Historical Developments and Perspectives in Inorganic Fiber Toxicity in Man

by Irving J. Selikoff*

The first patient known to have died from asbestosis (1900) began work in 1885, approximately 5 years after the industrial use of asbestos began in Britain. Mineral particles were found in his lungs. No special comment was made of their fibrous nature then nor when the first case was reported in 1924. The various neoplasms attributed to asbestos in the next decades posed an additional question: What influence did the fibrous shape of the particles have on carcinogenic potential? The cogency of the problem was amplified by the identification in humans of asbestoslike neoplasms with a fiber other than asbestos (erionite) and by the production of such neoplasms in experimental animals with a variety of man-made inorganic fibers, often used as substitutes for asbestos. The lessons learned about asbestos may help guide us in evaluating current fiber problems.

Introduction

The first recorded case of asbestos-associated disease was seen in 1899 by Dr. H. Montague Murray, a physician at the Charing Cross Hospital in London. The case was a man with marked dyspnea employed for only 12 years in the carding room of a recently established asbestos factory. Death occurred a year later and, at autopsy, fibers of the mineral were seen (together with what were recognized as asbestos bodies when the slides were reviewed in 1970s). Nevertheless, there was no special comment made that the dust to which exposure had occurred was fibrous in nature (1). Nor was there recognition that special potential toxicity that might be associated with the fibrous nature of the dust, although public health authorities responsible for maintenance of hygienic precautions in workplaces were then aware of excessively dusty conditions and worker complaints (2,3), and it had been categorized by HM Factory Inspectors in 1898 as one of the four most hazardous occupational dusts.

These positions are easily understood. First, although it was known, in general, that some dusts could be extremely toxic and others apparently benign, reasons for such differences had not been worked out. Knife grinders of Sheffield inhaled dust, as did bricklayers of Manchester and agricultural laborers of Wales, but their shorter span of life demonstrated that there was something special about the dust to which they were exposed. Gradually, however, the special role of crystalline silica in the various dusts was deciphered, and was well established in 1916 by the brilliant Milroy Lecture of E. L. Collis (4–6). This impressive display of the power of

occupational toxicology and clinical epidemiology served to focus attention on quartz: so much so that the potential toxicity of inorganic dust particles thereafter was generally gauged by their content of respirable quartz.

Emphasis on quartz did not prevent identification of clinical disease associated with asbestos fiber inhalation. Such cases were seen by physicians among employees of the growing asbestos industry. The first such case in the medical literature was reported in 1924 by W. E. Cooke. The Cooke case opened a new era, with the observations detailed in the *British Medical Journal.* A further description of the case was published in the same journal in 1927 (8), allowing the condition to be named "pulmonary asbestosis." It stimulated wide discussion at the next meeting of the British Medical Association and attracted the attention of the Medical Inspectors of Factories, who sought out other cases. Further, with awareness of additional instances of illness among workers exposed to this dust, a survey was undertaken of employees of one of the largest British asbestos plants. The findings led to general appreciation that an important pneumoconiosis, without appreciable amounts of quartz, existed (9).

Among the new findings in the rapidly burgeoning medical reports, two stood out. The first was pleural disease, which was detailed in the 1924 and well illustrated in the 1927 description of Cooke's case and was soon amplified by additional radiological descriptions. This abnormality further separated asbestosis from the other pneumoconiotic dust diseases, since pleural abnormalities were not a feature of either silicosis or coal workers' pneumoconiosis. Second, the strikingly unusual finding of filamentous structures, both uncoated (understood to be asbestos fibers) and coated, again was unique. The coated structures occasioned a vigorous

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debate at first, since their initial identification did not establish them as related to the mineral fibers inhaled [Cooke even considered (10) that the "curious bodies" might be organic in nature]. Soon, however, their significance was clarified, with their designation changing from "curious bodies" (11) to "asbestosis bodies" to "asbestos bodies" (12). Further, it was rapidly established that their central core need not be an asbestos fiber, but that other inorganic materials, if they were fibrous in form, could also stimulate the tissue reactions that produce a coating, and the term "pseudo-asbestos bodies" (13) was used, later to be generalized as "ferruginous bodies" (14).

