review of his work history indicated experience with bench-scale reactor operation; this job included hand cleaning of small reactor vessels. Thus, the association of hand cleaning of reactors and AOL disease was striking. Because of job progression practices, practically all persons suffering from AOL had worked at other PVC production jobs at one time or another. Since the lowest paying jobs, ie, reactor cleaning and bagging-packing, are given to newcomers, most production workers were given these jobs before progressing upward into the skilled jobs. The fact of this upward progression is underlined by work histories

Table 8.—Prevalence of AOL by Diagnostic Category and Reactor Cleaning Exposure (Job 17)

	Prevalence		
	Reporting Reactor Cleaning Experience, 1961-1966	Reporting Any Reactor Cleaning Experience, by Follow-up	Questionable or no History, Reactor Cleaning
Definitive cases (ie, diagnostic categories 5 and 6) of AOL, 25			
Total workers at risk, reactor cleaning, 1,047	$\frac{18^*}{1,047} = \frac{1}{58} =$ case per workers	$\frac{24}{1,047} = \frac{1}{41} =$ case per workers	$\frac{1}{1,047} =$ case per workers
Total man-years, reactor cleaning experience, 1,082	$\frac{18^*}{1,082} = \frac{1}{60} =$ case per man years	$\frac{24}{1,082} = \frac{1}{45} =$ case per man years	$\frac{1}{1,082} =$ case per man years
Definitive and possible cases (diagnostic categories 3, 5, and 6), 41			
Total workers at risk, reactor cleaning, 1,047	$\frac{(18^*+10^*)}{1,047} = \frac{1}{37} =$ case per workers	...	...
Total man-years, reactor cleaning, 1,082	$\frac{(18^*+10^*)}{1,082} = \frac{1}{39} =$ case per man years	...	...
Total PVC work force, male			
Men at risk, 4,751	$\frac{28}{4,751} = \frac{1}{170} =$ case per male employees in PVC study population	$\frac{(28+6\dagger)}{4,751} = \frac{1}{140} =$ case per male employees in PVC study population	$\frac{7\ddagger}{4,751} = \frac{1}{679} =$ employees in PVC study population
Total man-years in PVC population, 21,510	$\frac{1}{768} =$ case per man-years in PVC study population	$\frac{34}{21,510} = \frac{1}{633} =$ case per man-years in PVC study population	$\frac{7}{21,510} = \frac{1}{3,073} =$ man-years in PVC study population

* By analysis of survey data.
† Based on postsurvey follow-up; six workers in diagnostic categories 5 and 6 were determined to have had reactor cleaning experience; similar data not available for diagnostic category 3 population.
‡ Assumes that six workers in diagnostic category 3 had had no reactor cleaning experience.

of men with AOL; only experience as bagger-packer or reactor operator approached the frequency of experience of reactor cleaning.

Reactor cleaning has a strong association with AOL. The prevalence of AOL in reactor cleaners was one case per 72 workers at risk (total population at risk, 1,047) among all workers having a history of such job experience. For job categories larger than 500 men, the prevalence rate of AOL by job was greatest for bagger-packers (one case of AOL per 86 workers at risk out of a total population of 860) and reactor operators (one case per 69 at risk out of a total population of 893). On the basis of man-months at risk, the prevalence of clear-cut AOL was even more strikingly associated with reactor cleaners; this job had a prevalence rate of one case per 721 man-months at risk (12,984 total man-months at risk). Among those jobs reporting 5,000 or more man-months at risk, no other job category approached this prevalence rate.

The question might be asked whether plants with AOL differed from plants free of this disorder in regard to the duration of duty tours in reactor cleaning. Analysis did not indicate that men in the former group of plants worked longer tours on this high-risk job.

In addition to the 25 clear-cut cases of AOL, there remained some question whether individuals demonstrating Raynaud's phenomenon with nondescript or borderline x-ray films might have represented early or minimal cases of this disorder. Review of the x-ray films and medical questionnaires of the 74 men in diagnostic category 3 (ie, Raynaud's phenomenon) revealed 16 men who might have been manifesting an early phase or minimal degree of AOL. Eight of these men had marginal defects, about whose presence the radiologists could not agree, and two more had widening of the tuft and shaft, with soft-tissue clubbing (one of the latter subsequently developed multiple osteolytic lesions). The other eight had three, five, six, or eight other symptoms of AOL on history but no bony abnormalities.

Among these 16 individuals about whom there is suspicion of AOL, we found that ten of them reported experience in reactor cleaning. This reported experience in reactor cleaning was somewhat similar to the work history found among those men with clear-cut AOL, ie, 18 men of the 25 cases. It would be of interest to determine the probability of finding that among 16 men chosen at random from the study population, ten or more would report such work experience. Among 5,011 individuals surveyed, 1,047, or 21%, reported experience in this specific job. Considering this entire study population, the probability that within a random sample of 16 men we would find by chance ten or more reporting experience in reactor cleaning is only 0.00038 (ie, 38 chances in 100,000). This determination is based upon application of the cumulative probability distribution, where

$$\sum_{x=10}^{16} \frac{(16!)(0.21^x)(0.79)^{n-x}}{x!(n-x)!}, \text{ where } n = 16$$

It is apparent that time alone will tell whether these last eight individuals will develop AOL. Nevertheless, because we know that at least one individual in this suspicious group subsequently has developed clear-cut AOL, we believe that 25 cases underestimates the total number of AOL cases in the population study. Therefore, we have considered that in addition to the 25 clear-cut cases, these 16 might also be categorized in the AOL group for statistical purposes, providing a total number of 41. On this basis, the prevalence of cases in the general plant population of AOL is calculated in Table 8.

Experience Among Compounding Workers.—One of the reasons for performing this study was to determine whether fabricators handling PVC polymer risked development of AOL. None of the cases of clear-cut AOL occurred among this group of 1,257 employees despite there being 57,657 man-months experience. Among the 557 men working as compounders, there was only one case of Raynaud's phenomenon. The prevalence of Raynaud's phenomenon among compounders was one case per 6,406 man-months experience while in reactor cleaners, this diagnosis occurred with a prevalence of one case per 721 man-months exposure. Comparing those plants with cases of AOL with compounding plants by χ^2 analysis, significant symptoms (vs) occurred considerably more frequently in the plants with cases ($P < 0.01$) [redacted] than in those compounding only. In this group of compounders, there were no persons showing x-ray film defects of a questionable nature without Raynaud's phenomenon (diagnostic category 4). In summary, it would appear that manipulation of the finished PVC resin is probably not associated with a risk of contracting AOL.

Comment

The disease acroosteolysis appears to be clearly associated with hand cleaning of polymerizers. In those plants using high-pressure water lances or solvents for cleanup of polymerizers, there were possible cases in only one. There appeared to be a correlation between the extent of degassing prior to entry into the reactor.[2]

At this time, work practices, rather than any one specific ingredient or combination in the process, appear to determine whether this disease will occur. In view of the low prevalence, the probability of the occurrence of AOL is correspondingly low in a small plant. However, smaller plants without cases at the time of the survey should not consider themselves immune to this problem.

Indeed, several plants with relatively small populations do have this disease among their workers. An examination of the intimate details of their work practices might clarify these ambiguities. While plants with cases of AOL provided gloves for their reactor cleaners, we observed inconsistent usage. Furthermore, while the standard procedures used to "air out" the reactor before entry are well designed to minimize exposure, these were frequently found, upon worker inquiry, to have been "short-cut."

That host characteristics may be determinant of the pathogenesis of AOL is suggested by the low prevalence of this condition, ie, idiosyncratic "sensitization" or "susceptibility" must be seriously considered. It will be recalled[2] that a number of inadequately defined low molecular weight, partially polymerized materials are believed to reside in the reactor scrapings. In this connection, the sensitizing propensities of dextranpolyvinyl pyrrolidine plasma extenders should be recalled.[7] While it is difficult to see how a high molecular weight (MW 10,000) compound could be absorbed percutaneously, the possibility of respiratory tract absorption and systemic distribution must remain open. In addition, because this appears to be a systemic disease, we are more inclined toward the pulmonary portal of entry rather than the transdermal route of absorption.

The possibility might be considered that this disease is caused by several agents, each one producing a specific component of the picture. In this connection, there is existent a report of Plesitzer and co-workers[8] which notes the occurrence of Raynaud's phenomenon resulting from VC exposure. Is it possible that the Raynaud's component of AOL stems from residual, unreacted VC associated with the PVC remaining on the reactor walls? Contrariwise, the bone changes in animals produced by VC monomer by Viola[9] did not appear to be associated with vasomotor lability.

To answer some of these questions, more data are required. A more complete chemical characterization of the residual PVC which remains on the reactor walls is essential. Animal exposure to these various possible components are desirable.

Finally, medical surveillance for symptoms of Raynaud's phenomenon and periodic hand x-ray films appear indicated for the present. It may transpire, as more men and man-years experience accumulate, that those manufacturers now free of AOL among their workers will, as time goes by, see development of some cases. This caution particularly applies to employees in the PVC synthesis area. It must be emphasized that the limitations of any retrospective epidemiological study make impossible any definitive prediction of future consequences of PVC manufacture. Since such studies can only describe events of the past and up to instant of the survey, the recommendations as to work practices and medical surveillance become especially pertinent for the safety of these workers.

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Occupational Acroosteolysis

II. An Industrial Hygiene Study

Warren A. Cook; Paul M. Giever, MPH; Bertram D. Dinman, MD, ScD; and Harold J. Magnuson, MD, MPH, Ann Arbor, Mich

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Warren A. Cook; Paul M. Giever, MPH; Bertram D. Dinman, MD, ScD; and Harold J. Magnuson, MD, MPH, Ann Arbor, Mich

An industrial hygiene survey was conducted in respect to occupational acroosteolysis (AOL) in 32 plants engaged in production and compounding of polyvinyl chloride. This survey was limited to inspection of facilities, interrogation of technical personnel, and statistical analyses. All manufacturing processes and chemicals utilized were explored. A major objective was the identification of variables in processes and chemicals that were peculiar to those plants affording known cases of AOL. No such processes or chemicals were found. The survey brought to light a number of situations suspected of relationship to the precise cause of AOL, some of which require additional exploration. Most positive of these was the finding that essentially all of the persons who developed AOL had served as reactor cleaners using manual methods.

