OCCUPATIONAL TUMOURS OF THE BLADDER

by

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PREFACE

The work which is the subject of this thesis was done by me at The Clayton Aniline Company Ltd. to which organisation I have been the sole medical officer for 20 years.

The Company manufactures some heavy chemicals but is engaged principally in the manufacture of synthetic dyestuffs and pigments and of the intermediate chemicals used in their synthesis.

At least 123 men who were engaged in this work are known to have developed tumours of the bladder. In a few instances the tumours were in the ureter or the pelvis of the kidney and these cases are included under the present title.

The thesis is set out in the following order. There is first a short history and explanation of the origin and development of the synthetic dyestuffs industry in general and of that in the Clayton Aniline Company Ltd. in particular. The historical background of occupational tumours of the bladder is then traced and the incidence of the disease abroad and in Britain described. The compounds which have been suspected or proved to cause the disease in workmen are considered together with the methods of their manufacture and the risks involved. The industrial, epidemiological and experimental evidence of their carcinogenicity or otherwise is evaluated. Their metabolism and mode of action is considered. Much of the work

on the metabolism of one of these compounds (benzidine) was done under my direction in the Works Medical Department.

Against this background my own work on the problem of occupational tumours of the bladder is prescribed.

The relevant compounds are discussed; these are the carcinogens which have been manufactured at Clayton and certain other compounds pertinent to the subject. Of the latter some have not been manufactured at Clayton and some are thought not to be carcinogenic. The conditions existing from time to time and the populations exposed are described.

There follows a detailed description and statistical analysis of the incidence of the disease in the Clayton factory.

The difficulties of achieving early diagnosis and the relative merits of various screening methods are compared. Clayton was one of the two factories in which exfoliative cytology was first used for the early detection of tumours of the urinary tract in workmen at risk. Its original introduction into industrial medical practice and the successful development of the application of cytodiagnostic methods to the Clayton works population is detailed at some length.

The clinical, histological and pathological features of the tumours are described and an account is given of the incidence of recurrent tumours, treatments and age factors.

The legislation relating to the actual working conditions

LIST OF CONTENTS

PART I - GENERAL

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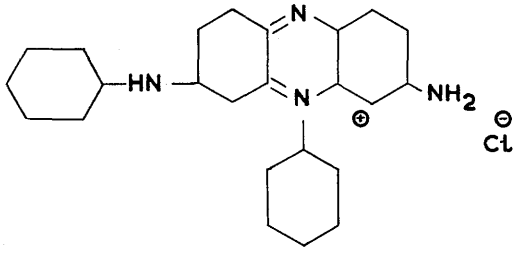
ORIGIN AND HISTORY OF CHEMICAL DYESTUFFS

Faraday discovered benzene in 1825 and Hofmann isolated it from coal tar in 1845, yet as late as 1847 Berzelius was writing in support of the belief that a "vital force" was necessary for the production of organic compounds. Organic chemistry was then in its infancy and synthetic dyes were undreamed of. Compounds which are commonplace to-day were unknown or merely of academic interest.

In 1856 aniline was a rare, almost precious, substance and toluidine was even rarer. In that year William Henry Perkin, then aged only 18, was working in Hofmann's laboratory in London attempting to make quinine from the toluidine derivative allytoluidine by oxidizing it with potassium bichromate. The experiment was unsuccessful but Perkin tried again this time using impure aniline sulphate from which he obtained a dark resinous mass which practically every other chemist of his time would have thrown away. Perkin, however, studied it and discovered it could dye silk a brilliant mauve, a shade which at that time was obtainable only from natural colour and which had always been very fugitive especially on silk usually fading to red within 24 hours. He sent his new dye which he called mauveine to Sir R.Pullar of Perth, head of the Scottish firm as well-known then as it is now. Pullar liked it and was prepared to use it if he could obtain it in sufficiently large quantities.

Perkin thereupon set up a factory at Greenford Green in Essex to make mauveine on a commercial scale and he took out his first patent in 1856, one hundred and two years ago. This was the start of the coal tar or aniline dye industry which was soon to become important in many countries.

After numerous experiments, Perkin decided that the reduction of nitrobenzene was the best source of aniline. He succeeded in devising and setting up plant for its manufacture on the requisite scale. The aniline which he obtained and the aniline manufactured for the next two generations contained many impurities, the most important of which were ortho and paratoluidine. On the relative amounts of these depended the colour of the mauveine and that of many other products. Mauveine would not dye cotton or wool and this limited its application. He turned his attention to this aspect of the problem and discovered a method of applying it to these materials thereby extending its use enormously. Perkin's mauveine was used



MAUVEINE.
(Chief constituent; homologues are also present.)

for dyeing many different textiles and paper and as a pigment until the turn of the century when it was superseded by newer dyes. Some mauveine as made by Perkin is, however, still available and a piece of silk dyed by it is attached, (in Vol.II).

Perkin's discovery stimulated research into the subject all

over Europe. In the same year Natansen in Poland produced a new purple dye by heating aniline with ethylene dichloride. This was soon to sweep the market. Two years later Hofmann obtained a similar product from aniline and carbon tetrachloride. In 1859 Verguin working with Renard Frères et France of Lyons discovered a process using stannic chloride and aniline, and this firm was the first to manufacture it industrially. The dyestuff was named magenta to commemorate the French victory over the Austrians in the battle of Magenta in 1859. The Germans took it up with enthusiasm and named it fuchsin, a pretty play on their word for fox (fuchs) and the name (Renard) of the French originators. In 1860 Medlock devised a method of manufacture using arsenic acid with aniline which was widely adopted. In 1869 Coupier of Paris developed a process using nitrobenzene which was first successfully carried out on an industrial scale by the firm of Meister, Lucius and Bruning at Hochst-am-Main. This process superseded the arsenic acid method everywhere. As with mauveine the production of colour depended on toluidines being present; it is now known that pure aniline yields a quite different substance of the induline type. In 1887 Caro developed acid magenta, a trisulphonic acid derivative which greatly widened its application and its use in industry.

Picric acid was also used as a dye. A well-known firm of Burton brewers (Allsops) was disconcerted by the popularity of a rival beer which had an enhanced bitter taste compared with their own. They employed a firm of analysts to find the reason for this

and one of their chemists Peter Griess found that picric acid had been added to it. Following this Griess subsequently became head chemist at Allsops, where, working in his spare time, he developed the diazo reaction which he had discovered previously whilst a student at Marburg in 1858. On this reaction depends the synthesis of a large class of dyestuffs comprising thousands of azo-dyes which are the foundation of the dyestuffs industry. In this class are many colours in which benzidine, alphanaphthylamine and betanaphthylamine are used as components and although these intermediates have, or have had, other uses inside and outside the dye industry, their large scale manufacture and use has been predominantly for the production of azo colours.

Benzidine was first discovered by Zinin, a Russian chemist in 1853. He showed that azobenzene when treated with ammonium sulphide and boiled with sulphuric acid gave the sulphate of a base which he called benzidine. This was confirmed by Hofmann in 1862, who identified and isolated the intermediate hydrazobenzene which he found was easy to convert to benzidine by the action of a mineral acid. Finally Fittig showed that the base was 44' diaminodiphenyl. An early use of benzidine was in the manufacture of Palatine orange (tetranitrodiphenyl) which quickly became obsolete as a dyestuff. Following Bottigers major discovery in 1885 of the direct cotton dyestuffs many of which,such as Congo Red, are made from benzidine, benzidine began to be made in very large quantities and this has continued to the present day. It was not, however, until 1902

that the first commercial patent for its manufacture was registered by Lillienfeld in Berlin. This was an electrolytic reduction of 4-aminobenzoic acid.

Alphanaphthylamine was discovered also by Zinin eleven years previously in 1842. It was first prepared by the ammonium sulphide reduction of alphanitronaphthol and subsequently many different reducing agents have been used in its manufacture, for example, iron and acetic acid in 1854, tin and hydrochloric acid in 1861, zinc and hydrochloric acid in 1870, and alcoholic potash in 1877. On the industrial scale the reduction of alphanitronaphthalene is still the method employed.

Betanaphthylamine was first recorded in Germany by Lieberman and Schneiding (1875) who obtained it by the reduction of 1-bromo betanitronaphthalene with tin and hydrochloric acid. In 1880 it was commercially manufactured in Germany by heating betanaphthol with ammonia at 160^{o}C under pressure (D.R.P.14612) a principle substantially similar to that which was used in The Clayton Aniline Company in Manchester until its manufacture was abandoned in 1950.

Until about 1876 the British chemical industry was pre-eminent in the manufacture of dyestuffs but after that it was increasingly outstripped by its German and Swiss competitors until by 1914 Britain was virtually dependent on them for dyestuffs and many other chemicals. The stimulus and stark necessity of war forced an effort from the British industry which rendered it independent of foreign suppliers, an economic and strategically vital independence which it has

maintained ever since.

History of Manufacture in The Clayton Aniline Company Limited.

The Clayton Aniline Co.Ltd. of which I have been medical officer for 20 years, was founded in 1875 in Manchester and has manufactured aniline from that time. The cases of occupational tumours of the bladder which are the subject of this thesis arose there. It was one of the few dyestuffs manufacturing companies in England which survived the Continental competition and between 1875 and 1914 it continued to make coal tar chemicals. It carried out the refining of coke oven benzole to obtain benzene, toluene and naphtha. From these were manufactured nitrobenzene, aniline, paranitroaniline and various other nitro and amino compounds. It listed about 20 dyes, the principal ones being aniline black, nigrosine, primuline and some stilbene colours. Primuline was developed at Clayton by A.G.Green, later Professor of Colour Chemistry in Leeds.

Some indication of the comparative British and German output during these years can be had from the numbers of patents taken out between 1885 and 1900 which were quoted by Green at the meeting of the British Association in 1901 :-

England

Brooke, Simpson and Spiller	7
The Clayton Aniline Co.Ltd.	31
Levinstein and Co. (later I.C.I Dyestuffs Blackley)	19
Read Holliday & Co.	28
Claus and Ree	9
W.G.Thompson	2
Total British patents	96
Total German patents	948

This accords with an estimate (C.A.C.Quarterly, 1951) that by the beginning of the 1914 War about 80% of all our supplies of dyestuffs for textiles came from Germany.

In 1909 as a result of the English Patent Act of 1907 which required the compulsory manufacture of products in order to maintain patent rights, certain reciprocal arrangements were made with the Society of Chemical Industry in Basle (now Ciba Ltd.) which culminated in that organisation eventually purchasing the whole shareholding of the company and taking over effective control in May 1911.

At the outbreak of the war in 1914 about 200 tons of trinitrotoluene were being made annually at Clayton for dye manufacture. This substance was of great importance as an explosive and so its production was rapidly expanded to 3000 tons a year. In 1917, because of the urban location of the factory, manufacture was discontinued for safety reasons. The trinitrotoluene plant was then turned over th the manufacture of several compounds which are used in the intermediate stages of dyestuffs manufacture. One of these

was benzidine which was made by the zinc reduction process.

Betanaphthylamine manufacture was begun in 1920 in another department and continued until it was given up voluntarily in 1950 because of the health hazard associated with it. Alphanaphthylamine was made for a short period from 1926 to 1930. At all other times it has been bought from other manufacturers and used on a fairly large scale. Magenta was manufactured from 1920 to 1926 and since then has been bought only at intervals and then on a comparatively small scale. Several other substances which have been suspected of being carcinogenic have been manufactured or used and will be referred to later. All these intermediates have also been used in the colour factory in the synthesis of azo-dyes and other compounds. There has been a rapid development of the manufacture of many other intermediates and of all types of synthetic coal tar dyes, particularly azo colours, vat dyes and triphenylmethane colours. Auramine has never been manufactured by this company.

Thus ,up to the end of the First World War while the dyestuffs and chemical industry had grown to large proportions in Germany, and to a somewhat lesser extent in Switzerland, a few companies here in Britain had maintained a small steady production in the face of their continental competitors. It was not, however, until after the First World War that the naphthylamines, benzidine and magenta, all compounds subsequently to be indicted as bladder carcinogens, were manufactured on a substantial commercial scale in this country.

As already described The Clayton Aniline Company was among the largest British manufacturers.

HISTORY OF OCCUPATIONAL TUMOURS OF THE BLADDER.

Towards the end of the 19th century skin cancers in chimney sweeps and workers in shale oil, tar and similar industries had come to be accepted as occupational in origin. The occurrence of lung tumours in the Schneeberg miners at Joachimstall in Bohemia had already been reported. No occupational tumours in organs remote from the site of contact had been recognised.

At a congress of the German Surgical Society in 1895 Rehn, a surgeon in Frankfurt-am-Main which was the centre of an important chemical industry, discussed the frequent occurrence of haematuria in chemical workers in his practice. He reported among them three cases of men who had bladder tumours, two with papilloma and one with carcinoma, and mentioned a fourth man who had not been examined cystoscopically but who also was presumed, for good reasons, to have had a tumour of his bladder. All of these men had worked in the fuchsin room in one factory, and a total of 45 men at the most were known to have worked there during the period when these men had been exposed. The three men with bladder tumours, recorded by Rehn, had been employed in this shed for 15, 29 and 20 years and had had haematuria for 4 years, $1\frac{1}{2}$ years and 6 months respectively. Rehn concluded that :-

1. the fumes which develop during the manufacture of fuchsin lead

to disturbances in the urinary system,

2) after years of work in the fuchsin industry tumours of the bladder may occur as a result of continuous irritation,

3) the injurious effect is mainly due to the inhalation of aniline vapour.

Thus early these tumours were attributed to exposure to aniline and the name "aniline-cancer" was to stick for many years before it was finally accepted that aniline is not a significant cause and the misnomer was dropped. Despite the convincing evidence of certainly three, and probably four, cases of men with bladder tumours in a population of 45 in one workshop some scepticism was expressed about their occupational origin. Grandhomme (1896), an official of the works previously owned by Meister, Lucius and Bruning, the firm which introduced the nitrobenzene process for the manufacture of fuchsin about 1869 and which had made it on a large scale since then, writing on the sanitary and social aspect of his factory, expressed strong doubts as to the connection between the occupation and the disease. He claimed that in the same room and over the same period described by Rehn (i.e. 1883 -'95) 493 operatives had remained healthy and that in other factories 4000 operatives had worked on similar processes and under similar conditions and no bladder tumours had been diagnosed. He agreed that aniline might irritate the mucous membrane of the bladder and produce pain and haemorrhage but maintained that it had no connection with the production of tumours.

Although one may suspect that Grandhomme was not disinterested and that his motives were not altogether altruistic, it is nevertheless still accepted that heavy exposure to toluidines and some other aromatic amines, many of them not carcinogenic, can cause acute haemorrhagic cystitis.

Bachfield in 1898 supported Grandhomme's view when he reported 63 cases of poisoning by aniline, toluidine or nitrobenzene from a factory in Offenbach. Of these, 16 had dysuria and haematuria but no tumours were observed. Later in the same year Leichtenstern (1898) attributed a bladder tumour to naphthylamine. This was 18 years after the manufacture of betanaphthylamine was begun in Germany and about the same time after the alpha-isomer began to be widely used. It is the first mention of naphthylamines as a cause of tumour.

In 1904 Rehn made a report of a further 20 cases to the Surgical Congress which then asked him to compile material for a comprehensive survey of the incidence of tumours of the bladder in aniline factories. He investigated the workmen at 18 factories and found a total of 38 cases which had arisen in seven of the factories. In addition to aniline and fuchsin, benzidine and naphthylamine were now identified as significant contacts. Several other authors reported other cases from the same area but most of them were probably included in Rehn's 1906 report (Wendel, 1900, 3 cases: Posner,1904, 1 case: Straus,1904, 1 case: Randesheuse 1904, 2 cases: Schedler, 1905, 2 cases: Seyberth, 1907, 5 cases: Labour

Inspector's Report, 1909, 2 cases: Cesabianco, 1911, 1 case).

The cases hitherto reported had nearly all come from the Frankfurt area and those like Grandhomme who were sceptical of their occupational source, or were unwilling to admit it, were very ready to suggest a geographical origin for them, although Schedler in 1905 had reported two cases from Basle which he ascribed to aniline. Any credence which the geographical theory had gained was exploded in 1912 when Leuemberger produced 18 cases in aniline dye workers in Basle. Adding to them the 41 cases previously reported, he reviewed all the existing reports.

He compared the incidence in aniline dye workers with that in the general population in Basle. He showed that the incidence of deaths from tumour of the bladder had increased from 7 per thousand of the average population of the city for the decade 1871 - '80 to 20 per thousand for the decade 1901 - '10. Further, during 1901 - '10 the number of workers in aniline and aromatics in Basle was 840; the total male working population was 56,900. During this time 6 workers in aniline died of bladder tumour compared with 12 men in the rest of the male population. From these data he calculated that the deaths due to tumour of the bladder among workers in aniline dyes were 33 times that of those in the rest of the male population.

He also cited figures from the records of the Basle Surgical Clinic. During the forty years 1861 - 1900, when the chemical

industry was growing, 15,800 patients were recorded, among whom were six cases of tumours of the bladder, none of whom was known to have worked with aniline; in the next ten years 1901 - 1910, during which the chemical industry had developed, there were 16 cases of bladder tumour in 8,650 patients. Of these 16 cases, 12 were aniline workers or dyers. Of all tumours treated during this latter ten year period 7.8% were bladder tumours. In Vienna where there was no chemical industry, bladder tumours constituted 0.39% of all tumours. In Frankfurt where the chemical industry was heavily concentrated they comprised 25 - 30% of all tumours by 1918 (I.L.O. Report, 1921).

By 1913 Schewin (1920) had collected 100 cases which he discussed at a conference of factory doctors in Leipzig in that year. He had personally seen 38 cases of industrial origin against only one of non-industrial origin. The rest of his 100 cases had previously been reported.

Thus by 1913 Rehn's observation that bladder tumours were an occupational disease of aniline workers had been confirmed and had come to be accepted by those working in this field in Europe. The great bulk of the aniline and synthetic dyestuffs industry was still located in Germany and Switzerland and no cases had yet been reported from elsewhere. In England, Legge, H.M.Senior Medical Inspector of Factories in his Annual Reports for 1912 and 1913, following a visit to Frankfurt in 1911, had called attention to the hazard, but no cases were reported in England despite the fact that this warning must have increased the likelihood of any occupational cases being

recognised. The German and Swiss industries, aware of the risk and alert to it, made considerable improvements in their methods of working. As their industry expanded before and during the First World War, new plants were built and re-organisation and amalgamations into large combines tended to concentrate the dangerous manufactures into fewer factories where, on the whole, working conditions were better, populations larger and supervision closer.

At the end of the war, the subject of industrial tumours of the bladder was again discussed in Germany by the Congress of Factory Doctors in 1920. A Commission of Inquiry composed of representatives of doctors, manufacturers, government and workers was appointed to study the question. Curschmann, the secretary, conducted a survey by circulating a questionnaire and he reported later the same year on the results. He revealed that 28 new cases had arisen since 1913. In addition to these his report included several which had been previously reported, several which were not tumours but other "troubles of the bladder" and one which was described as a cancer of the kidney. He estimated the total number of cases since Rahn's first report todate at 177 but the report of an I.L.O. study in 1921 revised his estimate pointing out that many cases had been included in more than one report. This I.L.O. study gave the number as 87 excluding Nassauers' (1919) 32 cases, as there was doubt whether they had been previously included in other reports.

The I.L.O. report summed up the position in Germany and

Switzerland up to 1920 and made recommendations for industrial and medical prophylactic measures. The report recommended the keeping of detailed records; it listed many compounds which were suspected by various authors as causative agents. Aniline was the substance most often named, although the report concluded, among other things that it was not possible to determine the substance capable of engendering tumours; that one could go no further than to incriminate the amine compounds, particularly benzidine and betanaphthylamine. This was the first time such emphasis had been placed on these two compounds which were later to figure so largely in this problem.

By the end of the 1914-18 war, the dyestuffs industry throughout the world had, to a large extent, been redeveloped and manufacture in the allied countries had increased to a level comparable with the crippled German output. The problem of bladder cancer in these countries outside Germany and Switzerland was forgotten, if it had ever been seriously believed or heard of, and a complete repetition of the German and Swiss experience was set in motion in Great Britain, Italy, France and the United States of America.

Great Britain.

In Great Britain, Ross (1918) writing on oocupational cancer of the bladder stated that although the aniline dye industry was not of a large size the Chief Inspector of Factories "refers to a series of 14 cases of villous growth of the bladder in a works where the

men concerned are engaged in handling aniline dyes". I have not been able to trace any published or private reports of these cases. Hueper (1954) and several other writers have, presumably on the strength of this paper, mistakenly credited Ross as being the first to discover or describe the existence of occupational bladder tumours in Britain. Henry, Kennaway and Kennaway (1931) found some barely conclusive evidence from an examination of death certificates that there was a higher incidence of deaths from tumours of the bladder and prostate in workers in coal gas, pitch and tar than in the general population. They also found 61 fatal cases of cancer of the bladder in chemical workers and dyers but could not obtain reasonably accurate figures of the population at risk. Bridge, H.M.Senior Medical Inspector of Factories in his Annual Report in 1926 recorded 12 chemical workers who had died from the disease in the preceding four years.

Wignall (1929) the appointed surgeon to the British Dyestuffs Corporation (later Imperial Chemical Industries Ltd.) delivered a paper on the "Incidence of Disease of Bladder in Workers in Certain Chemicals" to the Section of Occupational Diseases of the 97th Annual Meeting of the British Medical Association in Manchester. This is the first report from a factory doctor in England of an incidence of occupational tumours of the bladder in a defined industrial population. His paper in many ways is reminiscent of Rehn's although he does not mention him. Like Rehn, he describes

a high incidence of cyanosis from methaemoglobinaemia among his workmen, and of gross haematuria from the cystitis induced by some aromatic amines. He then describes in some detail 14 cases of tumour, papillomata and carcinomata, of the bladder arising in his factory, 7 of whom had worked in alphanaphthylamine, 3 in colour manufacture, 2 in benzidine and the others in other intermediates. A further 8 men whose illness had arisen before 1910 might have had tumours due to alphanaphthylamine but his information on these cases is not complete.

Betanaphthylamine is not mentioned but his successor in the factory, Goldblatt (1956), states that Wignall had at that time no reason to suspect that benzidine and betanaphthylamine, which were extensively used in the factory were able to lead to bladder tumours. Macalpine (1929) the urologist who treated Wignall's cases, published a detailed surgical description of 7 of them. Apart from another reference by Bridge in 1936 no further cases were published in England until two years after the last war (Goldblatt 1947). Müller (1951) remarked that little interest in these diseases had been shown in England during the Second World War. This was completely unjustified as reports from Goldblatt (1947 and 1949a) and myself (Scott 1952) unquestionably showed.

In 1949 Goldblatt reviewed his experience during the period 1934-47 from two British chemical factories manufacturing intermediates, dyestuffs, and many other compounds. In his series there were 99 cases of workmen who developed bladder tumours of whom 59

had died, and "as to causative agents, alphanaphthylamine, betanaphthylamine and benzidine were manifestly involved". He also attributed 3 cases of papilloma to aniline, but retracts this in a more recent publication (1956) and agrees that later rigorous studies by other investigators appear to rule aniline out completely. These three cases mentioned by Goldblatt are of interest in that they are the only inculpation of aniline as a causative agent in post-war England. No other observers appear to have had reason to suspect it. (Scott, 1952, 1953, 1954, Williams 1958).

Goldblatt's papers evince the enormous interest, care and work which he had maintained in this problem in his factories during the war years. Data were carefully recorded throughout; regular examination of all workers at risk and routine urine tests were maintained; continuous medical supervision of workers and of the working environment was carried out and the investigation and treatment of suspected and established cases of tumour were vigorously pursued. It is an index of the care he directed to this problem that the average daily excretion of aromatic amine in the urine of alphanaphthylamine workers was estimated during the difficult war years of 1942, 1943 and 1944.

In a paper read to the International Congress of Industrial Medicine at Lisbon in 1951 I presented a further 66 cases from another factory[x] in England (Scott 1952). These cases were attributed to benzidine, alphanaphthylamine, betanaphthylamine and various combinations of these. In addition to the usual medical

x The Clayton Aniline Co.Ltd.

and statistical details I gave the history of the manufacture of benzidine and betanaphthylamine in this factory with diagrammatic illustrations of each. From these histories it can be seen that many improvements in plant and process working were instituted and that some of the most important of these were introduced during the war years of 1939-45 thus further demonstrating the efforts made in England during the war to improve conditions and lessen risk. Goldblatt's papers were published four years and two years respectively before Müller's statement that little interest had been shown in England during the war and my own paper was delivered to the International Congress in the same year as Müller made this statement.

Germany 1920 - 1958.

Meantime in Germany there was a succession of reports of cases from 1920 onwards from Oppenheimer (1920, 1926 a & b, 1927) who suggested in 1920 that not only operatives but also people living in the vicinity of the works might develop the disease, Bauer (1926), Ullman (1926 & 1933), Brezina (1929), Simon (1929, 1930 a,b,c, 1932), Sebening (1930) and Sieben (1931). Buttner (1931) found that the German literature had reported on 300 cases by that time - not a surprising figure in view of the size of their industry and the time which tumours had had to develop.

In 1940 Gross reported on 85 cases which had occurred in a Ludwigshaven factory. He attributed 36 to betanaphthylamine, 3 to

benzidine base, 13 to mixed exposures and he gave aniline as the cause in 33 cases. He is reported to have confirmed the aniline cases when examined by the Allied Commission in 1945 (B.I.O.S. Final Report No.784, 24) although he then qualified it by saying that very few men in comparison with the number of workers exposed to aniline had been affected. On raising this important point with him since then, I have received a personal communication in which he refutes his 1940 view entirely. He writes (14.11.57) "both betanaphthylamine and aniline seem to be extremely dangerous. I have not said or written so. This opinion concerns betanaphthylamine only and, as we know now, benzidine too, but never aniline".

Since then at a meeting of the bladder cancer working group of the Deutsche Forschungsgemeinschaft held in Bad Godesburg in November 1957 which I attended, the most recent German totals of cases were reported. Badische Aniline at Ludwigshaven now have 191 known cases, Beyers at Leverkusen have 132, Hochst at Greisheim 23 and Bayers at Offenbach 22. These figures have been collected since a similar meeting held in 1954 had re-stimulated interest in the problem in Germany. Except for these two meetings in 1954 and 1957 no further reports have emerged from Germany since the last war. The proceedings of the 1957 meeting will be circulated privately among the 20 attending members but it is unlikely that they will be published.

Switzerland 1920 - 1958.

In Switzerland, Müller who had succeeded Leuenberger as urologist in Basle, supplemented his predecessor's cases in 1933 by a collection of 54 further cases of bladder tumour and followed this by several subsequent publications (1933, 1934, 1936, 1940, 1945, 1949) culminating in his outstanding treatise of 1951, the most comprehensive review of the subject which had so far been written. He added a further group of 85 cases bringing his total up to 139. (Müller gives his total number as 161 but 22 cases were of haemorrhagic cystitis without tumour). He considers aniline to be decidedly dangerous and incriminates it in 22 cases, benzidine in 36, betanaphthylamine in 37, various combinations of these in 8 and other substances several times. His colleagues Uebelin and Pletscher (1954), the medical officers of the factory where the majority of his cases originated, in describing 100 cases from their factory, most of them undoubtedly in Müllers series, modified this view. They said that the effects of aniline were formerly held to be the principal cause of bladder tumours in dyestuff workers but to-day this opinion is doubted, and it is probable that benzidine and betanaphthylamine are primarily responsible. In their works 300 workmen were directly exposed to these two compounds and of their cases they attribute 20 to benzidine, 25 to betanaphthylamine, 20 to a mixed exposure of these two and the remainder to mixed exposure of one or the other of them with

other amines. No tumours arose among 500 workmen in contact with aniline alone or with aniline together with other amines.

United States of America

If the U.S.A. had appeared fortunate or provident in having had no industrial bladder tumours, any complacency which might have been felt there must have been dispelled in 1934 when 27 cases were reported by Gehrmann. The first case had arisen in 1931 - about 16 years after manufacture of coal tar dyes in America had begin to assume the proportions of an important industry. Further cases quickly followed and by 1934 it was deemed expedient to hold a "Symposium on Aniline Tumors of the Bladder" at which papers were presented on the incidence (Gehrmann), the etiology (Ferguson), the chemical and industrial aspects (Gehrmann), the pathology (Gay), the incidence, diagnosis and results (Anderson) and the treatment (Washburn). Except for two alphanaphthylamine workers all the men had been exposed to either betanaphthylamine or benzidine, or both, and only two had not been exposed to betanaphthylamine; no tumours were found in aniline workers. Routine cystoscopy of all workers, which will be discussed later, had already been applied and recommendations for safe working methods were put forward. Three years later Evans (1937) reported 83 cases which included those of Gehrmann, and he blamed naphthylamines, benzidine and "other nitro and amido compounds" as causative agents, but again aniline was specifically excluded from the list of suspected carcinogens.

In a communication to the IXth International Congress of Industrial Health in 1948 Gehrmann,Foulger and Fleming (1949) were convinced that aniline did not induce bladder tumour, a conviction that has not been disproved and, in fact, has since been universally agreed. As betanaphthylamine was the only compound able to produce tumours experimentally and as every case of tumour they had met with had had exposure to it at some time, they refused to accept benzidine in the role of a bladder carcinogen until an incidence of tumours, higher than that in the general population occurred in benzidine workers who had had no contact with betanaphthylamine or, although he did not specifically say so, presumably until tumours were induced in experimental animals with it.

Both these requisites were soon to be satisfied. I reported a new series of cases in England, amongst whom were 23 benzidine workers, from a total working population since 1918 of 198 men who had never had contact with betanaphthylamine or any other known or suspected carcinogen (Scott 1952). Meantime, tumours had been induced with benzidine in experimental animals by Spitz, Maguigan and Dobriner (1950). Maguigan (1950) also recorded nearly 200 cases of industrial bladder tumour which had appeared in America up to the time of his writing - a figure which is not surprising when one considers the size of the post-war American industry and the fact that 85 cases had already arisen in the six years between 1931 and 1937.

Italy

The experience in the other countries in Europe which had not started manufacturing dyestuffs on a large scale until the First World War was remarkably similar to that in England and America. In Italy the first bladder tumour in a dyeworker to be attributed to his occupation occurred in 1931 - the same year as the first American case. This first Italian case was one of 11 reported by Di Maio, a Milanese urologist, in 1937. In 1948 in London at the IXth International Congress he presented a further report. His results are summarised in Table I.

TABLE I

Italian cases in 1947 (Di Maio)

	Department			
	Benzidine	Betanaph-thylamine	Alphanaph-thylamine	Aniline
No. employed	213	40	30	619
No.with tumours	22	9	2	1

In addition he lists 68 cases with "congestive" lesions of the bladder which he believed to be precancerous and of which 8 subsequently became cancerous. At the same Congress, Barsotti

and Vigliani (1949) described 33 cases of tumour and 58 of "congestive lesion" from benzidine, betanaphthylamine and alpha-naphthylamine but they found none due to aniline. Their cases undoubtedly overlapped Di Maio's and were probably mostly included in his series. Bellesini (1949) described a factory manufacturing benzidine by the zinc reduction process for a total period of 15 years where none of the 54 workmen had developed tumours. Goldblatt (1956) later reveals from his personal knowledge, that subsequent cystoscopy of these men revealed five tumours at the first sitting.

France:

In France there had been no reports of any occupational tumour of the bladder up to 1947. As late as 1941 Hugeuin said that occupational bladder cancer, so widely known in America, was practically unknown in France. Müller (1951) remarks that the Congress of the French Society of Urologists had bladder papilloma as its subject in 1946 but chemical aetiology was not discussed. In view of the incidence in other countries and the similar manufacturing conditions existing in France it was too much to hope that none had arisen up to that time and it was not surprising when, in 1947, Billiard Duchesne disclosed 17 cases from the Rouen and Le Havre area. At the International Congress of Industrial Health in London in the following year he was able to report a total of 34 known cases in France which had arisen since 1937 (Billiard Duschesne 1949). These included the cases previously published by

Desoille, Hochfeld and Aboulker (1948) by Douiller (1949), Delinotte Arnaud and Chatain (1949) and Aboulker, Gaultier, Benguigi and Smagghe (1949). Again his experience agrees with that of most other post war observers that the tumours are due to contact with benzidine and the naphthylamines.

Other Countries.

Occupational bladder tumours in aniline dye workers are not a monopoly of the Western world. Rosenbaum and Gottlieb as early as 1926 reported 13 cases in a population of 9000 operatives in Russia and cases had occurred in Japan (Nagazio and Kimosita 1940) by the beginning of the Second World War.

Survey by Association of British Chemical Manufacturers.

Thus,by the early 1950's there existed a large body of opinion, supported by a great weight of epidemiological evidence, which agreed on the occupational nature of bladder tumours in dyestuffs operatives and which indicted certain compounds as causal agents. The original cases were attributed to aniline or to fuchsin (magenta) or to a combination of them and some years later benzidine, alphanaphthylamine and betanaphthylamine emerged as the most likely responsible compounds. Aniline was given a clear bill by most observers. Fuchsin was not mentioned in the later reports. It must be remembered, however, that as the century advanced its manufacture declined compared with that of the other suspected agents and in later years it has been made only on a comparatively small scale. Neverthless five cases have recently arisen in a

small factory in England (Ashworth, personal communication, shortly to be published) and these will be considered later.

Two major surveys have been described, one by Rehn who reported in 1906 and one by Curschmann who reported in 1920. The results of these surveys went a long way towards confirming the industrial nature of these tumours and indicating the agents causing them. A third survey, this time on a major national scale, was inaugurated in Great Britain in 1947 when the Association of British Chemical Manufacturers (A.B.C.M.) decided to conduct and finance a major research project on industrial "papilloma of the bladder", as it had come to be known, in England. This intentional euphemism had come to be used because of the fearful sound of the word cancer to English ears and in order not to encourage cancerphobia by its use. The A.B.C.M. among other measures appointed a "Scientific Committee", under the chairmanship of Professor Alexander Haddow, to guide research work into the cause, consider diagnostic methods and examine preventive techniques. A sub-committee was formed, under the chairmanship of Mr N.Strafford,to provideaccurate methods for the analysis of suspected compounds under industrial conditions. The Scientific Committee was disbanded in 1954 and succeeded by a smaller permanent one, the Papilloma Committee under the chairmanship of Mr J.D.Rose and having as its two medical members Dr.M.H.C.Williams and myself.

In 1948 Dr.R.A.M.Case was appointed to a research fellowship created by the A.B.C.M. at the Chester Beatty Institute, to conduct an investigation, in the first place by an extensive field survey, to establish whether aniline, benzidine, beta or alphanaphthylamine are implicated and what factors affect production of tumours of the bladder in workmen in the industry.

Case and his co-workers obtained from the relevant member firms of the A.B.C.M. a register of names of men who had had any contact of over six month's duration with the named compounds (the "Nominal Roll") and a list of all men then known by the firms to have developed bladder tumour. They also obtained from the records of hospitals in the appropriate areas the names of men who had been treated for bladder tumour in the neighbourhood of the relevant factories and, from the Registrar General, the names of all males dying between 1921 and 1949 whose death certificates mentioned bladder tumour. Coroners records and death certificates which mentioned the chemical industry as the occupation of the deceased were also used.

By the beginning of 1952 they (Case, Hosker, McDonald and Pearson 1954) had found 455 cases of bladder tumour from the British chemical industry 444 of which had occurred after 1921; of these 444 men there were 341 whose names were on the nominal roll of men who had worked in contact with the described substances in the factories of the member firms. This group of 341 from a nominal roll of 4,622 was examined statistically in detail.

Of these 341 men, 298 (87.4%) had had contact with benzidine, betanaphthylamine or alphanaphthylamine or some combination of these and 32 (9.4%) were not known to have had such contact. Case and his co-workers found that the overall risk of dying of a bladder tumour, if on the nominal roll was 30 times greater than that of the general population - a statistical finding remarkably similar to the figure of 33 times reached by Leuenberger forty years earlier by much cruder methods.

They also found that betanaphthylamine was the most potent agent and that the relative potency was in the ratio of betanaphthylamine 5: mixed exposure 2.7: benzidine 1.7; alphanaphthylamine 1: . The chance of a workman in betanaphthylamine developing a bladder tumour was 61 times greater than that in the general population, that of a benzidine worker 19 times greater and that of an alphanaphthylamine worker 16 times greater. Their statistical proof of the industrial carcinogenicity of betanaphthylamine, benzidine, and alphnaphthylamine was overwhelming.

They found no statistical evidence to suggest that aniline had caused occupational bladder tumours in the British chemical industry between 1910 and 1952 (Case and Pearson 1954) but the manufacture of magenta and auramine "appears to have a definite occupational hazard of causing tumour of the urinary bladder" but "it should not be assumed that the finished products are necessarily dangerous". This again confirmed the earlier observations made by Rehn in 1895 that fuchsin manufacture was dangerous. Case

and Hosker (1954) have estimated statistically the number of cases which may be expected to arise in the future from people already exposed. Case (1953) set out a method by which it is possible for a firm in Britain to estimate the number of deaths that might arise by the non-occupational risk in a given population. A comparison of this with the actual number might usefully detect unsuspected dangers. Case and Lea (1955) have since set out a simpler method which can be more generally applied to other forms of cancer as well.

The results of the A.B.C.M. study were given to the Factory Department of the Ministry of Labour and to the Ministry of Pensions and National Insurance, and in 1953 papilloma of the bladder was prescribed in Great Britain as an industrial disease in chemical workers under certain conditions. A pamphlet setting out the nature of the study, the results, the knowledge available and the means of prevention was issued to management and workers throughout the industry, by the A.B.C.M. (A.B.C.M.1953). Meantime the analytical sub-committee had completed its work and it subsequently published analytical methods for determining benzidine and betanaphthylamine (Butt & Strafford, 1956). Diagnostic techniques had been studied and appraised in two of the member companies, in The Clayton Aniline Co.Ltd. by myself and in The Imperial Chemical Industries Ltd. by Drs.Crabbe, Cresdee and Williams. The results were published in 1952 and 1956 (Crabbe, 1952, Crabbe, Cresdee, Scott and Williams 1956).

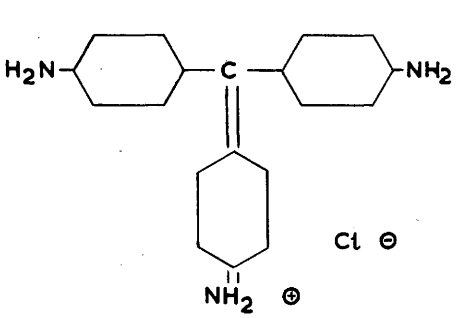
Dr.Williams and I were invited by the A.B.C.M. to draw up a "code of industrial practice" to cover the manufacture and use of known and suspected carcinogens. Our recommendations for safe working were accepted in toto by the Association and were circulated to the member firms in 1953. They were published in 1957 (Scott and Williams 1957). They have since been circulated in extenso by the International Labour Office in English and French to its member countries.

RELEVANT COMPOUNDS

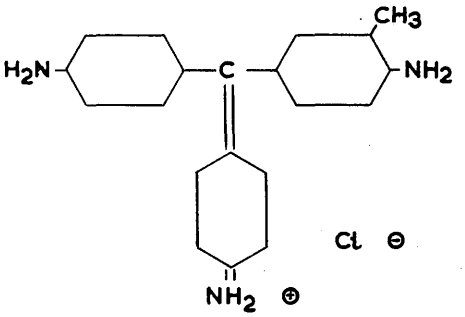
In considering the compounds which have been suspected or proved to be capable of causing occupational tumours in workmen, the history of the manufacture of each one will be described and special reference will be made to their manufacture at The Clayton Aniline Co.Ltd. The experimental evidence relating to their carcinogenicity will be reviewed and an assessment of their potency will be made.

Fuchsin (Magenta).

Fuchsin was the first of the triphenylmethane group of dyes to be manufactured commercially. In Rehn's time it was made by oxidising crude aniline with nitrobenzene in the presence of ferric chloride. As with Perkin's mauveine the shade of fuchsin produced depended on the purity of the aniline used and the most important factor was its relative content of toluidines and xylidines all of which have a higher boiling point than aniline.



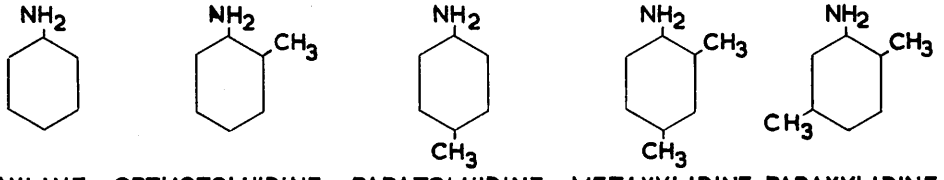
PARAROSANILINE HYDROCHLORIDE.



ROSANILINE HYDROCHLORIDE.

Hence by using crude aniline of varying boiling points a dye ranging from red to blue could be produced at will. As early as

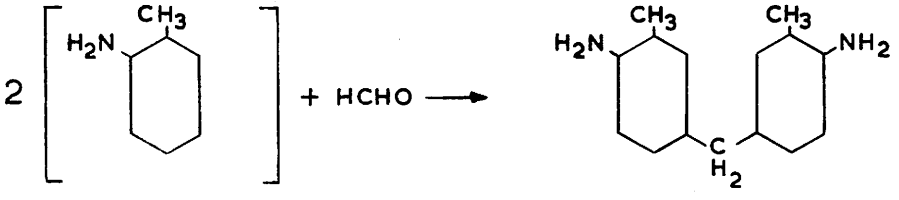
1864 it had been shown that pure aniline did not produce fuchsin. The formulation of the dye depended on the CH_3 group in the toluidine producing the central carbon atom which is necessary for the triphenylmethane structure. The fuchsin at this time was a mixture of salts of "rosaniline".



ANILINE. B.P. 180°C. ORTHOTOLUIDINE. B.P. 200°C. PARATOLUIDINE. B.P. 200°C. METAXYLIDINE. B.P. 212°C. PARAXYLIDINE. B.P. 215°C.

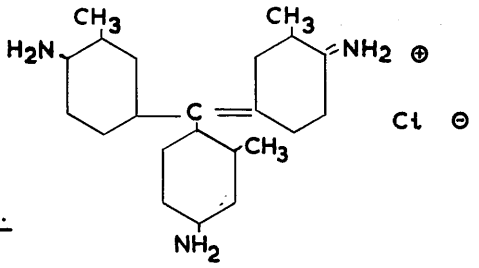
It was later found to be possible to produce the desired colour with accuracy by using pure aniline and the exact proportion of toluidines or xylidines required.

Several other amines were also present in the aniline of the last century. Walpole, Williams and Roberts (1952) pointed out that Hofmann (1862) had identified a new amine, xenylamine (4aminodiphenyl) in the distillation residues of aniline and that Jackson (1875) had isolated methylated xenylamines and naphthylamines from the aniline of his time. The original benzene, therefore, must have contained not only toluenes and xylenes but also naphthalene and diphenyl which were also nitrated and reduced when aniline was made. For the past 40 or more years, and since the 1914 war in England, fuchsin has been made by condensing ortho toluidine with formaldehyde to form ditolyl



ORTHOTOLUIDINE DITOLYL BASE.

The ditolyl base is filtered and dried and is then reacted with ortho toluidine hydrochloride using nitrotoluene as an oxidizing agent, to give "magenta" of a slightly different formula from the original dye but which is a more stable and constant product.



MAGENTA.

The statistical evidence of Case and his co-workers has confirmed the original observations of the danger to workmen who have been engaged in the manufacture of magenta. The original writers' opinions that aniline was the carcinogenic agent were based on reasonably adequate evidence at that time. The suggestion of Walpole, and his co-workers, that these early tumours were due to impurities in the aniline, supported by their experimental results (to be discussed later) makes it still valid, especially when one considers the heavy exposure which must have been commonplace. The fact that since 1910 when pure or purer aniline was used in Germany no tumours have been attributed to it supports their proposition. Neverthless, Case and Pearson's magenta cases all arose in association with the more modern magenta process in which aniline is replaced by ortho-toluidine. Ashworth's five cases were from a factory making magenta from orthotoluidine where no other suspected carcinogens have been used.

It has been suggested that the toluidine is the offending agent but there is no firm evidence to support or contradict this. Animal experiment has so far been negative (Williams 1958) but it must be remembered that experiments have not yet been on a sufficiently extensive scale to be regarded as conclusive. Haematuria from acute cystitis is a common symptom in men exposed to toluidines. It is described by Rehn and many subsequent writers - several cases will be reported later in this work - but it is not accepted as a necessary precursor of tumour (Goldblatt, Scott, Williams). Bleeding usually occurs when exposure has been heavy and may be taken as some index of the conditions existing. Where haematuria has been common, it can be presumed that the exposure has been heavy not only to toluidine but to the other amines present at the same time. More positive evidence than exists at present would be required before it could definitely be concluded that toluidines are causative agents. Similarly, in the absence of conclusive proof, such as animal experiments might afford, it is impossible to make any informed judgement as to the role of the magenta itself.

As Scott and Williams (1957) stated "it is not possible to say at this moment whether the cause of the magenta tumours in England is due to intermediates, to impurities in the magenta process or to the final product itself."

Magenta was made at The Clayton Aniline Co. from 1920 to

1926 by the formaldehyde - ortho toluidine process. Its manufacture was discontinued in January 1926 and from then until 1938 small quantities were bought for the preparation of acid magenta. The total number of men known to have worked on magenta manufacture is 19. As luck would have it, after its manufacture ceased 4 of these men were engaged in making pyrogen sulphur melt colours some of which involved the use of benzidine. There were, therefore, 15 men who had been exposed to magenta and not to benzidine and 4 of those have so far developed tumours. At the same time 2 of these men who have been exposed to both benzidine and magenta have also contracted the disease.

Aniline.

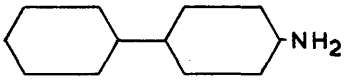
Aniline is manufactured by the reduction of nitrobenzene by iron filings in the presence of hydrochloric acid. The iron is oxidised to ferric oxide and the aniline is distilled off and purified by a series of distillations and condensations.

NITROBENZENE. ANILINE.

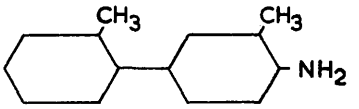
Animal experiments with aniline have failed to yield any convincing proof of its carcinogenicity. Hartwell (1951) lists 17 series of experiments in rabbits, rats and mice. Roffo (1931) using resin pearls impregnated with the chemical reported 3 bladder papillomata in rats but he obtained similar results in his

control animals and this experiment can be discounted as evidence. Wamazki and Sato (1937) claim to have induced papillomata in 12 of 37 rabbits by introducing 1% solution into the bladder but their experiment is not convincing and solutions of 5% and 10% yielded negative results. No tumours of the bladder were reported by the other workers. Goldblatt (1957) says that aniline has not been found to be tumour-inducing in any experimental animal. Beremblum and Bonser (1937) and Gerhman, Foulger and Fleming (1949) have also failed to induce tumours in carefully set up and controlled experiments.

Walpole, Williams and Roberts suspected that the alleged carcinogenicity of the aniline of last century was due to the naphthylamines and aminodiphenyls it contained and they tested both 4 aminodiphenyl and 3:2' dimethyl 4 aminodiphenyl on rats (1952) and the former on dogs (1954).



4 AMINODIPHENYL.



3:2' DIMETHYL 4 AMINODIPHENYL.

Both compounds were found to be highly carcinogenic, the former more effective as a bladder carcinogen in the dog than either benzidine or 2acetylaminefluorene and at least as potent as betanaphthylamine. They suggested that the compounds were metabolised to orthohydroxyamines and that on this orthohydroxylation depends their carcinogenicity, a suggestion which was to be

extended and developed later.

The inference that those aminodiphenyls and naphthylamines present in the early aniline were sufficient to account for the tumours which had been attributed to it was not accepted by Walpole, Williams and Roberts in their first paper. They did not believe that the small quantities present could have accounted fully for the early tumours especially as the greater part of these impurities was left in the distillation residues so that even less significant amounts would have been present in the distillate. In their second paper in 1954 however, they modify this view and remark that this amine (4aminodiphenyl) might have been partly responsible for "aniline cancers of the bladder in Germany before 1920". This revised view seems more reasonable because although the dose and time necessary to induce a tumour in man is not known, it is highly probable that quite small doses for a short time may be sufficient eventually to do so.

Hamilton (1921) suggested that arsenic might be the responsible agent. Her contention was based on two facts; first that fuchsin was originally made by the arsenic acid method (but not since about 1870 !), and secondly that arsenic was present as an impurity not only in the iron and zinc used for the reduction of nitro benzene to aniline or benzidine but also in the sulphuric acid and in the metal of the vessels used in the process. Small amounts of arsine were often liberated and as late as the time at which she was writing, haemolysis from it was frequently observed in workmen.

Kennaway (1925) finally dispelled this hypothesis. Apart from the increasingly conclusive proof pointing to other substances he cited his own 38 consecutive cases of arsenical tumour in none of which had there been any bladder tumours. He knew of only one case in the literature of a person exposed to any of the other cancer-producing materials (i.e. not aromatic amines) developing cancer of the bladder and that was an inoperable tumour in a tar worker who had previously undergone operation for warts.

