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ASBESTOS CANCERS AS AN EXAMPLE OF THE PROBLEM OF COMPARATIVE RISKS

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Occupational exposures to several dusts have caused an excess of respiratory tract cancers - for example, arsenic, chromates, fluorspar, haematite, nickel, uranium. Here the agent is thought to be the element or its salt, or ionising radiation, or the two operating together. Professor Maltoni and Dr. Mole will be discussing examples of these.

I will limit my remarks to asbestos and some other mineral fibres for two reasons. First, present evidence suggests that the physical properties of the fibres rather than their chemical composition are especially important in the cancers they induce; and second, because "asbestos" is a commercial term of a small sub-group of fibrous silicates, but there are many other fibrous silicates and other fibrous minerals* widely distributed over the surface of the earth, so that the dust from these - even though in very small amounts - has been in the general air since time immemorial and may be seen in airborne dust and in lung residues. (1).

These simple observations indicate that even though there may not be a threshold level below which no effect is produced in a strict biological sense, there is a practical level below which no serious disease is produced.

Our knowledge of the carcinogenic effects of asbestos is almost entirely derived from occupational and para-occupational exposures in the past. The question is, therefore, do we yet know enough about the effect of varying intensity and type of exposure in industry to specify what may be acceptable conditions within industry in the future, as well as to the general public?

Types of Cancers

Table I shows the types of asbestos and the cancers with which they are associated. Nearly all of it is chrysotile (about 4 million tons/year), but it should not be assumed, as used to be done, that the biological effects of all types are the same. The cancers widely accepted as due to asbestos are bronchial and mesotheliomas of the pleura and peritoneum. But an excess of gastro-

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* These include calcium silicates (woolastomite, cement dust); sepiolite (hydrous magnesium silicate); hornblende (amphibole mineral variety); diatomaceous earth (amorphous silica); fibrous clay minerals (kaolinites, bentonites); and naturally occurring fibrous minerals, such as pyroxene minerals; amphibole minerals (other than commercial varieties); serpentine minerals (antigorite); and oxide minerals (brucite, magnesium hydroxide).

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intestinal tumours has been reported in several large cohort mortality studies of asbestos workers (2,3,4,), though the excess has been much smaller than for the lung cancers. Larynx, pancreas, and lymphomas have also been suggested. There is still uncertainty about the causal relationship of these other cancers with asbestos.

Cancer Sites	Types of Asbestos
Bronchial	Chrysotile (95%)
Mesothelial	Amphiboles
Pleural	Amosite
Peritoneal	Crocidolite
	Anthophyllite
G.I. Larynx Others	?

Table I: Asbestos and Cancers

A pattern of recent research

The last 15 years has seen the results of many epidemiological studies into the incidence of asbestos-related cancers (5), and also parallel animal experimental studies to explore mechanisms as to how such remarkably stable and inert minerals are carcinogenic. The pattern of this work illustrates one of the themes Dr. Higginson has been developing at the IARC; a combined epidemiological and experimental programme of research in which the work in each field stimulates and orientates that in the other. The experimental work has been mainly aimed at discovering physical or chemical factors responsible for the carcinogenesis, and it has not been aimed at defining a TLV for man by extrapolation from studies in animals. These approaches and their inter-relations are shown in Fig. 1.

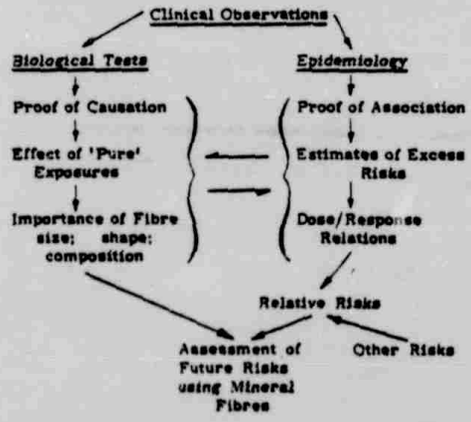


Fig. 1: Research into Asbestos Cancers

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Biological tests

The cancers proved in man to be caused by asbestos are also induced in rats and other small animals. For example, intra-pleural injection of all types of asbestos causes a high incidence of mesotheliomas (6), and although by this route part of the defence mechanisms of the lungs are effectively by-passed, the technique is very useful to study the effect of particle shape and composition in the induction of a tumour known to be caused by asbestos in man. Present evidence suggests that to produce mesotheliomas the fibres may have to be $\geq$ 4μm in length and less than about 1μm diameter. Larger fibres > 3μm diameter and rounded particles rarely or never cause mesotheliomas by this route. When it is possible to produce narrow sized ranges of fibres for both diameter and length, it should be possible to specify fairly precisely the critical dimensions for the induction of mesotheliomas. Much effort is being put into preparing such test samples of fibres at present because the results of such experiments are likely to influence the way new man-made mineral fibres are produced in the future and also the way fibrous dusts are sampled in air and water.