POLYVINYL chloride (PVC) has been in production and widespread use for more than 30 years. An extensive account of the chemistry, methods of production, materials utilized, properties, and uses of the PVC resins was recently published in a series of technical articles by Albright.[1-5] Uses include such diverse products as floor tiles, films for food wrappings, sheeting for shower curtains, phonographic records, and coatings for cables.

As an indication of the magnitude of the PVC industry, the average operating capacity in this country for the year 1969 was about 3 billion lb.[6] Much PVC is produced in other countries. Even with this extensive production involving thousands of operators, the occurrence of occupational acroosteolysis (AOL) among these workers was not recognized until about 1961.[7]

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The clinical and epidemiological aspects of this condition are discussed in separate papers in this issue of the ARCHIVES.[8,9]

Industrial Hygiene Survey

Surveys were made of 32 plants by the authors of this paper, most of the plants being visited by a team of one physician and one industrial hygienist. Twenty-six of these were polymer production plants. Vinyl chloride monomer production plants and plants engaged in compounding and fabricating of the polymerized resin were a part of the manufacturing complex at a number of these locations. Five plants conducted compounding and fabricating operations only, and one plant produced only the vinyl chloride monomer. These plants were located throughout the United States and one in Canada.

This survey was designed to obtain information on equipment used, procedures followed, materials involved, extent of exposure to these, and names and descriptions of jobs in order to compare practices in the plants where cases of AOL occurred with those in plants experiencing no cases.

The extent of exposures was estimated on the basis of general observation, a knowledge of the physical, chemical, and physiological prop-

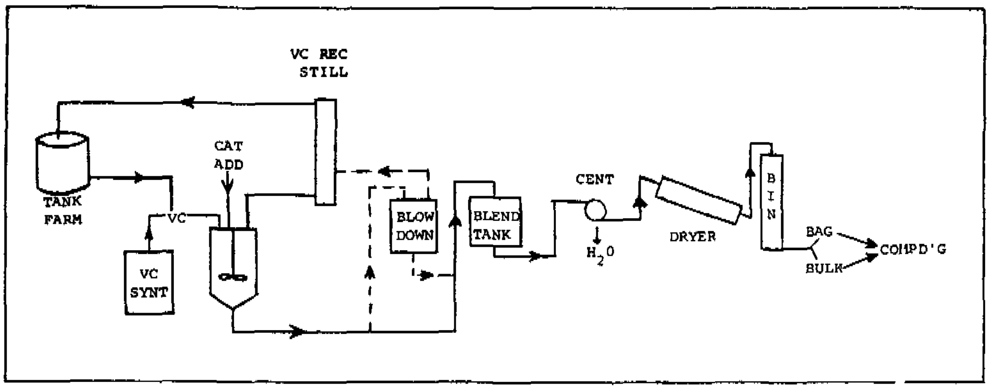

Fig 1.—Flow diagram for production of PVC from vinyl chloride monomer.

erties of the materials, and discussion with technically informed persons at the plants. By setting up three broad categories of duration and of relative severity of the exposure, semiquantitative estimates were made. Since materials responsible for causing AOL might be absorbed either through the respiratory tract or through the skin or both, such estimates were made for each of these avenues of absorption.

Production Operations

Vinyl Chloride Production.—The two processes for production of vinyl chloride described by Albright[1,2] were found to be in current use. One of these involves the reaction of hydrogen chloride with acetylene in the presence of a mercuric chloride catalyst. In the other process, 1, 2-dichloroethane is pyrolyzed in the presence of chlorine as a catalyst for the production of vinyl chloride and HCl. In some plants, both methods were used, with the HCl produced in the latter of these processes being used in the former.

Polyvinyl Chloride Production.—Polyvinyl chloride can be produced in accordance with four processes, each with many variations among different plants. The final polymer may have a molecular weight varying from 50,000 to 150,000, depending on conditions under which it is produced. The production processes are designated as suspension, emulsion, bulk (or nonsolvent), and solvent. A typical procedure is presented in the flow-sheet (Fig 1). The essential steps of these operations are outlined in this paper. For more complete details, reference may be made to the papers by Albright.[3-5]

In the widely used suspension process, deionized water is first introduced into a large autoclave, usually glass-lined, followed by a wide variety of additives. These include suspending agents such as polyvinyl alcohol, methyl cellulose, and gelatin, emulsifying agents such as sulfonated oils, surfactants such as sorbitan monolaurate, and buffers such as sodium bicarbonate. Trichloroethylene may be added to produce the lower molecular weight polymers. Catalysts are added to initiate the polymerization. These are nearly all organic peroxides, with lauroyl peroxide and diisopropylperoxydicarbonate (IPP) being used at the greater number of plants. The reactor is then closed, evacuated to remove oxygen, and vinyl chloride, normally a gas, is piped in as a liquid under pressure from the tank farm or the vinyl chloride plant. In some plants, the catalyst is added to a charge tank from which it is introduced into the closed reactor following addition of the vinyl chloride.

The mixture is agitated with rotating propeller blades, and steam initially is directed into the reactor jacket to raise the temperature to 50 or 55 C. Since the polymerization reaction is exothermic, cooling water must be run into the jacket after the reaction has begun to avoid excessive heating. After ten to 16 hours, the polymerization is essentially complete, and the reactor is brought down to atmospheric pressure. In most plants, it is placed under vacuum for removal of unpolymerized vinyl chloride monomer and transfer to the monomer recovery area. The suspension of PVC is then discharged into a blowdown tank below the reactor. This tank is placed under vacuum for transfer of remaining vinyl chloride to the recovery area. In some plants, the blowdown tank is eliminated. The general appearance of the charging floor of a polymer plant is shown

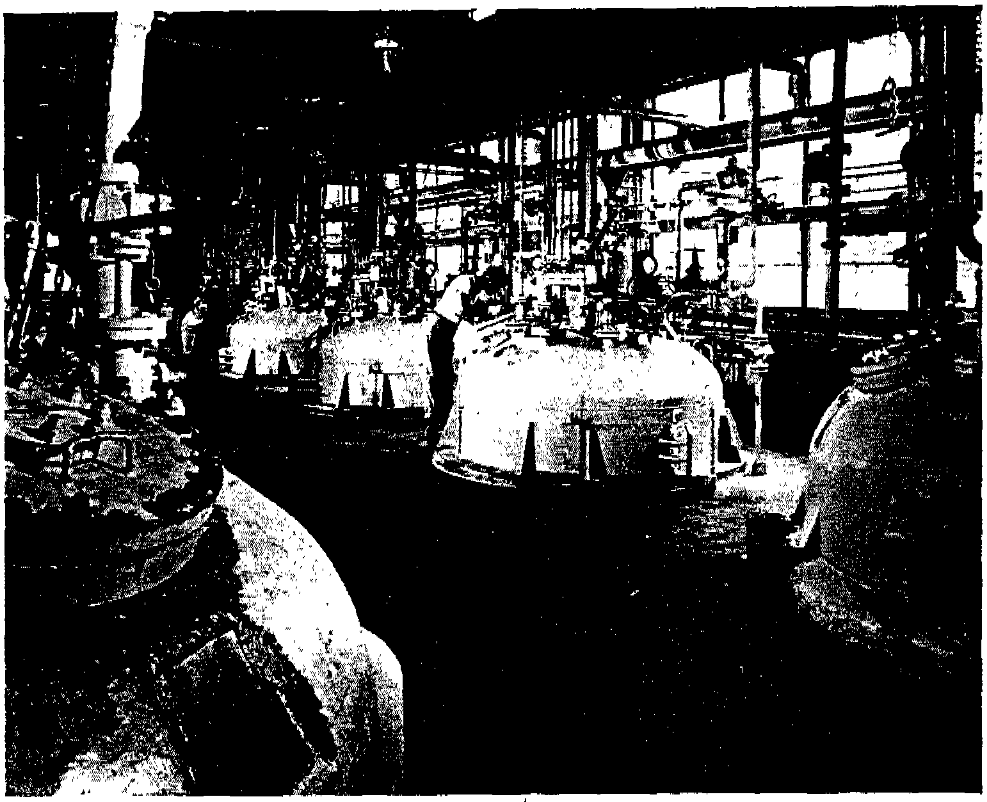

Fig 2.—Charging floor of PVC production plant showing top portion of reactors.

in Fig 2. The reactors extend for ten feet or so down to the floor below.

The polymer slurry is pumped to blend tanks, then to centrifuges for removal of much of the water. The dewatered polymer is passed through a rotary dryer with heated air, the temperature of the polymer being kept below 140 F to avoid degradation. The dried granular polymer is pneumatically conveyed into a cyclone separator, with finer particles being removed from the air stream by means of a filter-type collector. The polymer particles are sized by vibrating screens, then bagged for transfer to compounding and fabricating plants or shipped in bulk. In some plants, the polymer is stored in bins prior to being shipped.

In the emulsion process, the equipment and process is essentially the same as in the suspension process up to the drying operations. In order to produce the finer polymer particles characteristic of the emulsion process, a wide variety of emulsifying agents is used. These may be soaps such as ammonium or sodium laurate, surfactants such as salts of naphthalene sulfonic acid, or various synthetic detergents. Water-soluble initiators such as ammonium persulfate and hydrogen peroxide are used as catalysts. Since the fine polymer particles cannot be readily separated from the emulsion by centrifuging or filtering, a spray dryer is employed in this process.

The bulk process is similar to suspension polymerization but is characterized by the precipitation of the polymer from the liquid phase, as about 10% of the vinyl chloride becomes polymerized.

Solution polymerization is much the same as suspension polymerization, but no water is introduced. Instead, the polymerization is conducted in such solvents as cyclohexane, acetone, or *n*-butane.

