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TUMOURS OF THE URINARY BLADDER IN WORKMEN ENGAGED IN THE MANUFACTURE AND USE OF CERTAIN DYESTUFF INTERMEDIATES IN THE BRITISH CHEMICAL INDUSTRY

PART I. THE ROLE OF ANILINE, BENZIDINE, ALPHA-NAPHTHYLAMINE, AND BETA-NAPHTHYLAMINE

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The Scope of the Report

The genesis, history, and achievements of the Association of British Chemical Manufacturers' research scheme for the investigation of tumour of the urinary bladder in a section of the chemical industry have recently been described in some detail by the Association (1953). The present paper is the result of a five-year field survey of the problem conducted in the factories of, and amongst the work-people employed by, a group of interested member firms of the Association which had contributed towards the cost of the research. Part I has been written in two sections, the one, in narrative form, is the report proper and does not presuppose any detailed medical or statistical knowledge on the part of the reader ; the other is an appendix where some of the statistical manipulations to which the data have been subjected are set out in full. In Part II, which will be published in this journal shortly, the results relating to auramine or magenta reported herein will be considered in more detail. Both parts have been used as a basis for the recent legislation whereby tumour of the bladder occurring in certain occupations has been prescribed for benefit under the National Insurance (Industrial Injuries) Act (Statutory Instrument. No. 1740, 1953).

It was laid down in the terms of reference that the function of the field survey was to establish whether the manufacture or use of aniline, benzidine, α-naphthylamine or β-naphthylamine could be shown to produce tumours of the urinary bladder in men so engaged. Accordingly, the scope of this report has been limited to this topic, with but minor digressions to consider other possible causative substances. Furthermore, many medical aspects of the problem have been ignored or simplified. Both cancer of the bladder and papilloma of the bladder have been considered as an entity, after a purely statistical investigation to see that they could be so considered, and treatment has been ignored.

Historical

In 1895 the German surgeon Rehn reported what he considered to be an undue incidence of bladder tumours in a group of men employed in the manufacture of fuchsine (magenta), and he concluded that aniline was the most suspicious of the substances used in this process. From this supposition the term " aniline tumour of the bladder " stemmed, and has since become current in medical textbooks. Since this time there have been numerous reports from Great Britain, Germany, Japan, Switzerland, France, Italy, and America on this topic, and unanimity of opinion has been reached only about β-naphthylamine, which has been generally accepted as a cause of human bladder cancer. α-Naphthylamine has been suggested as a possible cause by some authorities, and strenuously denied this status by others. Those who believe that α-naphthylamine is dangerous seem to have tacitly accepted that the substance acts

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because it always contains a small proportion of β-naphthylamine. Benzidine has also been a subject of controversy, and, though American opinion on the whole seems to favour the theory that this substance is not a cause of bladder tumour, the opposite view seems to be held in Europe. There never appears to have been much evidence to implicate aniline as such, although the original observations on the manufacture of magenta were certainly valid.

Hueper, Wiley, and Wolfe (1938) conclusively showed that β-naphthylamine, in its commercially available form, caused bladder tumours in dogs, and Bonser (1943) confirmed these observations using a partially purified product. No convincing evidence of induction of bladder tumours by aniline, α-naphthylamine or benzidine in dogs or other animals has yet been produced although Baker (1950) claims bladder tumours in mice from 3 : 3′ dihydroxy 4 : 4′ diaminodiphenyl which he considered to be a metabolite of benzidine ; and Spitz, Maguigan, and Dobriner (1950) have induced tumours in other situations with benzidine itself. The evidence that pure β-naphthylamine or one of its metabolites are the only active carcinogens concerned in the production of tumours by this substance is not yet completely convincing, despite the work of Bonser, Clayson, and Jull (1951) who induced bladder tumours in mice by implanting paraffin wax pellets containing 2-amino-1-naphthol into the bladder, since Case and Pearson (1952) have demonstrated carcinogenic impurities in commercial β-naphthylamine and in what had previously been considered as " pure " β-naphthylamine. For the purposes of this report, therefore, the terms aniline, benzidine, and naphthylamine will mean these substances as encountered in industrial practice, and will not mean these substances as pure chemicals in the sense that an organic chemist might use such a term.

Goldblatt (1947) and Müller (1949) have reviewed the risk in industry at length, and Bonser (1947) has discussed the experimental aspects of the problem.

Sources of Information

The following sources of information have been available :—

Cases of Bladder Tumour in the Industry.—This is found in cases reported by firms ; cases found in hospital records and confirmed by firms ; cases found in hospital records and confirmed by the patient or near relative ; cases found from an examination of death certificates where the chemical industry was mentioned as the occupation of the deceased ; cases found from a cross-check between a nominal roll of persons known to be at risk and all the names collected by the means listed above ; cases found in coroners' records.

The Populations at Risk.—The firms participating in the scheme were asked to provide a nominal roll of all workers known to have had any contact with aniline, benzidine, α-naphthylamine or β-naphthylamine, stating the age of the worker and the dates between which he was exposed to these substances. Twenty-one firms complied with this request to the best of their ability, and a reasonably complete nominal roll from 1920 was compiled.

Natural History of the Incidence of the Disease in Males in General Population.—All death certificates mentioning bladder tumour for males dying in England and Wales between the years 1921 and 1949 were available. Many hospitals collaborated by allowing the use of their records for recent years.

Processes and Local Conditions.—All the participating firms cooperated by allowing complete facilities to inspect processes, and by collecting works-history data of cases known to have occurred in their factories.

Many other firms, members of the A.B.C.M. but not participating in the scheme, helped by giving information about ex-employees who developed bladder tumour.

The Nature of the Problem

Tumour of the urinary bladder occurs in both sexes in the general population. It is more frequent in males (about 2·5 males to 1 female) and is predominantly a disease appearing in the later years of life. Only 14% of all adult male deaths in England and Wales from the disease occur before the age of 55. Although the disease may be divided roughly into papilloma and cancer of the bladder, death certificates show that at death 88% of the deaths from bladder tumour are attributed to cancer and 12% to papilloma or benign tumour. This figure applies to all male deaths in England and Wales. In the cases found in the chemical industry this proportion is 94% cancer and 6% papilloma. This difference is of no statistical significance ; in other words, there is no special tendency for industrial tumours to be either more or less predominantly papilloma than non-industrial ones, as judged from death certificate data. The disorder, tumour of the bladder, must be regarded as a killing disease ; only 20% of all cases found by this survey in the dyestuffs industry survived more than 10 years from the first recognition of the disease. Since, as will be shown later, the age of onset of the industrial form of the disease depends almost entirely on the age of entry into the relevant occupations, this high case mortality is serious. All patients who develop bladder tumour are not, of course, eventually certified as having a bladder tumour at death. Out of 819 cases notified by hospitals and known to be dead, 666 (81·3%) had a mention of bladder tumour on the death certificate.

Limitations of the Statistical Analysis

The accuracy of any statistical analysis is limited by the accuracy of the information upon which it is based. In the present study it often happened that the only data now in existence are those provided by the participating firms, and such data were not recorded for this purpose. Although such information has been examined most carefully as to its validity before incorporating it in this report, and where corroborative evidence, such as coroners' and factory inspectors' reports, was available, such additional information was always sought, the underlying possibility of inaccuracy must be borne in mind in interpreting the results.

There will be a tendency for the information to become less reliable as the period for which it is collected becomes more remote, and, as with some other occupational hazards which also occur in the general population, some of the cases which should properly have been assigned to occupational causes will have escaped notice as such, especially in areas of the country where medical opinion has not been focused on the hazard.

In the statistical analysis, only cases appearing on the nominal roll are used, and care was taken to ensure that no cases were placed on the nominal roll solely because it was known that they had developed a tumour. Thus, although in more remote times the nominal roll itself is too small, the tendency will always be to underestimate the industrial hazard through failing to trace all cases.

Certain conclusions drawn have only a statistical significance, with which implication the word is used in this report, therefore extrapolation from these conclusions should only be made with caution. For example, it will be shown that there is a slightly increased tendency for men entering the hazardous occupation at a more advanced age to develop tumours than for men entering at an earlier age. This does not necessarily imply any biological difference in susceptibility since, for instance, it could be explained on the hypothesis that older entrants are given more responsible jobs which would necessarily involve more exposure to the dangerous material.

Another example of the limitation of the term " significant " occurs where the statistical analysis of the data shows that the induction time* is independent of the exposure time. This does not mean that such a conclusion would be reached by animal experiments, or even by a very detailed analysis of short exposure times, but that within the rather coarse groupings of exposure times and induction times used, the two times are independent. Therefore it is legitimate to use the observed shape of the distribution of induction times as a basis for analysing the expected rate of appearance of cases.

The scope of the analysis is limited severely by the small number of cases that can be expected to occur since 1945, a date when, in accordance with earlier appreciation of the risk, certain sweeping changes in plant design were introduced. It is quite impossible at this stage to predict what effects these changes may have, and it will be realized that the slight reduction of risk noted in the post-1930 period is a mean value, and does not necessarily take into account the progressive results of these changes, which will have to await the judgment of posterity. Another limitation is the lack of knowledge of the relative importance of the different routes by which the dangerous substances may enter the human body, and of precise data about the operative concentrations of the substances met with and the amounts absorbed and eliminated.

Results

In all, by February 1, 1952, 455 cases of bladder tumour had been found in the British chemical industry. Four hundred and forty-four of these cases were found in and after 1921, the first year in which death certificates were available for a systematic search. Table 1 shows the distribution of these cases within the industry. Of the 341 cases occurring in employees of the member firms participating in the scheme, 298 (87·4%) had had contact with benzidine, β-naphthylamine, or α-naphthylamine, and only 32 (9·4%) were known not to have had such contact. It is necessary, as a starting point, to assess whether or not these 341 cases are more than could reasonably be expected by chance, on the assumption that the industry is exposed to only the same risk of developing bladder tumour as the general population. To do this it is necessary to form an estimate of the number of cases expected on this assumption, and this requires a knowledge of the population at risk. The nominal roll provides such knowledge in some detail, and of the 311 cases

* The length of time between first exposure to risk and the recognition of the tumour.