When the fibres are inhaled it is the diameter rather than the length which controls entry to the periphery of the lung; also curly fibres, such as chrysotile, are more readily arrested in the upper respiratory tract by impaction than the straight fibres of amosite or crocidolite. This may be one of the reasons why the incidence of mesotheliomas in those exposed only to chrysotile is much lower than those exposed to crocidolite or amosite (7).

The composition and chemical structure does not seem very important because all types of asbestos and some very fine glass fibres and ceramic fibres have all produced mesotheliomas by intra-pleural inoculation. The animal experimental results have given no support to hypotheses that trace elements or adsorbed hydrocarbons might be important in the production of the pleural tumours (8). But an interesting recent observation (9) is that fully magnesium leached chrysotile, even though fibrous, produces very few mesotheliomas compared to the untreated mineral. An important result of the experimental work has been a better understanding of the likely mesothelioma risk of man-made mineral, and other fibres. In general the fibres are too large in diameter and the airborne concentrations too low for many to reach deep into the lung. In addition, man-made fibres do not break down within the lung into fine fibrils as occurs with asbestos (10, 11). Thus present evidence indicates the chances of present man-made mineral fibres of a critical size reaching the periphery of the lung in significant amounts must be far less than in the case of the natural fibrous minerals.

Inhalation of asbestos produces in rats a small incidence of bronchial cancers and even fewer mesotheliomas (12). So far nothing is known about the importance of fibre size in the production of the bronchial tumours.

Feeding rats with asbestos, as well as detailed autopsies of rats inhaling the mineral, (during which they will ingest an appreciable amount when cleaning their fur), has shown no excess of gastro-intestinal tumours (13, 14).

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Epidemiology

Proof of association between asbestos and cancers of a particular site is based in part on case/control studies of pathological material, and in part on the causes of deaths in cohorts of asbestos-exposed workers. The pathological studies give no measure of the magnitude of the risk and are, therefore, of little predictive value. The simple cohort studies do give a measure of the excess risk for each type of cancer, but due to the long latent period for cancer induction, often 20 or more years, they refer to conditions many years in the past. Such studies, many of which have received wide publicity in the general press, are also of little use for prediction of risks in the future or of extrapolation to the general population.

Dose response studies

For such predictions cohort studies, in which the workers can be sub-divided on the basis of duration and intensity of past exposure, are required. Ideally we need quantitative information on past dustiness, but useful information has been obtained by the detailed historical study of the factory or mill, making the maximum use of the knowledge of long-term employees, and relating these to such dust measurements as there have been. In this approach the men's jobs can often be grouped into those with markedly different dust exposures, so that mortality experience can be related to dose. The advantage of this approach is that groups of employees are identifiable, who almost certainly had exposures several orders of magnitude greater than the general population, and yet show no excess cancer risk or a small one compared to those who have been most heavily exposed.

Men born 1891-1920 Deaths/1000 to 1969

	Dust Exposure (particle/years)					
	<10	10-	100-	200-	400-	800+
All Cancers	58	61	54	41	67	79
* Lung "	10	13	13	16	21	32
Abdominal "	18	14	19	12	26	29
No. of Men	2810	2329	1124	1007	837	588

*Including Mesotheliomas (5)

Table II: Chrysotile Mining and Milling, Quebec

Table II is an example from the chrysotile mining and milling industry in Quebec, where about half the world's asbestos is produced. Only in the two highest exposure groups is there an increase of cancer risks relative to the lowest exposed group. For the whole group of workers there was no lung cancer excess over the general population. Thus the least exposed group were not at a significant excess risk despite being exposed to far more asbestos dust than

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members of the general population. Similar patterns have been reported in the asbestos cement industry, and for lung cancer and mesotheliomas in factories manufacturing asbestos products (15, 16, 17).

Differences within the Industry

Table III summarizes differences in proportional mortality within the industry for lung cancers and mesotheliomas (18). As is often the case in epidemiology, the interpretation of findings is not simple; in this case because the type of asbestos fibre used and the type of industrial process are to some extent confounded. Many manufacturing processes use more than one type of asbestos, often all three of the major types - chrysotile, amosite, and crocidolite. In mining and milling exposures to one type do occur, but unfortunately for the epidemiologist crocidolite and amosite are mined only in South Africa where the opportunities for quantitative epidemiology are slender because of the paucity of records.

Asbestos	Lung Cancer	Mesoth:	No. of Surveys	Total Men
* Insulation	18 - 26	5 - 9	6	26,500
* Factories	8 - 21	1 - 7	5	10,800
+ Mining and Milling	2 - 10	0 - 0·2	3	13,700
Gen: Popl:				
E and W	9			
U.S.A.	5	0·0001		
Canada	5			

* Mixed fibre exposures

+ Chrysotile (2); Anthophyllite (1);

Table III: Proportion (%) of All Deaths due to Lung Cancer and Mesotheliomas in Cohorts of Asbestos Workers and the General Population

The percentage of lung cancers and mesotheliomas is highest in the insulators; less in the factories making asbestos products; and least in mining and milling, but the mining and milling covers only chrysotile and anthophyllite. In the two large chrysotile-exposed cohorts, one in Quebec and the other in Italy, no general excess of lung cancers was shown, and no or a very few mesotheliomas.