Thus, by the mid-1930s, a new pneumoconiosis was medically established and unusual features agreed upon. The disease was due to a fibrous dust, unrelated to crystalline silica content, the pleural surfaces could frequently be involved, and the scarring produced could be extremely damaging (pulmonary insufficiency), even fatal. The next 30 years were marked by continuing accumulation of information concerning disease hazards associated with exposure to the dust, including the fact that the particles were fibrous in form. Nevertheless, the fact that we were dealing with fibers was not one of the outstanding questions explored during this period. Rather, scientific and medical studies were driven by accumulating knowledge of the spectrum of disease hazards. The initial finding of lung cancers among asbestos-exposed workers in 1935 (15,16) added impetus as did the initial reports of pleural and peritoneal mesothelioma in the 1950s (17–19) with even greater emphasis stimulated by the reports of the frequency of pleural mesothelioma and the fact that it could be produced by much lighter exposure (environmental, family contact) than that which caused serious pulmonary and pleural fibrosis (20,21). Moreover, data became available indicating that a much larger number of people had been and were being exposed to asbestos (22), including the many hundreds of thousands using asbestos products in their work, products which had been produced by considerably fewer individuals in the factories in which they were manufactured. The dimensions of the problem were greatly extended, qualitatively and quantitatively.

It was at this point that focus and attention were added to the fibrous nature of the dust, for a very good reason. Augmented control measures were being considered. Among them, abandonment of the toxic fibrous dust was one of the options. But if this were to be adopted, the question of substitutes for asbestos had to be simultaneously considered. What would replace asbestos? For many applications, these also had to be fibrous in form. Some had already come into commercial use, including manmade mineral fibers such as fibrous glass and rock wool.* Inevitably, with the scientific in-

formation that had been gathered from 1930 on, questions arose as to whether the substitutes might not have toxicity similar to that of asbestos fibers.

This historical development was, in a sense, codified and stated almost in a form of scientific challenge by the observations and thesis of Merle Stanton in 1972 (23) when his experimental research, albeit limited, led him to consider the possibility that small inorganic fibers, in general, might be inherently toxic to tissues, particularly with regard to carcinogenicity (mesothelioma), and that the probability of tumor induction was related to their fibrous form, with a gradient that produced greater and greater risk as the fibers became longer and thinner.

The Stanton Hypothesis, 1989

Stanton's hypothesis has been and is being explored, probed, and tested in many ways (24). Not unexpectedly, questions have been raised and inconsistencies noted. These do not, however, in my opinion, make it less fruitful as an overall guide to studies concerning asbestos or for the evaluation of other inorganic fibrous materials, particularly those that might be used as substitutes for asbestos. Rather, they serve to refine and extend the overall concept.

Thus, Stanton's emphasis on the dimensions of fibers has been enriched by appreciation that chemical and physical characteristics are also of potential importance (25–27). For example, there has been increasing discussion concerning the possible different toxicities of the various fiber types, if not for asbestosis and lung cancer, then perhaps for mesothelioma; the "crocidolite hypothesis" (28) was modified to an "amphibole hypothesis" (29) which, in turn, has been further altered by some to a "tremolite hypothesis" (30) to explain mesotheliomas seen in chrysotile-exposed individuals.

Further, discrepancies between results of studies of fiber lung burdens and associated disease (31–33) have begun to be explained by such wry observations as those pointing to selective bias (34) perhaps almost inevitable in providing lung specimens for analysis, and by Sebastien's studies of the fiber burden of pleura, when considering pleural mesothelioma. He did not limit analytical measurements to what is in the pulmonary parenchyma, especially since findings at the two sites differ substantially, both quantitatively and qualitatively (35,36).

