Are Trace Metals Associated With Asbestos Fibers Responsible For the Biologic Effects Attributed to Asbestos?

Lewis J. Cralley, Ph.D. and William S. Lainhart, M.D.

In evaluating the role of trace metals associated with asbestos in relation to the biologic response to asbestos, it is necessary to: (1) review briefly the predominent biologic responses to asbestos along with the etiologic aspects and pathogenic mechanisms involved, (2) identify the trace metals associated with different types of asbestos, and (3) present evidence relating the biologic response of asbestos to the presence of trace metals.

Predominent Biologic Responses to Asbestos

Fibrogenic Response. — It is generally accepted that exposure to asbestos fibers may lead to a pulmonary fibrogenic response. This knowledge is so universal that its documentation is no longer necessary. It is not within the scope of this presentation to discuss either the characteristics of the fibrosis nor the dose-response aspects involved. This information is contained in many standard references on the pneumoconiotic diseases. The pathogenic mechanisms of injury, however, are pertinent to this discussion. The following theories have been proposed at one time or another to account for the pulmonary fibrosis resulting from the presence of asbestos fibers in the lungs: (1) mechanical: traumatic injury of the tissue by the asbestos fiber, (2) chemical: reaction of soluble components of the fibers with the tissues, and (3) surface action: absorption of proteins on fiber surface governed by crystallographic structure and surface areas of asbestos crystals. Previous publications[1,2] have reviewed these theories in detail along with supporting and conflicting evidence. It is generally accepted that none of the theories alone is adequate to explain the pathologic mechanisms of asbestosis. This leaves us with the conclusion that more than one factor as well as factors not considered heretofore may be involved.

Carcinogenic Response. — The scientific literature associating exposure resulting in asbestosis with increased risks for malignancies is voluminous. The malignancies relate predominately to the lung, pleura, or peritoneum, though other sites may also be involved. Data are meager relating exposures to specific types and characteristics of asbestos with specific types and sites of cancer. Researchers theorize that a number of etiologic agents[3-8] may be involved: (1) the fiber, per se, (2) trace metals associated with the fiber, (3) polycyclic aromatic hydrocarbons associated with the fiber, (4) additives in the mining, milling, and processing of asbestos, and (5) cigarette smoke in conjunction with asbestos exposure. Thus the asbestos fiber may be a cocarcinogen or may serve largely as a mechanical carrier of other agents to tissue sites. The precise agent or agents causing the cancer and the relationship with the asbestos fiber, however, are still to be definitively identified.

Asbestos Bodies. — Asbestos fibers in the body tissues give rise to asbestos bodies. The description of these bodies and their nature is contained in standard texts dealing with clinical aspects of asbestosis. Though asbestos bodies have been described in the literature for over 65 years and their origin has had considerable study, little is known of the meaning of their presence other than to denote that exposure to asbestos fibers has occurred.

Trace Metal Characteristics of Asbestos. — Metals associated with asbestos fibers originate from the mineralogy involved in formation of the fibers[9,14] and from the abrasive action of asbestos on the alloy equipment in which it is processed.[10] These metals and their compounds include manganese, chromium, nickel, iron, cobalt, vanadium, zinc, copper, titanium, zirconium, and lead. Only limited effort has been devoted to characterizing the overall trace metal content of asbestos-airborne dusts associated with different types of asbestos and various methods of processing. Work done has been selective and limited mostly to designated metals considered to be of physiologic importance in relation to the response being studied, i.e., nickel, chromium, cobalt, manganese, iron, etc.[10-17] Characterizing the trace metals in asbestos is difficult because great variation exists in the specific metals present in the original mineral and in the airborne concentration encountered, depending on type of asbestos, grade of fiber, and nature of the process. The trace metal content of asbestos dust has been shown to concentrate in the respirable fraction.[10,14,15]

Data for Table 1 were obtained on milled asbestos bulk fibers received in the United States for processing into

From U.S. Dept. of Health, Education and Welfare, Public Health Service, Health Services and Mental Health Administration, National Institute for Occupational Safety and Health, U.S. Post Office and Courthouse Bldg., Cincinnati, Ohio 45202.
Reprint requests to Dr. Lainhart.

