

OCCUPATIONAL TUMOURS OF THE BLADDER

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SYNOPSIS

Tumours of the bladder in workmen making dyestuffs were first observed in 1895, but only in relatively recent years have the responsible compounds been recognised. Similar cases have been known to occur in workers in the rubber industry. The actual tumours are similar to those of non-occupational origin, and substantially reduce the expectation of life. There is usually a long latent period between first exposure to a carcinogen and the ultimate development of a tumour. The manufacture or use of a known bladder carcinogen demands the highest standard of plant design and operation, together with careful medical supervision.

Historical Aspects

From the beginning of time mankind has used colour as a means of self-expression. His original primitive colourings were all derived from natural sources, but in 1856 William Henry Perkin discovered the first synthetic dyestuff which he called mauve. From that discovery there has developed the modern dyestuffs industry producing an immense diversity of colour whereby modern man—and woman for that matter—may express his aesthetic ideals.

The blessings thus conferred upon mankind have brought in their wake a tragedy in the form of an industrial disease known as Papilloma of the Bladder which is largely—though not entirely—peculiar to the dyestuffs industry. After Perkin's original discovery the manufacture of synthetic dyestuffs developed in England, Italy, France, and the United States of America, but particularly in Germany and Switzerland. One of the most important German centres was Frankfurt-am-Main, and in 1895, a Frankfurt surgeon named Rehn¹ noticed that he was treating for tumours of the bladder three men who had worked not merely in the same factory, but in the same shed in the same factory, making magenta. Rehn rightly concluded that these tumours were the result of the occupational environment of the workmen, but wrongly attributed them to exposure to aniline, which is one of the starting materials in this manufacture. This was the origin of the term "aniline cancer" and although it is now accepted that aniline has no carcinogenic effect whatsoever, the term is still occasionally used by people who should know better.

Since Rehn's original observation many reports have been published about the occurrence of bladder tumours in dyestuffs workers, and although a number of manufacturers refused to acknowledge that the nature of their employment could be in any way responsible, there did develop within the industry an increasing awareness that a serious bladder tumour hazard did exist.

There is not time today to discuss in detail the ways in which light eventually began to penetrate the darkness. In Great Britain the problem was discussed prior to the Second World War by the Factory Department, the chemical industry, and leading authorities on cancer research but the war delayed any concerted effort to obtain more detailed facts. At this point of time, the only point of common agreement concerned the part played by *beta*-naphthylamine, although other products were under suspicion. In 1946, however, the Association of British Chemical Manufacturers

formed a Scientific Committee "for the guidance of research work, aiming at (a) information on causation, (b) improved diagnostic methods, (c) improved methods of testing causative agents, and (d) information likely to improve preventive techniques". A Research Fellow was appointed to carry out a statistical investigation in the British chemical industry and he ultimately reported² that "contact with benzidine, *alpha*-naphthylamine, and *beta*-naphthylamine in either manufacture or use causes many more bladder tumours in workmen so exposed than would appear if no special risk were operating. Furthermore, both the onset of and death from these occupational tumours takes place at a much earlier age than in non-occupational cases". He also stated that there was no evidence of aniline causing an increased number of bladder tumours in men exposed to it. He further reported that there appeared to be a definite hazard associated with the manufacture of two specific dyestuffs, auramine and magenta, although pointed out that the dyestuffs themselves were not necessarily dangerous.³ There is in fact no evidence as yet as to any increased incidence of tumours in the industries using these dyestuffs, although it has been demonstrated that they have a carcinogenic action in experimental animals.

Chemical Causes

The compounds then which were specifically indicted as dangerous (both in manufacture and use) were *beta*-naphthylamine, *alpha*-naphthylamine and benzidine and the salts thereof. There is undoubted confirmatory evidence from animal experiments that both *beta*-naphthylamine and benzidine are potent carcinogens, but this is not so in the case of *alpha*-naphthylamine, however many tumours may have resulted from its manufacture and use. Commercial *alpha*-naphthylamine is not a pure product, and contains about 4-7% of the *beta* isomer. There is thus some doubt as to whether pure *alpha*-naphthylamine is carcinogenic or whether the undoubted danger arising from handling *alpha*-naphthylamine on an industrial scale results from the presence of the *beta* content. The point is largely academic as the commercial compound is invariably impure so that the hazard always exists.