Additional modifications have been forthcoming as data accumulate. For example, it seemed curious that mesotheliomas were reported in humans for all the common asbestos fibers except anthophyllite, even though this type of asbestos produced the neoplasm in animals and both lung cancer and asbestosis in man. New work in Finland, where much of the asbestos used has been anthophyllite, now shows substantial levels of anthophyllite in individuals with mesothelioma in that country (37).

Another unexplained observation was troubling. The most physiological route of exposure in animal studies was clearly by inhalation, yet few mesotheliomas were so produced. In collected series of more than 600 animals

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* It is a historic irony that the British Admiralty, after pioneering the use of "cotton silicate" in the 1890s, recognized this manmade inorganic fiber to present a potential health hazard and subsequently changed to asbestos for thermal insulation.

exposed to crocidolite by inhalation, only a handful of mesotheliomas were seen. On the other hand, the same fiber type, with exposure by injection or implantation into a mesothelial cavity, readily gave large numbers of mesothelial tumors. Pott has astutely pointed this out, noting that the nonphysiological route seemed much more predictive of mesothelioma potential in experimental studies than did physiological exposure, a lesson that could be relevant in the investigation of possible asbestos substitutes (38).

Additional discrepancies in the results of different studies could be explained by the recent appreciation that the standardized UICC asbestos materials (39) used in many studies were by no means standardized, in terms that would now be relevant, including trace elements or the presence of contaminating asbestos fibers other than those of the overall designation (chrysotile, amosite, crocidolite), as well as distribution of fiber dimensions, features that might be relevant to differences in experimental results. The UICC samples were analyzed for the tasks of their time, but they have been evaluated since in ways not originally foreseen.

Asbestos Disease, 1989

It may be useful to consider several aspects of the asbestos disease situation as research continues and expands into human fiber toxicity, particularly that potentially associated with asbestos substitutes and replacements.

Spectrum of Asbestos-Associated Disease

Adequate knowledge concerning the full dimensions of human disease associated with asbestos exposure has been hampered by a number of epidemiological constraints. The first is the size of populations studied. Since we generally compare what is seen among exposed groups with the same findings in unexposed groups (expected rates), we need to have available sufficient experiences to be able to judge whether or not there is an increase in incidence and whether that increase can be reliably said to be present, from a statistical point of view. This would, of course, be particularly true for diseases of lesser frequency. This constraint was very much in evidence in Richard Doll's classic report in 1955 of lung cancer among workers in the asbestos textile factory in which Cooke's case was employed; there were only 39 deaths among the 113 individuals being followed (40). While this was enough to identify a significant increase in lung cancer (11 cases versus fewer than 1 expected) there were simply not enough data to permit analysis of the incidence of other asbestos-associated diseases, including neoplasms of other sites. This difficulty exists in both clinical and mortality studies, and is even more obvious in the mortality studies because collection of series of deaths add the constraint of adequate time of observation during which deaths might occur.

A second governing problem is that of latency. The first 20 years of any mortality study of asbestos-exposed workers are unlikely to yield a sufficient number of deaths to permit evaluation of a significant increase in asbestos-associated deaths. In fact, the same difficulty might perhaps be ascribed to the first 25 years or, even, the first 30 years, if the population size is not sufficiently large and if the number of deaths, consequently, remains relatively small.

Thus, we need to be able to observe the experiences of large numbers of exposed individuals for sufficiently long periods of time. Practically, this translates into person-years of observation of those whose exposure began 25 or 30 or more years before.