TABLE 1

THE DISTRIBUTION OF CASES OF BLADDER TUMOUR WITHIN THE CHEMICAL INDUSTRY

Date Group	Member Firms Investigated								All Others										Total All Groups	
	Contacts Include α-Naphthylamine, β-Naphthylamine, or Benzidine		Contacts Known not to Include α-Naphthylamine, β-Naphthylamine or Benzidine		Contacts not Known		Total		Employers not Known		Member Firms not participating in Scheme and not Investigated		Existing Firms not Members of A.B.C.M.		Firms no Longer Existing		Total			
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Before 1900	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1
1900–1904	0	0	0	1	0	0	0	1	0	1	0	0	0	0	0	2	0	3	0	4
1905–1909	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1	0	2
1910–1914	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	1
1915–1919	0	1	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0	2	0	3
†																				
1920–1924	0	3	0	0	0	1	0	4	0	8	1*	3	0	1	0	0	1*	12	1*	16
1925–1929	2	13	0	5	0	0	2	18	0	9	0	5	0	1	1*	3	1*	18	3*	36
1930–1934	3	18	2*	2	0	1	5*	21	0	11	0	6	0	0	0	1	0	18	5*	39
1935–1939	14	24	4	2	0	1	18	27	0	12	0	7	0	0	0	1	0	20	18	47
1940–1944	22	50	5	2	3	2	30	54	0	12	0	5	0	0	0	0	0	17	30	71
1945–1949	50	50	5	3	0	2	55	55	0	8	1	8	1	0	0	0	2	16	57	71
‡ 1950–	31	13	1	0	1	0	33	13	0	0	0	0	0	0	0	0	0	0	33	13
Total	122	176	17	15	4	7	143	198	0	65	2	34	1	2	1	9	4	110	147	308
Total	298		32		11		341		65		36		3		10		114		455	

Breakdown of the 298 cases (Contacts include α-naphthylamine, β-naphthylamine, or benzidine):

- Contacts include only α-naphthylamine of these three substances: 28
- Contacts include only β-naphthylamine of these three substances: 59
- Contacts include only benzidine of these three substances: 38
- Contacts include two or more of these three substances: 173

Breakdown of the 32 cases (Contacts known not to include α-naphthylamine, β-naphthylamine or benzidine):

- Contacts include aniline (also auramine in two cases) but not magenta: 4
- Contacts include magenta: 9
- Contacts include auramine but not aniline: 4
- Contacts include only substances not mentioned here: 15

Key: * Case where it is unknown if the patient has died.
† Death certificates not searched systematically until 1921.
‡ 1950 and subsequent death certificates not available at date of analysis.

which had had contact with aniline, benzidine, β-naphthylamine, or α-naphthylamine, 262 were persons whose names appeared on the nominal roll. This figure of 311 consists of 298 cases with contact with benzidine, α-naphthylamine, or β-naphthylamine, four with contact with aniline only, and nine with contact only with magenta.

A qualification for the nominal roll was that the persons must have been employed in the chemical industry for more than six months, though not necessarily in contact with the suspected substances. This limit was imposed because many firms did not provide records of men with shorter employment times, and, where such records were provided, a very large proportion of men worked for only a week or so. It was felt that these men would contain a high percentage of migrant types, whom it would not be possible to trace. The nominal roll used contains records of 4,622 men, who entered the industry at different times and at different ages.

Now it is not possible to estimate the number of cases of bladder tumour that would be expected from the 4,622 men if no special risk were attached to their work, but it is possible to form a reasonable estimate of the number of death certificates mentioning tumour of the bladder which would be expected on this assumption (Case, 1953a, b). This expected number is between 3 and 5 for the 4,622 men, all due allowance being made for the age of the men and their date of entry into the work with the four substances mentioned; and the number of death certificates mentioning tumour of the bladder found amongst the 262 cases whose names appear on the nominal roll was 127. There is therefore no doubt that a risk of dying of tumour of the bladder exists amongst that group of people who have had contact with aniline, benzidine, β-naphthylamine, or α-naphthylamine. In this group, that is those men who are known to have had contact with any of the four substances named and have been employed in the chemical industry for more than six months, even though their period of contact with any of the four substances was not necessarily six months, the data indicate that the overall risk of dying of bladder tumour is approximately 30 times that of the general population.

The Localization of the Risk within the Industry

It is now necessary to examine this group more carefully to see where the risk lies, and to see which of the specific substances mentioned can be implicated and which exonerated as causative agents. It seems very unlikely that the employees of the 21 participating firms could fairly be regarded as having equal chances of exposure to the suspected substances, but statistical analysis is hampered because no actual measure of exposure exists. It was therefore decided to consider the nominal roll in three sections, an arbitrary classification being made as follows:—

Group I.—The nominal roll of those firms which manufacture any one or more of the substances, aniline, benzidine, α-naphthylamine, β-naphthylamine; it will of course consist of men exposed in both manufacture and use, since these firms also use these substances. This group consists of 3,198 men.

Group II.—The nominal roll of those firms which use but do not manufacture any of these substances, excluding those firms whose use is confined to the purification of the substances for sale as fine chemicals. This group consists of 1,275 men.

Group III.—The nominal roll of those firms which only purify any of these substances: this group consists of 149 men.

The distribution of the 311 cases of bladder tumour which had had contact with one or more of these four substances, with the number of death certificates mentioning tumour of the bladder expected and found, is shown for each group in Table 2 (Rank 9), and it is apparent that Groups I and II have an undoubted occupational risk of dying with bladder tumour. The one death in Group III is suspicious considering the low expectation of such an event.

It is convenient here to depart from a logical sequence of development, and to discuss an indication the justification for which will be dealt with more fully later. This is that the age of death was 51 in the one dead case in Group III, and that the age of onset was 29 in the other case. Both these ages are low compared with the most frequent age of death (65–70 years) or onset (60–70 years) found for bladder tumour in the general population and this fact lends weight to the suspicion that an occupational risk is operating.

Thus we may say that the occupational hazard at work is most intense in Group I, less so, but still definitely present in Group II, and probably still operating in Group III.

The Localization of the Risk to Particular Substances

It is now necessary to consider the evidence for the implication of each of these substances as a cause of bladder tumour, again using the death certificate criterion since this is the most precise measure available.

Aniline.—This is considered separately as a special case, since, as will be shown, the effect of the substance is different from that of the remaining three substances.

When the compilation of the nominal roll by member firms was first requested, the possible importance of magenta was not realized, but all manufacturers of magenta are automatically qualified for the nominal roll in virtue of the fact that they must handle aniline, and it is possible to divide the aniline nominal roll into two sections. (1) That derived from firms where it is known that magenta is not manufactured; (2) that derived from firms where it is known that magenta is manufactured. Only a small proportion of the names on the second list will have been exposed to the manufacture of magenta. Ranks 1, 2, and 3 of Table 2 show the tumour cases and the expectation of death certificates from the aniline nominal roll divided in this way for the three groups of firms. It can be seen from these figures that there is not a sufficient excess of certificates found over certificates expected to

TABLE 2

THE NUMBER OF DEATH CERTIFICATES EXPECTED IF NO SPECIAL RISK WERE OPERATING AND THE NUMBER OF CASES AND DEATH CERTIFICATES FOUND FOR THE VARIOUS EXPOSURE CLASSES

Rank	Class	Group	Total No. of Cases Found	Cases on Nominal Roll			Cases on Nominal Roll where Death Certificate Mentions Bladder Tumour	Expected No. of Such Cases	% of Expected No. Derived from Incomplete Data	Significance of Difference	
				Total	Alive	Dead					P
1	Aniline without magenta contact	I	4	4**	2*	2*	1	0·30	35·8	None	>0·1
		II	0	0	0	0	0	0·23		None	>0·1
		III	0	0	0	0	0	0·01		None	>0·1
		All	4	4**	2*	2*	1	0·54		None	>0·1
2	Aniline with possible magenta contact	I	8	5	3	2	2	0·30	15·6	Suspicious	0·025
		II	1	1	0	1	1	0·05		None	>0·1
		III	0	0	0	0	0	0·00		None	>0·9
		All	9	6	3	3	3	0·35		Significant	<0·02
3	All aniline	I	12	9**	5*	4*	3	0·60	20·3	Suspicious	0·025
		II	1	1	0	1	1	0·28		None	<0·1
		III	0	0	0	0	0	0·01		None	<0·1
		All	13	10**	5*	5*	4	0·89		Suspicious	0·025
4	Benzidine	I	38	34	21	13	10	0·54	3·7	Very high	<0·001
		II	0	0	0	0	0	0·17		None	>0·1
		III	0	0	0	0	0	0·01		None	>0·1
		All	38	34	21	13	10	0·72		Very high	<0·001
5	α-Naphthylamine	I	28	19	13	6	6	0·66	3·2	High	0·005
		II	0	0	0	0	0	0·04		None	>0·1
		III	0	0	0	0	0	0·00		None	>0·9
		All	28	19	13	6	6	0·70		High	<0·005
6	β-Naphthylamine	I	59	55	28	27	26	0·30	4·1	Very high	<0·001
		II	0	0	0	0	0	0·00		None	>0·9
		III	0	0	0	0	0	0·00		None	>0·9
		All	59	55	28	27	26	0·30		Very high	<0·001
7	Mixed Exposures	I	162	135	50	85	75	1·15	13·5	Very high	<0·001
		II	9	7	0	7	5	0·32		High	<0·005
		III	2	2	1	1	1	0·006		Significant	0·005
		All	173	144	51	93	81	1·48		Very high	<0·001
8	All classes, excluding aniline	I	287	243	112	131	117	2·65	7·3	Very high	<0·001
		II	9	7	0	7	5	0·53		High	<0·005
		III	2	2	1	1	1	0·02		Suspicious	0·025
		All	298	252	113	139	123	3·20		Very high	<0·001
9	All classes	I	299	252	117	135	120	3·25	9·3	Very high	<0·001
		II	10	8	0	8	6	0·81		High	<0·005
		III	2	2	1	1	1	0·03		Suspicious	0·025
		All	311	262	118	144	127	4·09		Very high	<0·001

* also manufacturer of auramine.

warrant saying that aniline, as manufactured or used between 1915 and 1950, is a cause of bladder tumour.