If we add to these quantitative cohort studies the results of 15 years' observations in Southern Africa, where chrysotile, amosite, and crocidolite are mined, it is fairly certain that mining and milling crocidolite is - by a factor of 100 or more - more likely to produce mesotheliomas than amosite or chrysotile. Studies in

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Finland suggest anthophyllite almost never causes mesotheliomas (19).

Cofactors

Cigarette smoking is most important in the production of bronchial cancer in asbestos workers. The effects of asbestos and cigarette smoke are multiplicative, not simply additive. Table IV shows this for both sexes (20,21,). Asbestos alone is apparently a weak bronchial carcinogen but it has not been possible to establish this very firmly, because there are few non-smoking asbestos workers with long exposures. It seems likely that stopping cigarette smoking is likely to have a much bigger effect on the incidence of lung cancer in asbestos workers than small changes in exposure to asbestos dust. No cofactors affecting the incidence of mesothelioma have been firmly identified.

	Observed	Expected		
Insulation		Non Occup:	Non Occup: and Occup: +	Non Occup: and Occup: ×
Cigarettes	24	2·98	18·9	22·6
Non-Smokers	0	0·05	2·8	0·4
Factories Male				
Cigarettes	25·5	9·9	25·1	26·4
Non-Smokers	0	0·0	0·9	0·1
Female				
Cigarettes	15·5	1·4	12·5	15·3
Non-Smokers	1·7	0·2	4·7	1·9

Table IV: Lung Cancer Deaths and Smoking fit with Additive (+) and Multiplicative (×) Hypotheses

Relative risks

These asbestos cancers should be seen in perspective in relation to other occupational cancers and occupational accidents (Table V). The information to do this precisely is not available, but the general pattern is well summarized by Pochin (22,23). All the figures are deaths per million per year. Cancers vary from about 700 for the nasal cancers in woodworkers to 24,000 for the beta-naphthalene manufacturers, with asbestos lung cancers at about 3,000. The occupational fatalities range from 3 in clothing manufacturers up to 11,000 for the professional divers (24). For both occupational cancers and accidents there is a big range of risk for different types of job. In general the cancer risks are the bigger, but affect a selected group of workers.

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Cancers			Accidents	
Wood Workers	Nasal	700	Clothing Mf:	3
Asb: Industry	Lung	2,000 M 4,000 F	Bricks and Cement	80
			Ship Building	160
Rubber Workers	Bladder	7,000	Coal face	600
Nickel Refining (up to 1925)	Lung	15,000	Company Directors	1,800
			Deep sea fishing	3,000
β Naph: Mf:	Bladder	24,000	Prof: Divers	11,000

Table V: Estimated Occupational Mortality/M/year

Finally, compare these occupational risks with risks run by all from accidents, our personal habits, and our age (Table VI). Traffic accidents are about one quarter that of working on the coal face, but cigarette smoking at 20/day is about double that of heavy asbestos exposure. This is, of course, due to cigarette smoking affecting several diseases. The last column shows how rapidly age creeps up on us and perhaps indicates that those who research into occupational hazards should be in the 30's to see things in perspective!

General Accidents; Personal Habits; Your Age (Male)

Accidents		Your Age	
Traffic	150	12	350
Home	130	30	1,000
Suicide	80	42	3,000
All	460	53	10,000
Cigarettes		63	30,000
20/day	5,000	77	100,000

Table VI: Estimated Mortality/M/year in U.K.

SUMMARY

Major differences in excess cancer risks have occurred in the asbestos industry in the past; part of this difference is probably related to dustiness, part to the

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type of fibre used. In the case of mesotheliomas there is evidence of a major effect of the fibre type in the order of risk, crocidolite > amosite > chrysotile > anthophyllite.

Differences of risk within an industry indicate that there is a dose response relation for both bronchial cancers and mesotheliomas. Also that in some instances it has been possible to identify lightly exposed groups in which no excess risks were detectable. As these least exposed groups are likely to have had several orders of magnitude heavier exposure than the general population, the risks to the general public are likely to be negligible.

Bronchial cancers in absolute numbers are the major excess risk and are highly smoking-related. Stopping cigarette smoking is likely to be of paramount importance in reducing the excess cancer risks in asbestos-exposed individuals.

Cancers in other sites which may possibly be related to asbestos exposure need further study even though the magnitude of the excess risk has been small compared to the lung cancers.

In my view it is now possible to use the epidemiological evidence and experimental results to predict with fair confidence the physical and chemical characters and dose of natural and man-made fibres which will not cause a significant hazard in the future.

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