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Industrial Medicine and Hygiene (E. R. A. Merewether, editor), London: Butterworth, pp. 185-188, 215-224 and 557-562, 1956

CHAPTER 3

INDUSTRIAL CARCINOGENESIS AND TOXICOLOGY

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PART I: *Occupational Carcinogenesis*
PART II: *Some Aspects of Industrial Toxicology*

PART I

Occupational Carcinogenesis

SOME GENERAL CONSIDERATIONS

THE LACK of knowledge of causes of spontaneous cancer in man is often held to be the most serious handicap in real advance towards cure. But in the case of occupational cancer the causes are in several instances known, but cure in the sense of chemotherapy is far off. On the other hand, prevention is a more attainable target, when a cause is known.

It may be helpful to quote from one or two statements recently made by Haddow (1951): " . . . the cancer cell is but a modification of the normal cell "; " . . . conversion to malignancy may be due to a subtle and elusive re-orientation of enzyme construction quite unaccompanied by any gross changes affecting protein structure or immunological specificity and that there is on this account little or no protective reaction on the part of the host such as occurs in infections "; " . . . the malignant cell appears highly stable, if not indeed irreversible, as is shown by the manner in which its newly acquired genetic properties are transmitted and maintained, quite indefinitely and with no sign of reversion ".

In occupational carcinogenesis no less than in spontaneous carcinogenesis these statements are equally justifiable, and indeed cast a certain light on certain facts, whilst making it more difficult to understand others.

In occupational carcinogenesis the outstanding characters are: that the tumours are not distinguishable from non-occupational tumours: the causes are either known or can be reasonably assumed to be known; the time of

Industrial carcinogenesis and toxicology (1956)
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induction of the tumours from the first exposure is usually very long; the tumours may first show themselves many years after exposure to the " carcinogen " has completely ceased.

Since there is no particular reason to regard a worker who enters a particular industry with a cancer hazard as specially susceptible to the particular form of cancer frequently found in it, we must consider that the tumour arises from the action of the occupational hazard (or a derivative of it) on the special tissue cells and that these cells are so modified as to take on the character of tumour cells.

Now, whereas in the case of spontaneous tumours no one can say how long the hidden process of change has been going on, in the case of occupational tumours a pretty good estimate can be made on how long the attack by the carcinogen may have been going on.

Table I shows the order of times involved :

TABLE I

SHOWING THE AVERAGE PERIOD FROM START OF WORK TO APPEARANCE OF TUMOUR

Disease	Occupation	Carcinogen	Appearance of tumour (years)
Cancer of lung	Chemical worker	Chromate	14·5
Cancer of bladder	Dyestuffs worker	Aromatic amines	17–19
Cancer of lung	Asbestos worker	Asbestos	7–21
Cancer of skin	Tar distiller	Tar	23
Cancer of skin	Pitch worker	Pitch	23
Cancer of skin		Arsenic Medication	up to 30
Cancer of nose and lung	Copper and nickel workers	? Arsenic	11–12 (1–30)
Cancer of scrotum	Mule spinner	Mineral oil	46

What are the factors necessary to induce the tumours, for it is almost impossible to imagine that the known occupational hazard can take so long to reach the effective point of action or to initiate the essential biochemical or pathological process?

We hold the view that the occupational hazard is a local potentiator (Goldblatt, 1947) of particular tissues and that the essential excitor of the carcinogenic process is endogenous in origin.

It is quite certain that occupational carcinogens are not equally potent against all tissues, for example aromatic amines do not produce lung or skin tumours, mineral oils do not produce lung tumours, chromates never produce skin tumours although irritation of skin is common, arsenic never produces bladder tumours in spite of great and maintained absorption and excretion of arsenicals.

Although a single kind of occupational " carcinogen " may induce tumours in more than one location or organ, there does seem to be some predilection for particular kinds of cell.

No advance will, in our view, be made until some picture of the char-

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(2) Experimentally it should be possible to simulate the disease in animals by procedures comparable to those arising in the course of the occupation, or other appropriate means.

(3) Failure of experimental efforts need not preclude prescription of the disease. In certain cases it may be necessary to demonstrate the material concerned in the tissues, organs or secretions of the subject.

This, or something like it, might be sufficient if the world were peopled only with honest men and if the response of appropriate animals were similar to that of human beings.

The fact is, however, that we have to make judgments on the evidence before us in a given case. The dilemma is often very great.