Table 1. — Designated Metals in Under Ten-Micron Fraction of Mine Milled Asbestos Fibers*

Type	Source	No. Samples	ppb Ni	Cr	Co	Mn
Chrysotile	Africa	3				
	range		1980-2180	1475-1741	55-97	499-855
	average		2048	1648	76	684
	Canada	3				
	range		1533-2730	553-1865	43-72	552-1586
	average		2006	1317	64	898
	Russia	3				
	range		1643-1788	1349-1478	71-76	676-749
	average		1720	1403	73	718
Crocidolite	Africa					
	North Cape	8				
	range		85-488	97-320	0-93	539-3409
	average		207	207	36	1886
	Transvaal	5				
	range		87-467	53-208	0-87	519-811
	average		255	124	52	668
Amosite	Africa	7				
	range		104-290	123-440	0-84	2756-13919
	average		207	261	20	6375
Anthophyllite	Finland	1	927	55	31	1448

* Sample sieved through a ten micron diameter pore screen

asbestos products. The bulk fibers were screened through a 10 μ diameter pore size sieve[19] to obtain the fraction that would simulate respirable dust at the milling operations producing the fiber. The metals, by specific kinds and concentrations, vary greatly in different types of asbestos—but have a number of similarities within the same type of asbestos. For example, the metal content of chrysotile is, in general, similar regardless of source. No specific metal characterization is available to distinguish chrysotile by its source of origin. In crocidolite, however, manganese is much higher in fiber from the North Cape area compared to fiber from the Transvaal area. The source of the excess manganese is believed to be the processing equipment, especially the hammer mill, since the country rock around the North Cape fiber is much harder than the rock around the Transvaal fiber. As seen by the data, the ratios of manganese, chromium, cobalt, and nickel vary appreciably according to type of asbestos fiber.

Table 2 gives data on comparative levels of designated metals in different size fractions of mine milled asbestos fibers. The milled fiber was sieved through a 10 μ diameter pore sieve[19] to obtain a fraction that would simulate airborne exposure at operations producing the fibers. The two fractions were analyzed for designated metal content. It is apparent that the metals in the mine milled bulk asbestos are concentrated in the under ten-micron size fraction. Also, the metal contents of the bulk UICC samples (Asbestos reference samples prepared by the International Union Against Cancer[18]) are much lower than the under ten-micron size portion of the corresponding mine milled asbestos fibers. Research data on animals exposed to these or similarly prepared samples, though extremely important for reference purposes, are not directly applicable to conditions representing worker exposure since there may be several orders of differences in the magnitude of exposure to trace metals in the respective groups.

Evidence Relating Biologic Response of Asbestos to Presence of Trace Metals

Only minor attention has been directed to research for defining the role of trace metals associated with asbestos dust in relation to biologic response. This work has been confined largely to animal research on asbestos fibers and carcinogenesis in which the asbestos was analyzed for designated trace metals, i.e., nickel, cobalt, chromium, manganese. The data on the concentration of metals occurring either alone or in combination in the asbestos, did not correlate well with prevalence of tumors observed in animals. For this reason, the role of these metals in asbestos carcinogenesis remained obscure and was given little further attention. A recent hypothesis,[20] however, should redirect further attention to the importance of trace metals in the biologic response to asbestos. The hypothesis relates the biologic response of asbestos to the electromotive interaction of the metals and minerals present with the fiber serving as a transport mechanism to different tissue sites. The electromotive interactions of the metals and minerals serve to: (a) concentrate metals lower in the electromotive series such as nickel to localized tissue sites, (b) greatly increase the residency time of metals lower in the electromotive series at localized tissue sites, (c) create a subsequent flooding effect at localized tissue sites when the metals lower in the electromotive series go into solution, and (d) release the metals lower in the electromotive series in more biologically active form. The cations of these metals are not in equilibrium with anions, as occurs when the metal compounds, as minerals, go into solution.