Two other points require mention. (1) While, as the figures stand, there is only just enough excess of death certificates found over death certificates expected to be statistically significant in the magenta group, the whole picture is more strongly suggestive that magenta may be dangerous, since it is known that the nominal roll for the magenta group is much too large. (2) Two of the four cases occurring in the aniline group are also concerned with the manufacture of auramine, and there is some reason, as will be seen later, to suspect this substance.

Thus aniline, on present evidence, does not appear to be a cause of bladder tumour. If this conclusion is accepted for the purposes of this analysis, then men who have had contact with aniline and one other of the three substances benzidine, α-naphthylamine, or β-naphthylamine, can now be allocated to contact with that other substance only.

α-Naphthylamine, β-Naphthylamine, and Benzidine.—The remainder of the 311 cases which had had contact with one of the four substances mentioned above can be subdivided into the following exposure classes :—(1) Those who have had contact with benzidine only of the three substances. (2) Those who have had contact with α-naphthylamine only of the three substances. (3) Those who have had contact with β-naphthylamine only of the three substances. (4) Those who have had a mixed contact with two or more of the three substances.

Ranks 4 to 8 of Table 2 show the tumour cases, the number with bladder tumour death certificates, and the number of death certificates expected if no special risk existed for these exposure classes and for the three groups of firms. These data show that benzidine, α-naphthylamine, and β-naphthylamine are associated with an increased death certification rate from tumour of the bladder. It will also be seen that only 2·6% of all the cases with bladder tumour death certificates would be expected to be of natural occurrence. If this ratio is even approximately valid for the remainder, it means that the whole group of cases can be considered as consisting of virtually only occupational tumours, and accordingly will be so considered.

It is necessary to examine the works history of the cases to see what types of job give rise to this risk. The nominal roll does not give full occupational details, so that differential rates cannot be obtained. The job-analysis of the 298 cases which had contact with one or more of the three substances under consideration is set out in Table 3 for each exposure class of substance and for each group of firms, and an inspection of Table 3 shows that the substances benzidine, α-naphthylamine, and β-naphthylamine can cause bladder tumour in workers engaged in

TABLE 3

JOB ANALYSIS

Job	Group	I					II	III	
	Manufacture (M) or Use (U)	Benzidine	α-Naphthyl-amine	β-Naphthyl-amine	Mixed	Total Group I	Total Group II	Total Group III	Total All Groups
Scientific staff	M	0	0	0	0	0 } 2	0	0	0 } 4
	U	0	0	0	2	2	0	2	4
Foremen	M	2	1	5	5	14 } 21	0	0	14 } 21
	U	0	1	1	6	7	0	0	7
Processmen, pressmen, filtermen, labourers	M	25	17	37	56	135 } 224	0	0	135 } 226
	U	8	5	9	67	89	2	0	91
Stillmen not included in above..	M	1	2	0	1	4 } 4	0	0	4 } 6
	U	0	0	0	0	0	2	0	2
Weighmen	M	0	0	0	0	0 } 2	0	0	0 } 2
	U	0	0	0	2	2	0	0	2
Dryers and ovenmen	M	0	0	1	0	1 } 12	0	0	1 } 12
	U	2	2	2	5	11	0	0	11
Grinders	M	0	0	0	1	1 } 7	0	0	1 } 11
	U	0	0	0	6	6	4	0	10
Maintenance men, plumbers, and fitters	M	0	0	0	0	0 } 12	0	0	0 } 13
	U	0	0	4	8	12	1	0	13
Coopers and cask washers ..	M	0	0	0	0	0 } 3	0	0	0 } 3
	U	0	0	0	3	3	0	0	3
Total	M	28	20	42	63	153 } 287	0	0	153 } 298
	U	10	8	17	99	134	9	2	145
Total		38	28	59	162	287	9	2	298

either the manufacture or use of the material, and that the risk spreads through a wide variety of methods of coming into contact with the substances. A multiplicity of processes is covered by the jobs mentioned in the table, the extent of which is indicated by the following list.

Cases have been caused by the manufacture of both naphthylamines, their distillation, their flaking or stoving, their sulphonation, and the manufacture of sodium naphthionate ; the manufacture and use of the free bases, their hydrochlorides, and their sulphates.

The manufacture of benzidine and its isolation as the base ; the monohydrochloride, the dihydrochloride, and the sulphate, the use of benzidine and its salts.

The manufacture, drying, and grinding of finished colour prepared from the naphthylamines and benzidine, and the hand mixing of finished colour so produced.

The care and maintenance of plant for manufacturing the substances and for their sulphonation or conversion into finished colour.

The washing of casks contaminated with α-naphthylamine, β-naphthylamine, and benzidine, and the weighing out of these materials.

The purification of β-naphthylamine and benzidine, the total time involved being less than 100 working hours, has apparently caused one case, and longer exposure as a supervising chemist another case.

It is necessary to consider the characteristics of occupational tumours of the bladder in order that the course of events may be understood. The methods of determining the factors at work are technical, and the factors largely interdependent. It is therefore difficult to develop the argument in a strictly logical sequence ; some of the characteristics will be used before their meaning is discussed and, in general, the technical process of arriving at the characteristics will be dealt with in the statistical appendix. In these statistical procedures, unless otherwise stated, only the cases derived from Group I α- or β-naphthylamine, benzidine, or mixed contacts will be used. This is to avoid using a heterogeneous group, and to provide a standard measure of risk. The number of cases in the other two groups is too small to allow statistical conclusions to be drawn about the characteristics of induced tumours, but the cases can be used for comparison with Group I (see Table 9).

The first characteristics to be considered will be

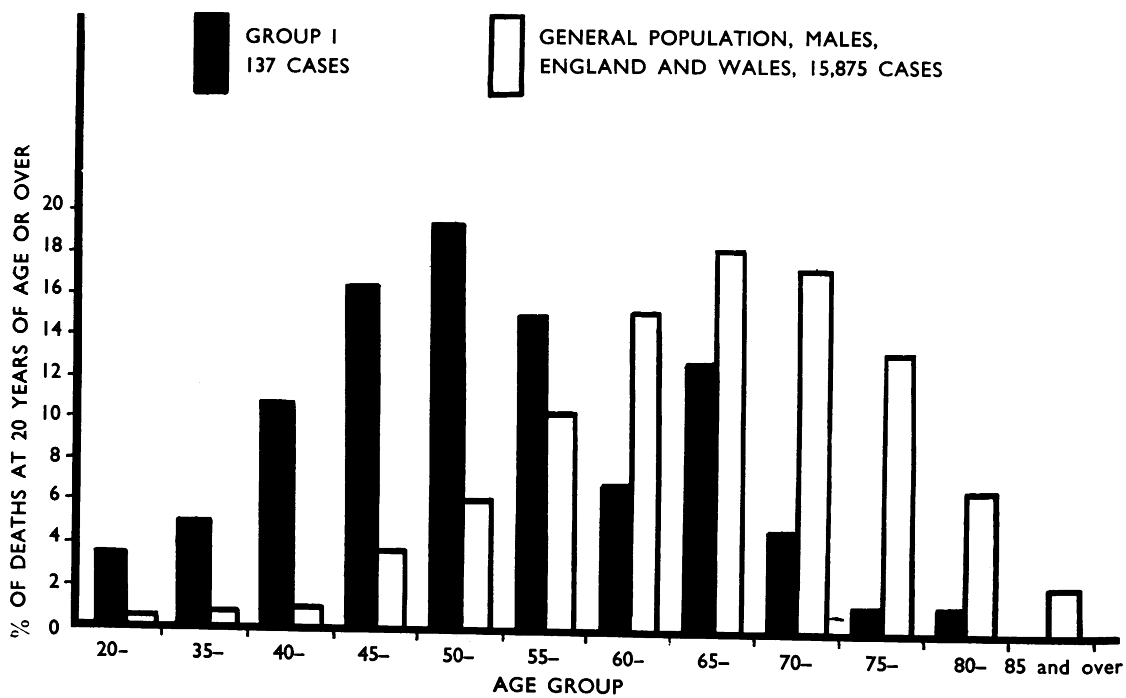

FIG. 1.—The age at death.

the age at which the tumours appear, and the length of time which elapses between the first exposure to risk and the recognition of the tumour. These will be termed the age of onset and the induction period respectively. The age at which naturally occurring tumours appear in the general population is required, but, since there is not enough information available to form a reliable estimate for the whole country, this cannot be determined at present, though such an estimate can be made for Birmingham and district (see Statistical Appendix). However, the age at death for all males in England and Wales whose death certificates mention bladder tumour can be determined for any year from 1921 to 1949, and therefore these figures are compared with the age at death of the 137 cases from Group I whose death certificates mention tumour of the bladder. (These cases are not all derived from the nominal roll.) Fig. 1 shows the percentage at each age group of the total number of deaths in each of these two groups for persons over 20 years of age.

It is shown that these 137 cases from firms in Group I died of bladder tumour at an earlier age than would be expected from the data relating to England and Wales, the most frequent age of death in the occupational group (50–55 years) being 15 years earlier than the most frequent age (65–70 years) in the general population. Thus the occupational hazard produces not only an increased number of deaths from bladder tumour, but also death from this complaint at an earlier age.

It now becomes pertinent to enquire whether this earlier age at death from bladder tumour is due first to a more limited survival time from the outset of the disorder; secondly to a selectively greater susceptibility to the disorder in younger men; and thirdly to a relationship between the age at exposure to risk and the age at onset, or whether some combination of these factors is at work. The first of these hypotheses cannot be tested directly by comparison with survival times since proper hospital records have not been available for a long enough period. An approximate answer can be given by comparing the age at onset of the group of chemical workers with the age at onset of a group of 750 male cases of bladder tumour reported from the Birmingham hospitals between 1936 and 1951. This comparison is given in Fig. 2, which shows clearly that the movement to lower age groups is still very marked, the most frequent age of onset of the chemical workers in firms in Group I (40–50 years) being 20 years earlier than the most frequent age of onset for Birmingham males (60–70 years). It is thus apparent that the earlier age at death is not due to a more limited survival time.