It is perhaps appropriate to mention at this point that the order of potency of these three carcinogens as reflected in Case's survey was *beta*-naphthylamine, benzidine, *alpha*-naphthylamine in decreasing order.

Certain substituted benzidines, *viz.* *ortho*-tolidine, dianisidine and dichlorbenzidine, are widely used in the dyestuffs industry, although on a much less scale than benzidine.

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These products are almost invariably made on the same plant as benzidine, and no population of workmen is known which has been engaged in the manufacture of these compounds without also having been exposed to benzidine itself.⁴ There is therefore no statistical evidence which can demonstrate that these compounds are or are not dangerous, but there is experimental evidence which suggests that all of these analogues of benzidine are carcinogenic, although to a lesser extent than benzidine. One must therefore make the recommendation that where these products are handled in industry, they should be treated with the same care and respect as is given to benzidine itself.

Having mentioned certain substituted benzidines, mention should also be made of three substituted naphthylamines which are widely used, *viz.* phenyl-*alpha*-naphthylamine, phenyl-*beta*-naphthylamine and ethyl-*alpha*-naphthylamine (Fig. 2). Whereas in the benzidine analogues there has been ring substitution, these compounds are all substituted in the amine group. It can be stated quite clearly however suspicious these compounds might sound by virtue of their names, none is believed to be carcinogenic.

Apart from the two dyestuffs auramine and magenta, all of the other compounds mentioned are used mainly as intermediates in dyestuffs manufacture. But this is not necessarily their only use. One very important compound used in the rubber industry from 1926 until 1949 was a formaldehyde condensation product of *alpha*- and *beta*-naphthylamine. This material was used as an antioxidant in rubber and contained about 2.5% of free naphthylamine,

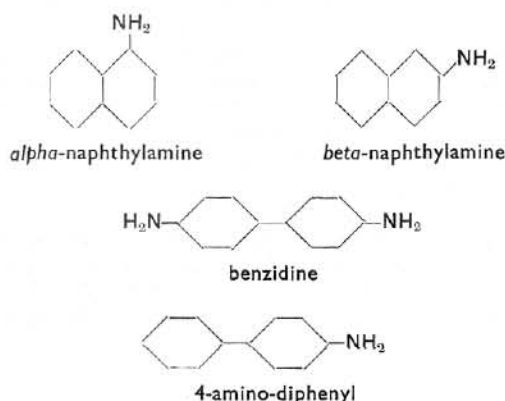


Fig. 1.—Some chemicals known to cause bladder tumours

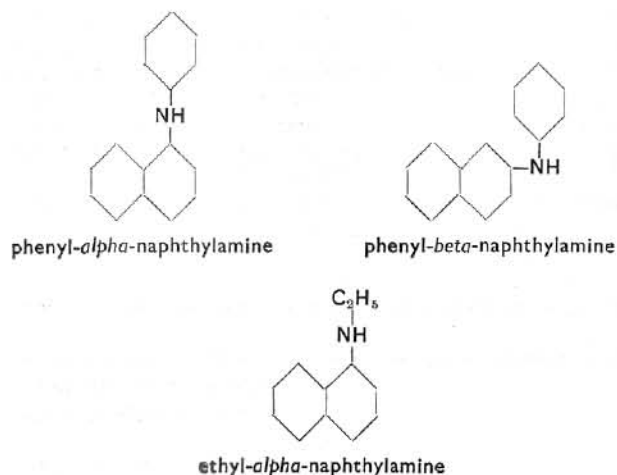


Fig. 2.—Some compounds which are thought not to be carcinogenic

which tended to vapourise at the temperatures reached during the processing of the rubber "mix". There has been an undoubted incidence of tumours in workmen so exposed, although possibly less than might have been anticipated.

An antioxidant derived from 4-amino-diphenyl (Fig. 1) was used in the United States of America for a number of years. Experimental work carried out in Great Britain demonstrated that this amine (which is related to benzidine) was a potent carcinogen.^{5,6}

After this work had been published, the American company making this compound discovered a number of cases of bladder tumours amongst their employees and gave up the manufacture. There is recent information, however, to the effect that a large number of cases have developed since.