Fibrogenic Response. — There are no data which relate the fibrogenic response of asbestos fibers to the minerals and metals associated with the fibers. A number of observations have been reported, however, which indicate that factors other than the fiber alone may be involved.[2 21 22] These data show that synthetic chrysotile fibers produced much less or no fibrogenic response compared to natural chrysotile. Finely ground asbestos is much less reactive in producing fibrosis compared to coarse fiber. The metal content of the fiber could be important. In the synthetic fiber the level of trace metals is very low. In finely ground asbestos, the presence of metals such as manganese may influence significantly the actions of metals such as nickel which are present in natural asbestos and in which elemental metals higher in the electromotive series are of a very low order of magnitude or are absent. Though speculative, it is conceivable that the presence of trace metals could modify

Table 2. — Comparative Levels* of Designated Metals in Different Size Factors of Nine Milled Asbestos Fibers

Type	Source	No. Samples	Ni	Cr	Co	Mn
			µg/g			
Chrysotile	Africa	3				
	over 10-micron†		1588	1294	58	305
	under 10-micron‡		2048	1649	76	684
	Canada	3				
	over 10-micron		1356	591	46	452
	under 10-micron		2086	1317	57	898
	Russia	3				
	over 10-micron		1353	793	78	530
	under 10-micron		1720	1400	73	718
	UICC§					
	Africa	1				
	bulk		1482	1378	54	393
	under 10-micron		1290	1050	33	245
	Canada	1				
	bulk		802	317	45	444
	under 10-micron		665	288	23	227
Crocidolite	Africa					
	North Cape	5				
	over 10-micron		25	26	9	723
	under 10-micron		170	239	7	1914
	Transvaal	2				
	over 10-micron		15	15	13	410
	under 10-micron		120	162	15	721
	UICC	1				
	bulk		8	20	10	833
	under 10-micron		30	34	11	800
Amosite	Africa	6				
	over 10-micron		55	27	22	7539
	under 10-micron		193	273	6	5071
	UICC	1				
	bulk		33	31	11	13347
	under 10-micron		79	65	8	12650
Anthophyllite	Finland	1				
	over 10-micron		547	1075	72	538
	under 10-micron		827	55	31	1448
	UICC	1				
	bulk		414	584	24	986
	under 10-micron		397	407	18	752

* Values expressed are average values.

† Fraction of sample retained on a ten-micron diameter pore sieve.

‡ Fraction of sample passing through a ten-micron diameter pore sieve.

§ A special blend of the designated asbestos for use as reference samples.[17]

the fibrogenic response of asbestos fibers. This aspect merits further consideration in relation to asbestos dust and to other non-fibrous pneumoconiosis-producing dusts.

Asbestos Bodies. — As with the fibrogenic response of asbestos, there are no definitive data that relate presence or absence of asbestos bodies with the presence of specific trace metals and minerals associated with the asbestos fibers. Recent reports[23 24] show that the number of bare fibers in the lungs far exceeds the number of coated fibers. The cause of this phenomenon is unknown. Though suppositional, it is conceivable that if elemental metals higher than iron in the electromotive series are present, they may interfere with the availability of iron for complexing with protein in forming the coating around the fiber. Further research into this aspect may give clearer meaning to the presence of asbestos bodies.

Carcinogenic Response. — A number of publications have suggested that trace metals associated with airborne exposure to asbestos dust may be related to cancer observed in exposed groups.[6 7 10 25 28] This appears rational since either some of the metals or their compounds have been shown to be carcinogenic. A major hindrance to acceptance of this relationship by many has been lack of reasonable correlation between cancers observed in animals and metal content of the asbestos under investigation. The hypothesis on the electromotive interaction of metals and minerals[20] gives new perspective on the relationship of their presence in asbestos and the carcinogenic response.

Since the nature of the associated minerals and alloys, their solubility, etc., are extremely variable and largely unknown, it is not surprising that the total metals, either individually or combined, did not correlate with the prevalence of cancer observed in any particular investigation. To further define the importance of the electromotive interaction of elemental metals and minerals associated with asbestos and carcinogenicity, it was deemed essential to go to relatively pure forms of specific metals and their compounds without a multitude of concurrently unknown exposure factors being present as is the case with asbestos. Dr. F. William Sunderman, Jr.[29] is conducting this investigation using the model he previously established. Fisher strain, male rats (24 of each series) were given intramuscular (thigh) injections of designated combinations of elemental metals and nickel sulfide (Ni_3S_2) suspended in 0.5 ml of penicillin solution. The concentrations per injection were: 2.5 mg Ni_3S_2 and atomic equivalents of elemental metals as the Ni in the 2.5 mg. Ni_3S_2. Full details of methodology and procedures and preliminary findings 17 months after injection are contained in the preliminary report.[30] The tumors have not been characterized in detail. They are predominently fibrosarcomas and rhabdomyosarcomas with an appreciable number having metastasized to other organs. Limited data from this investigation are presented in Table 3. At 510 days after injection 91.7% (22 out of 24) of the rats injected with nickel sulfide had tumors at the site of injection; 97.8% (23 out of 24) of the rats injected with nickel sulfide and elemental chromium had tumors at site of injection with tumors occurring somewhat earlier than in rats dosed with nickel sulfide alone; 91.7% (22 out of 24) of

