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THE INCIDENCE OF BLADDER TUMOURS IN A DYESTUFFS FACTORY*

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The incidence of bladder tumours in workers in the dyestuffs industry was first described by Rehn in 1895 and 1906. Leuenberger reported 41 cases in 1912, and by the third decade of this century in Europe exposure to beta naphthylamine and to benzidine had been accepted as a cause of bladder tumours by Kennaway (1924), Berenblum and Bonser (1937), Goldblatt (1949), and Müller (1951). In the U.S.A. Gehrmann, Foulger, and Fleming (1949) are less certain of the carcinogenicity of benzidine than the European investigators and have suggested that it cannot be accepted as a bladder carcinogen until it is known that benzidine workers without any exposure to beta naphthylamine have developed tumours of the bladder.

This paper describes 23 cases of papilloma and carcinoma of the bladder among workers exposed only to benzidine, and reviews in all 66 cases not previously reported of confirmed bladder tumours arising in a dyestuffs factory. Fifty-eight cases were found in the section where intermediates are manufactured and eight in the colour factory where the intermediates are handled. No cross transfers have taken place and the populations have remained distinct. Only the men for whom data are complete have been included in this series. In addition there are 11 former employees believed to have died of bladder tumour whose histories are not yet fully traced, and two men reported to have developed tumours with whom contact has been temporarily lost. A voluntary system of compensation, by *ex gratia* payments, should help to ensure that the histories of men who develop tumours after leaving the factory will be known.

Manufacture of Intermediates

In Table 1 it will be seen that of the 58 patients 19 have died. All except three of these 58 patients have been employed in the manufacture of benzidine, alpha naphthylamine, or beta naphthylamine, or in various combinations of the three. Twenty-three had worked solely on benzidine in a separate building and had never had contact with naphthylamines. Fifteen had worked solely on beta naphthylamine and had not had contact with benzidine. The 16 mixed exposures arose either in the still house, where benzidine and naphthylamines were sent to be distilled, or in the sulphonation building where alpha and beta naphthylamine were sulphonated. The percentage of beta isomer in the alpha naphthylamine was about 4. There have been no transfers between these departments. Three cases arose in men with other exposures.

TABLE 1

CASES OF TUMOUR OF THE BLADDER IN THE MANUFACTURE OF INTERMEDIATES

Type of Exposure	Total	Alive	Dead
Benzidine	23	15	8
β Naphthylamine ..	15	9	6
α Naphthylamine ..	1	1	0
Mixed benzidine α & β naphthylamine	16	11	5
Other	3	3	0
Total	58	39	19

Benzidine.—Benzidine manufacture by the zinc reduction method was started in 1918. It was first produced as the sulphate which was then converted to the base, and until 1944 either the sulphate, the base, or both have been isolated. Since 1944 the hydrochloride has been made. These and other changes in the process are shown diagrammatically in Fig. 1. Ortho-dichlorbenzene was used as a diluent until 1926 when it was replaced by a solvent, paraffin oil. In 1947 solvent naphtha was substituted

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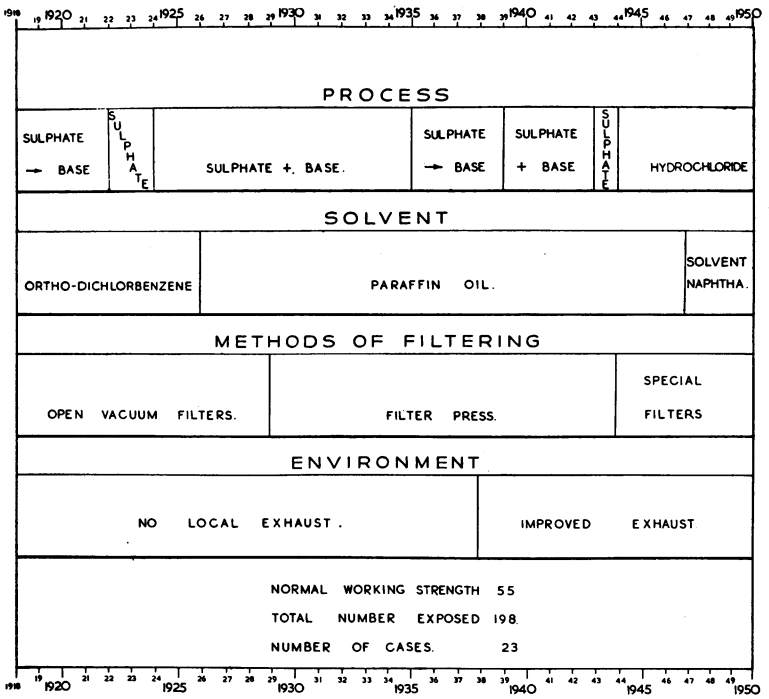