Natural History of the Disease

The chemicals which have been definitely proven to cause bladder tumours in man, *beta*-naphthylamine, benzidine, 4-amino-diphenyl and commercial *alpha*-naphthylamine, are all primary aromatic amines (see Fig. 1). They may enter the body by absorption through the intact skin, by inhalation of dust or vapour, or by ingestion. The most important of these, and the most difficult to prevent, is skin absorption. One of the most unfortunate features is that except with large doses sufficient to cause symptoms of acute poisoning, such absorption appears to produce no ill-effect. Nevertheless symptomless but irreversible changes do take place which may ultimately be followed by a tumour of the bladder.

As with other tumours of occupational origin, there is characteristically a long latent period between first exposure to the carcinogen and the eventual onset of the disease. This latent period is often about 20–25 years, but may be very much shorter or substantially longer. Indeed once significant exposure has occurred, the workman is at risk for the rest of his life—latent periods as long as 40 or 45 years have been recorded.

It is customary in the industry to refer to the disease as "Papilloma of the Bladder". Using the word in its scientific sense, the term "papilloma" implies that the tumour is benign. In fact, while many of these tumours appear to be benign in their early stages, all are potentially malignant and some appear to be frankly cancerous from the start. They cannot be differentiated in any way from tumours of non-occupational origin although in general they tend to appear in younger age-groups.

The onset of bladder tumours tends to be insidious, and the growth may be advanced before any symptoms or signs occur. Most commonly the first symptom is the presence of blood in the urine, or possibly discomfort on emptying the bladder, or frequency thereof. Any such symptom occurring in a dyestuffs worker requires full investigation of the entire urinary tract. Should blood appear in the water without any other symptoms it frequently disappears again within a few days, and it is all too easy to presume it wrongly to be merely the effect of a temporary disorder which has righted itself.

Methods of treatment are precisely the same as for spontaneous tumours. Recurrences are far from uncommon however, either at the original site, or elsewhere in the bladder. After all, the entire bladder lining has been exposed to the offending compound, and may well respond with a further growth at any point. Most early cases can be treated quite simply by burning off the new growth, but other cases may require removal of part or whole of the bladder or treatment with deep X-rays.

Because of this tendency to recur, once a diagnosis has been made it is essential that these cases be regularly examined for the rest of their lives. This enables recurrences to be recognised at the earliest possible stage.

There is no doubt that in these cases the expectation of life is substantially reduced. The average survival time is about five or six years. This figure is depressed by the group of cases in which diagnosis occurs late, and who die within two years. On the other hand, where diagnosis occurs early, the expectation is substantially better than this, and it is not uncommon for death to occur from some unrelated disease. Thus early diagnosis is of prime importance.

Diagnosis in Industry

Diagnosis of tumours of the bladder is customarily made by carrying out cystoscopy. This involves passing into the bladder a tube with light and lenses which enables the surgeon to visualise the whole of the inside of the bladder. It will be appreciated that this is not a particularly pleasant experience for the patient. Even if carried out under a general anaesthetic, there is still considerable post-operative discomfort.

It has been suggested that in order to ensure diagnosis at the earliest possible stage, regular cystoscopy at about yearly intervals should be carried out on workmen exposed to carcinogens. Such a routine has been attempted in a number of countries, but so far as one can gather, without great success, and it has never been attempted in Great Britain. There are a number of objections. Tumours frequently develop many years after a workman has ceased exposure, and while he may agree to regular cystoscopy during his period of contact, he is unlikely to agree indefinitely. After a series of negative cystoscopies, there may be a refusal to undergo further examination at the very time when it is most desirable. All authorities in Britain, and many abroad, are now agreed that routine cystoscopy is neither practicable or desirable.⁴

What is done in Britain, however, with considerable success, is routine examination of the urine. Such examinations can be performed at frequent intervals without inconvenience or discomfort. Two types of test are carried out. Firstly, simple microscopic examination which will detect the presence of small numbers of red blood cells or pus cells, and secondly a much more complex technique (Papanicolaou) which will enable tumour cells to be recognised. Neither of these tests should be regarded as diagnostic in itself but as an indication for cystoscopy. It is obvious that many conditions other than tumours will produce small amounts of blood or pus. Furthermore, bladder tumours will not necessarily exfoliate cells into the urine (although they usually do) which can lead to false negative results; and one may find cells which look like tumour cells but are not, thus producing false positive results. Nevertheless these examinations have proved of great value for routine screening, and a well-known Manchester surgeon has stated that "on account of routine medical examination in industry, occupational bladder tumours tend to be seen at an earlier stage than those arising spontaneously".⁷