Copolymer and Terpolymer Production.—In addition to the production of the homopolymer PVC, many of the plants also produce copolymer and terpolymers, including vinyl chloride. The greater percentage of the monomer tends to be the vinyl chloride in all of these. The copolymer vinyl chloride-vinyl acetate is in highest production among this group but is a minor product in comparison to the homopolymer. Other copolymers are vinyl chloride-vinylidene chloride and vinyl chloride-lauryl-vinyl ether. An example of a terpolymer is vinyl chloride-*n*-butyl maleate-dibutyl maleate.

Processes, additives, and catalysts essentially identical to those used for the homopolymer are employed in the production of the copolymers and terpolymers with the addition to the reaction mixture of the additional monomers.

Vinyl Chloride Recovery.—The unpolymerized vinyl chloride removed from the batch following completion of polymerization is conveyed to a vinyl chloride recovery area by the suction pump that places the reactor and the stripping tank under reduced pressure. Here the vinyl chloride gas that is removed is placed under pressure to condense it together with water vapor to a liquid. The water and the vinyl chloride are immiscible, permitting their separation. In some plants, an inhibitor, usually phenol, is added to the vinyl chloride to prevent spontaneous polymerization during its distillation, the method used for its purification. The recovered vinyl chloride, with the higher boiling phenol remaining in the still, is then pumped to storage for reuse.

Table 1.—*Absolute Pressure-Time Values*

Absolute Pressure-Time Values Below 10			Absolute Pressure-Time Values of 10 or Above		
Plant Code	No. of Reactor Cleaners	No. of Expected AOL Cases	Plant Code	No. of Reactor Cleaners	No. of Expected AOL Cases
		Plants With AOL Cases			
EE	31	0.8	B	216	5.8
			E	165	4.5
			F	16	0.4
			R	39	1.1
Plants With Possible AOL Cases					
CC	32	0.9			
Totals	63	1.7		436	11.8
		Plants With No AOL Cases			
P	30	0.8	D	27	0.7
Q	22	0.6	H	26	0.7
V	91	2.5	L	28	0.8
W	50	1.4	S	17	0.5
			T	9	0.2
			Z	17	0.5
			AA	8	0.2
Totals	193	5.3		132	3.6
		Plants Started in Operation in 1965 or 1966			
DD	21	0.6	C	54	1.5
			J	13	0.4
Totals	21	0.6		67	1.9

Table 2.—*Classification of Standard Job Titles*

Job Title	Code	Job Title	Code
Additive makeup (other than catalyst)	1	Monomer recovery operator	14
		Monomer supervisor	15
Bagging and shipping operator	2	Plant guard, security officer	16
Catalyst makeup man	3	Reactor cleaner	17
Clerical, other office, staff	4	Reactor cleaner, solvent	18
Compounding and fabricating	5	Reactor operator	19
Dryer operator	6	Slurry blender	20
General laborer, custodial	7	Supervisor, polymer	21
Laboratory supervisor	8	Tank farm operator	22
Laboratory technician	9	Utilities area operator (water treatment, etc)	23
Maintenance, electrical	10		
Maintenance, mechanical	11	Warehouse operator	24
Monomer maintenance operator	12	Transfer operator	25
Monomer operator	13	Other than PVC	30

Reactor Cleaning Operations.—After the polymer has been discharged from the reactor and the pressure brought to atmospheric, the reactor is aerated. This is accomplished by dropping a flexible duct connected to a portable blower to the bottom of the reactor, with discharge normally through the open manhole at the top of the reactor into the charging-floor area. The loose residue is washed out with water, after which one or two men enter the reactor to remove the skin of polymer remaining on the reactor surfaces. The usual method is by manual scraping with putty knives. Residue on the agitator blades may require hammer and chisel for removal and sometimes even axes.

Four plants use water jets with pressures of from 300 to 3,000 lb/sq in for the cleaning operation. One of these used water jets only in one of two production buildings, as the structional features interfered with movement of the portable high-pressure water unit about the building. Three other plants have been using solvents for reactor cleaning. One of these started to use this method late in 1964, a second in 1966, and the third from the beginning of plant operation in 1966. The reactor is filled with the solvent which must be heated and agitated for a prolonged period, as the PVC is difficulty soluble.

Polyvinyl Chloride Compounding.—Com-

Table 3.—Magnitude of Dosage Expressed as Single Concept

Magnitude* of Dosage	Severity/Duration Exposure Parameters† Less Than 1 hr/Week	1-8 hr/Week	More Than 8 hr/Week
Slight			
1	Negligible	None	None
2		Negligible	None
3			Negligible
4	Moderate	None	None
5	Moderate	Negligible	None
6	Moderate		Negligible
Intermediate			
7	Appreciable	None	None
8	Appreciable	Negligible	None
9	Appreciable		Negligible
10		Moderate	None
11		Moderate	Negligible
12			Moderate
Major			
13	Appreciable	Moderate	None
14	Appreciable		Moderate
15		Appreciable	None
16		Appreciable	Negligible
17		Appreciable	Moderate
18			Appreciable

* Expressed in order of increasing dosage received from exposure, which is the summation of the three columns to the right.
† Severity of exposure is estimated as none, negligible, moderate, or appreciable for indicated durations.

pounding consists of mixing PVC with a multiplicity of plasticizers, antioxidants, pigments, emulsifiers, stabilizers, and other special compounds in ribbon blenders and mills. The mixtures are then passed through roll mills or mixers, such as are used in the rubber industry, where the temperature may rise sufficiently to vaporize some of the plasticizer and other volatile constituents. The compounded polymer is then extruded through rolls or dies to form sheets, films, or pellets. These are used in fabricating operations.

Job Classification

Many variables were introduced in the plants surveyed and even in different units of the same plant in regard to nearly every phase of the operations. Investigation of unit jobs in the plants disclosed a wide assortment of job titles. In fact, a job title as used by the technical supervisors often differed from that for the same job in the same plant as listed by the personnel department.

Furthermore, a job assignment in one plant might include a different group of unit operations than in another plant. Also, the proportion of time devoted to the several unit operations often differed. To compound the difficulties of classification, workers would frequently rotate through several jobs at a weekly, monthly, or other period.

A classification of 26 job titles for the statistical purposes of this study was prepared (Table 1). These job titles corresponded to comparable operations in all the plants and to a common group of types of exposures to production materials. Every job in each of the plants was given its fraction of time related to the job title as defined for the study. Details of the manner in which this was done are discussed in the accompanying paper on epidemiological aspects of AOL.[8]

Job Progression.—Often the first job assignment of the new employee is that of reactor cleaner. Unless there are many reactors, this work does not require the entire time of the employee. Part of his time may be spent in bagging or shipping finished polymer or in the handling of catalysts and other additives.

As job openings arise and with accretion of seniority, this employee may progress to higher skilled jobs such as reactor, monomer recovery or dryer operator, or any combination of these at any one time.

In plants producing other products in addition to vinyl chloride polymers, employees may transfer between these product areas either as full time for a period of months or dividing their time within a given week or even day. The latter occurs particularly among maintenance personnel.

Where production of vinyl chloride is part of the operation, operators may rotate between jobs in the production of the monomer and those associated with the production of the polymer.

The length of time spent at various jobs is a function of production needs, economic conditions, plant growth rates, and activity of other product lines.

Occupational Exposures to Materials

Extent of Exposures.—Information was obtained not only on each of the materials used or produced but also on the extent of exposure to each. Since this is a function of both duration and severity, each of these factors was estimated. The duration of exposure was recorded as less than one hour a week, from one to eight hours a week, or more than eight hours a week; the severity as negligible, moderate, or appreciable. Since it was not known whether the materials might be absorbed through the respiratory tract, through the skin, or both, the extent of exposure as related to each of these avenues of absorption was recorded.

For statistical purposes, it was desirable to combine these two factors of exposure into a single dose value. Although admittedly the effect of exposure to materials with differing physiological responses would vary somewhat with different combinations of degrees of duration and severity, the 18 possible combinations of duration and severity were listed in increasing order of dosage and classified in three groups of dose values designated as slight, intermediate, or major. These combinations are presented in Table 2.

Materials Involved.—A total of 227 different materials were used or produced in the formation of PVC, the copolymer vinyl chloride-vinyl acetate, and other copolymers and terpolymers incorporating vinyl chloride. These materials included monomers, polymers, catalysts, dispersants, inorganic compounds for coalescence regulation, emulsifying agents, surfactants, and organic solvents (including hydrocarbons, both aliphatic and aromatic, ketones, esters, and chlorinated hydrocarbons). This total of 227 materials does not include the many more used in the compounding and fabricating plants.

A computer analysis of exposures to these materials was undertaken, but up to the present time, this has disclosed no constellation of materials introduced into the batch at the plants exhibiting cases of AOL that was not used in plants without cases. However, special consideration was given to certain suspect materials and also to certain details of procedure.

Vinyl Chloride Exposures.—In evaluating the role of vinyl chloride as a possible influence in the causation of AOL, the estimates of the extent of the exposure of reactor cleaners and reactor operators were reviewed. Since the authors conducted no air analyses, they had to judge the presence of vinyl chloride in the charging floor area principally on the basis of general ventilation provided and odor observed. The odor of vinyl chloride could be detected in the immediate vicinity of reactors as they were first opened and also when they were first being vented into the charging room area. Air analyses conducted by others have shown vinyl chloride concentrations in the reactor prior to ventilating to be in the order of 3,000 ppm. The lower limit of detection of vinyl chloride by odor is accepted as 400 ppm. Except under the foregoing conditions, the odor of vinyl chloride was not observed in the general room air.

Table 4.—*Use of Inhibitors With Vinyl Chloride*

	Use of Inhibitors	
	In Virgin Vinyl Chloride	In Vinyl Chloride Recovery
Plants with AOL cases or possible cases	2	2
Plants without AOL cases	3	4

The reactor cleaner enters the reactor after the aeration has reduced the vinyl chloride exposure to what is considered satisfactory limits, normally 15 or 20 minutes. The test is either by sniffing at the manhole opening or by use of a flammable vapor indicator. With the lower explosive limit of vinyl chloride at 4%, it requires 400 ppm for the usual type of flammable vapor indicator to give a positive reading.