FIG. 1.—Diagram of history of benzidine manufacture from 1918 to 1950.

for the paraffin oil. Open vacuum filters were used until 1929 when they were replaced for technical reasons by a large filter press. In 1944 specially designed vacuum filters were installed. In 1938, after the first cases of bladder tumour had occurred, an exhaust ventilation system was installed. This has since been improved from time to time.

The usual number of men employed in the building housing this plant is about 55, of whom a special squad of six now work the benzidine process; the total number who have been exposed in this building for six months or more over the whole period is 198. Since 1935 there have been 23 cases none of which has been exposed to naphthylamines.

Beta Naphthylamine. — The manufacture of beta naphthylamine was started in 1920. It was manufactured in one building, distilled in another (where benzidine was also distilled for many years), and sulphonated in a third. Apart from the still house, with a normal complement of two men, the workers on these processes were never exposed to benzidine.

The process is in two stages and is shown diagrammatically in Fig. 2. The first, heating beta naphthylamine with ammonium sulphite and ammonia in autoclaves, varied little from the beginning. The second stage, that is the separation of the amine from the autoclave charge, was improved from time to time. From 1920 to 1933 the charge was filtered, stoved, distilled, set in open trays, broken up by hand, and ground. From 1933 to 1938 stoving was omitted and a flaker replaced the trays and the grinding. From 1938, when the hazard was apparent, all washing and drying was carried on in closed vessels, and molten beta naphthylamine was piped to the still, distilled and flaked. In 1947 the

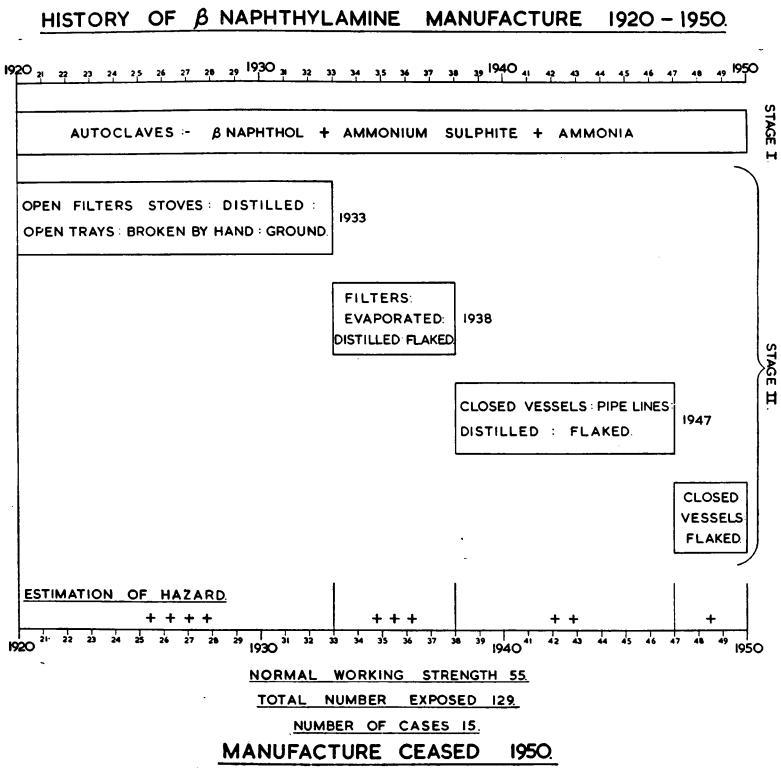

FIG. 2.—Diagram of history of β naphthylamine manufacture from 1920 to 1950.

product was flaked without distillation. After separation the amine was then sulphonated in another building.