Table 3. — Tumors Observed at Site of Injection 17 Months After Injection[a]

Dose Combination	Rats	Tumors	Rats with Tumors, %	Median* Latency Period, Days
No metals	24	0	0	—
Elemental chromium	24	0	0	—
Elemental manganese	24	0	0	—
Elemental copper	10	0	0	—
Elemental chromium + manganese	24	0	0	—
Aluminum oxide†	24	0	0	—
Nickel sulfide	24	22	91.7	289
Nickel sulfide + elemental copper	10	10	100.0	281
Nickel sulfide + elemental chromium	24	23	95.8	260
Nickel sulfide + aluminum oxide†	24	22	91.7	328
Nickel sulfide + elemental manganese	24	15	62.5	387
Nickel sulfide + elemental chromium and manganese	24	3	12.5	

* 50% of rats in each series

† Contained 15.0% elemental aluminum

the rats injected with nickel sulfide and elemental aluminum had tumors at site of injection with tumors occurring at a somewhat later period than that for rats injected with nickel sulfide alone even though only 15% of the total aluminum was present in the elemental form; 62.5% (15 out of 24) of rats injected with nickel sulfide and elemental manganese had tumors at site of injection with tumors occurring at a much later date than that for rats injected with nickel sulfide alone; 12.5% (3 out of 24) of rats injected with nickel sulfide, elemental chromium, and elemental manganese had tumors at the site of injection with tumors occurring at a dramatically much later date than that for rats injected with nickel sulfide alone.

The latency period in days from injection until 50% of animals in each series developed tumors were: nickel sulfide alone, 288 days; nickel sulfide and elemental chromium, 260 days; nickel sulfide and aluminum (15% in elemental form), 328 days; nickel sulfide and elemental manganese, 384 days; nickel sulfide and elemental chromium and elemental manganese, only 3 out of 24 rats developed tumors in 510 days. In another series, elemental copper was given with the nickel sulfide since copper is lower than nickel in the electromotive series and should have no electromotive interaction with nickel sulfide. There was no appreciable difference in this group in either latency period or number of tumors compared to animals injected with nickel sulfide alone. The latency periods from injection until 50% of the rats developed tumors for each series were 282 and 288 days respectively. These data give strong support to the hypothesis of the electromotive interactions of metals and metal compounds and their carcinogenic action.

Summary

There is no definitive evidence that relates the fibrogenic properties of asbestos fibers or their potential to form asbestos bodies to trace metals associated with the fibers. Such a relation would be largely speculative. Bits of evidence are available, however, which could explain how the presence of trace metals may play a modifying role in these biologic responses to asbestos. Further research is recommended to determine the actuality of such a relationship.

A considerable body of evidence exists relating trace metal contents associated with asbestos fibers with the carcinogenicity of asbestos. Evidence is presented supporting the hypothesis that the electromotive interactions of the metals and minerals present are important determinants in the carcinogenic action of asbestos. Research is continuing on this inter-relationship.

References

1. Vigliani EC: The Fibrogenic Response to Asbestos, *La Medicina del Lavoro*, **59**:401-410, 1968.

2. Gross P, et al: Problems in the Pathology of Asbestos, Pneumoconiosis Proceedings of the International Conference — Johannesburg 1969. pp 126-132. Edited by H. A. Shapiro, Oxford University Press, 1970.

3. Working Group on Asbestos and Cancer, Geographical Pathology Committee of the International Union Against Cancer, *Arch Environ Health* **11**:221-229, 1965.

4. Cralley LJ, et al: Research on Health Effects of Asbestos, *Jour Occup Med* **10**:38-41, 1968.

5. Cooper WC: Asbestos as a Hazard to Health, *Arch Environ Health* **15**:285-290, 1967.

6. Wright GW: Asbestos and Health in 1969, *Amer Rev Resp Disease* **100**:467-479, 1969.

7. Cooper WC, et al: Panel on Asbestos: Asbestos the Need for and Feasibility of Air Pollution Controls. National Academy of Sciences, Washington, D.C., 1971.

