TUMOURS OF THE URINARY TRACT AS AN OCCUPATIONAL DISEASE IN SEVERAL INDUSTRIES

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by

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PREAMBLE

THE SUBJECT OF occupational tumours of the urinary tract is one with many facets, and because of space it is necessary to neglect almost entirely some of the most fruitful experimental work that has been done in the field of cancer research and also the long struggle of many workers in many countries to get the idea that urinary tract neoplasia may sometimes have an occupational basis accepted. Fortunately both these aspects have been admirably described elsewhere (Goldblatt and Goldblatt, 1956; Williams, 1958).

This paper attempts to outline present knowledge of the epidemiology of urinary tract neoplasia in relation to occupation as it occurs in this country, and to indicate where there are gaps in this knowledge. It also tries to give a picture, necessarily incomplete, of what has been done by Industry to combat the scourge, and what remains to be done by Industry, the Medical Profession and other organizations and individuals to complete this conquest.

DEFINITION OF THE DISEASE

The pathological definition of the industrial form of the disease is given in the Prescribed Industrial Disease regulations (M.P.N.I. 1962) as follows:

" PRESCRIBED INDUSTRIAL DISEASE NO. 39: Primary neoplasm of the epithelial lining of the urinary bladder (Papilloma of the bladder), or of the epithelial lining of the renal pelvis or of the epithelial lining of the ureter."

However, most of the work discussed below refers almost entirely to tumours of the urinary bladder. This is because all the epidemiological studies were of necessity directed to this organ because the most vital investigatory weapon, a national register of death certificates of all deaths from the disease, was available only for the bladder. Despite this limitation it is probable that all the conclusions that have been drawn apply to tumours of all parts of the urothelium, from the renal tubules downwards. The limitation to the epithelial lining of the renal pelvis written into the regulations is in fact based on guesswork or " general principles " and should not be taken as a proven pathological concept.

THE OCCUPATIONAL DISEASE AND HOW IT IS CONTRACTED

Occupational tumours of the urinary tract are now known to be caused by a variety of chemicals, mainly those of a class known as aromatic amines, but not all such amines possess the dangerous property.

The substances concerned may enter the body by being inhaled as dust or vapour, may be absorbed readily through the skin, or may be ingested and absorbed through the alimentary tract. They are mainly encountered in the dyestuff manufacturing section of the chemical industry, where they are both manufactured and used and where they are known by their own chemical names. At one time they would have persisted in small amounts as impurities in finished dyestuffs, presenting a danger both to those who used the colours and those who dried or ground them. To-day, at least in the larger firms, this danger has been virtually removed.

The substances are, however, also sold to other users either as the named chemicals or as complex compounds under a variety of trade names. Here the firms using such products might in some instances have been unaware of the nature of the substances that they were handling.

PATHOLOGY AND PROGNOSIS

The tumours that arise may be, initially, histologically benign papillomata. If detected and treated at this stage the prognosis can be good, but if untreated the tumours may progress rapidly to frank and invasive malignancy, and may then present a hopeless prospect. Sometimes, as far as can be judged, the tumours may be malignant from the earliest moment at which they can be detected with the methods currently available.

NATURE OF THE DISEASE

Just under 3,000 males in this country die of urinary tract tumours each year, 2,000 of these being in the bladder, and perhaps 1 per cent of these deaths can with some certainty be called occupational. However, in some industries nearly all the urinary tract neoplasms that occur are occupational, but clinically the occupational and non-occupational are indistinguishable. Differentiation must therefore be made on the occupational history, and the incrimination of a substance or process must be made on epidemiological evidence based on an accurate knowledge of the frequency of the disease in the general population and in the industry concerned.

Official statistics by themselves are insufficient, for in any large community the manifestations of industrial disease are diluted by the large number of the population who are not exposed to the hazard. This effect is illustrated by Figure 1.

For this reason epidemiological studies are best carried out on defined groups of workers who are known to have worked on the processes

under investigation. In order for this to be done the close co-operation of the industry concerned must first be obtained.

An epidemiological investigation may also show disturbances of the age-distribution of disease as well as a quantitative difference; but though a shift of age-distribution suggests an environmental factor, the absence of a shift is no conclusive disproof that such as factor is present.

OCCUPATIONAL TUMOURS OF THE BLADDER

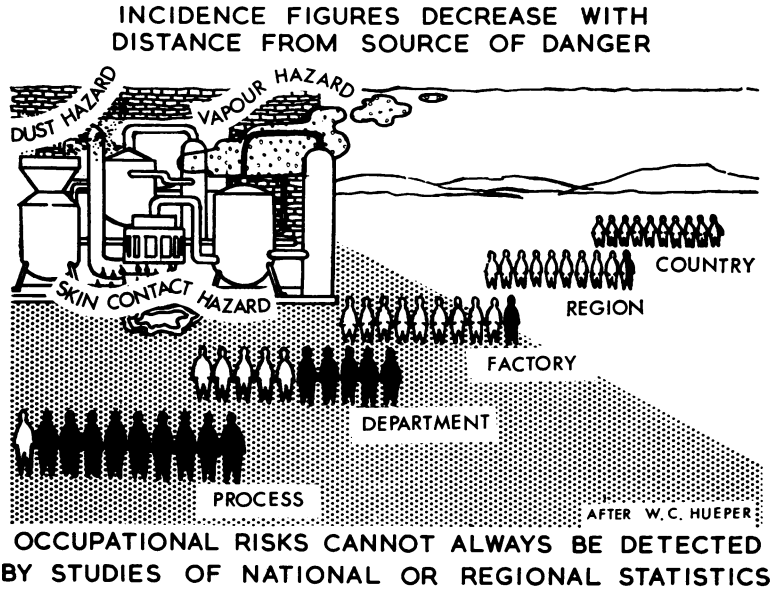


Fig. 1. To show how the apparent intensity of the risk becomes diluted as we study figures for aggregates of people of whom those at risk form only a small part. For this reason epidemiological surveys conducted without the close co-operation of the industry are relatively insensitive instruments. The three sources of danger are also shown.