The manufacture of beta naphthylamine and its handling in the colour factory ceased in 1950 because of the health hazard involved. The normal working complement was about 55 men, and the total number exposed for six months or more since 1920 was 129. Fifteen cases of tumour have occurred in this group since 1934.

Alpha Naphthylamine.—Alpha naphthylamine was manufactured in this factory for four years only, from 1926 to 1930, by the nitration of naphthalene and subsequent iron reduction of alpha-nitronaphthalene. The usual number of men employed on this process was three, and the total number who worked on it for six months or more was four. None of these men has developed bladder tumour.

One case, which might be attributed to alpha naphthylamine in the manufacture of intermediates, developed a tumour after being employed for 18 years in the manufacture of naphthionate of soda from alpha naphthylamine. During this process a distillation residue containing about 17% of beta naphthylamine (from the 4% beta impurity) was recovered as a molten product, set in trays, broken up by hand, and transferred to casks. It has previously been suggested by other investigators (Goldblatt, 1949; Müller, 1951) that the beta naphthylamine impurity in alpha naphthylamine is the causative factor in tumour production, and this man was, owing to the nature of the process, more heavily exposed to the residue with a high beta naphthylamine content than to technical alpha naphthylamine.

Aniline.—The manufacture of aniline by the iron reduction process started before 1900 and has always been carried on in separate buildings. The total number exposed over six months since 1920 is 76. Previous records are not dependable. The normal working complement is 11. No cases of bladder tumour have been found among men in this process although some men have worked since the early days of primitive plant and bad conditions, and some exposures up to 45 years are substantiated. In Europe tumours attributed to aniline have been reported by Gross (1940) 33 cases, Goldblatt (1949) three cases, and Müller (1951) 22 cases, but Gehrmann and others (1949) reported that they had found no tumours in men from an aniline plant with a substantial number of employees who had worked thus exposed up to 25 years.

Other Exposures.—One man was employed on the manufacture of beta naphthylamine for three months, and for the next 27 years worked as a boiler fireman in the factory, an occupation which did not bring him into contact with intermediates. Müller (1951) reports the case of a stoker who developed bladder carcinoma after three years' exposure to firing anthracene vapours, and quotes Rosner, Young, Russell, and O'Donovan as reporting bladder carcinoma in addition to skin and scrotal carcinoma in tar and fuel operatives. The observations of Henry, Kennaway, and Kennaway (1931) do not show any increased incidence for this class for the 1921–28 period in England and Wales. As no other exposure under four years is known to have occurred in this series, he has not been included with the beta naphthylamine cases, although exposures as short as six months have been accepted by Gross (1940).

Another, a process worker, developed a papilloma after 28 years on the manufacture of ortho-toluidine and chlor-toluidines. He had no contact with benzidine. The nearest process to him in this building, however, was one in which alpha naphthylamine sulphate, which contained about 4% beta naphthylamine sulphate, was baked to make naphthionic acid. No other cases have arisen in this shed.

The third, a process worker, developed carcinoma of the bladder after working for five years on the manufacture of amino salicylic acid. In the next unit in the same building dianisidine was made. Neither of these substances has been reported previously as causing bladder tumours, although Perlman and Staehler (1933) included dianisidine in a list of substances which they mentioned as possible causes.

Exposure and Latent Periods.—The shortest period of exposure, excluding the one doubtful case

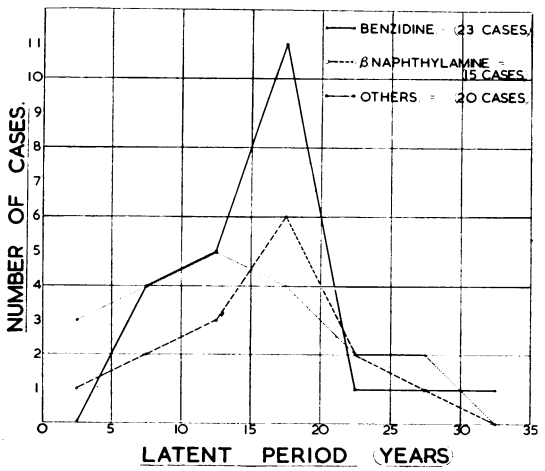

FIG. 3.—Graph of time from starting work to diagnosis of tumours.

of the boiler fireman, was four years and the longest 32 years, with an average of 16 years for all the manufacturing group. The latent period (Fig. 3), that is the time from starting work to diagnosis of tumour, showed no appreciable difference between the 23 benzidine cases with a range of eight to 32 years (average 15·9 years) and the beta napthylamine cases with a range of five to 27 years (average 15·5 years). The 20 mixed and other exposures with a range of seven to 22 years tended on the whole to appear earlier but their average latent period was 16 years (Fig. 3).