8. Selikoff IJ, Hammond EC, and Churg J: Asbestos Exposure Smoking and Neoplasia, *JAMA* **204**:106, 1968.

9. Speil S and Leineweber JP: Asbestos Minerals in Modern Society. **2**:166-208, 1969.

10. Cralley LJ, Keenan RG, and Lynch JR: Exposure to Metals in the Manufacture of Asbestos Textile Products, *Amer Indus Hyg* **28**:452-461, 1967.

11. Harrington JS: Chemical Studies of Asbestos, *Ann NY Acad Sci* **132**:31-47, 1965.

12. Holmes A, Morgan A, and Sandalls FJ: Determination of Chromium, Cobalt, Iron, Nickel, and Scandium in the International Union Against Cancer (UICC) Asbestos Reference Samples by Neutron-Activation, UKAEA Unclassified Report AERE-R 5910, 1968.

13. Morgan A, and Holmes A: Neutron Activation Techniques in Investigations of the Composition and Biologic Effects of Asbestos. Pneumoconiosis Proceedings of the International Conference, Johannesburg, 1969. Edited by H. A. Shapiro pp 52-56, Oxford University Press, 1970.

14. Gibbs GW: Qualitative Aspects of Dust Exposure in the Quebec Asbestos Mining and Milling Industry. Inhaled Particulates III, Vol. 2, 783-797. Edited by W. H. Walton, Unwin Brothers Limited, The Gresham Press, Old Woking, Surrey, England, 1971.

15. Gibbs WG, and Lachance M: Dust Exposure in the Chrysotile Asbestos Mines and Mills of Quebec, *Arch Environ Health* **24**:189-197, 1972.

16. Rendall REG: The Data Sheets on the Chemical and Physical Properties of the UICC Standard Reference Samples. Pneumoconiosis Proceedings of the International Conference, Johannesburg. Edited by H. A. Shapiro, pp 23-77, Oxford University Press, 1970.

17. Timbrell V: Characteristics of the International Union Against Cancer Standard Reference Samples of Asbestos. Pneumoconiosis Proceedings of the International Conference, Johannesburg, Edited by H. A. Shapiro, pp 28-36, Oxford University Press, 1970.

18. Trimbrell V: Characteristics of the International Union Against Cancer Standard Reference Samples of Asbestos. Pneumoconiosis Proceedings of the International Conference, Johannesburg. 1969 Edited by H. A. Shapiro, pp 28-36, Oxford University Press, 1970.

19. Kupel RE, Kinser RE, and Mauer PA: Separation and Analysis of the Less Than 10-Micron Fraction of Industrial Dusts, *Amer Ind Hyg Assoc J* **29**:364-367, 1968.

20. Cralley LJ: Electromotive Phenomena

in Metal and Mineral Particulate Exposure: Relevance to Exposure to Asbestos and Occurrence of Cancer. *Amer Ind Hyg Assoc J* 32:653-661, 1971.

21. Valagar AG, Kogan FM, and Fralova NH: Comparative Assessment of Biological Aggressivity of the Natural and Synthetic Asbestos Potogency Pneumokonioyov — Proceedings of the Federal Symposium of USSR pp 73-81, Snerdlovsk, 1970.

22. Webster I: The Pathogenesis of Asbestosis Pneumoconiosis. Proceedings of the International Conference, Johannesburg. 1969. Edited by H. A. Shapiro pp 117-119. Oxford University Press, 1970.

23. Langer AM, Baden V, Hammond EC, and Selikoff IJ: Inorganic Fibers, Including Chrysotile, in Lungs at Autopsy: Preliminary Report. Inhaled Particulates III. Edited by W. H. Walton, Vol. 2, pp 683-694. Unwin Brothers Limited. The Gresham Press, Old Woking, Surrey, England 1971.

24. Gross P, deTreville RTP, and Cralley LJ: Studies on the Carcinogenic Effects of Asbestos Dust. Pneumoconiosis Proceedings of the International Conference, Johannesburg. Edited by H. A. Shapiro. pp 220-224. The Oxford University Press, 1970.

25. Donna A: Experimental Asbestos Tumors Induced by Chrysotile, Crocidolite and Amosite in Sprague-Dawley Rats, *Med Lav* 61:1-32, 1970.