The truth may be obvious to the clinical observer, but the experimentalist may be unable to help him. A great deal of work remains for investigators to do in this field.

CHROMIUM

Incidence

There is good reasonable suspicion that chromium compounds can lead to cancer of the respiratory tract, and various investigators had come to a conclusion of this kind. Gross and Alwens (1938) had found 39 cases of bronchogenic carcinoma among 2,000 workers in the German chromate industry.

By 1943 Gross and Koelsch had found 8 additional cases in the chrome colour industry.

It is instructive to tabulate the age incidence at death among these 47 cases:

Age Group	*Frequency*
21–30	1
31–40	6
41–50	10
51–60	19
61–70	11
	47

Although most of the cases were over 45 years of age at death, the numbers less than 40 years of age at death are, in our view, strongly in favour of an occupational factor being engaged. In this 1943 series the substances involved were lead and zinc chromates, and these authors were particularly impressed by the much greater solubility in water of zinc chromate compared with that of lead chromate. They suggest that zinc chromate dust may be a specially dangerous hazard to the lung.

Two cases of bronchogenic carcinoma in workers exposed to lead and zinc chromates were described by Letter Neidhardt and Klett (1944).

In their B.I.O.S. (British Intelligence Objective Subcommittee) report Weldon and his colleagues (1947) dealing with information obtained at the German chromate factories at Leverkusen and associated centres

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acteristic biochemical activities of individual cell-types is obtained, and how known carcinogens can affect it.

As we have said, knowledge of causes is vital for prevention of occupational cancer. Chemotherapy of cancer, however, does not call for knowledge of causes, for the good reason that the cause of the growth is not necessary for the continued life and development of the tumour.

This is particularly clearly shown by the fact that the tumour may appear many years after all contact with the occupational hazard has ceased. In other words, once the cancerizing process has established a focus, however small, of autonomous growth, however slow, the initiating process is no longer essential, but the cancerized cell will multiply true to type.

Chemotherapy must, therefore, be directed to the cell. Either it must be killed, or its growth inhibited. Reversion to normality does not seem a possible goal.

DIFFICULTIES IN ESTABLISHING THE EXISTENCE OF AN INDUSTRIAL DISEASE

It is hardly necessary to stress the immense difficulties which derive from the character of the disease which is indistinguishable from the non-occupational counterpart of it.

In the case of occupational tumours this is especially the case. There is nothing to distinguish the scrotal cancer of a mule-spinner, the pitch wart of a lens-maker or the bladder tumour of a dye-maker as clinical entities from the non-industrial disease. Except in statistical factors as, for example, the frequency of a particular location in the mule-spinner's tumour (left side of scrotum), the frequency at different ages in the dye worker, and the association with a known carcinogen, the occupational and non-occupational are indistinguishable. The difficulty is reflected in the frequent differences of opinion expressed by different authorities when trying to attribute a case to the proper cause.

ANIMAL EXPERIMENT

No amount of animal experiment can resolve this aspect of the matter. Animal experiments can, if the experiments have been positive, answer the question: could the particular job give rise to the disease with a high degree of probability? But if the experimental work has been negative, it can give no answer at all.

Even to attain this degree of probability a great deal of luck must be had in the experiments.

The following postulates would seem reasonable in defining occupational disease:

(1) Statistically the incidence of the disease in the occupation must be highly significant and it must arise from that occupation but not necessarily in the course of it.

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there was 1 milligram per gramme of nickel in the lung even 8 years after cessation of exposure. If Løken's results were correct, there must have been some 1·2 grammes of nickel in the lungs—a wellnigh incredible figure—completely out of harmony with Barnes and Denz's conception of non-retention unless there was very great difference, as seems likely, in the physical form and states of the nickel.

ASBESTOS

The association of what appears to be purely mechanical trauma with a later development of neoplastic change has a long history both in the experience of myriads of medical observers and in that of theorists who invoked it in the exposition of a theory of cancer. If such an association is looked at askance it is not because it is denied that it can occur, but rather that it is too facile and even sterile an explanation. Of the tens of millions of mechanical traumas occurring daily, the number which can be later recognized as having possibly initiated a neoplastic process *in situ* is minute. Most pathologists would sum the matter up by saying that if trauma is followed by the development of a tumour at the site of the original trauma, then that site was not normal at the outset.