This is illustrated by Figure 2, a comparison of the age of onset of bladder tumours in a group of chemical workers, where virtually all the cases were of occupational origin, and of all the males recorded as suffering from bladder tumours in Birmingham in the years 1936–49. The most frequent age of onset is 20 years earlier in the chemical workers than in the Birmingham controls, but had the structure of the chemical industry been such that men did not start work on the dangerous processes

until they reached the age of 40 years, instead of 20 years as in fact happened, then the most frequent age of onset would have been the same in both groups.

CHEMICAL INDUSTRY

Within the chemical industry itself, the observations of a German surgeon, Rehn (1895), directed suspicion to an aniline dye works where several men suffered from bladder tumours. He considered that aniline

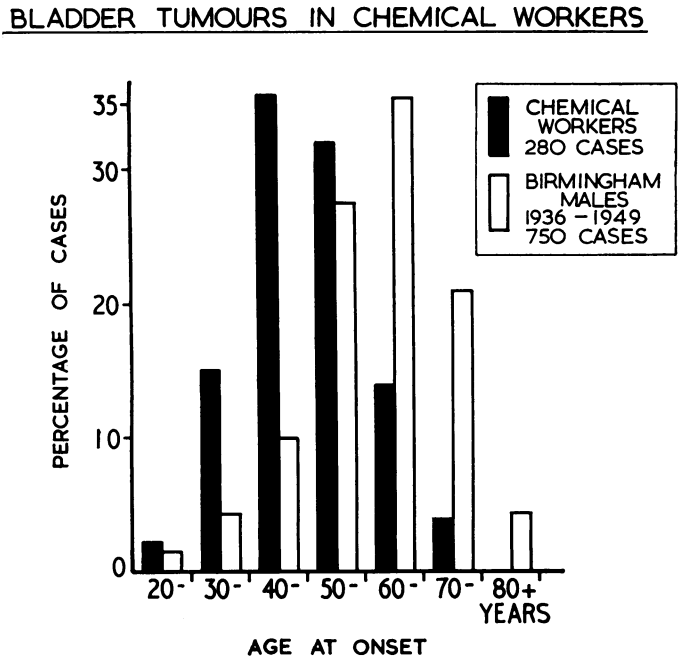


Fig. 2. To show how the age at onset of the disease in chemical workers using the dangerous substances was some 20 years earlier than that found in a control group of patients. However, had the structure of the chemical industry been such that men did not enter the dangerous occupations until the age group 40–45, the most frequent age at onset would have been the same in both groups.

was the most suspicious chemical used, and from this idea the still-current but incorrect name "aniline tumour" of the bladder arose. Suspicion followed the aniline dye industry as it spread from country to country, but only after an interval of 15–20 years, during which time a false sense of security had been engendered.

In retrospect, it now seems astonishing that the epidemiological evidence that had accrued, although it was fragmentary, should have been so lightly discounted.

EXPERIMENTAL BACKGROUND

To some extent this was due to the failure of experimental scientists to produce bladder tumours in their experimental animals with any of the suspected chemicals. This situation changed when Hueper *et al.* (1938) induced bladder tumours in dogs by oral administration of com-

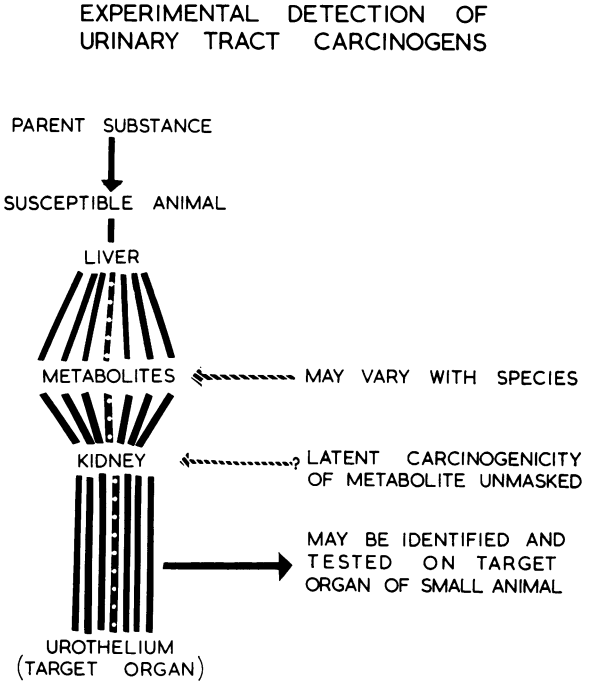


Fig. 3. To show how a probably non-carcinogenic substance may be metabolized to a carcinogenic substance, possibly in more than one stage. The induction time in the known susceptible animal, the dog, is of the order of 5–15 years, according to the amine given, and so the susceptible animal system itself is not very useful for screening. The isolation of all possible metabolites, with subsequent testing by pellet implant into rats and mice, is also obviously impracticable if a large range of new substances is to be tested, both because of the numbers of animals involved and because there is no certainty that the susceptible animal will be the same one in each case.

mercial β-naphthylamine. This discovery resulted in extensive and intensive biochemical studies (Boyland, 1965; Clayson, 1962) which disclosed a complex picture of the parent substance, used in industrial processes, being transformed in the body to another substance, not met with to any extent in industry, which is itself carcinogenic. This situation is shown in Figure 3.

A substance administered to a susceptible animal is metabolized, probably mainly by the liver, into a series of compounds. The chemical

nature of these metabolites, or the proportion of each metabolite, may differ in different species. One or more of these metabolites may be carcinogenic or may possess latent carcinogenic properties which are unmasked at some point between excretion by the kidneys and final voiding from the bladder.

Since the most susceptible animal at present known is the dog, and since the time taken for a urinary tract tumour to develop may be between five and fifteen years from starting the experiment, identified metabolites have been tested by being implanted as pellets in a relatively inert base into the bladder of rats and mice.