Where air analyses have been made in a small number of plants with more sensitive instruments, such as the gas chromatograph, it has been found that the vinyl chloride concentration inside the reactor during scraping operations tends to be below 100 ppm and usually about 50 ppm. With the residue containing some unpolymerized vinyl chloride, small amounts of this gas are released as scraping is carried on. Air analyses have shown vinyl chloride concentrations close to the hand during scraping in the range of 600 to 1,000 ppm.

Although this study provided no evidence to suggest that vinyl chloride per se is the etiological agent, the measurement of vinyl chloride concentrations may serve as a useful index to the adequacy of reactor ventilation.

Inhibitors in Vinyl Chloride.—An inhibitor, usually phenol, may be added to the

Table 5.—*Reactor Cleaning Procedures*

Plant Code	Hand Scraping: After Every Batch	Hand Scraping: Less Than Every Cycle	Cleaning by Water Jet	Cleaning by Solvent
Plants with AOL cases				
B	X			
E	X			
F	X			
K	X (through 1964)		From 1965	
R	X			
U		Every 5-12 cycles (building A)	From 1962 (building B)	
EE	X			
Plants with possible AOL cases				
BB		Every "several" cycles		On glass-lined, intermittently in 1966, entirely by December 1966
Plants with no AOL cases				
A	X (to September 1964)			From September 1964
C	X			
D			From 1962	
H	X			
J		Every 2½ cycles		
L		Every 4-8 days		
N	X			
P		Weekly through 1964, every 2 weeks 1965-1966	From 1965	
Q	X			
S	X			
T	X (emulsion)	Every 1-3 cycles (suspension)		
V		Every 10 cycles		
Z	X			
AA		Every 4 or more cycles		
DD	X			
GG				From start of operations

vinyl chloride to prevent spontaneous polymerization in storage. An inhibitor may also be added to the vinyl chloride recovered from the reactor. The phenol is removed by treatment with caustic soda prior to its transfer to the reactor. The practice over the years covered by the study is presented in Table 3. The use of the inhibitor in the virgin vinyl chloride at two of the positive plants and three of the negative plants, with inhibitor being added in the vinyl chloride recovery operation in two positive plants and four negative plants, leads to the conclusion that inhibitors probably are not a factor in AOL causation.

Catalyst Exposures.—Since the catalysts are all active compounds, they were suspect as a possible factor in the causation of AOL. Contact with these inorganic and organic peroxides occurs as they are handled prior to their introduction into the reactor and also during reactor cleaning if any unreacted catalyst remains in the residue. Twenty-two of the 26 plants used lauroyl peroxide. Eight of these were plants with AOL cases or possible AOL cases, and 14 were plants without AOL cases. The next most common organic peroxide was the IPP, and it, too, was in use in both the positive and the negative plants, in four of the former and in eight of the latter. No catalyst or group of catalysts was used in all positive plants and in no negative plants.

Constituents of Scrapings.—Other suspect materials are constituents of scrapings removed from the reactors during manual cleaning. These are believed to include some partially polymerized resins, along with some unreacted catalysts and additives, and unpolymerized vinyl chloride. Little specific information is currently available concerning these constituents. It has been reported that lauroyl peroxide is definitely associated with residual PVC particles, whereas little of the IPP remains unreacted in the polymer.[4]

Further investigation of the scrapings from the reactor may be expected to furnish information that may lead to a better understanding of the factors involved in causation of AOL. A difficulty in such investigation is that the composition of the scrapings is continually changing from the time they are removed from the surfaces of the reactor. It is obvious that comparatively small molecules of partially polymerized vinyl chloride are increasing in size with passage of time, and active constituents such as residual cat-

Table 6.—*Reactor Cleaning Procedures*

Method	Positive Plants	Negative Plants
Manual scraping after every reactor cycle	7	9
Manual scraping after 2-3 cycles	0	2
Manual scraping after 4-12 cycles	2	4
Water-jet cleaning	2	2
Organic-solvent cleaning	1	2

alyst and vinyl chloride monomer are decreasing or may no longer be present.

Procedures Affecting Exposures of Reactor Cleaners

Since all but one of the 25 operators diagnosed as positive for AOL had worked as reactor cleaners and the one exception had cleaned laboratory reactors,[8] additional inquiry was made of procedures that might affect the exposures of this group of workers.

Reactor Cleaning Procedure.—The number of man hours required to clean the reactors depended not only on the number of reactors but also on the frequency of cleaning. In 16 of the 26 production plants, reactors were manually cleaned after every batch. This was true of six of the seven positive plants and one of two plants with possible AOL cases. In only nine of the 17 plants with no AOL cases were reactors manually scraped after every batch.

The procedures followed in each of these plants appears in Table 4 and an analysis of the types of procedure by positive and negative plants in Table 5.

Procedures Following Completion of Polymerization.—Since vinyl chloride and other volatile components of the residue remaining on the reactor surfaces following discharge of the batch might be factors in AOL causation, information was obtained concerning the degree of vacuum applied to the reactor prior to opening it and the length of time that the reactor was under this reduced pressure. The amount of volatile materials remaining in the residue on the reactor surfaces was considered to be roughly proportional to the absolute pressure and inversely proportional to some function of the time. Since the rate of removal of volatile material would tend to decrease with time, the logarithm of this factor was used in calculating an absolute pressure-time (AP-T) value. It was hypothesized that the relative amount of volatile materials remaining in the residue following application of vacuum would approximate a nondimensional value obtained by dividing the absolute pressure in inches of mercury by the logarithm of the time in minutes during which the vacuum was applied. Thus, the lower the AP-T value, the less is the amount of volatile materials remaining in the residue.

Another factor affecting removal of volatile materials is the temperature range over the period that the reactor is under vacuum. The variables in temperature control were so diverse that this factor defied classification and could not be incorporated in the parameter under consideration. Actually, variations in degree of vacuum and timing of its application were such that meaningful calculation of an AP-T value could be accomplished only for five of the seven positive plants, one of the two with possible cases, and 14 of the 17 negative plants.

In the subsequent discussion of these values, the three plants that started in operation as recently as 1965 and 1966, all with no AOL cases, are not included as it is not known whether sufficient time had elapsed for cases to have developed by the terminal date of the study period. These plants are listed separately in Table 6.

The AP-T values ranged from 0.5 to 21. The AP-T values were 10 or above (an entirely arbitrary division line) for four of the five positive plants and for one of the two plants with possible AOL cases. Four of the negative plants gave AP-T values below 10, and seven gave values of 10 or above.

Consideration is directed to the number of reactor cleaners and the corresponding number of expected AOL cases in the two groups of positive plants as compared with those in the negative plants.

The total number of reactor cleaners at risk in the positive or possibly positive plants with an AP-T value of less than 10 is 63; that in such plants with an AP-T value of 10 or more is 436. The relation of these two totals is to be compared with that of the negative plants in which 193 reactor cleaners at risk are in the four plants with an AP-T of less than 10 and 132 are in the seven plants with an AP-T above that value.

The number of expected cases of AOL for each plant is also listed in Table 6. These values were obtained by dividing the number of reactor cleaners at risk by 37 This

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figure derives from the paper on epidemiological aspects of AOL[8] which reports the prevalence of AOL or possible AOL as one case per 37 reactor cleaners at risk.

Of the negative plants with an AP-T value of 10 or more, none of those in operation earlier than 1965 had enough reactor cleaners at risk to expect an AOL case, whereas two of the four plants with an AP-T value under 10 have enough workers to expect cases. Cases would be expected from the total population of reactor cleaners in the entire group of the seven negative plants with AP-T values of 10 or more, but the total number would be 3.6, as compared with 5.3 expected cases from the entire group of four negative plants with an AP-T value of less than 10. This contrasts with expected cases in the group of positive plants with an AP-T value of less than 10 as 1.7, compared with 11.8 in such plants with an AP-T value of 10 or more.

The proportion of the number of reactor cleaners in the negative plants with an AP-T value of less than 10 to the total number in such plants was 193 to 325. This proportion for the positive plants was 63 to 499. A χ^2 test demonstrated that the probability of this difference between the negative and the positive plants occurring by chance is less than 0.001.

In order to make this comparison between the positive and negative plants with AP-T values below and above 10, it was necessary to oversimplify a multiplicity of varying details of operational procedures from the time the polymerization is completed to the time the cleaner enters the reactor. Accordingly, any interpretation of the findings that reduction of the AP-T value below 10 by reducing the absolute pressure or keeping the reactor at reduced pressure for a longer time or both may results in reduction in development of AOL cases should be approached with great caution.

Preventive Measures

The present knowledge as to AOL is such that categoric statements as to preventive measures are not justified. However, on a somewhat speculative basis, some measures are indicated that may be conducive to AOL prevention:

1. Although some manual removal of residue from reactor surfaces may be required when solvents or high-pressure water jets are used for cleaning, the more extensive employment of these methods would greatly reduce the number of man hours required for conducting this operation by manual methods.

2. The adequacy of ventilation of reactors prior to entry should be checked with flammable vapor indicator equipped with a scale of greater sensitivity than 1% of the lower explosive limit of vinyl chloride or with other instruments of such sensitivity.

3. Further investigation of the constituency of the scrapings from the reactor surfaces should be considered, as such information might disclose the factor responsible for the causation of the disease.

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Occupational Acroosteolysis

III. A Clinical Study

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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 anteceded 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, hypothroid 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 uneaten 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 regions, using sodium floride 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

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		Cryoglobulins
α-2		LE cell	Immunophoresis
β		Direct Coomb's	IgA
γ		Latex-rheumatoid factor	IgM
		Cold agglutinins	IgG

months. The length of the interval bore no 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).

ounces of whiskey per month. Three of the men rarely drank milk, and the other (case 4) averaged two glasses each day. Dietary histories indicated calcium intakes between 1,000 mg and 1,300 mg/day except for one patient (case 2) whose usual intake was 518 mg/day. This patient's normal dietary intake of phosphorus averaged 2,400 mg/day while the others took in between 1,500 and 1,800 mg/day. None had unusual food cravings or aversions.