It is worth noting that, of the men exposed to beta naphthylamine who developed tumour, the one with the longest latent period (27 years' exposure) was the only chemist in the series. As a chemist he would have had considerably less exposure than a process worker.

Handling of Intermediates

All of the eight cases reported in the colour factory have arisen among men who have worked on diazotization processes in colour synthesis. Seven have handled benzidine, and one both benzidine and alpha naphthylamine with the former as the major exposure. There have been no deaths among these men (Table 3). This factory, which opened in 1919, has used benzidine in one building and small amounts of alpha naphthylamine in another. The amount of benzidine used has increased eightfold over the past 31 years and has utilized practically the whole output from the intermediates section. Special precautions were extended in this factory at about the same time that cases arose among men manufacturing intermediates, but the first case did not arise in the colour factory until 1941. Since then only one man at a time has been handling and charging benzidine. The three men so employed consecutively have been volunteers. The first, who had 14 years' previous exposure to benzi-

TABLE 2

TYPES OF TUMOUR ENCOUNTERED IN THE MANUFACTURE OF INTERMEDIATES

Type of Exposure	Total Cases	Papilloma	Carcinoma	Papilloma Carcinoma
Benzidine	23	14^4	7^4	2
β Naphthylamine	15	8^1	7^5	—
α Naphthylamine	1	—	1	—
Mixed benzidine and α & β naphthylamine ..	16	5^2	9^3	2
Other	3	2	1	—
Total	58	29^7	25^{12}	4

The index figures relate to deaths.

Eight men left the firm and subsequently developed tumours. The period of exposure was from four to 11 years with an average of seven years. The average latent period ranging from nine to 20 years was 15 years, which is similar to the latent period for those who had not left the firm before developing tumours.

Types of Tumour.—Of the 58 cases, 29 had papilloma, 25 had carcinoma, and four had papilloma which recurred as carcinoma (Table 2). There is no striking difference in the incidence of benign and malignant tumours in the varying types of exposure in these small numbers, except that the men with mixed exposures had a higher proportion of carcinomata than other groups.*

* The pathology and treatment of these tumours will be the subject of another paper n collaboration with Mr. Poole-Wilson.

TABLE 3

CASES OF TUMOUR OF THE BLADDER IN HANDLING OF INTERMEDIATES (COLOUR FACTORY)

Type of Exposure	Total	Alive	Dead
Benzidine	7	7	0
Benzidine + α naphthylamine	1	1	0
Total	8	8	0

Exposure period ranged from 15 to 27 years (average 21 years)

Normal working strength ..	14
Total numbers exposed ..	86
No. cases	8

dine, developed a tumour a year later and was taken off at his own request ; the second was promoted to foreman after six years ; and the present one has handled and charged all the benzidine for three years. The latter two men have not developed tumours.

The normal working complement on the benzidine colours is 14 and the total number who have worked six months or more since 1919 is 86.

Exposure and Latent Periods.—All the men in this factory who developed tumours were still employed at the time of diagnosis and therefore the latent and exposure periods are the same. The shortest was 15 years and the longest 27 years with an average of 21 years. The cases among the men handling benzidine in the colour factory had a longer average exposure (21 years) than those manufacturing (16 years), and the first case among the handlers arose seven years later. It is reasonable to assume, therefore, that the intensity or the nature of the exposure in the manufacturing process was a determining factor in producing tumours earlier than in handling.