It is obvious that the initial identification of a susceptible animal must be made by allowing the tumour to develop in that animal. Therefore initial testing is lengthy, and there can be no guarantee that the right animal had been selected in the first place.

Quite apart from the great scientific value of this work, in this country led by Bonser, Boyland, Clayson, Walpole, Williams and their colleagues (see Goldblatt and Goldblatt, 1956), the complexity of the situation implies that no effective screening of new compounds that may be introduced into industry can at present be envisaged, for although a positive result should be accepted as implying human danger, a negative result does not mean safety.

For this reason the epidemiologist will have to act as a watchdog, and the epidemiological studies must be well designed and comprehensive.

COMPENSATION AND SHORTCOMINGS THEREOF

As has been said, suspicion that some substances used in the manufacture of dyestuffs caused bladder tumours in men exposed to them had been growing for many years. During the 1930s pressure grew for the disease to be scheduled under the Workmen's Compensation Act.

Many large firms in the British chemical industry thought this step premature until a proper epidemiological survey had been carried out, and they proposed that such a survey should be made. In the meanwhile, the employers' association entered into a " gentleman's agreement " that no man who contracted a tumour that could reasonably be called occupational would be worse off than he would have been if the disease had been scheduled.

In the event, however, war intervened, and the survey could not be started until 1948. When the results became available in 1953 (A.B.C.M. 1953) the old Workmen's Compensation Act had been superseded by the Prescribed Industrial Diseases Regulations (M.P.N.I. 1962), and it was written in to these that exposure to the now-recognized dangerous substances must have continued after 4th July 1948, the date that the regulations came into effect.

Since the average time from first exposure to the development of the disease is about 18 years, this meant that there was a class of men who

developed occupational tumours but who did not comply with this date rule.

Although the chemical firms who made the " gentleman's agreement " have honoured it both loyally and generously, the date limit has produced hardship to persons working in some other industries where the disease was subsequently found to exist. This matter has now been brought to the notice of the Ministry concerned, and it is hoped that careful consideration will be given to the complex legal situation that has inadvertently been created.

THE SURVEY

Let us now turn to the survey itself (Case *et al.*, 1954). By its terms of reference it was confined to four chemicals largely used as intermediates in the dyestuff industry, aniline, α-naphthylamine, β-naphthylamine and benzidine. Three of these, α-naphthylamine, β-naphthylamine and benzidine, proved to be potent carcinogens in man; aniline did not show this property. Subsequently animal experiments on dogs (Walpole *et al.*, 1954) suggested that 4-amino diphenyl was also dangerous, and a survey of an American factory where the substance was made confirmed this (Melick *et al.*, 1955).

The statement about the carcinogenicity of α-naphthylamine requires qualification. The substance as met with in the British chemical industry always contained about 5 per cent of the β isomer. Nevertheless, ancillary evidence (Scott, 1962) suggests that it is prudent to regard α-naphthylamine as potentially carcinogenic in its own right, and this is the view expressed in the British Code of Working Practice (Scott and Williams, 1957).

These chemicals were made largely for use as dyestuff intermediates, and would in general be transformed into harmless material in this process. Some would be purified and sold as fine chemicals for laboratory use, some would be sold to other industries, and some made into compounds for use in other industries.

The survey (Case *et al.*, 1954; Case and Pearson, 1954) also showed that the manufacture of the dyes auramine and magenta was attended by a tumour hazard, but was not able to determine whether this was due to the properties of the finished dyes or not.

SURVEY METHODS

We have already anticipated the results of the survey by stating what substances were found to be dangerous, but before these conclusions became acceptable it had been necessary to measure the frequency of bladder tumours in the chemical industry and in the general population. Since no measure of the *incidence* of bladder tumours was available we had to use the frequency of death where a bladder tumour was mentioned on the death certificate. A complete set of bladder tumour death certificates for England and Wales from 1921 on was made available, and

this was the most potent tool in the whole investigation. Twenty-one member firms of the Association of British Chemical Manufacturers (the A.B.C.M.) had provided a list of some 4,600 men who had worked in contact with aniline, α-naphthylamine, β-naphthylamine or benzidine at some time between 1921 and 1951.

RESULTS OF SURVEY

Proof of hazard

Working from the death certificates it was possible to calculate that four bladder tumour deaths would have been expected if the disease was affecting these men at the average rate for the country—127 were found.

Thus, for practical purposes, no great error is made if all these cases are regarded as being industrial in origin. In addition there were 135 other men who developed bladder tumours but who were either still alive or had died from some other cause; there is no reason to believe that the proportion of these which were due to occupational causes would differ from that found for the deaths.

Diversity of dangerous jobs

These men had worked in a diversity of jobs. Although the majority of the cases had occurred amongst processmen, pressmen, filtermen and labourers, victims were also found amongst company directors, scientific staff, weighmen, dryers and ovenmen, grinders of colour, maintenance men, plumbers, fitters, coopers and cask washers. The fact that the disease is no respecter of persons is an important one to bear in mind, for in the ordinary course of events one might fail to realize that men in some of these occupational groups were in fact at risk.

Severity of risk

How severe the risk is can be judged by the proportion of men who ultimately develop a bladder tumour. This differs according to the substance to which the man is exposed and to the extent to which he is exposed, and varied, in the section of the industry studied, from 10 per cent amongst workers in contact with α-naphthylamine (Fig. 6) to 100 per cent, the latter figure being reached in a small group of men who distilled β-naphthylamine. In the general population the corresponding figure would be much less than 1 per cent. This increasing incidence with increasing intensity of risk is shown in Figure 4, and this figure shows from facts what was illustrated from general principles in Figure 1, where the theory of an increasing proportion of cases with increasing exposure was illustrated.

Long and varied latent period

The disease manifests itself at differing times after the first exposure. The extremes are under 5 years, and over 50 years, but the most common

time is about 18 years. A consequence of this long induction time is the necessity for medical supervision throughout the remainder of their lives of workers who have been exposed to risk.