New data have recently become available that largely meet the two requirements outlined above. The mortality experience of 17,800 asbestos insulation workers, the total membership of the International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO, CLC in the United States and Canada, has been observed prospectively from January 1, 1967 to December 31, 1986. Four thousand nine hundred fifty-one deaths were seen, with each subjected to clinical, pathological, and demographic study. Causes of death were ascertained in two ways: on the basis of the death certificate designation (DC) and after review of all available medical/pathological data (best evidence, BE). Observed deaths were then compared with those expected by cause, taking age, year, and sex into account, with expected deaths calculated from death rates of the U.S. National Center for Health Statistics for white males, 1967 to 1986. The rationale for such an approach has been discussed (41).

Table 1 illustrates that the principal diseases causing death among asbestos-exposed workers remain those already identified. This is true whether contrasts are made between expected deaths (based upon death certificate data) and those recorded either on death certificates of the workers involved or ascertained following review of all available data. Expected deaths were 3450.5 and 4951 occurred. The principal cause of the excess deaths was cancer (761.41 expected at all sites; 2127 were so recorded on death certificate and 2295 found to have been present after examination of available material). The major cancers involved were bronchogenic carcinoma (268.66 anticipated, 1168 observed on best evidence) mesothelioma (458 occurred, although none were expected) and a modest increase in neoplasms of the gastrointestinal tract. Asbestosis also was a major cause of death, with 427 being seen.

A number of other cancers were increased in incidence, but were by no means as numerous as lung cancer, mesothelioma, or gastrointestinal cancer. Table 2 provides information concerning a number of these (larynx, oropharynx and buccal cavity, kidney, pancreas, gall bladder, and bile ducts). On the other hand, various other cancers were not observed in excess, including lymphoma and leukemia and carcinoma of the ureter, urinary bladder and prostate (Table 3).

Latency

Virtually no increases in death rates, either overall or for specific diseases, were seen in the first 15 years

Table 1. Deaths among 17,800 asbestos insulation workers in the United States and Canada, January 1, 1967 to December 31, 1986: principal causes of death.

		Observed deaths			
		Death certificate		Best evidence[b]	
Causes of death	Expected deaths[a]	Number	SMR	Number	SMR
All causes	3453.50	4951	143*	4951	143*
All cancer	761.41	2127	279*	2295	301*
Lung cancer	268.66	1008	375*	1168	435*
Pleural mesothelioma[c]	—	89	—	173	—
Peritoneal mesothelioma[c]	—	92	—	285	—
G.I. cancer[d]	135.69	188	139*	189	139*
G.I. cancer, extended[e]	191.66	324	169*	269	140*
Noninfectious respiratory disease	144.82	465	321*	507	350*
Asbestosis[c]	—	201	—	427	—
All other causes	2547.27	2359	93*	2149	84*

[a] Expected deaths based upon death rates 1967–1986 of the U.S. National Center for Health Statistics, for white males.

[b] Ascertained after review of autopsy, surgical and clinical material. Where no such data were available, death certificate diagnosis was used except for mesothelioma. Cases were accepted for this diagnostic category only after Mount Sinai's histopathology review and confirmation.

[c] Rates are not available since these have been rare causes of death in the general population.

[d] Includes cancer of stomach, esophagus, and colon/rectum.

[e] Includes cancer of stomach, esophagus, colon/rectum, liver, gall bladder, and bile ducts.

*$p < 0.001$.

Table 2. Deaths among 17,800 asbestos insulation workers in the United States and Canada, January 1, 1967 to December 31, 1986: less common asbestos-associated cancers.

		Observed deaths			
		Death certificate		Best evidence[b]	
Cause of death	Expected deaths[a]	Number	Ratio	Number	Ratio[c]
Cancer of larynx	10.57	17	1.61	18	1.70*
Cancer of oropharynx	22.02	38	1.73†	48	2.18*
Cancer of kidney	18.87	32	1.70†	37	1.96*
Cancer of pancreas	39.52	92	2.33‡	54	1.37*
Cancer of esophagus	17.80	29	1.63*	30	1.68*
Cancer of stomach	29.36	34	1.16	38	1.29
Cancer of colon/rectum	88.49	125	1.41‡	121	1.37†
Cancer of gall bladder, bile ducts	5.37	13	2.42†	14	2.61†

[a] Expected deaths based upon death rates 1967–1986 of the U.S. National Center for Health Statistics, for white males.