Co-carcinogenesis

The classical experimental basis for the effect of the super-imposition of trauma on an abnormal site is the *Deelman phenomenon*. Deelman showed in 1923 that if a tarred area of animal skin is injured by wounding or other physical effect, tumour formation might be hastened and its location thereby determined. This observation was later confirmed by other workers who used pure carcinogens and laid the foundation of what is now called co-carcinogenesis. Co-carcinogenesis may be defined as the augmentation of the action of a carcinogen by some suitable additional treatment which shows itself in increased numbers of induced tumours and/or shortening of the induction time. In general the term co-carcinogenesis is applied to an effect produced by local application of an agent to a tissue (Berenblum, 1947). A co-carcinogen is not itself a carcinogen although Anderson (1948) appears to think otherwise, regarding co-carcinogenesis as a synergy between subliminal doses of two or more carcinogens. Such mechanical irritation as strongly brushing the skin, and foreign body fibrosis, have been shown to be effective as co-carcinogens. Heat, cold, radioactive radiations, croton oil and resin, all possess co-carcinogenic power.

The precise nature of co-carcinogenesis is difficult to understand except as an expression of certain experimental facts. The significant matter from our present viewpoint is that for a co-carcinogen to produce its effects it must be applied after a preparation of the tissue has taken place by a carcinogen, or even after an overt carcinogenic response has regressed.

Although the whole conception of co-carcinogenesis has arisen from

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experimental work on mouse and rabbit skin, some such idea must be evoked by a problem such as that of asbestosis and cancer, until some more experimental evidence of direct carcinogenesis by asbestos or a decomposition product of it can be obtained. If such an idea is feasible, then we must also assume a pre-neoplastic preparedness in the organ in which the co-carcinogen (asbestos or the fibrous tissue in the peribronchiolar reaction) later induces a further development into true neoplastic growth. The preparedness of the tissue if it is to be regarded as more than a form of words is brought about by something independent of the asbestosis, and this must be regarded as an endogenous factor. But some special property must also attach to the asbestosis for the alleged cancer induction in this condition is not apparently found in the long-standing cases of silicosis.

We will first consider the evidence that asbestosis leads in a proportion of cases to cancer of the lung. As long ago as 1938 the suspicion arose that asbestos workers might be more than normally prone to lung cancer.

Nordmann (1938) analysed six cases of lung cancer and showed that the range of exposure periods was 7–21 years, and the range of intervals between entering the industry and death was 15 to 21 years. The malignant disease in some cases occurred years after leaving the industry. Half of these cases were comparatively young, 35–41 years of age at death. In one remarkable case a 71-year old woman had worked in asbestos for only 19 months. Later in the same year he referred to a further seven cases of associated asbestosis and lung cancer, including Gloyne's (1936) finding of six cases of carcinoma of the lung in 50 necropsy cases of asbestosis.

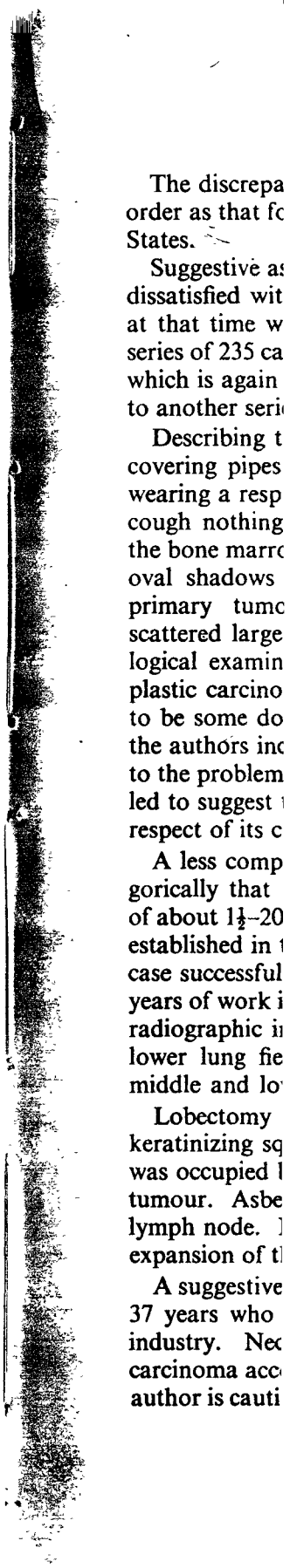
In the 1947 Annual Report of the Chief Inspector of Factories, Merewether tabulated the age incidence among 235 deaths caused by asbestosis: in 13·2 per cent of these cancer of the lung was present, and it is especially important to note that 4·8 per cent of the age-group 25–34 years and 5·6 per cent of the age-group 35–44 years had this condition. It will be seen that the over-all figure is closely in agreement with Gloyne's findings.