The variation of the latent period found in the chemical industry (Case *et al.*, 1954), where the risk had been more or less constant over the period studied and for some time before this period, is shown in Figure 5.

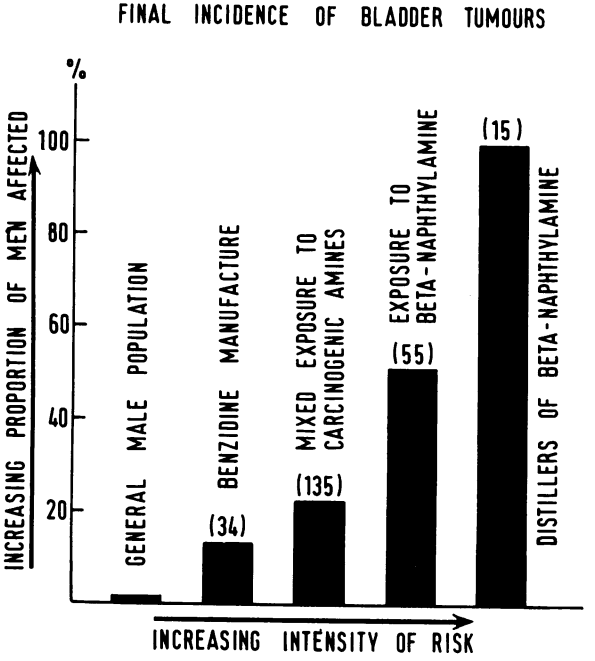


Fig. 4. To show the final incidence in different groups of men, reaching 100 per cent amongst the distillers of β-naphthylamine.

Consequences of long latent period

Because of this long mean latent period the incidence of the disease builds up slowly amongst men at risk, and this slow process often induces false confidence that no risk is at work in a particular factory.

The way in which the incidence rises is shown in Figure 6, and it can be seen that amongst α-naphthylamine workers, for example, the extent of the danger is barely appreciable even after 15 years from starting work in the hazardous process.

ACTION TAKEN

As might have been expected, the firms who called for the investigation to be made were not slow to take drastic action when the state of affairs began to become apparent.

Control of exposure

The manufacture of β-naphthylamine was abandoned, and plants for making the other dangerous intermediates were redesigned and rebuilt. Remote control techniques were introduced, dust hazard, skin contact hazard and vapour hazard reduced to vanishing point, and both personal and plant hygiene taught and practised. A strict Code of Working Practice (Scott and Williams, 1957) recommended by the British dyestuffs industry was drawn up and this has been widely observed.

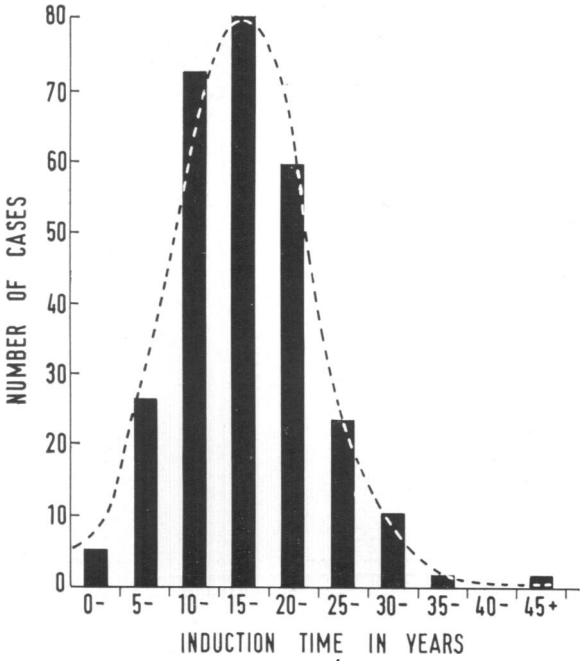


Fig. 5. To show how the induction times vary from less than 5 years to over 45 years, with a mode at 15–20 years. When dealing with a situation where the risk has remained fairly steady for several decades, as in the chemical industry at the time of the survey, the curve tends to normality.

Need for international agreement on control of exposure

Nevertheless, two of these most modern plants, one which made benzidine and one which made α-naphthylamine, have recently been closed because in each case one man who had worked on the plant contracted a bladder tumour (*Lancet*, 1965*c*). The firm concerned, although not convinced that both cases were of occupational origin, deemed it wise to cease manufacture, with the result that benzidine, and some chemicals made from α-naphthylamine, will be imported.

Now I think that most humane men will agree that it is obviously improper to expect men in other countries to face a risk which a firm

considers unacceptable in its own factories; but, on the other hand, it is arguable that, if the substances concerned are really vital to human well-being, then the solution might be to have one extremely well-designed plant which could serve the world demand, and so reduce the risk to an absolute minimum.

This at once raises the question of the necessity for international agreement on the methods of safe manufacture and usage of the carcinogenic substances, and there is now reason to believe that this matter will be discussed at the International Labour Organization in Geneva.

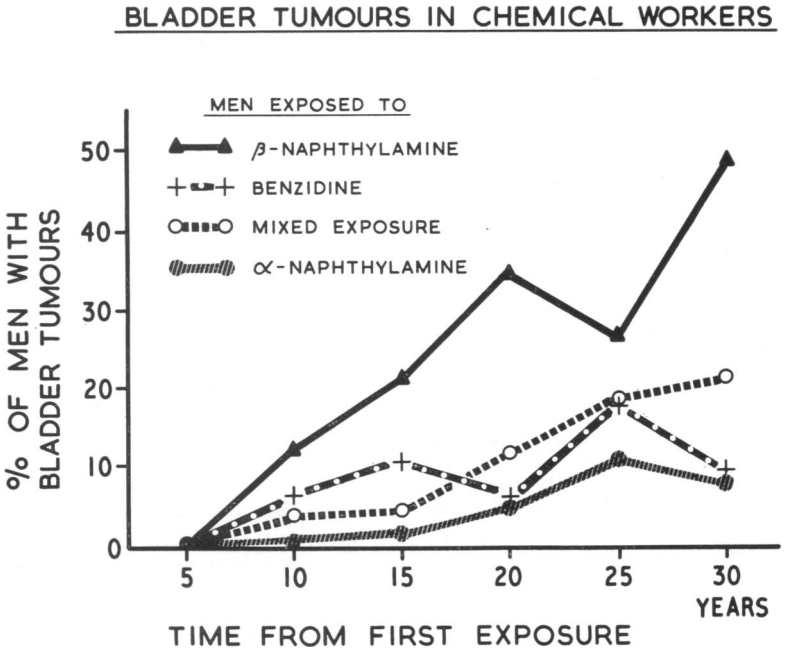


Fig. 6. To show how the incidence of the disease rises with the passage of time in the men employed on different processes.