26. Webster I: Asbestos Exposure in South Africa. Pneumoconiosis Proceedings of the International Conference, Johannesburg. Edited by H. A. Shapiro, pp 209-212. Oxford University Press, 1970.

27. Dixon JR, Lowe DB, Richards DE, Cralley LJ, and Stokinger HE: The Role of Trace Metals in Chemical Carcinogenesis: Asbestos, *Cancer Res* 30:1068-1074, 1970.

28. Contract EHS-C-0109. Electromotive Interactions of Metals in Asbestos Carcinogenecity. F. William Sunderman, Jr., M.D., Professor and Head Department of Laboratory Medicine, University of Connecticut, School of Medicine, Hartford, Connecticut.

29. Cralley LJ, and Sunderman FW: Interactions of Metals and Carcinogenecity. American Industrial Hygiene Conference (ACGIH) May 15-19, 1972. To be published.

Some Ancient Mysteries Reexplored

I. Women are Sinister*

Carey P. McCord, M.D.

That title in no way implies that women are evil, devious or capricious. That word "sinister" has more than one meaning, and one meaning is "left" just as dexter is "right." Many women, without being naturally left-handed, do many things with the left hand that expectedly would be done with the right. Many public buildings have two front doors, side by side. Neither may be marked "entrance" or "exit," but the customary way of entering is through the right-hand door. Some women regardless of the direction from which they approach the door consistently reach for the left one, often times after passing by the right door, the proper one. All this is so well established that most of the entrances to supermarkets, even when electrically operated, are on the left. This is equally true for the exit. Airports usually pose no such situation. There, ordinarily two electrically operated doors spring open, thus offering no choice for either men or women.

The most striking phenomenon connected with women's sinisteristics has to do with the side of buttons on garments. On men's overcoats, jackets, vests, sweaters, shirts, and underwear, the buttons are on the right and the buttonholes are on the left. Not so with women's garments. Somewhat invariably, the buttons are on the left and the buttonholes are on the right. When women are questioned about this, they point out that that practice is a long tradition in the women's garment trade. What they don't know is that long before there was any women's garment trade, women in their own households diligently sewed buttons on in the same manner. During that period women, with their own hands, made garments for their husbands and male children. The wonder is that by habit they did not sew buttons on the left side for one and all. Not so. It does appear that this sex differentiation long ago was established, and for a long time, there has been close adherence.

In the kitchen, most of the utensils such as skillets do not involve handedness. A few do. There is one type of strainer which is provided with a handle. To carry out its intended use, the handle only can be gripped with the right hand while the heavier vessel with its contents to be strained must be held in the left hand. This just suits the women cooks, but for most males the position is definitely awkward.

Many belts on garments are removable. On replacement, the male ordinarily will start the end of the belt through the loops using his right hand and moving to the left. At the end this places the buckle on the left. Women are prone to do just the opposite. With their left hand they start the belt through the loops at the right, ending up with the buckle on the right. The net result is the same, but the difference in this practice by the men and women is striking.

At any cocktail party for both men and women, look about you. Men will be seen holding their drinks with their right hand while women, but by no means unfailingly, will be seen sipping at drinks brought to their lips with the left hand.

When a group of men and women, or boys and girls, are out for a spin in an open car, they may wish to wave at passing friends. Men do the waving with the right hand; women are given to waving with the left hand.

In some restaurants, the handles on the coffee pots for table-serving are not vertical but horizontal. The handle reaches out horizontally from the side of the pot. This device has been provided to avoid the waiter or waitress from coming too close to the customer. In pouring coffee, the proper position for filling the cup is from the customer's right side. Just the same, numerous waitresses may be seen pouring the coffee with the left hand, thus defeating the very intent of the innovation. Male waiters do just the opposite.

Surely there must be some deep psychological reason for all such sex-linked activities and there is. This series of articles proposes to explore old mysteries, but provides no guarantee that a final solution will appear. In this instance there is a solution. For many centuries women have carried babies around on their right arms. The left arm has long been woman's free arm—the arm ready to carry out endless activities. It is probably true that this has gone on for so long that woman's disposition to depend on the left arm now reaches into the genes. That point is not pressed, but the fact remains that women are sinister.

*For reprints write the author at the Institute of Environmental and Industrial Health, School of Public Health, University of Michigan, Ann Arbor, Michigan 48104.