In a further report* carrying this analysis up to the end of 1954, he found that amongst 344 deaths, in 55, or 16·0 per cent, cancer of the lung was present.

In their series of papers on asbestosis Lynch and Cannon (1948) give an analysis of the post-mortem examination of 40 cases of asbestosis among which 3 cases of carcinoma of the lung were found associated with medium or advanced grades of asbestosis, which, according to these authors, is seven times the general incidence in the United States.

In a more recent study of the clinical picture and pathology of asbestosis, Behrens (1952) estimated that of 309 cases of asbestosis reported in the literature there were 44 cases of carcinoma of the lung (14·2 per cent) whereas in a series of 2,204 cases of silicosis only 32 such tumours were found (1·4 per cent).

* Annual Report Chief Inspector of Factories for 1954, pp. 190–193.



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The discrepancy between the two incidences in Switzerland is of the same order as that found in the smaller series by Lynch and Cannon in the United States.

Suggestive as these and other data are, Stoll, Bass and Angrist (1951) were dissatisfied with the statistical weight one could put upon available figures at that time which included, in addition to those of Lynch and Cannon, a series of 235 cases of asbestosis with 31 carcinomas of the lung (13·2 per cent) which is again almost identical with the finding of Behrens. They refer also to another series of 115 cases with 14·8 per cent lung tumours.

Describing the case of a worker who had been engaged for only 6 years covering pipes with asbestos and who had refused to take precautions by wearing a respirator, they point out that except for weakness and persistent cough nothing noteworthy was found until malignant cells were found in the bone marrow. Radiographs of the chest showed numerous large discrete oval shadows which were interpreted rather as metastatic deposits than primary tumours. Post-mortem examination showed asbestosis with scattered large nodules and metastases in kidneys, brain and liver. Histological examination confirmed the presence of asbestosis bodies and anaplastic carcinoma of the lung, with numerous metastases. There appeared to be some doubt about the primary focus of malignancy in this case, and the authors inclined toward a multiple origin. Whether this case is relevant to the problem of asbestosis cancer is open to question, but the authors were led to suggest that asbestos must itself be regarded as a direct carcinogen in respect of its composition as a silicate.

A less compromising attitude is taken by Werber (1952) who states categorically that in 7–17 per cent of cases of asbestosis after a latent period of about 1½–20 years, as a result of epithelial metaplasia, carcinoma becomes established in the lung. Werber then reports what appears to be a clear-cut case successfully operated on. The patient was a man of 58 years who, after years of work in asbestos with complaint of irritant cough, showed, in a mass radiographic investigation, a well-marked dense round shadow in the right lower lung field associated with bilateral finely granular shadows in the middle and lower fields, more marked on the right side.

Lobectomy of the right lower lobe confirmed the presence of a non-keratinizing squamous cell carcinoma. Nearly the whole of the lower lobe was occupied by an almost certainly bronchogenic (postero-lateral segment) tumour. Asbestosis bodies were found in the lung and in an excised hilus lymph node. Recovery was uneventful and x-ray examination showed later expansion of the upper and middle lobes.

A suggestive case is also described by Cureton (1948) of a young woman of 37 years who 15 years before had left asbestos work after 7 years in the industry. Necropsy showed a predominantly squamous-celled bronchial carcinoma accompanied by asbestos bodies and fibrosis in both lungs. This author is cautious about the relation between the neoplasm and the asbestosis

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but points out that the woman was very young for a squamous growth.

As in the case of most other occupational tumours, it is commoner to find workers without the neoplastic reaction than with it, even after all the apparently necessary and sufficient conditions for its development have been found to exist. Many such cases have been amply described. We give one or two from the Continental literature.

Having worked for 22 years consecutively applying insulating (asbestos) material to articles, a man aged 40 years was killed in a street accident, never having complained of respiratory troubles. Franchini and Canepa (1949) performed the post-mortem and found a fracture of the base of the skull as the immediate cause of death. The lungs were massively and extensively fibrosed mainly in the middle and lower lobes, with lymphocytic infiltrations and thickened elastic tissue; many asbestosis bodies were found occupying the lungs and lymph nodes. No mention of neoplastic change is made. It is specially interesting that, as in so many other cases, the massive pulmonary changes should have been unaccompanied by complaint.