Prescription as industrial disease

As a result of this survey occupational bladder tumours were listed in the Prescribed Industrial Diseases List as P.D. 39 (Statutory Instrument 1953), and the Association of British Chemical Manufacturers continued their voluntary scheme to mitigate the effects of the date bar in these regulations.

Danger to men already exposed

However, even if the measures taken prove to have been completely effective, and therefore no more men were exposed to danger, the long latent period in the development of the disease implies that cases will develop in men already exposed until about the end of the century.

In 1952 the best estimates that could be made suggested that, in the group of men in the survey, only half the potential cases of the disease had become manifest, leaving another 243 cases yet to develop (Case *et al.*, 1954). This estimate, divided into the different classes of compounds and types of exposures concerned, is shown in Table I. So far as can be seen at present, this forecast is not a gross overestimate.

Medical care for men already exposed

Because of this situation the British chemical industry looked around for some method of identifying these potential cases whilst the disease was in its earliest stages, for it is, I think, generally accepted that early diagnosis offers the best chance of effective treatment.

TABLE I

BLADDER TUMOURS IN CHEMICAL WORKERS

Analysis at February 1952

To show the 1952 balance sheet of the number of men in the survey who had already contracted the disease, and the number of new cases to be expected from these same men if all risk had been withdrawn (Case *et al.*, 1954).

Men exposed to	*Cases found*	*New cases expected*	*Total*
Benzidine	34	24	58
Alpha-naphthylamine ..	19	51	70
Beta-naphthylamine ..	55	38	93
Mixed exposure	135	130	265
Total	243	243	486

Men at risk, 2,466

In America routine cystoscopy of workmen had been advocated (Gehrmann, 1934), but it was thought that this regimen would be unacceptable to the British working man.

One firm therefore instituted an experimental exfoliative cytological urine screening scheme, and this proved so successful (Crabbe *et al.*, 1956) that after the experimental period was over it was expanded to cover all the member firms of the Association of British Chemical Manufacturers who wished to take advantage of it.

The British chemical industry, as represented by the Association of British Chemical Manufacturers, is thus seen to be keenly aware of the risk, active in combating it, and in general generous in compensating for it. Unfortunately, it soon transpired that this industry was not the only one affected.

RUBBER INDUSTRY

Discovery of risk

Quite early in the survey of chemical workers an almost fortuitous discovery was made. As part of the epidemiological survey of the general population, the County Borough of Birmingham was selected for study

because it was a large industrial city without any large-scale dyestuff industry. It also had extremely good tumour follow-up records dating back to 1936. These records were so complete that morbidity rates for the city could be calculated.

It at once became apparent from the records that an undue number of patients who suffered from bladder tumour had worked in one large rubber works. In the years 1936–50, four cases would have been expected amongst all skilled rubber workers in Birmingham if no risk was at work; 22 were found (Case and Hosker, 1954).

At the same time it came to light that one of a class of compounds called antioxidants which was put into rubber to stop it perishing was made from α- and β-naphthylamine and that some cases of bladder tumour had occurred amongst the men making it.

TABLE II

NUMBER OF DEATH CERTIFICATES WHERE TUMOUR OF THE BLADDER WAS MENTIONED RELATING TO WORKERS IN RUBBER OCCUPATIONS

(Rubber industry only)

To show the continuing excessive number of deaths from bladder tumours amongst rubber workers.

Date	1936 *to* 1951	1952 *to* 1956	1957 *to* 1961	1962 *to* 30*th June* 1965	
England and Wales	26	20	27	25	Found
	15.9	9.8	11.0	10.8	Expected
Birmingham C.B.	6	10	12	6	Found
	3.1	1.3	1.5	1.5	Expected
England and Wales except Birmingham C.B.	20	10	15	19	Found
	12.8	8.5	9.5	9.3	Expected

These figures include men who at the time of death were either occupied or retired.

The rough estimate of the risk just quoted, made by a rather primitive epidemiological technique, so convinced the chemical industry who made the antioxidant of the danger that, as early as 1949, they promptly stopped making it and another similar one and destroyed existing stocks. The rubber industry itself stopped using the compound.

Need for further investigation

Now it might have been expected that a finding of this sort would have led to a detailed epidemiological study of the rubber industry, similar to the one carried out in the chemical industry, to see just how far the risk extended, if the antioxidants which had been withdrawn were in fact the only dangerous ones, and which men were most at risk, in order to assess priorities for continuous medical supervision.

In fact, the Rubber Manufacturing Employers' Association (the R.M.E.A.) decided against such a procedure lest employees were unduly

alarmed (Gunter, 1965). Such an investigation has not been carried out to this day, despite increasing public alarm at the lack of it, and the bladder tumour deaths in the industry continue at a high level, which may or may not simply be due to the back-log of cases in men exposed before the suspect antioxidants were withdrawn. The figures for skilled rubber workers in Birmingham and in the rest of England and Wales, together with the number of such deaths expected at national rates, are shown for successive periods of time in Table II.

Difficulty of protecting workmen

The process of making rubber articles is complex, presents opportunities for men to be exposed to dust and vapour, and is difficult to protect in the way that chemical plants can be protected.