Gross's personal communication to me, quoted earlier, is perhaps enlightening in that it suggests that aniline was blamed in a generic sense when the actual agents which were responsible were benzidine, betanaphthylamine and some other amines. Nassauer (1919) claimed that the "irritating substance" was always aniline and so dangerous did he consider it that he allowed only three months employment at a time in the benzidine department where aniline was liberated as an impurity in the process at that time. This practice must have increased the numbers at risk to an enormous extent in a plant where exposure must have been heavy. Hamilton likewise stated that it was said (although she does not state who said it, it was, in fact, Nassauer) that in the making of benzidine there may be more actual exposure to aniline vapour than in the manufacture of aniline itself and she inferred that the aniline vapour rather than the benzidine was the danger.

Since the early 1930's , however, all observers have agreed

that there is no evidence to suggest that aniline is the active carcinogen in cases that have arisen in their generation and this certainly coincides with the time since reasonably pure aniline has been manufactured.

It is, therefore, suggested that while some, and possibly many, of the so-called aniline tumours in the earlier years were due to carcinogenic impurities in the aniline, many of the others were loosely ascribed to aniline when in fact another compound such as benzidine or betanaphthylamine was being worked. It must be borne in mind that cases arising in Britain from exposure to magenta after the First World War remain to be accounted for and it cannot be taken as certain that all of the early German fuchsin cases were due to impure aniline.

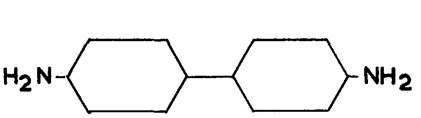
Under modern conditions of manufacture of aniline, which takes place in an enclosed system, exposure to the vapour or liquid and absorption of it either through the skin or by inhalation is so low as to be practically negligible. Williams (1957) suggested the possibility that aniline is a very weak carcinogen and that the advent of modern conditions lowered absorption to levels below those capable of producing tumours. British experience does not support this view. No cases of aniline tumours are known to have arisen in England despite three quarters of a century's experience of manufacture during the first 50 years of which conditions of constant and heavy exposure must have prevailed.

It has been manufactured in The Clayton Aniline Company since 1875 and up to the 1920's conditions are admitted to have been bad by modern standards. They were improved between the wars but it was not until 1940 that a completely enclosed modern plant was constructed. Certainly exposure must have been heavy even in the first 20 years of this century and until 1940 it was more than we would consider safe to-day. Records are good for the past 40 years and some go back to 1900. Since 1920 there has been a working population of 78 men who have worked on this plant (men with less than six months service are excluded). Turnover has been so low that there have only been two new workers on this plant, one processman and one crane man, since it was described by me in 1952. The majority of these 76 men have very long periods of employment - up to 45 years - most of it under the more primitive conditions of the earlier years. No tumours have arisen among these aniline manufacturers nor could any tumours be attributed to aniline in any other part of the factory.

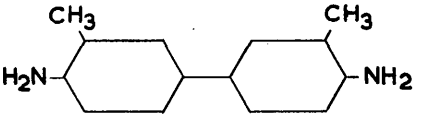
The experience at Clayton, therefore, accords with the view that aniline is not carcinogenic in man under industrial conditions even in the earliest days of its manufacture.

Benzidine (4:4' diaminodiphenyl). Its Homolgues and Derivatives.

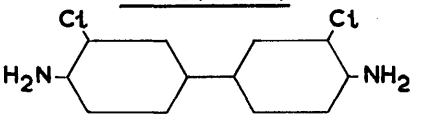
Benzidine and its derivatives, the most important of which are tolidine, dichlorbenzidine and dianisidine are used largely for the manufacture of azo dyes.



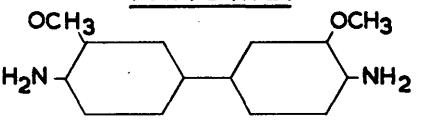
BENZIDINE.



TOLIDINE.



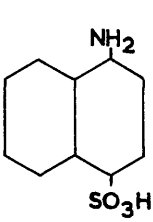
DICHLORBENZIDINE.



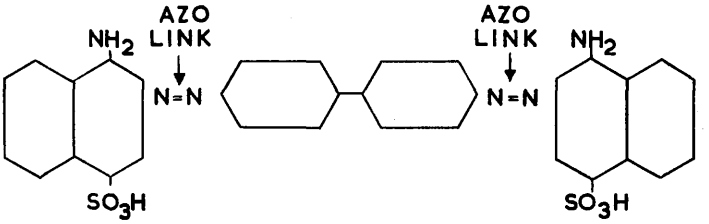
DIANISIDINE.

This process depends on the diazotization by nitrous acid of an aromatic amine which produces the "azo" linkage, i.e. two nitrogen atoms united by a double bond. The molecule is highly reactive at this point and will unite or "couple" with, for example, an amine. Many of the resultant compounds are colours.

Benzidine manufacture began to assume large proportions about 1880 when the azo dye Congo Red was first made on a commercial scale.



NAPHTHIONIC ACID.

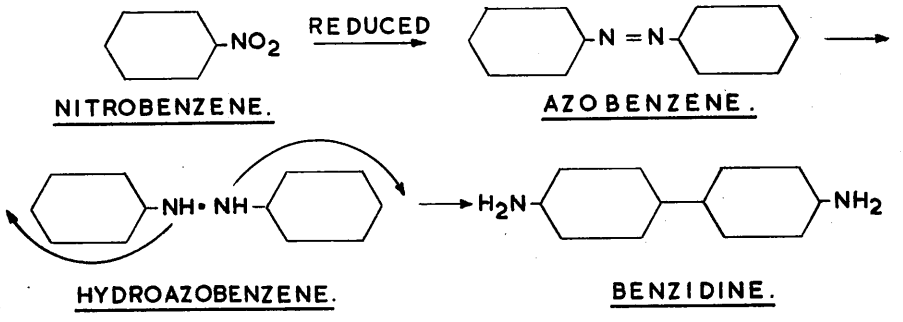


CONGO RED.

It was quickly followed by many similar dyes using benzidine, alpha-naphthylamine, betanaphthylamine and many other aromatic amines for diazotisation and a great variety of aromatics and aromatic amines as coupling agents. There is virtually no limit to the changes which can be rung and many thousands of azo colours have been listed. Many of them have stood the test of time by virtue of their shade, their affinity for certain materials, their brilliance, their fastness to light, sweat, washing and their many other properties.

Benzidine is also used in the manufacture of certain other types of colours.

In the manufacture of benzidine, nitrobenzene is reduced in an alkaline medium. (It will be recalled that reduction of nitrobenzene in an acid medium results in the formation of aniline). The reduction is affected either by zinc or iron and caustic soda, by sodium amalgam or by electrolytic means. The nitrobenzene is reduced through azobenzene to hydroazobenzene - some factories, for example, one I visited in Germany, start with azobenzene which is made in another plant. The hydrazobenzene is then converted by the addition of hydrochloric acid to benzidine.



(The arrows indicate the conversion mechanism.)

Dichlorbenzidine, tolidine and dianisidine are made similarly from chlornitrobenzene, nitrotoluene and nitroanisole.

Benzidine manufacture (Fig.1) was started in The Clayton Aniline Company in 1918 following preliminary experimentation and trials in 1917.

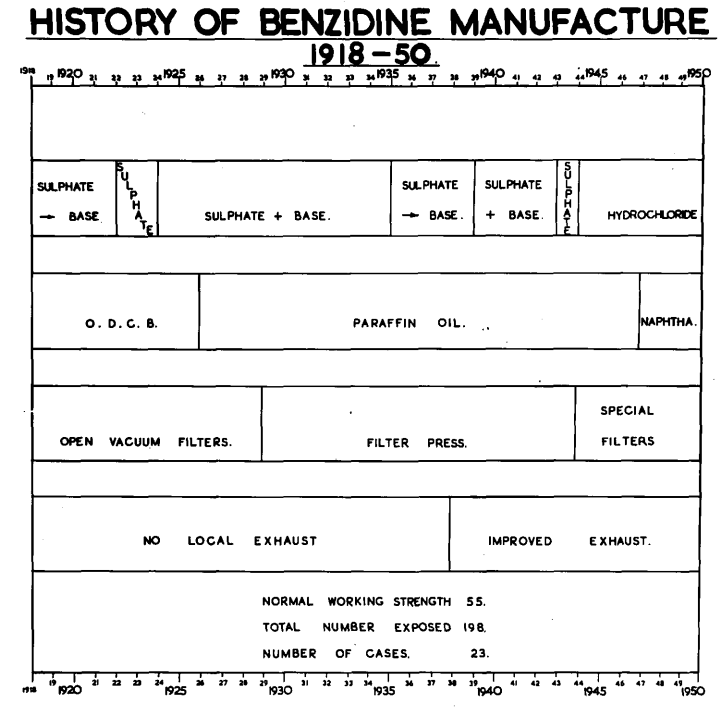


FIG. 1.

It has always been made by the zinc reduction process. A solvent was introduced into the process in order to keep the reduction reaction smooth. Orthodichlorbenzene was used for this purpose until 1926 when it was replaced by paraffin oil. In this process the hydroazobenzene is formed as granules and these are filtered out and re-charged in the next stage. In 1947 this method gave way to the use of solvent naphtha, which dissolves the hydrazo-benzene and keeps it in solution until the conversion by hydro-chloric acid. Benzidine dihydrochloride is thereby formed and

precipitates out. It is redissolved by adding water and heating. The aqueous solution of the amine is separated from the upper solvent layer by running off and the benzidine dihydrochloride is then salted out.

Benzidine was first produced as the sulphate which was then converted to the base and until 1944 either the sulphate or base or both have been made. From 1944 to 1951 the hydrochloride was manufactured.

Open vacuum filters were used until 1929 when they were replaced for technical reasons by a large filter press. Contact was heavy at this stage. It could not be reduced to the level thought desirable, and so in 1944 specially designed covered vacuum filters were substituted. (It is of interest to note that in November 1957 filter presses were seen in a German factory making benzidine). Some exhaust ventilation was installed in 1938 and this was added to and improved from time to time since then.

In 1951 a completely new plant was opened. In this the manufacture of benzidine and its derivatives is now carried on separately from other manufactures. Benzidine is not isolated; it is tetrazotised in the usual way with nitrous acid and the resulting tetrazonium dichloride now containing virtually no benzidine and still in the enclosed system, is conveyed by pipeline to the colour factory several hundred yards away. It is then

distributed to the azo dye manufacturing vessels without leaving the enclosed system.

By 1949 the danger to workers in benzidine of contracting bladder tumours had been agreed by observers in all countries except for those in America whose doubts were resolved soon afterwards. The epidemiological evidence of its carcinogenicity to workers was incontrovertible, the danger existing both in its manufacture and in its use. It had been held that all stages of the manufacturing process were hazardous as men engaged in the reduction to hydrazobenzene were apparently affected equally with those doing the conversion to benzidine and its separation. Other men engaged on other processes in the same building were also affected and the whole operation was regarded as dangerous until Barsotti and Vigliani (1949) described a factory where hydrazobenzene was made in one building and conveyed to another factory for conversion to benzidine. No tumours had occurred among the men making hydrazobenzene - the exposure times are not given - but tumours had arisen in some of the benzidine men. No tumours have so far been induced in experimental animals with hydrazobenzene (Hartwell, 1951). Scott and Williams (1957) believe that the hazard exists after the conversion of hydrazobenzene to benzidine.

The accepted industrial carcinogenicity of benzidine to workmen had naturally led to many experiments being made on animals

but until 1950 all had negative results. As early as 1920 Jaffe sensibly suggested that negative results should be published so that other workers would not repeat fruitless experiments. Bierich (1922), Kennaway (1924), Berenblum and Bonser (1937), Yoshildi et al (1941), Gehrmann, Foulger and Fleming (1949) all reported animal experiments with benzidine in which no tumours were induced. The last named used dogs and continued their experiments for five years.

In 1950, Spitz, Maguigan and Dobriner published a report of the successful induction of tumours in rats and dogs by the administration of benzidine. A high proportion, 10% of about 500, of the rats developed tumours of a sebaceous gland adjacent to the external auditory meatus and adenocarcinomata of the colon, but not bladder tumours; of 11 dogs, seven on benzidine and four on benzidine sulphate, seven survived and three of these were eventually reported to have developed papillomata and carcinomata of the bladder after periods up to 10 years. The rat tumours were similar in type and distribution to those occurring with 2acetylaminofluorene in that they were found in the liver, colon and auditory sebaceous gland. A much smaller proportion (4.3% of 105) of rats who received orthotolidine contracted tumours.

The doses given were high and administration was prolonged - the dosage to the rats was of the order of 15 mg. per week of benzidine injected over periods averaging 2 years. The explanation

of the failure of previous experimenters to induce tumours may lie in inadequate dosage given for insufficient periods, or to their using unsuitable species. For example, Beremblum and Bonser in 1937 used rats and rabbits - the latter species has since proved to be relatively insusceptible to induced bladder tumours - and they gave much lower doses. In one series of 9 rabbits who survived, the experiment was continued for 4 years but in another series of 29 rats it was discontinued after 76 weeks.

Thus the carcinogenicity of benzidine was placed beyond any doubt by the epidemiological evidence and animal experiments. The results of Spitz and her co-workers have been confirmed several times since and many compounds related to aminodiphenyl and diaminodiphenyl (benzidine) have proved carcinogenic in animals (Walpole, Williams and Roberts 1954, Miller, Sandin, Miller and Rusch 1956).

Certain homologues and derivatives of benzidine, of which orthotolidine, dichlorbenzidine and dianisidine are the most important are used for similar purposes to those of benzidine. No population of workmen is known which has been exposed to these homologues without also having been exposed to benzidine itself. Most factories which manufacture benzidine make the homologues as well, but one at Grenoble in France makes benzidine only and some cases of tumour have arisen there (Williams, personal communication). The homologues have hitherto been less in demand than benzidine and, therefore, have been made on a much smaller scale so that

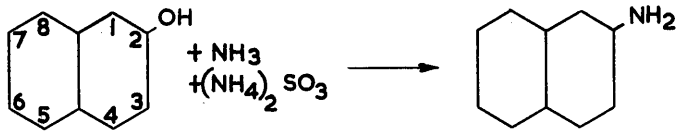
exposure to them has been less, both in amount and in total time than it has to benzidine.

Orthotolidine was found by Spitz to be a weaker carcinogen than benzidine but so far no animal experiments have been published in which tumours have been induced by dichlorbenzidine or dianisidine. Animal experiments now in progress support the view that the two latter compounds are much less active even than orthotolidine, (Walpole and Williams, personal communication) and it is thought that these conclusions can be held also to apply to man (Scott and Williams 1957).

It is, however, anticipated that the demand for some of these materials will increase rapidly for the making of certain paints and pigments so that the scale of their production may come to rival that of benzidine. Meantime, one must reserve judgement on the carcinogenicity of these homologues and, if large amounts of them are to be handled, they should, as Scott and Williams recommend, be treated industrially in a similar fashion to benzidine itself.

Beta-naphthylamine (2 Naphthylamine).

The manufacture of betanaphthylamine has been carried out by the same fundamental principle since its inception as a commercial product about 1880 until it was given up in 1950. It was made by the action of ammonium sulphite and ammonia on betanaphthol (2hydroxynaphthalene) in autoclaves under pressure at 150°C. This is known as Bucherer's reaction.



BETANAPHTHOL. BETANAPHTHYLAMINE.

When the reaction was completed the betanaphthylamine was isolated by being filtered off, dried and distilled. It was then allowed to solidify and either broken into lumps or more finely prepared by flaking it or grinding it to a powder.

Betanaphthylamine is a whitish powder or a dull grey red flaked product depending on its purity and its physical state.

It is apparently a harmless substance and acute toxic effects do not occur readily. Müller has described two men who developed acute haemorrhagic cystitis as a result of massive exposure to it, but no such effects have been recorded at Clayton at least in the last 25 years of its manufacture. It is non-irritant and has not caused dermatitis in the workmen.

Manufacture of betanaphthylamine started at The Clayton Aniline Co. in 1920, and Fig.2 is a diagramatic representation of its history in the firm.

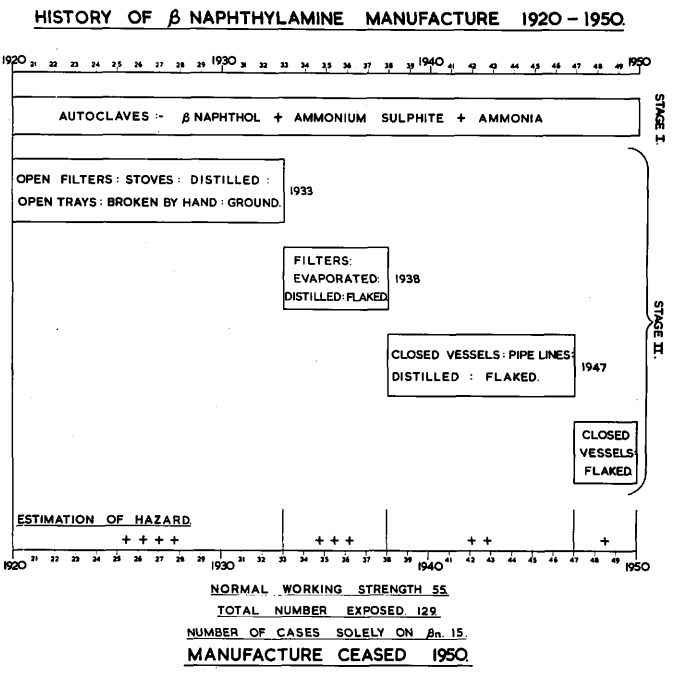
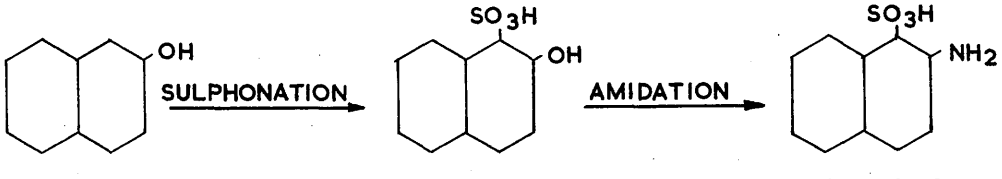


FIG. 2.

The first stage of the process, the heating of betanaphthol with ammonium sulphite and ammonia has been virtually the same throughout. The second stage, that of separation of the amine from the liquors in the autoclave has been progressively improved. For the first 13 years until 1933 the charge was filtered in open filters and dried in large stoves which the workmen had to enter. It was purified by being distilled in another building, (where for many years benzidine was also distilled) and the molten amine was run on to shallow trays to cool and solidify. When solid it was broken up by hand into small pieces and finally ground in a mill

to a fine powder. In 1933 stoving, setting in trays, breaking up by hand and grinding were omitted. The distilled product was "flaked" by being run on to a drum revolving against a knife edge. It solidified on the surface of the drum and was scraped off in flakes. In 1938 more enclosure of the process was attained by keeping the reacted charge in the closed vessels and washing out the other products from them; the betanaphthylamine was then dried in these vessels and piped molten to the still where it was distilled and then flaked as before. By 1947 further improvements which had been impossible during the war were applied to keep exposure to a minimum. The flaker was enclosed and elaborate improved exhaust ventilation applied to it; distillation was omitted to minimise vaporization.

Finally, in 1950 the manufacture and use of betanaphthylamine in this Company was abandoned because of the danger associated with it. Other organisations followed this lead and by 1952 it had been stopped everywhere in Great Britain. Sulphonation of beta-naphthol followed by amidation is now the method used for preparing the sulphonic acids in the synthesis of the dyestuffs for which betanaphthylamine was previously used as an intermediate.



BETANAPHTHOL. OXY TOBIAS ACID. TOBIAS ACID.

The total number of men who had had over six months' employment in the autoclave shed was 129 and the normal working strength was 55. An average of two men were employed in the stillhouse.

A rough estimation of the hazard existing during these periods is indicated in the diagram. Conditions in the first 13 years of manufacture were bad and exposure must have been heavy. There must have been heavy skin and atmospheric contamination in the stoving, handling and breaking up of the amine and the workmen's clothing, hair and skin became powdered with it in the grinding. Some dust must have been inhaled and swallowed. Melting and distillation under the conditions prevailing must have resulted in a high vapour content in the atmosphere and a correspondingly high intake by inhalation. The working place was heavily contaminated with dust and the risk of absorption even when the process was not running must have remained high. The vapour and the dust constituted a danger to men working in adjacent processes and in neighbouring sheds.

In view of the German and Swiss experience even before 1920 it may seem strange that the hazard was not recognised in England earlier. Yet itmust be remembered that the same lack of realization, or lack of action, ruled in America, France, Italy and even in experienced Germany and Switzerland for long after the First War. It is only fair to say that the Swiss gave up

its manufacture in 1938 and that Britain would have abandoned it much earlier than 1950 but for the war. It is still manufactured in the U.S.A., in Ttaly and in Czechoslovakia. One German factory is known to buy it from the last source (Communication to meeting of Cancer Commission. Deutsche Forschungagemeinschaft, November 1957).

There has long been a remarkable agreement among all reporters about the carcinogenicity of betanaphthylamine. It was the first of the compounds suspected of causing occupational tumours of the bladder to be proved capable of inducing tumours in experimental animals. Many attempts had been made to induce tumours in animals with it before success was achieved. Schar (1930) claimed to have induced bladder papillomata in one rabbit in a series of six who had been exposed for over two years to the inhalation of betanaphthylamine vapour in air but his interpretation of the histology is suspect and his experiment is not convincing. Perlmann and Staehler (1932) described bladder tumours in 6 of 31 rabbits receiving daily injections of it. Berenblum and Bonzer (1937) failed to confirm either of these results despite heavy dosage over long periods in a large series of rabbits and rats. All their results were negative.

A preliminary paper in 1937 from Hueper and Wolfe followed by a full report from Hueper, Wiley and Wolfe (1938) described the successful induction of tumours, papillomata and carcinomata, in

female dogs after subcutaneous and oral dosage for two to three years. They had also used rabbits and failed to induce tumours in them. The dog was later to prove to be the most suitable species of animal for this work. The tumours in the dogs were similar to those seen in dye-workers in that they continued to grow and to recur after cessation of the treatment and in one dog the tumour arose several months after administration ceased. In several of their dogs they observed lesions which they considered to be pretumourous and which were similar in description to those described by Di Maio in dye-workers. Their results have been confirmed by other workers, notably Bonser (1943) who virtually excluded impurities as the cause by inducing tumours in dogs with a highly purified compound in similar dosage over five years. Case and Pearson (1954) nevertheless maintained that impurities in the betanaphthylamine might possibly still be the cause as they had isolated small amounts of the carcinogen 3:4:5:6 dibenzcarbazole from the so-called pure compound.

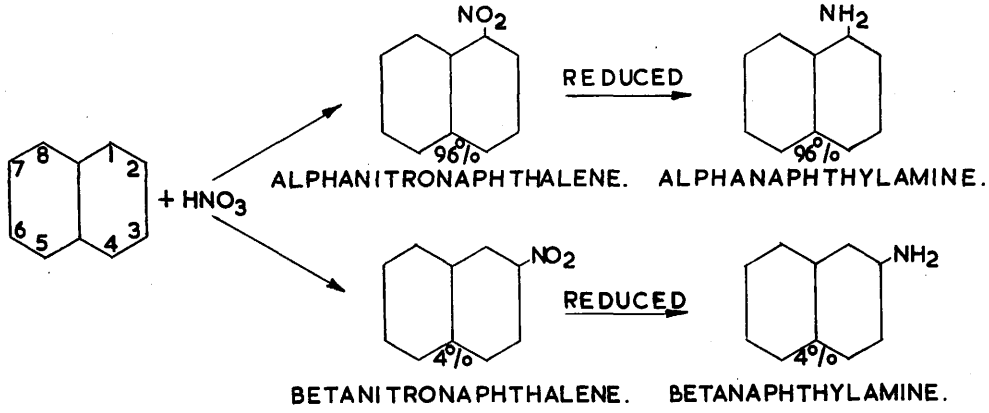
Later work on the metabolism of betanaphthylamine and other amines in animals and in man sheds a great deal of light on the way in which they act and supports the view that the carcinogenicity of betanaphthylamine does not depend on impurities in it. This will be discussed in the chapter on the mode of action.

There is undoubtedly overwhelming evidence that betanaphthylamine is a highly active carcinogen not only to laboratory animals

but to man under industrial conditions of manufacture and use, so much so that its manufacture has been given up in Britain solely because of the danger associated with it.

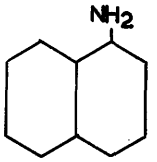
Alphanaphthylamine. (1naphthylamine).

Alphanaphthylamine is used in industry for similar purposes to those for which betanaphthylamine is used, that is for the manufacture of azo dyes, condensation colours and for certain rubber processess. It is manufactured by the nitration of naphthalene to alpha-nitro-naphthalene and its subsequent reduction. When naphthalene is nitrated the product consists of about 90 - 96% of alpha-nitro-naphthalene and about 10 - 4% of beta-nitro-naphthalene so that subsequent reduction and isolation yields the corresponding proportions of alphanaphthylamine and betanaphthylamine.

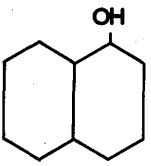


Under present day conditions of manufacture the beta-isomer content can usually be kept down to about 4% .

Alphanaphthylamine is also used for the manufacture of alphanaphthol by hydrolysis.

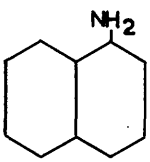


HYDROLYSIS

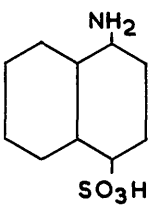


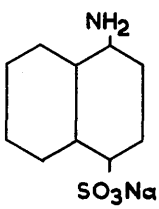
ALPHANAPHTHYLAMINE. ALPHANAPHTHOL.

This is in contrast to betanaphthylamine which is made from betanaphthol prepared more directly from naphthalene. Sulphonated naphthylamines are used widely in the colour industry and among the most widely used are naphthionic acid and sodium naphthionate which result from the simple sulphonation usually by sulphuric acid of alphanaphthylamine under controlled conditions.



+ H_2SO_4





NAPHTHIONIC ACID. SODIUM NAPHTHIONATE.

This sulphonation is "preferential" to the alpha-isomer. Virtually only the alphanaphthylamine is sulphonated in this process with the result that most of the betanaphthylamine content is left unreacted so that when the naphthionic acid is isolated the residue

contains a much higher proportion of betanaphthylamine than the original compound - often as high as 30%.

Alphanaphthylamine was manufactured in The Clayton Aniline Co., by the method described, for only four years, from 1926 to 1930. The usual number of men employed on this process was three and a total of four men in all were engaged on it for over six months. None of these has so far developed bladder tumour. Both before 1926 and after 1930 it has been bought from other manufacturers and used in large quantities for the large scale manufacture of alphanaphthol, sodium naphthionate and a wide range of azo dyes and other colours. The total number of men engaged in work involving its use in these respects is 88 and 4 of them have so far developed tumours.

The carcinogenicity of alphanaphthylamine has not been so readily accepted and agreed upon as that of betanaphthylamine despite the number of cases which have been attributed to it in many countries (Table 2).

TABLE 2.

No. of cases attributed to alphanaphthylamine from literature.

Year	Author	Country of origin	No. of cases
1929	Wignall	England	7 (+8 doubtful)
1937	Evans	U.S.A.	20
1949	Gehrmann et al	U.S.A.	2
1948	Di Maio	Italy	2
1948	Barsotti	Italy	2
1948	Duchesne	France	2
1948	Goldblatt	England	11
1952	Scott	England	1 (now 4)
1954	Case et al	England	28

The 28 cases found by Case et al in England almost certainly include those of Wignall and Goldblatt and the one of mine. Di Maio's and Barsotti's are probably the same two cases. Hence a total of 56 reported cases is estimated but, apart from Müller's in 1951, no reports have been published from America or Europe during the last ten years and many more cases may have arisen from these sources in the meantime.

While there can be no doubt that "technical" (i.e. commercial)

alphanaphthylamine is dangerous under industrial conditions of manufacture and use,it is not universally agreed whether it is a carcinogen per se or only by virtue of its beta-isomer content. No experimental tumours have so far been induced by it in animals. Schar (1930) claimed to have induced papillomata in two rabbits with it but one must agree with Beremblum (1932) that the histological appearances in the photomicrographs are not convincing and that they fail to support the findings described in the text. His experiments have not been confirmed.

I suggested that the tumours which arise in alphanaphthylamine users more heavily exposed to the residues in naphthionic acid manufacture might be due to their high betanaphthylamine content (Scott 1953). I advised that one must reserve judgement about the carcinogenicity of pure alphanaphthylamine itself as it is not used in the industry but that one must treat its manufacture and use with the same care and respect that must be accorded to betanaphthylamine and benzidine.

Since then the evidence on which alphanapthylamine may be considered to be carcinogenic per se has accumulated. In 1954 the A.B.C.M. survey (Case et al) revealed 28 cases of bladder tumour in workers in alphanaphthylamine (apart from other cases in workers exposed to it in combination with other amines such as betanaphthylamine and benzidine), 20 of whom had been engaged in its manufacture and 8 in its use. The average latent period from beginning of

exposure to onset of tumour was 22 years, (S.D. 6 years) and this was significantly different from that of betanaphthylamine which was 16 years (S.D.6). Case concluded therefore, that the betanaphthylamine content of the alphanaphthylamine may not be the sole active agent (unless it is assumed without evidence that alphanaphthylamine exerts a delaying action on the rate of development of betanaphthylamine tumours) and that alphanaphthylamine itself is capable of causing tumours in man. The longer development may account for the delay in alphanaphthylamine becoming accepted as a carcinogen in the industry and for the small number of cases reported in the earlier literature.

Although no tumours have been induced in experimental animals with alphanaphthylamine, one of its metabolites 1 amino 2 naphthol has been found to induce tumours in five mice out of six when implanted into the bladder (Clayson, 1953). This is also one of the metabolites which are excreted in the urine in man.

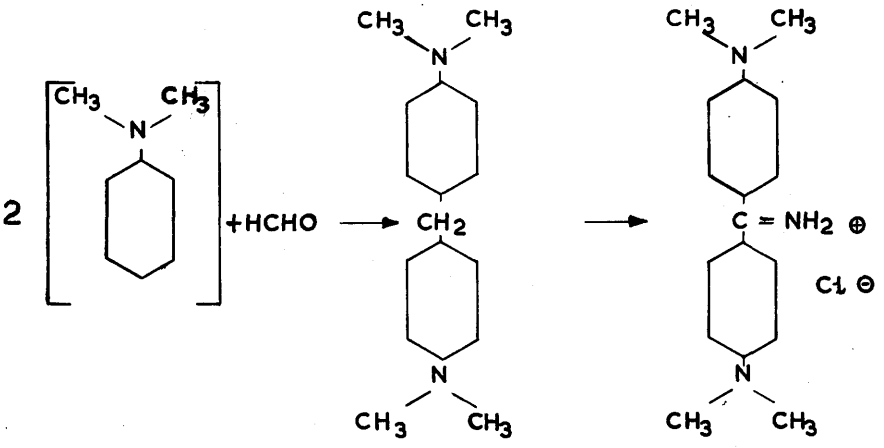
It is, therefore, difficult to escape the conclusion that alphanaphthylamine is carcinogenic to man. Even if it were not itself a carcinogen it is never found in industry without at least 4% of betanaphthylamine in it and in some processes this figure rises to 30% in the residues. The carcinogenicity of betanaphthylamine is not in doubt. One must consider alphanaphthylamine, therefore, as it is found in industry ("technical alphanaphthylamine") and there can be no doubt epidemiologically and theoretically of

the risk attached to it. No refuge should be sought on the grounds that it takes longer to act and is less potent than either betanaphthylamine or benzidine. Scott and Williams (1957) recommend a standard of precautionary measures in its manufacture and use as high as that recommended for benzidine.

Auramine.

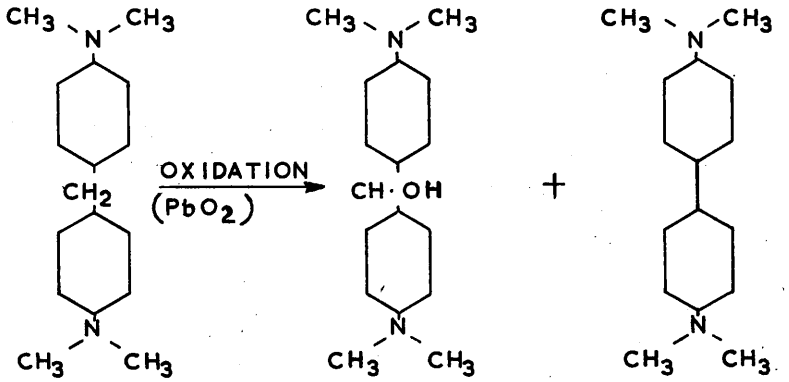
Case et al (1954) found evidence that the manufacture of auramine may cause tumour of the bladder in workmen engaged in its manufacture. There was a statistically significant excess in the number of deaths certified as being due to bladder tumour among them. The age at onset and at death tended also to be lower than in the general population.

Auramine has been manufactured and used since 1884 for the colouring of paper and some textiles. Dimethylaniline and formaldehyde are reacted to produce Michler's base (tetramethyl diaminodiphenyl methane) which is converted to auramine by heating it with sulphur and ammonium chloride in the presence of ammonia.



No tumours from auramine had been reported before Case, but Müller has described two cases, which he attributed to dimethylaniline in men making auramine from it. No other cases of tumour from it seem to have appeared before 1954 and Scott and Williams raised the point that the tumours in Case's series may have been due to other chemicals handled in the auramine shed. They advised further examination of this possibility but no further evidence has come to light.

Another possible explanation is now suggested. In a paper by Kehrmann, Roy and Ramm (1922) it is pointed out that Michlers base can be oxidised by lead dioxide and sulphuric acid to tetra methyl benzidine, a potent carcinogen (Walpole and Williams (1958).

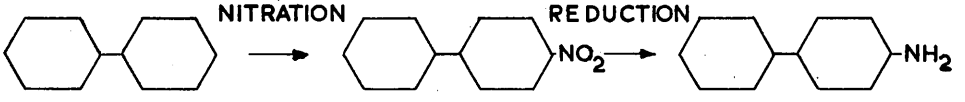


So far there is no evidence that such impurities have been present in auramine or at any stage of its manufacture at any time in Britain or the Continent. No work on its metabolism is known to have been done but it is possible that tetramethylbenzidine is formed in the body.

Auramine has never been manufactured at The Clayton Aniline Co. but dimethylaniline and Michler's base, hydrol and ketone have been made for 25 years. The normal working complement is 2 men and a total of 20 men have been exposed in all. No tumours attributable to these have arisen.

Xenylamine (4amidodiphenyl)

Unlike most of the intermediates implicated as industrial bladder carcinogens, xenylamine manufacture was not started on an industrial scale until 1938 when it was first made in the U.S.A. for use as a rubber antioxidant. The method was the familiar one of nitration (of diphenyl) and subsequent reduction.



DIPHENYL. 4: NITRODIPHENYL. 4: AMIDODIPHENYL. (XENYLAMINE)

Some 2nitro and hence 2aminodiphenyl are found at the same time.

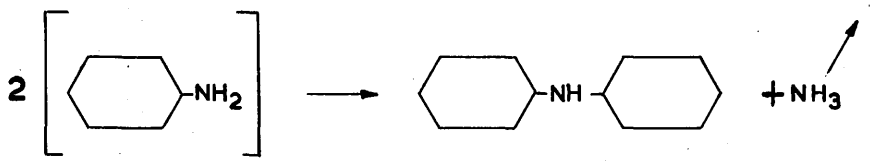
In 1952 Walpole, Williams and Roberts published the first proof of its carcinogenicity. They induced tumours with it in rats and in 1954 confirmed this by using dogs. They pointed out that it may be capable of causing bladder tumours in man.

In 1955 Melick, Escue, Naryka, Mezera and Wheeler confirmed Walpole and his colleagues' prognostication when they reported 19 cases among 171 men who had been engaged in its manufacture and

use, that is to say that within 20 years of starting its manufacture 11% of the men exposed to it had developed bladder tumours. Its manufacture was forthwith stopped in the U.S.A. Scott and Williams recommended that it should not be started in Britain and in fact it has never been made in this country.

Diphenylamine.

Diphenylamine like many of the other intermediates considered has been made since about 1880, at first in Germany and later all over the world. It is made by the reaction of aniline or aniline hydrochloride under high temperature and pressure.



ANILINE. DIPHENYLAMINE.

A small amount, usually about .025%, of 4aminodiphenyl is also formed in some processes (Stagg and Reed, 1957) and is likely to be present in the finished product, while as much as 1% may be present in the residues. The manufacture of diphenylamine has increased rapidly in amount during the last 15 years for rubber anitoxidants and insecticides such as phenothiazine and it is still increasing. More men are likely to be exposed to it for more continuous periods. Müller attributed two tumours

to it in 1933, but no other reports of its carcinogenicity have been published.

It has been manufactured at The Clayton Aniline Co. since 1921. Until about 10 years ago the old method of condensation of aniline with its hydrochloride was used; since 1948 it has been made by condensing aniline using phosphorous trichloride as a catalyst in high pressure autoclaves. Amounts of 4aminodiphenyl of the order of 0.005 and 0.01% have been identified in this process and of 0.2% in the residues since Stagg and Redd's method of determining it was applied early in 1957. No tumours have arisen which could be attributed to it. Careful watch is being kept on what may ultimately prove to be a dangerous manufacture and working conditions are carefully safeguarded.

Other Compounds.

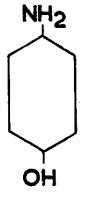
Several other compounds which are made and used in the dye industry must be considered. It has never been suggested that either alphanaphthol or betanaphthol, neither of which are amines, are carcinogenic and there has been no evidence to indicate that they are likely to be so. As alphanaphthol is made from alphanaphthylamine it must be ensured that the final product is free of amine. Phenylalphanaphthylamine and ethylalpha-naphthylamine have not been shown to be, and are not believed to be, dangerous except when made from alphanaphthylamine, the handling of which may constitute a danger. They can be made safely from alphanaphthol.

Phenylbetanaphthylamine is sometimes thought to be carcinogenic because of its name but there is no evidence to suggest that it is dangerous and it is not considered to be an industrial carcinogen (Scott and Williams). It was made at Clayton from 1932 to 1942, from betanaphthol and aniline, on a fairly large scale and no tumours have been attributed to it among the men who were engaged on its manufacture and use.

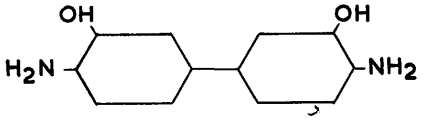
THEORIES OF CAUSATION AND METABOLISM

Theories of the cause of bladder carcinoma have been largely influenced by the general conception of the aetiology of cancer accepted at the time and by the existing state of knowledge. Bayle (1833) first suggested a possible cause in a gouty diathesis accompanied by urinary calculus; Waldeyer (1873) suggested an epithelial origin and Lubarsch (1901) distinguished tumours arising from embryonal rests from the far more numerous ones of different origin. The knowledge that bilharziasis was directly related to a type of bladder tumour strengthened Rehn's contention that in his cases the tumours were due to inflammation and irritation caused by earlier cystitis and calculi.

Rehn in his first paper quoted Engelhardt as showing that aniline is excreted in the urine as a conjugate of paraaminophenol. Adler (1907) showed that 3 3' dihydroxybenzidine was found in the



PARAAMINOPHENOL.



3:3' DIHYDROXYBENZIDINE.

urine of animals given benzidine. Engel (1920) confirmed these experiments but was unable to find anything then known to be

carcinogenic in the urine although Oppenheimer (1920) had suggested that it was a metabolite of benzidine or aniline which was specially active on the bladder epithelium. Schar (1930) and Perlmann and Staehler (1932) who claimed to have induced tumours in animals with alphanaphthylamine and betanaphthylamine were likewise unable to demonstrate a carcinogenic agent in the urine.

Tumours were eventually induced in animals with betanaphthylamine by 1937 by Hueper and his co-workers, with benzidine by 1950 by Spitz and her co-workers and with 4aminodiphenyl by 1952 by Walpole, Williams and Roberts. These three are the only compounds imputed to be causes of occupational bladder tumours in man, which have been confirmed as carcinogens by experiments on animals. In most of the experimental animals, tumours have been induced by them in many organs, but the dog is the only animal in which bladder tumours have appeared readily or early. In men exposed to these compounds under industrial conditions careful investigation has failed to reveal an incidence of tumours in organs, other than the bladder and renal pelvis, higher than that in the general population. Man and the dog are the only known animals who have this high susceptibility of the bladder to tumours induced by aromatic amines. Why do man and the dog react differently in this respect from other species and why should the bladder be attacked?

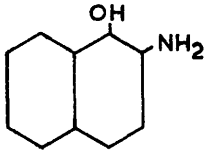
Bonser and her co-workers (1951) suggested and investigated three possible reasons for this species difference in response,

(1) that it might be because of a difference in metabolism from other species, or (2) that metabolite(s) may be at maximum concentration in the urine, or (3) because in man and the dog the urine is acid.

They conducted a series of experiments in an attempt to determine these several points. First they reconfirmed the high susceptibility of the dog to betanaphthylamine by inducing bladder tumours in six animals out of six in under four years. In three of the dogs the urine was kept alkaline by the administration of sodium bicarbonate and no difference in tumour induction compared with the other three was observed. This was regarded as sufficient evidence to dispose of the third theory - that the pH of the urine was important.

Using larger numbers of different animals, rats (25) mice (49) and the same number of rabbits (6), they found that tumours of the bladder could be induced only occasionally and after a long time in rats and rabbits and not at all in mice although the mice readily developed benign and malignant hepatomata.

Previously Engel (1920), Wiley (1938) and Manson and Young (1950) had shown that 2amino 1 napthol was a metabolite of beta-naphthylamine in man, dogs and rats respectively.



2 AMINO I NAPHTHOL.

Clayson (1950) had developed a method for estimating 2amino-1 naphthol conjugates and this enabled Bonser and her colleagues to study species differences in the mode of urinary excretion of the metabolite after administration of various doses of beta-naphthylamine. They found that there was an approximate correlation between the relative susceptibility to induced bladder tumours in the dog, mouse, rat and rabbit and the amount of 2amino 1 naphthol conjugates they excrete after dosage with beta-naphthylamine. In the dog the concentration of 2amino 1 naphthol conjugates in the urine was about 200 times that in the blood plasma. They concluded that not only was there a species difference in metabolism of betanaphthylamine in the dog but there was also a maximal concentration of the metabolite in the urine.

The presumption that this metabolite was the active carcinogen was attractive, and they tested this theory on three mice using a method devised by one of them (Jull, 1951) which consisted of implanting 2amino 1 naphthol in wax pellets into the bladder. One developed a papilloma, one a carcinoma and one metaplasia and hyperplasia "amounting almost to a papilloma". Further experiments (Bonser, Clayson, Jull and Pyrah 1952) on a larger scale confirmed these results. This time betanaphthylamine was also tested by implanting it in mice bladders and no tumours were induced by it. Sarcomata at the site of injection of 2amino 1 naphthol confirmed that it is a local carcinogen whereas no local tumours could be induced at the site of injection with betanaphthylamine in mice,

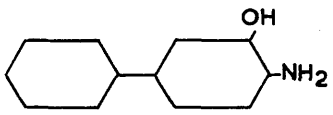
rats or rabbits. In 1954 Bonser and her co-workers described a method of introducing carcinogens in oil into the bladders of dogs by catheter, a technique which may facilitate further experiments in this species and render comparison with other species easier.

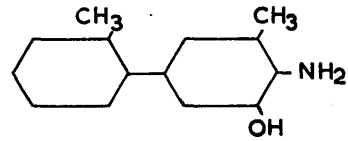
It seems reasonable at this stage to conclude that this metabolite, 2amino 1 naphthol, is the active, or one of the active, substances in the production of bladder tumours in man and the dog. It is not the only metabolite nor is it suggested that it is necessarily the only carcinogenic metabolite of betanaphthylamine but the fact that it is formed in higher percentages from betanaphthylamine in these species and concentrated so highly in the urine must be a determining factor in the localisation of the initial disease to the bladder.

The position with benzidine is similar in many ways. Baker (1950 and 1953),working in my laboratory, isolated 3:3' dihydroxybenzidine from the urine of men working on benzidine and induced tumours in the bladder and livers of mice with it. He fed it to rats and induced tumours including ear gland tumours, similar to those reported by Spitz and her co-workers with benzidine. The tumours appeared in a shorter time than those induced by benzidine itself. Three of the rats developed bladder tumours. This suggested that a similar mechanism (i.e. by an active metabolite) was operating in the case of benzidine to that of 2acetylaminofluorene (Bielschowsky 1944) and betanaphthylamine.

Clayson and Bradshaw (1955) identified 3hydroxybenzidine as a minor metabolite in dogs but did not report finding the 3:3' compound. Müller, Sandin and Miller and Rusch (1956) investigating 4 acetylaminodiphenyl, N:N diacetylbenzidine and eighteen related compounds did not find 3hydroxybenzidine or its acetyl derivative to be carcinogenic in rats, but they fed them for only 8 and 10 months respectively and terminated their experiments after 13 months. Bonser and her co-workers' rat experiments with 2amino 1 naphthol were sustained for twice as long.

Walpole, Williams and Roberts in their 1952 paper, which described the successful induction of tumours in rats with 4amino diphenyl and 3:2' dimethyl 4aminodiphenyl, suggested that in each case the effective carcinogen is an orthohydroxyamine formed in the body by metabolic hydroxylation.



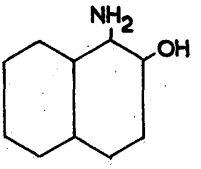


ORTHOHYDROXY 4 AMINO DIPHENYL. ORTHOHYDROXY 3:2' DIMETHYL 4 A.D.P.

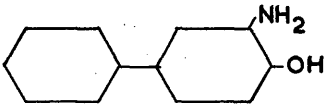
They further postulated that the higher activity of the 3:2' dimethyl homologue is due to the preferential direction of the hydroxy group into a position ortho to the amino group under the influences of the 3 methyl group, so that there is formed a large amount of the "orthohydroxy" metabolite, which they presumed to

be the active one. Again, in 38 rats which developed tumours out of a group of 46, only one had a bladder tumour but in their next experiments (1954) on two dogs both had developed advanced bladder tumours $2\frac{3}{4}$ years after the start of dosing. This again confirms the "species difference" of the dog's susceptibility to induced bladder tumours. They suggested a working rule that if a compound does not produce tumours at the site of injection then it is not a direct or local carcinogen and that if tumours are produced in organs remote from the site of administration then the carcinogen must be a metabolite.

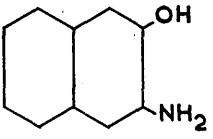
Clayson (1953) propounded a similar hypothesis and further developed the theory that hydroxylation in the position ortho to the amino group renders certain aromatic amines carcinogenic. He illustrated his hypothesis by comparing large numbers of published experiments and pointed out that this route of conversion is facilitated if the position para to the amino group is blocked as it is in benzidine and betanaphthylamine. The experimental testing of his hypothesis requires proof of the carcinogenicity of the ortho hydroxyamines and Dr.Bonser's department of which he is a member, has set up experiments on mice using the wax pellet implant technique, with 1 amino 2 naphthol, 3 amino 4 hydroxydiphenyl, 3 amino 2 naphthol, 1 amino 2 naphthol 4 sulphonic acid, 3:3' dihydroxybenzidine and orthoaminophenol.



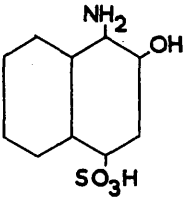
1 AMINO 2 NAPHTHOL.



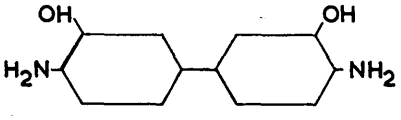
3 AMINO 4 HYDROXY DIPHENYL.



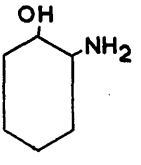
3 AMINO 2 NAPHTHOL.



1 AMINO 2 NAPHTHOL 4 SULPHONIC ACID.



3:3' DIHYDROXYBENZIDINE.



ORTHOAMINOPHENOL.

Clayson states that 1 amino 2naphthol a metabolite of alpha-naphthylamine has already induced tumours in five mice out of six in experiments in his department, but no results regarding the other compounds have been published.

Walpole, Williams and Roberts extended their theory to include compounds with a single ring such as orthotoluidine. Clayson could not agree with them. There is no published evidence that amines with only a single ring are active and he considers that the hypothesis should be confined to compounds with more than one ring. Walpole and Williams (1958) pertinently point out that orthotoluidine has never been tested on the dog and they now have experiments in progress.

Before one could accept the proposition that single ring compounds can be carcinogenic one would require either incontrovertible evidence of industrial tumours in workers exposed only to them, or proof of their carcinogenicity in experimental animals. This does not mean that in the absence of such proof one should relax the stringency of the precautions applied in industrial practice.