Some details of family history are recorded in Table 4. A firm history of hypertension was present in either the father or the mother in three of the four patients, and one half also had immediate family members with diabetes mellitus though none personally evidenced the disease. Notably, the fathers of all four men had heart diseases.

The associated symptoms and signs of joint involvement are listed in Table 5. Intermittent transient orthostatic tinnitus was mentioned by three of the four patients. This occurred upon rising from sitting or recumbency. The one patient not having tinnitus (case 3) had chronic postnasal drip, nasal stuffiness, and a prior history of childhood bronchial asthma.

Table 2.—*Clinical Features of Patients With AOL at Onset*

Clinical Features	Case 1	Case 2	Case 3	Case 4
Blanching,				
Onset	Sudden	Gradual	Gradual	Sudden
precipitated by cold	+	+	+	+
Associated symptoms:				
Fingertip tenderness,	+	+	+	—
Tingling of the hands,	—	—	—	+
Joint pain	Elbows	Coccyx	—	1 hip, 1 wrist, 1 knee, hands
	Low back			Low back Sacro-iliac
Joint stiffness	Hands	Hands	Hand	—
	—	Knees	Knees	—
Subcutaneous nodules			+	
Muscle swelling			+	
Exposure-to-first blanch interval	1 mo	6 mo	18 mo	23 mo
Intermittent tinnitus	+	+	—	+
Palpitations with exertion	+	+	+	—

Table 3.—*Habits and Dietary Histories of Patients With AOL*

Features	Case 1	Case 2	Case 3	Case 4
Cigarette smoking (pack-yr)	9	25	0	15
Average coffee consumption (cups/day)	9	3	0	0
Alcohol per month				
Beer (12-oz unit)	3	13	8	120
Whiskey (oz)	1	4	0	8
Milk (glasses/day)	Rarely	Rarely	Rarely	2
Calcium intake (mg/day)	1,045	518	1,327	1,096
Phosphorus intake (mg/day)	1,519	1,587	2,457	1,797

Table 4.—*Diseases in Family Member of Patient With AOL*

Family Member	Case 1	Case 2	Case 3	Case 4
Father	Diabetes mellitus	Heart disease	Heart disease, Chronic lung disease	Congestive heart failure, Hyperlipemia, Hypertension
Mother	...	Hypertension, Obesity	Hypertension	Obesity
Brother	Emphysema	...	...	...

Physical Examination.—The major physical findings were restricted to the skin and joints, as shown in Table 5. Synovial and skin thickening were observed by two or more clinicians independently. Dupuytren's contractures were present bilaterally in one patient (case 1). The extensor ligaments of the wrist were thickened in another (case 2). The distal phalanges of the hands of one patient (case 3) were shortened.

Laboratory Parameters.—The numerous clinical laboratory parameters depicted in Table 1 were found to be essentially normal. All four men vacillated between negative and positive calcium balances day-to-day during the two-week period. Except for one patient (case 2), all averaged a positive balance ranging from 33 to 246 mg/day. This patient managed a deficit of 27 mg/day, which was primarily a function of renal excretion. All had positive phosphorus balances except this patient, whose phosphoturia always accounted for more than his stool losses.

Five-hydroxyindole acetic acid determinations were performed on 24-hour urine spec-

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	PIP† MP‡ Knees	PIP† −	− −	− −
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.

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 reports.

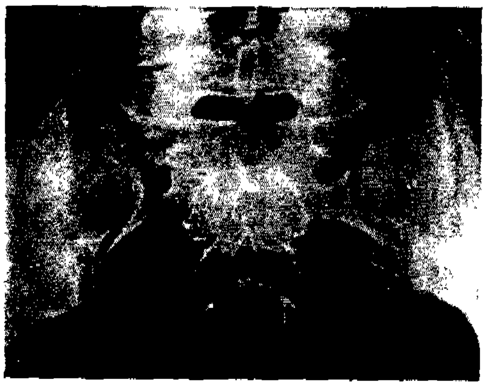
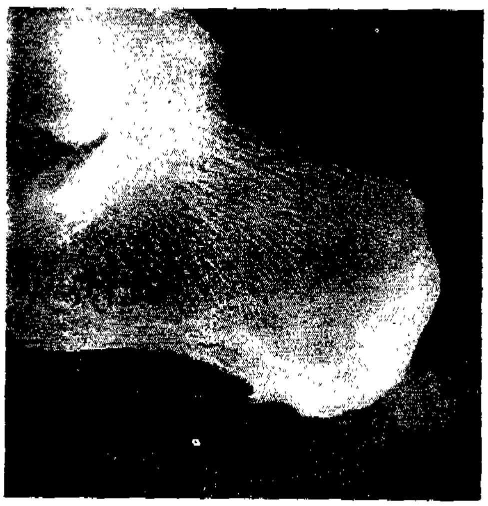


Fig 3.—Erosive and sclerotic changes in sacro-iliac joints bilaterally (case 1).

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



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, 1966, 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 13, 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

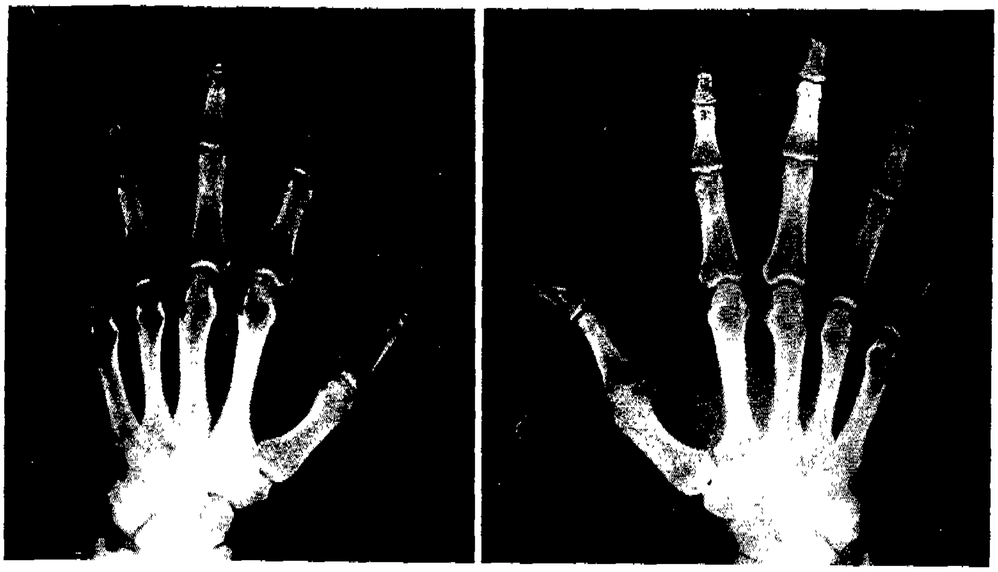


Fig 5.—Left hand shows marginal defect at tip of distal phalanx of second finger, with transverse defect in distal phalanx of third finger. Right hand shows transverse defects in distal phalanges of second and third fingers and an additional distal marginal defect of second finger (**top** [case 2]). Scintigram shows uptake of sodium fluoride ^{18}F (**bottom**).

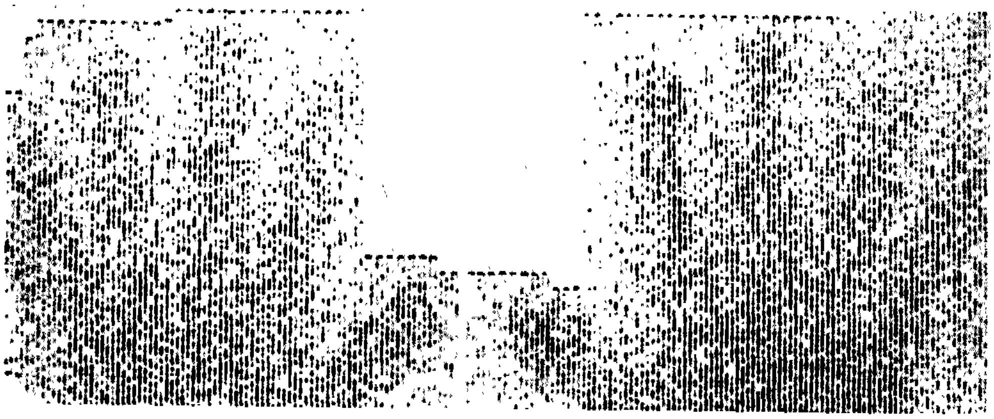


Fig 6.—Sacro-iliac joints show erosive and sclerotic changes, more marked on left (case 2).

Table 6.—*Five-hydroxyindole Acetic Acid and Catecholamine Studies in Patients With AOL*

	Case 1			Case 2			Case 3			Case 4		
Urinary Excretion	Mg	Urine Volume	Creat-inine	Mg	Urine Volume	Creat-inine	Mg	Urine Volume	Creat-inine	Mg	Urine Volume	Creat-inine
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 phalangal 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.