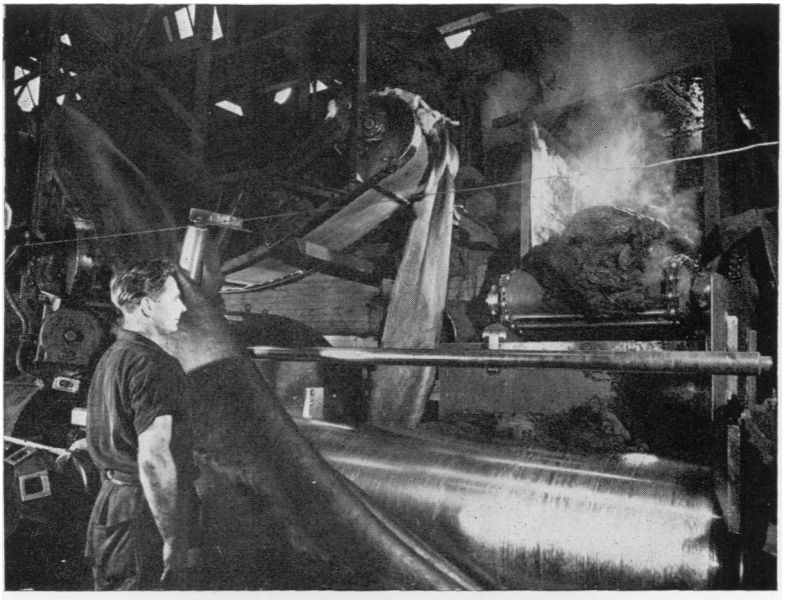
This difficulty is illustrated by Figures 7 and 8. Figure 7 shows how a man preparing the uncured rubber as it passes through heated rollers is exposed to vapour arising from it, and Figure 8 shows how a man opening the steam-heated moulds after the rubber is cured is also likely to breathe the vapours of substances which have been volatilized during the process.

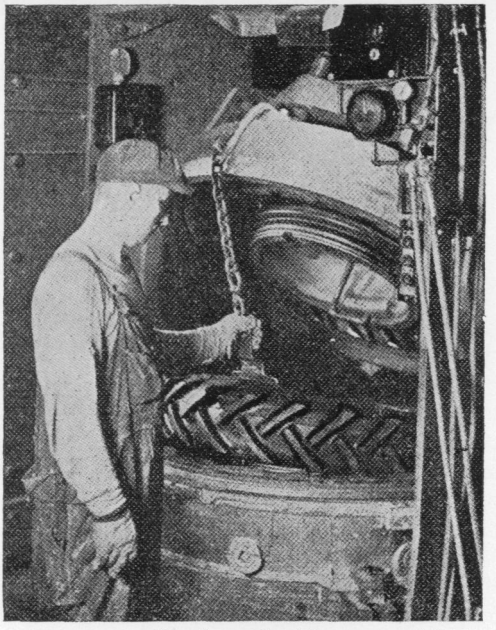
In both cases it is difficult to totally enclose the plant. The alternative, to enclose the man, is not well tolerated in such hot and active occupations.

Urine screening

When the success of the exfoliative cytology urine screening techniques had been established, the R.M.E.A. (1961) set up a Health Research Unit and offered its member firms a screening service. Unfortunately, not all rubber manufacturers are members of this association, nor can the R.M.E.A. compel its members to make use of the service.

An example of the results of failure to accept such advice was recently brought to public attention by an inquest held at Bath (*Lancet*, 1965*b*). It transpired that there had been a cluster of 13 cases of bladder tumours at a rubber factory in the West Country, and initially the firm was unaware of some of these cases. Six deaths had occurred, against 1.3 expected at national rates. Twice the R.M.E.A. Health Research Unit had advised the firm that, because they had used the suspected antioxidants, they should have their employees screened. Twice the firm had turned the suggestion down, and it was only after an earlier coroner's inquest on a cable worker in January 1965 (*Lancet*, 1965*a*) that screening had been introduced. This occurrence emphasizes both that a lack of real awareness of the danger had persisted in some sections of the rubber industry, and also that coroners' inquests have great value in educating the public and in disseminating important information.





(Fig. 7 reproduced by courtesy of Dunlop Rubber Co. Ltd.)
(Fig. 8 reproduced by courtesy of McGraw-Hill (Shreve, 1945))

Figs. 7 and 8. To show how a rubber worker comes into contact with the fumes from hot rubber, and to illustrate the difficulty of totally enclosing the plant,

CABLE INDUSTRY

Until a few years ago, when suitable plastics became widely available, large quantities of rubber were used in the electric-cable-making industry. The rubber mixes used were similar to those used in the rubber industry itself, and some had contained the suspected antioxidants.

Lack of appreciation of risk

Although the firms who used these materials were told that they were suspected carcinogens by the manufacturers, the warning did not seem to have been clearly understood, for the cable industry claimed to be unaware of the danger to its employees until the coroner's inquest on a former cable worker early in 1965 (*Lancet*, 1965*a*). Indeed, although they had been invited by the R.M.E.A. some years ago to join in the urine screening scheme, this offer was turned down. Davies (1965) recently showed that there is quite a serious hazard in the cable industry by demonstrating a highly significant excess mortality from bladder tumours in workers in the rubber mill of one cable factory to whose records she was given access, but so far no survey capable of defining the full extent of the risk has been made.

Since the withdrawal from use of two suspected antioxidants in 1949, the cable industry has undergone extensive regrouping, with the result that some factories were closed and their labour force disbanded. This creates a serious problem because many men who may have had heavy exposure, and who certainly should be under continuous scrutiny by urine screening, have moved to other jobs and may still be unaware of the threat to their health and lives.

Need for national urine screening scheme

The lack of an adequate survey, which would have made it possible to see where the risk really lies, has made it impossible to establish a programme of screening priorities, starting with men most in danger. Because of this, the efforts so far made by the Ministries of Labour and Health (Gunter, 1965) to trace and screen those at risk may be thought by some to smack more of a conciliatory gesture to public opinion than of a serious medical programme.