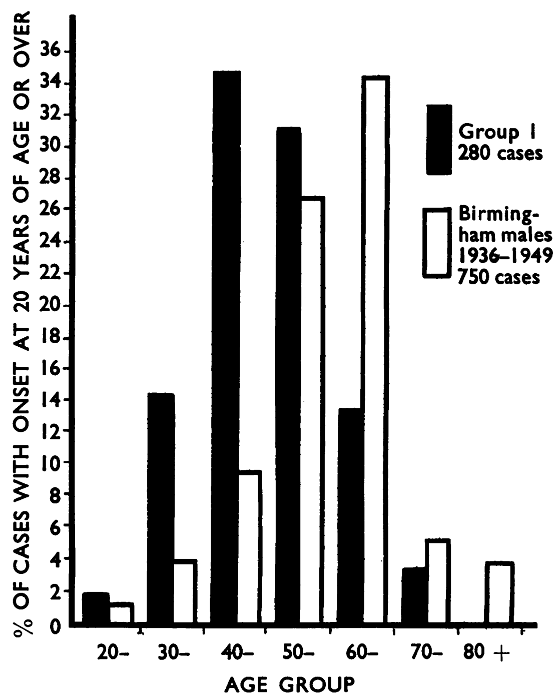

FIG. 2.—The age at onset. In a further seven cases, ages at onset were not known.

The second hypothesis was tested by calculating the number of cases that would be expected from persons entering any of the hazardous occupations (exposure to benzidine, α-naphthylamine, or β-naphthylamine) in the different age groups at the time of entry, on the assumption that this played no part in the production of tumours, and comparing the expected number with the number actually found, and these figures are shown in Table 4. It is shown that an older age of entry into risk increases somewhat the chance of developing a tumour, and therefore the earlier age of onset is not due to an increased susceptibility of younger persons.

The third hypothesis was tested by plotting the average age of onset against the age at entry in age groups. The result of this calculation is shown in Fig. 3. This shows that the age of onset is dependent almost entirely upon the age of entry, the induction period being nearly constant. The lack of complete agreement shown can be accounted for by the increasing loss of men who might otherwise develop bladder tumours by death from other causes in the older age groups. For all practical purposes, the younger a man is when he enters risk, the younger will he be when he gets a tumour, and the most common time to develop a tumour will be between

TABLE 4

NO. OF EXPECTED CASES IF AGE AT ENTRY HAD NO EFFECT ON INCIDENCE AND NO. FOUND

Age at Entry	Expected No. of Cases Allowing for Death from All Causes at 1931 Rates	Tumours Found
Under 20	22	13
20–	109	90
30–	74	75
40–	29	52
50–	5	8
60 and over	0	0
TOTAL	239	238
Unknown	—	5
	Total	243

$\chi^2 = 27{\cdot}6$
$n = 4$
$P < {\cdot}001$

15 and 20 years after starting work in the dangerous environment.

The apparent constancy of the average time from first exposure to development of a tumour for each age group of entry into risk suggested that the induction time should be studied further. Accordingly, the induction times of all cases in each exposure class were examined, and the average time and the scatter around it determined. The values are benzidine exposures 16 (S.D. 5) years, α-naphthylamine exposures 22 (S.D. 6) years, β-naphthylamine exposures 16 (S.D. 6) years, mixed exposures 18 (S.D. 7) years, and the mean for the combined series 18 (S.D. 7) years. The mean induction time for benzidine and β-naphthylamine is the same, but there is a real difference between this time and that for α-naphthylamine, where the mean time is six years (37·5%) longer. The spread of the induction times for all the cases pooled together is shown in Fig. 4. (The superimposed normal curve is discussed in the appendix.) This shows that while the most frequent induction time is between 15 and 20 years from exposure, tumours can develop within five years or after 45 years from the first entry into risk. This is of practical importance because it means that it is possible for a case of bladder tumour to be of occupational origin even if the induction time is very short or very long.

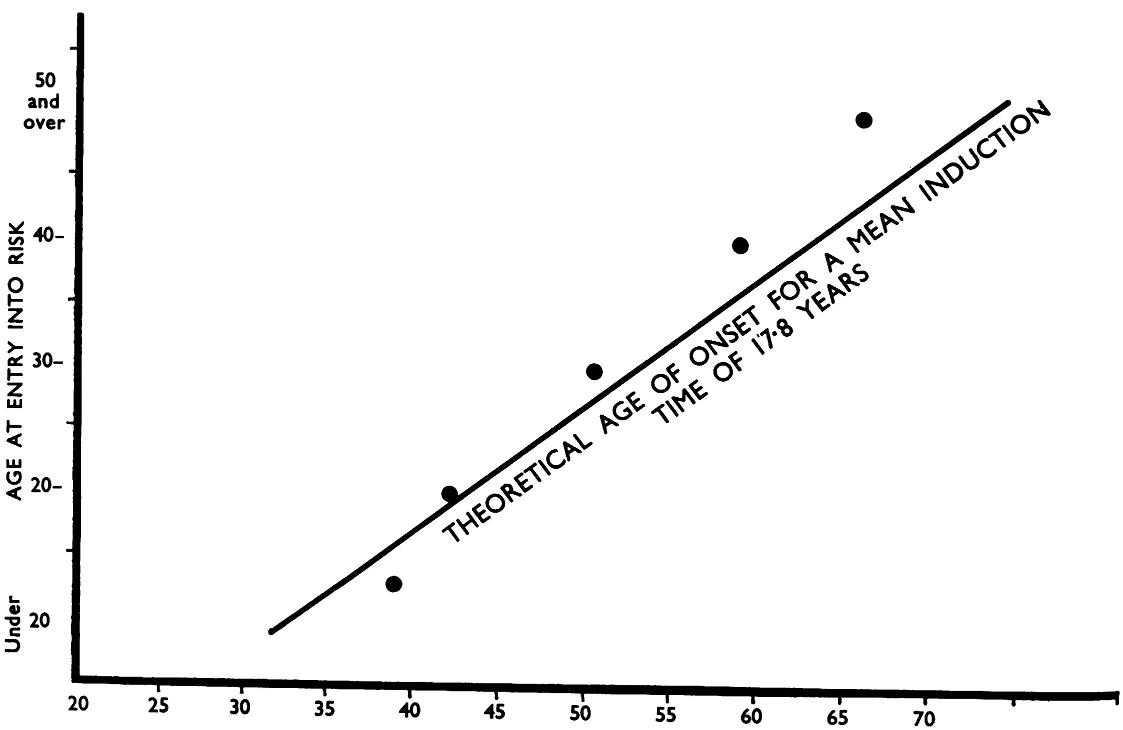

FIG. 3.—Age at entry and age at onset.

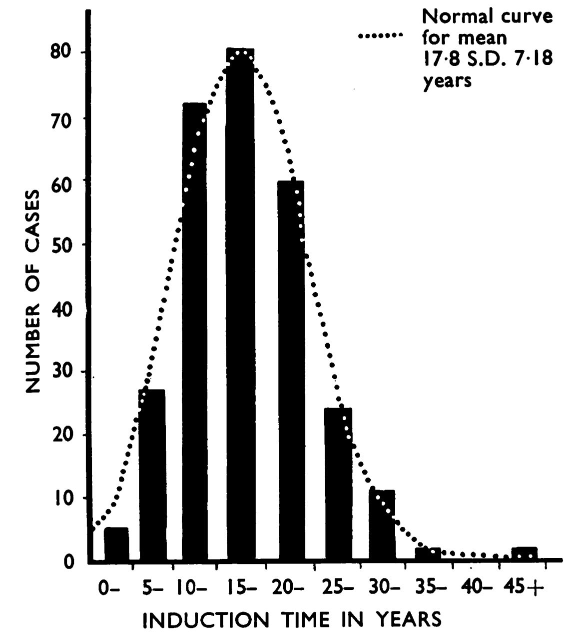

FIG. 4.—The distribution of induction times in Group I (281 cases). In a further six cases induction times were not known.

It is necessary to see whether the variation in induction time is an expression of the dose of the noxious material encountered. If it is such an expression, then men receiving a smaller dose should tend to get tumours after a longer interval, and men receiving a larger dose after a shorter interval. No direct measure of the dosage received is available but it is reasonable to suppose that the length of exposure will be some sort of indication of the amount of the substance encountered. However, there will obviously be a number of patients who have worked in the hazardous environment until the onset of the disorder, and here of course the length of exposure and the induction time will be identical. There will also be a number of men where the induction time exceeds the exposure time. In all, there are 281 cases in Group I where both the exposure and induction times are known. These 281 cases are shown in Table 5, subdivided into groups according to the length of the two times. The number of cases in each group that would be expected if the exposure time did not affect the induction time has been calculated and is also shown. The method of calculation is discussed in the appendix. There is no trend to suggest that there is an association between short exposure times and long induction times, or vice versa, and the deviations from the expectation are no more than could be reasonably attributed to chance variations of sampling.

Another more approximate measure of the severity of exposure might be the supposition that manufacturers of a substance will be more heavily exposed than users. If this is so and if the severity of exposure did affect the induction time, then the manufacturers should show a preponderance of shorter induction times and a shorter mean induction time. Table 6 shows the number of cases in each group of induction times that would be expected in users if severity of exposure had no effect, and if there were equal numbers of users and manufacturers, and also the number actually found. The observed differences are no greater than could easily occur by chance. The mean induction time of the manufacturing group (17·7 years) does not differ from that of the using group (18·3 years) by more than might occur by chance. Thus it may be concluded that the severity of exposure, as judged by these methods, has no effect on the induction time of the disorder. The mean induction time in Groups II and III combined, where, as will be shown later, the risk is much smaller, does not differ materially from these figures. It would therefore appear that this mean induction time is characteristic of the particular substance concerned, and not dependent on the severity of the exposure. The fact that, within the terms chosen for the analysis, these factors are independent makes it possible to use the observed distribution of the induction times as a basis for calculating the expected appearance of tumours, and the underlying principle of the subsequent analysis rests upon this independence.

Another implication of the independence is that the difference of the mean induction times for α-naphthylamine and β-naphthylamine suggests that the β-naphthylamine content of the α-isomer may not be the sole active agent, unless α-naphthylamine exerts a delaying action on the rate of development of β-naphthylamine tumours.