Age at Diagnosis of Bladder Tumours

Of the 66 cases, 40 entered the industry before the age of 30, 17 between the ages of 30 and 40, and nine after the age of 40. It will be seen from Table 4 that of those under 30 the average age of onset of tumour was 42 and of death was 44 ; of those between 30 and 40 the average age of onset was 51 and of death 54 ; and in those over 40 the average age of onset was 58 and of death 66. From the Registrar General's figures for 1947 the average age of death of 1,417 males in England and Wales who died of neoplasms of the bladder, urethra, and ureter was 67·5 years. Stocks (1950) took records of cases of cancer of the bladder and ureter from 275 hospitals in England and Wales in 1945. He found that the average age of all cases at first attendance was 62·3 years and at death 66·3 years. These figures emphasize the shortened expectation of life of men who are exposed to carcinogens before the age of 40 and develop bladder tumour. Thus, there is a strong argument in favour of excluding young entrants from processes where the hazard of bladder carcinogens can even be suspected. It has been the policy in recent years in this factory to debar men under 30 from such plants and to prefer healthy men over 40.

TABLE 4

AGE AT DIAGNOSIS OF BLADDER TUMOURS (ALL CASES)

Age on Entry	Under 30	30–40	Over 40
Number of cases	40	17	9
(Number of deaths)	(10)	(5)	(4)
Average age at diagnosis of tumour	42	51	58
(Range)	(25–52)	(41–62)	(47–66)
Average at death	44	54	66
(Range)	(34–51)	(51–60)	(61–69)

Future Prevention

Methods of prevention at first followed the usual lines. Technical improvements in the plants and processes, some of which have been indicated, have been applied. Men are carefully selected by pre-employment examination with consideration given to age, family history, and previous health ; strict hygienic measures such as special working clothing and daily bathing are obligatory ; regular medical supervision is carried out ; and although routine periodic cystoscopy of all workers is not yet applied, routine examination of the urine for red and white blood cells is done on all workers monthly. But with the possibility of such a high morbidity and early mortality arising from these processes more radical measures were deemed to be essential. Delayed by the war with its greater priorities, a new benzidine plant in which all possible precautions are taken to obviate contact between the operator and the carcinogens has now been built on a new site and will be in production this year. The old plant will be pulled down. Apart from a small number of key men, whose experience is needed and who will be selected from those who have had tumours and are cured, new men from the older age groups, with no previous exposure, will be selected and trained for this job. Thus, should any of these new men develop tumours it will be possible to attribute them solely to exposure on this plant when assessing the incidence.

Beta naphthylamine manufacture ceased a year and a half ago, as soon after the war as technical exigencies permitted, and sulphonation of beta naphthol followed by amidation is now the method used for preparing beta naphthylamine sulphonic acids in the synthesis of the colours for which beta naphthylamine was previously used as an intermediate.

In the future it should be possible to know whether or not these hazards have been controlled, but the time necessary for the development of tumours may be so long that we cannot be sure that the problem has been mastered until a whole generation has been unaffected. A list has been compiled, and is kept up to date, of all men who are known to have worked more than six months with carcinogens

since 1918. As even shorter exposures may come to be accepted as sufficient to initiate a tumour, careful records are now kept of any exposure, however short, and no cross transfers are permitted between departments where carcinogens are manufactured or used.

Summary

Sixty-six cases of bladder tumours in a dyestuffs factory are reported.

The methods and history of manufacture and handling are described.

Of the 66 cases there were 30 (23 in the manufacturing section and seven in the handling section) whose exposure was to benzidine, and which had never been exposed to beta naphthylamine. Benzidine is therefore considered to be as dangerous a carcinogen, industrially, as beta naphthylamine.

The role of beta naphthylamine as a bladder carcinogen in manufacture and experimentally has previously been accepted, and 15 cases are attributed to it alone and others to mixed exposures. Beta naphthylamine as an impurity cannot be eliminated as a cause of bladder tumours in men who worked on alpha naphthylamine.

No cases have been traced which can be attributed to aniline, despite the longer time of manufacture and periods of exposure, and the similar numbers engaged on it compared with benzidine and beta naphthylamine.

Three other exposures are described in which the cause of tumour was doubtful or unknown.

Exposure, latent periods, and ages at diagnosis and death are discussed.

Men under the age of 30 should not be employed in the manufacture or handling of substances known or suspected to be bladder carcinogens and, when possible, healthy men over 40 should be employed on these processes.

This paper would not be complete without an expression of gratitude to Mr. J. B. Macalpine and his successor Mr. D. S. Poole-Wilson, the urologists who have had these cases under their care.

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