These efforts have consisted in sending out several thousand cards to persons who might possibly have been at risk, advising them to seek the advice of their family doctor, and of issuing instructions to certain pathological laboratories to undertake the necessary tests.

The cards themselves, although issued by the Ministry of Labour, were apparently sent out by the firms thought to be concerned, who at that stage could have hardly been expected to have the knowledge of the problems involved. From various personal communications I know that cards have been received by workmen's widows, by female typists, and by male clerks, most of whom could hardly have been in imminent

danger. Pathologists have made frantic phone calls to cytological experts to complain that they have neither the facilities nor the knowledge to undertake the screening, and family doctors have given advice to enquirers that showed that they had no conception of the problem that they had been asked to tackle, or even of the nature of the test which was available.

In my view, what we need is a carefully planned campaign directed to identifying and instructing the men most in need of surveillance, coupled with an intensive educational programme aimed at other men at risk, those employers not already fully aware of what is at stake, hospital pathologists, and general practitioners. Ministry assistance to train technicians and provide facilities will also be required.

ANTIOXIDANTS

One particular problem that concerns both the rubber and the cable industry is the chemical nature of the source of the danger. The suspected antioxidants were withdrawn because, being made from α- and/or β-naphthylamine, they contained traces of these substances as impurities, for it was then thought that these impurities were themselves responsible for the carcinogenic action. This view has recently been challenged (Watts, 1965) by one firm who manufactured the most suspect one, and it was suggested that the finished product itself might have been the carcinogenic agent.

If this is so, the situation could be very serious, for it would mean that we have a hitherto unsuspected class of carcinogenic chemicals to deal with, and other methods of making antioxidants, although not starting from known carcinogens, might yield a dangerous end-product.

This is another reason to keep pressing for the institution of a searching and comprehensive epidemiological study of all branches of rubber-using industries, not merely of the large firms who are members of the Employers' Association.

GAS WORKS

A recent epidemiological study by Doll *et al.* (1965) has indicated that workers in the retort houses of gas works also have an excess risk of contracting bladder tumours. Since β-naphthylamine has been identified in both coal tar (Thorpe and Whiteley, 1939) and gas works pitch (Hoffman and Beonte, 1933) this is not surprising. However, so far no systematic testing of the atmosphere of gas works in order to detect and estimate the naphthylamine content of the air at various situations has been published. Again, in my view, such a survey is urgently needed.

OTHER INDUSTRIES AND OCCUPATIONS

Since coal tar and pitch are extensively used in making patent fuel, and melted by passing live steam through the mix, it is quite likely that men employed on this process are at risk, for both the naphthylamines are easily vaporized by steam.

α-Naphthylamine and benzidine are used outside the chemical and rubber-using industries; textile printers used to, and, for all I know, still do, develop dyes on the cloth with these agents. No survey in this industry has been reported, nor is there any special urine screening scheme operated for them by their industry.

Benzidine has been used in medicine as a test for blood, and many pathologists and others may have been exposed. α-Naphthylamine is a commonly used reagent in testing water supplies and the effluents of some electro-plating processes.

A study of death certificates certainly raises a clinical suspicion that some of these classes of people may be at risk, and it should not be impossible to conduct an efficient epidemiological survey based on the national register of bladder tumour death certificates and the records of, for instance, the Pathological Society, the Institute of Medical Laboratory Technicians, and similar professional organizations.

Rat catchers, or perhaps I should say rodent operators, may also have been exposed to α-naphthylamine present as an impurity in the rodenticide Alpha-Naphthyl-Thio-Urea, commonly called Antu.

FUTURE NEEDS

Thus we see that the danger of being exposed to substances which may produce occupational tumours of the urinary tract is insidious, furtive, and more widespread than has commonly been believed, and although more is known about this disease than about most occupational cancers there are gaps in our knowledge at nearly all levels.

In the preceding pages I have tried to indicate some forms of action that I believe should be taken, but some other tasks remain. One of the most urgent of these is to spread the knowledge that we already have amongst medical men, some sections of industrial management, and the men on the factory floor. This has already been effected in the large firms in the chemical industry and in some of the large rubber works.

Lack of awareness amongst medical practitioners

For many years the urologist as well as the general practitioner seems to have regarded industrial bladder tumours as a problem peculiar to a few centres of the north of England, where dyestuffs were made. In fact, the problem concerns the medical profession in nearly all parts of the country. This point is illustrated by Figure 9, where the county of residence of men who were certified as having died with bladder tumours in the years 1945–64, and who were also stated on the death certificate to be employed in, or retired from, the cable-making or rubber industries are shown. Nearly half the cable workers came from the Greater London area, but the largest groups of rubber workers were found in the Midlands or the North-West. Scattered cases occurred over most of the country (Davies, 1965).

Although not all of these deaths were due to occupationally induced tumours, the medical attendant of the deceased should have considered this possibility in each case.