This is of importance because if after a period of exposure to asbestos dust a certain measure of fibrosis is developed and thereafter the industry is left, we may picture a static non-symptomatic, non-progressive fibrosis, but a continuing process of cancerization in a certain number of cases. Whether the preceding fibrosis is necessary for the subsequent neoplastic process or whether the latter is conceivable without the former, it is not as yet possible to say.

The entry of any particles or fibres into the lung, even when they are soluble in water, produces a phagocytic response from the septal cells in the alveolar walls and giant cells with many nuclei soon develop. In the case of a soluble compound the ultimate degeneration of the dust cell permits the second stage of the absorption of the compound. This is readily shown experimentally with any of the common laboratory animals. The lung presents a temporary barrier to soluble particles; in the case of insoluble particles the barrier is more permanent, depending on the size of the particles. The smaller particles may be taken up by phagocytic cells arising from various sources and disposed of in lymph glands, in the interstitial tissue of the lung and even to some extent in organs from which they can be excreted. Everything depends upon the size.

Phagocytic cells may, however, be completely frustrated both by the nature and size of particles. In such cases they surround the foreign material and a process of local fibrosis sets in, the foreign unattackable material remaining more or less *in situ*.

A small particle (2–3 micrograms) will ultimately enter the alveoli and the fibrous reaction will start from the alveolar walls and lymphatics, if it cannot otherwise be disposed of. If the particle is big (10–15 micrograms) and cannot therefore proceed into the ultimate air passages, it is held up and the reaction occurs more proximally in the bronchiolar tree.

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In respect of the basic features of the body's reaction to asbestos fibres there is nothing to choose between them and particles of silica. The particular differences, which are undoubtedly observed, arise from different physical form; difference in solubility; difference in size, and the possible difference in carcinogenic properties.

The term asbestos is vague and industrially may refer to any of a series of complex silicates. It belongs to a group of crystalline magnesium silicates, which include talc (steatite) $Mg_3H_2(SiO_3)_4$, Meerschaum $Mg_2H_2(SiO_3)_3.H_2O$, possessing varying degrees of resistance to heat and to chemical agents. It is best as recommended by Spencer (1937) to preface the word asbestos with the particular mineral from which it is derived, for example serpentine asbestos and amphibole asbestos (hornblende). Unfortunately, more words than one are used in this industry for the same natural product.

The common forms, with country of main origin, used in the various industries with which our present theme is concerned are:

(1) *Serpentine asbestos* (*Canadian*) (chrysotile*; amiant). Chrysotile is the most used of the fibrous silicates. Empirical formula : $H_4Mg_3Si_2O_9$ $(= 3MgO.H_4(SiO_3)_2)$.

As mined the following is the analytical composition of an average sample of the naturally found mineral (serpentine: hydrous magnesium silicate):

	per cent
SiO_2	43
Al_2O_3	0·52
$FeO.Fe_2O_3$	1·0
MgO	41·36
H_2O	13·79

(2) *Amphiboles.* Empirical formulae:

$H_2Ca_2Mg_5(SiO_3)_8$	Tremolite (Italian)
$H_2Ca_2(MgFe)_5(SiO_3)_8$	Asbestos (amphibole asbestos)
$CaMg_3(SiO_3)_4$	Actinolite
$H_2Na_2Fe''Fe_2'''(SiO_3)_8$	Crocidolite (Blue asbestos—South Africa, Australia)

(3) *Amosite asbestos* (*South Africa*) (ferro-anthophyllite). Empirical formula: $H_2(MgFe)_7(SiO_3)_8$.

Their commercial value is due to the long fine, infusible, non-conducting fibres in which these silicates exist and can be worked and it is this character which motivates the characteristic changes in the lungs when inhaled over considerable periods. In the mining of serpentine and of the asbestos from it as a mass of fine, silky crystals in Canada, Cartier (1949) found that he could divide the 3,242 workers of whom 40 per cent had been in the mines for 10–40 years into two groups, one exposed to the dust of serpentine, which remained free from asbestosis and the other, exposed in grinding,

* Not to be confused with chrysolite which is an isomorphous mixture of Mg_2SiO_4 (forsterite) and $FeSiO$ (fayalite).