Preventive Measures

Plant design and operation

The major difficulty in developing effective preventive measures against this kind of hazard is that because of the long latent period prior to the development of tumours it takes many years to demonstrate whether or not a plant is being operated safely. Furthermore, because the hazard is so remote, because these dangerous products produce no immediate ill-effects, because it is difficult to comprehend the degree of scrupulous care required to handle these materials safely, workmen and supervisors tend to work less safely than they ought. It is all too easy to say that everything

ought to be totally enclosed, and that safety devices should be outwith the workman's control. The chemical plant was never invented that didn't require maintenance and the more complex the handling devices that are installed, the more easily they break down. Enclosed systems have to be opened up. Products have to be discharged and packed.

The most satisfactory preventive measure is always to eliminate the offending material altogether. This has been possible with *beta*-naphthylamine, the main use of which was an intermediate for Amido G Acid and Amido J Acid, both important for dyestuff synthesis. These compounds are both naphthylamine sulphonic acids, and an alternative chemical route was established by sulphonating *beta*-naphthol before adding the amino-group to the molecule, thus obviating the formation of naphthylamine. The sulphonic acids themselves are free from hazard. It has never been found possible to make *beta*-naphthylamine safely, and by means of this alternative route, although more expensive, it has been possible in Germany, Switzerland and the United Kingdom, and to a large extent in the United States, to abandon *beta*-naphthylamine manufacture.

4-amino-diphenyl, whose main use was for a rubber antioxidant, was never manufactured in England. Many other rubber antioxidants are available, and when the hazard was discovered it was possible for its manufacture to cease in the United States of America.

It has not, however, been possible to eliminate benzidine, the substituted benzidines, or *alpha*-naphthylamine. There is no alternative route to the products derived from these intermediates. Serious problems arise therefore from their manufacture and use.

A full account of precautions has been given in the A.B.C.M.'s Code of Working Practice recommended for the manufacture and use of products causing tumours of the bladder.⁸ They state that the object in all plant design must be to contain the carcinogens within an enclosed system wherever possible whether they are present as powder, liquid, or vapour. All operations involving manual handling of carcinogens ought to be studied with a view to eliminating that particular operation.

For example, hydrazobenzene is manufactured as an intermediate for benzidine and is believed by most, although not all, authorities to be carcinogenic. In some plants, hydrazobenzene is isolated, discharged into drums, and then charged again from drums into a reaction vessel for conversion into benzidine. How much less exposure occurs on those plants where the hydrazobenzene filter cake is slurried up and transferred by pipeline to the reaction vessel within an enclosed system.

Any operation where the carcinogen sees the light of day is potentially dangerous. Sampling, filtration, drying, distillation, and flaking are all hazardous procedures. The use of dip pans and dipsticks are obviously not free from risk and should be replaced by small vented cabinets for sampling, or automatic depth recorders. Filter presses and open nutsches are obviously unsatisfactory for the isolation of carcinogens as it is impossible to discharge filters of this type without fairly gross contamination. Rotary vacuum filters, or automatically discharging pressure filters, are much more satisfactory. Distillation residues are a common source of hazard, and probably the ideal means of disposing of these is to run them off molten to a furnace where they can be burned. Care must be taken to ensure that the carcinogen is destroyed, and not merely distilled to the outside atmosphere.

Three of the most hazardous procedures in dealing with carcinogens are drying, grinding, and flaking. They are especially hazardous as all of these operations are invariably dusty, though flaking is less so than others. Where it is technically possible it is of course far better to handle

products of this type as a wet paste (which obviates the dust hazard), and this is now done in respect of benzidine and its analogues. For packaging in drums, a water content of about 30% is best. If too much water is present, the paste is sloppy and tends to splash about causing contamination of skin and overalls. If too little water is present, the paste is sticky and difficult to discharge from drums. Ideally, of course, it is more satisfactory not to pack it into drums at all, but to transport it in bulk as a slurry. Quite recently a special road tanker, with a rotating tank almost like a cement mixer in principle, was designed and built for the bulk transport of benzidine slurry, but unfortunately this never became operational as the manufacture ceased. An even better solution is to tetratosise the benzidine *in situ* within the closed system so that it never sees the light of day, but this presents technical difficulties unless the usage of benzidine is adjacent to the site of manufacture.