Why the bladder should be especially singled out for attack in man would appear, therefore, to be determined by the formation of a metabolite, which is a local carcinogen and its being excreted in sufficient concentration in the urine to exercise an effect on the epithelium of the urinary tract. Ferguson (1934) held that the agent circulated in the blood and exercised its harmful effect in the terminal capillaries of the bladder mucosa. He believed that in this way the whole of the bladder was affected and that recurrences arose because of this and not from implants or seedlings.

Hueper (1938) was able to identify betanaphthylamine in the liver, kidneys and bladder wall of mice one or two hours after it was injected but none was found in the bladder epithelium. In a second series injected with betanaphthylamine three times at four day intervals none of these organs showed any betanaphthylamine

after the third day following the last injection, although traces of it persisted in the urine longer than in the parenchymatous organs. These observations indicate that when the organism is floodedwith the compound betanaphthylamine may be deposited in the organs as an acute toxic effect but Hueper held "the main and probably only contact of the epithelium with the carcinogenic agent takes place on the mucosal surface".

Many other writers from Oppenheimer and Engel(1920) up to the present day have also preferred the theory that prolonged contact of the bladder epithelium with urine containing the harmful agent causes the change. This seems a more reasonable view and would account for the bladder being the site of the tumours in man and dogs. Many people (e.g. Hueper, Gay 1935) have cited, in support of this, the location of the bladder tumours in these species - in man around the ureteral openings and the trigone and in the dog on the anterior and lateral surfaces of the bladder - and have suggested that because of the posture adopted by each the urine is more in contact with these areas. This postulation has been widely upheld but it is difficult to accept it when one reflects that the bladder is only potentially a hollow viscus and that when part full it contains virtually no air or gas and the whole surface of the wall, as the bladder is contracted down, must be in contact with the urine. Gay in 1937,when he described a larger series than he had in 1934,took the view that the distribution of the lesions did not support the theory of a urogenous

origin, as the majority of the lesions in his cases were situated above the level of the ureteric orifices. On these grounds he then supported the haematogenous theory.

The contention that a urine borne carcinogen is the active agent has been further strengthened by more recent work. Scott and Boyd (1953) fed betanaphthylamine to three groups of dogs; in the first group with normal bladders all kinds of bladder tumours resulted; in the second group the ureter of one kidney was implanted into the sigmoid and tumours arose in the bladder but not in the colon of these animals; in the third group both ureters were diverted to the sigmoid and no tumours were found in either the bladder or the colon but in some of these animals there were tumours in the ureters and metaplastic changes in the pelvis of the kidneys. McDonald and Lund (1954) separated pouches off the bladder of dogs so that the urine could not get in contact with the mucosa in them and fed the animals betanaphthylamine. Tumours developed in the bladder but none appeared in the pouches. McDonald and Thorson (1956) placed fragments of papilloma from other dogs fed betanaphthylamine in similar pouches in another series of dogs on normal diet and several of these became implanted and grew in the mucosa of the pouch. All these experiments suggest that while the carcinogen reaches the bladder in the urine rather than by the blood stream there is also a susceptibility of the urinary tract epithelium to react to it and that the "receptiveness" of the bladder epithelium may also be an important factor in the

initiation of the tumours.

Boyland, Wallace and Wallace (1955) think that the tumours are due to an excess of the enzyme glucuronidase in the urine which liberates a free animophenol from the excreted metabolite. They found a high glucuronidase content in the urine of men who had bladder tumours and also in those who had been treated and were free of tumours. They have suggested that this enzyme might be inhibited by the administration of saccharolactone especially in the event of accidental massive exposure. The problem in industry, however, is one of long term exposure possibly to very small doses. The threshold of the dose is unknown and may be very low. Prolonged exposures over 15 - 20 years are more important than accidental contamination and it is not proposed to use saccharolactone. Prevention must lie in directions other than the administration of uncertain long term antidotes.

To sum up, it would require a great deal more evidence than exists at present to support the view that the activity of the carcinogen in the bladder depends on its reaching it by way of the blood stream. The conclusion that it reaches the epithelium of the urinary tract by being conveyed there in the urine and that it acts upon it directly is inescapable.

PART II

"OCCUPATIONAL TUMOURS OF THE BLADDER ARISING AT THE CLAYTON ANILINE FACTORY"

ANALYSIS OF RESULTS

Introduction.

In 1950 a works register (the "nominal roll") was compiled recording the names and working histories of all men who were known to have been engaged for more than six months in the manufacture of or use of aniline, alphanaphthylamine, betanaphthylamine, benzidine, and magenta. Men with less than six months employment were omitted partly because it was difficult to get details of some of those who had worked for very short periods and partly because, in the absence of any known experience to the contrary, six months exposure was regarded as a reasonable minimum time necessary to initiate a bladder tumour in industrial conditions. The nominal roll is brought up to date annually but aniline is now omitted as it has not been shown to be carcinogenic.

By the end of 1957, when the list was closed for the purpose of this analysis, the names of 667 men (excluding the aniline workers) were on the roll. At the same time 123 men were known to have developed tumours of the bladder. A system of checking the names of men whose death certificates mentioned tumours of the bladder or chemical work, set up in the Factory Department by courtesy of H.M. Senior Medical Inspector has helped to ensure that men who develop tumours after leaving the factory are traced. The normal expected number of cases in similar members in the general population would not exceed three cases in thirty years.

Of the 123 men who developed tumours, 87 were engaged in that section of the works where carcinogens were manufactured, 28 in processes entailing their use and 8 were ancillary workers - 2 chemists, 2 fitters, a weighman, a transport worker and a man who worked as a boiler fireman for 28 years following three months exposure to betanaphthylamine.

It is obviously impossible to determine which individuals in a working population will develop tumours. Individual predisposition has been suggested as an explanation of the fact that they appear in some workmen whilst others placed in apparently similar circumstances escape. Gross (1958) suggests that chemical and other types of carcinogen merely activate latent oncogenic viruses. If this is true, then he contends that those who develop cancer represent only a small fraction of those actually carrying the seeds of the disease. In industrial practice, however, many other factors are operating. Some are impossible to measure; conditions in the factory have varied from time to time and have progressively improved during the past twenty years; dirty workers will absorb a higher dose than clean workers. Familial tendencies are impossible to estimate; two pairs of brothers (cases 11 and 12, and 65 and 86) contracted the disease but each had worked on the same job as his brother, and other workmen on it also developed tumours of the bladder. The predisposing influence of good or poor general health and intercurrent

disease is also impossible to assess but I have already emphasized (1954) that good health and strong physique have no relation to a man's resistance to carcinogens.

There are, however, several measurable factors which may influence the incidence of tumours. These include the duration of exposure to the dangerous chemical, the time which has elapsed since first entry into the dangerous occupation, the type of work upon which the men have actually been engaged, and the compound handled.

Incidence

In the present series the overall incidence of tumours is 18.4%. This crude figure is of little value on its own. For instance, roughly one half of all the men have entered the industry within the last 12 years and would be unlikely to have developed tumours as yet.

The incidence among the total population at risk according to length of exposure is given in Table 3. It rises with the duration of the exposure until it is 71% for men who have been exposed for more than 30 years.

TABLE 3

Incidence by Length of Exposure

	Total Years of Exposure				
	0-10	11-20	21-30	31+	Total
Population at risk	429	139	75	24	667
No. of cases	26	51	29	17	123
Incidence per cent	6	37	39	(71)	18.4

More information is required in order to be able to assess the extent of the hazard to which certain groups of men are exposed. It appears probable that not only the actual duration of exposure but also the period of time which has elapsed since first entering the hazardous occupation influences the incidence (Table 4).

TABLE 4.

Incidence by Date of Entry

	Date of Entry							
	After 1951	1947-1951	1942-1946	1937-1941	1932-1936	1927-1931	1922-1926	Before 1922
No.at risk	157	97	63	110	80	62	59	39
No.of cases	-	1	2	9	16	28	46	21
Incidence per cent	-	1	3	8	20	45	78	54

It is impossible in the present series however to be able to distinguish a difference in these two factors which in any event are very closely correlated.

In order to assess the effect of the type of work, the men who were exposed to benzidine have been grouped in three categories, those who were directly engaged in the manufacturing processes, those who worked in the same building but were not directly concerned with the manufacture ("services men")and those who used the chemical for the synthesis of dyestuffs in an entirely separate building ("users"). The incidence of tumours in these three groups is shown in Table 5.

TABLE 5.

Manufacturers, Services Men and Users, Exposed to Benzidine.

Job.		Date of Entry			
		Before 1927	1927-1936	1937-1957	Total
Manufacturers (142)	Pop.at risk	20	13	109	142
	No.of cases	13	8	4	25
	Incidence per cent.	(65)	(62)	4	18
Services (149)	Pop.at risk	17	56	76	149
	No.of cases	1	3	3	7
	Incidence per cent	(6)	5	4	5
Users (86)	Pop.at risk	21	30	33	86
	No.of cases	10	4	1	15
	Incidence per cent.	(48)	(13)	(3)	17

Although the numbers who started work more than 20 years ago, that is before 1937, are somewhat small, there is a very highly significant difference between the experiences of the manufacturers and the service men. Twenty-one of the 33 men in the former group have developed tumours, compared with 4 of the 73 service men. The users have an incidence between these other groups, 14 tumour cases out of 51 men at risk. These findings indicate that there has been a greatly increased hazard for men directly engaged in manufacture and, to a lesser extent, in handling the chemical compared with men working in less close proximity. This is obviously of great importance in the prevention and control of the hazard.

The incidence according to age at entry and length of exposure in the three categories of workers with benzidine is shown in Table 6. Again the numbers are small but there is no evidence to suggest that older men entering the industry get a higher incidence of tumours than their younger colleagues. This is of the greatest importance in the selection of workers and will be referred to later.

In the case of the men who have worked solely with benzidine, alphanaphthylamine and magenta it has been possible to allocate accurately the compounds to which they have been exposed. The numbers involved with the last two compounds are too small for fruitful analysis.

TABLE 6.

Incidence by age at entry. Length of exposure - Benzidine workers.

Type of Work.	No. of Men with	Length of Exposure (Years)							
		Under 11		11-20		21 -			
		Age at entry		Age at entry		Age at entry		Total	
		Under 31	31 & over	Under 31	31 & over	Under 31	31 & over	Under 31	31 & over
Manufacturers.	Pop.at risk	20	86	10	14	11	1	41	101
	No.of cases	1	5	7	6	5	1	13	12
Services	Pop.at risk	30	59	29	20	7	4	66	83
	No. of cases	1	1	1	2	1	1	3	4
Users	Pop.at risk	9	18	17	16	19	7	45	41
	No.of cases	-	2	3	1	6	3	9	6

It has not been possible to allocate with the same accuracy the men who worked in betanaphthylamine manufacture. Many of them were called upon to distil benzidine and use alphanaphthylamine in their section of the factory so that, while a proportion of them have worked exclusively on betanaphthylamine, many have had mixed exposures. It is not easy to trace the history of every man on this plant and attempts to do so cause a great deal of alarm, but when a man develops

a tumour a complete history is obtained and checked against his own account.

For this reason the incidence of tumours in the betanaphthylamine men cannot be given accurately nor can the potency of betanaphthylamine be compared with the other compounds at the present stage. This aspect of the problem, however, has already been well covered (Case et al) and the greater potency of betanaphthylamine as a carcinogen is generally accepted.

Discussion of Incidence.

Apart from any possible individual predisposition or personal factor in actual working, the incidence has been influenced by the date of entry into the industry, the length of exposure, the type of work done and the type of compound worked. One cannot easily separate these factors as more than one, and often all of them, have been operating at the same time.

Although it is impossible to forecast which men will develop tumours it would be useful to know the final total yield of cases which can be expected. Case and his co-workers estimated by an elaborate statistical method that eventually, when all the workers on their nominal roll will have died, 20% will have died of the disease.

The groups of workers described by Gross, by Hueper and by Goldblatt all had a crude incidence varying from 50 - 100% at

the time of their writing and it can be presumed that their death rates would be higher than 20%. Müller's workmen already had a 33% incidence in 1951 and they may well have an ultimate death rate higher than one in five. Williams (1958) has reported that 94% of 78 men who had worked for five years or more distilling benzidine and betanaphthylamine under poor conditions had developed tumours 30 years after starting.

One cannot compare these results with each other or with the present series as the groups are comprised differently and it is not known precisely which workers have been included. Williams' analysis is based on men with five or more years exposure under bad conditions whereas Case's figures were derived from men with over six months' exposure who were employed by a number of firms many of whom made or used only small amounts of carcinogens sporadically.

My results come from a factory where the carcinogens have been made and used on a large scale all the time; there is no doubt that in the earlier years exposure must have been heavy although it has decreased progressively over the last 20 years as conditions have improved. Already 18.4% of the men on the nominal roll are known to have developed tumours and there may be others who have not yet been traced. There is no evidence that the annual yield is tending to drop and tumours have already been seen among the men who started within the last 20 years. It is only within the last ten years that conditions have been brought up to

the standard now considered satisfactory so that it is unlikely that the full effects of improvements in conditions will be felt for another decade at least.

Latent and Exposure Periods.

Industrial bladder tumours arise after a long latent period between entry into the industry and onset of the tumour. This latent period is not necessarily the same as the period of exposure as many men leave the industry and subsequently develop tumours. In those who remain in the industry until the tumour appears the period of latency and of exposure is, of course, the same.

The range of the latent period is wide but there has been a surprisingly constant average throughout the sixty three years since the hazard was first described. In 1927 Oppenheimer's cases had a range of 1 - 45 years with an average of 18 years. Müller in 1936 described the range as 2 - 28 with an average of 18; Goldblatt in 1947 gave the range of 4 - 48, average 19. In 1952 describing the earlier cases now included in this analysis I found the range at that time was 4 - 33 years and the average 16 years. Many other writers have had similar averages (Anderson 13 years, Buttner (1931) 17 years, Heuschen (1937) 17 years, Hueper 11 - 15 years). Hueper (1950) analysed 277 cases from the European literature and summarized the percentage incidence according to years of latency (Table 7) and Evans (1937) tabulated his 83 American cases similarly with a similar result.

TABLE 7

Latent Periods in Years (Hueper 1950).

Latent Period in years	1 - 5	-10	-15	-20	-25	-30	-35	-40
No. of cases	32	49	69	74	28	13	6	6
Percentage	11.5	17.7	24.9	26.4	10.1	4.7	2.2	2.2

In the present series the latent periods ranged from 4 to 41 years, the average was 20.4, and the most frequent period was between 15 and 19 years (Table 8 and 9). Five men developed tumours 35 or more years after starting in the dangerous work.

TABLE 8.

Latent Periods in Years (Present Series)

Latent Period	0 - 4	5 - 9	10-14	15-19	20-24	25-29	30-	Total
No. of cases	2	9	23	35	21	15	18	123
Percentage of total cases	1.6	7.3	18.7	28.5	17.1	12.2	14.6	100

Most writers have given average latent periods for their collected cases as a whole but a few have attempted to analyse them according to the chemical involved. Beremblum (1932) pointed out that the average latent period varied according to the department and that in fuchsin workers it was 24 years but in benzidine workers

only 12 years. In Müller's series the range of the latent period was given for various carcinogens but not the average.

Case and his co-workers (1954) in their statistical analysis of the collected cases in Britain found that the mean latent period, or induction period as they called it, for betanaphthylamine and benzidine was the same, (16 years S.D. 5 and 6 years) and that it did not differ significantly from that due to mixed exposures, (18 years S.D.7). There was, however, a significant difference in that of alphanaphthylamine which was 22 years (S.D.6). They considered that this longer latent period was a characteristic of alphanaphthylamine and a proof that it was carcinogenic per se and not only on account of its betanaphthylamine impurity.

In the present series there were no statistically significant differences between the average latent periods for the various compounds although the 4 cases exposed to alphanaphthylamine had very short latent periods (18, 16, 14 and 14 years) in marked contrast to the experience of Case and his colleagues (Table 9).

The range of the average latent period is remarkably constant whether the initial tumour be papillomatous, carcinomatous or multiple and the malignant tumours do not develop more quickly than the benign.

TABLE 9

Mean Latent Period in relation to Compound used.

Compound	No. of Men with tumours.	Mean Latent Period in Years		
		Papilloma	Carcinoma	Total
Ben.	48	18.2	21.25	19.2
An.	4	(16.0)	(14.5)	(15.3)
Bn.	23	21.1	18.45	19.8
Other	11	25.4	23.7	24.9
Mix.	37	22.15	20.9	21.6
Total	123	20.45	20.4	20.4

Variations in the latent period may be due to a variety of possible causes, and it has not been possible to determine the most important. The nature of the carcinogen is not necessarily the only factor. The intensity or length of exposure may also be important. Hueper (1950) showed that in experimental dogs dosed regularly with 250 mgms. of betanaphthylamine bladder tumours appeared in $1\frac{1}{2}$ - 3 years but if dosage was stopped after six months the first tumours did not appear until after 5 years. Case and his colleagues failed to confirm that intensity of length of exposure influenced the latent period. Williams (1958) suggests

this was because of the relatively small number of men who developed tumours following short exposures or to the wide variations of the degree of exposure in the different factories from which their material was drawn.

Wide variations in the exposure period have also been observed. Müller (1951) states that over the whole of the tumour material seen at Basle the exposure varies from 3 months to 36 years but he gives no further details of the man whose exposure was so short. Koelsch (1935) contended that only six months exposure to betanaphthylamine was sufficient to induce a tumour ultimately but he did not cite any cases in support of this theory. Goldblatt (1949 b) described one case of a man who developed a small papilloma after three months in the industry. This he regarded as non-occupational without giving any reason for this assumption. Many exact reports of exposure (and latent) periods of one year are available, e.g. Hueper (1938), Oppenheimer, Evans, etc. and short exposures of several months must be regarded as dangerous. I have taken six months as the qualifying period for registration on my nominal roll.

Equally interesting and important is the length of time which may elapse between the cessation of work with carcinogens and the onset of tumour. In 1954 I gave details of eight workmen who developed bladder tumours on an average 7 years (1-13 years) after leaving the work. Their average latent period was 15 years - little different from that of those men who stayed on and developed

the disease. This is different from Hueper's finding in animals that early cessation of dosage lengthened the induction period. This suggestion is confirmed in the present larger series. Twenty-five men who left the industry have now developed tumours at some time after their exposure to the hazard had ceased. There is little difference between the latent periods for these men (mean 21.5 years) and those of the other 98 men (20.1 years) despite the fact that the first group had an average exposure of only 9.9 years whilst in the second group it was 20.1 years. Table 10 shows that 10 of the 25 men who had left the industry had actually had less than five years exposure although their latent periods ranged from 5 to 34 years.

TABLE 10

Length of exposure and latent periods of 25 men who left the industry before onset of tumour.

Length of exposure (years)	Latent Period (years)							Total
	0-4	5-9	10-14	15-19	20-24	25-29	30-	
0-4	1		2	2	1	2	2	10
5-			2	1	1	1		5
10-			1	1		2		4
15 -				1		1		2
20-					1	1		2
25 -						1		1
30 and over							1	1
Total	1	-	5	5	3	8	3	25

These figures stress the fact that removal from contact after short exposures does not eliminate the prospect of developing a tumour and does not necessarily postpone its onset. These points are of great importance in prevention because replacing men on this work after short periods of exposure would certainly increase the numbers at risk and might well increase the ultimate yield of tumours.

Fifteen of these 25 men who developed tumours after leaving the industry have so far survived for periods up to 16 years, 8 of them for more than 5 years. Of the 10 who died, 1 survived 13 years before dying of arteriosclerosis at the age of 77; the other 9 all died from tumours of the bladder within 7 years, 6 of them under 5 years after the onset of tumour. It follows, therefore, that removal from exposure does not mitigate the severity of the disease if it arises subsequently.

Perhaps the most sinister and disquieting observation arising from the study of these 25 men is the time which elapsed between their leaving the industry and the onset of the disease. This averaged 11.7 years but 4 men had been out of the industry for over 20 years, and 1 of them (Case No.59), who had worked for only 1 year and 7 months in betanaphthylamine manufacture, developed a carcinoma of the bladder 29 years after leaving the industry during all of which time he had worked as a railway porter. It is feared that other men with similar histories may not have been traced and many may well have forgotten the names of the chemicals and some

even the name of the firm with which they were associated for such a short time so long before.

The first 66 cases in this series were described by me in 1952 and the average latent period for these at that time was 16 years (range 4-33). The lengthening of this by over 4 years to its present average of 20.4 years (range 4-41) is not statistically significant. The average latent period in my 1952 series was longer in users (21 years) than in manufacturers (16 years) and there was a suggestion that mixed exposures tended on the whole to induce tumours earlier but neither of these findings are confirmed in this larger series. The average latent period for the magenta workers who developed tumours tended to be longer but their number is too few for one to draw any conclusions or make any comparison with other writers.

The duration or nature of the exposure has never been found to have any influence on the type of tumour. Benign and malignant tumours and all gradations between them appear apparently indiscriminately and independently of these factors. In 1952 I noted thatmen who had tumours following exposure to more than one compound had a higher proportion of carcinomata than those whose exposure had been to only one carcinogen. This is no longer the case as the numbers of papillomata (15) and carcinomata (16) in the mixed exposure group is virtually equal (Table 23). Earlier diagnosis may be responsible for this in that a greater number of tumours are detected before demonstrably malignant changes are manifest.

AGE FACTORS

The average age at onset of chimney sweeps who developed scrotal cancer prior to 1853 was between 30 and 40 years (Curling, 1853). These men had started work when they were 4 - 10 years old. By the end of the century the effects of the law forbidding boys to start work as sweeps until they were sixteen were seen when the average age at onset had risen to 40 - 50 years (Butlin, 1892. By 1935 the average age was 61.9 years but by this time improvements in hygiene may well have had a beneficial effect as great as raising the age at entry (Henry, 1937).

I have always insisted that the age at onset of occupational bladder tumours is directly related to the age of entry into the industry which entails exposure to carcinogens (Scott, 1952, 1953, 1954). I also showed that the average age at death from such tumours is similarly related to the age of entry.

Curschman in 1920 and Beremblum (1932) had already indicated that the onset of the tumours did not depend on the age of the workers. Hueper in his 1938 treatise noted a shift towards the younger age groups in his own and Evans' series of occupational bladder tumours compared with those of unknown aetiology, and in 1952 agreed that "the manifestation age of environmental and occupational tumpurs is directly related to the age at onset of the carcinogenic exposure". In Goldblatt's 1949 series 33% of the 93 cases were diagnosed before the men reached the age of 45 and the mean age at onset was 50.55. Case and his co-workers

(1954) confirmed this tendency when they found that the mean age (40.5) at onset of bladder tumours in 137 chemical workers was 20 years earlier than that in 750 men who had bladder tumours of unknown origin. They also found a similar difference, 15 years, in the most frequent age at death from bladder tumours in chemical workers (50 to 55 years) compared with other males. Stocks (1950) took records of cases of cancer of the bladder and ureter from 275 hospitals in England and Wales in 1945 and found that the average age of all cases at first attendance was 62.5 years and at death 66.3 years. From the Registrar General's figures for 1947 the average age at death of 1,417 males who died of neoplasms of the bladder, ureter and urethra was 67.5 years.

Case and his colleagues showed that the earlier age at death from occupational bladder tumours was due neither to a shorter survival time from the onset of the disease nor a selectively greater susceptibility to the disease in young men, and they confirmed that it was dependent on the age at first exposure to risk. I had already (1952) emphasized the shortened expectation of life of men who are exposed to bladder carcinogens before the age of 30 and the importance of this in the control of the disease in industry.

In the present series the average age at onset of tumour is 49.7 years (Table 11). This confirms my earlier results and is in accord with the experience of other writers. The majority (75, i.e. 61%) of the 123 men who have so far developed bladder

tumours entered the industry before they reached the age of 30.

TABLE 11

123 Cases of Bladder Tumour by Age at Entry.

	Age at entry			Total
	Under 31	31-40	Over 40	
No. of cases	75	35	13	123
Mean age at onset	46.9	52.9	50.7	49.7
Mean latent period	19.8	19.6	16.5	20.4

TABLE 12

55 Fatal Cases by age at Entry.

	Age at entry			Total
	Under 31	31-40	Over 40	
No. of cases	27	18	10	55
Mean age at onset	43.7	54.2	61.5	50.4
Mean age at death	49.6	57.4	66.1	53.7

Thirteen (11%) started after they were 40. Fig.3 shows the ages at onset in five year groups. The average age at onset in the men who have subsequently died is given in Table 12 and the ages at death in five year groups are shown in Fig.4. Of those who started under the age of 30 and later died of bladder tumour the average age at onset was 43.7 years, whereas of those who entered the industry when they were over 40 and later died of tumour the average age at onset was 61.5 years.

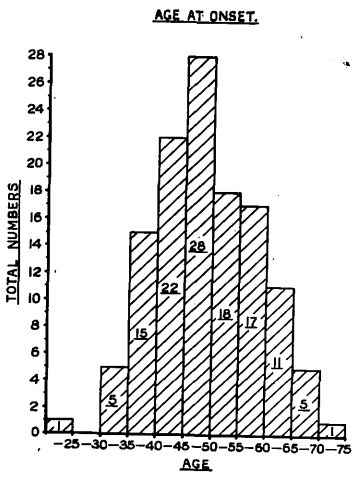


FIG. 3.

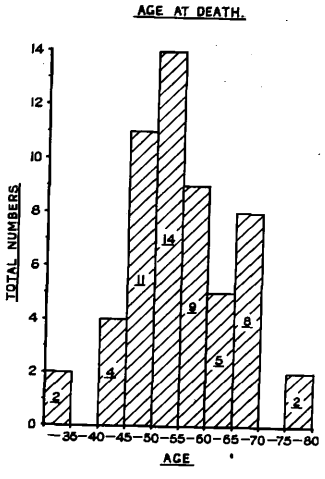


FIG. 4.

The ages at death are of the greatest importance. Whereas the mean age at death for those who entered the industry before they were 30 was 49.6 years, it was 66.1 years for those entering over 40 which approximates to the age at death for non-occupational tumours. It was figures such as these which led me in 1950 to exclude men under the age of 30 from starting work where carcinogens are manufactured and eventually to insist that only men over 40 should be engaged. This was to exclude younger entrants who would have their lives shortened should they develop tumours despite modern precautions.

It will also be noted from Fig.3 that the age at which the tumours appeared tend to be much younger than that for non-occupational tumours appearing on the average about 15 years earlier than in Stock's series. This shift to the younger age groups at onset of a tumour may be used as an indication that a hazard is operating in cases where there may be doubt as to the occupational origin (Case et al 1954). It will be noted from Table 11 that the average latent period (16.5 years) for men starting over the age of 40 is shorter than that for men (19.8) who started before the age of 30. Despite this, it must be remembered that there is no evidence to suggest that the incidence of occupational bladder tumours is higher in older men entering the industry (Table 6).

Another fact which is apparent is the considerably worse prognosis for the older men. There were 10 fatal cases among 13 who started over the age of 40 compared with 27 fatal cases amongst the 75 in the youngest age group.

DIAGNOSIS

Introduction.

Occupational tumours of the urinary bladder once established differ little in their clinical features from those arising in the general population. There is, however, one important practical difference in that they usually arise in men who are known to have been at risk. Consequently such men can be kept under supervision so that the tumours may be detected at as early a stage as possible. It cannot be in doubt that, apart possibly from the degree of malignancy, the most important single factor in the effectiveness of treatment is the stage of a tumour when it is first discovered.

Tumours appearing in the general population are usually heralded by symptoms such as haematuria, dysuria, frequency of micturition or pain, and these symptoms may not supervene until the tumour has grown to a considerable size, become fungating, infiltrated into surrounding tissues, or even formed metastases. In Riches' (1958) series of over 500 patients with tumours of the bladder haematuria was present in 97% of them when first seen. Routine clinical examination is unlikely to detect the symptomless tumours at an early stage and it has never seriously been advocated as a useful measure in this respect. Whilst mass screening of the general population for the detection of bladder tumours by any known methods will be shown to be impracticable on account of the difficulties of applying it, and would be unrewarding because of

the comparative rarity of non-occupational vesical tumours, nevertheless the high incidence of such tumours in groups of chemical workers not only justifies the application of mass screening methods to them but renders it imperative if all possible care is to be afforded the workers at risk.

In this section the various methods which have been used to screen industrial populations at risk for the early detection of tumours of the bladder are described. Regular periodic cystoscopy of exposed workers and the routine examination of the urine for microhaematuria are evaluated as screening techniques.

The history of the application of cytodiagnosis to the urine of workmen is given. Its introduction and development at Clayton are described. The successful results in new cases, and the disappointing results in old cases, are analysed and compared with those obtained by other writers. Reasons are given for the striking differences in these results. A comparison of the old techniques with a modified Papaniculaou technique and an evaluation of their merits is made.

Screening Methods.

In 1920 Oppenheimer recommended regular microscopical examination of the urine for red blood cells and Nassauer suggested that pus cells might have some significance. This was taken up by the Germans (Gross), the Swiss (Müller) and, in the earliest days, by the Americans (Anderson). It was adopted in Britain

from 1934 onwards (Crabbe, Cresdee, Scott and Williams 1956) and was the method of screening relied upon in this country until the introduction of cytodiagnostic techniques in 1951. Workers in many other countries relied upon the routine cystoscopy of all their workers at regular intervals usually of a year.

Routine Cystoscopy

In America, when the first bladder tumours arose in men in the Wilmington works in 1931, routine cystoscopy of all exposed workmen at regular intervals was introduced and it was even extended to the pre-employment examinations of new recruits. In the 22 months between December 1931 and October 1933, 532 men from that factory were cystoscoped and 25 of them were found to have tumours of the bladder (Gehrmann 1934). By 1937 (Evans 1937) 2,868 cystoscopies had been performed and 83 cases of tumour detected. These examinations are said to have been done annually and the rate of yield of tumours is interesting :- 49 men were found to have tumours when being cystoscoped for the first time, 16 at the second cystoscopy, 15 at the third and one each on the fourth, fifth and sixth occasion. The quickly diminishing number of tumours found after the first three annual cystoscopies suggests that a pool of undiagnosed tumours was awaiting the investigators when they started. As the years went on the number of examinations with a normal result must surely seriously discourage a workman from submitting himself to an uncomfortable surgical procedure.

Müller relates how the Americans at a conference with him

and his colleagues in 1934 convinced the Swiss that they should apply routine periodic cystoscopy to their workmen at risk, and in 1937 he introduced it for contacts with benzidine, beta-naphthylamine and other dangerous substances. In the five years before 1937 using the wet smear technique for occult haematuria he had performed 152 cystoscopies and detected 15 tumours, whereas in the fifteen years after 1937 doing annual cystoscopy of all men at risk, he performed 968 cystoscopies and detected 35 tumours. Between 1947 and 1950 he did 499 cystoscopies and found 22 tumours. This means that before routine cystoscopy was introduced he was doing an average of 30 cystoscopies per annum, in the first 10 years after its inception he averaged 42 per annum and for the last 4 years preceding his report he averaged 125. From these figures it can be inferred that, unless the total number of the employees was as low as 125, annual cystoscopy has not been applied even to the majority of the men at risk even during the period of greatest activity in 1947-50.

Wolfe (1937) details the difficulties he encountered in America in applying routine endoscopic examination to all workmen. The time lost following the examination, the attribution of extraneous complaints to it, labour unrest, the opposition caused by preliminary treatments, such as meatotomy, all engendered many persistent refusals to be examined or treated. In the face of this discouragement he persevered and apparently was able to maintain a reasonably wide cover. He describes 984 original and

repeat cystoscopic examinations in one plant, of which 329 were done in 22½ working days - the imagination boggles at the effects such a heroic procedure would have had on a population of British workmen. Despite the obvious difficulties, the reports of Gehrmann and his colleagues in 1949 showed that the Americans were still continuing to apply annual cystoscopy as a method of control in their factories, and it has not been given up so far as is known. It is, however, extremely doubtful if all workers submit to it regularly. (Sundry personal communications, Williams, Case, etc.)

In Italy annual cystoscopy had been adopted before 1937 (Di Maio) and was still being advocated with enthusiasm at the International Congress in London in 1948 by Barsotti and Vigliani (1949) whose figures do not, however, convince one that they were entirely successful in getting their workmen to submit. Only 13 of 106 men engaged in benzidine utilisation and only 9 of 36 men in one group of benzidine reduction workers were cystoscoped. They were more successful with their betanaphthylamine men of whom 33 out of 40 were examined. Workers were not obliged, but were advised, to submit periodically to cystoscopy at the works surgery and they say that in many of these workmen cystoscopy could be repeated several times. One must infer that the others declined to submit themselves for repeat examinations. They also cystoscoped workers attending other kinds of work for "control purposes" but they do not specify any further details of these examinations.

The French practice seems to have been less unanimous.

Billiard-Duchesne (1949) advocated systematic cystoscopy of all workers. He applied it in two factories and found six tumours in 55 workmen. In other factories which he mentions it does not appear to have been accepted. Alboulker, Gaultier, Benguign and Smagghe (1949) used the wet smear technique for occult haematuria but they did not apply routine cystoscopy to all their workers.

In Great Britain routine cystoscopy has never been applied to working populations. Although Goldblatt in 1947 advocated that it should be performed on all exposed men before starting work and at least once a year thereafter, he never applied it to his own workers. In 1949, he declared that the attitude of workers in Britain towards cystoscopy was far from favourable, an understatement such as one does not usually get from him. There are other more valid objections and drawbacks to its regular use. (Scott,1953; Crabbe, Cresdee, Scott and Williams, 1956). It is often an uncomfortable procedure and undesirable sequelae can occur so that its application might lead to refusal to undergo it at the very time when it has become most necessary; many men might leave after one or two cystoscopies rather than continue in employment where they had to undergo it, and their replacement would increase the numbers at risk; a tumour could arise and become inoperable in less than a year after a negative result had led to a false sense of security; it would be impossible or impracticable to extend regular cystoscopy to all those workers whose exposure has been relatively slight but who may have a

remote chance of developing bladder tumours, for example laboratory workers and men who have worked in areas adjacent to the dangerous ones. In addition to these practical disadvantages all investigators in Britain are agreed that periodic cystoscopy would not be accepted by British workmen, either as part of the pre-employment examination or as a regular routine thereafter, and it has never been introduced in this country. This does not, of course, apply to the follow-up and re-examination of men who have developed tumours.

Haematuria

As routine periodic cystoscopy was not considered to be an acceptable and efficient means of screening in Great Britain some other method of deciding when cystoscopy should be done had to be applied. Until the end of 1950 the examination of wet smears of urinary deposits was the only other useful method available and was the one depended upon in this country. It was introduced into The Clayton Aniline Company in 1936 and was the chief screening method used there until cytodiagnosis was started in 1951. As urine can be collected and examined without discomfort or difficulty the test was extended to all workers in the factory and to those members of the staff who had even the most remote contact with carcinogens. It is still done at monthly intervals and there have never been any objections or refusals. It has been part of the factory routine for many years.

Wet Smear Technique.

The exact technique is described in Appendix A. The presence of large numbers or the persistence of small numbers of red blood cells in the urine of a man who has had a "sufficient" exposure to carcinogens was almost invariably regarded as an indication for cystoscopy (Scott 1954) but as haematuria is not specific for bladder tumours many other factors had to be considered. Haematuria, occult or gross, can be occasioned by many causes other than tumour, for example, infection, trauma, calculi and divers other bladder, prostatic and renal diseases. Acute haemorrhagic cystitis is a common manifestation of the absorption of certain chemicals such as the toluidines and 5 chlor 2 toluidine which are often made and used in dyestuffs factories (Goldblatt 1949, Scott 1953). Red blood cells are also found in the urine of some apparently healthy individuals.

Red blood cells had been observed in the urine of a disturbingly large proportion (8%) of recently employed men on their first routine test after starting. There was no apparent cause for this and none of them had been exposed to the amines which cause haemorrhagic cystitis. These cases raised difficulties in assessing the results of the tests. It was impossible to be certain if the men were healthy and the microhaematuria transient or of no significance. The urine of the new recruits was, therefore, examined from 1948 onwards so as to eliminate any men who had microhaematuria before they started. It was hoped in this way to avoid periodical

confusion in the appraisal of urine tests in the future.

During the period of three years - 1948 to 1950 - approximately 2000 men (1,926) between the ages of 20 and 55 years were examined prior to engagement in the factory but not specifically for work carrying a risk of tumour of the bladder. Apart from those rejected because of various disabilities, 142 (7.4%) were rejected because of some abnormality of the urinary system (Table 13).

TABLE 13.

Pre-employment Examinations 1948 - 50.

Total no. examined		1,926		100%
Total no. accepted		1,738		90.2%
Rejected for all causes		188		9.8%
Rejected on "general grounds"	46		2.4%	
Rejected for urinary abnormality	142		7.4%	

The urinary abnormalities for which these 142 men were rejected fell into three groups - albuminuria without red blood cells, a history of urinary disease and the presence of microscopic haematuria of undetermined origin (Table 14).

TABLE 14.

142 men rejected because of urinary abnormality

Albumen without R.B.C's	17
History of urinary disease	5
Red blood cells in Urine	120

The presence of albumen alone did not necessarily entail rejection. If it was postural or present only in small amounts and there was no evidence of any disability it was not disqualifying but no man with albuminuria was allocated to a hazard plant. When it was severe or if accompanied by other factors such as cardiovascular or renal impairment it caused rejection in 17 cases. Of the five men who had a history of genito-urinary disease four had had a nephrectomy and one an operation for renal calculus. One man had a history of a previous attack of visible haematuria of unknown cause and when examined had many blood cells in his urine; he is included in the next group.

The largest number of men rejected (6.2%) were those who had a "significant" amount of blood in the urine (more than 6 - 8 R.B.C's per low power field on microscopy of centrifuged urine deposit) in the absence of any detected disease or disability.

As the pre-employment examinations were strictly for the placing of male applicants for employment a certain degree of selection had already been exercised by the personnel department before the men were submitted for medical examination and the obviously unfit and undesirable had been eliminated. The circumstances and the need for a prompt assessment precluded the use of any elaborate laboratory methods such as Addis counts of cells in the urine, nor was it possible to do further investigations on the men rejected except in a few cases. All of them were advised to consult their own doctors who were informed of the reason for

rejection. Only three men are known to have had further investigation, including cystoscopy, and in each it failed to reveal any lesion.

The possibility that many of these cases were due to infection is discounted by the fact that no acute gonorrheal infections were found in the series nor were there any men with a sufficiently large number of leucocytes in the urine to be described as pyuria.

The presence of the blood cells was not related to any particular age group. Fig.5 shows the percentage of applicants in each age group against the percentage of men with blood in the urine in each age group, and the proportion is constant. It was not possible to assess any dietetic influence but the men were all more or less in the same working class social group.

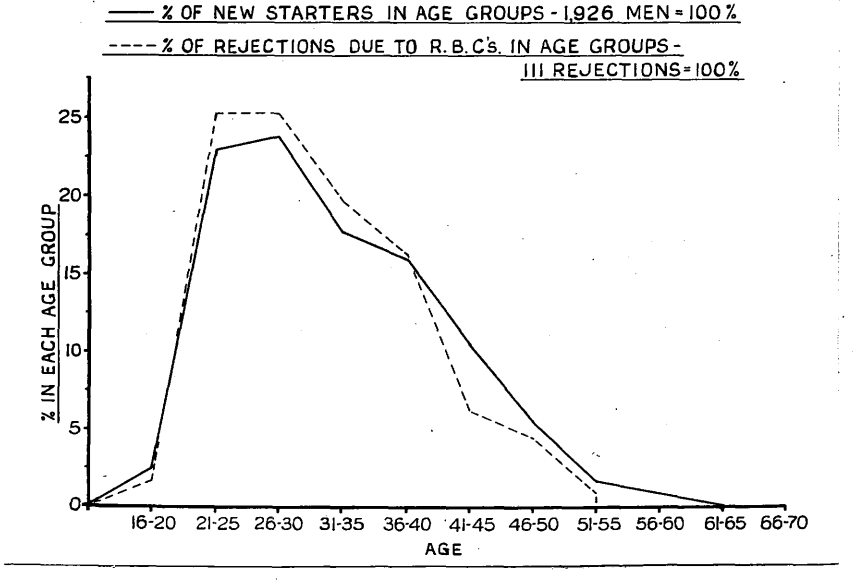


FIG. 5.

There is the possibility that different men may excrete blood cells at different times. Table 15 shows that the percentage of men in 1950 who had occult blood in the urine on their first routine test after starting work was much lower than it was in 1947 before applicants with occult blood were rejected.

TABLE 15.

Men with microhaematuria on first urine test after starting.

		Total new starters in plants	Show blood on first urine test after starting.	%
1947	No.pre-employment R.B.C.test	202	16	8.0
1950	Clear at pre-employment R.B.C.test	337	4	1.2

These results suggest that at least a proportion of the rejected men would have continued to show blood in their urine.

No similar healthy population which has not been exposed to chemicals was available for comparison and enquiries failed to elicit any other similar survey of healthy men or new entrants - even in the atomic industry.

No reason, therefore, was found to explain the microhaematuria in these men and it was presumed that they were healthy but this was largely speculation until the publication of Green, O'Shaughnessy and Hendricks (1956) six years later strengthened the opinion that the majority of the rejects had no serious

uro-genital lesions. These writers described the results of the urological investigation of 500 patients referred to them because of the presence of symptomless microhaematuria which had been detected incidentally in the course of examination for complaints unconnected with the genito-urinary system. Of these patients nearly 80% were over 40 years of age and more than half were over 50 so that one could reasonably expect a higher incidence of disease among them than in The Clayton Aniline group with its higher proportion of younger people. Nevertheless, they found that only 10% of these people had "moderate to great" lesions of the genito-urinary tract, and only 2% had tumours; half of the remaining 90% had an "insignificant" lesion which required little or no treatment and in the other half no lesion whatsoever was found. The incidence of significant lesions was not greater in those who had the higher degrees of microhaematuria. There was no indication in the urinary examination (which did not include the study of exfoliated cells) which patients were likely to have a detectable lesion and which were not.

It is, therefore, reasonable to conclude that at least a very large proportion of the men rejected for employment at Clayton on account of microhaematuria were healthy. But where bladder carcinogens are contacted the presence of blood cells in the urine must always be regarded as a possible sign of bladder tumour. These men were rejected lest they should continue to pass blood in their urine and difficulty should arise in the assessment of their wet

smears in the future and to eliminate those who might have urinary tract disease or a predisposition to it.

Haemorrhagic chemical cystitis.

The occurrence of acute haemorrhagic cystitis in workers in certain amines has been recognised since last century. It was described by Rehn and many other of his contemporaries and most of them attributed it to aniline and toluidines. Müller (1951) refers to two instances in young men after two days of heavy exposure to betanaphthylamine, Goldblatt (1947, 1949b) cites benzidine and chlor-aniline as causes and Melick and his co-workers (1955) found it in workers in 4 amino diphenyl. Aniline has not been reported as a cause during the last thirty years. By far the most active of the commonly used chemicals in this respect are the toluidines and 5 chlor 2 toluidine. Goldblatt (1949b) thinks the other two isomers of chlor toluidine may be inactive. Currie (1933) gives details of 11 cases of haematuria from cystitis arising in workers manufacturing 5 chlor 2 toluidine; in one group of 13 workers there were 9 men who developed haematuria. All the men had sufficiently heavy exposure to induce some degree of cyanosis from methaemoglobinaemia as well. Both the haematuria and the cyanosis cleared up rapidly on removal from exposure. These acute attacks of cystitis are not thought to be precursors of tumours and it is not suggested that 5 chlor 2 toluidine is carcinogenic (Goldblatt 1949, Scott 1954, Williams 1959, etc.). Truhaut (1952) goes so far as to state that it should be absolutely struck off the list of

substances causing bladder cancer.

Manufacture of 5 chlor 2 toluidine hydrochloride has been carried out at Clayton since 1929. One man operated the process for many years until 1953. He has never complained of haematuria or had blood cells in his urinary deposit on regular monthly tests. Since then another experienced man has replaced him and he also has had no complaint or signs of cystitis.

In the manufacturing process the temperature does not exceed 100°C. and the final material is kept in a wet paste as far as demands permit so that vapour and dust are not great. From time to time a dry product is required and the amine has to be dried on trays in a large stove so that the risk from volatilization and dusting is increased.

The compound has been used in another part of the same building, being condensed with other compounds of low toxicity to form an intermediate of the Ciba-naphthol series. Three to four men at a time have been engaged on this job which normally operates for one or two periods of three to four weeks each year. The condensation is done at high temperature so that there is a potential vapour risk. All the men have their urines examined daily while they are on this work. If blood cells are found in the urine of any man he is taken off immediately. Despite this, and despite the most stringent precautions which are taken on the plant, three cases of gross haematuria arose during the past three years 1954 - 57.

The following summary of the three cases, none of whom became cyanosed, illustrates several points which arose.

Case No.M. 50031 (Age 31). Started March 1954. In May 1954 had worked 3 days on Ciba naphthol. No blood cells had been seen in his urine which was examined daily. On the evening of the third day whilst at home he started passing blood painlessly. He was sent into hospital by his own doctor. Cystoscopy revealed dense congestion and inflammation of the bladder mucosa ("haemorrhagic cystitis"). This cleared up in three days and he was well on discharge. There was no recurrence of blood in his urine up to his leaving the company on 14.1.55.

Case No.J. 50002 (Age 24). Started October 1955. On 17th October, 1956, after working a week on Ciba-naphthol, his daily urine test revealed 6-8 red blood cells per low power field. His job was immediately changed so that contact with 5 chlor 2 toluidines was eliminated. Next day he had a moderate degree of visible haematuria which lasted one day. Microhaematuria gradually decreased and took 10 days to disappear entirely. He is still employed and has had no further symptoms or signs of urinary trouble.

Case No.B. 50016 (Age 52). Started 14.1.57. On 28.5.57 he was engaged in cleaning out stoves which had contained 5 chlor 2 toluidine. That evening he suddenly developed severe dysuria and frequency. The urine was blood stained. His symptoms cleared up in two days, but he had another slight attack on the fourth day. The microhaematuria gradually subsided and by June 3rd his urine contained no blood. Stained smears of exfoliated cells showed normal (Class I) cells throughout. His urine has been clear on subsequent examination.

Other similar cases have been recorded in earlier years and all have cleared in a few days under simple treatment; fortunately none has developed clot retention.

Thus the significance of occult blood in the urine of workers in a chemical factory can be very difficult to assess, and a single sample can be misleading. If there is micro-haematuria in a specimen from a man with a history of recent contact with certain amines, further examination after removal from exposure may be necessary. The persistence of small number of blood cells or the sudden appearance of large numbers has usually been regarded as an indication for cystoscopy but such signs are in no way specific for tumour even in men with histories of long and heavy exposure to carcinogens. Each case had to be considered individually, taking into account the history of exposure to carcinogens,before deciding if cystoscopy should be advised, bearing in mind the importance of keeping the number of negative cystoscopies as low as possible in order to avoid the risk of refusal in the future.

Nevertheless, although the application of the wet smear technique had disadvantages and short-comings many presymptomatic diagnoses have been achieved by this method. The average number of men employed during the past 15 years has been about 1,800 and approximately 22,000 wet smears have been examined from them each year. During the eleven years from 1940 - 1950, 40 men whose urine was being examined regularly by the wet smear test, developed tumours. In 16 of these men there was no indication whatsoever that a tumour was present until blood cells were observed on microscopy of their urine. In 12 cases small numbers of blood

cells considered to be insufficient in quantity to warrant advising cystoscopy, were present. In 12 men symptoms or gross haematuria were the first indications of bladder trouble. The wet smear technique, therefore, was unsatisfactory in detecting the presence of tumour in 24 men out of 40.

CYTODIAGNOSIS.

The disadvantages of depending on the detection of micro-haematuria or on regular routine cystoscopy for the early diagnosis of tumours of the bladder kept one on the alert for any other means of screening the workmen. Fragments of tumour and tumour cells were sometimes identified on routine examination of unstained wet smears of urinary deposit from men known to have tumours. This was not a new observation as desquamated cells were said to have been seen in the urine as early as 1864 (Sanders). It was not, however, until the introduction of differential staining by Erlich in 1891 that the accurate assessment of such cells became possible. In 1903, Albarren and Imbert suggested a search for neoplastic cells in the urine in cases of inexplicable haematuria. Stennius (1924) and Heiburg (1926) tried to assess the malignancy of cells in urine by measurements of the cells and of their nuclei. Parmenter (1925) thought the urine could usefully be examined for tumour cells as well as blood cells before cystoscopy.