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screening, suction and bagging to the dust of the dried separated fibrous silicate, in which all the cases of asbestosis developed. Among the 22 cases of asbestosis found by radiography and confirmed post-mortem, there was no mention of any cases of cancer of the lungs. More clinical and occupational data on these cases would have been desirable. On the basis of the findings elsewhere, 1 or 2 cases of lung cancer would have been expected. On the experimental side Cartier implies that his clinical data are confirmed by exposure of animals to the two kinds of dust.

Cartier makes two statements of considerable interest as to the severity of asbestosis among his miners.

(1) During his 3 years of clinical observation (more than 10,000 complete medical examinations) no worker has died of uncomplicated asbestosis under the age of 60 years, even after 20–30 years' severe exposure to asbestos dust; nor has he seen among asbestosis cases as severe cyanosis or dyspnoea as that seen in asthmatics, lung cancer or advanced tuberculous cases. From this he concludes that pure asbestosis is not as severe a disease as it is considered in Great Britain and elsewhere where manufacturing processes are carried out with the separated asbestos.

(2) Pure asbestosis, often even radiologically very advanced, is found among workers who show no clinical signs, no diminution of respiratory function and can without discomfort carry out their habitual tasks.

The claim by Cartier amounts to this, that asbestosis as usually described is really a mixed disease, complicated by cardiopathies and even tuberculosis, and that " pure " asbestosis as seen by him is by no means a severe condition. Having been in close association with such notable authorities as Gardner and Vorwald, these statements cannot be ignored because of relatively short experience of the industry. It may be that Cartier considers a life of 60 years amply sufficient for the relatively few cases who develop the disease severely enough to die from it. He does not, however, in this paper give the populations at risk so that we cannot calculate essential data. It may be relevant to his thesis that the population around the Thetford mines is almost entirely pependent upon them for their " gagne-pain ".

Cartier's second statement is, however, borne out by the case of Franchini and Canepa. It will be recalled that whereas the general view in Great Britain is that the symptomatic picture is more severe in asbestosis than in silicosis, the reverse view is held in America. The long period of absence of symptoms has been known for many years, but the diminution in vital capacity is demonstrable even when the worker is perhaps unwilling to admit any respiratory abnormality. As was pointed out over 20 years ago by Merewether and Price (1930) and Merewether (1930), the worker is inclined to attribute his discomforts to causes other than his work.

A more normal case history is that given by Luton, Champeix and Faure (1951) who describe what is stated to be the first case of asbestosis reported in France. This was a man aged 62 years who, having worked for 11 years

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in an asbestos cloth factory ($2{\cdot}25–4{\cdot}0 \times 10^6$ particles (1–2 μ) per litre of air) complained of dyspnoea on exertion and was somewhat cyanosed. Radiographically the fibrotic condition progressed in the middle and lower lobes until he died 7 years later. Necropsy findings were of the classical kind: diffuse fibrosis, thickened plurae, no nodulation, many asbestosis bodies with giant cells and many mineral particles in the lungs.

Dust particles were found also in the vessels of the liver, kidney and spleen. No mention is made of metaplasia or neoplastic changes. These authors discount the possibility of a chemical influence of asbestos particles on the pulmonary tissues.

We have been at some pains, but without success, to elicit any statement or evidence in the literature of asbestosis which could be interpreted as more than a verbal attribution of the effects of asbestos particles to irritation. For the fibrotic effects there does not seem any reason to seek causes other than sharp " insoluble " foreign bodies larger than a critical size. The work of King, Clegg and Rae (1946) in which they pursued the mechanical action theory of Gardner, presented a reasonably full picture of the response of the lungs of rabbits to insufflation of small (2·5 μ) and large (15 μ) asbestos fibres. Gardner and his school had emphasized that, as we have already mentioned, with asbestos particles size is everything, small particles being innocuous, big particles hazardous, and that this distinguishes their effects from those of silica and quartz which are entirely the result of small particles. Nevertheless, King, Clegg and Rae did find some effect from the inhalation of small (2·5 μ) particles of asbestos, which might be described as a diffuse fibrous tissue reaction affecting mainly the interstitial tissue and alveolar walls with hyperplasia of the bronchial nodes and some nodular areas of giant-cell reaction. Phagocytosis of these small particles was probably easy enough to restrict the reaction to the locations mentioned. With larger fibres (15 μ), the foreign body giant-cell processes were apparently overlapped by a more permanent reaction, nodular in distribution, which fixed the asbestos particles *in situ*.

King, Clegg and Rae make the significant comment that these nodular, somewhat acellular, areas of intra-alveolar connective tissue were strictly comparable to, if less intense than, those produced by quartz, which means that the lung does not distinguish them.