[b] Ascertained after review of autopsy, surgical and clinical material. Where no such data were available, death certificate diagnosis was used.

[c] Calculated for information only, since it used best evidence versus death certificate diagnoses, not strictly comparable due to different quality of ascertainment and verification.

*$p < 0.05$.

†$p < 0.01$; range 0.010 but less than 0.050.

‡$p < 0.001$; range 0.001 but less than 0.009.

Table 3. Deaths among 17,800 asbestos insulation workers in the United States and Canada, January 1, 1967 to December 31, 1986: cancers not found with increased incidence.

		Observed deaths			
		Death certificate		Best evidence[b]	
Cause of death	Expected deaths[a]	Number	Ratio	Number	Ratio[c]
Cancer of bladder	20.77	17	0.82	22	1.06
Cancer of prostate	52.56	59	1.12	61	1.16
Leukemia	28.74	32	1.11	33	1.15
Lymphoma	43.24	33	0.76	39	0.90
Melanoma (skin)	12.65	11	0.87	9	0.71
Brain tumors (all)	26.35	40	1.52*	3	1.25
Cancer	22.55	29	1.29	7	1.20
Cancer of liver	11.06	31	2.80†	12	1.00

[a] Expected deaths based upon death rates 1967–1986 of the U.S. National Center for Health Statistics, for white males.

[b] Ascertained after review of autopsy, surgical, and clinical material. Where no such data were available, death certificate was used.

[c] Calculated for information only, since it used best evidence versus death certificate diagnoses, not strictly comparable due to different quality of ascertainment and verification.

*$p < 0.05$.

†$p < 0.001$.

after onset of exposure and comparatively little after that until 25 or 30 years had passed. If the same were to be true for disease that might be associated with man-made mineral fibers, for example, the first 30 years of observation of cohorts of individuals exposed to such fibers would provide little information with regard to potential neoplastic toxicity; epidemiologically, such information would constitute empty data. Figures 1 and 2 depict the incidence of deaths of asbestosis and peritoneal mesothelioma following onset of work exposure.

Parenthetically, if we were to truncate epidemiological mortality studies of asbestos-exposed workers at age 65, a practice sometimes recommended for cancer studies in general, it would be difficult to fully appreciate the importance of latency in the evaluation of the incidence of asbestos-associated cancer. Figures 3 and 4 indicate that approximately one-third of the deaths of mesothelioma, for example, occurred after age 65.

Populations at Risk

With growing awareness of the hazards of asbestos exposure, searching inquiries have been directed beyond previously studied populations such as mining and milling, product manufacturing, shipyards, insulation work, brake repair and brake lining, family contact and neighborhood disease, etc. The numerical scope of the problem has been considerably expanded by recent investigations of asbestos-associated disease among such diverse groups as railroad workers (42–44), merchant marine seamen (45,46), as well as a variety of construction trades, custodians and building maintenance workers, power production and public utilities, and maintenance and repair in a wide variety of situations. Still incompletely quantified populations are being added to the more than 10 million survivors of the 27,500,000
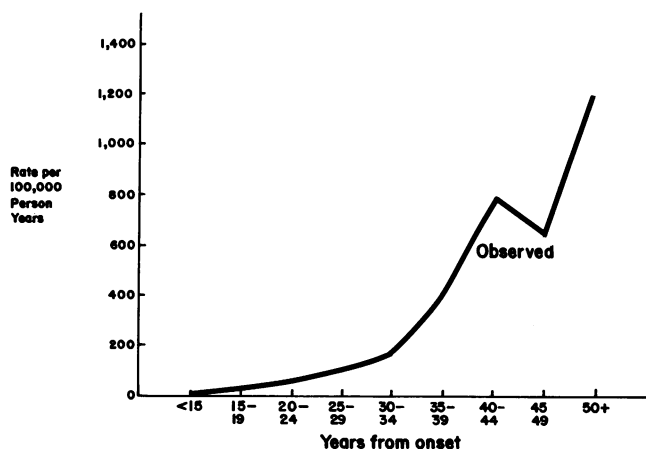