Papanicolaou, following the successful application of his technique of exfoliative cytology to the diagnosis of cancer of the cervix uteri (Papanicolaou and Traut 1943) extended it to the urine (Papanicolaou and Marshall 1945, Papanicolaou, 1947). He reported his findings from cytological studies of the urine in 240 hospital patients. Of these, 76 had tumours (55 of bladder, 12 of kidney, 1 of renal pelvis, 8 of prostate) and tumour cells

were found in the urines of 43 (57%). A further 21 were suspicious or doubtful, 7 were slightly suspicious and 5 were negative. There were also two false positive findings. Schmidlapp and Marshall (1948) treated 333 patients whose smears had been classified by Papanicolaou. Despite an encouraging number of true positive results they reported that the technique was not dependable in the detection of benign tumours - they had 36 patients with histologically benign papillomata in 27 of whom the smear was negative and in 8 of whom it was suspicious. Chute and Williams (1948) applied the technique to the urine of 168 hospital patients with encouraging results in malignant neoplasms (55% true positive in 59 patients with tumours and 12% false positive results in the others) but their results in cases of benign papilloma were not dependable. Possible reasons for this are discussed later. Although in 1950 Cromwell and Papanicolaou (1952) had suggested the screening of dyeworkers at risk by this method it has not yet been extensively applied in America. Within the past few months it is being introduced there by Melicow for the screening of 4 amino diphenyl workers on the advice and under the guidance of British industrial physicians (sundry personal communications and correspondence).

In 1951 the stained smear method of Papanicolaou was introduced into three British factories (Crabbe 1952; Crabbe, Cresdee, Scott and Williams, 1956) one of which was The Clayton Aniline Company. It has been used in this factory as the principal

method of control screening of workers since then. The other two factories belonged to Imperial Chemical Industries Ltd. and Drs.Crabbe, Cresdee and Williams were their medical officers. In the 1956 paper the joint results obtained by examining the urine of some 1800 workers and the cystoscopic findings amongst 91 men are reported. Of these I contributed approximately 1500 men who were on routine test and 44 of the 91 men who were cystoscoped. Since the joint paper was written further cases of bladder tumour have been diagnosed by cytodiagnosis and confirmed by cystoscopy in The Clayton Aniline Company's factory and my complete results are now described and discussed.

When the technique was introduced at Clayton in January 1951, wet smears were being done at monthly intervals on all workers and this has been continued. At first if any wet smears showed epithelial cells or blood cells a stained smear was made by Papanicolaou's method and examined. One also examined stained smears from all workers at least annually and at more frequent intervals from those men at high risk due to long or heavy exposure to carcinogens. The two latter types of survey were done for the first four years, but it was found that a great deal of time and energy was wasted on preparing smears, many of which were acellular when examined. Furthermore, it seemed desirable that a more frequent check should be maintained on those workers at high risk. If the urines of all the men were to be fully processed each month it would have necessitated doing something of the order of 1500

stained smears every month, a number which was administratively and economically impossible. Therefore, from 1955 stained smears were prepared only from those urines with cells in the wet smear. Much time previously wasted in preparing and examining acellular material has thereby been saved. With experience, variations in cell structure were noted in the wet smear and were confirmed on examining a stained smear. In this way it was found that cells which were atypical or abnormal could be distinguished on the wet smear. Stained smears were thereafter prepared for further examination and classification only from urines containing abnormal or atypical cells and from those containing blood cells.

With the adoption of this procedure, which was finally worked out and applied by the beginning of 1955, an average of 100 stained smears require to be prepared and examined each month from the 1500 or so men who are on monthly urine test.

Phase Contrast Microscopy

The fact that atypical and abnormal epithelial cells could be distinguished from normal cells in wet smears of urinary deposit under the microscope using conventional illuminants suggested that if phase contrast microscopy were applied it might be possible to make a direct reading. This would eliminate the time spent in preparing and examining stained smears.

In order to test this hypothesis 1,000 urine deposits were examined using phase contrast microscopy. It was found that the classification of the cells present corresponded in all cases to

that made by the same reader on the same urine stained by the Papanicolaou technique. It was concluded that direct readings by phase contrast microscopy can readily be made on unstained wet smears. The re-training of a technician or technologist used to examining stained material would not be difficult. The advantage expected of phase contrast microscopy was the saving of the time spent in preparing and staining smears. In fact little time was saved as a fresh specimen had to be prepared for each urine so that it could be examined under a high power objective using a cover slip. A batch of 20 Papanicolaou smears can be stained and mounted in about 30 minutes.

The great disadvantage of phase contrast microscopy was found to be the absence of a permanent preparation. This is essential for (a) the confirmatory examination by the medical officer of a technician's findings, (b) the re-examination of suspicious smears and their comparison with subsequent specimens, (c) reference back in the case of readings which subsequently appear to be false and (d) teaching and demonstration purposes. These considerations outweighed the apparent advantages and it was decided to discard phase contrast microscopy and to concentrate on increasing the efficiency of the stained smear technique.

Stained Smear Technique.

The original technique (Crabbe 1952) consisted essentially of fixing the urine with an equal volume of 95% ethanol and centrifuging 40 mls. of it. Smears were made by spreading a small amount

of the deposit on a slide and placing it in a fixative solution. It is then stained, counterstained and mounted. The technique is described in detail in Appendix A. While it is preferable to use fresh urine (Sarvaya, Saudin and de Almeida, 1954, state that it should be processed within one hour) it has been found that unfixed urine will keep several hours and fixed urine as long as 96 hours at room temperature.

Most urines examined from symptomless, healthy workmen are crystal clear and yield little deposit and few cells. As there is a marked increase in the exfoliation of bladder epithelium after exercise (Hyman, Solomon and Silberblatt, 1956) urine is collected from men at work, when they are active, in order to get the maximum possible number of cells in the specimen. The collection of clear urine in two pots appeared unnecessary and during a trial period of two months in 1955 smears were prepared from each pot and from a mixture of the two specimens. There was rarely any difference in the smear whichever specimen was used and since then one pot specimens have been collected. Occasionally when there is a heavy cellular deposit a two pot specimen may be required.

In industrial practice most of the urines yield little cellular deposit. The addition of the 95% abohol often precipitated a heavy deposit of amorphous debris and also halved the possible cellular yield in the final deposits. It was found after a series of trials that the ommission of alcohol for fixation did hot affect the cells if they were processed within four hours of

micturition and alcohol fixation was therefore discarded.

The smears made from many of the urines showed so few cells that a great deal of time had to be spent in searching for them. Some method of concentrating more cells into a smaller area was sought. Deden (1954) used 400 ml. of urine, allowed it to settle for six hours and centrifuged the deposit. This is cumbersome and is impracticable in mass screening. Rofe (1955) concentrated the cells by differential centrifugation. A modification of his method was eventually developed and is the one now used. Fig.6 shows a random smear prepared after ordinary centrifugation of clear urine and Fig.7 shows a smear from the same specimen after special concentration. It will be seen that many more cells are available in each field for examination.

Deden (1954) found that staining by haematoxylin and eosin was as reliable as Papanicolaou's stains. A series of smears stained by each method confirmed Deden's opinion. It was found, however, that examining H & E stains for long periods was much more tiring to the eyes than the Papanicolaou stains and the latter are preferred and used.

Variations in staining were troublesome until trials showed that standardization of the pH of the urine and of the stains gave uniform results. Leishman's stain was also tried in order to get more delicate nuclear staining but was abandoned because all attempts to stain smears in batches with it resulted in uneven and unsatisfactory staining.

The use of a tissue processor for staining was also tried as it was thought that automatic staining might save time and standardize results. Against controls stained by hand there was some distortion of the cytoplasm and the nuceli were poorly defined. This was probably due chiefly to the time taken (75 secs.) to change over from one bath to another so that the smears tended to dry out, and partly to the limited number of operations possible. Automatic staining has, therefore, not been introduced. In any case the time that might have been saved by its use is small compared to that required to examine the slides.

The technique of preparation and staining of the smears which was finally adopted is detailed in Appendix A.

Classification of smears.

Papanicolaou (1954) described and depicted in his Atlas the criteria of malignancy. His classification of smears is as follows :-

Class I. Absence of atypical or abnormal cells.

Class II Atypical cytology but no evidence of malignancy.

Class III Cytology suggestive of, but not conclusive for malignancy.

Class IV Cytology strongly suggestive of malignancy.

Class V Cytology conclusive for malignancy.

Crabbe, Cresdee, Scott and Williams emphasize that the interpretation of the smears is difficult and requires a thorough knowledge not only of the criteria of malignancy but also of the numerous variations from normal due to non-neoplastic conditions.

We stress that it takes many months of instruction and practice to train a technician to make a reliable assessment of exfoliated cells.

As Papanicolaou points out, exfoliated cells differ greatly in appearance from corresponding cells in tissue section. No single criterion is sufficient to establish conclusively the presence of malignancy and he bases his classifications on structural modifications of cells and their nuclei, and changes in the inter-relationships of cells as evidenced in cell clusters and tissue fragments. Crabbe (1959) includes as the main criteria enlargement and prominence of the nucleus with an alteration in the amount and pattern of chromatin, marked irregularity in nuclear shape and abnormality in size, and he notes that mitotic figures, though uncommon, are sometimes seen; the cells may be large and bizarre in shape and phagocytosis of other cells by malignant ones is common. Figs. 8 and 9 show malignant cells illustrating many of these criteria in smears from the urine of men under routine test.

As a practical working method in screening the Clayton workers, Class I and II have been regarded as negative, Class III as suspicious and Class IV and V as positive. A positive result is regarded as an indication for investigation (including cystoscopy of the genito-urinary tract). Suspicious smears are regarded as positive if blood is also present or if exposure to carcinogens is deemed to have been significant but otherwise the examination

is repeated until a definite appraisal can be made. Many of the case histories illustrate the application of these principles.

Results of cytodiagnosis

The results cover the seven year period 1951 - 58. Special reference will be made to the last three years when the improvements in cytodiagnostic technique and interpretation had been fully developed.

Approximately 1500 men were examined regularly when new starters and leavers are taken into account. Table 16 shows the number of hourly paid male employees on the tests. A number of the staff were also examined.

TABLE 16

Men on routine urine tests

	Total at Jan.1st (A)	New Starters during year (B)	Leavers during year (C)	Overall Total (A + B)
1951	1472	627	498	2099
1952	1601	81	778	1682
1953	904	534	240	1438
1954	1198	392	294	1590
1955	1296	282	248	1578
1956	1330	100	261	1430
1957	1169	212	179	1381
1958	1202			

The results are divided into two main groups, first those men who had never previously had bladder tumour and secondly,

those who had developed, and been treated for, tumours and who were under regular follow-up review. The results in these two groups are so strikingly different that they are described and discussed separately.

Cytodiagnosis in men with no previous tumour.

In the first group 55 men were cystoscoped because of the findings in the routine urine tests or because of the onset of symptoms and 35 new cases of bladder tumour were discovered. The results are summarized in Table 17.

Smear results compared with cystoscopic findings in 55 men

	Tumour Present				No tumour found		
	True Pos.	Prob. True	False Neg.	Total	False Pos.	True Neg.	Total
Symptoms and/or R.B.C's	10	2	3	15	1	15	16
No. " "	17	3	-	20	2	2*	4
Total	27	5	3	35	3	17	20

* cystoscoped at own request

There were 27 men with positive Papanicolaou smears in whom tumours were found on first cystoscopy (true positives). Of these 10 had symptoms or a degree of microhaematuria sufficient in themselves to be an indication for cystoscopy; the other 17 had not at any time had symptoms or blood cells in the urine or any indication, other than the stained smear, that a tumour was present

Five other men with positive smears, but in whom no tumour was found when they were first cystoscoped, were found to have tumours on re-examination at varying intervals up to 18 months later and are regarded as probably true positives. Three men who had negative smears were investigated because of sudden haematuria in one, and the persistence of red blood cells in the urine of two, and they were found to have bladder tumours (false negatives).

No tumour has been found in 20 men who have been cystoscoped for various reasons. Three examinations were made on men whose smears were considered to be positive (false positives) and 17 on men whose smears were negative (true negatives), 15 because they had symptoms or occult haematuria and two at the men's own request for an examination to allay their fears.

Discussion of results.

Of 35 men whose stained smears were positive 27 (77%) were found to have bladder tumours on first cystoscopy. When the 5 "probably true positives" are included this figure becomes 32 (91%).

Men who had negative Papanicolaou and negative wet smears were presumed to be clear of tumours in the absence of symptoms and they were not investigated further. During the period under review all the tumours which were found were at an early stage of development when first seen. This supports the view that no tumour remained undetected until it was at a late stage. In the three cases in which a tumour was found associated with a negative stained smear, two of the men had increasing microhaematuria which

prompted further examination but the other had only an insignificant number of blood cells in the urine before a sudden haematuria supervened. In each case the Papanicolaou smear was positive after initial out-patient cystoscopy and before the men were admitted to hospital for treatment, so that the detection of the tumour by stained smear examination would probably not have been long delayed had the other reasons for initiating investigations not arisen.

The ability to distinguish normal cells on the unstained wet smear leads one to the conclusion that urines which are classed as normal in this way are rightly regarded as negative for tumour. During the last 3-year period 1955-57 approximately 40,000 urines were examined by this method and 2,544 were selected for staining and further examination. Deducting 820 smears from men with new tumours or established tumours which had previously been treated there were therefore 1724 true negative stained smears and approximately 39,000 true negative smear examinations in all. During this period the presence of only one bladder tumour has been revealed other than by routine urine examination (Case No.41) and it is reasonable to presume that this is the only false negative result, using the two techniques, in about 39,000 examinations.

Both tests have been applied throughout. Table 18 shows the results of the application of the wet smear technique for microhaematuria and Table 19 those of the Papanicolaou technique

since the latter was introduced in 1951.

TABLE 18

Wet Smear Results.

Cystoscopy	Red Blood cells or symptoms		Total
	Present (Positive)	Absent (Negative)	
Tumour present	15	20	35
No tumour present	16	4	20
Total	31	24	55

TABLE 19

Papanicolaou Smear Results.

Cystoscopy	Papanicolaou Test		Total
	Positive	Negative	
Tumour Present	32	3	35
No Tumour Present	3	17	20
Total	35	20	55

These data emphasize the great superiority of the Papanicolaou technique over the wet smear technique for the detection of blood cells. With the latter there were 20 (36.4%) false negative results whereas with the Papanicolaou technique there were only 3 (5.5%). Moreover there were 16 (29%) false positive results with the wet smear and only 3 (5.5%) with the Papanicolaou smear.

The improvements in the technique and the experience gained in the interpretation and classification of the smears would be expected to improve the results. Table 20 shows the results for the past three years 1955 - 57 during which 21 new cases of bladder tumour have arisen in men still at work and under supervision.

TABLE 20

Tumours arising in the past 3 years.

	Papanicolaou smear			
	True Pos.	False Pos.	False Neg.	Total
Blood cells and/ or symptoms	1	0	1	2
No blood cells or symptoms	19	0	0	19
No. of men with tumours	20	0	1	21

There were during this period 19 men (90%) with symptomless tumours which were detected by the Papanicolaou before there was any other indication whatsoever of their presence.

False positive results.

There were eight men whose smears were positive but in whom no tumour was found when they were first investigated. Five of these men were found to have tumours on subsequent urological investigation at intervals varying from five to 18 months later and they have been tabulated as "probably true positives". The following case is representative :-

> Case No.122. This man was aged 56 when the tumour was found in 1954. He had worked on magenta manufacture for 3 years 1922 - 25 and had used benzidine in small amounts for 19 years 1930 - 49. In January 1954 a wet smear of his urine contained a few red blood cells and a Papanicolaou smear revealed "many malignant cells and clusters - Class V - positively malignant". Cystoscopy was done on 25.1.54 but no tumour was seen in the bladder; intravenous pyelography revealed no abnormality. Exfoliated malignant cells continued to be present in the urine and he was re-investigated four months later. On 25.5.54 cystoscopy showed widespread papillomatosis of the bladder which proved on biopsy to be papillary carcinoma.

Von Hamm and Menzies (1953) found malignant cells in vaginal smears from laboratory animals some time before experimentally induced carcinomata of the cervix uteri could be identified, and it seems reasonable to presume that cells with malignant characteristics were exfoliated from early foci of tumour formation which were too small to be demonstrable by the most careful investigation. Melicow and Hollowell (1952) described 30 cases of carcinoma in situ from the Squier Urological Clinic in New York. Among these

were 17 in the bladder epithelium while two involved the ureter and one the renal pelvis.

It is possible that the appearance of malignant cells in one case in this series in which no cause has been found may prove to have a similar explanation :-

> Case No. F.M. 53035: Born 10.10.02. He worked in a process using benzidine for 20 years 1931 - 51. A carcinoma of the colon was successfully removed by right hemicolectomy in 1954. In March 1956 cells with characteristics suggestive of malignancy (Class IV) were observed in his urine. On 21.8.57 he complained of severe lower chest and abdominal pain radiating to the left arm and was admitted to the Manchester Royal Infirmary as an emergency on 21.8.57. Investigations and liver function tests confirmed a diagnosis of acute pancreatitis. He was discharged from hospital on 27.9.57. He was cystoscoped as an out-patient on 19.10.58 and no bladder tumour was found. Smears up to 17.3.58 have been Class I. He is being kept under observation.

It remains to be seen if this man will eventually develop a tumour. Roland and Marshall (1957) held that unexplained positive smears should be followed up indefinitely. Crabbe, Cresdee, Scott and Williams had four men (the above case is not one of them) who had repeatedly shown malignant cells in their smears over periods of up to two years but in none of them had a tumour been found. Two of these men were from The Clayton Aniline Co.Ltd. and are included in the present series (Case Nos. 47 and 127). Both of them have since been found to have tumours on follow-up cystoscopy and are now included in the "probably true positive" group.

One of two men in the series who developed the initial

tumour in the renal pelvis had malignant cells in his urine for a year before a diagnosis of tumour was confirmed. There was a gradual progression of the classification from normal to frankly malignant over a few months and this has been observed in many of the cases.

Case No.127 H.C.: Born 9.6.05. This man worked on or near the benzidine manufacturing unit for 13 years 1939 - 52. Stained smears of his urine were classified as I or II until 1st November 1955. A reading of Class II - III was made on that day and again on 30th November and 3rd January 1956. On the 2nd February 1956 it was Class III - IV and on the 2nd March Class IV. Three further smears during the same week were Class IV. Some blood cells were also present then. Fig.10 is a photomicrograph of the smear on 2nd March. In view of these findings he was cystoscoped on 26th March 1956. No tumour was present in the bladder. Straight x-ray of the urinary tract showed no abnormality and an intravenous pyelogram revealed good excretion and no abnormality of the renal or pelvic outlines.

He continued to exfoliate Class IV or V cells and he was admitted to Salford Royal Hospital on 22.12.56. Cystoscopy again revealed an apparently normal bladder. On retrograde pyelography the appearances were suggestive of tumour at the right pelvi-ureteric junction and this was confirmed on an intravenous pyelogram.

On 15.1.57 right nephrectomy and ureterectomy was performed by Mr D.S.Poole-Wilson and a papillo-carcinoma of the renal pelvis was found. Section showed this to be invasive. Smears were Class I after his operation.

He subsequently developed bilateral pulmonary tuberculosis of which he died on 18.12.57. At post-mortem examination his bladder, left kidney and renal pelvis were clear of tumour.

Papanicolaou (1954) stated that there was evidence that exfoliation appears early in tumours of the pelvis of the kidney.

He cites two cases in which the diagnosis was made by the examination of ureteral urine and was confirmed by nephrectomy performed on the strength of the urinary findings. Owing to the limitations of diagnostic methods the detection of renal pelvic and ureteral tumours at as early a stage as those in the bladder is difficult and it is likely that exfoliation does not necessarily take place earlier from these tumours than from bladder tumours but that it occurs before the growth is sufficiently advanced to be demonstrable by other methods. For this reason it is probable that renal pelvic tumours will give rise to positive readings on urinary smears before they can be demonstrated by conventional methods.

Two of the men whose smears were classified as positive were investigated and were found to have symptomless renal calculi. Ferguson (1949) held that certain non-neoplastic conditions can produce cells almost identical to malignant cells. Papanicolaou in his Atlas pointed out that renal calculi may cause the appearance of atypical transitional cells which are mostly small or medium sized and that their differentiation from malignant cells is at times difficult. The smears from each case showed clusters of cells which were not unlike those from a benign papilloma. There was, however, ample cytoplasm between the nuclei and the cell membranes and the outline of the clusters was smooth and well-defined; there were some erythrocytes and leucocytes in each case. Fig.11 is a photomicrograph (Case No.

59028) showing these several points. It was thought that one could in the future recognise these appearances as typical of the presence of renal calculi and differentiate them from those of benign papilloma. Smears from two patients in Salford Royal Hospital who were known to have renal calculus were made and this impression was strengthened. Fig.12 shows a photo-micrograph from a smear of one of these patient's urine and the same characteristics are evident. This can be compared with Figs. 13 and 14 which are from benign papillomata.

Crabbe (1959) feels it is far worse to miss detecting a tumour until it becomes inoperable than for a man to undergo what he describes as a "negative cystoscopy" and that, therefore, false positive results are far less undesirable than false negatives. No one could seriously refute this statement. Deden (1954) looking at the same point from another aspect is of the opinion that if one aims to be so cautious as to exclude any false positive the result would presumably be to get too low a number of correct positive findings and thus reduce the clinical value of the procedure. These views are merely speculative. The point has already been made that in approximately 40,000 examinations in the last three years, only one case arose which was not first detected by the smear technique. In all other cases a positive smear gave an indication that a tumour was present and in a few apparently false positive cases it preceeded the appearance of the tumour by some months. Furthermore, in

only one case does a false positive smear remain unexplained.

False negative results.

Three men (Case Nos. 22, 23 and 41) whose Papanicolaou smears were negative were found to have tumours when cystoscoped. Two were investigated because of the presence of significant numbers of red blood cells in the wet smear and one (No.41)because of the sudden onset of haematuria. Thus if both techniques are taken into account there was only one false negative.

> Case No.41: Born 12.1.07. This man had been engaged in the manufacture of beta-naphthylamine for 23 years, 1927 - 50. Wet and stained smears examined at monthly intervals had been consistently negative, the latter was Class I on every examination except for a Class II reading on 14.10.55. The last urine test previous to the onset of symptoms was on 16.1.56 and it was again negative. On 18.2.56 he had a sudden attack of haematuria. Cystoscopy on 24.2.56 revealed a tiny benign papilloma which was destroyed by diathermy. Biopsy confirmed that the tumour was a benign papilloma.

In each of these three cases the clinical appearances were those of a benign papilloma and this was confirmed by biopsy in two of them. In the other case (No.22) the biopsy material showed oedematous bladder wall only. Soon afterwards this man passed large numbers of cells with the characteristics of malignancy and he has continued to do so. He is discussed more fully in the consideration of established cases(page 149).

Crabbe, Cresdee, Scott and Williams had a false negative finding in a man with a solid type of carcinoma covered with slough and calcareous deposit which presumably sealed off any

cells which might have exfoliated. No advanced or solid carcinomata occurred in the present series and the three false negative Papanicolaou findings were all associated with tiny benign papillomata.

Benign Papillomata.

Papanicolaou in his discussion of the criteria of malignancy states that Class V is the only conclusive group and that a varying degree of error in interpretation is to be expected in each of the other four groups. Many authors (Chute and Williams, 1948, Schmidlapp and Marshall 1950, McDonald 1954, Deden 1954) stress the difficulty of detecting benign papillomata because the cells exfoliated from them would not be expected to show the usual criteria of malignancy and would be similar to the normal. In fact Dean (1948) and Leadbetter (1955) maintained that they showed no recognisable difference from normal cells. Osborn (1953) thought that even fragments of tissue voided in the urine from benign papilloma showed little cellular variation from each other or from the normal, but three years later (1956) he said that cytology of the urinary tract was of the greatest value in diagnosing both benign and malignant tumours and that the cells from each are easily distinguished from the other.

Crabbe, Cresdee, Scott and Williams (1956) reported 56 new cases of bladder tumour. Among these were 29 cases of clinically benign papilloma which had been detected by the appearance of positive smears and of which 15 were confirmed on biopsy. In

three cases clumps of cells which were considered to be benign papilloma cells were seen and in each the presence of a benign papilloma was confirmed on cystoscopy. My co-workers and I were convinced that, contrary to many opinions, it is possible to detect a significant proportion of benign papillomata by the stained smear technique. My own experience since then has strengthened me in this conviction.

The reading and interpretation of large numbers of smears have resulted in a greatly improved perception of the characteristics of cells exfoliated from benign papillomata and malignant neoplasms. The results still show that while both types of tumour may exfoliate cells with malignant characteristics, some benign papillomata will exfoliate cells, which while not having the criteria of malignancy have specific characteristics by which they can be classified as having originated from benign papilloma. Figs. 15 and 16 show two examples of such smears. They are from Cases No.51 and 66 respectively. The cells are clustered in groups, are fairly small but have a high nuclear cytoplasmic ratio and there is nuclear hyperchromasia; there is little variation in the size or shape of individual cells within the clusters. Occasionally a small piece of tissue is identified as having been shed from a benign papilloma and Fig.17 shows such a particle from Case No.38.

There were 32 men in whom the onset of a tumour was associated with a positive Papanicolaou smear (Table 21).

TABLE 21

32 men with tumours whose Papanicolaou smears were positive

	Papilloma	Carcinoma	Total
Class IV or V	16	10	26
Papilloma cells	6	0	6
Total	22	10	32

In 6 the smear contained cells typical of benign papilloma and in 26 the smears were classed IV or V, in fact, the appearances were suggestive of or conclusive for malignancy. Of these 32 men, 10 had clinical carcinomatous lesions all confirmed by biopsy and 22 had clinically benignpapillomata of which 14 were confirmed by biopsy. The latter include the 6 cases (Nos. 20, 38, 40, 46, 51, 66) in which only clumps of benign papilloma cells were seen.

Thus, 16 men out of the 22 with benign papillomata had apparently malignant cells in the urine. It is difficult to explain this finding in such a high proportion of men with benign tumours, unless malignant changes are already taking place in these tumours. If this is so then one would expect a higher eventual incidence of malignancy over all the period than there actually is.

The degree of innocence or malignancy of the simple histologically benign papilloma is a very controversial point (Crabbe 1959). Some (e.g.Demming 1950) regard it as benign throughout, others (e.g. Marshall 1956) take the easier way of regarding it as being in a distinct class by itself and many (Ash 1940, Wakeley and Graves 1958) regard the papilloma as a potential source of cancer. Wakeley and Graves held that "some benign growths will remain benign, some will become malignant soon and some will have malignancy thrust upon them" (the last from super-added irritant). Dukes(1947, 1952) held that some benign neoplasms contain a focus of carcinoma which is not invasive and Macalpine (1947) thought that a urinary papilloma may be benign in one part and malignant in another.

The one very important conclusion that can be drawn with certainty from the results in this series is that it is possible to detect benign papillomata by cytodiagnostic techniques but it has not been found possible to predict the nature of the tumour from the appearance of the exfoliated cells except in the small number of men in whose urine benign papilloma cells could be identified. If, as some claim, normal looking cells are, in fact, exfoliated from a benign papilloma and are not identifiable in the urine then it could be expected that the degree of malignancy of the tumour would be very low. Such a false negative reading would not be so serious as it would be in the case of a malignant tumour or one potentially malignant. The more

malignant a tumour is the more readily does it exfoliate in the early stages (Chute and Williams 1948, Booth 1959 in print) and the more likely it is to be detected.

Contrary to the many opinions expressed previously, it has been found that the cytodiagnostic technique is capable of detecting a significant proportion, and probably most, of the benign papillomata. Many of the opinions to the contrary were expressed in the early days of its application and were founded on the results in various series of hospital patients in whom new untreated tumours and advanced or previously treated tumours were indiscriminately mixed.

Cytodiagnosis in the follow-up of old cases.

The high liability to recurrence makes it essential that regular review of all those who have bladder tumours should be maintained for the rest of their lives. The possibility that examination of smears could be substituted at least in some measure for cystoscopic examinations was naturally attractive and it was hoped that it would prove dependable in this respect. The results (Table 22) have utterly dashed this hope.

The table shows the results for the 2½ year period up to January, 1958. This period is chosen because the improvements in technique had been established by then and the readings are likely to be more accurate than in the earlier days of its use. Despite this it is obvious that the results are quite inconsistent and that no dependence can be placed on them.

TABLE 22

Results of 130 review cystoscopies and smears of 47 men who have had tumours.

Smear Results	Cystoscopy			
	Negative (No tumour found).	Suspicious	Positive (Tumour Present)	Total
Negative	46	4	19	69
Suspicious	10	1	0	11
Positive	19	2	29	50
Total	75	7	48	130

Marshall and Whitmore (1956), because they had a "moderate number" of patients who had positive smears for some time before cystoscopic observation could detect a recurrence, concluded that the Papanicolaou smear technique had become a useful adjuvant to follow up examinations. This would only hold good if a large proportion of recurrences were detected and if one could be reasonable certain of the absence of recurrences in those with negative smears. It is disappointing that, in the present series, in 19 instances patients with negative smears had recurrent tumours on cystoscopy and only in 46 instances out of 69 (66.6%) was a negative smear completely vindicated on cystoscopy. In fact,

there are only 76 agreements (46+29+1) between the smear and the cystoscopy results in 130 cases, that is to say, in almost half of them they did not correspond.

Melicow (1952) found nests of malignant cells in sections of grossly normal areas from cystectomized bladders which had had tumours. He suggested these might be carcinoma in situ and that they were foci from which fresh neoplasms would spring. It is possible that malignant cells may be exfoliated from similar nests in the bladder of workmen who have been treated for tumours and have no demonstrable recurrence.

While one cannot, therefore, agree with Marshall and Whitmore that smear control is of much value in follow-up it might be expected that individuals with consistently negative smears would have a better prognosis than those with positive smears. Here again the facts are inconsistent and disappointing. Only 9 men among the 47 old cases have had consistently negative smears during the $2\frac{1}{2}$ year period. Each has been cystoscoped two to four times and only four have been clear of recurrent tumour throughout; three have had one recurrence, one has had a recurrence on two occasions and one on three occasions. All the recurrences have been clinically benign papillomata. In several other instances the agreement between the smears and cystoscopic findings has been highly inconsistent, for example, one man (Case No.40) had one recurrence following two successive positive smears, six months later there was

another recurrence following two successive negative smears and since then no recurrence has been found following consistently positive smears.

The appearance of positive smears in treated cases has accompanied or heralded the onset of recurrent tumour in only a third of those cases in which they were seen. Remembering that positive smears were observed in some of the new cases up to 18 months before a tumour could be demonstrated by other methods it is probable that recurrence will eventually be found in a proportion of the others. There are 19 such cases (Table 22) and the following Case No.22) is given as an example :

> Case No.22. W.L. Born 20.12.12. This man was a benzidine user for 17 years from 1931 until 1948 after which he continued to work as foreman in the same department.
>
> In May 1952 he had numerous erythrocytes in his urine. A stained smear was negative. Cystoscopy revealed a small clinically benign-looking papilloma of the bladder but biopsy showed oedematous bladder wall only and no evidence of tumour. He is one of the three false negatives described in the Papanicolaou smear findings in the new cases.
>
> On 16.3.55 his smear was Class III - IV and it has been either Class III or Class IV on every monthly occasion until 18.9.56 when a reading of Class V was made. On 10.2.58 and 13.3.58 it was again Class V. A photomicrograph of a smear from this man is shown on Fig.18 and many criteria of malignancy can be seen.
>
> No recurrences have so far been detected on investigation at intervals of three to six months since 1952; the most recent was in August 1958. Cystoscopy and retrograde and intravenous pyelography have failed to reveal the presence of a tumour and one can only wonder what the prognosis will be.

Discussion and evaluation of cytodiagnostic technique.

The difference in the results and in the dependability of the test in old and new cases is striking. Equally striking is the difference between my series of initial tumours and those described by other observers (Papanicolaou, Schmidlapp and Marshall, Chute and Williams, Deden, Marshall and Whitmore, etc.) many of whose results have been widely quoted as evidence that the technique had only a moderate value in diagnosis. Careful appraisal of their results suggests that in none of these studies was any differentiation made between new cases and those with advanced or previously treated tumours.

Papanicolaou in his 1947 paper does not state if his patients were new cases or had previously had tumours, but he describes them as "recent cases"; 8 of his 19 men with "suspicious" smears had tumours on investigation and 8 had none (one was "doubtful") - a finding rather similar in some ways to those in my series of treated cases.

Chute and Williams' 1948 report has been quoted as a reflection of the value of the technique by many writers (Crabbe, 1952, Poole Wilson, 1953, Crabbe, Cresdee, Scott and Williams, 1956) but Chute and Williams themselves state that they realise their observations were not controlled as closely and accurately as possible. All their smears were from hospital patients and they had only 3 cases diagnosed by the smears which were previously unsuspected or unknown to have tumours. They were so highly

selective in their material that all "doubtful" (i.e. suspicious) smears were excluded and all those patients in whom a definite diagnosis of some disease could not be made were discarded. So selective were they in fact, that they had 338 specimens from 256 patients and reported only on 194 smears from 168 patients. Most patients had only one specimen examined and they thought that repeated examination would have resulted in a higher percentage of positive results - 45% of their negative readings proved to be false. Furthermore, that many of their patients had previously had tumours might be inferred from their cases of prostatic cancer with positive smears of whom half had already been on stilboestrol treatment.

Schmidlapp and Marshall in 1948 reported on 333 of Papanicolaou's cases and they included " a large percentage" of patients with genito-urinary neoplasms. The high proportion of correct results they give in their table refers to malignant tumours only. No differentiation was made between new cases and those with advanced or previously treated tumours. The apparent anomaly of many of their results, e.g. 27 false negative smears in 36 patients with benign papillomata, is similar to that of my series of old cases and in the light of my experience it is suggested that it would probably not have arisen in new cases. On these figures has been based the assumption by many writers that the technique is undependable in cases of benign papillomata.

Deden in his 1954 thesis did not describe or evaluate his old and new cases separately. He had hospital patients only, most of them with advanced inoperable disease and few in which the diagnosis of tumour was unsuspected or even in doubt. The urines he collected were so "dirty" and thick with blood, pus and debris that he had to devise a tedious and time consuming method of separating the exfoliated cells out of the deposit.

The application of cytodiagnosis to patients with advanced recurrent disease accompanied by haematuria or pyuria has not, therefore, been succesful. The presence of blood or pus cells in large numbers obscures the exfoliated cells and limits the degree to which they can be concentrated in the smear. In the industrial population exfoliation of malignant cells has been detected at a very early stage before blood or pus appear in any quantity, and a reliable reading has been made more easily. The confusion arising from the inclusion of old or advanced cases is eliminated.

In no other series reported except that of Crabbe, Cresdee, Scott and Williams, have the results of new and old cases been separated so that, with this exception, one cannot compare the results of any other series with the present one.

Cytodiagnosis as a screening technique.

The results during the past seven years have proved that cytodiagnostic techniques can successfully be used to screen an industrial population especially if both wet and stained smears

are used in conjunction. The most important advantages which have been gained from their use are the detection of tumours at a very early stage of development, the ease and convenience of the examination compared with routine cystoscopy so far as the workman is concerned, the frequency with which the examinations can be made and the large number of people with minimal exposures to carcinogens to whom they can be extended.

Poole-Wilson (1953), only two years after cytodiagnosis was started on the workmen he examined urologically, noted that occupational bladder tumours tended to be seen at an earlier stage than those in the general population. He is now certain that the bladder tumours seen in workers referred to him are all at a much earlier stage than is usual in hospital practice (personal communication). The size of tumour seen is usually about 4-8 mm. high.

Had routine cystoscopy been applied to the Clayton workmen even annually it would have required something of the order of 5000 cystoscopies in the seven years to cover all the workmen at greatest risk, if there had been no refusals, compared with the 55 which in fact were done (excluding the follow up examinations of men who had had tumours before).

The fact that early diagnosis was achieved in all the cases detected and that, with one exception, no tumours appear to have been missed using both tests makes reasonable the conclusion that cytodiagnostic techniques offer over-riding advantages in

screening industrial workers who have been exposed to bladder carcinogens.

The possibility of using such methods to screen the general population in cancer detection programmes has been widely canvassed, especially in the U.S.A., since Papanicolaou first suggested in 1945 that it might be useful in this sphere as well as in the detection of carcinoma of the cervix uteri. The total number of new tumours which have arisen in the Clayton workmen over the past three years has been 21, an average of 7 per year in approximately 2000 men, i.e. an incidence of 3.5 per thousand per year. Since the incidence in the chemical industry is 34 times greater than in the general population one would expect about 1 per ten thousand per year in the latter. The detection of the 21 new cases of tumour involved nearly 40,000 urine examinations and the chemical workers were examined monthly so that it is likly that in a similar number of examinations of the general population no new cases of tumour, or only one, would be disclosed. It appears, therefore, that examinations of the general public could not be made at sufficiently frequent intervals to make application of the technique valid and that the incidence of bladder tumour in the general population is too low to make the work worth while.

On the other hand cytodiagnosis must be regarded as the method of choice and as being indispensable in the screening of industrial workers where a hazard of bladder tumour is known or suspected to be operating.

CLINICAL FEATURES

The tumours in the workmen, once established, had no distinguishing features from those which arise in the general population. Papillomata and carcinomata occurred without any apparent correlation to any particular substance or job, (Table 23) except that the comparatively small proportion of malignant tumours in the benzidine workers is possibly statistically significant ($P < 5\%$).

TABLE 23

Malignant and Benign Tumours according to compound worked.

	Papilloma	Carcinoma	Multiple	Total
Benzidine	30	15	3	48
Alphanaphthylamine	1	2	1	4
Betanaphthylamine	12	11	0	23
Other	8	3	0	11
Mixed	15	16	6	37
Total	66	47	10	123

The tumours were classified according to the biopsy findings or, if there were none, the clinical appearances. This division,

assumed to facilitate the analysis, is admittedly arbitrary but it avoids the dilemma of having to choose between the contradictory clinical, histological and cytological appearances which occur in some cases. Broadly, the tumours described as papillomata fall into Stage I of the classification described by Melicow (1955) and those described as carcinomata fall into Stage II, III or IV.

Poole-Wilson (1953) thought there was a tendency to greater multiplicity of tumours in those of occupational origin, although it was not marked. Winsbury White, Henderson and Wilkins (1950) hold that tumours appearing initially as frank carcinomata are commonly solitary. Wakeley and Graves (1958) make the point that the multiplicity of tumours and the co-existence of papillomata and carcinomata are due to the multifocal neoplastic change and the presence of different phases of this change simultaneously or at different times. Müller had 10 cases of multiple primary tumour in his 1951 series of 143 men with confirmed tumours - in three cases one of the growths was in the renal pelvis. Anderson reported 10 men who had multiple tumours in the bladder in 23 men in his series. There were also, curiously enough, exactly 10 men in the present series of 123 with multiple tumours on first examination and all were benign papillomata. Multiple recurrent tumours were seen more frequently on follow-up examination and are recorded simply as a recurrence.

In my first 66 cases in this series, reported in 1952,

exactly 50% of the tumours were malignant and now the incidence of malignant tumours has fallen to 42%. Table 24 compares the percentage incidence of malignant and benign tumours in four earlier series and the present one.

TABLE 24

Ratio of Malignant and Benign Tumours.

	No.of cases	Malignant %	Benign %
Müller 1949	111	71	29
Goldblatt 1949	75	64	36
Barsotti & Vigliani 1952	34	79	21
Scott 1952	66	50	50
Scott 1958	123	42	58

While it might be thought that improved working conditions may be held to have some influence in the reduction of the proportion of malignant tumours it has been shown that the type of compound and the nature of the job have no relation to the malignancy of the tumour. Some other factor must be operating. It is suggested that the explanation lies in the fact that owing to the improved diagnostic methods introduced in 1951 many tumours are now seen at an earlier stage and before malignant changes have begun.

Tumours of the renal pelvis.

Epithelial tumours of the renal pelvis and ureter are

comparatively rare. Riches, Griffiths and Thackray (1951) estimated that they constituted only 3% of all renal tumours. Riches (1958) had 43 in his series of 500 cases. Macalpine (1947) described four cases in dyeworkers all of whom had previously had bladder tumours. Moore (1942) found only 60 cases in the literature Goldblatt (1949) had two cases of renal pelvic tumours co-existing with or following occupational tumours of the bladder. Leuenberger (1912) and Sebening (1930) each had one case in which the tumour was in the renal pelvis only.

Among the 123 cases of tumour at Clayton there were 15 men who developed tumours of the renal pelvis, 13 following earlier bladder tumours. There were two men (Case Nos.60 and 127) in whom a renal pelvic tumour was the first manifestation of the disease (Case No.127 is discussed at length in the chapter on Diagnosis). The increase in the number of these tumours in recent years is probably due to the longer survival, resulting from earlier diagnosis and improved treatment, affording more time for renal tumours to develop before death supervenes.

Epithelial Hyperplasia.

Congestive lesions which were said to be the precursors of occupational bladder tumours were described by Gay (1934) and 1937) and at some length by Di Maio (1949). They have not been observed as a specific feature in my cases and it has not been possible to recognise pre-neoplastic congestive lesions. Poole-Wilson (1953), the urologist who examined and treated the

majority of these cases since 1945, stated that, while the mucosa over the area of tumour formation may be red or congested, he has not observed an abnormal incidence of vesical congestion or epithelial hyperplasia as a precursor of occupational tumours.

TREATMENT

A close appreciation of the treatment and its results has been maintained and a short account of them is given in this section. The treatments given total more than 123 because there were cases in which more than one type of treatment was applied. For example, when endoscopic diathermy was followed at a later or recurrent stage by radon seed implant or other radiation, both treatments are included. The therapeutic measures adopted at Salford Royal Hospital and The Christie Hospital and Holt Radium Institute, Manchester, where the majority of the men were treated have been according to the principles laid down for spontaneous tumours. (Poole-Wilson 1956, Gibson 1956, Millen 1956).

Diathermy. Benign pedunculated villous papillomata have, where possible, been treated by endoscopic fulguration. Recurrent tumours of this type have been kept under control as far as possible by this means. In all, 65 of the workmen had initial tumours treated by per-urethral diathermy. Of these 22 have had no recurrences, 31 up to three recurrences, 6 between 4 and 8 recurrences, and 6 have had more than 9 recurrences.

Radon Seed Implant. Localised malignant tumours which were not too deeply invasive were treated with fulguration and radon seed implantation through a suprapubic cystostomy. Nineteen men were treated in this way and only 2 have had more than 4 recurrences.

Irradiation. Tumours which have not been controlled by simple fulguration and carcinomata which were not amenable to treatment by other means were treated by deep x-rays or, as in 2 cases of

multiple superficial tumours, by intracavity irradiation. Eighteen men were thus treated by radiation. These include men in whom recurrent tumours of a malignant nature necessitated deep x-ray therapy and there were some advanced cases.

Nephroureterectomy. When operable, tumours of the renal pelvis and ureter were treated by nephroureterectomy. This operation was performed on 11 men, 2 of whom have survived over 10 years. Three others, all of whom have been operated on within the last 2 years, survive. Six have died, all within 3 years of the operation, one of pulmonary tuberculosis 11 months afterwards, and the others as a result of their tumours. In 2 men the tumours were inoperable and in 2 men they were discovered post mortem. In a further 2 men nephrectomy was performed for unilateral pyelonephritis.

Total cystectomy. As the whole of the bladder mucosa may be assumed to be potentiated by the carcinogenic mechanism total cystectomy has been advocated by many writers. Riches (1958) holds that it should not be left to be undertaken as a last resort for extensive or multiple papillary tumours. On the other hand Jacobs and Barr Stirling (1952) described the poor results from ureterovesical anastomosis in 476 patients with malignant bladder disease, of whom 75% were dead within a year, and from total cystectomy in 705 patients, of whom 54% were dead within a year. Only 2.2% survived the first operation for 5 years or more and only 20.4% the second. In the first group are included

many on whom cystectomy had been planned but who died of the preliminary operation. Winsbury White (1953) writes of the rearguard action some surgeons continue to fight in the losing battle to support cystectomy and Jacobs (1954) is impressed by the futility of the operation as a curative procedure for the advanced case. Poole-Wilson (1953) strikes a more hopeful note when he points out that it has, in practice, proved to be largely unnecessary. He writes, somewhat naively, that it has been found to be extremely unpopular with the workmen. In fact it is now almost invariably refused by our workmen all of whom have seen, or heard of, the physical, social and psychological effects of it on some of their mates. It is advised with the greatest reluctance and only when other measures offer no hope of a cure (Scott, 1953). As a result it has been done only in those patients in whom the prognosis is already poor. Five men have had the operation and all have died (Case Nos. 74, 82, 87, 96, 121). The longest survivor lived in discomfort and depression for 20 months (Case No.87). Three were dead within three months of ureter transplantation and before cystectomy could be done. The fifth died while still in hospital two months after the cystectomy. When a cystectomy is proposed or performed on one of the workmen the effect on the morale of the men who have tumours, and on those who know they may develop them, is disastrous and, in the Clayton experience at any rate, even more depressing than the death of one of the sufferers. Two men to whom the

operation was advised steadfastly declined to have it done although they were well aware of the consequences of their refusal. Both died in a few months from infiltrating carcinoma (Cases No.34 and 109).

Partial cystectomy. Seven men were treated by partial cystectomy, for solitary papilloma in six cases and for a malignant tumour in one case (No.65). The latter died of a perforated peptic ulcer seven months later and the genito-urinary tract was free of tumours at post mortem.

Others. In one man, (Case No.84) who was thought to have died of Paget's disease a large papilloma nearly filling the bladder was found on post mortem examination. Only one man (Case No.71) resolutely refused any kind of treatment from the beginning and he died in 1939 of an infiltrating carcinoma of the bladder and spinal metastases.

The numbers treated by each type of therapy were relatively small. There was considerable overlapping of treatment in many cases, some having,for example, radon seed implants for malignant recurrences soon after endoscopic fulguration. The men were not all treated by the same urologist nor did they attend the same hospital. It is not possible, therefore, to attempt to assess the relative value of each, or any, type of treatment in any grade of tumour and, with the exception of total cystectomy, no attempt has been made to do so.

RECURRENCES

All observers are agreed that the recurrence rate in occupational tumours of the bladder is high. Wakeley and Graves (1958) have suggested that recurrences even of simple papillomata are more frequent in spontaneous cases than they were usually thought to be. Comparative figures are not available but there can be no doubt about the high recurrence rate in dyeworkers who have developed the disease.

Of the 103 men who survived their initial tumour, 70 have already had at least one recurrence (Table 25). Six men - four of whom are still alive, two in good health - have had more than 8 recurrences. Only 6 men survived more than 10 years from the onset of their tumour without a recurrence.

TABLE 25
Recurrence rate in men who survived initial tumour.

Time elapsed since onset of first tumour	Pop. * at risk	Men who have had a recurrence			
		No. of recur.		Total	
		1	2+	No.	%age
Over 20 years	1	-	1	1	
At least 10 years	29	5	18	23	
" " 6 "	52	15	29	44	85%
" " 4 "	65	20	32	52	80%
" " 2 "	89	33	36	69	77%
Under 2 years (Cumulative Total)	103	33	37	70	68%

* 20 men who died as a result of their initial tumour are not included.

Table 26 shows the relative incidence of recurrences among men exposed to different compounds. There is no evidence of any correlation between the chemical involved and the frequency of recurrence.

TABLE 26

Recurrences according to compound.

Compound	Period since onset first tumour			
	0 - 4 years		5 years and over	
	Pop.*	No. of Recur.	Pop.*	No. of Recur.
Bz.	18	7	24	22
Bn.	4	3	14	11
Mixed	14	10	16	10
Other ⊖	8	3	5	4

* 20 men who died as a result of their initial tumour are not included.

⊖ Includes alphanaphthylamine.

The recurrences have not always been the same as the original tumour; while they have frequently been so, Table 27 shows that in 20 cases they were different from the original tumour, some papillomata recurring after carcinomata and some carcinomata succeeding benign tumours.

TABLE 27

Cases in which recurrence is different from original tumour

	COMPOUND					
	Bz.	An.	Bn.	Mix.	Others	Total
No. of cases	9	0	1	9	1	20
Mean latent period (Years)	15	-	34	18	31	18

DEATHS

So far 55 of the men who have had tumours of the bladder have died, 43 as a direct result of the tumour and 12 from other causes. Six of the 12 died of cancer in other sites (3 in the lung, one each in the liver, pancreas and oesophagus). The ages of the men at death and its implications have already been discussed (page 98).

The mean latent period in the men who have died from tumour was 18.9 years and of those who survive 21.2. The difference is not significant and it is possible to infer that those tumours which take shorter times to develop are not necessarily the most fatal and that those which incubate slowly are not necessarily of low malignancy once they are established.

Of the 10 men who developed tumours before 1937 only one (Case No.58) is still alive; 21 men have survived 10 years or longer after onset of their tumour, but 29 died within the first 5 years after it was detected, 12 of them in the first year (Table 28).

TABLE 28

Survival Time After Onset of Tumour.

Time since onset tumour	Living	Dead	
		Tumour	Other
Under 1 year	2	12	2
1 - 4 years	28	17	1
5 - 9 years	17	10	5
10 - 19 years	20	4	4
20 and over	1	-	-
T O T A L	68	43	12

There is no evidence that the type of compound has any effect on the death rate.

LEGAL POSITION

The Factories Acts and the more specialised section of them, the Chemical Works Regulations (1922) impose certain standards on all chemical works. The manufacture of the nitro and amido derivatives of benzene or its homologues is specially included in a section of the Regulations but no special regulations have been laid down concerning the carcinogenic aromatic amines. This is only of legal interest, in fact, the precautions applied by those manufacturing and using these carcinogens are much more rigid than are required for the nitro and amido derivatives of benzene.