In respect of small particles they suggested that if fibres $< 2{\cdot}5$ μ in size were insufflated, they would be completely removed from the alveolar wall and fail to produce interstitial fibrosis. It seems possible that in the case of Luton and his colleagues the smaller particles were phagocytosed and discharged into the circulation in the way probably envisaged by King and his co-workers, since they report having found dust particles in the vessels of the liver, kidney and spleen.

Summing up the many years of research of Gardner and his co-workers on the effects on animals' lungs of asbestos particles administered by

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inhalation, intratracheal insufflation, intravenously or intraperitoneally, Vorwald, Durkan and Pratt (1951) recall that ordinary industrial (asbestos) dust and, especially, long fibre asbestos dust from which the small fibres had been separated, produced characteristic peribronchiolar fibrosis which remained static on discontinuance of exposure, whereas to particles of 3 μ and less there was no tissue reaction (King, Clegg and Rae, 1946). On substituting Brucite (native magnesium hydroxide containing only 0·9 per cent silica as silicate—Brucite is a crystalline compound easily split into thin sheets and has a flexibility comparable to that of asbestos fibre), for the asbestos peribronchiolar fibrosis is similarly established, but dust of glass fibre which is not flexible and, of course, cannot be split does not, on long inhalation, lead to fibrosis.

The dependence of the fibrosis on physical form was, however, settled by the failure to induce fibrosis by long inhalation of asbestos which, having been fused and ground, no longer retained its original structure.

The Gardner school held that the combination of size, physical form and immobilization in a rhythmically moving organ is the determinant of the pathogenic effect. Effects somewhat similar to this pulmonary fibrosis can be obtained by injection of asbestos fibres into the peritoneum.

But at no stage in all these impressive researches was any clue obtained which might have offered any support to the possibility that asbestos could act as a carcinogen. There is no reliable criterion by which one can anticipate carcinogenicity and, as is well known, relatively minute changes in the structure of a chemical carcinogen are sufficient to diminish or eliminate carcinogenic action.

If asbestos is indeed to be regarded as a carcinogen, the need is felt to demonstrate some property which can be regarded as something more than inertness. The simplest such property is solubility. Solubility confers some activity on a compound as, for example, in the case of silica, the solubility of which in aqueous conditions is sufficient to found a chemical theory of silicosis.

Asbestos has, however, not given much evidence of a solubility which might be significant.

In analysing the working environment for asbestos dust Sundius and Bygden (1938) made the curious remark that only amphibole asbestos could be recognized in their analyses, in spite of the fact that the asbestos commonly used in industry contains mainly chrysotile and to a considerably lesser extent amphibole asbestos. This statement, if confirmed, might mean that chrysotile is dissolved in the analytical process. In fact, chrysotile is the least resistant of asbestos types to chemical and physical agents: it is decomposed by hydrochloric and sulphuric acids, it loses water at red heat and its fibres can be fused in the bunsen flame. (Crocidolite—blue asbestos—is also fusible to a black magnetic glass but is resistant to chemical agents).

Assuming that chrysotile might be capable of exerting some chemical

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effect by virtue of these and perhaps other related properties, the mind turns to the asbestos body which, lying in the lung tissues for long periods, might have some significance other than that usually attributed to them of being a structure in which the enclosed asbestos fibre can lie innocuous. In the experiments of Gardner and his school the injection of isolated asbestos bodies did not produce fibrotic reactions. But this need not deter us.

Cooke (1930), who, with MacDonald, discovered the asbestosis body, made the following comment: " they consist of central nuclei of asbestos spicules upon which colloidal aggregates of blood proteins, plus, possibly, soluble fractions of asbestos, and, in the case of chrysotile workers, iron salt, have been absorbed and moulded by currents in the bronchi and alveoli ".

In recent work Champeix and Bouteville (1950) examined asbestosis bodies in the electron microscope at magnifications of 25,000. It may be recalled that Champeix was associated with the view opposing a chemical factor in the aetiology of asbestosis (Luton and his colleagues).

Electron microscopy

The procedure to examine an object as delicate as an asbestosis body in the electron microscope presents much difficulty, and the interpretation of the photographs obtained should be correspondingly cautious.

Champeix and Bouteville treated expectorated material as follows:

Alkaline digestion of the diluted sputum with NaOH (equal volumes). After 10 minutes' warming in a porcelain dish, allowed to cool.