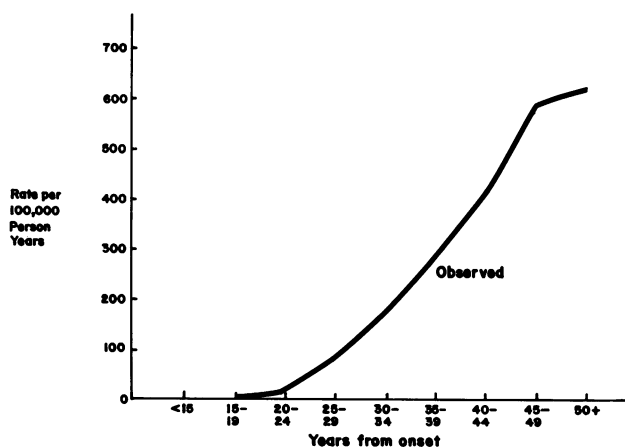FIGURE 1.   Deaths of asbestosis among asbestos insulation workers in the United States and Canada, 1967 to 1986.

FIGURE 2.   Deaths from peritoneal mesothelioma among asbestos insulation workers in the United States and Canada, 1967 to 1986.
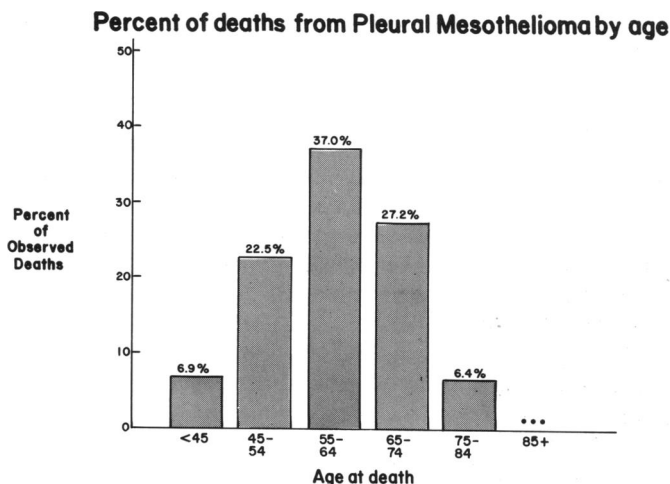

FIGURE 3.   Ages at death of asbestos insulation workers in the United States and Canada who died from pleural mesothelioma, 1967 to 1986.
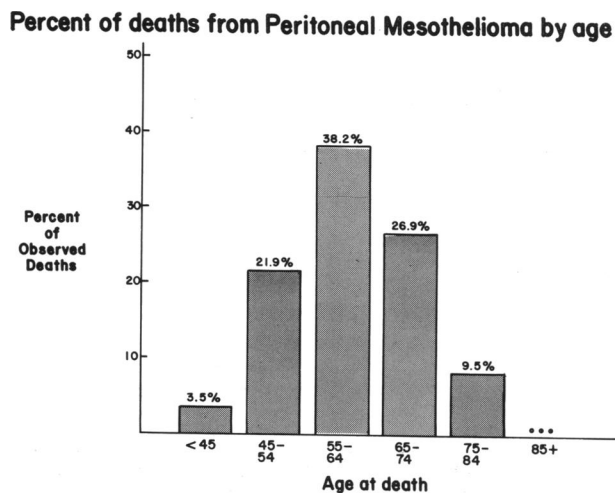

FIGURE 4.   Ages at death of asbestos insulation workers in the United States and Canada who died from peritoneal mesothelioma, 1967 to 1986.

workers previously enumerated in 10 of the most important asbestos-exposure trades, considered significantly exposed from 1940 to 1979 by Nicholson and his colleagues (47).