Severity of the Incidence in Population at Risk at Different Times

It is necessary to consider how the incidence in the population at risk varies at different times, and what factors influence this variation. Accordingly the nominal roll for Group I was divided into groups who started work in the hazardous occupations in the years 1910–1919, 1920–1924, 1925–1929, and so on in five-year groups to 1945–1949. Each group was further subdivided into the length of time which the man remained in the occupation. This subdivision was carried out for each class of benzidine

TABLE 5

NO. OF CASES FOUND AND EXPECTED IN EACH EXPOSURE TIME GROUP IF LENGTH OF EXPOSURE DOES NOT INFLUENCE INDUCTION TIME: GROUP I

Exposure Time in Years		Induction Time in Years 0–	1–	5–	10–	15–	20–	30 and over	Total	χ^2
0–	Found	0	1	0	2	1	3	0	7	χ^2 = 0·30, n = 1, P = ·75
	Expected	0·0	0·1	0·8	1·9	2·0	1·9	0·3	7·0	
1–	Found		4	10	9	12	19	0	50	χ^2 = 6·36, n = 3, P = ·075
	Expected		3·0	5·4	13·7	14·5	14·4	2·0	50·0	
5–	Found			17	20	12	9	0	41	χ^2 = 6·66, n = 2, P = ·04
	Expected			16·2	12·7	13·3	13·2	1·9	41·1	
10–	Found				41	8	7	1	16	χ^2 = 0·00, n = 1, P = ·99
	Expected				41·6	7·5	7·4	1·1	16·0	
15–	Found					47	11	2	13	χ^2 = ·007, n = 1, P = ·96
	Expected					43·7	11·4	1·6	13·0	
20–30	Found						33	12	127	χ^2 = 5·54, n = 4, P = ·25
	Expected						43·2	6·2	127·1	
Total	Found	0	5	27	72	80	82	15	281	χ^2 = 2·99, n = 4, P = ·6
	Expected	0·0	3·1	22·4	69·9	81·0	91·5	13·1	281·0	

Total: χ^2 = 18·87, n = 12, P = ·1

The dotted lines indicate groups combined in carrying out χ^2 test which is discussed in the statistical appendix.

TABLE 6

THE EFFECT OF MANUFACTURING OR USE ON THE INDUCTION TIME

Induction Time (years)	Under 5	5–	10–	15–	20–	Over 30	Mean and S.D.
Cases found in the manufacturing group	2	18	38	47	35	9	18·18 ± 8·5
Cases in user group calculated for a group of equal size	3	14	35	43	43	11	17·63 ± 7·3
Difference of Distribution χ^2 = 4·09, n = 4, P = ·4	The dotted line indicates groups combined together in carrying out the χ^2 test.					Difference of means χ^2 = 0·55, t = 0·72, P = ·4	

exposure, α-naphthylamine exposure, β-naphthylamine exposure, and mixed exposure, and also for all these exposures pooled together. The cases derived from the nominal roll were arranged in similar subdivisions, so that the percentage incidence arising from each subdivision could be calculated. Fig. 5 shows the percentage of the population in each group according to the date of starting developing bladder tumour, irrespective of the date of tumour development, age at entry, or length of service. This figure is calculated from the pooled classes. (The superimposed cumulative normal curve is discussed in the appendix.) It is seen that as the date of starting gets earlier the percentage of the population affected gets larger, until a steady level of just under 20% of the original population being

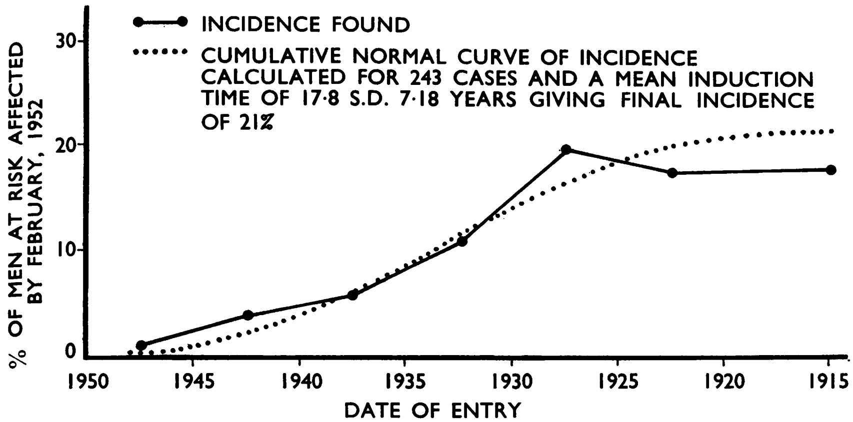

FIG. 5.—The crude incidence at different times. Pooled exposures in 243 cases of Group I.

effective exposure, which is defined as the length of time of exposure necessary for the particular class of exposure to produce the average risk for that class of exposure.

The number of cases of tumour occurring in each grouped length of exposure class, using the groupings shown, was found, and the figures expressed as a percentage of those expected if the length of exposure had no effect, i.e., the figure for the mean effective exposure is called 100%. The results of these calculations are shown for each class of exposure in Fig. 7. From this it can be seen that the length of exposure has in all classes a profound effect on the number of cases produced, and that the mean effective exposure is reached after a varying exposure time. It is also shown that the risk of developing a tumour increases to a maximum and then decreases for men who have been employed for a long time. This strongly suggests that for a given level of risk, where risk is the sum total of all factors causing bladder tumour, there are members of the population being considered who are susceptible to the disorder and members who are not. Altering the

affected is reached. It becomes necessary to find out which factors other than the induction times are responsible for the shape of this graph. It might be that in earlier times exposures were greater and protective methods less good ; it might be that men were exposed for longer periods in earlier years, or it might be that some combination of these factors is at work. It is also necessary to see whether each of the three substances produces a similar or dissimilar severity of incidence. Fig. 6 shows a graph for each of the four classes of exposure that were combined in Fig. 5. Although these graphs show obvious dissimilarity, a consideration of this must be postponed until the effect of the length of exposure has been evaluated.

There is already a suggestion that the severity of exposure affects the number of cases that will be found, since relatively fewer cases occurred amongst the employees of Group II and III firms. The length of exposure may, as said before, be regarded as some measure of the severity of exposure. The graphs already considered (Figs. 5 and 6) did not take any account of the length of exposure in each date group of entry into work. They may thus be regarded as being calculated from the mean

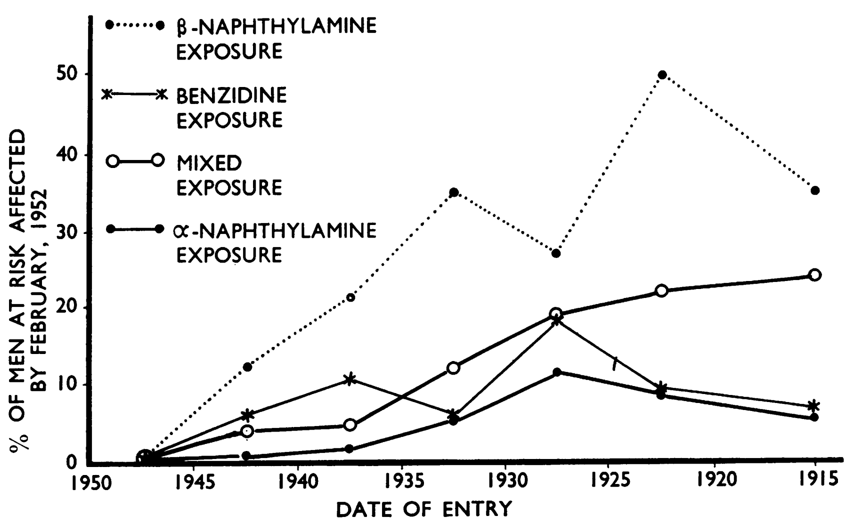

FIG. 6.—The crude incidence at different times by exposure class.

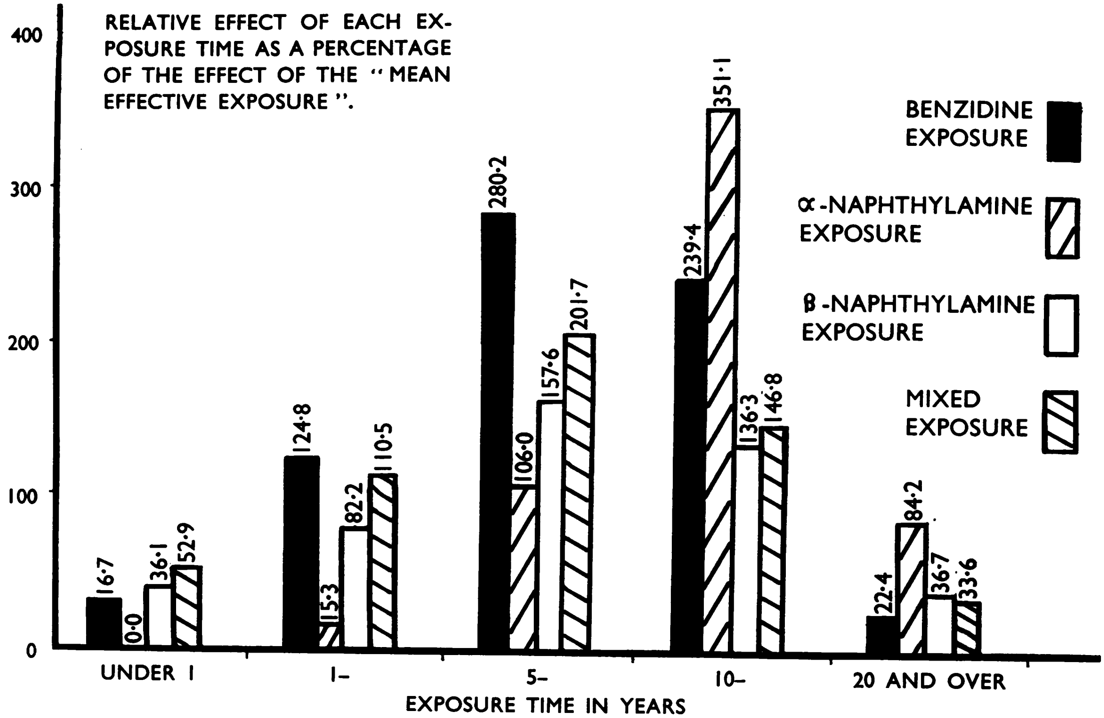

FIG. 7.—The effect of exposure time by exposure class.

level of risk will alter the relative proportions of these two groups, and it is probable that a high enough level would produce a 100% affected group and a low enough level an almost unaffected group. The fall in the severity of incidence after long exposure times means that most of the persons who will be affected have already contracted tumours, and so have been removed from the figures available for calculation. This apparent immunity is a statistical concept. It may be due to the fact that the population at risk consists of some who really have little or no contact with the substance concerned; that some of the men acquire a "know-how", either conscious or unconscious, that enables them to avoid risk; that inherently in themselves they possess a resistance; or that more than one of these factors is at work.