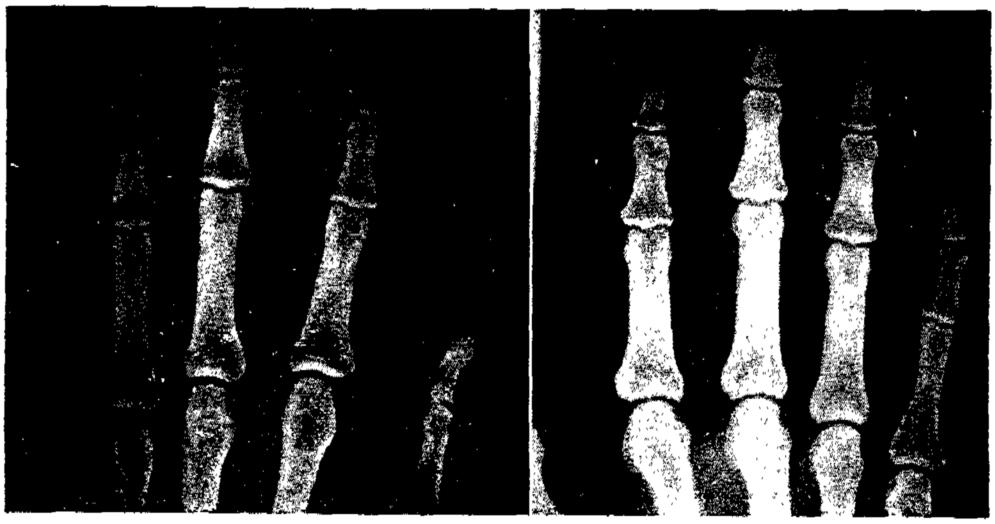
As shown in Fig 5, the left hand revealed a marginal defect at the tip of the distal phalanx of the second finger while the third finger showed a transverse defect in the distal phalanx. At the same time, the right hand presented transverse lytic defects in the distal phalanges of the second and third fingers and an additional distal marginal defect of the second finger.

Figure 5 compares a typical sodium fluoride ^{18}F scintiscan of the bands 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 1965.

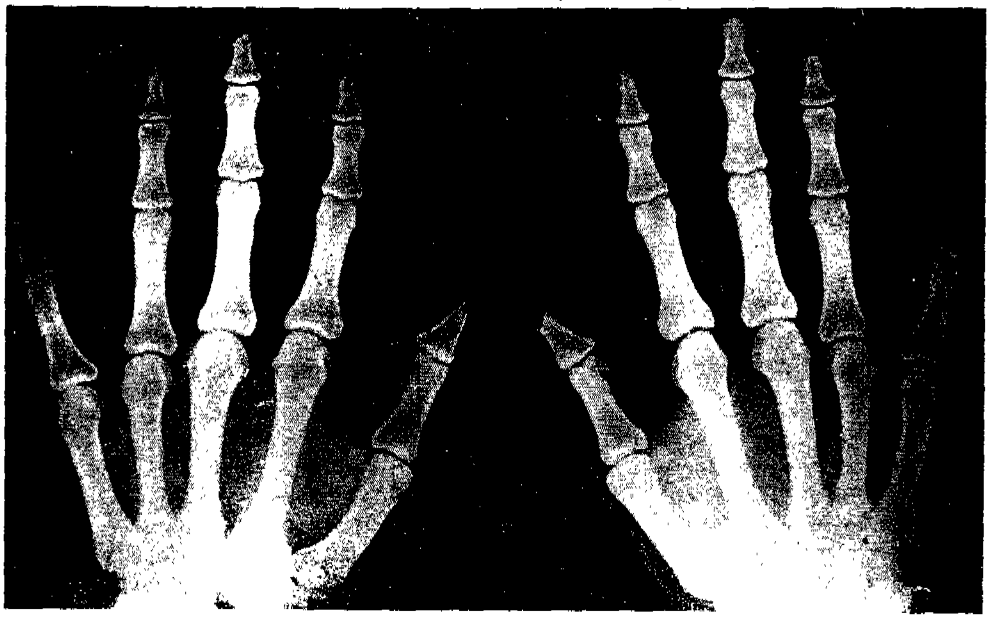
CASE 4.—Review of previous x-ray films made of this patient indicated that no abnormality of the hands was present on Feb 20, 1967, or Jan 23, 1968. On July 15, 1968, films of the sacro-iliac joints exhibited erosive and sclerotic changes, and the hands revealed marginal defect of the distal phalanges 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 8.—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).

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).



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 Adams[5] reported one case in which distal digit shortening occurred first, while Wilson et al[4] 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" ie, 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 reponses, 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 Nordin[10] 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.[1,3-8]

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, os calcis, 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 ^{18}F scintiscan data suggests that the more advanced osteolytic changes with transverse defects at this time were picking up more fluorine and probably calcium, indicating active remineralization. That the digits with marginal defects picked up less than the normal bones implies some type of uptake block or active demineralization. If the latter is true, it is all the more interesting that different bone lesions appear to be mineralizing and demineralizing in the same individual, even the same hand. The etiological agent or agents responsible and the pathogenical mechanisms remain obscure.

Medical Prevention.—The interval between the beginning of reactor cleaning and the onset of AOL appears highly variable, ie, one to 23 months. Accordingly, the frequency with which one examines reactor cleaners has no rational basis. By contrast, the occurrence of Raynaud's phenomenon should serve as a sufficient warning for further inquiry.

This is not to suggest that prudent medical practice does not require periodic examination of reactor cleaners and other groups of workers in whom AOL occurs. These groups should be surveyed periodically by use of hand roentgenograms and medical questionnaires. The form the latter might take has been discussed in the epidemiological segment in this series. But we would emphasize that prevention of AOL also requires the cooperation of supervision. This group should be alerted as to the possible significance of Raynaud's phenomenon in relation to AOL.

Upon the discovery of any case of AOL among workers at risk, such individuals should be removed from the job. X-ray films of the hand, back, and knees should be obtained. A medical history questionnaire, similar to those used in the epidemiological survey reported here, should also be procured. A medical evaluation for other causes of Raynaud's phenomenon is in order. In view of the unpredictable course of AOL, it would be wise to exclude any individual with Raynaud's phenomenon from reactor cleaning. Since seniority practices usually remove workers from reactor cleaning with the passage of time, such excluded workers probably would not return to this particular job. In view of the low prevalence of this disease, we believe that permanent restriction of these few workers from this job does not pose any undue administrative burden. Until more is known of the natural history of this disease, prudence would dictate the course as here recommended.

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Occupational Acroosteolysis

Report of 31 Cases

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In 31 cases of acroosteolysis of the hands of workmen associated with vinyl chloride (CH_2CHCl) polymerization processes, the osteolysis was specific to the distal phalanges of hands and was frequently associated with Raynaud's symptoms. Affected personnel ranged in age from 26 to 47. The disorder is believed to have resulted from a combination of physical insult, chemical insult, and personal idiosyncrasy. The specific causes are unknown. The prevalence was found to be less than 3% among employees performing similar work. No cases were found in workmen using or processing the polymer or manufacturing commercial resins.

During mid-1964, several complaints came to our attention of soreness and tenderness of the fingertips of workmen in a manufacturing plant polymerizing vinyl chloride (CH_2CHCl). Comprehensive examinations of these individuals revealed nothing of significance except a "Raynaud-like phenomenon" of the hands, and in some cases, definite changes of the distal phalanges were apparent on roentgenograms of the hands. Since then we have observed additional cases of this unusual syndrome. It is the purpose of this manuscript to summarize our observations.

Description of Syndrome

To date we have observed 31 cases of hand disorders among 3,000 personnel involved in vinyl chloride manufacturing and polymerization. All have been men, between the ages of 26 and 47. We have not observed any ethnic or racial tendency for the syndrome. The great majority have been characterized by two common factors: symptoms likened to those ascribed to Raynaud's phenomenon and acroosteolysis of the distal phalanges. A few have had no symptoms but have the roentgenographic evidence of acroosteolysis. Several of the patients have external skin lesions on the dorsal surfaces of the hands and forearms, with a rope-like appearance resembling changes sometimes seen in scleroderma. Some have clubbing of the fingers. Only a few of the cases have sought medical attention because of symptomatic complaints; the majority have been found through x-ray examinations of the hands.

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A summary of the physical findings of the observed cases is shown in Table 1, and a detailed description of the two predominantly common symptoms follows:

Raynaud's Phenomenon.—This symptom complex has occurred in varying degrees, with one or both hands involved. Generally, its effect is observed as marked discomfort on exposure to cold. None of the cases have exhibited vascular changes of the feet. A unilateral sympathectomy performed on one of the most seriously affected cases relieved most of the symptoms on that side. The acroosteolysis was not altered by the sympathectomy.

Roentgenological Changes.—The most unique characteristic of this syndrome is the unusual roentgenological findings. These are described as acroosteolysis and are illustrated in Fig 1. It may be present in all of the fingers and readily observable, or only in one finger and barely discernible, as illustrated in Fig 2. X-ray films of the feet, as well as those of the long bones and of the skull have been made in some of these cases, with no osteolysis found other than in the distal phalanges of the hands.

Acroosteolysis is a rare clinical entity, with only 72 cases of the familial type reported up to 1965, according to Cheney in his excellent review.[1] The diagnosis of acroosteolysis requires expert roentgenological technique and knowledge. It has been our observations that early cases of acroosteolysis will be missed by the roentgenologist not familiar with this condition. All of the cases on which we are reporting have been confirmed by at least two experienced roentgenologists working independently.

We established the following roentgenographic criteria for our diagnoses. These are the result of our having viewed several thousand x-ray films of the hand in our search for the cause of the syndrome.

1. General: Roentgenographically, acroosteolysis, as found in workers who are exposed to vinyl

chloride and polyvinyl chloride manufacturing processes, is somewhat different from that found in familial osteoporosis with acroosteolysis and in familial osteosclerosis with acroosteolysis. In osteoporosis with acroosteolysis there may be compression fractures in the spine, and basilar impression of the skull, along with destruction of the midphalanges. None of these findings have been seen in these workers. The changes in the distal phalanges are similar in both conditions.

Osteosclerosis acroosteolysis observed by Andren et al[2] (University Hospital, Malmo, Sweden) in twins showed diffuse sclerosis, with cortical thickening of the shafts of the long bones and clubbing of the metaphyseal ends. The phalanges of the hands and metacarpals were foreshortened, and the distal phalanges showed acroosteolytic changes. The feet showed the same changes, except that the distal phalanges were not fragmented.

There has been no evident destruction in the mid or proximal phalanges of the thumbs or fingers of these individuals and no evidence of a lytic, destructive lesion in the feet.