The building industry is of particular importance, not only because of the large number of workers who entered the various construction trades from 1950 to 1970, and therefore very much at risk of asbestos-associated cancer death for the next 40 years or so, but also because of the continued exposure of construction workers as they do maintenance and repair work in buildings and facilities still laden with asbestos installed in previous years. Recent studies have shown significant proportions of workers in such diverse trades as sheetmetal, pipefitting, plumbing, drywall construction, painting, carpentry, and electrical work to have radiological evidence of asbestotic abnormalities in clinical surveys. (48–50).

Research Perspectives Derived from Asbestos Experience

The unhappy experience with asbestos provides not only the stimulus for examination of potential toxicity of other fibers but perhaps useful general guidelines to their clinical and epidemiological evaluation. We know a good deal about the spectrum of disease with at least this one group of fibrous minerals (as well as with the zeolite, erionite) and, although different neoplasms and different diseases might well occur with other inorganic fibers that have been and will be proposed as asbestos replacements, there is a good chance that investigation of the increased incidence of the asbestos cancers will be helpful in evaluating substitutes for toxicity to humans. Too, it is likely that the same sort of latency is involved (with concordant age distribution) and there may even be such multiple factor interaction as that seen between asbestos and cigarette smoking (51,52).

Nevertheless, study of potential human toxicity of substitutes, while very important, is perhaps inadequate. Additionally, prevention of disease should be a concern, from the beginning. In this, I would include not merely primary prevention (avoidance of exposure) but secondary prevention of disease even should substantial exposure sometimes occur (perhaps inevitable if a substance is to be used at all).

Prevention of Clinical Disease among Those Exposed to Asbestos and Other Inorganic Fibers

Disease following asbestos exposure is not inevitable. Experience has shown us that even with significant exposure, not all individuals develop an asbestos-associated cancer or disabling asbestosis. Reasons for such differences in susceptibility have been but little explored (53); for example, we have few data concerning the significance of immunomodification not infrequently seen among asbestos-exposed workers. Similarly, a va-

riety of biological phenomena have been observed that may contain fertile hints with regard to differences in susceptibility. The lower frequency of disease in solid organs comes to mind (although some such disease is seen, as in pancreas and kidney, we do not see it in spleen, bone, muscle, prostate, liver, brain, or regional lymph nodes). Is this simply a reflection of different dose/response relationships, or a basic biological phenomenon? Epithelial surfaces seem particularly affected (respiratory tract, gastrointestinal), but this is not universally true. Although asbestos fibers are found in the urine of asbestos-exposed workers (52) and although kidney cancer is increased, we do not see similar increases in cancer of the ureter, bladder, or prostate. Erionite gives the same tumors (and pleural and parenchymal fibrosis) among exposed residents of the zeolite areas in Turkey, yet the fibers are physically and chemically distinct from asbestos varieties, albeit similar in their dimensions. Although asbestos fibers are transported across the placental barrier, mesothelioma in infants born to asbestos-exposed women has not been reported either at birth or in early life. For lung cancer, there may be important differences between small cell and nonsmall cell cancers, yet in asbestos-exposed workers, all cell types are seen, in the same frequency as in lung cancer in general. Further, some asbestos-exposed workers not only develop one or another of the asbestos cancers, but may have multiple primaries in, for example, the lung or stomach, as well as cancer known to be associated with asbestos exposure in other organs. Yet other individuals, with apparently the same exposure, develop no cancer, or only one at a single cancer site. Are these biological differences due to variations among individuals or to the nature of exposure?