Whatever the actual explanation of the graph, from a practical aspect it means that exposures of less than one year to benzidine, β-naphthylamine, and mixed exposures have already produced sufficient effect to make it impracticable to attempt to obviate the risk solely by reducing the employment time. α-Naphthylamine appears to require a longer exposure for equivalent effect, but too much reliance should not be placed on the low incidence found at very short exposures, since the number of cases available for study is very small, and therefore the conclusions tend to be unreliable.

Applying this knowledge of the effect of the exposure time on the number of tumours produced, it becomes possible to represent graphically the tumour incidence that would occur at different times if all the exposures had been of the same length, namely of the mean effective exposure. In this way the number of tumours that would have occurred in the nominal roll for each class of substance had the men been exposed for the mean effective exposure to a standard substance that has a mean potency can be calculated, and is shown in Table 7. (A standard substance is defined as a hypothetical substance whose activity in the production of bladder tumours represents the average activity of the substances actually met with by the men at standard risk, and a mean potency as the average measure of the power of the standard substance, with exposure for the mean effective exposure time to produce tumours in a population at risk of known size observed from the date of entry into risk after 1910 until 1952.) A comparison of these numbers

TABLE 7

EFFECT OF THE EXPOSURE CLASS

Exposure Class	Benzidine	α-Naphthyl-amine	β-Naphthyl-amine	Mixed Exposures
No. of cases expected ..	47·0	46·9	25·5	124·0
No. of cases found ..	34	19	55	135
Relative potency	72%	41%	216%	109%
Ultimate relative potency	68%	58%	185%	127%

with the numbers actually found gives a measure of the relative potency of each individual compound expressed as a percentage of the mean potency; where the relative potency is defined as the average measure of the power, expressed as a percentage of the mean potency, of a specified class of exposure, with exposure for the mean effective exposure time for that class of exposure, to produce tumours in a population at risk of known size, observed from the date of entry into risk after 1910 until 1952.

Statistical tests show that this relationship between the substances held true generally over the period between 1915 and 1950. Thus it can be said that, under the exposure conditions obtaining in the Group I firms between these dates, β-naphthylamine has been the most potent cause of bladder tumour, followed by mixed exposures, then by benzidine, with α-naphthylamine the least potent of these substances. β-Naphthylamine has been about five times as potent as α-naphthylamine, and three times as potent as benzidine.

However, the differing mean induction times for the different substances suggest that this may underestimate the relative potency of the substances with the longer induction times. Therefore a measure, called the "ultimate relative potency", has been calculated and is necessary to express what these relationships would be when all the expected cases at the mean risk have developed, on the assumption that men die of all causes at 1931 rates. This measure is defined as the measure of the power, expressed as a percentage of the ultimate mean potency, of a specified class of exposure, with exposure for the mean effective time for that class of exposure, to produce tumours of the bladder in a population at risk of known size observed until all have died, on the assumption that death from all causes acts at the 1931 rate for males in England and Wales. These ultimate relative potencies are also shown in Table 7. It can now be seen that the relative potencies of α-naphthylamine and mixed exposures have been underestimated and that of β-naphthylamine overestimated by the relative potency figures.

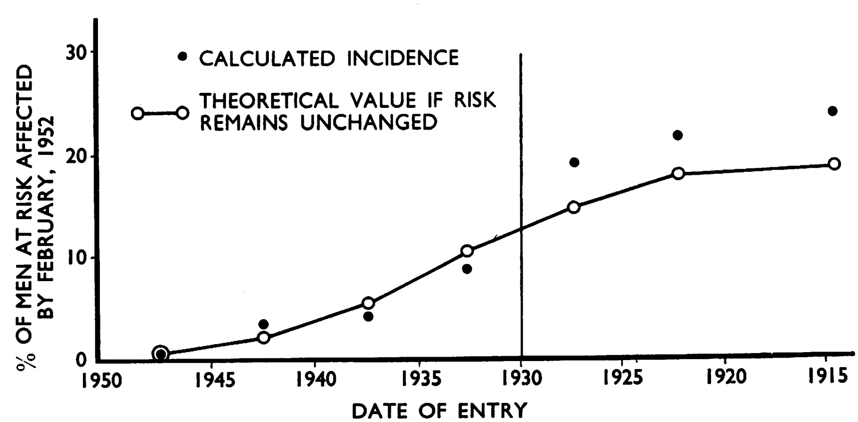

FIG. 8.—The incidence at different times calculated from the mean effective exposure time and the mean potency in 243 cases of Group I.

Effect of Changing Conditions and Altered Techniques on the Incidence at Different Times

The only factors so far investigated that affect the final incidence of tumours are the type of substance encountered and the length of exposure. Fig. 8 shows what the result would be if all the men had been exposed to each exposure class for the mean effective exposure time, and, by the use of the potency factors, if all the men were working at the mean potency. This removes chance influences due to the number of men working on a particular substance at a given time, and to different movements of labour that may take place at different times. The incidence in the population at risk entering the relevant occupations at different dates increases, slowly at first, then more sharply, and then again slowly, with the passage of time since starting work. The highest figure reached is about 24%, and a time will come when the final incidence is reached since deaths from all causes will leave no more men in the original population to be affected.

The data that have been collected about the induction times make it possible to calculate a

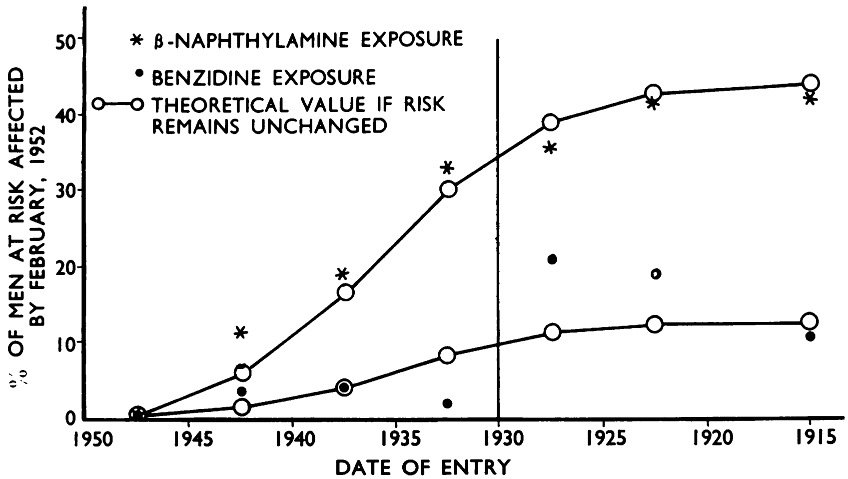

FIG. 9.—The incidence at different times by exposure class.

graph of the way in which the incidence figures would behave if it is assumed that the "danger-value" of exposure for a given time is constant between 1915 and 1950; in other words, that any alterations of plant and process have been without effect, and if it is further assumed that deaths from all causes affect the men at the rates found in the male population of England and Wales for 1931, this date being the nearest to the centre of the period being considered for which such information is available. Fig. 8 shows this curve as well as the values that were actually found.

Alterations of plant and technique which might be expected to have affected the risk were made first in about 1935, and developed progressively with additional impetus after 1945. Since it has already been shown that the full effect of exposure is not experienced until after an exposure time of more than five years, the men entering between 1930 and 1935 may be expected to benefit to some extent by any reduction of risk that has taken place between 1935 and 1940. If, therefore, this graph is considered as consisting of two groups of men, those entering before 1930 and those entering after 1930, it can be seen that the theoretical line underestimates the risk in the earlier period, and overestimates the risk in the later period. Statistical tests show that this difference of estimate is slightly more than could reasonably be expected to occur by chance. The analysis of the figures reveals that the mean post-1930 risk is about 66% of the mean pre-1930 risk, but it is safer to limit this conclusion more generally to stating that the risk is reduced just significantly. It is not possible yet to say that this improvement is progressive, since cases which may be expected to occur in men who entered after 1945 would be very few, and the results of improvements inaugurated then are not yet assessable.

How Individual Classes of Exposure Follow the Type of Theoretical Curve in Figs. 9 and 10

Figs. 9 and 10 show the theoretical expected incidence for the four exposure classes calculated on the assumptions that the risk remained constant throughout the whole period, and that the death rate from all causes was at the 1931 figure. The incidences actually found are also shown. An analysis of these curves shows that the mean post-1930 risks for benzidine and for mixed exposures are reduced by more than could be expected from chance sampling variations (to 39% and to 67% of the pre-1930 risk respectively) and also that the mean post-1930 risks for α-naphthylamine and β-naphthylamine have risen, being 118% of the

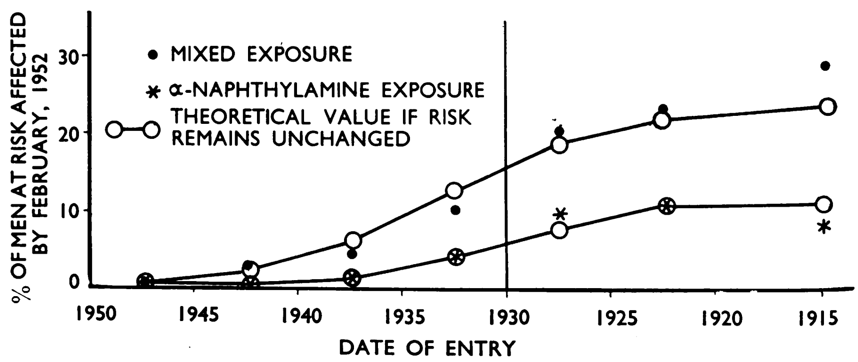

FIG. 10.—The incidence at different times by exposure class.

pre-1930 risk in each case, but this difference does not exceed what might be attributed to chance sampling variations. The slight total diminution of risk shown in Fig. 8 is derived from the benzidine and mixed exposures classes, though any quantitative estimate of the change should also be treated with reserve.