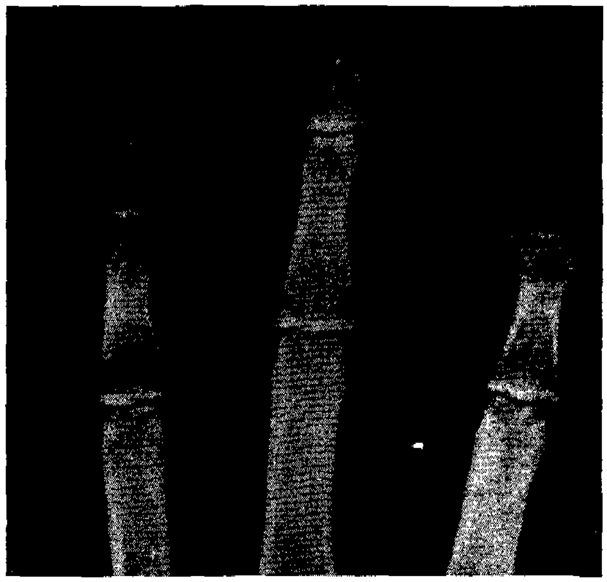
We have not observed any loss of calcium salt in the bones of the wrist and remaining bones of the hand and phalanges in any of these individuals, and there has been no evident sclerosis of the wrist and hand bones.

2. Mild stage: The earliest change found in acroosteolysis in these workers has been a loss of the cortex of one or more of the tufts of the distal phalanges, with no destruction of the tuft or shaft of the distal phalanx.

The next more advanced stage may be a small, half-moon cut in the cortex of the tuft of one or more

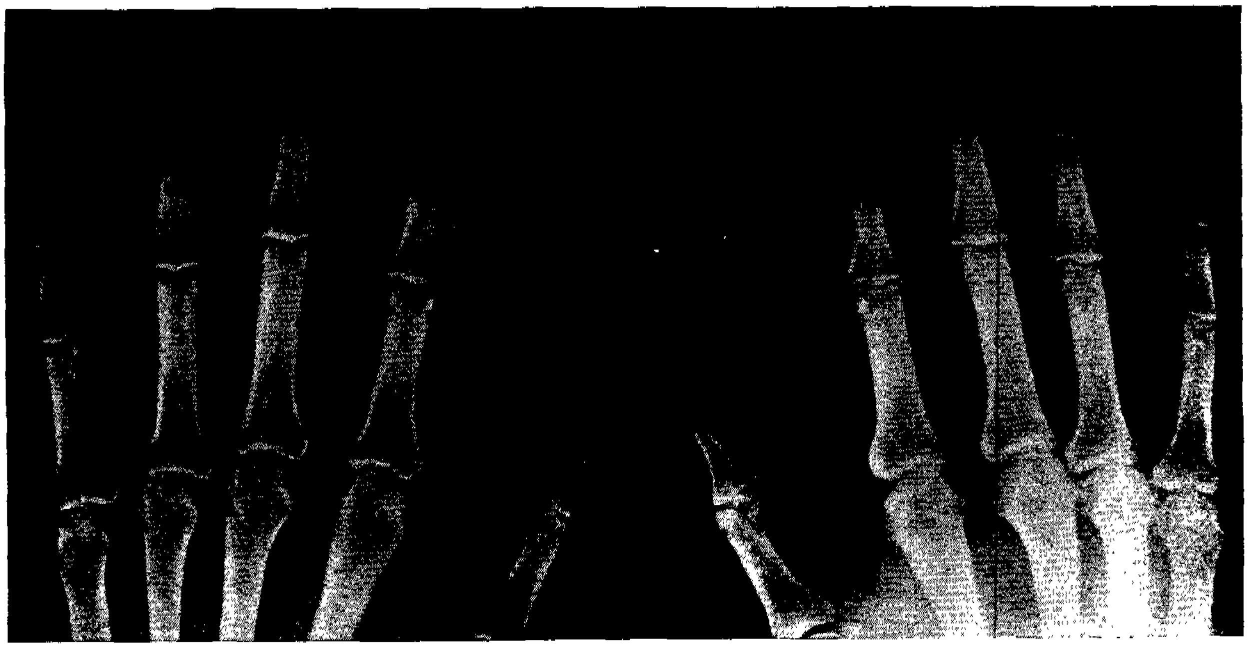
Table 1.—Summary of Symptoms and Findings

Symptoms	No. of Cases
Acroosteolysis without Raynaud's symptoms, one hand	4
Acroosteolysis without Raynaud's symptoms, both hands	5
Acroosteolysis with Raynaud's symptoms, one hand	5
Acroosteolysis with Raynaud's symptoms, both hands	17
Total	31
Clubbing of fingers	8
Skin nodules	8



2. Mild stage of acroosteolysis with half-moon defect of distal phalanx of mid finger.

1. Acroosteolysis with involvement of distal phalanges of all fingers.



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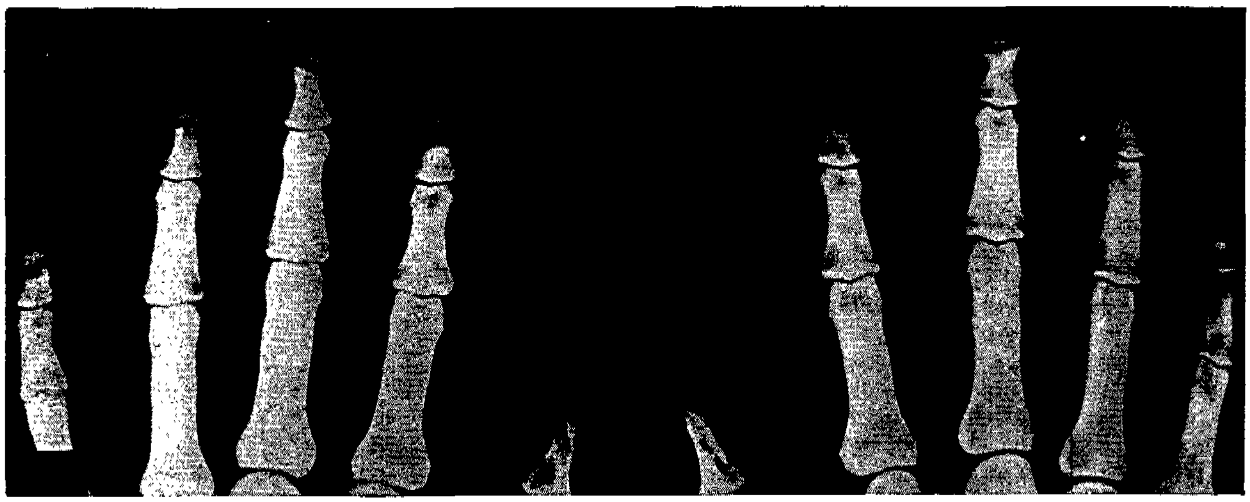
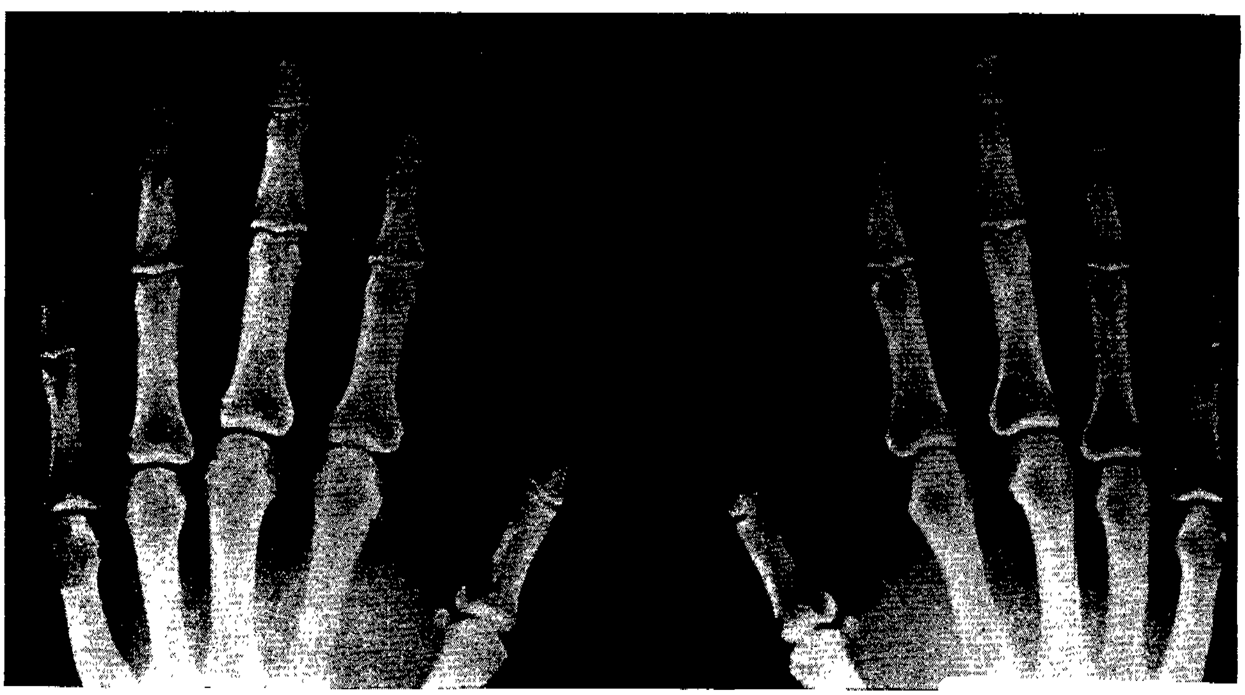
distal phalanges, or a so-called slice effect along one or more of the tufts. Figure 2 illustrates the small, half-moon cut in the cortex of the distal phalanx of the mid-finger.

3. Advanced stage: A more severe lytic destruction may be a complete loss of the tuft and a portion of the shaft of one or more distal phalanges as illustrated in Fig 1 in which the tuft of the distal phalanx of the right thumb and the tuft of the distal phalanx of the left fifth finger are completely absent. Additionally, there may be in the same hand a portion of the distal rim of the tuft remaining, with loss of the proximal portion of the tuft and a portion of the shaft of the phalanx, which can also be identified in the remaining phalanges in Fig 1. This loss may be of a transverse nature through the shaft and the tuft, or of an oblique type loss of bone structure.