By 1938 papilloma of the bladder had come to be recognised as a hazard of the dyestuffs industry and tentative discussions were held between interested parties to examine the possibility of its being scheduled as an industrial disease under the Workmen's Compensation Acts. It was generally agreed that this could not be conveniently accomplished. There were three main difficulties, all of which were successfully overcome fifteen years later; the evidence was hardly enough in quantity, or exactness; it was deemed impossible to formulate a satisfactory definition of the disease or of the nature of the work to which it was to be related; the diagnosis had to be confirmed by cystoscopic examination and it was not practicable for this to be done by the doctor certifying the disease for official purposes.

It may seem to-day that these objections could easily have been surmounted and it is possible that they would have been overcome had the climate of opinion at that time been more ready to

make public the knowledge that the disease was industrial. It is doubtful if the employers were altruistic enough to risk the adverse effect on the industry generally and on recruitment of labour in particular that the publicity of scheduling the disease would have caused.

A suitable and reasonably fair compromise was reached. An undertaking was given by the Association of British Chemical Manufacturers to H.M.Senior Medical Inspector of Factories, Dr. J.C.Bridge, representing the Home Office of which the Factory Department was then a part. It stated that "in the event of absence from work for the purpose of examination or treatment, illness or death directly due to papilloma attributable to exposure to betanaphthylamine or benzidine whilst not binding themselves to pay any specific scale of wages, grants or lump-sum compensation (the members of the A.B.C.M.) undertook to deal with such cases very sympathectically with the sincere intention that the men concerned should not suffer as compared with similar cases dealt with under the Workmen's Compensation Act". The agreement continued to be observed by the member firms after the introduction of the National Health Service and National Insurance (Industrial Injuries) Act in 1948.

By 1952 the survey which the A.B.C.M. initiated in 1947 had provided sufficient evidence of the incidence and extent of thedisease in industry to allow representation to be made by the employers to the Minister of Pensions and National Insurance that

it should be prescribed as an industrial disease. Reasonably wide definitions of the disease and the occupation were recommended to the Minister but he would not agree to include papilloma of the pelvis of the kidney or ureter in the definition of the disease nor would he include work in the homologues of benzidine in the definition of the occupation. This was on the grounds that all the recorded tumours of the ureter or renal pelvis in the industry had been accompanied, or preceded, by bladder tumours and no cases of industrial tumour resulting exclusively from exposure to the homologues of benzidine had been recorded. Apparently the Minister did not want at that stage to widen the scope of the prescription more than was necessary. The previous difficulty of diagnosis for the purpose of certification was easily overcome, it being agreed that a urologist's or an industrial medical officer's certificate would be accepted without its entailing a special ad hoc cystoscopic examination. Finally, on the 1st December, 1953 "papilloma of the bladder" was prescribed as an industrial disease under the National Insurance (Industrial Injuries Act (ref.) with the exact wording as follows :

Description of disease or injury	Nature of occupation
39. Primary neoplasm of the epithelial lining of the urinary bladder (Papilloma of the bladder)	Any occupation involving - (a) work in a building in which any of the following substances is produced for commercial purposes :- (i) alpha-naphthylamine, beta-naphthylamine or benzidine or any of their salts; (ii) auramine or magenta; (b) the use or handling of any of the substances mentioned in sub-paragraph (i) of paragraph (a), or work in a process in which any such substance is used or handled or is liberated; (c) the maintenance or cleaning of any plant or machinery used in any such process as is mentioned in paragraph (b), or the cleaning of clothing used in any such building as is mentioned in paragraph (a) if such clothing is cleaned within the works of which the building forms a part or in a laundry maintained and used solely in connection with such works.

By 1957 two cases of initial tumour of the renal pelvis had arisen at Clayton (Case Nos.60 and 127) and another case of papilloma of the ureter without previous or concomitant bladder tumours had been reported to the Papilloma Committee from another factory. In collaboration with Dr.M.H.C.Williams, I drew up evidence which was submitted to the Minister and to the Industrial

Injuries Joint Advisory Council with the recommendation that the definition of the disease should be extended to cover tumours of the ureter and renal pelvis. At the same time we pointed out that there was a great increase in the use of certain of the homologues of benzidine which had previously been used on a scale too small to yield an incidence of tumours exclusively attributable to them. We expressed our concern at the possibility that men might in the future develop tumours from these substances when benzidine was not associated with them and, by the terms of the definition, they would be excluded from benefit. The Advisory Council accepted our recommendations and made the appropriate representation to the Ministry with the result that on 7th July, 1958 the prescription of the disease was amended to read as follows:

Description of disease or injury	Nature of occupation
39. Primary neoplasm of the epithelial lining of the urinary bladder (Papilloma of the bladder), or of the epithelial lining of the renal pelvis or of the epithelial lining of the ureter.	Any occupation involving : (a) Work in a building in which any of the following substances is produced for commercial purposes:- (i) alpha-naphthylamine or beta-naphthylamine; (ii) diphenyl substituted by at least one nitro or primary amino group or by at least one nitro and primary amino group; (iii) any of the substances mentioned in sub-paragraph (ii) above if further ring substituted by halogeno, methyl or methoxy groups, but not by other groups; (iv) the salts of any of the substances mentioned in sub-paragraphs (i) to (iii) above; (v) auramine or magenta; (b) the use or handling of any of the substances mentioned in sub-paragraphs (i) to (iv) of paragraph (a), or work in a process in which any such substance is used or handled or is liberated; (c) the maintenance or cleaning of any plant or machinery used in any such process as is mentioned in paragraph (b), or the cleaning of clothing used in any such building as is mentioned in paragraph (a) if such clothing is cleaned within the works of which the building forms a part or in a laundry maintained and used solely in connection with such works.

The effect of this is that tolidine, dianisidine, dichlorbenzidine and certain other compounds such as xenylamine are now included in the definition of the occupation, while many other amino and nitro compounds not suspected of carcinogenicity are still excluded.

No further enactments or regulations have been promulgated in this country regarding occupational bladder tumours. In France, Italy and Switzerland naphthylamines and benzidine are included in the schedules of occupational diseases. So far as is known there are no specific regulations in the United States of America. Nothing is known of the legal position in the other countries, Japan, Czechoslovakia and Russia, where these compounds are manufactured.

PREVENTION AND CONTROL

The measures which have been adopted for the prevention and control of the hazard will not be described in great detail. They have been the subject of a recent publication of which I was co-author and which is appended in Volume II (Scott and Williams 1957). In this a comprehensive description of preventive measures is given. Only certain principles and the broad outline of the prevention programme will be considered here.

In the preventive field the simplest and most effective solution to the problem of industrial cancer in general and of industrial bladder cancer in particular is the complete prohibition of the dangerous compounds and processes. At first sight this would appear to be an attractive and easy solution to the doctor in industry, to the industrial administrator and to the legislator. The numbers of men affected by bladder cancer in the dyestuffs industry and the gravity of the disease leave no room for doubt that, unless safe measures can be adopted, prohibition would have to be insisted upon by the medical advisers to the industry.

The high potency of betanaphthylamine had become evident at Clayton during the war and it was later confirmed by the results of the A.B.C.M. field survey in 1954. By 1950 it had been decided at Clayton that it was impossible to devise and

operate safe plant in which it could be manufactured at an economic cost. Its manufacture and use was, therefore, given up by the Company in 1950, and the alternative methods described on page 53 were put into operation. The capital cost of installing the alternative process was high (of the order of £90,000 in 1950) and the running cost is many times that of the process in which the amine was used.

No alternatives are available for alphanaphthylamine or for benzidine and its homologues in the dyestuffs industry. A ban on the use of these compounds would, therefore, appear to be the rational consequence. Two factors of great importance however must be considered. First, these compounds are essential for a very large range of colours for wool, cotton, paper and many other fabrics. If prohibition were to be imposed it would result in grave damage not only to the chemical industry but to the textile, paint, rubber and many other industries as well. The loss of these chemicals would cause widespread unemployment and have serious adverse effects on our export trade and economy generally. I have recently discussed the moral and material justifications for continuing many highly dangerous manufactures and processes which are essential to maintain our modern standards of living (Scott 1959). The hazards associated with many dangerous or lethal materials are accepted when proper precautions are attached to their use. The second factor is that the potency of alphanaphthylamine, benzidine and its homologues

is of a considerably lower order than that of betanaphthylamine. This has been shown not only in the A.B.C.M. field survey but in animal experiments. In view of these considerations the manufacture and use of benzidine and its homologues has continued but a high standard of safe working practice is imposed.

At first the methods of prevention followed the usual lines. The diagram of the history of benzidine in Fig.1 and of betanaphthylamine in Fig.2 show some which were applied up to 1950. I have described (Scott, 1953, 1954) the medical supervision of men on these processes and how by 1950 the high morbidity and early mortality stimulated the intensification of efforts to make the processes safe. The old benzidine plant was scrapped and in 1950 a specially designed new building with modern plant was completed. In this benzidine and its homologues are made in a totally enclosed system so as to avoid contact between the operators and the chemicals as completely as possible. This was in production by 1951. Fig.19 is a photograph of the old plant and Fig.20 shows one of the new benzidine units. It is enclosed and draughted and it can readily be seen that the risk of contact with the materials used and produced is infinitely less than it was in the older plant.

Except for one foreman, a completely new force of men was employed and trained, none of whom had previously worked in chemicals and all of whom were over 40 years old. Thus if tumours should arise, they will not arise in young men. It would also

be possible to attribute them to work on this plant and not to previous contacts with chemicals.

Alphanaphthylamine is bought from another company and its use is confined to one part of the colour factory under strict conditions and to a limited number of men. Magenta has not been manufactured since 1926.

By 1950 the dangers associated with the carcinogenic amines were widely known and appreciated by the manufacturers but some users, especially those whose turnover was small, were thought to be still handling these substances in an unsafe manner. The progress made in the A.B.C.M. investigations was such that it was felt by its Papilloma Committee that the information gained should be utilized to attain the safest possible methods of working throughout industry.

Dr.M.H.C.Williams and myself, as the medical members of the Papilloma Committee, were therefore invited by the A.B.C.M. in 1952 to draw up a "code of industrial practice to cover the manufacture and use of known or suspected bladder carcinogens". In 1953 our recommendations were presented to the Association and accepted. They were circulated to all member firms with the advice that they should be implemented and so far as is known this has been done. The Committee decided that this information should not be restricted to the member firms or even to the British industry and a summarized version was published in 1957.

In the code of practice we cover many fundamental

industrial principles to be observed in order to avoid contact between the operator and the carcinogen. We make specific recommendations regarding the design and material construction of buildings, plant and machinery. We advise on general ventilation and local draughting. Old plants which cannot be rendered safe should be scrapped and replaced by plant conforming to the principles laid down. General methods of handling, separation, purifying, packaging and transporting of carcinogens are given. Detailed consideration is made of some twenty compounds known or suspected to be carcinogenic and methods for their manufacture and handling are advised. The danger to subsequent users in the factory or after sale is emphasized and the measures which should be taken to eliminate it are described. The absolute ban on betanaphthylamine is repeated.

Personal protective measures are recommended in detail in order to give an added margin of safety should the plant and process design fail to prove adequate against accidental failure or contamination. Working clothing, baths, protective clothing and breathing apparatus are discussed. Selection of workers with particular regard to age and previous history is important. Hours of work, overtime, and the limitation of the numbers of men to be exposed are discussed. Adequate records are essential and should be kept in detail in respect of men and of plant operations. Analyses for the detection and determination of amounts of carcinogens in the atmosphere, on clothing and on plants provide

a check on conditions. Estimations of amines in the urine provide an index of possible absorption.

The Code recommends that where there is a hazard of bladder tumours a medical officer should be employed - part time or full time depending on the amount of work involved - in order to ensure adequate supervision of the health of workers and of the plant hygiene. This work includes the screening of workers to achieve early diagnosis of tumours by cytodiagnostic and other examinations, co-operation with the family doctor and the urologist in the investigation and treatment of workmen and in the re-habilitation to work of those who develop the disease.

Before accepting the invitation to write the Code, both of us obtained an undertaking from our respective managements that we had complete freedom to draw up its provisions regardless of what the practice in our own works might be. It was also agreed that each company would conform to whatever recommendations were laid down. As was to be expected, little alteration had, in the event, to be made in the practice of either company, both of which had already instituted elaborate precautions. The working practice at Clayton now conforms to that laid down in the Code.

It is obviously too soon yet to be sure of the final success of the measures which have been adopted. All that can be done is to give certain results up to date. Since the new benzidine plant was started in 1951 ninety-one men have worked for more than

six months in it but only nine have been continuously engaged for 5 years or more. None of them has developed a tumour. The atmosphere is sampled continuously by two apparatus, one of which is moved from point to point throughout the building; the other is sited beside the benzidine conversion vessel where the highest readings might be expected. Twenty-four hour samples of air are analysed and the readings which have been obtained have always been virtually "background" (0.1 - 0.05 micrograms of benzidine per cubic metre of air) except in isolated instances when maintenance operations or accidental breakdown have given rise to higher readings. Any reading above 0.5 micrograms per metre is taken as an indication that some failure of the precautions has arisen and steps are taken to remedy it. Analyses of the urine of the men for amines, done as a spot check at irregular intervals, have so far shown negative results in the men in the new plant.

Elsewhere in the factory, the provisions of the Code are likewise implemented. It may be some measure of the success of banning betanaphthylamine on the one hand and of intensifying the precautions with other compounds on the other, that the average latent period is now 4 years longer than it was in 1951.

This figure is too tenuous for statistical proof to be significant and final judgement must be reserved for many years. It has been seen that the incidence is very significantly lower in service men than it is in manufacturers in the same building who are in closer proximity, so that even crude measures which

reduce the exposure could be expected to lead to an improvement. It may, therefore, not be too much to hope that the fine control now exercised in the prevention of this industrial disease will be successful.

THE HUMAN ASPECT

The medical officer in a comparatively small company the size of The Clayton Aniline Co.Ltd., is fortunately in much closer personal contact with the workmen than would be the case in a company employing many thousands of men. I have known for many years every man who has contracted the disease while still at work in the company. In the same way the members of the higher management have had an intimate and personal knowledge of their workmen. It is not surprising, therefore, that a high degree of confidence and good faith exists between all grades of men and management.

I have always advocated (1952, 1953, 1954; Scott and Williams 1957) that it is not possible to justify the concealment of a risk such as cancer of the bladder from men exposed to it and this policy has been accepted and freely applied at Clayton, I am quite certain that as a result of complete frankness better co-operation has been achieved with the workmen and a higher degree of confidence has been engendered in their minds. A full explanation of the hazard and of the importance of his meticulous observance of the precautions is given by me to every workman who has to work in the manufacture or use of carcinogens, so that he can understand what he must do to protect himself. Work on these processes is entirely voluntary and any man is taken off them and transferred to other work without penality if he so desires.

It is some indication of the confidence and good faith existing that this is seldom requested. A few men asked to be transferred when they have recovered from tumours but only one has done so on the grounds that he was afraid he might get one. He was the deputy to the 'benzidine' man in the colour factory and had only twice been called upon to stand in for him because of illness.

In the 20 years I have been at Clayton the attitude of the men to this hazard has been a constant source of wonderment to me. The quiet acceptance of the possibility of contracting tumours in those who have been exposed under the bad working conditions of earlier years may smack of fatalism but the attitude of other men who accepted the risk and continued to accept it from choice was, in some ways, gladiatorial. Even though preventive measures have been progressively improved there can be little doubt that it has taken a rare kind of courage or an unusual attitude of mind to enable men to carry on in this work, especially in the years of full employment.

In the first years when conditions were bad no danger was apprehended. From the later 1930's until 1951 danger money was claimed and paid. This payment must have encouraged men to accept the risk and the institution of precautions at the same time may have conferred some degree of reassurance. That the earliest attempts at prevention failed is now proved by the tumours which have arisen in men subsequently exposed. Although the present

prophylactic measures in force are thought to be effective, final proof must await the absence of tumours in a whole generation. I have condemned (1953, 1957) the payment of danger money to make up for unsafe plant and dangerous environment. The men and their unions have accepted this principle and danger money has not been paid at Clayton to men working on the new benzidine plant. This has not apparently affected their morale or their willingness to undertake the work. The shorter hours of work, the cleanness of the job and the opportunity to start a new career at the age of 40 may account for the popularity of this work.

Certain payments are made to those who suffer from the disease. Since 1938 ex-gratia payments in addition to the usual insurance benefits have been made to men who are off work because of tumours of the bladder. When the disease was prescribed under the Industrial Injuries Acts in 1953, these payments were continued and now a flat rate of £5 per week is paid. On retirement at 65 a special pension is paid to all men who have had tumours of the bladder. A pension is paid to the widow of every man who has had such a tumour irrespective of whether he died from it or from any other cause either before or after retirement. The same financial benefits are extended to those men who develop tumours after leaving the company and to those who leave the company after they have developed tumours. An average of 10 men at a time throughout the year receive the weekly ex-gratia payments for absence from work; some are off only a few days for

review cystoscopies but one or two have had continuous absences of several years.

While many men who had industrial tumours must have gone untraced in the past, it is probable that few, if any, which arise nowadays are not ultimately disclosed. The prospect of payments has undoubtedly helped in tracing men who develop tumours after leaving the company's service for work elsewhere. The local hospitals and many of the general practitioners know the circumstances and advise men who have previously been employed with us to report back to the company when they find they are suffering from tumours of the bladder. H.M.Senior Medical Inspector of Factories maintains for the industry a register of names of men, supplied by the firms concerned, who have had contact with the prescribed bladder carcinogens. All death certificates mentioning chemical work or bladder tumours are checked against it.

When a workman is known or suspected to have a tumour of the bladder arrangements are made with his doctor to refer him to a urologist for the necessary investigation and treatment. Close contact with the men's family doctors is maintained meticulously and their co-operation has been unfailing. There are advantages in having all the cases investigated and treated by the same urologist who thereby gains valuable experience of the aetiology and course of industrial tumours. Mr J.B.Macalpine, until he retired in 1945, and his successor Mr D.S.Poole Wilson, consulting urologists to the Salford Royal Hospital and the Christie Hospital

and Holt Radium Institute Manchester have treated the majority of the Clayton men. In 1951 a special monthly cystoscopic clinic for the Clayton dyeworkers was started at the former hospital and there the workmen are investigated and reviewed. When treatment is necessary it is done through the usual National Health channels.

The majority of the men who develop tumours can return to work after treatment. Where possible they have been encouraged to go back to their old jobs, so as to minimize any suggestion of invalidism. It might be argued that these men should not return to the same job but in fact the recurrence rate has not been apparently increased in those who do,and under present day conditions there is little likelihood of dangerous absorption. In practice the psychological effect of being able to return to full productive work is a major factor in assisting many sufferers to lead a normal social and working life. Unfortunately, these tumours, by their very nature, develop in the longer serving employees and recurrences are common so that the effects of age and ill-health combine to reduce the number of men who can do the work in which they were previously engaged. Of 50 men who have had tumours,and are still employed in the company, only 14 are now back at their old jobs or on similar plant work; of the remainder, 3 have been promoted to staff jobs (two foremen, one clerk) and 33 are doing sheltered work as messengers, gatemen, laboratory cleaners and the like. One of the last group (case No.25) although fully recovered was unwilling to return to work

with any kind of chemicals and alternative work was arranged for him on this account.

Several of the men who developed tumours after leaving the company had worked for many years in their next job and have been content to remain in that employment, for example one man (Case No.59) has worked for 29 years with British Railways. They are encouraged to keep in touch and I see them at regular intervals, usually at the time of their review examinations. Others have not had the same security in their subsequent jobs and six men have been re-employed by the company in order to afford them sheltered work and security of tenure with the added advantages of closer supervision of their health.

THE FUTURE

Many more men have still to develop tumours before the final yield in the present generation is complete. Already 123 cases have been fully recorded; many may still be untraced and some may be untraceable. There can be no doubt that tumours have yet to appear in a proportion of the men who were exposed when conditions were worse than would be accepted now and when betanaphthylamine was still being made and used. Until a whole generation has been unaffected there can be no absolute certainty that the rigid precautions in force today are effective. All that can be stated is that none of the men who started after 1950 has so far developed a tumour.

A careful watch is being kept on the incidence of the disease locally and nationally. The various interested bodies centralise their information through the Papilloma Committee of the industry. The records maintained at the Factory Department will provide starting material for subsequent field surveys and will make collation of information for them easier. It is intended that another survey will be conducted on a national scale in about 10 years time. By then it may be possible to include other industries in addition to the chemical and rubber trades.

Carcinogenic amines such as benzidine have been used in the paper industry for making security paper to make writing on bank cheques indelible, in medical laboratories for testing for occult blood and in chemical laboratories for spraying chromatographs. In the textile industry alone the use of benzidine and

naphthylamines in indirect dyeing and in textile printing has been extensive and in many instances no precautions have been taken.

Some concern has recently been expressed (Lancet 1958) at the possibility of carcinogens being present in foodstuffs colours. Certainly benzene-azonaphthol was until recently one of the permitted foodstuffs colours on the American list. This compound, when metabolized, would be likely to break through the azo linkage, into aniline and betanaphthylamine. Fortunately, so far as is known no such potentially dangerous colour has been used in food in Britain.

On the experimental side many new developments and lines of research are already foreshadowed. Walpole and Williams (1958) have recently published, as a guide to chemists who may contemplate their use, a summary of the results of new experiments on many diphenyl and stilbene compounds and the effects on their potency of ring substitution on their amino derivatives. Bonser, Clayson and Jull (1958) have similarly dealt with many chemicals, chiefly orthohydroxyamines and aromatic amines of two and three ring types. Their methods of testing for carcinogenicity by implantation in the mouse bladder is claimed by them to be the most important advance in the last decade. It must be borne in mind, however, that the metabolism of a compound has to be worked out before valid conclusions as to its carcinogenicity to man can be drawn from implantation experiments in

the mouse.

Radiochemical techniques will facilitate the study of the distribution of compounds in the body and of their excretion. Already Goldblatt (1958) and his colleagues (1954 and 1956) have used labelled betanaphthylamine for excretion studies in various animals. Boyland (1958) again suggests the prospect of prophylactic treatment of workers by administering saccharolactone as a routine. While one would agree with him that, if it works, it might be used in cases of accidental contamination to inhibit the formation of the carcinogenic metabolite in the urine, one can hardly accept the prospect of dosing men for all their working life as a practical proposition. Safe plant design and good working practice can obviate contact between operator and carcinogen and it is wrong to depend on anything else as a routine. Nevertheless the future may hold some hope that further developments may enhance and facilitate this line of attack when there is accidental failure of the industrial precautions.

In the future many new compounds will be introduced into the dye-stuffs industry. It will not be possible to forecast the carcinogenic potency of them all nor will it be possible to test them all on animals. Many years may elapse before their danger to workmen becomes apparent. Other compounds already manufactured on a scale too small to have revealed them as dangerous may come to be in greater demand and extension of their manufacture may eventually reveal unsuspected carcinogenicity.

New methods of manufacture and new processes may result in the formation of carcinogens as by-products or impurities.

The workman will in the future, as in the past, be unable to protect himself against these insidious dangers to his health and his life. The application of many diverse technical skills and professional disciplines will still be required to safeguard him. As has been shown in this thesis, a great fund of technological and medical knowledge exists and its application can almost certainly protect workers against the known hazards of today. As research advances and as new products and new dangers are introduced the lessons of the past must not again be forgotten. In the future research into combating these dangers and preventing new outbreaks of disease must be promoted and pursued as vigorously as the search for new and better products, so that an industry which brings so much colour and brightness into the lives of mankind does not darken and destroy the lives of those who work in it.

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VOLUME II

Contents

Perkin's Mauveine.

This silk is dyed with mauveine actually made by W. H. Perkin. I am indebted to the Dept. of Colour Chemistry, University of Leeds for the dyestuff.

CASE HISTORIES

The case history of each of the 123 men in the series is given in this section, set out in the following order:

i) Date of birth, of entering and leaving the industry, of onset of tumour, and of death: age on entering the industry, at onset of tumour and at death: exposure and latent periods. The date on which the diagnosis was first confirmed is usually taken as the date of onset. The ages and the exposure and latent periods are calculated to the nearest six months.

ii) Working history. The type of work done, the exposure to carcinogens or suspected carcinogens and its duration, are described briefly.

iii) History of onset. Special reference is made to the appearance of symptoms and to the results of routine screening tests if they were in operation at the time.

iv) The hospital attended and the urologist or consultant surgeon. In some cases more than one hospital or surgeon is mentioned. Many men were referred from other hospitals to The Christie Hospital and Holt Radium Institute, Manchester, for radiation treatment. It is referred to in the case histories as Christie Hospital.

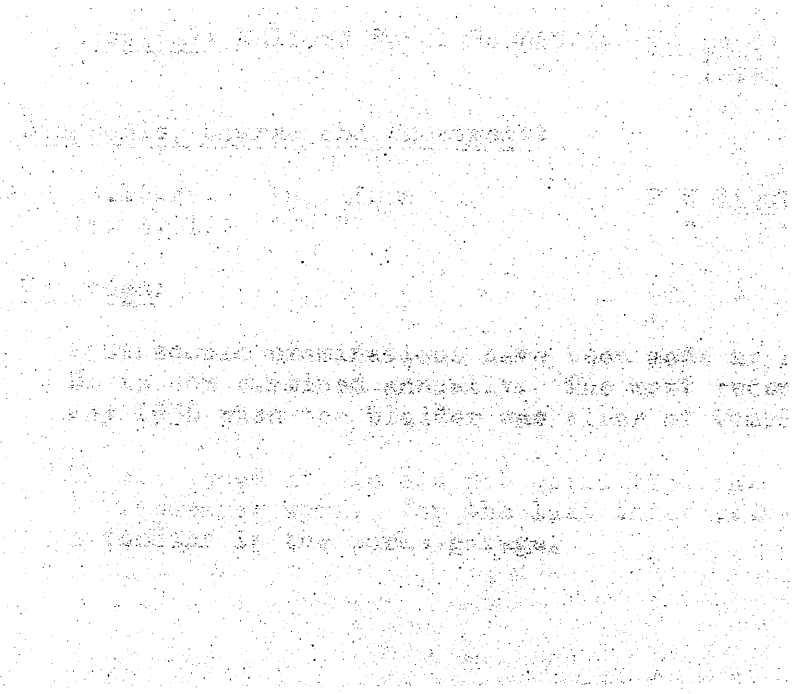
v) Diagnosis, course and treatment. The clinical appearance of the tumour, the histological classification when available, and the treatment are stated. The dates on which recurrences were diagnosed, and the type of recurrent tumours and their treatment are tabulated. Most of the men had follow-up cystoscopic examinations at regular intervals. Examinations on which no abnormality was detected are not recorded unless the result is of special interest.

vi) Progress. The progress of each case to the end of 1958 is summarised. The degree of recovery and the subsequent employment are described. Causes of death and findings on post mortem examination, when available, are given. Points of special interest and items of additional information are included.

The cases are presented in order of their serial numbers. It was found to be impracticable and confusing to present them in any other order.

Four men (Case Nos. 78, 92, 94, and 101) to whom numbers had been allocated were discarded from the series; two because they were eventually found not to have tumours of the urinary tract and two (who had died after leaving the Company) because the history of tumour of the bladder was doubtful. For this reason the serial numbers of the 123 cases go up to No.127.

Cases are referred to in the text by their serial numbers and a cross reference to the page number is given in the case histories which are mentioned.



CASE No.1 (J.A.)

Date of Birth:	4.11.97.	Age at Entry:	30 years
Date of Entry:	20.12.27.	Age at Onset:	49 years
Date of Onset:	3.12.46.	Latent Period:	19 years

Working History:

1927 - 46 Worked in the building in which betanaphthylamine was manufactured. For the first five years, 1927-1931, he did general work on the plant including the distillation of betanaphthylamine and the powdering of the distilled product.

From 1931 until 1946 he was employed on the filter-pressing of various naphthylamine sulphonic acids as well as the manufacture of betanaphthylamine.

History of Onset:

In late November 1946 he had sudden haematuria. He had had no previous symptoms or signs of bladder trouble and routine urine tests had been negative for blood cells.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpin later Mr.D.S.Poole-Wilso

Diagnosis, Course and Treatment:

3.12.46.	Papilloma	P U diathermy
19. 3.51.	"	" "

Progress:

Cystoscopic examinations have been made at regular intervals. He is now examined annually. The most recent occasion was in May 1958 when the bladder was clear of tumour.

He continued at his old job until 1950 when he was transferred to messenger work. For the last three years he has been an attendant in the works garage.

CASE No.2 (J.B.)

Date of Birth:	20.11.98.	Age at Entry:	41 years
Date of Entry:	27. 3.40.	Age at Onset:	46 years
Date of Onset:	15. 1.45.	Latent Period:	5 years

Working History:

1940 - 44 Worked as a general labourer on the manufacture of amino salicylic acid, amino p-cresol, diamino-diphenylamine sulphate, ortho-amino-phenol and nitro-aminophenol. Dianisidine was manufactured in the shed in which he worked and benzidine in the next shed.

He was employed as a coal-bagger for 20 years before entering the industry and had never worked in chemicals previously.

History of Onset:

On 31st December 1944 he experienced a scalding sensation on passing urine and two days later he passed blood in his urine. Routine urine tests for blood had been negative.

Hospital: Christie Hospital, Manchester. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

11. 2.45.	Carcinoma.	Deep X-ray therapy
9.11.49.	Left pyelonephrosis.	Left nephrectomy

Progress:

He was off work for several months and then returned to his usual job. Regular review examinations have been made.

In November 1949 he had a left nephrectomy for pyelonephrosis and stones. There was no evidence of tumour on microscopical examination.

After recovering from this operation he was taken off plant work and put on painting. In April 1950, following an operation for umbilical hernia, he was transferred to sheltered work in the Locker Room where he is still employed.

In 1953 he developed a urethral stricture due to instrumental trauma. This was dilated at increasingly frequent intervals until June 1958 when a first stage Swinney operation for its excision was performed. The second stage was completed on 11.11.58. and he is now making an apparently good recovery.

No recurrences of tumour have been seen since the original lesion 13 years ago.

CASE No.3 (L.C.)

Date of Birth:	29. 5.00.	Age at Entry:	21 years
Date of Entry:	19.10.21.	Age at Onset:	40 years
Date of Onset:	29.11.40.	Latent Period:	19 years

Working History:

1921 - 40 Engaged in the manufacture of benzidine azo colours. For fourteen years, 1926-1940, was handling benzidine daily.

History of Onset:

In November 1940 red blood cells were found in the urine on routine test at the factory. There were no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

29.11.40.	Papilloma	P U diathermy
24. 8.42.	"	" "
19. 9.47.	"	" "
29.11.57.	"	" "

Progress:

Regular cystoscopic examinations have been made since 1940. His general health has been good all the time. For 10 years, from 1947 until 1957 he had no recurrence.

He has continued at work but has not been employed on plant work since 1947 when he was transferred to the canteen.

CASE No.4 (J.C.)

Date of Birth:	30.12.03.	Age at Entry:	32 years
Date of Entry:	16. 1.36.	Age at Onset:	44 years
Date of Onset:	24.12.47.	Latent Period:	12 years

Working History:

1936 - 47 Worked as a process man in the sulphonation of betanaphthylamine to which he was exposed during the whole of this period.

History of Onset:

On 25.11.47 he had sudden haematuria. There were no previous symptoms. Routine examinations of his urine for blood cells had been negative.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

24.12.47.	Papilloma	P U diathermy
21. 8.52.	"	" "

Progress:

Regular review cystoscopic examinations have been made. The recurrence in 1952 was a tiny area of raised mucosa and it was uncertain if fronds were present. He is now reviewed annually.

He has continued work as a process man and is still doing a full job. His general health is good.

CASE No.5 (A.H.)

Date of Birth:	23. 7.05.	Age at Entry:	23 years
Date of Entry:	26. 3.28.	Age at Onset:	34 years
Date of Onset:	21.11.39.	Latent Period:	11 years

Working History:

1928 - 39 Worked on the manufacture of betanaphthylamine.

History of Onset:

Began with haematuria of sudden onset. Routine test of urine four months previously had shown no blood cells. In late 1939 the tests were perforce being done at irregular intervals.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

21.11.39.	Carcinoma	Gold seed implant 9.1.40.
28.11.52.	Papilloma	P U diathermy
9. 7.56.	Papillomatosis of left renal pelvis and ureter.	Nephroureterectomy

Progress:

He had a severe radiation reaction and was off work until October 1941. He then worked as a bath attendant in the Locker Room until 1950 when he was transferred to the Labour Department as a clerk, a position he still holds.

Apart from a small recurrence in 1952 he enjoyed good health until January 1956 when he had an attack of haematuria. On cystoscopy there was an area of roughness in the old tumour area which was apparently where one of the gold seeds had extruded. This was thought to account for the bleeding.

On review examination on 9.7.56. the left ureteric orifice was patulous and several fronds of tumour could be seen coming down from it. Further investigations indicated a non-functioning left kidney. The right kidney appeared normal. On August 7th a left nephroureterectomy was performed. There was papillomatosis of the pelvis and lower end of the ureter which on section proved to be benign.

He made a good recovery and returned to work three months after the operation. At his last review cystoscopy on 24.11.58. the bladder was clear.

CASE No.6 (H.J.)

Date of Birth:	10.12.98.	Age at Entry:	26 years
Date of Entry:	30. 3.25.	Age at Onset:	41 years
Date of Onset:	9. 2.40.	Latent Period:	15 years

Working History:

1925 - 27 Worked on sulphonations in primuline factory.
1927 - 36 Worked on the distillation of diamines and the stoving of paranitraniline. During this time was engaged in the department where betanaphthylamine was manufactured.
1936 - 40 Worked on the distillation of betanaphthylamine and on the purification of Tobias acid.

History of Onset:

In February 1940 he was referred to Salford Royal Hospital because of copious haematuria.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

9. 2.40.	Carcinoma	Biopsy - malignant.
11. 4.40.		Gold seed implant. Open (operation.
11. 1.44.	Papilloma	P U diathermy
4. 3.45.	"	" "
15.10.46.	"	" "
1.11.46.	Clot retention	Suprapubic cysotomy

Progress:

On initial cystoscopy there was seen an irregular raised area high up on the right lateral wall. On biopsy this proved to be malignant.

After the operation there was a prolonged radiation reaction and he was off work for a year. He did not return to plant work. He was employed as a Locker Room attendant for ten years. He was then transferred to the Works Police and for the past two years has been in charge of the car park.

His recurrences have been small benign papilloma which were easily fulgurated. Two misfortunes have beset him. He was operated on for clot retention in 1946. In 1951 he developed a urethral stricture due, presumably, to instrumental trauma. This has to be dilated every two months. Despite this he is uncomplaining and unfailingly cheerful. His general health is excellent.

CASE No.7 (J.L.M.)

Date of Birth:	28.8.03.	Age at Entry:	28 years
Date of Entry:	13.4.31.	Age at Onset:	46 years
Date of Onset:	31.3.49.	Latent Period:	18 years

Working History:

1931 - 49 Employed almost exclusively on the manufacture of naphthionate of soda. (The crude naphthionic acid contained alphanaphthylamine which was extracted from the salt with toluene.)

History of Onset:

In March 1949 there were moderate numbers of red blood cells in the urine on three consecutive routine tests. He had had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

9. 4.49.	Papilloma	P U	diathermy
8.11.49.	"	"	"
14. 9.51.	"	"	"
12.11.51.	"	"	".
28. 1.52.	"	"	"
8. 7.52.	"	"	"
30.12.52.	"	"	"
2. 9.53.	"	"	"
8. 7.54.	"	"	"
20.12.54.	"	"	"
16. 9.55.	"	"	"
5. 3.56.	"	"	"
15. 2.57.	"	"	"

Progress:

Since 1949 he has been employed as a messenger but has been off work frequently because of the recurrences. This case is of interest as frequent benign recurrences have been kept under control by per-urethral diathermy. He has had no recurrence now for nearly two years.

In August 1957, on a routine M.M.R of his chest, a large glandular shadow was seen at the right hilum. He was admitted to Park Hospital, Davyhulme. On thoracotomy enlarged glands were found at the right hilum, interlobar fissure and along the trachea. Biopsy of one gland showed Hodgkins' disease. He was transferred to the Christie Hospital where he had X-ray treatment. In May 1958 there was some regression of the X-ray appearances. His general condition has improved but he has not yet recovered sufficiently to return to work.

CASE No.8 (E.M.)

Date of Birth:	11.12.00.	Age at Entry:	36 years
Date of Entry:	20.10.36.	Age at Onset:	42 years
Date of Onset:	3. 6.43.	Latent Period:	7 years

Working History:

1936 - 39 Worked as a general labourer, mainly trucking raw materials in building where betanaphthylamine was made.

1939 - 43 Manufacture of Tobias acid and Bronner acid (2:6 naphthylamine sulphonic acid). At that time these were made on the same unit as betanaphthylamine and he also helped with its manufacture.

History of Onset:

He had haematuria in May 1943. He had had no previous symptoms and routine urine tests at the factory for blood cells had been negative.

Hospital: Salford Royal Hospital. **Surgeon:** Mr. J. B. Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

3. 6.43.	Papilloma	P U diathermy
10. 5.48.	"	" "
9. 5.50.	"	" "
13. 2.51.	"	" "
16. 5.52.	"	" "
25. 4.55.	"	" "
22.11.55.	"	" "
18. 3.57.	"	" "
27. 6.57.	"	" "
10. 9.57.	Papillomatosis left renal pelvis.	Left nephroureterectomy

Progress:

After treatment for papilloma in 1943 he returned to plant work for five years but since 1948 he has been employed on sheltered work as a messenger and bath attendant. He has had many periods off work because of the recurrences and cystoscopic reviews. In July 1957 he began to complain of vague but persistent pain in the left loin. Investigation indicated a tumour of the left kidney and a nephroureterectomy was performed on 10.9.57. Benign papillomatosis of the kidney and ureter was present and was confirmed on microscopy.

His general condition has been poor since the operation and he has not yet returned to work.

CASE No.9 (C.R.)

Date of Birth:	2.10.01.	Age at Entry:	30 years
Date of Entry:	6. 7.31.	Age at Onset:	47 years
Date of Onset:	13.11.48.	Latent Period:	17 years

Working History:

1931 - 48 Worked as a processman on the manufacture of betanaphthylamine.

History of Onset:

In November 1948 appreciable numbers of red blood cells were found in the urine on routine test. He had had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

13.11.48.	Papilloma	P U diathermy
15.12.50.	"	" "
13. 2.51.	"	" "
27. 4.51.	"	" "
18. 9.51.	"	" "
20. 2.52.	"	" "
27.10.52.	?Solid tumour	Biopsy - no malignancy. (P U diathermy.
17. 3.53.	Papilloma	P U diathermy
28. 9.53.	"	" "
21. 1.55	"	" "
10. 7.56.	"	" "
1. 6.58.	"	" "

Progress:

This man had six recurrences within two years between December 1950 and October 1952. It is interesting to note that the frequency of recurrences has abated and that he had none for two years from July 1956 until June 1958.

He was taken off plant work after 1951 and transferred to sheltered work in the Locker Room as a bath attendant. For the past four years he has been greenkeeper of the Works bowling green. His general health is now excellent.

CASE No.10 (J.S.)

Date of Birth:	30.5.06.	Age at Entry:	20 years
Date of Entry:	2.3.26.	Age at Onset:	38 years
Date of Onset:	29.6.44.	Latent Period:	18 years

Working History:

1926 - 31 Drying betanaphthylamine and H.Acid in stoves.
1931 - 33 Manufacture of 1:8 naphthylamine sulphonic acid.
1933 - 35 Manufacture of alphanaphthylamine sulphate.
1935 - 44 Manufacture of betanaphthylamine.

History of Onset:

He was referred to hospital by his own doctor on account of symptoms of acute cystitis and haematuria. Routine urine tests for R.B.Cs. at the factory had been negative.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

29. 6.44.	Papilloma	P U diathermy
23. 1.47.	"	" "
17.11.48.	"	" "
15. 1.49.	"	" "
3. 2.51.	"	" "
13. 7.51.	"	" "
21. 8.52.	"	" "
3. 2.53.	Papillomatosis left renal pelvis.	Nephroureterectomy (biopsy - benign papilloma)
4.10.54.	Papilloma (bladder)	P U diathermy

Progress:

He has had regular cystoscopic examinations since 1944. For the first nine years recurrences were frequent. They were kept under control by repeated diathermy but some anxiety was felt that this might cease to be effective.

From August 1952 onwards he had frequent attacks of haematuria. No tumours were seen in the bladder on cystoscopy on 27.10.52. and X-rays and intravenous pyelography were negative. On 28.1.53, when he was again investigated, retrograde pyelography showed a gross filling defect of the calices of the left kidney. It was excised and papillomatosis of the renal pelvis was present. It was confirmed on section.

Seeding from the tumour of the renal pelvis to the bladder is a possible explanation of the many recurrences before the kidney was removed in 1953 especially as there has been only one recurrence since then.

He was off work for a year after the nephroureterectomy. Since early 1954 he was worked regularly in sheltered jobs as a gateman and a laboratory messenger.

CASE No.11 (P.S.)

Date of Birth:	8.5.01.	Age at Entry:	19 years
Date of Entry:	1.8.20.	Age at Onset:	47 years
Date of Onset:	18.1.48.	Latent Period:	27 years

Working History:

1920 - 48 Worked in the betanaphthylamine manufacturing department. After a few months as a general labourer he worked as a processman on the manufacture of 1:8 and 1:5 betanaphthylamine sulphonic acids. He was also called upon to stove benzidine base from time to time during the two years 1928 to 1930.

History of Onset:

Investigation was done on account of the appearance of R.B.Cs. in his urine during routine monthly tests. He had had no symptoms or other signs suggestive of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

18.1.48.	Papilloma	P U diathermy
21.4.58.	"	" "

Progress:

Regular cystoscopic reviews were carried out at intervals at first of three months, gradually extending to one year between 1948 and April 1958. In 1953 he was found to have a urethral stricture probably due to instrumental trauma. This is dilated from time to time.

He is one of the few who survived over 10 years without a recurrence.

He continued at work as a process man until 1956 when he was transferred to work in a laboratory. He is still working and keeps in good health.

He is a brother of Case No.12.

This case is referred to on page 82

CASE No.12 (T.S.)

Date of Birth:	16.1.16.	Age at Entry:	23 years
Date of Entry:	4.9.39.	Age at Onset:	33 years
Date of Onset:	28.1.49.	Latent Period:	9 years

Working History:

1939 - 49 Worked on the manufacture of benzidine and, for two years 1943-45, also on the manufacture of tolidine.

History of Onset:

Increasing numbers of red blood cells were seen in the urine on routine tests from October 1948 to January 1949. He had had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

28.1.49.	Papilloma	P U diathermy
2.5.56.	"	" "

Progress:

Regular cystoscopic examinations have been made. The most recent was on 24.11.58. He continued at his work as a processman in the same department until it was closed in 1952. He was then transferred to another department where acetanilide is made.

His general health is good.

He is a brother of Case No.11.

This case is referred to on page 82

CASE No.13 (R.S.)

Date of Birth:	3.4.15.	Age at Entry:	19 years
Date of Entry:	8.2.34.	Age at Onset:	34 years
Date of Onset:	30.4.49.	Latent Period:	15 years

Working History:

1934 - 42 Worked as labourer in the Ice Plant. This involved taking ice into the Colour Factory where benzidine was used.
1942 - 45 Worked in Colour Factory as a processman.
1945 - 49 Worked in Ice Plant.

History of Onset:

In April 1949 he complained of dysuria and frequency of micturition. The urine was faintly blood-stained.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

30.4.49. Papilloma P U diathermy

Progress:

He has been reviewed at regular intervals and cystoscopy is now done every twelve months.

This case is of interest in that he has had no recurrence in nearly ten years.

He is still working in the Ice Plant on his usual job which is a fairly heavy one.

CASE No.14 (H.W.)

Date of Birth:	13.9.96.	Age at Entry:	31 years
Date of Entry:	1.7.27.	Age at Onset:	50 years
Date of Onset:	6.4.46.	Latent Period:	19 years

Working History:

1927 - 34	Worked on the manufacture of an intermediate made from alphanaphthylamine and metanilic acid.
1934 - 36	Left Company's employment.
1936 - 39	Labourer in the Engineering Department.
1939 - 41	Left Company's employment.
1941 - 46	Worked on the vacuum distillation of betanaphthylamine.

History of Onset:

In March 1946 routine examination at the factory revealed red blood cells. He had had no symptoms or other signs.

Hospital: Christie Hospital, Manchester. **Surgeon:** Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

23. 4.46.	Carcinoma	Open operation. Gold seed implant.
18. 2.48.	Papilloma	P U diathermy
5. 5.48.	"	" "
20.12.48.	"	" "

Progress:

On cystoscopy there was a solid tumour of the bladder. He was transferred to Christie Hospital for treatment.

This case is interesting in that after three recurrences within a year the bladder has been clear for ten years. Regular cystoscopic examinations have been made since 1946. In 1953 he developed a severe stricture of the urethra due to instrumental trauma. In 1955 it was impossible to dilate the stricture sufficiently to allow the cystoscope to pass and a two stage Swinney operation was completed in December 1956.

He has not worked since 1948 because of chronic bronchitis and dyspnoea and is usually confined to the house except in fine weather.

CASE No.15 (F.C.)

Date of Birth:	31.3.00.	Age at Entry:	34 years
Date of Entry:	12.5.34.	Age at Onset:	48 years
Date of Onset:	10.5.48.	Latent Period:	14 years

Working History:

1934 - 48 Worked as a process worker on the manufacture of azo colours some of which involved the handling of benzidine base.

History of Onset:

On 10.11.47 he consulted me with a history of slight haematuria of two weeks duration. Routine urine tests for blood cells had previously been negative. On cystoscopy by Mr. Poole-Wilson no definite tumour was seen in the bladder but there was a "mossy" area above the right ureteric orifice. It was decided to review him in six months. On re-examination on 10.5.48. there were three tiny papillomata in the area previously noted.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

10.5.48.	Papillomata	P U diathermy
28.4.52.	"	" "
24.2.53.	Carcinoma (biopsy - malignant)	Open operation. Gold seed implant.

Progress:

He continued work as a processman until 1953 when a malignant recurrence was found. He was off work for just over a year after his radon seed treatment. Since then he has been employed in a laboratory as a cleaner and messenger.

Regular cystoscopic review continues at six monthly intervals. His general health is good.

CASE No.16 (J.S.)

Date of Birth:	12.8.97.	Age at Entry:	34 years
Date of Entry:	15.1.32.	Age at Onset:	52 years
Date of Onset:	1.9.49.	Latent Period:	17 years

Working History:

1932 - 49 This man is a millwright. He has worked as a plant fitter in all sections of the Intermediates Department, in particular on the betanaphthylamine plant. He also did alterations to the benzidine plant during the time it was being changed over to the solvent process.

History of Onset:

For about two weeks in September 1949 he complained of suprapubic discomfort and had occasional terminal haematuria. Routine urine tests had previously been negative.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

1.9.49.	Papilloma	P U diathermy

Progress:

There have been no recurrences and review cystoscopies have now been extended to yearly intervals.

After treatment he resumed his usual work. His health has since been good.

In 1951 he was promoted to foreman, a position he still holds.

CASE No.17 (C.I.)

Date of Birth:	17.4.03.	Age at Entry:	23 years
Date of Entry:	28.4.26.	Age at Onset:	47 years
Date of Onset:	29.8.50.	Latent Period:	24 years

Working History:

1926 - 32 Worked on the milling of a wide variety of finished dyestuffs.

1932 - 50 Worked as a processman on the manufacture of azo colours, using benzidine almost continuously during the whole of this period and, in addition, from 1940 alphanaphthylamine at infrequent intervals.

History of Onset:

On 10.8.50. he noticed some burning and scalding when he passed urine. Next morning it was blood stained. Routine tests had been negative for blood cells.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

30. 8.50.	Papilloma	P U diathermy
9. 3.51.	"	" "
15. 8.51.	"	" "
5.11.51.	"	" "

Progress:

Apart from the short absences occasioned by recurrences he continued work as a processman until 1956 when he was transferred to a laboratory as a cleaner and messenger.

He is now examined annually and the bladder was clear of tumour in May 1958. His general health is good.

CASE No.18 (R.M.)

Date of Birth:	21.4.04.	Age at Entry:	20 years
Date of Entry:	4.3.24.	Age at Onset:	47 years
Date of Onset:	20.2.51.	Latent Period:	27 years

Working History:

1924 - 32 Worked on the manufacture of azo colours which entailed the continuous use of alphanaphthylamine.
1932 - 34 Worked on manufacture of azo colours using benzidine.
1934 - 51 Worked on shift doing general work in the same azo colour factory but not employed directly with benzidine or alphanaphthylamine.

History of Onset:

In March 1942 he was referred to Salford Royal Hospital because of the persistence of small numbers of red blood cells in his urine which were first observed on routine test.

On investigation the bladder was clear of tumour but there was a rough oxalate stone in the left renal pelvis. This was removed at operation and he made a good recovery.

His urine remained clear of blood or other abnormal constituents and he had no complaints until 1951. He consulted me on 5.2.51. complaining of severe spasmodic pain along the urethra which had been present intermittently for three days. There was no history suggestive of recent colic or bladder stone. He was referred to Salford Royal Hospital for investigation. No evidence of calculus was found but there was a small papilloma near the right ureteric orifice.