Reversal of Risk

Is it possible to reverse at least some of the risk among those already exposed to inorganic fibers? There is some evidence that this may be possible. First, it was reported in 1979 (54) that asbestos workers who stopped smoking, after 5 to 10 years, have approximately one-half to one-third the risk of dying of lung cancer compared to similar asbestos workers who continue to smoke cigarettes. Of course, this may be related not only to diminution of fiber risk but to the previously identified decrease in risk of death of lung cancer among cigarette smokers in general who stopped smoking.

Some additional, more direct, evidence has recently become available, the result of what almost may be termed a large-scale natural experiment. When, in 1964, the serious cancer and pneumoconiosis risk of asbestos-exposed insulation workers was reported (22), both the labor unions and many employers began to use at least the most obvious control measures. While these were by no means always rigorous, they did serve to begin to decrease asbestos exposure on the job. Such diminution was accelerated and amplified in 1972 and 1973 when asbestos was no longer included in newly manufactured insulation materials in the United States. This served to

further decrease exposure, although some continued during repair and maintenance work involving previously installed asbestos-containing insulation materials.

In the 20-year prospective study that was begun in 1967, we therefore had occasion to evaluate death rates in three periods of times: before removal of asbestos from new insulation materials (but with some use of better industrial hygiene precautions) (1967–1972); shortly after the removal of asbestos from these materials (1973–1979), and some years following removal (1980–1986). We have analyzed death rates for the major asbestos-associated diseases (asbestosis, bronchogenic carcinoma, pleural and peritoneal mesothelioma) for each of these three periods, comparing duration-from-onset categories. The data indicate that reduction in exposure had a measurable effect in decreasing death rates for asbestosis, bronchogenic carcinoma, and peritoneal mesothelioma, at least for those in the mid-period from onset (55). After 40 years from onset, reducing exposure did not seem to make any difference, nor was there reduction in death rates for pleural mesothelioma, even in the mid-period. These data indicate that reduction of exposure can be important in reducing risks for some individuals already exposed.

Preclinical Diagnosis

Clinical diagnosis of cancer, even when early in the course of disease that has appeared, is therapeutically disadvantaged—diagnosis is not early, in biological terms. The possibility exists that if the diagnosis could be established before clinical abnormality appears, management, including chemotherapy, might be more successful.

At one time, it was hoped that cytological evidence of neoplastic change, as in bronchial secretions, could serve this purpose in high risk asbestos-exposed groups. This has not proven to be the case (56). There has therefore been interest in identifying preclinical diagnostic approaches, perhaps cytological or immunological. An obvious candidate has been mesothelioma, derived from what is, in a sense, a specific tissue, with fairly unique histochemical and immunocytochemical features. Roboz and colleagues have undertaken experimental studies using transplanted human mesothelial tissue in the nude mouse and have found increasing concentrations of hyaluronic acid as the tumor grows (57). Whether this will prove to be useful for asbestos-exposed individuals being monitored for the development of pleural or peritoneal mesothelioma may be a suitable subject for investigation.

Molecular Epidemiology

Considering the wide agreement concerning the likelihood of a multistage process in the development of human cancer, it may well prove useful to investigate whether the sequential molecular changes in that process can be identified (58). If this is found to be the case, it would naturally follow that investigations could be

undertaken to see whether the sequence of changes leading to clinical cancer could be interrupted.

Ordinarily, it would be extremely difficult to investigate this attractive hypothesis, in view of the random nature of most neoplastic disease and the absence of knowledge concerning who might be at risk. With asbestos exposure, however, it might be feasible. Large populations of asbestos-exposed individuals have been identified. In many instances, these individuals are available for prospective surveillance, including a variety of tests that would explore molecular changes of the carcinogenic process that is under way. It is even conceivable that human gene therapy (replacement, correction, or augmentation) could be considered (59). Such prospective studies of defined populations at risk would be an appropriate extension of the epidemiological studies that have been accomplished to this point.

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