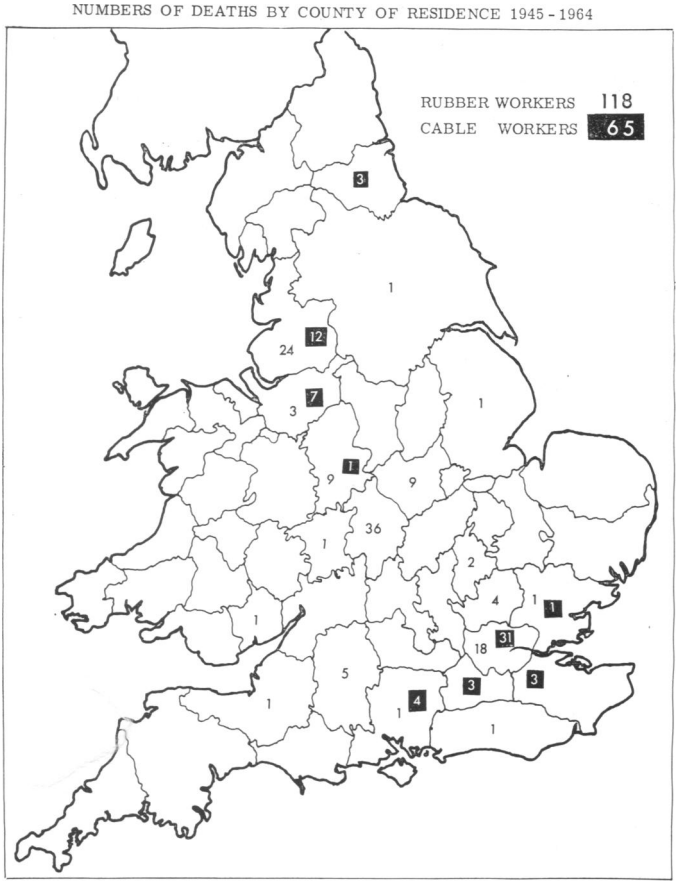


Fig. 9. To show the widespread geographical distribution of deaths from bladder tumours in men stated to be rubber or cable workers on their death certificates. Although not all of these were necessarily of industrial origin, the possibility that they were should have been considered by the medical attendant in each case. (Map: Davies, 1965.)

Inadequacy of advice about when to claim benefit

One consequence of this lack of appreciation of the situation has been that patients and dependants have not claimed the benefits that might have been due to them under the Prescribed Diseases Regulations because neither their medical attendant nor anyone else advised them to make a claim. Table III shows successful claims for compensation under

Prescribed Disease No. 39 regulations during the years 1954–63, and the number of death certificates showing that chemical, rubber or cable workers died with a bladder tumour during the same years. The discrepancy between the figures is probably grossly underestimated, for some of the claims referred to persons still alive, and not all workers in the suspect industries could be identified by the description of their occupations that appeared on the death certificates.

Reporting to the coroner

Another consequence of lack of knowledge has been a failure, except in a very few areas, to report cases of possible occupational death from urinary tract tumour to the coroner.

After the recent publicity (*Lancet* 1965*a*, *b*) given to the subject by two coroner's inquests, some coroners (Hails, 1965; Thurston, 1965) on their

TABLE III

INDUSTRIAL BLADDER TUMOURS
(PRESCRIBED DISEASE NO. 39)
Successful claims 1954–63

To show how few claims for benefit under P.D. 39 have been madei n the rubber and cable industries, compared with the number of deaths from bladder tumours amongst workers in these industries. Obviously, since many claims are made in relation to the living, this table grossly underestimates the disparity.

Industry	*Maximum No. of Claims*	*No. of Death Certificates*
Chemical	105	133
Rubber	33	77
Cable	1	36
	139	246
Other industries ..	7	Not obtainable
All industries ..	146	Not obtainable

own initiative have offered to help in research. Such help is warmly welcomed and I hope will be extended.

If an inquest had been held on, say, a cable worker some five years ago, and if it had been widely reported, urine screening might have been started in the rubber factory in the West Country, with a possible consequent saving of several lives.

Need for factory doctors to know causes of sickness amongst workers

There is also a need for many industrial medical officers, particularly part-time ones, to know more about the causes of illness amongst employees. Although there is now a good appreciation of the risk amongst the medical officers in the A.B.C.M. firms in the chemical industry, and perhaps in a few large firms in the rubber industry, elsewhere the situation leaves much to be desired.

In 1948 the medical officer of a large rubber works in Birmingham wrote:

" Your reference to a ' large bladder tumour problem ' rather surprises me. In this works of nearly 9,000 I can only ascertain the existence of 7 people with bladder trouble at all, and some of these are not in the nature of tumours."

At this point 18 cases of bladder tumour had been found in this works in the last seven years (Case and Hosker, 1954), and only one of the seven cases referred to was a tumour. This ignorance could possibly be understood in 1948, but in 1965 the Medical Officer of a cable factory wrote to one of my colleagues as follows:

" I find that the substance . . . was used in this factory up till 1947. . . . We have had only one case of Bladder Tumour in this factory i.e. . . ."

At this point three other cases had been found in this factory by this colleague. This continuing ignorance of the necessity to ascertain the causes of absence amongst workers in factories where hazards exist is neither understandable nor entirely excusable.

Need for liaison between management and workers

Management might in some instances learn from the experiences of the workmen. In the early part of the studies made on the rubber industry at least one patient suffering from an occupational tumour was suspicious about the number of other cases amongst his workmates, for he wrote:

" Re your enquiries regarding bladder trouble, all I can do is to say I worked in the Tube Dept. nearly 30 yrs on different jobs, I wasn't among the French chalk like some of them had to be, still it was in the air, I know of at least 6 cases in the same dept, which has seemed remarkable to me, I am afraid there is nothing I can add to this."

In 1965 a workman at another rubber factory, the one where the management had refused to institute urine screening on two occasions when advised to do so by the R.M.E.A., wrote a very similar letter in which he said:

" it was during this time, whilst handling rubber just cured, the bleeding of the bladder commenced. Whilst on the subject of bleeding I would add that I have seen quite a number of men who are rubber moulders, who suffer from this, but many have an idea that this is one of the hazards of rubber workers and do nothing about it."

In both instances better liaison might have ensured a proper appreciation of the risk at an earlier date.

Proposed legislation to control carcinogenic substances

Within the last two years legislation (Minister of Labour, 1964*a*, *b*; 1965) to prohibit or control the manufacture, use or importation of the known urinary tract carcinogens has been proposed. If framed effectively this would be very welcome, but, like so many other decisions about the

problems raised above, because of our incomplete knowledge of the whole situation it will be based, of necessity, to some extent on general principles only.

ENVOI

As John Hunter (1861) said:

" The man who judges from general principles only, shows ignorance: few things are so simple as to come wholly within a general principle.

"We should never reason on general principles only, much less practise upon them, when we are, or can be, master of all the facts; but, where we have nothing else but the general principle, then we must take it for our guide."

Our task is plain, let us set out to master the facts so far as we can, but, because many of the difficulties that I have discussed have stemmed from a failure to communicate such knowledge, let us make quite certain that these facts become public property.

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