Hospital:
Salford Royal Hospital.

Surgeon:
1942 - Mr. J. B. Macalpine.
1951 - Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

20.2.51.	Papilloma	P U diathermy
9.7.53.	"Suspicious area" (biopsy - no growth)	" "
12.8.57.	Papilloma	" "

Progress:

He has continued on his usual shift work and is in good health. He is reviewed regularly.

CASE No.19 (C.G.)

Date of Birth:	21.12.12.	Age at Entry:	25 years
Date of Entry:	6. 1.36.	Age at Onset:	40 years
Date of Onset:	28. 1.52.	Latent Period:	16 years

Working History:

1936 - 38	Worked for the first three months as a general labourer in the betanaphthylamine shed. Then employed in another building on non-carcinogenic intermediates.
1938 - 39	Worked a year and nine months on the manufacture of betanaphthylamine.
1939 - 42	Served in H.M.Forces.
1942 - 43	Worked on the manufacture of betanaphthylamine.
1943 - 45	Recalled to H.M.Forces.
1945 - 50	Worked on the manufacture of betanaphthylamine.
1950 - 52	Worked on the manufacture of Tobias Acid.

History of Onset:

In January 1952 a few red blood cells were noted on routine urine test; in a stained smear there were many Class IV cells and some clusters of cells suggestive of benign papilloma. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.
Christie, Manchester.

Diagnosis, Course and Treatment:

28.1.52.	Papillomata and ? carcinoma.	Transferred to Christie Hospital.
5.3.52.	Papilloma	P U diathermy
17.1.58.	"	" "

Progress:

On 28.1.52 two groups of benign papillomata were seen one above and behind the right ureteric orifice and one behind the left ureteric orifice. Below the latter the mucosa became piled up and gave the impression of a flat invasive tumour extending over an area of two centimetres in diameter. There was a small benign papilloma in the vault of the bladder. He was transferred to the Christie Hospital for biopsy and intra-cavity radiation.

Five weeks later, on March 5th, the same urologist (Mr. D. S. Poole-Wilson) again examined him. The indurated area which was thought to be a carcinoma had completely disappeared. The papillomata were diathermized. He has had only one recurrence and that was six years later.

He is in good health and still works as a process man on Tobias acid production.

CASE No.20 (L.N.)

Date of Birth:	13.3.08.	Age at Entry:	39 years
Date of Entry:	2.1.47.	Age at Onset:	44 years
Date of Leaving:	1.2.48.	Exposure Period:	1 year
Date of Onset:	28.1.52.	Latent Period:	5 years

Working History:

1947 - 48 Worked one month on dichlorpyrazolone and twelve months on paranitrotoluol sulphonic acid in the building in which naphthionic acid was manufactured but had no direct exposure to alphanaphthylamine.

This case is exceptional in that there was no significant exposure to any known carcinogen and his employment was of very short duration. There is no history of other employment in the chemical industry or in any industry where he would be likely to come in contact with carcinogens.

History of Onset:

In December 1951 he applied for re-employment. On examination many red blood cells were found in his urine; in a stained smear clusters of cells suggestive of benign papilloma were seen. On the 8th January 1952, while awaiting further investigation, he had slight haematuria.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

28. 1.52.	Papilloma	P U	diathermy
20. 6.52.	"	"	"
16. 9.52.	"	"	"
27.10.52.	"	"	"
20. 1.53.	"	"	"
26. 8.53.	"	"	"
29. 3.54.	"	"	"
30. 8.54.	"	"	"
15. 3.55.	"	"	"
27. 2.56.	"	"	"
5. 2.57.	"	"	"
11.11.57.	"	"	"

Progress:

He has had many recurrences but has been free of recurrent tumour for a year. He is now examined at intervals of six months. He was re-employed by the Company in December 1951 on sheltered work as a messenger and has naturally lost a great deal of time but he is now in good general health and is working.

This case is referred to on page 144

CASE No.21 (F.L.)

Date of Birth:	22. 9.05.	Age at Entry:	22 years
Date of Entry:	17.10.27.	Age at Onset:	46 years
Date of Onset:	29. 2.52.	Latent Period:	24 years

Working History:

1927 - 36 Process worker on the manufacture of azo dyes using benzidine sulphate.

1936 - 41 Worked on the manufacture of benzidine disulphonic acid.

1941 - 52 Worked on various intermediates in the building next to that in which benzidine was manufactured.

History of Onset:

On 19.2.52. a stained smear was prepared from his routine urine test. It showed Class IV cells. There were no blood cells and he had had no symptoms or other signs of bladder trouble.

Hospital: Christie Hospital, Manchester.

Surgeon: Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

29.2.52.	Carcinoma. (biopsy - malignant)	Open operation. Gold seed implant.
21.1.58.	Infiltrating recurrence. (biopsy - malignant)	Inoperable

Progress:

Regular review cystoscopic examinations have been made. On 1.4.57. the bladder was seen to be clear of tumour. He developed pain and haematuria about seven months later. On 21.1.58. a large infiltrating epidermoid carcinoma was present at the base of the bladder. Total cystectomy, even if it were to be considered, was impracticable.

He is still alive (December 1958) but is suffering the misery of inoperable cancer of the bladder and requires constant sedation.

CASE No.22 (W.L.)

Date of Birth:	20.12.12.	Age at Entry:	18 years
Date of Entry:	1. 5.31.	Age at Onset:	39 years
Date of Onset:	26. 5.52.	Latent Period:	21 years

Working History:

1931 - 42 Processman in the manufacture of azo colours using benzidine and alphanaphthylamine.
1942 - 48 Benzidine weighing and distribution.
1948 Appointed foreman in the azo colour department.

History of Onset:

On routine urine tests at the factory in March, April and early May 1952 there were numerous red blood cells in the deposit. there were no abnormal cells in the stained smears during this period. A cystoscopic examination was arranged for May 26th but on the 21st he had slight visible haematuria.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

26.5.52.	Papilloma (biopsy - negative)	P U diathermy
28.4.58.	Papilloma	" "

Progress:

On cystoscopy a thin fringe of papillomatous growth was present near the right ureteric orifice.

Follow-up review cystoscopies have been carried out regularly. In the later months of 1956 large numbers of Class V cells were persistently present in his urine. These were very similar in appearance to those seen in Case No.26 before a papillary carcinoma of the renal pelvis was found. Full investigation of the urinary tract as an in-patient in December 1956 failed to reveal any lesion. On cystoscopy on several occasions since, the last in August 1958, the bladder has been clear of tumour. The classifications of stained smears of his urine now range from I to V and are quite inconsistent. These findings are fully discussed in the text.

He has continued his work as a foreman and keeps in good general health.

This case is referred to on pages 141 and 149

CASE No.23 (T.B.)

Date of Birth:	14.10.13.	Age at Entry:	18 years
Date of Entry:	14.12.31.	Age at Onset:	39 years
Date of Onset:	27.10.52.	Latent Period:	21 years

Working History:

1931 - 34 Employed in the Colour Factory transporting ice in barrows.

1934 - 52 Worked on the manufacture of a number of azo colours which involved the use of benzidine. Until 1949 it was charged by him but after 1949 all benzidine was charged by the "benzidine man".

History of Onset:

In September and October 1952 routine tests of the urine revealed the presence of large numbers of red blood cells. Stained smears in March, April and October had been "negative" (Class I). He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. **Surgeon:** Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

27.10.52.	Papilloma (biopsy - benign)	P U diathermy
27. 1.58.	Papilloma	" "

Progress:

Cystoscopic examinations have been made at regular intervals; the last was in March 1958.

His general health is good and he is still working at his usual job.

This case is referred to on page 141

CASE No.24 (F.B.)

Date of Birth:	16.3.13.	Age at Entry:	33 years
Date of Entry:	22.8.46.	Age at Onset:	40 years
Date of Onset:	26.1.53.	Latent Period:	6 years

Working History:

1946 - 52 Worked on the manufacture of benzidine.
1952 - 53 Worked on other intermediates after benzidine manufacture was transferred to a new building in July 1952.

History of Onset:

Routine urine test showed a fairly large number of red blood cells in the deposit in October 1952 and again in December. In November the urine was clear. A stained smear on 15.10.52. was "suspicious" (Class III) but on 10.12.52. it was "negative", there being only a few atypical cells and many normal squamous and transitional cells present. In view of the microhaematuria, the exposure history, and the suspicious smear he was investigated.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.
Christie Hospital.

Diagnosis, Course and Treatment:

24.7.53.	Papilloma	P U diathermy
5.7.54.	"	" "
29.7.57.	Carcinoma	Transferred to Christie Hospital. Deep X-ray therapy.

Progress:

On review cystoscopy on 29.7.57. a flat invasive tumour about 1.5 cms. in diameter on the right postero lateral wall of the bladder was seen. A second smaller nodule about .75 cms. in diameter was present in the vault. He had a radical course of X-ray treatment at the Christie Hospital and made a good recovery. In May 1958 the bladder was clear of tumour. At his next review in September there was a recurrence of the larger tumour and on examination of biopsy material carcinomatous invasion was seen in the deeper layers.

He has continued at work except for a period of four months following X-ray treatment in 1957. He is still in good general health despite the malignant recurrence but he has not worked since May 1958. The urologist does not consider this a suitable case for total cystectomy.

CASE No.25 (S.H.)

Date of Birth:	26. 9.00.	Age at Entry:	31 years
Date of Entry:	13. 4.31.	Age at Onset:	53 years
Date of Onset:	26.10.53.	Latent Period:	21 years

Working History:

1931 - 47 Worked on the manufacture of alphanaphthol from alphanaphthylamine.

1947 - 51 Promoted to chargehand. In this capacity he also came into contact with betanaphthylamine manufacture until it was given up in 1950.

History of Onset:

On a routine test on 24.9.53. there were Class IV cells in the urine and large numbers of erythrocytes. The results of previous tests had been negative and he had had no symptoms or other signs of bladder trouble.

Hospital: Christie Hospital, Manchester. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

30.11.53. Carcinoma — Open operation. Gold seed implant.

Progress:

The report on the biopsy specimen taken at operation was "doubtful as the tissue was necrotic". He made a good recovery and returned to work in May 1954. He was unwilling to go back to any kind of plant work and after doing several odd jobs for two years is now employed in the Works Surgery as a cleaner and messenger.

Cystoscopic examinations have been made annually, the most recent in September 1958. There has been no recurrence so far. His general health is good.

This case is referred to on page 187

CASE No.26 (A.H.)

Date of Birth:	13. 2.05.	Age at Entry:	25 years
Date of Entry:	1.12.31.	Age at Onset:	49 years
Date of Onset:	25. 1.54.	Latent Period:	22 years

Working History:

1931 - 52 Worked as a processman in the building in which benzidine was made. From 1937 until 1941 he was engaged in its manufacture.

1952 - 54 Worked with many other intermediates not suspected of being carcinogenic.

History of Onset:

On routine examination of his urine in January 1954, Class V malignant cells were seen in the stained smear. There were no blood cells and he had had no previous symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

25. 1.54.	Carcinoma (section - papillary carcinoma)	Open operation. Gold seed implant.
2.10.56.	Carcinoma left renal pelvis. (section - epidermoid carcinoma)	Left nephroureterectomy

Progress:

He made a good recovery from his first operation. In October 1954 he returned to light work of a semi-clerical nature in the Milling Department. No tumours were seen in the bladder on review examinations up to and including January 1956.

In July 1956 he began to have intermittent haematuria. (Stained smears were consistently Class IV or V but by this time it was known that no dependence could be placed on Papanicolaou smears in old cases.) On 21st August on cystoscopy no tumour was seen in the bladder but retrograde and intravenous pyelography showed evidence of a tumour in the left renal pelvis. Nephro-ureterectomy was performed on 2nd October and the presence of a carcinoma in the renal pelvis was confirmed.

He made a good recovery and returned to his sheltered job after six months. In July he developed an incisional hernia in the nephrectomy scar and he was fitted with a surgical belt. He is still working.

At his most recent review in June 1958 no evidence of recurrent tumour was found.

CASE No.27 (H.T.)

Date of Birth:	13. 1.93.	Age at Entry:	31 years
Date of Entry:	1.11.24.	Age at Onset:	61 years
Date of Onset:	23. 3.54.	Latent Period:	29 years

Working History:

1925 - 39 Worked on the manufacture of azo colours involving the use of benzidine and alphanaphthylamine.
1939 - 47 Worked on the milling of various finished dry colours.
1947 - 54 Worked as a hoist man in the azo colour factory.

History of Onset:

In January 1951 he was referred to the urologist for investigation because of the presence of considerable numbers of red blood cells in three successive urine tests. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

In January 1951 investigation of the urinary tract failed to reveal the presence of any tumour but there was a small reddish area on the posterior wall of the bladder. About this time the Papanicolaou tests began to be used in the factory. They were negative in this case until January 1953 when Class IV cells were seen. The microhaematuria had persisted on and off all the time. Re-investigation for tumour in January 1953 was again negative and the small reddish area was unchanged. He was listed for re-examination in six months time but was not sent for until 1st March 1954.

In March 1954 the area on the posterior wall appeared to have increased in size and its appearance was suggestive of tumour formation. Biopsy yielded no evidence of papilloma or malignancy.

He was re-examined on April 12th and the clinical appearances were such that the urologist decided to treat the area as malignant. Radon seeds were implanted at open operation. A piece taken for section at operation again showed no evidence of malignancy.

He continued his usual work on the hoist until 1954 but he had a severe radiation reaction and has not worked since. His general condition is poor, he is old for his years and his bladder is still extremely irritable.

No recurrences have been seen at regular cystoscopic examinations.

CASE No.28 (H.M.)

Date of Birth:	11.4.13.	Age at Entry:	19 years
Date of Entry:	29.2.32.	Age at Onset:	41 years
Date of Onset:	27.5.54.	Latent Period:	22 years

Working History:

1932 - 35 Transported intermediates from warehouse to plant. These included benzidine and alphanaphthylamine sulphate.
1935 - 39 Worked on the manufacture of 5-chlor-orthotoluidine.
1939 - 45 H.M.Forces.
1945 - 54 Worked on the manufacture of azo colours involving the use of benzidine and alphanaphthylamine. After 1950 the weighing and charging of these substances were by the "benzidine man".

History of Onset:

In March and April 1954 a few red blood cells were seen on routine urine tests and these persisted on repeated tests. In May 1954 a stained smear was Papanicolaou class III. Because of the suspicious cells and the blood cells the smear was regarded as "positive". He had had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. later Christie Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

27.5.54.	Papilloma	P U diathermy
9.2.55.	Carcinoma	Open operation. Gold seed implant.

Progress:

The initial papilloma was just above the right ureteric orifice. On review again in January 1955 there was a clinically malignant growth on the posterior wall of his bladder but not where the original papilloma had been. Section of biopsy material did not reveal any tumour growth but the tumour was treated by gold seed implant because of the clinical appearances. The bladder has remained free of tumour up to his most recent review in July 1958.

He resumed his usual job after his first treatment but, since the radiation treatment, he has been transferred to clerical work.

CASE No.29 (J.M.B.)

Date of Birth:	14.7.99.	Age at Entry:	25 years
Date of Entry:	19.1.25.	Age at Onset:	40 years
Date of Leaving:	4.1.39.	Exposure Period:	15 years
Date of Onset:	- 6.42.	Latent Period:	18 years

Working History:

1924 - 39 Engaged in the manufacture of betanaphthylamine, and the distillation of betanaphthylamine, benzidine, tolidine and phenylbetanaphthylamine.

History of Onset and Course:

In 1954, fifteen years after he had left the Company, this man reported that he had papilloma of the bladder and asked to be re-employed.

He joined the Army in 1939, after leaving the Company earlier in the year. In early 1941 he had an attack of haematuria and was admitted to a military hospital but no cause was found. It recurred several times and he was admitted to the Victoria Hospital, Glasgow, in June 1942. A papilloma was found in his bladder and he was treated by diathermy. He was then discharged from H.M.F. In 1944 he had a recurrence and was treated at Ancoats Hospital, Manchester; from there he was transferred to Crumpsall Hospital, Manchester, where he has attended since.

He had four recurrences treated by per urethral diathermy between then and 1950 but has been clear since then.

He was re-employed by the Company in September 1954 on light work as a fitter's mate, but he has not worked since February 1957 because of severe intermittent claudication in both legs.

CASE No.30 (A.S.)

Date of Birth:	12.1.12.	Age at Entry:	27 years
Date of Entry:	22.5.39.	Age at Onset:	43 years
Date of Onset:	4.7.55.	Latent Period:	16 years

Working History:

1938 - 39 Worked as a scalesman weighing a variety of products including benzidine and alphanaphthylamine.

1939 - 46 H.M.Forces. Was prisoner of war in Japanese hands 1942-45.

1946 - 48 Worked in the manufacture of azo colours on units adjacent to those where benzidine was stoved and used.

1948 - 52 Worked in manufacture of a benzidine azo colour and acted as stand-in for benzidine distribution man.

1952 - 55 Worked in vat dyes and had no contact with known carcinogens.

History of Onset:

On 11.5.55, on routine urine test, there were Class III cells in the stained smear. On 10.6.55. the smear was Class IV - V. He had had no previous symptoms or signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.
Christie Hospital.

Diagnosis, Course and Treatment:

18. 8.55.	Papilloma (?Carcinoma)	Biopsy
21.10.55.	Carcinoma	Deep X-ray therapy
15.12.56.	Papilloma	P U diathermy

Progress:

On cystoscopy in August 1955 there was a lesion on the left side of the bladder very suggestive of early superficially infiltrating carcinoma. Biopsy material showed an indefinite picture- "some superficial inflammation and a projection of tissue like a small papilloma which has been burnt". (No treatment had been given). On October 11th the appearance of the bladder was unchanged and further biopsy material still showed no definite evidence of tumour growth. The clinical appearances were so characteristic of carcinoma that he was transferred to the Christie Hospital for a full course of deep X-ray therapy.

He made a good recovery and resumed his usual work in February 1956. Except for one small recurrence in December 1956 he has remained in good health since.

CASE No.31 (H.P.M.)

Date of Birth:	22.7.98.	Age at Entry:	14 years
Date of Entry:	26.9.12.*	Age at Onset:	57 years
Date of Onset:	4.7.55.	Latent Period:	33 years

Working History:

1912 - 22 General labouring with no exposure to known carcinogens.
1922 - 24 General work on all products in azo colour factory.
1924 - 48 Worked as a processman in the manufacture of benzidine azo colours.
1948 - 53 Worked on azo colours not involving the use of known carcinogens.
1953 - 55 Worked on stoves drying finished colours.

* For the analysis of this tumour case his starting date has been taken as 1922, the year in which he was first exposed to carcinogens.

History of Onset:

Stained smears of urine on routine test in March 1955 were Class II, in April Class III-IV and in May Class IV. Several repeat smears were consistently Class IV. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

4.7.55.	Papilloma (biopsy)	P U diathermy

Progress:

On cystoscopy a cluster of low growing papillomata were seen just below the left ureteric orifice. A biopsy was taken and the growth was fulgurated. Microscopy of the biopsy material showed papilloma with an area of apparently solid growth with mitotic activity and cell irregularity but no evidence of invasion.

He has had no recurrence up to his most recent review examination in November 1958.

He returned to work on his old job for a year and was then transferred to work as a laboratory attendant and messenger.

CASE No.32 (J.E.B.)

Date of Birth:	6. 8.03.	Age at Entry:	30 years
Date of Entry:	4.12.33.	Age at Onset:	52 years
Date of Onset:	4. 7.55.	Latent Period:	22 years

Working History:

1933 - 39 Worked on the manufacture of benzidine.
1939 - 55 Worked in the same department on other intermediates.

History of Onset:

Routine urine tests were negative until May 1955 when a stained smear was Class III. A very few red blood cells were present. In June the stained smear was Class II but in view of his exposure and the urinary findings cystoscopy was advised.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

4.7.55.	Papilloma (biopsy - benign papilloma)	P U diathermy

Progress:

No recurrences have been observed up to his last review examination in August 1958. He continues work at his usual job and is in good health.

CASE No.33 (G.G.)

Date of Birth:	13.8.98.	Age at Entry:	20 years
Date of Entry:	- 7.15.*	Age at Onset:	57 years
Date of Onset:	5.9.55.	Latent Period:	37 years

Working History:

1918 - 55 Worked with the Transport Department. Never worked in the plants. The transport of aniline and benzidine formed a considerable part of his work. For the first 20 years the benzidine, often as a slurry, was transported in casks with open tops or sacking over them and there was considerable exposure.

* The latent period is calculated from 1918 when benzidine manufacture was started.

Previous health: Amputation left leg 3" below knee - gunshot wound 1917.

History of Onset:

In June 1955 on routine test of his urine a stained smear was Class II. In July it was Class III and on August 28th and September 1st it was Class V. There were no symptoms or other signs of bladder trouble.

Hospital: Christie Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

5.9.55.	Papillary carcinoma (biopsy - carcinoma)	Deep X-ray therapy
24.1.58.	Papilloma	P U diathermy

Progress:

The tumour, which was above the left ureteric orifice, was fulgurated. Biopsy showed the presence of transitional cell papillary carcinoma. In view of this he was re-admitted in December 1955 for a course of deep X-ray therapy and was finally discharged from hospital on 7th March 1956. There was a severe and prolonged radiation reaction and he did not resume work until January 1957.

He has made a very good recovery and has had only one recurrence, a benign papilloma. Because of his old leg amputation and his long absence from work he was put on sheltered work as a gate-man on his return and is still working on this job.

CASE No.34 (W.W.)

Date of Birth:	7.10.91.	Age at Entry:	29 years
Date of Entry:	11. 3.20.	Age at Onset:	64 years
Date of Onset:	5. 9.55.	Age at Death:	66 years
Date of Death:	28. 5.58.		

Working History:

1920 - 24 Worked on the manufacture of magenta.
1924 - 55 Worked on the manufacture of rhodamine. For a short time he had contact with dimethylaniline.

History of Onset:

Routine urine tests were negative until August 1955 when stained smears were Class V.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

5.9.55.	Papillary carcinoma. (biopsy - transitional cell carcinoma)	Open operation. Gold seed implant (30.9.55).
18.3.57.	Carcinoma. (biopsy - carcinoma)	Declined total cystectomy.
30.9.57.	Massive carcinoma.	Inoperable.

Progress:

At preliminary cystoscopy there was a small papilloma over the right ureteric orifice. A biopsy specimen was taken. Examination of this showed a poorly differentiated transitional cell carcinoma. At open operation on 30.9.55. a gold seed implant was carried out.

At review cystoscopy on 21.1.57. a pink grnaular raised area at the centre of the gold seed implant area was diathermized after a biopsy was taken. Section of the biopsy material showed epidermoid carcinoma.

Total cystectomy was advised as the only possible course of treatment but he steadfastly declined it.

He died on 28.5.58. At post mortem examination there was a large recurrent carcinoma of the bladder infiltrating the paravesical tissue and adjacent glands. No other secondaries were present.

This case is referred to on page 163

CASE No. 35 (J.M.)

Date of Birth:	22.12.92.	Age at Entry:	30 years
Date of Entry:	1. 3.23.	Age at Onset:	63 years
Date of Onset:	5. 9.55.	Latent Period:	32 years

Working History:

1923 - 39	Worked on the manufacture of benzidine azo colours.
1939 - 48	Worked on the manufacture of alphanaphthylamine azo colours.
1948 - 51	Worked on the manufacture of other azo colours until he contracted severe sensitization dermatitis from dinitrochlorbenzene and was transferred.
1951 - 55	Analytical department as a sampler.

History of Onset:

On routine urine test on 17.7.55. the stained smear was Class III, on 17.8.55 and 10.9.55 it was Class IV. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

5.9.55.	Papilloma (biopsy - transitional cell papilloma)	P U diathermy
19.7.56.	Papilloma	" "

Progress:

He was three months off work following an operation for umbilical hernia in April 1956. Apart from this he continued at work until he retired at the age of 65 in December 1957.

His general health is still good and no tumour was found at his most recent follow-up review in August 1958.

CASE No.36 (F.H.)

Date of Birth:	14. 2.12.	Age at Entry:	27 years
Date of Entry:	1. 6.39.	Age at Onset:	43 years
Date of Onset:	24.10.55.	Latent Period:	16 years

Working History:

1939 - 51 For the first two years, 1939-41, worked on benzidine manufacture, and thereafter worked on a variety of products on the vat next to it.
1951 - 55 Similar work but no exposure to benzidine.

History of Onset:

In September 1955 at routine monthly urine test the stained smear was Class IV and this was confirmed on a repeat specimen. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

24.10.55.	Papilloma	P U diathermy
20.12.56.	"	" "

Progress:

He has continued at work and is in good health. At his most recent follow-up cystoscopy in April 1958 the bladder was clear.

CASE No.37 (J.W.S.)

Date of Birth:	30. 8.08.	Age at Entry:	23 years
Date of Entry:	23.11.31.	Age at Onset:	47 years
Date of Onset:	24.10.55.	Latent Period:	24 years

Working History:

1931 - 40	Worked on the manufacture of betanaphthylamine.
1940 - 45	Worked on the manufacture of alphanaphthol using alphanaphthylamine.
1945 - 51	Worked on the manufacture of betanaphthylamine.
1951 - 55	Worked on the manufacture of other intermediates.

History of Onset:

Routine urine tests were negative until September 1955 when stained smears were Class IV. A stained smear in October was again Class IV. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

24.10.55.	Papilloma (biopsy - papilloma)	P U diathermy
19. 3.57.	Papilloma	" "
1. 6.58.	"	" "

Progress:

He returned to work after treatment for his original tumour but has been off work since 16.1.57 with emphysema and chronic bronchitis.

CASE No.38 (N.T.)

Date of Birth:	30.4.03.	Age at Entry:	20 years
Date of Entry:	7.9.23.	Age at Onset:	53 years
Date of Onset:	3.1.56.	Latent Period:	32 years

Working History:

1923 - 24 Records of this man's early working history are sketchy and his own recollection of it is confused. It is certain that at one period he worked with Case No.34 on the manufacture of magenta.

1926 - 39 Worked as a processman on the manufacture of rhodamine.

1939 - 56 Worked as an electrician's mate - would be in all departments of the factory from time to time.

History of Onset:

On 9.12.55. and the following day he passed a little blood in the urine at the end of the stream. He had had no previous symptoms. No blood cells or abnormal cells had been seen on routine urine tests. On 30.9.55. a routine stained smear was Class I and on 29.11.55. it was Class II. In a smear from the blood stained urine a small piece of tissue was identified as benign papilloma (Fig 17).

Hospital: Ancoats Hospital, Manchester. Surgeon: Mr. G. O. Jelly.

Diagnosis, Course and Treatment:

3.1.56.	Papilloma	P U diathermy

Progress:

He continues at work as an electrician's mate and has been in good general health since he was treated. At his last cystoscopic review in July 1958 the bladder was clear.

This case is referred to on pages 143 and 144

CASE No.39 (G.E.)

Date of Birth:	20.11.09.	Age at Entry:	35 years
Date of Entry:	13. 8.46.	Age at Onset:	46 years
Date of Onset:	21. 1.56.	Latent Period:	11 years

Working History:

1944 - 45 Warehouseman.
1945 - 50 Worked on the manufacture of benzidine azo colours.
1950 - 56 Worked as benzidine distribution man weighing and charging all the benzidine. For the last four years it was in an enclosed system and there was no direct contact.

History of Onset:

In January 1955 he complained that he felt burning on micturition. Stained smears of urine deposit were Class I. There were no blood cells. When he was investigated no tumour was seen in the bladder and X-rays and pyelography were normal. The burning cleared up in a few days and he had no further symptoms or signs.

Eleven months later, in December 1955, Class IV cells were seen in stained smear on routine test and in repeat tests. There were no symptoms or other signs at this time.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

24.1.56.	Papilloma (biopsy papillary carcinoma)	P U diathermy

Progress:

The papilloma was tiny and was fulgurated after the biopsy specimen had been resected. Radiation treatment was not considered to be necessary.

At his most recent cystoscopy in September 1958 the bladder was still clear of recurrent tumour.

He continues to work on benzidine distribution.

CASE No.40 (W.B.A.)

Date of Birth:	28.10.99.	Age at Entry:	34 years
Date of Entry:	16.12.33.	Age at Onset:	56 years
Date of Onset:	23. 1.56.	Latent Period:	22 years

Working History:

1933 - 34	General labourer transporting materials in a building where benzidine was being manufactured but did not handle it.
1934 - 44	Worked on the manufacture of nitrobenzene sulphonic acid and other non-carcinogenic intermediates.
1944 - 46	Worked on the manufacture of dichlorbenzidine and para anisidine. (benzidine and tolidine for six weeks only).
1946 - 47	Worked on the manufacture of para anisidine.
1947 - 52	Worked on the manufacture of benzidine, tolidine, and dichlorbenzidine.
1952 - 56	Worked on the manufacture of other non-carcinogenic intermediates.

History of Onset:

Routine urine tests were negative until October and November 1955 when stained smears were Class III. In December 1955 and January 1956 the smears were "positive" and clumps of benign papilloma cells were present. There were no other signs or symptoms of urinary disease.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

23.1.56.	Papilloma (biopsy - papilloma)	P U diathermy
8.3.56.	Papilloma	" "
18.9.56.	"	" "
30.9.58.	"	" "

Progress:

He has kept on at his usual job as a processman and is in good general health.

This case is referred to on pages 144 and 148

CASE No.41 (J.H.M.)

Date of Birth:	12.1.07.	Age at Entry:	20 years
Date of Entry:	6.9.27.	Age at Onset:	49 years
Date of Onset:	27.2.56.	Latent Period:	28 years

Working History:

1927 - 50 Worked on betanaphthylamine manufacture.
1950 - 56 Worked on the manufacture of the sulphonic acids of various other intermediates.

History of Onset:

On the 18th January 1956 he had a sudden severe haematuria. Routine urine tests had been negative and stained smears had been Class I except for a Class II smear on 14.10.55. A specimen of urine at routine test two days before the onset of the haematuria showed no blood cells and was Class I.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

27. 2.56.	Papilloma (biopsy - papilloma)	P U diathermy
5. 6.56.	Papilloma	" "
6.12.56.	"	" "

Progress:

He has continued at work but has been transferred to a lighter job as a messenger and gate man.

His general health is good and the bladder was clear of tumour on cystoscopic examination in May 1958.

This case is referred to on pages 133 and 141

CASE No.42 (G.A.)

Date of Birth:	25.10.12.	Age at Entry:	19 years
Date of Entry:	19.10.31.	Age at Onset:	44 years
Date of Leaving:	21. 8.35.	Exposure Period:	4 years
Date of Onset:	30. 9.56.	Latent Period:	25 years

Working History:

1931 - 35 Worked on the manufacture of various beta-naphthylamine sulphonic acids and on the distillation of benzidine, tolidine and other products. He also assisted at busy times in the manufacture of alphanaphthylamine sulphate.

Before entering the chemical industry he was five years in engineering. After leaving the Clayton Aniline Company he worked at another firm for 10 years on the manufacture of sulphur dioxide and thereafter worked with several engineering firms.

History of Onset:

Twenty-one years after leaving the Company he was admitted to hospital with gross haematuria. There was a history of a similar attack four years before which had cleared up in 24 hours and had given no further trouble.

Hospital: Manchester Royal Infirmary. Surgeon: Mr. R. Newell.

Diagnosis, Course and Treatment:

30.9.56. Papillomata P U diathermy

Progress:

There were three papillomata in the bladder. His general health has remained good and the bladder was clear when he was last reviewed in October 1958.

He was re-employed at Clayton when he developed the tumour in 1956 and has worked regularly since then as a works window cleaner.

CASE No.43 (W.P.)

Date of Birth:	28.5.07.	Age at Entry:	43 years
Date of Entry:	27.4.50.	Age at Onset:	50 years
Date of Onset:	12.1.57.	Latent Period:	7 years

Working History:

I have been unable to trace any significant exposure in this case except that he worked in the factory for seven years before developing a tumour. Before that he worked 28 years in a wood saw-mill.

1950 - 53	Worked as a filter-press cleaner handling chiefly sulphurised dinitro-oxydiphenylamine, indophenols and tolazine.
1953	(February-April) Worked on service team delivering ice and salt to plants.
1953 - 57	Worked in warehouse handling packaged materials.

History of Onset:

He had a sudden attack of haematuria on 24.11.56 which lasted six days. No blood had been seen on routine tests of his urine and stained smear results had been consistently Class I or Class II.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

12.1.57.	Papilloma (biopsy - benign)	P U diathermy
19.5.58.	Papillomata	" "

Progress:

He has continued at his work as a warehouseman.

The fulguration in May 1958 was for recurrent papillomata at the internal meatus and left lateral lobe of the prostate. Following this he developed a prostatic abscess in July. It eventually discharged spontaneously. This has now cleared up and he is in good general health and is back at work.

This case is of particular interest in that he is the most recently employed worker to develop a tumour of the bladder. Despite the fact that there has been little or no known direct exposure to carcinogens he is accepted as a case of occupational tumour because of his seven years' work in the factory.

CASE No.44 (G.M.)

Date of Birth:	22.11.97.	Age at Entry:	22 years
Date of Entry:	11. 5.20.	Age at Onset:	59 years
Date of Onset:	29. 9.57.	Latent Period:	37 years

Working History:

1920 - 42 Worked on the manufacture of benzidine.
1942 - 55 Worked on the manufacture of alphanaphthylamine sulphonic acids.
1955 - 57 Worked on the manufacture of amino benzoic acid, dimethylaniline and other products.

History of Onset:

In November 1955 the stained smear of the urinary deposits was Class III on routine test. In December it was again Class III but in January 1956 it was Class V. On this finding cystocopy, X-rays and pyelography were done on 23.1.56. No tumour was found.

The stained smears continued to be positive and a repeat investigation, made in July 1956, did not reveal any abnormality. He was reviewed again in April 1957 and on this occasion, fifteen months after the positive smear was first recorded, there was a papilloma in the bladder. This case is discussed in the text in considering "false positive" cytodiagnostic results.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

29.4.57.	Papilloma (biopsy - papilloma suspicious of early malignant changes)	P U diathermy

Progress:

No recurrences have been seen on review cystoscopies. He has continued at work but was transferred to a sheltered job as a cleaner in the transport department.

CASE No. 45 (H.H.)

Date of Birth:	1. 2.04.	Age at Entry:	29 years
Date of Entry:	9.12.32.	Age at Onset:	53 years
Date of Onset:	28. 1.57.	Latent Period:	24 years

Working History:

1932 - 39	Worked on benzidine manufacture.
1939 - 45	H.M.Forces.
1945 - 52	Worked on benzidine manufacture.
1952 - 55	Worked on the manufacture of cibanaphthol and cibanaphthol R.C.T. using 5-chlor-orthotoluidine.
1955 - 57	Worked on the manufacture of 5-chlor-orthotoluidine.

History of Onset:

He had one attack of haematuria in July 1955 which was ascribed to exposure to 5-chlor-orthotoluidine. This cleared rapidly and stained smears were Class I or II until December 1956 when a smear was Class III. The next month, in January 1957, the smear was Class IV. No other symptoms or signs were evident.

Hospital: Salford Royal Hospital. **Surgeon:** Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

28.1.57	Papilloma (biopsy - "Trans. cell papilloma. One suspicious area of possible invasion")	P U diathermy
28.4.58.	Papilloma	P U diathermy
10.9.58.	Papillomata	" "

Progress:

He has continued working on process work but has been transferred to a job where he will not be exposed to carcinogens or to compounds likely to cause cystitis.

His general health is good.

CASE No.46 (A.T.)

Date of Birth:	2.4.94.	Age at Entry:	30 years
Date of Entry:	26.2.24.	Age at Onset:	63 years
Date of Onset:	28.1.57.	Latent Period:	33 years

Working History:

1924 - 30 Worked on the manufacture of naphthionate of soda and sulphanilic acid. During this time it is possible that he came into contact with betanaphthylamine.
1930 - 48 Worked on the manufacture of oxy Tobias acid.
1948 - 57 Worked on the manufacture of naphthionate of soda which involved the use of alphanaphthylamine.

History of Onset:

On routine urine tests there was one Class III smear in early 1955. They were Class I until December 1955 when the smear was again Class III. In January 1956 it was Class IV and clumps of benign papilloma cells were present. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

28.1.57.	2 papillomata (biopsy - ulceration and inflammation)	P U diathermy

Progress:

The biopsy result was indefinite but the clinical appearances were indubitable.

He has been clear of recurrences up to and including his most recent review in November 1958.

Because of his age he was transferred to light work as a laboratory cleaner after his operation. His general health is good.

This case is referred to on page 144

CASE No.47 (F.J.L.)

Date of Birth:	26.8.98.	Age at Entry:	22 years
Date of Entry:	6.9.20.	Age at Onset:	59 years
Date of Onset:	12.3.57.	Latent Period:	37 years

Working History:

1920 - 28 Worked on the manufacture of H.Acid entailing some exposure to alphanaphthylamine.
1928 - 33 Worked on the manufacture of azo colours using benzidine.
1933 - 35 Office work.
1936 - 57 Canteen and Locker Room foreman.

History of Onset:

On routine urine test on 13.7.55. the stained smear was Class IV. Several repeat smears yielded similar readings. On cystoscopy, X-ray and pyelography on 5.9.55 no evidence of tumour was found.

The stained smears of the urine continued to be Class IV. He was again investigated eight months later in May 1956 and again no evidence of tumour was found.

Class IV cells were still being exfoliated when he was re-investigated on 12.3.57. A tiny papilloma was then present in the vault of the bladder.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

12.3.57. Papilloma P U diathermy

Progress:

On cystoscopy in March 1957 an area of red velvety mucosa with frond formation was diathermized. Biopsy was attempted but a good piece was not obtainable. On review examination three months later the area was healed. No further abnormalities have been seen and the bladder was clear in April 1958.

He continued to work in the Locker Room until he retired at the age of 60 in August 1958. His general health is excellent.

This case is referred to on page 137

CASE No.48 (J.H.)

Date of Birth:	15. 6.00.	Age at Entry:	29 years
Date of Entry:	9.10.29.	Age at Onset:	46 years
Date of Leaving:	10. 5.40.	Exposure Period:	11 years
Date of Onset:	20. 6.46.	Latent Period:	17 years

Working History:

1929 - 40 Worked in the department where benzidine was made and from 1937 to 1940 was engaged in its manufacture.

History of Onset:

In June 1946, six years after leaving the Company's employment, he had painless haematuria and attended hospital. In 1955 he reported to the Company that he was suffering from papilloma of the bladder.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

A case report obtained from the hospital in 1955 states that four small papillomata were found originally on 20.6.46. and small recurrences had been found on several occasions since then. He has been followed up closely since he got in touch with me in 1955. He had recurrences in August 1957 and in June 1958. All the treatments have been by endoscopic diathermy.

Since leaving Clayton he had been continuously employed as a concreter. In 1957 he was having difficulty in keeping up with such heavy work and he was re-employed by the Company in September of that year as a laundry worker - a light job which he is still doing.

His general health is good.

CASE No.49 (R.M.)

Date of Birth:	30.4.00.	Age at Entry:	39 years
Date of Entry:	1.9.39.	Age at Onset:	57 years
Date of Onset:	30.9.57.	Latent Period:	18 years

Working History:

1939 - 52 Worked as a general labourer on the manufacture of betanaphthylamine. There was some contact with alphanaphthylamine.

1952 - 57 Worked as a cleaner in Transport Department.

History of Onset:

Stained smears from routine urine tests were Class III in July 1957 and Class IV in August and September 1957. He had had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr. D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

30.9.57.	Papilloma (biopsy - benign)	P U diathermy

Progress:

Three weeks after his diathermy treatment he was found to have a mass over the pubis which was thought to be due to extravasation of urine. This resolved very slowly and at the end of six months had disappeared. He was then symptom free.

In 1952 he was transferred to light sweeping-up duties because of chronic bronchitis. His general health is still poor, and he has not yet resumed work although the bladder was clear at his most recent review in July 1958.

CASE No.50 (E.C.)

Date of Birth:	3.10.06.	Age at Entry:	25 years
Date of Entry:	19.10.31.	Age at Onset:	43 years
Date of Leaving:	12. 7.37.	Exposure Period:	6 years
Date of Onset:	28. 3.50.	Latent Period:	18 years

Working History:

1931 - 37 Worked on the manufacture of betanaphthylamine.

History of Onset:

In March 1950, thirteen years after leaving the Company, he was admitted to Christie Hospital, Manchester because of a history of three years' haematuria.

Hospital: Christie Hospital. Surgeon: Mr. Wilson Hey.

Diagnosis and Treatment:

In June 1951 I was informed of this case by a letter from the R.S.O. at the hospital.

At operation on 28.3.50 "a large carcinoma of the bladder was excised completely and the bladder closed. At the beginning of June 1950 he began a course of X-ray therapy." The report on the excised tumour was "epidermal carcinoma invading the bladder wall."

Progress:

He has made a good recovery apart from one small papillomatous recurrence which was fulgurated in September 1955. At the most recent review cystoscopy in June 1958 the bladder was clear.

When he left the Company in 1937 he removed to Southport and took up clerical work. He had difficulty in keeping a job because of the time he lost for review examinations and the seasonable nature of the work. In view of this he was re-employed by the Company in 1957 as a clerk in the Transport Office. He is still working there and is in good health.

CASE No.51 (J.M.)

Date of Birth:	25.11.02.	Age at Entry:	21 years
Date of Entry:	23.11.23.	Age at Onset:	55 years
Date of Onset:	27. 1.58.	Latent Period:	34 years

Working History:

Worked as a scalesman handling and weighing out raw materials and intermediate products including tolidine, dianisidine and dichlorbenzidine but he has not been engaged on actual process work. The shed in which he worked was next to the benzidine shed and formed part of the same department.

History of Onset:

Routine urine tests were clear until December 1957 when a stained smear was Class III. Two stained smears in January 1958 were "positive". The cells were of the type by then recognised as having been exfoliated from benign papilloma (Fig 15). He had had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

27.1.58.	Papilloma (biopsy - benign)	P U diathermy

Progress:

He is still working on his usual job as a scalesman but does not handle carcinogens or suspected carcinogens.

This case is referred to on pages 143 and 144

CASE No.52 (H.D.)

Date of Birth:	14.4.94.	Age at Entry:	45 years
Date of Entry:	5.7.39.	Age at Onset:	55 years
Date of Leaving:	19.9.44.	Exposure Period:	5 years
Date of Onset:	19.9.49.	Latent Period:	10 years

Working History:

1939 - 44 Employed as a "cask man" in intermediates department, looking after and washing the casks, including those used for benzidine.

In 1944 he contracted severe sensitization dermatitis and left the Company's employment.

History of Onset:

He was referred to hospital by his own doctor on account of symptoms of bladder trouble. He wrote to the Company soon afterwards stating that he was suffering from papilloma of the bladder.

Hospital: Ancoats Hospital. Surgeon: Mr. G. O. Jelly.

Diagnosis, Course and Treatment:

19.9.49.	Papilloma	P U diathermy

Progress:

No recurrences have been seen at regular review cystoscopy; the most recent review was in September, 1958.

He still has recurrent dermatitis. He has been unable to work for the past eight years because of osteoarthritis of the spine and chronic bronchitis with dyspnoea.

CASE No.53 (W.G.)

Date of Birth:	31. 7.00.	Age at Entry:	27 years
Date of Entry:	15.11.27.	Age at Onset:	44 years
Date of Onset:	19. 7.44.	Age at Death:	58 years
Date of Death:	28. 9.58.	Latent Period:	17 years

Working History:

1927 - 28 Worked on the manufacture of H.Acid.
1928 - 31 Worked in intermediates department powdering betanaphthylamine.
1931 - 44 Worked on the sulphonation of betanaphthylamine.

History:

This man developed symptoms of bladder trouble in 1944 and was referred by his own doctor to Manchester Royal Infirmary where a papilloma was diagnosed and treated by per-urethral diathermy.

He thereupon left the Company's employment and firmly refused all offers of ex gratia payments or advice.

In 1951 a relative who worked at Clayton informed me that he had had a recurrence and had diathermy treatment. Attempts were again made to get in contact with him and to get his consent to have the hospital reports sent to me, but again he refused all co-operation.

He died on 28.9.58. and the death was certified as "cancer of the bladder". The death occurred after the list was "closed" for the analysis of this series of cases and is not included in it.

One cannot but respect his spirit of pride and independence however financially misguided it may have been. His widow has accepted the usual pension which the Company offered.

CASE No.54 (J.M.)

Date of Birth:	27.7.98.	Age at Entry:	25 years
Date of Entry:	1.9.23.	Age at Onset:	41 years
Date of Onset:	26.8.39.	Age at Death:	60 years
Date of Death:	9.5.58.	Latent Period:	16 years

Working History:

1923 - 32 Worked on the manufacture of benzidine.
1932 - 39 Worked on the nitration and isolation of a variety of intermediates.

History of Onset:

No exact record.

Diagnosis, Course and Treatment:

26.8.39.	Papilloma	P U diathermy	
23.6.52.	Papillomata	" "	(4 areas)
9.4.57.	Carcinoma	" "	

Progress:

He left the Company in January 1941 when he took over a small coal business which he ran until he died.

Regular review examinations were continued. In January 1943, having been clear of tumour for nearly four years, four papillomatous areas were seen, one of which was possibly malignant. The biopsy result was "doubtful". They were all fulgurated and no recurrence was seen until April 1957, when there was a small tumour which proved on biopsy to be a papillary carcinoma. It was treated by fulguration. When he was cystoscoped in October 1957 the bladder was clear.

In early 1958 he had a fall and bruised his ribs. After this he gradually deteriorated and by March there was weakness in the left arm and leg. By the end of the month there was left hemiplegia. He died on May 9th. At post mortem examination there were widespread metastatic deposits of papillary carcinoma, confirmed histologically.

As he died after the lists were "closed" for the analysis of this series of cases he is not included in the "deaths".

CASE No.55 (R.C.)

Date of Birth:	28. 8.10.	Age at Entry:	23 years
Date of Entry:	1.12.33.	Age at Onset:	39 years
Date of Leaving:	1.10.37.	Exposure Period:	4 years
Date of Onset:	18. 6.49.	Latent Period:	16 years

Re-employed: 27. 4.44.
Left: 1.10.45.

Working History:

1933 - 37 Worked on the manufacture of betanaphthylamine.
1944 - 45 Worked in engineering department - no contact with chemicals.

History of Onset:

After he had left the Company he was referred by his own doctor, in June 1949, to hospital with a history of two attacks of haematuria, one four years before and one two days previously.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

18.6.49.	Papilloma	P U diathermy

Progress:

The clinical appearances were those of a papillary carcinoma but there is no record of a biopsy.

Follow-up cystoscopies were done in May and December 1950 and the bladder was clear. He failed to attend when he was sent for six months later. All efforts to get in touch with him by the hospital and by the firm have failed and nothing has been heard of him since. Although his present address is unknown he is presumably still alive as no death certificate has been reported.

CASE No.56 (R.W.)

Date of Birth:	2.8.01.	Age at Entry:	25 years
Date of Entry:	13.7.26.	Age at Onset:	43 years
Date of Onset:	26.1.45.	Latent Period:	19 years

Working History:

1926 - 45 Worked on the manufacture of azo colours which entailed the use of benzidine.

History of Onset:

He started with haematuria in January, 1945. A few red blood cells, not considered to be in sufficient number to warrant cystoscopy, had been present in the urine on routine tests some 12 months before, but none had been present in the more recent specimens.

Hospital: Christie Hospital. **Surgeon:** Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

26.1.45.	Carcinoma	Open operation. Gold seed implanted.

Progress:

Section of the tumour showed it to be a transitional cell carcinoma.

This man did not return to the Company's employment as he was afraid to return to any kind of chemical work. He was off work for a year and then took a job as a lavatory attendant at a local pleasure garden where he still works.

He attended hospital for review cystoscopies until January, 1950 and no recurrences were seen. For the next eight years he persistently declined to have further examinations. In early January, 1958 I persuaded him to be re-examined. Cystoscopy on the 9th January showed the bladder to be clear of tumour. He is to be reviewed in January, 1959.

CASE No.57 (D.H.)

Date of Birth:	29.8.96.	Age at Entry:	38 years
Date of Entry:	4.2.35.	Age at Onset:	52 years
Date of Leaving:	10.4.42.	Exposure Period:	7 years
Date of Onset:	16.8.48.	Latent Period:	13 years

Working History:

1935 - 42 Worked on the manufacture of benzidine.

History of Onset:

Six years after he left the Company he was referred to hospital by his own doctor presumably for symptoms of bladder trouble. After he had been treated he reported to the Company that he was suffering from papilloma of the bladder.

Hospital: Christie Hospital. Surgeon: Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

16. 8.48.	Papilloma	P U diathermy
23. 4.49.	"	" "
1. 3.50.	"	" "
15.11.50.	"	" "
21. 7.51.	Carcinoma	Open operation. Gold seed implant.

Progress:

At review cystoscopy in July 1951 there was a small hard ulcerating tumour which was clinically malignant. A week later radon seeds were implanted. A biopsy was then taken but failed to reveal any carcinoma. The piece taken showed largely a necrotic ulcer. Since then there has been no recurrence but he had very frequent attacks of cystitis for the first four years. The bladder was clear when he was last examined in January 1958.