4. Healing stage: In this phase, there is often definite fragmentation of the remaining tuft and of the filled-in area where the previous destruction was noted through the shaft of the distal phalanx. This may go on to a complete bony union or remain as a fibrous union with fragmentation. In Fig 3 and 4, x-ray films of the same individual well demonstrate this. This employee had almost complete reunion of the multiple fragments when first seen in November 1965 and again in November 1966 (Fig 3). In the latter, the completely healed shafts and tufts of the distal phalanges are indicated by no residual fragmentation with fibrous union. There is a definite shortening of the shaft and a widening of



3. ***Above***, **Acroosteolysis with marked fragmentation of distal phalanges in November 1965.** ***Below***, **Same individual in November 1966.**



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the shaft and tuft, both in the transverse and the anteroposterior diameter. This is most likely due to a combination of constant pressure, and by the normal tension of the soft tissues, particularly the tendons to the distal phalanges.

Occupational Aspects of Syndrome

Based upon our observations of these 31 cases, it appears as if this syndrome may be of occupational origin and is somehow related to the process of vinyl chloride polymerization. Its specific cause if not presently known. We are performing extensive research in an effort to find the cause. Two other papers referring to the condition have appeared in the literature. The publication by Suciu et al[3] contains no specific information, and merely alludes to some hand problem. That of Cordier et al[4] presents case histories with symptoms similar to many of the cases we describe. This syndrome differs from idiopathic and familial acroosteolysis in that only the hands are involved.

Vinyl Chloride Polymerization Process

Polyvinyl chloride is a widely used synthetic resin. It has been manufactured commercially for more than 30 years and is used in upholstery fabric, floor and wall tile, wire insulation, phonograph records, and many other commonly used commodities. For many of these uses, the resin $(CH_2CHCl)_x$ is mixed with other materials to achieve the desired physical characteristics. The hand syndrome occurs apparently only in those people exposed to vinyl chloride or to other chemicals used in the manufacturing process of the resin itself or both. In addition to our examinations of 3,000 personnel performing vinyl chloride manufacturing and polymerization, we have examined more than 1,000 individuals who handle the finished resin or who process it into plastic products. *No cases of acroosteolysis have been found in these 1,000 persons.*

Table 2.—Age Distribution of Cases

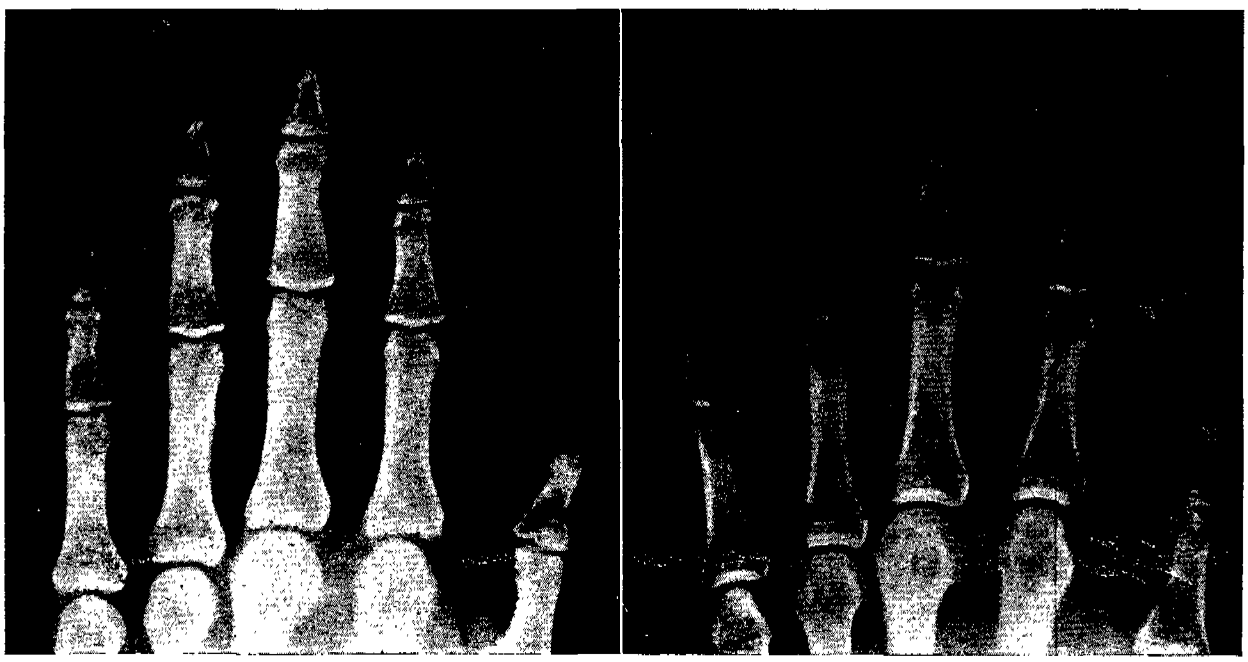
Age Group	Acroosteolysis Without Raynaud's Symptoms	Acroosteolysis With Raynaud's Symptoms
20-29	1	4
30-39	4	12
40-49	4	6

Basically, the manufacture of polyvinyl chloride consists of polymerizing vinyl chloride. The reaction is accomplished in closed containers (polymerizers) with suitable catalysts and emulsifiers.

Copolymers, formed by combining vinyl chloride with other monomers, create variations of the homopolymer. These are commercially produced. Following polymerization, the resin is washed, dried, and sold as a finely divided white powder.

The polymerization operations are carried out in closed processes and provide little opportunity for employee exposure. Following the completion of the polymerization reaction, periodic cleaning of the walls and agitator of the polymerizer is necessary. The frequency of this cleaning and its method varies with the type of material used in these vessels and with different manufacturers. The most common practice has been to accomplish the cleaning manually by using hand scraping techniques, with workers spending several hours each day on this job assignment. Personnel performing this job are commonly referred to as "polycleaners."

4. *Left,* Healed acroosteolysis with only minor roentgenographic changes. *Right,* Same individual one month after crushing injury to midfinger.



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Epidemiology

We have attempted to study the relationship of job history to the occurrence of the disease. Twenty-seven of our 31 cases have either been on the "polycleaner" job assignment at the time the syndrome appeared or have had that assignment at some time in the past. This job assignment is the only one showing any positive correlation with the occurrence of the syndrome.

Attack Rate.—The syndrome has a low attack rate. Our experience indicates it occurs only in less than 3% of all production employees who at one time have had polycleaning experience.

Age Distribution.—The youngest of our cases is 26 years old, and the oldest is 47, with the majority falling in the 30 to 39 age group. The complete distribution is shown in Table 2.

The appearance of the syndrome among younger employees may be influenced by the fact that the polycleaning job is one of the initial job assignments into which employees in such plants are hired.

Incubation Period.—If this syndrome is related to occupational factors, as we believe, then the time of exposure to these factors should be significant. We have investigated the time spent on polycleaning and, although accurate job-time assignment information is difficult to develop, it appears as if none of these cases has had less than 12 months polycleaning experience.

Comment

To our knowledge, this is a unique and, with the exception of references 3 and 4, previously unreported disorder. The specific cause is presently unknown, although it appears to be related to the manufacture of vinyl chloride and polyvinyl chloride. Not only are the x-ray findings of themselves unique, but when accompanied by the symptoms of Raynaud's phenomenon, the syndrome becomes extremely specific. As far as we are aware, this has not been an observed response to any toxicant in any of the animal species. We have attempted to arrive at an explanation of its cause, as well as the physiological mechanism whereby the extreme specificity for the distal phalanges of the hands occurs, but have been unsuccessful. We believe the condition is the result of three factors, all of which must be present for occurrence: (1) a chemical insult, (2) a physical insult, and (3) a personal idiosyncrasy. The chemical insult could occur from one or more of the monomers, catalysts, and intermediate reaction products existing in polymerizers. A low degree of exposure to these could occur from contact with the solid, slightly moist, residue in the polymerizer or to small quantities of vapor, absorbed either percutaneously or by inhalation. Research studies are in progress in an attempt to verify the chemical insult factor theory.

The physical insult is present in all "polycleaners" to some degree through the prolonged hand scraping operations as well as the occasional use of hammers to remove the residues. In support of the physical insult factor, we have quite recently observed the effects of a finger injury to an existing case of this syndrome. Figure 4 (*left*) shows an x-ray film of the left hand of the first of these cases of acroosteolysis (accompanied by Raynaud's symptoms and skin nodules on the dorsal surfaces of the hands). The bone damage is quite limited. Figure 4 (*right*) shows the same hand with the roentgenogram taken four months after a crushing injury to the mid finger, with lysis having resulted to the tuft of the distal phalanx. We believe this activity was stimulated by the trauma.

Personal idiosyncrasy appears to be an important factor because of the low incidence of occurrence of the disorder. This is especially significant because, although all polycleaners are subjected to essentially similar chemical and physical insults, the incidence of this syndrome is very low, and the explanation for this can only be made on the basis of personal idiosyncrasy. We suspect pertinent factors here are related to the individual's vascular system, the nerves controlling the blood supply to the fingers, and to the specific type of collagen in the individual's hands. We are in the process of investigating these factors.

We have observed no serious disability in any of these cases. A few have been partially disabled because of hand soreness, to the extent that some restriction in manual activity was necessary. Improvement in the symptoms, as well as in the roentgenological findings, has occurred in many cases without adequate explanation.

We wish to emphasize that no cases have been found, after extensive search, in individuals either working with the finished polyvinyl chloride or its copolymers, or in processing the polymer into plastic products. In these processes, more exposure to the polymer occurs than does in the manufacturing of the polymers themselves.

We presently believe that personnel assigned to polycleaning should be evaluated, prior to assignment, for any evidence of collagen disease, osteolysis of the hands, or abnormal response of the hands to cold insult. Any evidence of the existence of any of these factors should contraindicate the assignment of an individual to "polycleaning," and thus remove, or at least minimize, the personal idiosyncrasy factor.

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