Homogenized fluid divided among several centrifuge tubes and centrifuged cautiously to avoid disintegration of the asbestos bodies.

Decanted and residues spread on several slides.

To examine in the optical microscope, mount in Canada balsam.

To examine in the electron microscope the smear allowed to dry and with a micro-manipulator a single asbestosis body is lifted on to the collodion membrane of the object carrier. This operation is difficult and delicate and the hazard of fracture of the asbestos body is great.

As regards the general morphology of the asbestosis body, the electron microscope confirms in greater detail and without deformation the findings with the optical method—the central, needled fibre ($\frac{1}{2}$–1 μ thick, length always > 10 μ) surrounded by an amorphous, somewhat opaque rounded envelope (2–3 μ thick) in parts appearing as if burst and giving a general impression of a colloidal, proteinous gel: the extremities ovoid, ellipsoid, fusiform or sometimes angular.

Two observations suggested solution of the asbestos fibre: (1) there were no fibres less than 10 μ in length in any asbestosis body; (2) removal of the colloidal envelope of the asbestosis body by means of the micro-manipulator shows the central fibre with one edge semi-transparent as if it were being dissolved away.

These facts lead the authors to some dubiety on whether the fibrosis is

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due to a maintained mechanical irritation produced by the insoluble amphibole, or to a chemical effect brought about by the dissolving silicate. It may be recalled that Alden and Howell (1944) stated that amosite needles are capable, where embedded in epithelial tissue in the skin, of eliciting a non-inflammatory epithelial proliferation. This statement was made from observations on amosite workers who developed hyperkeratotic epithelial thickening after penetration by a small splinter-like fibre. X-ray examination and biopsy show no evidence of a foreign body in these " corns ".

Solubility of asbestosis bodies

More work is required on this problem especially quantitative studies of the solubility of asbestos types in a variety of conditions, together with an identification of the products after solution. The question is not one of explaining fibrosis of the lung by a chemical process, for this is almost decisively negatived by the undoubted fact that the smallest particles of asbestos have not in fact produced a fibrosis in the experience of most investigators. The question is rather one of finding a product of solution which, by entering the modified squamous epithelium of the lung, or by changing its environment, can lead to de-differentiation or to tumour formation. The majority of pulmonary tumours in men are anaplastic or undifferentiated or (epidermoid) squamous epitheliomata and they constitute a type of new growth in the lung which has hitherto eluded the experimentalist. Probably the only claim to have induced a true cancer in the lungs of mice was that made by Nordmann and Sorge (1941) who exposed 100 mice to undefined asbestos dust and stated that 20 per cent of the animals developed cancer. There is considerable doubt, however, whether the evidence presented is really acceptable.

In fact, cancer of the lung (truly so called—not adenomas as found and induced in mice) has not hitherto been produced by inhalation of any material. W. E. Smith (1952) in a very forceful consideration of the experimental aspects of cancer of the lung concludes " that we are singularly ill-equipped for the experimental study of one of the chief problems of human cancer ".

Until this charge is successfully answered we may for practical purposes regard asbestos or a derivative of asbestos as a probable co-carcinogen in that proportion of cases of diffuse fibrosis of the lung in which the necessary preparedness of the lung has been brought about, probably endogenously. Such a view has, at least, the merit of less sterility than the common panacea for carcinogenic dilemmas, irritation.

AROMATIC AMINES

Of the few identifiable chemical agents which may without doubt be accepted as standing in the line of causality of particular types of human neoplastic disease, certain aromatic amino intermediates in the dyestuffs industry occupy the most interesting and, from the point of view of the experimentalist, the most fruitful position. Not only have they been repeatedly reported in

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preparation for treatment of woodworm, and there had clearly been much skin contamination. The preparation contained *o*- and *p*-dichlorobenzene, DDT (2–3 per cent) and pentachlorphenol (some 5 per cent). The cases all did well after intervals up to 3 months. The question as to which of these compounds was responsible was left in doubt as experiment with rabbits and with fowl (notoriously sensitive to agents attacking nerve tracts) were negative as far as the central nervous system was concerned.

Nevertheless, there is every reason to suspect pentachlorphenol which may, in man, have acted in part in co-operation with DDT, the insecticidal action of which is enhanced by it and which, in conditions of free absorption, itself can induce polyneuritis, weakness, disturbances of hearing and vision, muscle pain, and the like, even in 2 per cent solution. Such DDT effects pass off in some 4 weeks.

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