He suffers from chronic bronchitis and has not worked since the onset of his carcinoma in 1951.

CASE No.58 (W.H.)

Date of Birth:	10. 4.93.	Age at Entry:	26 years
Date of Entry:	13. 5.19.	Age at Onset:	40 years
Date of Onset:	3.11.33.	Latent Period:	14 years

Working History:

1919 - 24 Worked on the manufacture of nigrosine.
1924 - 33 Worked on benzidine azo colours and on stoving finished colours.

Diagnosis, Course and Treatment:

This man left the Company's employment in 1937 and from his records it appears that, at that time, it was not realised that he had had an occupational tumour of the bladder in 1933.

In 1952 in the course of the A.B.C.M. field survey he was traced through the Christie Hospital records. From these it was learned that he had had haematuria in 1933 and was treated at Stockport Infirmary for a papilloma of the bladder by suprapubic diathermy.

He apparently remained well until 1951 when haematuria recurred and he was treated at the Christie Hospital for "multiple papillomata" by a cobalt radiation source in a balloon.

He has not been seen since then but no record of his death has been traced or reported.

This case is referred to on page 167

CASE No.59 (R.K.)

Date of Birth:	14. 2.07.	Age at Entry:	18 years
Date of Entry:	2.12.25.	Age at Onset:	48 years
Date of Leaving:	2. 7.27.	Exposure Period:	1 year 7 months
Date of Onset:	- 1.55.	Latent Period:	29 years

Working History:

1925 - 27 Worked in a chemical works for only 19 months. He was engaged in the betanaphthylamine manufacturing department at the time when the amine was distilled, broken up by hand and ground. There is no precise record of the job that he did and his own memory of it is not clear, but he remembers it was on the stoves. At that time and as a youth of 18 in that department, it is likely that he would be employed as a stove-boy in the stoves where betanaphthylamine was dried as this was the usual job preliminary to becoming a process man at 18.

After leaving the Company in 1925 he worked for 29 years as a railway porter and is still working at this job.

History of Onset:

He was referred to hospital by his own doctor because of the onset of symptoms of bladder trouble. I first learned of this case from the urologist after the operation.

Hospital: Christie Hospital. Surgeons: Dr. Ralston Paterson and Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

2.1.55.	Carcinoma of the bladder (biopsy - pleomorphic carcinoma)	Deep X-ray therapy

Progress:

Regular cystoscopic examinations have been made. In December 1955 there was still a large sloughing area over the site of the tumour on the anterior wall of the bladder near the bladder neck. Biopsy of this area showed inflammatory reaction only. In May 1956 only one tiny slough remained and the rest was healed. On re-examination in May 1957 healing was found to be complete. The bladder was clear of tumour in August 1958.

He has continued his usual work with British Railways and his general health is good. He comes to see me at the factory regularly twice a year.

This case is referred to on pages 96 and 188

CASE No.60 (J.K.)

Date of Birth:	22. 4.90.	Age at Entry:	38 years
Date of Entry:	28. 6.28.	Age at Onset:	64 years
Date of Leaving:	20. 4.42.	Age at Death:	68 years
Date of Onset:	13.12.54.	Exposure Period:	14 years
Date of Death:	10. 9.58.	Latent Period:	26 years

Working History:

1928 - 42 Worked chiefly on the manufacture of rhodamines and supervised other manufactures in the same shed. He was exposed to the following:- rhodamines, fluorescin, phthalic anhydride, resorcin, aniline, dimethylaniline, methane base, Michler's hydrol, betanaphthol and several triphenylmethane colours.

No direct contact with any of the recognised carcinogens has been traced but in view of his 14 years in the chemical works in a department next to that in which naphthylamines were sulphonated his tumour is regarded as occupational.

History and Progress:

After leaving the Company in 1942 he worked as a watchman in an engineering works until he retired in 1952.

In December 1954 he had several attacks of painless haematuria and was referred by his own doctor to Crumpsall Hospital, Manchester. He was admitted for investigation. On intravenous pyelography the right kidney was seen to be enlarged and there was some hydronephrosis; the left kidney appeared normal. No abnormality was seen in the bladder on cystoscopy. Retrograde pyelography showed the presence of right hydro ureter and incomplete filling of the right renal pelvis.

A right nephrectomy was carried out on 25.2.55. There was gross papillomatosis of the renal pelvis. Histologically this proved to be a transitional cell papilloma; there was no infiltration of the wall of the pelvis but cytologically it was regarded as malignant.

He made a complete recovery for three years but died from metastates in April 1958. His death occurred after the list was "closed" for analysis of these cases and he is not included in the deaths.

This case is of particular interest as the initial tumour was in the renal pelvis and no tumours developed in the bladder.

It was largely on the strength of this case and Case No.127 that in 1957 the definition of the prescribed disease was enlarged to include tumours of the pelvis of the kidney or ureter.

This case is referred to on pages 158 and 171

CASE No.61 (F.H.)

Date of Birth:	27. 3.99.	Age at Entry:	27 years
Date of Entry:	1. 3.26.	Age at Onset:	54 years
Date of Leaving:	1. 8.42.	Exposure Period:	16 years
Date of Onset:	1.11.53.	Latent Period:	27 years

Working History:

1926 - 42 Worked in the azo colour factory on the manufacture of colours which involved the use of benzidine and alphanaphthylamine.

History of Onset:

In November 1953, eleven years after leaving the works, he had a sudden attack of haematuria.

Hospital: Manchester Royal Infirmary. Surgeon: Mr. P. Newell.

Diagnosis, Course and Treatment:

Nothing was known of this case at the factory until he reported it a year after onset in November 1954 and applied for ex-gratia payments.

A report from the surgeon stated that when first seen he had a papilliferous neoplasm about 5 cms in diameter in the right lateral wall of the bladder. Biopsy showed it to be a transitional cell carcinoma. He was treated by radon seed implantation.

There have been no recurrences. He continues at his usual work as a watchman at an engineering works where he has been employed since he left Clayton in 1942.

CASE No.62 (T.W.)

Date of Birth:	20.5.91.	Age at Entry:	31 years
Date of Entry:	2.2.22.	Age at Onset:	53 years
Date of Onset:	15.6.44.	Latent Period:	22 years

Working History:

1922 - 40 Worked on the manufacture of a variety of sulphonated naphthylamines.

1940 - 44 Worked on manufacture of betanaphthylamine and its distillation. Also distilled benzidine during this period.

History of Onset:

He had a sudden haematuria in October 1943.

Hospital: Salford Royal Hospital. Surgeon: Mr.J.B.Macalpine.
Christie Hospital. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

11.11.43.	Carcinoma	Partial cystectomy
21. 5.48.	Papilloma	P U diathermy
13. 4.49	"	" "
15. 7.49.	Carcinoma	Deep X-ray therapy

Progress:

The initial tumour in 1943 was a papillo-carcinoma on section. No biopsy was made of the recurrence in 1949. No recurrences have been seen since 1949. The most recent review was in March 1958.

He returned to work and continued in sheltered employment as a gate-man until he retired in 1956 at the age of 65.

He is still alive and well.

This case is of some interest in that two carcinomata in the bladder have been successfully treated at an interval of six years.

CASE No.63 (E.N.M.)

Date of Birth:	14.8.88.	Age at Entry:	28 years
Date of Entry:	- - 16.	Age at Onset:	68 years
Retired:	31.5.48.	Exposure Period:	32 years
Date of Onset:	16.1.57.	Latent Period:	41 years

Working History:

1916 - 48 Joined the Company as a graduate chemist in 1916. He set up and developed the benzidine plant and was the plant chemist and manager of the department until he became General Manager of the Company in 1946. He retired in 1948.

History of Onset:

Nine years after he retired he had a sudden attack of haematuria on 4.1.57. His urine was examined at the factory. It was impossible to distinguish any cells other than blood cells until a small piece of white tissue the size of a pinhead was picked out from the clots. On smearing and staining this it showed cells recognisable as having originated from a benign papilloma.

Hospital: Christie Hospital, P.P.H. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

16. 1.57.	Papilloma	P U diathermy Biopsy: "Papilloma; tumour of transitional type. Down-growth cannot be assessed."
22.10.58.	Papilloma	P U diathermy

Progress:

On review cystoscopy in August 1957 the bladder was clear. He has severe osteoarthritis of both hips but otherwise is in good health.

This is the longest latent period in the series (41 years).

CASE No.64 (J.B.)

Date of Birth:	13.12.11.	Age at Entry:	18 years
Date of Entry:	28. 7.30.	Age at Onset:	45 years
Date of Leaving:	1.11.40.	Exposure Period:	10 years
Date of Onset:	2. 8.57.	Latent Period:	27 years

Working History:

1930 - 40 Worked on the manufacture of betanaphthylamine.
1940 - 46 H.M.Forces.
1946 - 57 Worked at Imperial Chemical Industries Ltd. Was using benzidine 1946-49.

History of Onset:

I was informed by the Medical Officer at I.C.I.Ltd. that this man had developed a papilloma of the bladder.

Hospital: Ancoats Hospital. Surgeon: Mr. J. H. Tasker.

Diagnosis, Course and Treatment:

2.8.57. Papilloma P U diathermy

Progress:

This man still works at I.C.I.Ltd. and in order to obviate administrative difficulties he has been admitted to their ex-gratia payments scheme and is "followed up" by their medical officer who keeps me informed of his progress. There can, however, be little doubt that the significant causative exposure was the 10 years to betanaphthylamine at Clayton.

CASE No.65 (E.Y.)

Date of Birth:	24.6.04.	Age at Entry:	19 years
Date of Entry:	12.6.23.	Age at Onset:	53 years
Date of Leaving:	26.1.27.	Age at Death:	54 years
Date of Onset:	16.9.57.	Exposure Period:	3 years 6 months
Date of Death:	19.4.58.	Latent Period:	34 years

Working History:

1923 - 27 Worked on the manufacture of betanaphthylamine and at times handled alphanaphthylamine.

1927 - 57 After leaving the factory he did a number of jobs, none of which was in chemical work.

History of Onset:

He was admitted to hospital in September, 1957 with gross painless haematuria, thirty years after leaving the factory. I was informed by the house surgeon that he was an in-patient.

Hospital: Manchester Royal Infirmary. Surgeon: Mr. R. Newell.

Diagnosis and Treatment:

16.9.57.	"Papilloma" (section - transitional cell carcinoma.)	Open operation. Excision of tumour.

Progress:

A large papilloma was found on cystoscopic examination. The bladder was subsequently opened, the tumour was excised and its base diathermised. No radiation treatment was given. Section of the excised tumour showed it to be a transitional cell carcinoma. He made a good recovery.

Seven months later he had a perforated peptic ulcer and died of enteritis following an operation.

On post mortem examination the bladder and kidneys were found to be free of tumour.

As his death occurred after the case list was "closed" for the analysis he is not included among the deaths in this series.

His brother (Case No.86) who worked in the same department also developed a tumour of the bladder.

This case is referred to on pages 82 and 163

CASE No.66 (S.P.)

Date of Birth:	15.11.92.	Age at Entry:	32 years
Date of Entry:	6. 1.25.	Age at Onset:	63 years
Date of Onset:	23. 1.56.	Latent Period:	31 years

Working History:

1925 - 31 Worked on the manufacture of hydrochloric acid.
1932 - 54 Worked on the Duron sulphuric acid concentrators as a processman until 1951 and thereafter as foreman. From 1932-40 benzidine was ground in the vicinity of the Duron units.

History of Onset:

In July 1954 he complained of dysuria and frequency of micturition. The cells in the stained smear of the urinary deposit were Class I but there were large numbers of red and white blood cells present. He was investigated and on cystoscopy no tumour was seen in the bladder but there was basal cystitis. The symptoms cleared up after a course of urinary antiseptics.

There were no further symptoms or signs until November 1955 when a stained smear was Class III. In December and in January 1956 it was Class IV and there were present many clumps of cells recognizable as having originated from a benign papilloma (Fig 16). There were no symptoms or other signs of bladder trouble at this time and no blood cells were present in the smears.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

23.1.56.	Papilloma	Diathermy

Progress:

He returned to work after treatment and continued until he retired at the age of 65 in December 1957. He is in good health.

Regular cystoscopic examinations are made.

This case is referred to on pages 143 and 144

CASE No.67 (T.D.)

Date of Birth:	29. 5.00.	Age at Entry:	22 years
Date of Entry:	19.10.22.	Age at Onset:	44 years
Date of Onset:	14. 7.44.	Latent Period:	22 years

Working History:

1922 - 44 Worked as a processman in the manufacture of azo colours. From 1930 to 1942 he handled benzidine and ortho-tolidine daily. At other times he worked on various units and handled benzidine sporadically.

Previous Health:

1934 Perforated duodenal ulcer - operation
1936 Perforated duodenal ulcer - operation
1938 Recurrent duodenal ulcer - gastroenterostomy.

History of Onset:

Red blood cells were present in his urine on routine test at the factory in May 1944. He had had no previous symptoms. He was referred to Ancoats Hospital, Manchester, at the wish of his own doctor.

Hospital: Ancoats Hospital, Manchester. Surgeon: Mr. G. Hughes. later Mr.G.O.Jelly.

Diagnosis, Course and Treatment:

14.7.44.	Papilloma	Suprapubic cystotomy and excision of papilloma.
14.3.49.	? Papilloma	Suspicious area fulgurated per-urethram.

Progress:

Regular review cystoscopies have been continued since 1944. In 1952 he developed an incisional hernia in his suprapubic scar. This was repaired on 18th April, 1953.

In the early part of 1957 he began to go downhill and in June was again admitted to Ancoats Hospital for investigation. X-rays of his chest revealed tuberculous infiltration at the right apex. Five weeks later this was found to be spreading rapidly. He was admitted to Monsall Hospital, Manchester, on 20th July, 1957 and was an in-patient until April 1958 on antibiotic treatment. On discharge his general condition was very much better and his chest lesion had healed satisfactorily.

His general health has been poor for over 20 years. He was at work on and off after the onset of his papilloma in 1944. When he developed pulmonary tuberculosis in 1957 he was put on retirement pension to help him financially. He made a good recovery and in September 1958 he applied to be re-instated. An easy job was found for him and he is now working in the Locker Room on the issue of clothing.

He has remained free of bladder trouble since 1949 and was last cystoscoped on 7th October, 1958.

CASE No.68 (J.H.)

Date of Birth:	28.6.02.	Age at Entry:	30 years
Date of Entry:	- - 32.	Age at Onset:	56 years
Date of Leaving:	4.1.40.	Exposure Period:	8 years
Date of Onset:	- 1.58.	Latent Period:	26 years

Working History:

1932 - 40 Worked on the caustic melt autoclaves in the building in which betanaphthylamine was manufactured. Was also engaged in the sulphonation of alphanaphthylamine from time to time.

History of Onset:

In January 1958, 18 years after leaving the Company, he had a sudden attack of haematuria.

Hospital: Christie Hospital. Surgeon: Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

- 1.58.	Papillomata	P U diathermy

Progress:

Several small papillomata were treated by per-urethral diathermy. At review examination in June 1958 the bladder was clear of tumour.

Since leaving the Company in 1940 he has worked at another firm as a storekeeper and is still in the same job. His general health is good.

CASE No.69 (A.A.)

Date of Birth:	18.4.82.	Age at Entry:	42 years
Date of Entry:	28.6.24.	Age at Onset:	58 years
Date of Onset:	31.5.40.	Age at Death:	63 years
Date of Death:	- - 45.	Latent Period:	16 years

Working History:

1924 - 40 Worked on the manufacture of benzidine.

History of Onset:

No record.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine.

Diagnosis, Course and Treatment:

31.5.40	Papilloma	P U diathermy

Progress:

Regular follow-up cystoscopic examinations were made. The bladder remained clear of tumour until his death in 1945 from cerebral thrombosis.

CASE No.70 (T.B.)

Date of Birth:	21.11.65.	Age at Entry:	57 years
Date of Entry:	24.11.22.	Age at Onset:	?66 years
Date of Onset:	? - - 30.	Age at Death:	67 years
Date of Death:	10. 9.31.		

Working History:

1922 - 30 Worked on the manufacture of betanaphthylamine.

History:

This case came to light in the course of the A.B.C.M. field survey.

A coroner's certificate stated the cause of death as cancer of the bladder. It had been confirmed on post mortem examination.

CASE No.71 (L.B.)

Date of Birth:	6. 2.92.	Age at Entry:	30 years
Date of Entry:	19. 1.22.	Age at Onset:	42 years
Date of Onset:	11. 5.34.	Age at Death:	47 years
Date of Death:	- 10.39.	Latent Period:	12 years

Working History:

1922 - 37 Worked on the manufacture of betanaphthylamine and benzidine.

History:

He first attended Ancoats Hospital in 1934 and a copy of the hospital report to his doctor has been obtained. At cystoscopy there were said to be multiple small haemorrhages in the mucosa of the bladder and these were diathermized. No tumour formation was seen.

He left the Company's employment in August 1937.

In a hospital report from Salford Royal Hospital dated 26.8.39. it is stated that he was referred to the urologist there in 1937 on account of haematuria but he never attended. When seen in August 1939 there was a large carcinomatous growth at the base of the bladder. Total cystectomy was advised but he refused it. He also declined any other form of treatment such as implantation of radium or deep X-ray therapy.

He died from infiltrating carcinoma and spinal secondaries in October 1939.

This case is referred to on page 163

CASE No.72 (J.A.B.)

Date of Birth:	2.11.01.	Age at Entry:	26 years
Date of Entry:	25.10.27.	Age at Onset:	37 years
Date of Onset:	9. 3.39.	Age at Death:	42 years
Date of Death:	6.10.43.	Latent Period:	11 years

Working History:

1927 - 39 Worked on the manufacture of benzidine and tolidine.

History of Onset:

On routine urine test in March 1939 there were large numbers of red blood cells in the urinary deposit. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine.

Diagnosis, Course and Treatment:

9. 3.39.	Papilloma - bladder.	P U diathermy
13.11.42.	" "	" "
1. 2.43.	Papilloma - left renal pelvis and ureter	Left nephrectomy, 16.4.43. " ureterectomy, 7.5.43.
25. 9.43.	Papilloma - bladder	Fulguration failed.
6.10.43.	" "	Open operation. Diathermy. Reactionary haemorrhage. Died.

Progress:

He returned to work on his old job and continued at it, apart from the periods when he was under treatment, until his death in October 1943. Regular review examinations were made.

In April 1943 a mass was palpable in the left renal area. On excretion urography no shadow was seen on the left side. At operation on 16.4.43. a left nephrectomy was performed and the ureter was excised on 7.5.43. There was a papilliferous growth at the upper end of the ureter and nearly the whole of the kidney was replaced by neoplasm.

In September he had severe haematuria from a papilloma in the bladder which could not be controlled per urethrally. Suprapubic diathermy was carried out on October 6th. He had severe reactionary haemorrhage following the operation and died the same day.

This case is fully reported by Macalpine (1947) in his description of two cases of papilloma of the renal pelvis in dyeworkers.

CASE No.73 (J.W.B.)

Date of Birth:	26.12.76.	Age at Entry:	43 years
Date of Entry:	8. 9.19.	Age at Onset:	62 years
Date of Onset:	28.11.38.	Age at Death:	65 years
Date of Death:	28. 5.42.	Latent Period:	19 years

Working History:

1919 - 38 Worked on the distillation of betanaphthylamine, benzidine, tolidine and phenyl betanaphthylamine.

History of Onset:

There is no exact record of the initial symptoms or signs.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine.

Diagnosis, Course and Treatment:

1.12.38.	Papilloma	P U diathermy
1. 3.41.	"	Suprapubic diathermy (biopsy - "no malignancy")

Progress:

He returned to his old job and worked until his health began to fail in September 1941.

Regular cystoscopic reviews were continued, the last being in May 1941.

He died in May 1942 of an ascending urinary tract infection. On the post mortem examination there were numerous infiltrating papillomata in the bladder and advanced bilateral pyelonephritis.

CASE No.74 (J.R.B.)

Date of Birth:	- - 95.	Age at Entry:	30 years
Date of Entry:	10.12.25.	Age at Onset:	51 years
Date of Onset:	21. 1.46.	Age at Death:	51 years
Date of Death:	21. 4.46.	Latent Period:	20 years

Working History:

1925 - 31 Worked on the manufacture of benzidine.
1931 - 35 Worked on the manufacture of azo colours but, so far as can be traced, not on those for which carcinogens were used.
1935 - 46 Worked on the grinding and warehousing of finished colours.

History of Onset:

Started with a slight haematuria in January 1946. Routine tests for blood cells had previously been negative.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

21.1.46. Malignant papillomata. Transplantation of ureters.

Progress:

There were two malignant papillomata on the right side of the bladder and some papilloma formation round the bladder neck. The urologist's opinion was that no treatment other than cystectomy was practicable.

The first stage, ureterosigmoidostomy, was performed two weeks later. The patient gradually went downhill and died on 21.4.46. of ascending infection of the kidneys and uraemia three months after the operation.

This case is referred to on page 162

CASE No.75 (E.C.)

Date of Birth:	8. 1.06.	Age at Entry:	18 years
Date of Entry:	15. 5.24.	Age at Onset:	34 years
Date of Onset:	19. 7.40.	Age at Death:	34 years
Date of Death:	11.10.40.	Latent Period:	16 years

Working History:

1924 - 40 Worked on the manufacture of alphanaphthylamine sulphate from alphanaphthylamine.

History of Onset:

Large numbers of red blood cells were present in wet smears of urine on a routine test and on a repeat test.

Hospital: Salford Royal Hospital. Surgeon: Mr.J.B.Macalpine.

Diagnosis, Course and Treatment:

19.7.40.	Carcinoma (biopsy - malignant)	Open operation. Radon seed implant.

Progress:

In July 1940 there was a solid growth above the left ureteric orifice and he was listed for admission. At open operation in October radon seeds were inserted. On section the tumour was a carcinoma and was more anaplastic than transitional cell in type.

He developed a fulminating pneumonia and died two days after the operation.

CASE No.76 (G.F.)

Date of Birth:	14.12.96.	Age at Entry:	26 years
Date of Entry:	17.11.22.	Age at Onset:	42 years
Date of Onset:	1.11.38.	Age at Death:	47 years
Date of Death:	29. 5.44.	Latent Period:	16 years

Working History:

1922 - 44 Worked on the manufacture of benzidine.

History of Onset:

This man was referred to hospital in October 1938 "because of the presence of microscopic blood in the urine" according to the records. Routine urine tests had been introduced only a short time before and were done about every six months at that time.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine.

Diagnosis, Course and Treatment:

17.11.38.	Papilloma	P U diathermy
31. 1.44.	Carcinoma right kidney. ?Papilloma left renal pelvis.	

Progress:

On regular follow-up examinations no recurrent tumour was found until 31st January 1944.

On that day no neoplasm was seen in the bladder but excretion urography showed a non-functioning right kidney and a large left kidney the upper calyx of which was dilated and at its junction with the pelvis proper there was a filling defect suggestive of a tumour in this situation. In view of the non-functioning right kidney no steps were taken to explore the left kidney. It was decided to review him in six months.

He was re-admitted early on 23rd May 1944 with anuria and he died in uraemia six days later.

On post mortem examination there was a large papillocarcinoma of the right kidney which had invaded the duodenum and other neighbouring organs. In the pelvis of the left kidney there was a small sessile papilloma.

This case is reported at length by Macalpine (1947).

CASE No.77 (E.E.H.)

Date of Birth:	2.10.08.	Age at Entry:	17 years
Date of Entry:	8. 3.26.	Age at Onset:	32 years
Date of Onset:	25.11.40.	Age at Death:	33 years
Date of Death:	15.12.41.	Latent Period:	15 years

Working History:

1926 - 30 Worked on the manufacture of alphanaphthylamine sulphate from alphanaphthylamine.
1930 - 33 Worked on caustic soda powdering.

History of Onset:

There is no precise record of the history of onset in this case but there is a note in the man's case history dated 25.11.40. to the effect that the urine had shown no abnormalities on microscopical examination and that there were no physical signs on examination. He may have been referred to hospital by his own doctor because of symptoms of bladder trouble.

Hospital: Crumpsall Hospital, Manchester. later Christie Hospital. Surgeon: Mr. T. Moore. Dr. Ralston Paterson.

Diagnosis, Course and Treatment:

25.11.40.	Papillomata	P U diathermy
25. 1.41.	Papillomatosis	Deep X-ray therapy

Progress:

In November 1940 several small papillomata were seen and fulgurated. Biopsy of portions of these showed benign papilloma. He was listed for review in two months.

Two months later there were still one or two papillomata in the bladder and several "suspicious" areas. He was referred to the Christie Hospital for a course of deep X-ray therapy which was completed on February 17th.

He was re-admitted to Crumpsall Hospital early in December and died there on the 15th. On post mortem examination there were multiple papillomatosis of the bladder, a recto-vesical fistula and bilateral pyelonephrosis.

CASE No.79 (J.E.J.)

Date of Birth:	11.12.76.	Age at Entry:	47 years
Date of Entry:	27.11.23.	Age at Onset:	62 years
Date of Onset:	1. 8.38.	Age at Death:	69 years
Date of Death:	16. 7.45.	Latent Period:	15 years

Working History:

1923 - 34 Worked on the manufacture of benzidine.
1934 - 38 Did odd jobs in various parts of the factory.
1938 - 42 Worked as a locker room attendant.

History of Onset:

There is no record of the exact premonitory symptoms or signs. the earlier history is taken from hospital reports.

Hospital: Ancoats, Manchester. later Salford Royal Hospital.

Surgeon: Mr. J. B. Macalpine.

Diagnosis, Course and Treatment:

1. 8.38.	Papilloma	Suprapubic diathermy (Ancoats)
7.12.39.	"	P U diathermy (Salford)
14. 8.41.	"	" " "
11. 6.42.	Papillomata	" " "

Progress:

The recurrences in June 1942 are interesting. There were about 12 small papillomata scattered over the left lateral wall. They were completely cleared by diathermy and did not recur.

He left the Company on 3.9.42. but continued to attend hospital for review examinations. There were no recurrences up to the time of his death from pneumonia in 1945.

CASE No.80 (E.K.)

Date of Birth:	20.9.84.	Age at Entry:	37 years
Date of Entry:	20.2.22.	Age at Onset:	55 years
Date of Onset:	11.4.40.	Age at Death:	55 years
Date of Death:	23.8.40.	Latent Period:	18 years

Working History:

1922 - 29 Worked on the manufacture of sulphanilic acid in the same building as the distillation of betanaphthylamine, benzidine and tolidine was carried out.

1929 - 40 Worked on the manufacture of the sulphonic acids of a variety of intermediates.

History of Onset:

Microhaematuria was found at routine tests in March 1940 and in repeat tests.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine.
Christie Hospital, Dr. Ralston Paterson.
Manchester.

Diagnosis and Treatment:

11.4.40.	Carcinoma	Palliative X-ray

Progress:

At cystoscopy at Salford Royal Hospital on 11.4.40. there was a deeply ulcerated carcinoma in the vertex extending under the mucosa from the ulcer itself down the anterior wall. The area was about the size of half-a-crown.

He was transferred to the Christie Hospital for partial cystectomy and gold seed implantation but on admission on 27.6.40. glandular metastases were present. Palliative X-ray treatment was given. He died of carcinomatosis two months later.

CASE No.81 (J.W.L.)

Date of Birth:	29.10.95.	Age at Entry:	33 years
Date of Entry:	6. 7.28.	Age at Onset:	52 years
Date of Onset:	17. 1.48.	Age at Death:	52 years
Date of Death:	19. 3.48.	Latent Period:	20 years

Working History:

1928 - 48 Worked on the manufacture of benzidine.

History of Onset:

In January 1948 was referred to hospital for investigation because of the presence of red blood cells on routine and repeat urine examinations.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis:

17.1.48.	Papilloma	P U diathermy

Progress:

On cystoscopy on 17.1.48 there was a small pedunculated papilloma on the left lateral wall of the bladder. He was admitted two weeks later and it was fulgurated by per urethral diathermy.

Soon afterwards his health failed and he died of carcinoma of the liver on 19.3.48.

At the post mortem examination (which I attended) the liver was grossly enlarged and there were many nodules of carcinoma in it. The bladder, renal pelvis and ureters were clear of tumour and no primary cancer was found elsewhere. The cancer of the liver was thought to be a primary growth, but unfortunately a histological report could not be obtained as the pathologist lost the sections or did not prepare any.

CASE No.82 (F.M.)

Date of Birth:	17. 8.00.	Age at Entry:	29 years
Date of Entry:	25. 9.29.	Age at Onset:	41 years
Date of Leaving:	11.10.37.	Age at Death:	48 years
Date of Onset:	30. 1.42.	Exposure Period:	8 years
Date of Death:	6. 2.49.	Latent Period:	12 years

Working History:

1929 - 37 Worked on the manufacture of betanaphthylamine and the handling of alphanaphthylamine.

History:

He left the Company in 1937 and nothing more was heard of him until it was learned that he died in hospital in February 1949. The following history of the course of his illness is taken from the Christie Hospital records.

6. 2.42. A history of haematuria three years previously. Was well until three months ago.
Cystoscopy: area $\frac{3}{4}$" diameter over left ureter, sessile and raised, and very suggestive of malignancy.
Treatment: open operation and gold seed implant.

16. 3.45. Papilloma on left lateral wall diathermized.

26.11.47. New lesion on vault, definitely neoplastic.

3.12.47. Cystoscopy: tumour in vault confirmed, also an extra-vesical area of tumour on right lateral wall of pelvis.
Operation: bilateral transplantation of ureters.

10. 2.48. Deep X-ray therapy to right side of pelvis.

From this date the patient's general and local condition deteriorated and he died of infiltrating carcinoma on 6.2.49.

There is no record of a post mortem examination.

This case is referred to on page 162

CASE No.83 (J.M.)

Date of Birth:	3. 2.83.	Age at Entry:	42 years
Date of Entry:	19. 1.25.	Age at Onset:	57 years
Date of Onset:	19.11.40.	Age at Death:	61 years
Date of Death:	15. 1.44.	Latent Period:	16 years

Working History:

1925 - 26 Worked on the stoving of various intermediates.
1926 - 44 Worked on the manufacture of benzidine and tolidine.

History of Onset:

In October and November 1940 there were many red blood cells in the urine on routine tests. He had no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

19.11.40.	Papilloma	Diathermy

Progress:

He had regular follow-up cystoscopic examinations; the last was on 26.3.42. when the bladder was clear of tumour.

A few months later he developed a malignant stricture of the oesophagus from which he died on 15.1.44.

CASE No.84 (W.H.T.)

Date of Birth:	2.10.90.	Age at Entry:	32 years
Date of Entry:	27.11.22.	Age at Onset:	57 years
Date of Onset:	21.10.47.	Age at Death:	57 years
Date of Death:	21.10.47.	Latent Period:	25 years

Working History:

1922 - 47 Worked on the manufacture of benzidine sulphur colours, diphenylamine and primuline. For the last 13 years he was foreman of this department.

History:

In August 1947 he was admitted to Stockport Royal Infirmary with a diagnosis of Paget's disease of bone. His condition deteriorated rapidly and he died on 21.10.47.

On post mortem examination there was a large cancerous mass nearly filling the bladder. This had not been diagnosed during life.

The cause of death was certified as carcinoma of the bladder.

This case is referred to on page 163

CASE No.85 (A.S.)

Date of Birth:	4.11.97.	Age at Entry:	23 years
Date of Entry:	17. 3.21.	Age at Onset:	40 years
Date of Onset:	11.10.37.	Age at Death:	49 years
Date of Death:	18.12.46.	Latent Period:	16 years

Working History:

1921 - 46 Worked on the manufacture of benzidine.

History of Onset:

Was referred to hospital for investigation and cystoscopy in September 1936 because of the presence of red blood cells in the urine. The tests were introduced in the factory in that year and the microhaematuria was found on the first test of this man's urine.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine
Christie Hospital. later Mr.D.S.Poole-Wilson

Diagnosis, Course and Treatment:

11.10.37.	Carcinoma	Fulguration. Deep X-ray
29.10.38.	Papilloma	Diathermy (therapy.
7. 2.39.	"	"
15.11.40.	"	"
15.12.41.	"	"
20. 8.42.	"	"
19. 3.43.	"	"
1.12.46.	Carcinoma - bladder.	
	" - left kidney.	

Progress:

Regular follow-up examinations were made at intervals of three to twelve months. No recurrences were seen on cystoscopy between March 1943 and April 1946. He returned to his usual work after treatment was completed in 1937 and except for absences due to recurrences and reviews he continued at work until 11.11.46. On that date he had sudden haematuria and was admitted to hospital.

He died on 16.12.46. The post mortem findings were (1) old telangiectatic areas in the bladder due to X-ray treatment (2) one small area of malignant growth in the bladder (3) a large carcinomatous mass in the right kidney possibly primary (4) secondary carcinoma left kidney (5) haemorrhages into both supra renals.

CASE No.86 (M.Y.)

Date of Birth:	1. 5.06.	Age at Entry:	16 years
Date of Entry:	12.11.22.	Age at Onset:	41 years
Date of Onset:	24.11.47.	Age at Death:	41 years
Date of Death:	13.12.47.	Latent Period:	25 years

Working History:

1922 - 47 Worked on the manufacture of betanaphthylamine.

History of Onset:

No exact record. He was admitted to Ancoats Hospital on 24th November 1947 with a provisional diagnosis of prostatic abscess, having been referred to out patients by his own doctor.

Hospital: Ancoats Hospital. Surgeon: Mr. G. O. Jelly.

Diagnosis:

24.11.47. Carcinoma of the bladder. Inoperable.

Progress:

After admission the clinical signs were indicative of a breaking down carcinoma of the prostate or base of the bladder.

He died in uraemia on 13.12.47.

At post mortem examination - there was a large infiltrating papillary carcinoma of the bladder (later confirmed on microscopy). There was pyonephrosis of the left kidney and the right kidney was necrotic.

He is a brother of Case No.65.

This case is referred to on page 82

CASE No.87 (J.J.W.)

Date of Birth:	6.3.00.	Age at Entry:	30 years
Date of Entry:	7.3.30.	Age at Onset:	44 years
Date of Onset:	9.6.44.	Age at Death:	46 years
Date of Death:	7.4.46.	Latent Period:	14 years

Working History:

1926 - 39 Worked on the manufacture of a variety of naphthylamine sulphonic acids.
1939 - 44 Worked on the distillation of benzidine, tolidine, betanaphthylamine and other products.

History of Onset:

In May 1944 many red blood cells were seen in the urinary deposit on routine test and on a repeat test.

Hospital: Christie Hospital. Surgeon: Mr. J. M. Macalpine.

Diagnosis and Treatment:

9.6.44.	Carcinoma (section - epidermal carcinoma)	Total cystectomy

Progress:

The tumour was a carcinoma originating at the vesical outlet and was sessile. It extended back along the trigone for some distance towards the left ureteric orifice.

In September 1944 a total cystectomy with transplantation of the ureters into the pelvic colon was done.

He survived nearly two years but control was poor and he was seldom able to go out. He died in uraemia in April 1946.

This case is referred to on page 162

CASE No.88 (A.W.)

Date of Birth:	23. 6.89.	Age at Entry:	35 years
Date of Entry:	1.10.24.	Age at Onset:	56 years
Date of Onset:	16. 3.45.	Age at Death:	62 years
Date of Death:	26.12.51.	Latent Period:	21 years

Working History:

1924 - 25	Worked on the manufacture of betanaphthylamine disulphonic acids. Exposure to betanaphthylamine would be heavy during this period.
1925 - 29	Employed in a "non-carcinogic plant" breaking and grinding solid caustic soda.
1929 - 40	Manufacture of naphthionate of soda - small quantities of alphanaphthylamine are present as an impurity in the crude naphthionic acid.
1940 - 45	Manufacture of H.Acid.

History of Onset:

On 16th February 1945 began passing blood in his urine. This persisted until he had treatment. Routine urine examination for blood cells had been negative.

Hospital: Salford Royal Hospital: Surgeon: Mr.J.B.Macalpine.
Christie Hospital, later Mr.D.S.Poole-Wilson.
Manchester.

Diagnosis, Course and Treatment:

16.3.45.	Papilloma	P U diathermy
20.5.46.	Carcinoma	Deep X-ray therapy

Progress:

There was a prolonged radiation reaction and he did not work after 1946. An ulcerated area persisted for three years; a biopsy specimen of this area was taken in May 1948 but no malignant changes were seen in it.

His last cystoscopy was on 14.11.51. No recurrent tumour was seen but a plaque of debris was diathermized although it was not regarded as being tumour formation. On discharge from hospital he was in good general condition.

He took ill at home on Christmas Day and died on the 26th December 1951. The cause of death was certified by his own doctor as carcinoma of the bladder. A post mortem examination was not made.

CASE No.89 (A.M.)

Date of Birth:	5. 1.09.	Age at Entry:	21 years
Date of Entry:	13.12.29.	Age at Onset:	25 years
Date of Onset:	- 4.34.	Age at Death:	42 years
Date of Death:	14. 6.51.	Latent Period:	4 years

Working History:

1927 - 30 Worked on the stoving of betanaphthylamine.
1930 - 34 Worked on the manufacture of alphanaphthylamine sulphate.

History:

He developed a papilloma of the bladder in April 1934 and was treated at Ancoats Hospital by electrocautery. He then left the Company and obtained an indoor job as a clerk in the Post Office, a situation he held until his death.

In late 1950 he had haematuria and was admitted to Crumpsall Hospital, Manchester, under the care of Mr. D. S. Poole-Wilson. He was found to have small multiple papillomata of the bladder and these were fulgurated. There was also a large tumour of the left kidney. This was removed at operation on 28.12.50. On section it proved to be a transitional cell epithelioma, doubtless derived from the renal pelvis.

He went steadily downhill and died at home on 14th June 1951. There was no post mortem examination.

This case is of particular interest because of the early age at onset. He is the youngest man in the series to have developed a tumour of the bladder.

CASE No.90 (R.W.)

Date of Birth:	15. 2.83.	Age at Entry:	35 years
Date of Entry:	6. 3.18.	Age at Onset:	? 54 years
Date of Onset:	? - - 37.	Age at Death:	54 years
Date of Death:	12.12.37.	Latent Period:	19 years

Working History:

1918 - 37 Worked on the manufacture of betanaphthylamine and various naphthylamine sulphonic acids.

History:

This case came to light during the A.B.C.M. survey when his death certificate with the cause of death as "cancer of the bladder" was noted.

No inquest was held. It has not been possible to trace any further information about this case from hospitals, relatives or workmates.

CASE No.91 (E.W.)

Date of Birth:	28.4.00.	Age at Entry:	24 years
Date of Entry:	8.4.24.	Age at Onset:	37 years
Date of Leaving:	16.4.25.	Age at Death:	42 years
Date of Onset:	- - 37.	Exposure Period:	1 year
Date of Death:	30.6.42.	Latent Period:	13 years

Working History:

1924 - 25 (Clayton records)	Worked on the manufacture of H.Acid - would involve exposure to alphanaphthylamine and possibly betanaphthylamine.
1925 (Inquest Report)	Worked three months at Levensteins (later I.C.I.Ltd.) as a labourer.

History:

This case came to light after he died when enquiries were made by the Coroner's Officer. The history is gained from the inquest report. His widow said he had worked at Levensteins before the First World War and for three months after he was demobilised.

After leaving Clayton in 1925 he had worked as a boot repairer until his death in 1942.

He first attended hospital in 1937 and attended several times after that. On the last occasion he was in hospital for 10 days before he died.

The pathologist who made the post mortem examination gave evidence that there was a malignant tumour infiltrating the bladder wall and advanced pyelonephrosis of both kidneys with abscess formation.

A verdict of death from natural causes was returned by the jury!

CASE No.93 (J.F.)

Date of Birth:	10.3.84.	Age at Entry:	36 years
Date of Entry:	30.8.20.	Age at Onset:	47 years
Date of Onset:	- 5.31.	Age at Death:	48 years
Date of Death:	4.2.32.	Latent Period:	11 years

Working History:

1920 - 31 Worked on the manufacture of betanaphthylamine.

History:

This is one of the earliest known cases to arise in the factory. It came to light when a summary of the inquest proceedings was found in an old file in the Labour Department. The history is gathered from the report of the inquest held 10.2.32.

In May 1931 he complained of gastric trouble, sickness and vomiting. He became worse in July and was admitted to Crumpsall Hospital, Manchester. He died on 4.2.32.

At post mortem examination there was extensive carcinoma of the bladder. The other organs were healthy.

An open verdict was returned.

CASE No.95 (S.H.)

Date of Birth:	10.1.99.	Age at Entry:	28 years
Date of Entry:	25.7.27.	Age at Onset:	39 years
Date of Onset:	- - 38.	Age at Death:	39 years
Date of Death:	2.7.38.	Latent Period:	11 years

Working History:

1927 - 38 Worked on the manufacture of benzidine.

History:

This case came to light when the death certificate was noted in the course of the A.B.C.M. field survey.

The death was certified as cancer of the bladder.

No details of the medical history can be traced.

CASE No.96 (A.F.)

Date of Birth:	5.10.99.	Age at Entry:	32 years
Date of Entry:	22. 4.32.	Age at Onset:	42 years
Date of Onset:	22. 4.43.	Age at Death:	52 years
Date of Death:	4. 6.52.	Latent Period:	11 years

Working History:

1932 - 35 Worked on the manufacture of chlor-toluidine sulphonic acid in the building where benzidine was manufactured.

1935 - 43 Worked on the manufacture of benzidine.

History of Onset:

In April 1943 he had slight haematuria of sudden onset. Routine microscopy of urine at factory had revealed no R.B.Cs. until then.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

22.4.43.	Papilloma	P U diathermy
17.5.47.	"	" "
23.2.51.	"	" "
8.5.51.	Carcinoma (biopsy - transitional cell carcinoma)	Deep X-ray therapy
4.5.52.	Recurrence	1st stage total cystectomy (uretero-sigmoidostomy)

Progress:

This man resumed work as a processman after treatment for his initial papilloma in 1943 but did not work on benzidine. He continued at work until 1951. During this period regular cystoscopic review was carried out at intervals of three to six months.

In February 1951 an area of recurrent papilloma near the internal meatus was treated by diathermy. Three months later in this area there was a solid tumour the surface of which was necrotic. Biopsy revealed a transitional cell carcinoma. The response to deep X-ray therapy was unsuccessful and a two stage cystectomy was planned.

Transplantation of the ureters into the sigmoid colon was performed in May 1955. Following this operation he deteriorated steadily and died in uraemia on 4.6.52.

This case is referred to on page 162

CASE No.97 (P.F.)

Date of Birth:	- - 80.	Age at Entry:	39 years
Date of Entry:	- - 19. *	Age at Onset:	68 years
Date of Retirement:	4.7.47.	Age at Death:	68 years
Date of Death:	- - 48.	Latent Period:	28 years

Working History:

* This man worked at Clayton on and off from 1900 but there are no records of this early employment. For the analysis of the tumour cases his starting date has been taken as 1919, the year in which he was first exposed to betanaphthylamine.

* 1919 - 22 Worked on the sulphonation of betanaphthylamine.
1922 - 26 Left Company.
1926 - 47 Worked on the manufacture of various intermediates and had intermittent contact with betanaphthylamine.

History:

He retired in 1947 at the age of 67. Nothing further was heard of him, except that he had died in 1948, until, in the course of the A.B.C.M. survey his death certificate with cancer of the bladder as the cause of death came to light.

CASE No.98 (T.E.)

Date of Birth:	- - 76.	Age at Entry:	36 years
Date of Entry:	- - 20. *	Age at Onset:	66 years
Date of Leaving:	15.3.40.	Latent Period:	22 years
Date of Onset:	- - 42.		
Date of Death:	6.8.42.		

Working History:

* Although this man started work at Clayton in 1912, the year 1920 is taken as the date of entry for the purpose of the analysis of the tumour cases, i.e. the year in which the manufacture of betanaphthylamine started.

* 1920 - 40 Worked as a pipe fitter in the department in which betanaphthylamine was manufactured. He maintained the plant in which it was made.

History:

He retired in 1940 and nothing further was heard of him until, in the course of the A.B.C.M. field survey, his death certificate was noted to have as the cause of death - "(a) carcinomatosis (b) carcinoma of the bladder."

CASE No.99 (A.G.H.)

Date of Birth:	25.3.01.	Age at Entry:	23 years
Date of Entry:	1.3.24.	Age at Onset:	49 years
Date of Leaving:	1.2.46.	Age at Death:	49 years
Date of Onset:	- 7.50.	Exposure Period:	22 years
Date of Death:	3.9.50.	Latent Period:	26 years

Working History:

1924 - 25 Worked on the stoving of betanaphthylamine.
1925 - 46 Weighman handling benzidine and alphanaphthylamine.

History:

This case came to light through the A.B.C.M. survey when the death certificate mentioning carcinoma of the bladder was noted. His occupation was given on the certificate as - "formerly a fish fryer."

Enquiries revealed that he had been ill only about six weeks before he died.

There was no post mortem examination.

CASE No.100 (C.B.)

Date of Birth:	26.6.78.	Age at Entry:	45 years
Date of Entry:	10.8.23.	Age at Onset:	69 years
Date of Leaving:	25.3.44.	Age at Death:	69 years
Date of Onset:	- - 47.	Exposure Period:	21 years
Date of Death:	- - 47.	Latent Period:	24 years

Working History:

1923 - 44 Worked on the manufacture of azo colours some of which entailed the use of benzidine.

History:

This case was reported to me on 15.5.51. by the Nuffield Department of Occupational Health, University of Manchester, to whom enquiries had been made by the widow. The man left the Company in 1944. He was admitted to Manchester Royal Infirmary three years later and was found to be suffering from cancer of the bladder from which he died soon afterwards. No post mortem examination was made.

CASE No.102 (H.N.)

Date of Birth:	25. 5.96.	Age at Entry:	25 years
Date of Entry:	7.11.21.	Age at Onset:	56 years
Date of Onset:	- 3.52.	Age at Death:	56 years
Date of Death:	28. 6.52.	Latent Period:	30 years

Working History:

1921 - 24	Worked on the manufacture of magenta.
1924 - 26	Left Company.
1926 - 29	Worked on the manufacture of aniline.
1929 - 52	Worked on the grinding and milling of a large variety of finished colours and some intermediates e.g. paranitraniline and 5-chlor-2-toluidine.

History:

This man was admitted to Ashton Infirmary in March 1952 with a provisional diagnosis of enlarged prostate. Routine urine tests had been negative.

At operation an inoperable carcinoma of the bladder was found. He died on 28th June 1952.

An inquest was held. The pathologist's report was that he died of a cancer of the bladder of a type similar to that found in people who work in aniline dyes, with secondaries in the abdomen and chest. I had not been informed that a post mortem examination was to be made and was not present at it.

CASE No.103 (T.D.)

Date of Birth:	11.11.95.	Age at Entry:	24 years
Date of Entry:	10. 1.20.	Age at Onset:	51 years
Date of Onset:	11. 4.47.	Age at Death:	57 years
Date of Death:	8. 9.52.	Latent Period:	27 years

Working History:

Sept 1920 - Jan 1921 Employed in the colour department on the stoving of betanaphthylamine and other intermediates and finished colours.

1921 - 47 Worked as a boiler fireman exclusively.

History of Onset:

Referred to hospital by his own doctor because of symptoms of bladder trouble.

Hospital: Manchester Royal Infirmary. Surgeon: Prof. A. M. Boyd.

Diagnosis, Course and Treatment:

11.4.47.	Papilloma	Suprapubic cystotomy and excision of papilloma

Progress:

Regular follow-up examinations were carried out and no recurrences were seen. The last examination was in April 1951.

He continued at work until he developed a primary carcinoma of the bronchus in 1952. It was inoperable when found. He died of secondaries in the brain on 8.9.52. No post mortem examination was made.

CASE No.104 (G.H.)

Date of Birth:	5.10.86.	Age at Entry:	41 years
Date of Entry:	5. 9.27.	Age at Onset:	63 years
Date of Onset:	21. 9.49.	Age at Death:	66 years
Date of Death:	25.11.52.	Latent Period:	22 years

Working History:

1927 - 29 Worked on the manufacture of melantherine BH and JH.
1929 - 49 Worked on the manufacture of 5 chlor-2 toluidine in a plant where benzidine was used extensively for azo colour manufacture.

History of Onset:

In April 1949 he had slight transient haematuria which was attributed to chlortoluidine cystitis. He was moved to other work where he did not come in contact with this amine but in August he had another attack of haematuria and was referred to hospital.

Hospital: Salford Royal Hospital. **Surgeon:** Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

21.9.49.	Papilloma (biopsy - malignant papilloma)	P U diathermy
19.4.51.	Papilloma	" "

Progress:

He returned to sheltered work as a messenger. Regular review examinations were made and no recurrences were seen in the bladder after 1951.

In late 1952 he developed carcinoma of the head of the pancreas which was considered to be a primary growth. He died on November 25th. No post mortem examination was made.

CASE No.105 (A.H.)