With *alpha*-naphthylamine it has been possible to devise a system of bulk storage and transport in the molten state, and this system is most satisfactory for large users. It is still necessary however to carry out some flaking for the smaller user, and in such cases the flaker must be totally enclosed and draughted.

The point was made earlier that even the best designed, most completely enclosed and most safely operated plant did at some time require to be opened up for maintenance or inspection. Such work must be carried out with the strictest precautions, and every care must be taken to clean plant out before opening up the closed system, and to detox chemically any traces of active carcinogen which might remain.

In discussing preventive measures we have so far referred primarily to plant operating precautions. A number of non-medical measures are advised as well and we will refer to these briefly.

Non-medical preventive measures

In the first place in any factory where a hazard of this nature exists it is obviously desirable that there should be a medical officer who fully understands the problem. The urine examinations essential for early diagnosis have already been described and when a case is discovered the medical officer must co-operate closely with the patient's general practitioner and with the surgeon responsible for treating the case.

Full records are absolutely essential of where and when any carcinogenic material is used, how much, methods of handling, design of plant, of plant hygiene precautions, and details of any untoward incidents. Full records must be kept of individuals employed on such a process, with date of exposure, date of birth, details of other employment, record of sickness absence, and particulars of death certificate. The importance of such records cannot be over-emphasised. All medical men concerned with such cases have experienced great difficulty because of the inadequate records of the past, and it is absolutely vital to have information of who worked with what and when. The information may be necessary 40 years later, not merely to show that a man's work may have been responsible for his tumour, but in some cases to establish it has not.

Care is required in the selection of workers for processes of this type. Ideally men over 40 should be employed, because even if a man does absorb a hazardous dose—and the aim must always be to ensure he does not—the long latent period, considered in association with the normal expectation of life, will substantially reduce the chance of a tumour developing. Obviously a high standard of personal hygiene is desirable along with sufficient intelligence to understand the nature and degree of the hazard, to appreciate the need for clean and careful working, and to carry out all instructions

correctly. Only men in good health should be chosen, and a history of any bladder trouble of any sort should exclude a candidate. Previous exposure to carcinogens is also undesirable.

There is no justification whatsoever, when a man is working with a known carcinogen, in concealing from him the danger of the material. Sir Thomas Legge,⁹ the first Medical Inspector of Factories pointed out many years ago, "All workmen should be told something of the danger of the material with which they come in contact and not be left to find out themselves, sometimes at the cost of their lives".

There will be little need for me to mention the need for special working clothing and protective clothing. Full working clothing must be supplied and changed at frequent intervals, preferably daily, and certainly immediately after any contamination. No man should be permitted to wear any of his own personal clothing on the plant, and separate lockers should be provided for home and working clothing to ensure no cross contamination takes place. A clean smock should be worn during meals so that tables and food do not become contaminated.

Protective clothing will depend upon the nature of the work to be done. Gloves which become contaminated on the inside—and this is a frequent occurrence—must be destroyed at once. Where respirators are required to protect against dust or vapour, air-fed hoods or suits are much preferable to dust respirators—"Martindale" type respirators are positively dangerous, giving a sense of false security and permitting the passage of vapour and the finer dust particles.

Before finishing work, a bath or shower is essential. This must be compulsory and should be taken in working time.

It is customary to provide soft drinks in considerable quantities for men in such processes, the reasoning being that any product which may be absorbed is diluted and washed out of the body more quickly.

Conclusion

One could go on indefinitely, but space has permitted only a superficial review of this tragic problem. In describing preventive measures the A.B.C.M.'s Code of Practice has been frequently quoted, and this must be the bible of anyone interested in the manufacture or use of bladder carcinogens. It will be evident that where such materials exist, every step of every process, every piece of plant, every action of every processman and fitter, must be scrutinised with great care to ascertain if there is any way in which it can be made safer. It is a problem which can be solved only by co-operation between doctor, chemist and engineer; by the most skilful chemical and engineering techniques aided by the application of medical principles.

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