The theoretical graphs for the mean risk over the whole period conform reasonably closely to the curve that has been found for the exposure classes α-naphthylamine, β-naphthylamine, and (apart from the diminution of risk since 1930 already noted) mixed exposures. In the case of benzidine the scatter of the observed values around the theoretical graph will be seen to be greater. Detailed histories of changes in industrial technique are not available for all firms or for all of the exposure classes, but 68% of the benzidine cases are contributed by one firm, and were engaged in the manufacture of this substance. Scott (1952) has given a historical summary of the manufacture of benzidine by that concern. It is of interest to attempt to correlate this history with the graph of the tumour incidence for the exposure class benzidine, and this is done in Fig. 11. In drawing the comparison, the assumption has again been made that a change of process will affect men who entered in the five-year period before the change was made, but not men who entered more than five years previously. The figures given are the incidences found expressed as percentages of the incidences that would be expected if the risk had been constant throughout the period. The last three groups are combined because a comparison of cases with very low expectation figures is not precise, since the actual cases can only be whole numbers. There is a suggestion that the isolation of the base, as opposed to the conversion of the sulphate to the base, increases the risk. Such a deduction should be treated with reserve, since this type of analysis can be fallacious. There is not enough evidence to make any comment about the isolation of the hydrochloride.

HISTORY OF BENZIDINE MANUFACTURE (SCOTT, 1952)

BENZIDINE PROCESS : ZINC REDUCTION.
PRODUCT ISOLATED AS :—

1950 · 1945 · 1940 · 1935 · 1930 · 1925 · 1920 · 1915

HYDROCHLORIDE	SULPHATE	SULPHATE AND BASE	SULPHATE CONVERTED TO BASE	SULPHATE AND BASE	SULP	HATE	SULPHATE CONVERTED TO BASE

HISTORY AS IT WILL AFFECT THE INCIDENCE IN EACH DATE-OF-ENTRY GROUP :—

1950–1945	1945–1940	1940–1935	1935–1930	1930–1925	1925–1920	1920–1915
HYDROCHLORIDE	SULPHATE AND BASE HYDROCHLORIDE	SULPHATE CONVERTED TO BASE SULPHATE AND BASE	SULPHATE CONVERTED TO BASE SULPHATE AND BASE	SULPHATE AND BASE	SULPHATE CONVERTED TO BASE SULPHATE AND BASE	SULPHATE CONVERTED TO BASE

CHANGES INTRODUCED THAT WILL AFFECT EACH DATE-OF-ENTRY GROUP :—

1950–1945	1945–1940	1940–1935	1935–1930	1930–1925	1925–1920	1920–1915
	ISOLATION OF HYDROCHLORIDE	DISUSE OF SULPHATE CONVERTED TO BASE	RE-USE OF SULPHATE CONVERTED TO BASE	DISUSE OF SULPHATE CONVERTED TO BASE	ISOLATION OF BASE	

NO. OF CASES FOUND IN EACH PERIOD AS % OF NO. OF CASES EXPECTED IF RISK HAD REMAINED CONSTANT AT THE MEAN RISK :—

1950–1945	1945–1940	1940–1935	1935–1930	1930–1925	1925–1920	1920–1915
	300·0	78·1	20·4	180·0	153·8	73·1
COMBINED POST-1935 106·6						

DATE-OF-ENTRY GROUP

FIG. 11.—The possible effect of the history of benzidine manufacture on the severity of incidence at different times.

Total Expected Number of Cases from the Nominal Roll in Group I Only

The type of graph shown to fit the observed incidences of bladder tumour in the various classes (see Figs. 9 and 10) makes it possible to calculate the numbers of cases that will be expected to occur on the assumptions that the death rate from other causes remains at the 1931 level, that none of the men on the nominal roll received further exposure after the end of 1950, and that the cases occur at the mean risk for the pre-and post-1930 periods for the men who entered at these times. By assuming in this way that conditions have remained static, it is practicable to obtain an indication of the number of cases which may still be expected in the population here considered, but since conditions have not in fact remained static the figures obtained are only a rough measure of the problems to be faced. They are shown in Table 8.

TABLE 8

NUMBER OF CASES EXPECTED FROM GROUP I

Exposure Class	Total No. of Cases Expected	No. of Cases Already Found	Further Cases to be Expected
Benzidine	58	34	24
α-Naphthylamine ..	70	19	51
β-Naphthylamine ..	93	55	38
Mixed exposures ..	265	135	130
Total	486	243	243

Another Measure of the Severities of the Risks in Each Exposure Class and in the General Population

In considering the risk involved in exposure to the three substances benzidine, α-naphthylamine, and β-naphthylamine, only patients who were dead, and where death certificates mentioning bladder tumour had been issued, could be used in determining the risk. It is now possible to devise another measure which will utilize the information from all the cases on the Group I nominal roll. This measure is the final incidence, after allowing for deaths from all causes at the 1931 rate, that will be reached for each class of exposure, and the comparison is with the final incidence for the general population. This can be calculated from the final incidence of death certification with mention of bladder tumour, together with the percentage certification with mention of bladder tumour of the cases in the hospital survey. The final incidence of death certification with mention of bladder tumour used is the figure for 1931 (0·56%) for men entering at age 34, this being the average age of entry for the period investigated. From this we find that the final incidence of cases of bladder tumour in the male general population is 0·70%, while the final incidences for benzidine, α-naphthylamine, β-naphthylamine, and mixed exposures in Group I are 13%, 11%, 43%, and 23% respectively.

This confirms the previous test and further provides a rough estimate of the severity of the hazard, the benzidine hazard being 19 times, the α-naphthylamine hazard 16 times, the β-naphthylamine 61 times, and the hazard from mixed exposures 33 times as great as that in the general population. In addition to the increased number of cases found, the occupational cases occur at a much earlier age than the non-occupational ones.

The Severity of the Risk in Groups II and III Firms

From the foregoing it is possible to calculate the number of cases that would have been expected from the nominal rolls of Group II and Group III firms if the risk were the same as in Group I, and to compare this expectation with the number of cases found whose names appear on the nominal rolls as having had contact with benzidine, α-naphthylamine, or β-naphthylamine. These figures are shown in Table 9. Both Group II and Group III firms have a lesser risk than Group I firms but the risk in Group III firms is not as small as was suggested by the figures derived from death certificates only.

TABLE 9

SEVERITY OF RISK IN GROUPS II AND III FIRMS COMPARED WITH RISK IN GROUP I FIRMS

Group under Consideration	No. of Cases Expected	No. of Cases Found	Potency of Risk as % of Group I Risk
Group II	48·7	7	14·4
Group III	4·1	2	48·7
Groups II and III combined	52·8	9	17·0

These figures also offer an additional means of testing the hypothesis that the mean induction time is not dependent on the severity of exposure. If it were, the mean induction time for these nine mixed exposure cases in the combined two groups should be longer than for the mixed exposure cases in Group I, and longer than the α-naphthylamine cases also. In fact, the mean induction time (21 S.D. 9 years) is not materially different from that of mixed exposure cases in Group I (18·3 S.D. 7. $P = 0{\cdot}25$), and is shorter, though not materially so, than that of the α-naphthylamine cases from Group I firms (22·5 S.D. 7. $P = 0{\cdot}55$).

A Possible Bladder Tumour Hazard in Other Dyestuffs Processes

It is now necessary to devote some attention to the cases that were found outside the groups which come into contact with benzidine or the naphthylamines. It has already been shown that aniline does not appear to present a hazard, but that the manufacture of magenta (fuchsine) appears suspicious.

The manufacture of auramine is also under suspicion. Four cases have appeared in auramine workers who have not had contact with either aniline, benzidine, or the naphthylamines, and two cases whose only contact with these substances has been with aniline. Nine other cases had worked on the manufacture of auramine, but also had contact with benzidine, α-naphthylamine, or β-naphthylamine. These nine cases were included in their appropriate exposure classes for the last three substances.

Two of the six auramine cases without such contact are still alive and three have bladder tumour death certificates. While it is impossible to say whether this figure represents an excess of cases over what might be expected if no occupational risk were present, unless the size of the population at risk is known, three death certificates seem highly suspicious when it is remembered that the total expectation from the 4,622 men on the combined nominal roll for aniline, benzidine, and α- and β-naphthylamine lay between three and five.

Fifteen cases amongst employees of member firms were found who were known not to have had contact with aniline, magenta, auramine, benzidine, or the naphthylamines. Seven of these have bladder tumour death certificates. The processes worked are shown in Table 10. These numbers are too small to allow a comparison between the age of onset and the age at death with those of the general population to be made, but there is no trend observable in this table to suggest that any of the processes listed there are to be suspected, but it is perhaps relevant to note that Henry, Kennaway, and Kennaway (1931) considered that occupations involving exposure to coal-gas, tar, pitch, or soot carried a risk of occupational tumour of the bladder. Two of the cases listed would fall into this category of worker, rather than into occupations proper to the chemical industry.

There are in addition 36 cases amongst past employees of member firms not participating in the scheme where it has been established that the men never had contact with aniline, auramine, benzidine, α- or β-naphthylamine, and of these, 34 have death certificates of tumour of the bladder. The seven cases with death certificates of tumour of the bladder from the previous group (Table 10) who had not had contact with benzidine or β-naphthylamine were combined with this group of 34, and their ages at death compared with the ages at death in the general population are shown in Fig. 12.

TABLE 10

PROCESSES WORKED BY CASES AMONG EMPLOYEES OF MEMBER FIRMS WITHOUT CONTACT WITH ANILINE, MAGENTA, AURAMINE, BENZIDINE, OR NAPHTHYLAMINES

Age at Onset	Age at Death	Processes	Length of Service
61	61. Died of other causes	Dinitrobenzene and dinitrotoluene	8 years
?	57	Diphenylamine, phenyl-peri-acid, primuline, sulphur colours, phenyl-beta-naphthylamine, o-nitro-aniline	25 years
66	67	Nitric acid manufacture	22 years
?	59	Picric acid manufacture	27 years
46	48	Manufacture of alizarine derivatives	28 years
?	74	Producer gas, handling tar and pitch Ice plant	5 years 1 year
50	53	Manufacture of sulphuric acid	2 years
?	48	Manufacture of dinitrophenol	5 years
53	Alive	Di-β-chloroethyl ether mono- and di-nitrations	7 years
59	Alive	Sodium hydrosulphite	1 year
47	Alive	Manufacture of amido-salicylic acid but worked in the same shed as a dianisidine plant	5 years
42	Alive	Para-, ortho- and chloro-para-toluidine. Next to sodium naphthionate plant	23 years
60	Alive	Use of acetie acid and acetic anhydride	2 years
74	Alive	Coal gas worker	3 years
		Chemical occupation not stated, but contact with any suspected chemical denied	46 years
57	Alive	Chemical occupation not stated, but contact with any suspected substance denied. However, his work was in a benzidine shed.	18 years

This figure shows that there is a movement towards the younger age groups and the statistical calculations show that, when allowance has been made for the fact that deaths at over the age of 65 may be missing from the chemical workers series because the death certificate might give the occupation as " retired, previous occupation unknown ", the shift is still real and is more than could reasonably be caused by chance sampling errors.

Thus, although it is impossible to say whether or not more tumours have occurred amongst chemical workers who have not had contact with aniline,

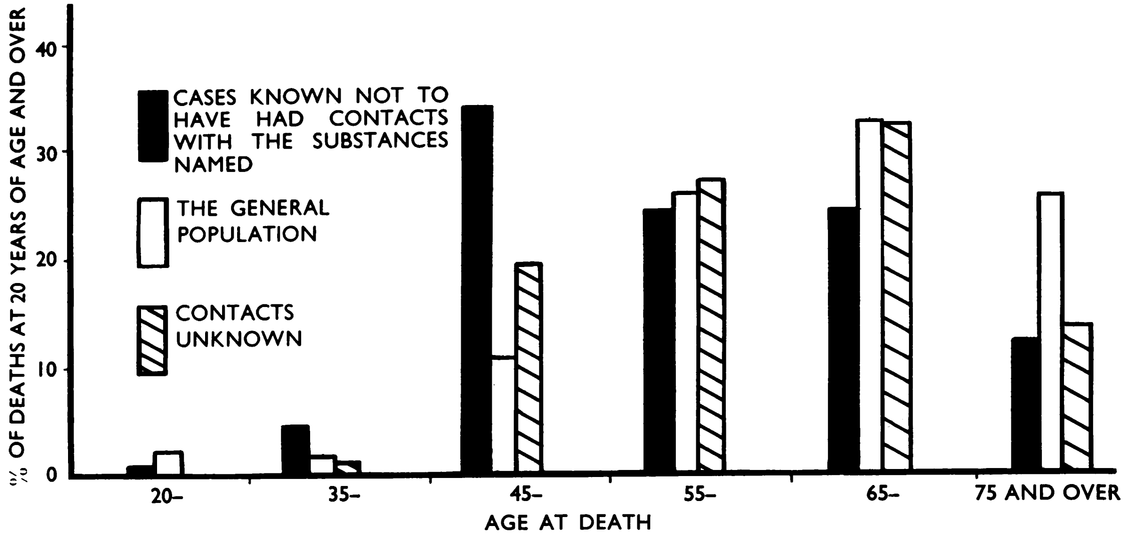

FIG. 12.—The age-distribution at death in 41 cases known not to have had contact with aniline, benzidine, α-naphthylamine, or β-naphthylamine, 81 cases with unknown contacts, and in the general population.

auramine, benzidine, α-naphthylamine, or β-naphthylamine than would be expected if they contracted the disease at the average rate for the general population, it is possible to say that the deaths occurred from bladder tumour at an earlier age than would be expected. This suggests that an environmental risk is operating in this group, but there is no evidence of the causes of the risk.

There now remains for consideration a group of cases whose contacts are unknown. These include 65 men whose employers are unknown, 10 men employed by firms no longer existing, three men employed by firms not members of A.B.C.M., and 11 men amongst the cases from participating firms. Of these 89 cases, 81 have death certificates mentioning tumour of the bladder.

The age distribution at death of these 81 cases is also shown in Fig. 12. Again there is a very slight movement towards the younger age groups, but this is no greater than could reasonably be attributed to chance sampling fluctuations, allowing for the possible loss of cases aged over 65 because of retirement. It is not possible to say whether or not an environmental risk is at work amongst this group.

Discussion

In general, each result has been discussed as it was achieved. Therefore no further discussion of the foregoing is needed. Certain general topics are however raised, and these are dealt with below.

It does not fall within the scope of this report to suggest alterations in industrial practice. However, it might not be out of place to make some suggestions for future investigation of the risk, so that changes due to better industrial practice can be assessed at an early date.

First, it is apparent that an accurate picture of what is happening can be obtained only from a study of both the population at risk and the cases derived from this population. Therefore it is important that accurate records of men employed should be kept, and their age, date of starting work, and occupational history noted. It would be desirable if records of causes of death of employees or past employees were also kept. It would then be possible for a firm concerned to make an estimate of the number of cases that might occur by the ordinary risk of the disease and the observed number, and so see what processes came under suspicion. The methods for doing this are set out and discussed elsewhere (Case, 1953b) and could be used by either the medical officer or the personnel management department.

Secondly, the number of cases that may be expected in the future makes early diagnosis important. The work of Crabbe (1952) using exfoliative cytology suggests that this method appears to offer advantages over older techniques. It might therefore be advisable to consider how far such a method could be applied in the dyestuffs industry generally.

Thirdly, it would seem desirable at this stage to emphasize the need for more experimental work. If trace substances in intermediates play any part in the production of tumours, a possibility suggested by Case and Pearson (1952) and the unpublished work of Case (1948–52), quite different protective measures may be needed from those that would be required to prevent contact with the intermediates themselves. A prerequisite of protection is a knowledge of the forces against which protection is required.

Summary and Conclusions

This statistical survey demonstrates that contact with benzidine, α-naphthylamine, and β-naphthylamine in either manufacture or use causes many more bladder tumours in workmen so exposed than would appear if no special risk was operating. Furthermore, both the onset of and death from these occupational tumours takes place at a much earlier age than in non-occupational cases.

There is no evidence that aniline causes an increased number of bladder tumours in men who manufacture or handle it. There is, however, some evidence to suggest that the manufacture of magenta and auramine may cause tumours, and further details will be published in this journal later.

There is some evidence that work in the chemical industry which does not involve contact with any of these substances may cause earlier deaths from bladder tumour than occur in the general population, although figures are not available to measure whether a greater number of tumours is produced than would occur in the general population.

β-Naphthylamine has been the most potent cause of occupational bladder tumours between 1915 and 1951. In those firms which manufacture aniline, benzidine, α-naphthylamine or β-naphthylamine, the ratios of the potencies of β-naphthylamine, mixed exposures, benzidine, and α-naphthylamine in manufacture or use have been respectively 5·2, 2·7, 1·7, 1·0. However, when all the cases expected from this group have appeared, this ratio should change to 3·8, 2·0, 1·2, 1·0. This difference of ratio is due to the different times required for the tumours to become manifest.

The tumours appear after an induction period of an average length of 16 years for β-naphthylamine and benzidine and 22 years for α-naphthylamine. However, tumours may appear in less than two years from the first exposure or after more than 45 years from first exposure. Thus the length of time between the first exposure and the development of a tumour should not be considered as a bar to recognizing the tumour as being of industrial origin.

The average induction time is not appreciably influenced by the severity or duration of the exposure. It therefore appears to be a characteristic of the causal agent. This suggests that it is possible that the β-naphthylamine content of α-naphthylamine is not the sole causative agent in the latter substance unless it is assumed that α-naphthylamine could retard the production of β-naphthylamine tumours.

In the largest group available for study, that is the group of firms which manufacture aniline, benzidine, and either α- or β-naphthylamine, the final proportion of all workers employed for more than six months who had any contact, in the manufacture or use, with the latter three of these substances was about 20%.

Calculations suggest that, in the absence of any further exposure after 1951, this group of 2,466 men, which has already given rise to 243 cases, may be expected to produce a further 243 cases, making 486 cases in all. This calculation indicates only an approximate expectation, since many relevant conditions may be expected to have altered.

In other words, in this section of the chemical industry (Group I) one in 10 of the men exposed in the way defined above between 1915 and 1950 has already developed bladder tumour, and this figure may be expected to reach one in five before all the men are dead from all causes. The severity of the risk seems to have been mitigated slightly for men employed since 1930, and the data suggest that this comes from a diminution of risk in persons exposed to benzidine and mixed exposures. However, the risk is still such that taking the average post-1930 values, one in six of all men employed in contact with any of these substances may be expected to develop a tumour, whereas before 1930, one in four would be expected to do so. Since these data were collected, the manufacture of β-naphthylamine has been abandoned in Great Britain, and major alterations in techniques of manufacture and handling of α-naphthylamine have been introduced.

The actual risk of developing a tumour is influenced to a small extent by the age at which a man starts work in a hazardous occupation, there being a slightly increased susceptibility in older men. For all practical purposes, however, the age at which he is likely to develop a tumour, if he does so, is almost entirely dependent on the age at which he starts, being on the average 18 years later.

The length of exposure to a hazardous environment affects the chances of a man developing a tumour, but exposures of less than one year to β-naphthylamine, benzidine, or mixed exposures carry a definite risk. α-Naphthylamine requires a longer exposure to produce an equivalent effect but too much reliance should not be placed on the absence of any cases with under one year's exposure, since the number of cases that could be expected if a risk is present is very small.

The use of sulphates or hydrochlorides instead of bases does not remove the risk, but there is evidence to suggest that the manufacture of benzidine sulphate followed by conversion to the base may be less hazardous than the direct isolation of the base.

The original paper contains a nine page statistical appendix that is not included here.