Date of Birth:	25. 3.86.	Age at Entry:	32 years
Date of Entry:	18.10.18. (1915)*	Age at Onset:	64 years
Date of Onset:	7. 3.50.	Age at Death:	67 years
Date of Death:	16. 4.53.	Latent Period:	32 years

Working History:

* He started work at Clayton in 1915, but for the analysis of the cases his date of entry is taken as 1918, the year in which benzidine manufacture was started.

1918 - 50 Worked on manufacture of benzidine and tolidine.

History of Onset:

In February 1950 red blood cells were present in fairly large quantities in three successive urine tests; the first was on routine examination.

Hospital: Christie Hospital. Surgeon: Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

7.3.50.	Carcinoma	Open operation and gold seed implant

Progress:

At operation on 5.4.50. there was a nodular growth above the right ureteric orifice about 3 cms in diameter which appeared to be indurated and was drawing up the adjacent bladder mucosa. Below this and behind the interureteric bar there was a small diverticulum inside which was a papilloma. The diverticulum was excised. The nodular tumour was diathermized and implanted with radon seeds.

The bladder was clear of visible recurrence when he was reviewed in November 1951.

He made a poor recovery from his initial operation and did not return to work. In October 1952 there was recurrent infiltrating growth in the left pelvic wall. He died in April 1953 of secondary carcinomatosis and extensive local growth in the pelvic cavity, confirmed on post mortem examination.

CASE No.106 (J.O.)

Date of Birth:	3. 5.04.	Age at Entry:	27 years
Date of Entry:	- - 31.	Age at Onset:	47 years
Date of Leaving:	- - 40.	Age at Death:	49 years
Date of Onset:	1. 2.51.	Exposure Period:	9 years
Date of Death:	13.10.53.	Latent Period:	20 years

Working History:

1931 - 40 Worked on manufacture of benzidine, tolidine and dianisidine - chiefly on drying the products in stoves.

History of Onset:

In January 1951, eleven years after leaving the Company, he was referred by his own doctor to the Christie Hospital because of haematuria and dysuria.

Hospital: Christie Hospital. Surgeon: Mr. D. S. Poole-Wilson.

Diagnosis, Course and Treatment:

1.2.51. Carcinoma Gold seed implant

Progress:

There was a flat papillomatous tumour above and behind the interureteric bar. This was treated by open operation diathermy and gold seed implant. On biopsy the tumour was seen to be a transitional cell carcinoma.

In the following October the mucosa at the site of the implant was still ulcerated but in February and August 1952 and in March 1953 the bladder was healed and no tumour was seen.

In June 1953 he developed venous obstruction with oedema of the right leg and a pelvic mass was palpable per rectum.

He died of infiltrating carcinoma of the pelvic structures on the 13th October 1953.

CASE No.107 (J.M.)

Date of Birth:	4. 9.94.	Age at Entry:	29 years
Date of Entry:	26. 9.23.	Age at Onset:	47 years
Date of Onset:	21. 8.41.	Age at Death:	59 years
Date of Death:	15.12.53.	Latent Period:	18 years

Working History:

1923 - 26 Worked on the manufacture of benzidine and tolidine.
1926 - 41 Worked on the manufacture of various other intermediates, in the shed in which benzidine was made.

History of Onset:

In 1942 there was microhaematuria in successive routine urine tests.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine.

Diagnosis, Course and Treatment:

21.8.42. Papilloma P U diathermy

Progress:

A "suspicious" mossy area was diathermized in 1949 but no other abnormality was seen in the bladder on regular review examinations.

He continued at his usual work until he retired because of chronic bronchitis at the beginning of 1952.

He died of myocarditis and bronchitis in hospital on 15th December 1953.

CASE No.108 (J.H.)

Date of Birth:	31.3.00.	Age at Entry:	31 years
Date of Entry:	9.4.31.	Age at Onset:	49 years
Date of Onset:	20.1.49.	Age at Death:	53 years
Date of Death:	11.1.54.	Latent Period:	18 years

Working History:

1931 - 39 Worked in the shed in which benzidine was made as general labourer with occasional spells on vacuum stove (dianisidine, para-amido-phenol base).
1939 - 47 Worked on ice distribution and on vacuum stove.
1947 - 49 Worked on the manufacture of nitro diazo, paranitro-orthotoluidine, cresapol, ortho-nitrotoluol sulphonic acid, nitrobenzene sulphonic acid, nitrochlortoluene sulphonic acid, chlornitraniline, meta-nitro-paratoluidine, ortho-nitrophenol sulphonic acid and dinitronaphthalene.

History of Onset:

Referred to hospital for investigation because of symptoms of bladder trouble. Routine urine tests for blood cells had previously been negative.

Hospital: Salford Royal Hospital. later Christie Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

20.1.49.	Carcinoma	Open operation and G.S.I.
3.4.51.	Keloid in scar;	Excised.
	3 stones in bladder.	Removed.
26.5.53.	Keloid in scar.	Excised and irradiated.

Progress:

On section the tumour proved to be an epidermal carcinoma.

He returned to light work in June 1949 as a joiner's labourer. He had regular periodic cystoscopic examinations. The last one was on 26.5.53. when the bladder was clear.

In early November 1953 he complained of severe headache and of stumbling to the left side when walking. He died at home in the following January of secondaries in the brain and lungs. No post mortem examination was made.

CASE No.109 (C.W.)

Date of Birth:	25. 4.00.	Age at Entry:	22 years
Date of Entry:	9.12.21.	Age at Onset:	38 years
Date of Onset:	4. 8.38.	Age at Death:	54 years
Date of Death:	17. 8.54.	Latent Period:	17 years

Working History:

1921 - 38 Worked on the manufacture of alphanaphthol and various naphthylamine sulphonic acids using alpha- and betanaphthylamine. Was chargehand from 1928-38.

History of Onset:

No record.

Hospital: Manchester Northern. later Salford Royal Hospital.

Surgeon: Mr. K. H. Watkins. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

5.3.38.	Papillomata	P U diathermy (Northern Hospital)
12.1.39.	Papilloma	" " (Transferred to Salford Royal Hospital)
25.5.41.	Carcinoma	Open operation. Gold seed implant.
15.1.46.	Papilloma	P U diathermy
8.7.46.	"	" "
14.9.46.	"	" "
9.9.50.	"	" "
13.1.51.	"Suspicious" area	" "
- 2.53.	Carcinoma	- - - -

Progress:

The original tumours, which were multiple, were fulgurated in two separate sessions at the Northern Hospital.

In May 1941 a nodular sessile tumour was seen on the posterior wall of the bladder which, on biopsy, proved to be malignant. This was treated by open operation and gold seed implant.

He continued at work. After 1938 his duties were mainly supervisory and in 1943 he was promoted to foreman.

He had several recurrences which were successfully fulgurated but in January 1952 a mass of low growing nodular carcinoma was seen on the anterior wall of the bladder and there was a nodular area on the vault. Between these two areas the appearance of the mucosa was suggestive of infiltrating carcinoma.

He was advised to have a total cystectomy but calmly declined the operation as he had seen two of his mates who had had it. He was well aware of the consequences of his considered refusal.

He survived an unexpectedly long time before he died of infiltrating carcinoma on 17th August 1954. He never appeared to regret his decision.

This case is referred to on page 163

CASE No.110 (A.W.)

Date of Birth:	29. 3.96.	Age at Entry:	28 years
Date of Entry:	17. 3.24.	Age at Onset:	40 years
Date of Leaving:	24.10.34.	Age at Death:	47 years
Date of Onset:	- 8.36.	Exposure Period:	10 years
Date of Death:	30.12.43.	Latent Period:	12 years

Working History:

1924 - 34 Worked on the manufacture of betanaphthylamine - chiefly engaged on drying it in stoves.

Previously, for a year, 1920-21, and for 2½ months in 1922 he had worked in another chemical factory (I.C.I.Ltd.) part of the time on the boilers and part on the manufacture of aminoazo-toluene.

History:

Nothing was heard of this man after he left in 1934 until 1955 when his widow applied to the Company for a pension because of his death from cancer of the bladder 12 years previously.

It was confirmed that he had had a partial cystectomy for carcinoma of the bladder at Ancoats Hospital in August 1936 and that the cause of his death in December 1943 had been certified as "cancer of the bladder".

The short periods of employment at I.C.I. were considered to be insignificant and an ex gratia pension was granted.

CASE No.111 (B.P.)

Date of Birth:	25.12.96.	Age at Entry:	24 years
Date of Entry:	1. 9.20.	Age at Onset:	56 years
Date of Onset:	23. 6.52.	Age at Death:	59 years
Date of Death:	3. 9.55.	Latent Period:	32 years

Working History:

1920 - 50 Worked on the manufacture of betanaphthylamine. In the earlier years one of his jobs was to break up betanaphthylamine in open trays by hand.
1950 - 52 Worked on other products in the same building.

History of Onset:

In April, May and June 1952 stained smears were Class III and a moderate number of red blood cells were present in routine urine tests.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

21.7.52. Papilloma P U diathermy

Progress:

No recurrent tumours were seen in the bladder on regular review examinations.

The last cystoscopy was on 25.4.55. four months before his death, when the bladder was clear. His general condition gradually deteriorated after this and he died at home on 3.9.55. The signs and symptoms were typical of cerebral arterial degeneration. His own doctor certified the cause of death as "cancer of the bladder" and this was not disputed. No post mortem examination was made.

CASE No.112 (W.H.)

Date of Birth:	23.10.98.	Age at Entry:	41 years
Date of Entry:	5. 2.40.	Age at Onset:	50 years
Date of Onset:	3.11.48.	Age at Death:	57 years
Date of Death:	14.11.55.	Latent Period:	9 years

Working History:

1940 - 42 Worked on the manufacture of nitro diazo, paranitrochlor benzol sulphonic acid, and similar intermediates, which were made in the benzidine shed.

1942 - 48 Worked on the manufacture of benzidine.

History of Onset:

Routine urine tests showed small numbers of red blood cells persisting for several months from August 1948.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

13.12.48.	Papilloma	P U diathermy
24. 2.49.	"	" "
26. 7.49.	"	" "
22. 9.52.	"	" "
8.12.52.	"	" "
25. 8.55.	Carcinoma of right kidney with metastases.	Inoperable

Progress:

He returned to his usual plant work for two years and was then transferred to work as a fitter's mate.

Cystoscopic examinations were made regularly. After four recurrences had been treated the bladder was clear for nearly three years after 1952.

In March 1955 he had slight haematuria. On cystoscopy there was considerable prostatic hypertrophy which was thought to account for the haematuria. On 5th August 1955 he was again cystoscoped and the bladder was clear. Barely three weeks later a fixed mass was palpable in the right loin and this was undoubtedly a carcinoma of the kidney. An attempt was made to remove the kidney in October but it was inoperable. A piece removed for section showed the presence of "atypical carcinoma".

He died a few days later on the 14th November 1955.

CASE No.113 (W.F.)

Date of Birth:	27.9.02.	Age at Entry:	22 years
Date of Entry:	17.9.24.	Age at Onset:	38 years
Date of Onset:	27.2.41.	Age at Death:	53 years
Date of Death:	20.9.55.	Latent Period:	16 years

Working History:

1924 - 27 Worked as a still-man in the diamine factory.
1927 - 36 Worked on the distillation of betanaphthylamine, benzidine, tolidine, phenylbetanaphthylamine and diphenylamine.
1936 - 41 Weighman in betanaphthylamine department.

History of Onset:

He had haematuria of sudden onset in February 1941.

Hospital: Salford Royal Hospital. Surgeon: Mr. J. B. Macalpine.

Diagnosis, Course and Treatment:

27.2.41.	Carcinoma	Partial cystectomy

Progress:

He returned to his work as a weighman until 1947 when he was transferred to the Works Police.

Regular review examinations were made.

This case is of particular interest in that he had no recurrences after his initial treatment. He died suddenly of coronary thrombosis 14 years later.

CASE No.114 (F.S.)

Date of Birth:	1883.	Age at Entry:	35 years
Date of Entry:	1918.	Age at Onset:	48 years
Date of Onset:	1931.	Age at Death:	48 years
Date of Death:	1931.	Latent Period:	19 years

Working History:

1918 - 31 Worked on the manufacture of alphanaphthol from alphanaphthylamine and on the manufacture of betanaphthylamine. Also distilled benzidine and tolidine.

History of Onset:

It was stated in evidence at the inquest on this man that he complained of difficulty in micturition for 6 months before his death.

Hospital: Crumpsall Hospital.

Diagnosis, Course and Treatment:

24.6.31. Inquest report. Carcinoma of the bladder.

History:

This death occurred several years before it was generally recognised in Britain that such tumours of the bladder were occupational. Nevertheless an inquest was held and the following history is culled from the notes which were taken at the time.

Inquest 24.6.31. He had complained of passing blood early in the year and was admitted to Crumpsall Hospital, Manchester, in May 1931.

On post mortem examination there was a tumour in the bladder which was breaking down and there was inflammation of the kidneys. The pathologist stated that there was nothing to differentiate between what was found and a growth produced by natural causes.

An open verdict was returned.

CASE No.115 (J.E.D.)

Date of Birth:	16. 1.01.	Age at Entry:	25 years
Date of Entry:	12. 9.26.	Age at Onset:	39 years
Date of Onset:	20. 8.39.	Age at Death:	54 years
Date of Death:	4.12.55.	Latent Period:	13 years

Working History:

1926 - 39 Worked on the manufacture of benzidine.

History of Onset:

No record.

Hospital: Salford Royal Hospital. later Christie Hospital.

Surgeon: Mr. J. B. Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

25. 8.39.	Papilloma	P U diathermy
14.11.47.	Carcinoma	Deep X-ray
10. 8.55.	Metastasis Scapula	Deep X-ray

Progress:

Regular review examinations were made until 1943 when he was discharged from hospital as he had had no recurrences. He continued at work until 1947.

In September 1947 there was marked microhaematuria on successive routine urine tests at the factory and he was referred back to hospital. On cystoscopy a carcinoma was seen on the right side of the bladder and he was transferred to Christie Hospital for radiation therapy.

He was admitted there in December 1947 and on re-examination several foci of neoplasm were seen in the bladder wall. He was treated by a course of deep X-ray therapy. In July 1948 the bladder was seen to be clear of tumour and it remained so on regular follow-up examinations until the last one in October 1954 by which time they were being done annually.

In August 1955 a lump appeared over the right scapula. This proved on biopsy to be secondary carcinoma. It was treated by deep X-ray. Other secondaries appeared in the ribs soon afterwards and he died at home on 4th December 1955. No post mortem examination was made.

CASE No.116 (J.C.)

Date of Birth:	9.10.77.	Age at Entry:	38 years
Date of Entry:	1. 3.16.	Age at Onset:	75 years
Date of Onset:	26. 5.52.	Age at Death:	78 years
Date of Death:	25.12.55.	Latent Period:	36 years

Working History :

1916 - 18 Worked on the manufacture of sulphuric acid.
1918 - 26 Worked on the manufacture of betanaphthylamine.
1926 - 45 Worked in acid department on the recovery of sulphuric acid.
1945 - 52 Worked as a clogger - repairing clogs and protective footwear.

History of Onset:

In April 1952 on routine urine tests a stained smear was Class IV and there were many red and white blood cells in the wet smear.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

26.5.52.	Papilloma	P U diathermy
11.8.55.	Papillomatosis left kidney.	Nephroureterectomy

Progress:

After treatment he continued to work as a clogger until he retired in January 1953 at the age of 75. He was reviewed regularly and no recurrences were seen in the bladder.

In early August 1955 he had several attacks of haematuria. Investigations revealed the presence of a tumour in the left renal pelvis. A nephroureterectomy was performed on 1.9.55. Papillary carcinoma was confirmed on section.

A few weeks after the operation, on December 8th, he was re-admitted with a mass of secondary carcinoma in the nephrectomy wound. He died on Christmas Day 1955.

The clinical findings were confirmed on post mortem examination.

CASE No.117 (W.H.S.)

Date of Birth:	31.10.01.	Age at Entry:	28 years
Date of Entry:	27. 5.29.	Age at Onset:	46 years
Date of Onset:	24.12.47.	Age at Death:	54 years
Date of Death:	27. 1.56.	Latent Period:	19 years

Working History:

1929 - 32 General labourer in yard of benzidine plant.
1932 - 45 Worked on the manufacture of benzidine disulphonic acid, nitrodiazo N.S., meta-nitroparatoluidine, metanilic acid and p-nitro p-anisidine.
1940 - 45 Worked on the manufacture of various alphanaphthylamine sulphonic acids.
1945 - 47 Worked on benzidine manufacture.

History of Onset:

He had haematuria early in December 1947. Prior to this routine urine tests had shown a few red blood cells in February 1946 but had otherwise been negative.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

24.12.47.	Papilloma	P U diathermy
15. 5.48.	"	" "
10. 7.48.	"	" "
10.11.48.	"	" "
29. 3.51.	"	" "
22. 9.53.	"	" "

Progress:

He returned to work as a processman but was not in contact with carcinogens.

Regular cystoscopic review examinations were made.

On 28th November 1955, two years after the last recurrence, he had an epileptiform fit and was subsequently admitted to Salford Royal Hospital. He was found to have a carcinoma of the lung with secondaries in the brain. The neoplasm in the lung was considered to be a primary tumour. The bladder was clear of tumour on cystoscopy at that time.

He was discharged from hospital and died at home on 27.1.56. No post mortem examination was made. The cause of death was certified as:

I Primary carcinoma of right bronchus
II Papilloma of the bladder.

CASE No.118 (S.K.)

Date of Birth:	1. 8.94.	Age at Entry:	35 years
Date of Entry:	25. 9.29.	Age at Onset:	48 years
Date of Onset:	12.11.42.	Age at Death:	61 years
Date of Death:	9. 4.56.	Latent Period:	13 years

Working History:

1929 - 42 Worked on the manufacture of sulphanilic acid and the distillation of many chemicals including betanaphthylamine, benzidine and alphanaphthylamine.

History of Onset:

In late October 1942 he complained of a dull pain in his abdomen and frequency of micturition. On one occasion he had seen blood in his urine. Routine urine tests had previously been negative.

Hospital: Salford Royal Hospital. later Christie Hospital. Surgeon: Mr.J.B.Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

12.11.42.	Papilloma	P U diathermy
10.12.43.	"	" "
24. 4.44.	"	" "
14. 5.45.	"	" "
13. 7.45.	Pyonephrosis	Right nephrectomy
13. 4.46.	Carcinoma (bladder)	Diathermy and gold seed implant

Progress:

Regular review examinations were made.

In 1945 the right kidney was removed because of pyonephrosis. There was no neoplasm on histological examination.

At review in April 1946 a clinically malignant recurrent tumour was seen in the bladder above the interureteric bar. He was transferred to Christie Hospital and in August a gold seed implantation was done. On section the tumour proved to be a transitional cell carcinoma.

He had a severe radiation reaction and was off work for six months. He returned to light plant duties for four years. He had frequent attacks of cystitis and in 1951 was transferred to the Works Surgery as a cleaner. In late 1955 he began to go downhill and in October a secondary mass was present behind the left clavicle. No tumour was seen in the bladder in April 1955, the last occasion on which he was cystoscoped. He died of secondary carcinomatosis on 9.4.56.

CASE No.119 (S.T.H.)

Date of Birth:	29. 6.91.	Age at Entry:	48 years
Date of Entry:	11. 9.39.	Age at Onset:	56 years
Date of Onset:	17.12.47.	Age at Death:	65 years
Date of Death:	5. 7.56.	Latent Period:	8 years

Working History:

1939 - 47 Worked on the manufacture of benzidine and tolidine.

History of Onset:

In December 1947 he had a sudden attack of haematuria. There had been no blood cells on routine urine tests until then.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

15. 1.48.	Papilloma	P U diathermy
4.11.49.	"	" "
19. 5.50.	"	" "
5. 8.55.	"	" "

Progress:

This man developed chronic bronchitis with dyspnoea in the late 1940's. Because of this he only worked for short periods after 1948 and he finally ceased work in 1951.

In the beginning of 1956 he began to lose weight rapidly. He was admitted to hospital. Investigation showed a filling defect in the left renal pelvis and a shadow in the upper lobe of the right lung. A diagnosis was made of carcinoma of the left renal pelvis with secondary deposit in the lung.

He died on 5th July 1956. On post mortem examination there was a large tumour in the upper lobe of the right lung, a mass of tumour tissue in the abdomen involving the pancreas and a tumour of the left renal pelvis. The histological findings were surprising. The lung tumour was a primary oat-celled carcinoma and the mass in the abdomen was secondary to it. The renal pelvic tumour was a papillocarcinoma.

An inquest was held and the verdict was that death was due to "natural causes due to primary carcinoma of the lung."

CASE No.120 (T.R.)

Date of Birth:	17. 7.04.	Age at Entry:	21 years
Date of Entry:	17.11.25.	Age at Onset:	50 years
Date of Leaving:	5. 9.30.	Age at Death:	52 years
Date of Onset:	1. 6.54.	Exposure Period:	5 years
Date of Death:	25. 1.57.	Latent Period:	29 years

Working History:

1925 - 30 Worked on the sulphonation of betanaphthylamine and on the milling of benzidine and tolidine.

History of Onset:

In 1954, 24 years after leaving the factory, he had haematuria for seven weeks. A year before that there was blood in the urine on one occasion only.

Hospital: Ancoats Hospital.
later Christie Hospital.

Surgeon: Mr. G. O. Jelly.
later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

1.6.54.	Papilloma	P U diathermy
21.9.55.	Carcinoma	Radon seed implant

Progress:

In June 1954 there were two areas of tumour formation in the bladder, one apparently benign and the other larger area having clinical appearances suggestive of papillocarcinoma. No biopsy material was taken. Both areas were fulgurated.

Three months later one small papilloma and three "suspicious" areas were fulgurated. Ten months later, in April 1955, the bladder was clear.

He was re-employed by the Company on sheltered work as a gateman in October 1954 and worked until August 1955. At that time on review examination there was a nodular ulcerated neoplasm on the posterior wall of the bladder. He was transferred to the Christie Hospital where a radon seed implant was carried out on 26.9.55. He had a severe radiation reaction and never worked again.
In August 1956 a nodule could be felt over the left external iliac vessels. Soon afterwards there were deposits in the pelvis and a large mass of glands in the groin.

He died on 25.1.57. On post mortem examination the bladder was clear of tumour. There was involvement of the right and left superficial inguinal glands extending along the lumbar iliac group and secondaries in the brain. Both suprarenals were replaced by neoplasm.

CASE No.121 (L.C.)

Date of Birth:	8. 1.05.	Age at Entry:	32 years
Date of Entry:	19.11.36.	Age at Onset:	52 years
Date of Leaving:	27. 5.44.	Age at Death:	52 years
Date of Onset:	- 11.56.	Exposure Period:	8 years
Date of Death:	20. 3.57.	Latent Period:	20 years

Working History:

1936 - 38 Worked on the manufacture of betanaphthylamine.
1938 - 44 Worked as a fitter's mate - no direct exposure to chemicals.

History of Onset:

Twelve years after leaving the Company he was referred to hospital by his own doctor because of a six weeks history of frequency of micturition and haematuria.

Hospital: Ancoats Hospital. **Surgeon:** Mr. G. O. Jelly.

Diagnosis, Course and Treatment:

5.12.56.	Carcinoma (biopsy - carcinoma)	Total cystectomy

Progress:

On cystoscopy in December 1956 he was found to have an advanced carcinoma of the bladder with very small capacity. A total cystectomy was subsequently performed. The sections showed carcinoma with little penetration of the muscle wall and no secondaries were seen in the lymph nodes examined. Excision was thought to be complete.

He developed a urinary fistula through the abdominal wound and several abscesses which discharged. He died on 20th March 1957 three months after the operation. On post mortem examination there was a large pyonephrosis on one side and a severely infected kidney on the other.

This case is referred to on page 162

CASE No.122(A.W.)

Date of Birth:	14.3.98.	Age at Entry:	24 years
Date of Entry:	7.3.22.	Age at Onset:	56 years
Date of Onset:	25.1.54.	Age at Death:	59 years
Date of Death:	13.4.57.	Latent Period:	32 years

Working History:

1922 - 25 Worked on manufacture of magenta.
1925 - 30 Worked on manufacture of triphenylmethane colours.
1930 - 49 Used benzidine in manufacture of sulphur colours.
1949 - 54 Hypertension. Light work as messenger.

History of Onset:

In January 1954 on routine urine tests stained smears were Class V.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson. later Christie.

Diagnosis, Course and Treatment:

25.1.54.	? Papilloma	- - -
25.6.54.	Malignant papillomatosis. (biopsy - papillary carcinoma)	Central source cobalt radiation.
17.4.56.	Carcinoma	Inoperable

Progress:

When he was investigated on 25th January 1954 no tumour was seen in the bladder and no evidence of tumour was found elsewhere in the urinary tract.

Malignant cells continued to be exfoliated. On 25th June 1954 there was widespread papillomatosis of the bladder which on biopsy proved to be papillary carcinoma. He was transferred to the Christie Hospital and treated by intracavity cobalt radiation.

In March 1955 he developed pulmonary tuberculosis. After six months chemotherapy in a sanatorium he was discharged well.

In April 1956 there was a mass of secondary carcinoma on the left side of the bladder invading adjacent structures. He died on 13th April 1957 of ascending pyelonephritis and recurrent carcinoma of the bladder, confirmed on post mortem examination. The tuberculous lesion in the lung was healed.

This case is referred to on page 136

CASE No.123 (G.W.)

Date of Birth:	12.1.02.	Age at Entry:	34 years
Date of Entry:	- 9.35.	Age at Onset:	52 years
Date of Leaving:	- 4.49.	Age at Death:	55 years
Date of Onset:	17.2.54.	Exposure Period:	14 years
Date of Death:	3.7.57.	Latent Period:	19 years

Working History:

1934 - 35	Worked on the manufacture of benzidine azo colours.
1936 - 38	Warehouseman weighing benzidine and alphanaphthylamine.
1938 - 39	Warehouse weighman - but no carcinogens.
1939 - 45	H.M.Forces.
1945 - 49	Warehouse weighman - but no carcinogens.

History of Onset:

Five years after leaving the Company he consulted his doctor because of haematuria of four months' duration.

Hospital: Ancoats Hospital. Surgeon: Mr. G. O. Jelly.

Diagnosis, Course and Treatment:

17. 2.54.	Papilloma	P U diathermy
30. 4.54.	"	" "
15.12.54.	"	" "
	(on urethral margin)	
16. 3.55.	Papilloma	" "
3.10.55.	"	" "
19. 1.56.	"	" "
4.10.56.	"	" "
	(on urethral margin)	
24. 1.57.	Papilloma	" "
21. 2.57.	"	" "
3. 7.57.	Carcinoma	Prostatectomy and excision of prostatic urethra.

Progress:

He was re-employed by the Company in August 1954 as a watchman. He was never fit for any but the lightest work, but, apart from the necessary absences for treatment he kept at work all the time. He was reviewed regularly and had many recurrences.

In July 1957 there was a malignant recurrence at the base of the bladder extending into the prostate. This was excised together with the prostate. He collapsed and died the same day. On post mortem examination death was found to have been due to air embolism. There were secondaries in the para aortic glands confirmed histologically.

CASE No.123 (G.W.)

Date of Birth:	12.1.02.	Age at Entry:	34 years
Date of Entry:	- 9.35.	Age at Onset:	52 years
Date of Leaving:	- 4.49.	Age at Death:	55 years
Date of Onset:	17.2.54.	Exposure Period:	14 years
Date of Death:	3.7.57.	Latent Period:	19 years

Working History:

1934 - 35	Worked on the manufacture of benzidine azo colours.
1936 - 38	Warehouseman weighing benzidine and alphanaphthylamine.
1938 - 39	Warehouse weighman - but no carcinogens.
1939 - 45	H.M.Forces.
1945 - 49	Warehouse weighman - but no carcinogens.

History of Onset:

Five years after leaving the Company he consulted his doctor because of haematuria of four months' duration.

Hospital: Ancoats Hospital. Surgeon: Mr. G. O. Jelly.

Diagnosis, Course and Treatment:

17. 2.54.	Papilloma	P U diathermy
30. 4.54.	"	" "
15.12.54.	"	" "
	(on urethral margin)	
16. 3.55.	Papilloma	" "
3.10.55.	"	" "
19. 1.56.	"	" "
4.10.56.	"	" "
	(on urethral margin)	
24. 1.57.	Papilloma	" "
21. 2.57.	"	" "
3. 7.57.	Carcinoma	Prostatectomy and excision of prostatic urethra.

Progress:

He was re-employed by the Company in August 1954 as a watchman. He was never fit for any but the lightest work, but, apart from the necessary absences for treatment he kept at work all the time. He was reviewed regularly and had many recurrences.

In July 1957 there was a malignant recurrence at the base of the bladder extending into the prostate. This was excised together with the prostate. He collapsed and died the same day. On post mortem examination death was found to have been due to air embolism. There were secondaries in the para aortic glands confirmed histologically.

CASE No.124 (S.P.)

Date of Birth:	7. 8.80.	Age at Entry:	35 years
Date of Entry:	1. 9.15.	Age at Onset:	62 years
Date of Retirement:	31.10.41.	Age at Death:	77 years
Date of Onset:	21.10.42.	Exposure Period:	26 years
Date of Death:	12. 8.57.	Latent Period:	27 years

Working History:

1915 - 41 Was the chemist in charge of an intermediates plant. From 1920 onwards he had close contact with the manufacture of betanaphthylamine and before that with its development and starting up.

History of Onset:

A year after he retired he had haematuria of gradual onset.

Hospital: Salford Royal Hospital. Surgeon: Mr.J.B.Macalpine.

Diagnosis, Course and Treatment:

19.11.42.	Papilloma	P U diathermy
7. 1.43.	"	" "

Progress:

Regular cystoscopic examinations were made. He had no further recurrences after February 1943.

He died on 12.8.57. of cerebral arteriosclerosis.

CASE No.125 (W.McN.)

Date of Birth:	30. 8.02.	Age at Entry:	14 years
Date of Entry:	1.11.16.	Age at Onset:	42 years
Date of Onset:	13. 7.44.	Age at Death:	55 years
Date of Death:	14. 9.57.	Latent Period:	28 years

Working History:

1916 - 19	Laboratory boy. There are no records of the exact work he did but his own recollection and that of an older chemist is that he worked on the betanaphthylamine process when it was being developed and piloted in the laboratory.
1920	Left the Company.
1920 - 44	Re-employed as a processman on the manufacture of toluidines. Had contact with paratoluidine, orthotoluidine, chlorparatoluidine and mononitrotoluol.

History of Onset:

A few red blood cells were present in a routine urine test in 1944. Before the next test he had an attack of haematuria.

Hospital: Salford Royal Hospital. Surgeon: Mr.J.B.Macalpine. later Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

13. 7.44.	Papilloma	P U diathermy
26. 4.45.	"	" "
25.10.54.	"	" "
14.12.55.	"	" "

Progress:

He continued at his usual work until 1951 when he developed auricular fibrillation and was transferred to light work in a laboratory.

Regular review examinations were made. He had three tiny benign recurrences and it is interesting that there was an interval of nine years between the two of them.

He died on 14.9.57. of right heart failure after an illness of two months.

CASE No.126 (J.B.)

Date of Birth:	16. 7.00.	Age at Entry:	24 years
Date of Entry:	20. 3.24.	Age at Onset:	55 years
Date of Onset:	26. 9.55.	Age at Death:	57 years
Date of Death:	28.11.57.	Latent Period:	31 years

Working History:

1924 - 26 Worked on the manufacture of magenta.
1926 - 30 Worked on the manufacture of triphenylmethane colours.
1930 - 42 Worked on the manufacture of sulphur melt colours using benzidine.
1942 - 55 Worked on the manufacture of triphenylmethane colours.

History of Onset:

Stained smears from routine urine tests were Class III-IV in August 1955, Class III in September 1955 and Class IV on a repeat test. There were no symptoms or other signs of bladder trouble.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

26. 9.55.	Papillomata (biopsy - papilloma)	P U diathermy
26.11.56.	Carcinoma (biopsy - carcinoma)	Deep X-ray

Progress:

The initial papillomata were two tiny benign growths which were well pedunculated and situated above the right ureteric orifice. Histologically the section of the biopsy material was benign papilloma.

He returned to work after treatment. At review cystoscopy in May 1956 the bladder appeared clear.

He was next examined on 26.11.56. A flat nodular invasive tumour surrounded the internal meatus and extended up to the trigone on the right lateral wall. On biopsy it proved to be a transitional papilliferous carcinoma. A course of deep X-ray therapy was given.

Response to treatment was poor and he died a year later of recurrent carcinoma of the bladder and iliac glands with secondaries in the lung. This was confirmed on post mortem examination.

CASE No.127 (H.C.)

Date of Birth:	9. 6.05.	Age at Entry:	34 years
Date of Entry:	29. 8.39.	Age at Onset:	51 years
Date of Onset:	15. 1.57.	Age at Death:	52 years
Date of Death:	18.12.57.	Latent Period:	18 years

Working History:

1939 - 41 Worked on the manufacture of benzidine.
1941 - 50 Worked on the manufacture of other intermediates in the same plant in which benzidine was made.
1950 - 57 Transferred to Locker Room owing to chronic bronchitis.

History of Onset:

In March 1956 stained smears from routine urine tests were Class IV (Fig 10). Investigations failed to reveal any tumour. The stained smears continued to be positive and he was again investigated in December 1956. The history of the onset of this case is described fully in the text.

Hospital: Salford Royal Hospital. Surgeon: Mr.D.S.Poole-Wilson.

Diagnosis, Course and Treatment:

15.1.57.	Carcinoma of left renal pelvis. (section - invasive papillo carcinoma)	Left nephroureterectomy

Progress:

For a few months after the operation his progress was moderately satisfactory but his chest condition soon began to deteriorate. This was attributed to the chronic bronchitis.

He died at home in December 1957, and a post mortem examination was ordered by the Coroner. This revealed extensive bilateral pulmonary tuberculosis. The bladder and remaining kidney and ureter were clear of tumour.

This case is of special interest for two reasons:-

I The exfoliation of malignant cells in the urine for eighteen months before a tumour of the renal pelvis was diagnosed by conventional means.

II The fact that the initial tumour was in the renal pelvis and there was no tumour in the bladder. It was largely on the strength of this case and Case No.60 that tumours of the renal pelvis or ureter were added to the definition of the prescribed disease in 1957.

This case is referred to on pages 137, 138, 158 and 171

HISTORY OF BENZIDINE MANUFACTURE

1918 – 50.

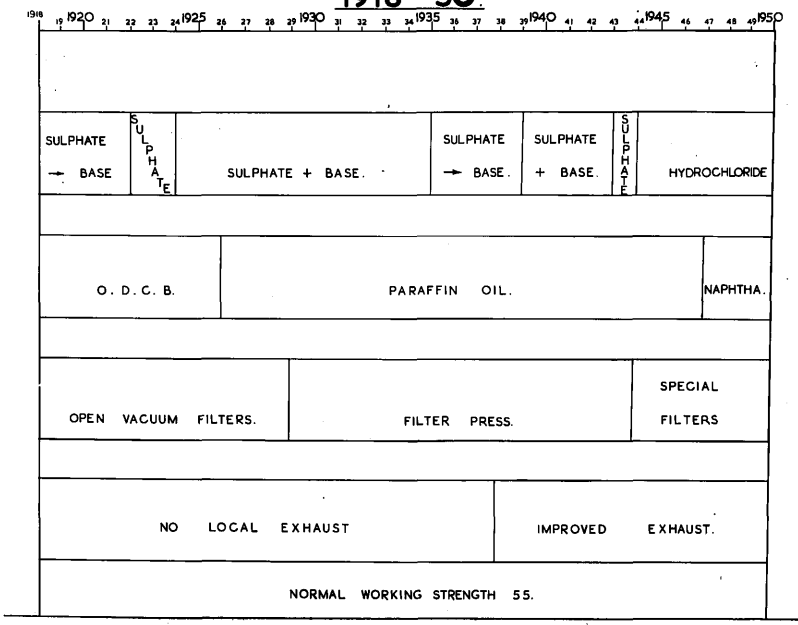


Fig. 1.

HISTORY OF β NAPHTHYLAMINE MANUFACTURE 1920 – 1950.

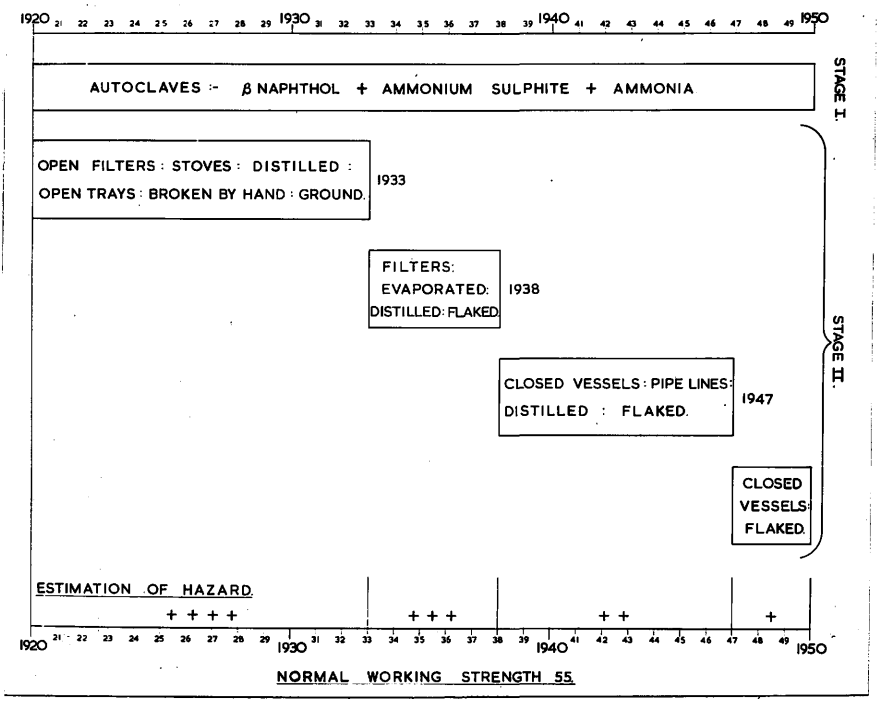


Fig. 2.

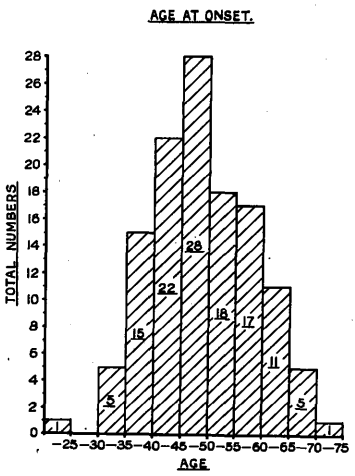


Fig. 3.

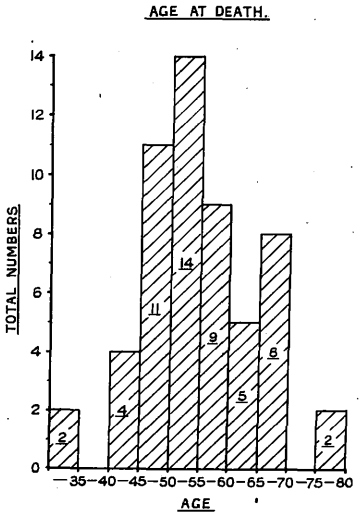


Fig. 4.

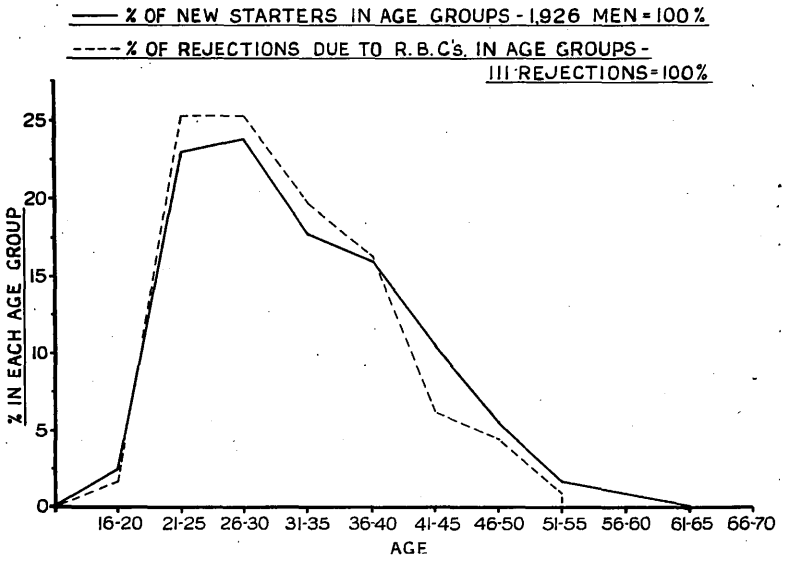
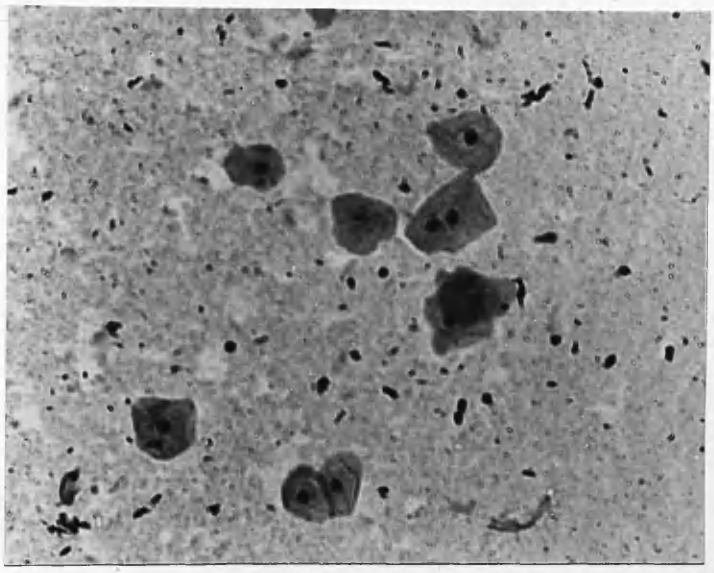
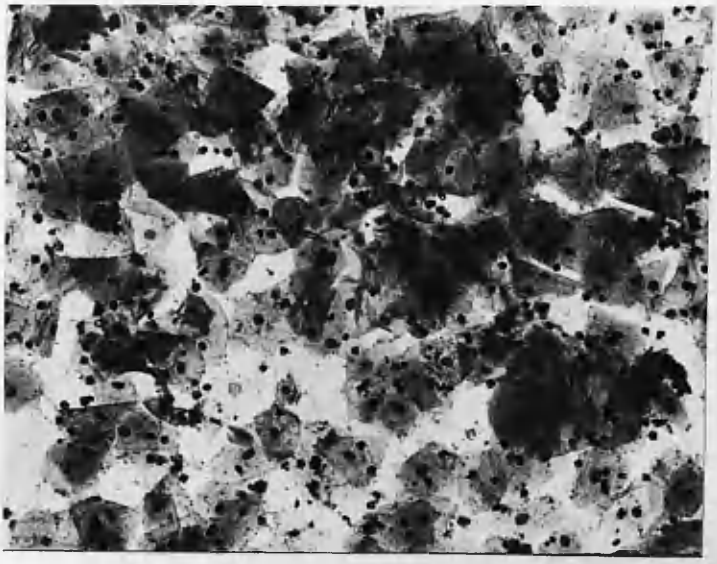


Fig. 5.



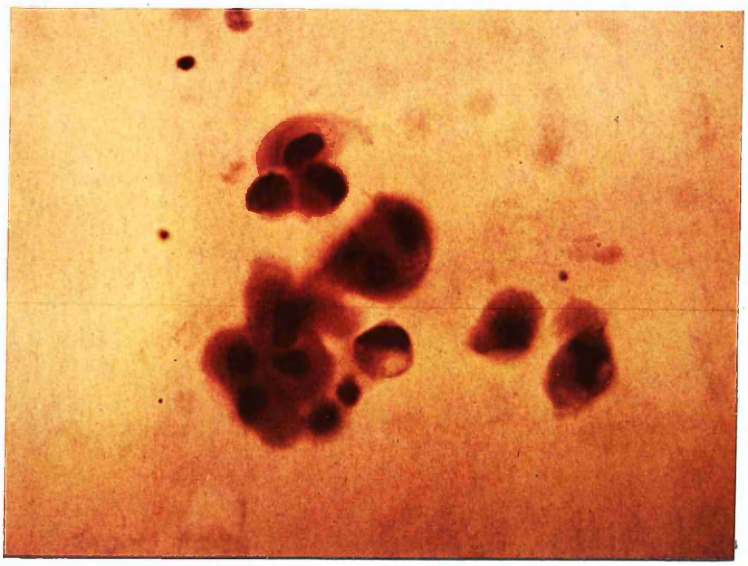
x 200

Fig. 6. Standard Smear.



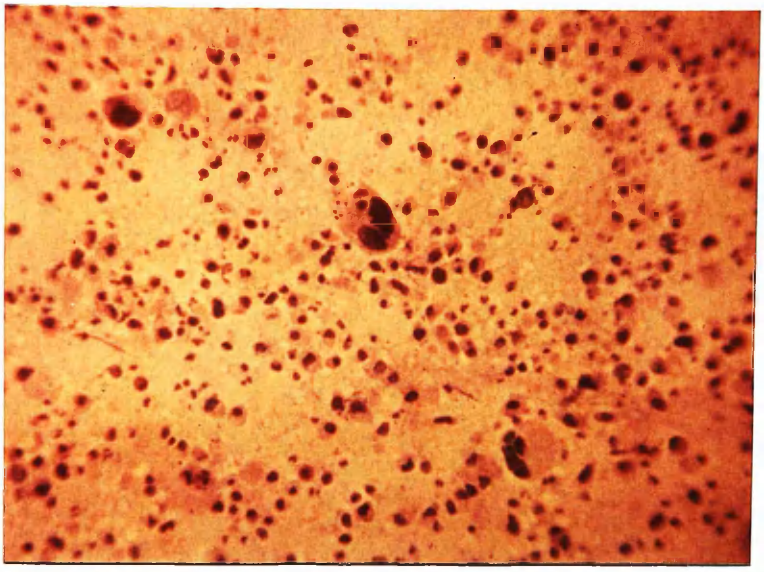
x 200

Fig. 7. Concentrated Smear.



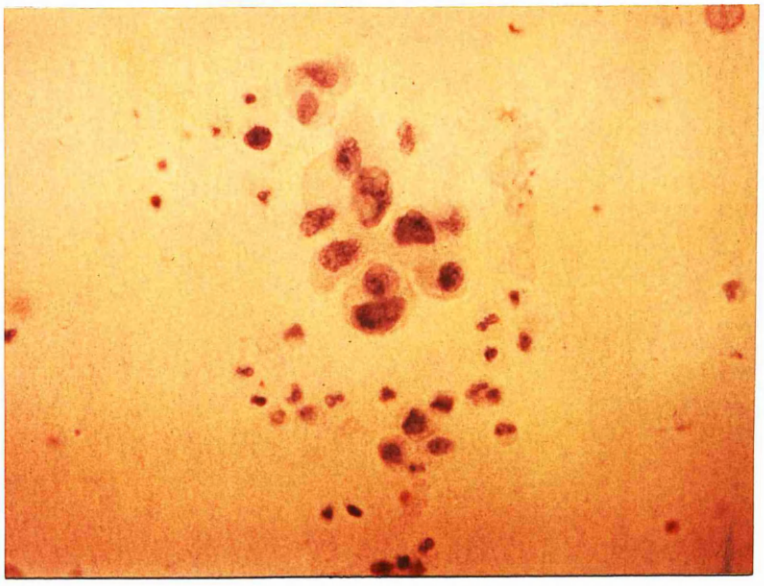
x 650.

Fig. 8. Malignant Cells. (Case No. 33.)



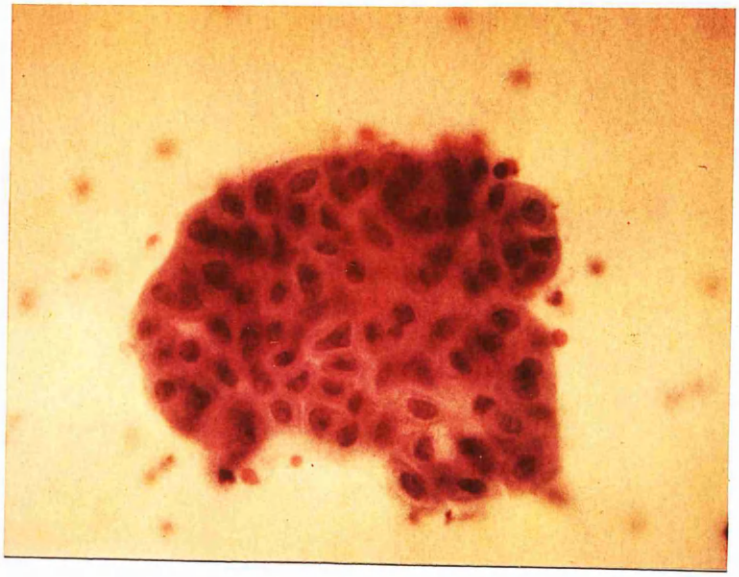
x 280.

Fig. 9. Malignant Cells. (Case No. 26.)



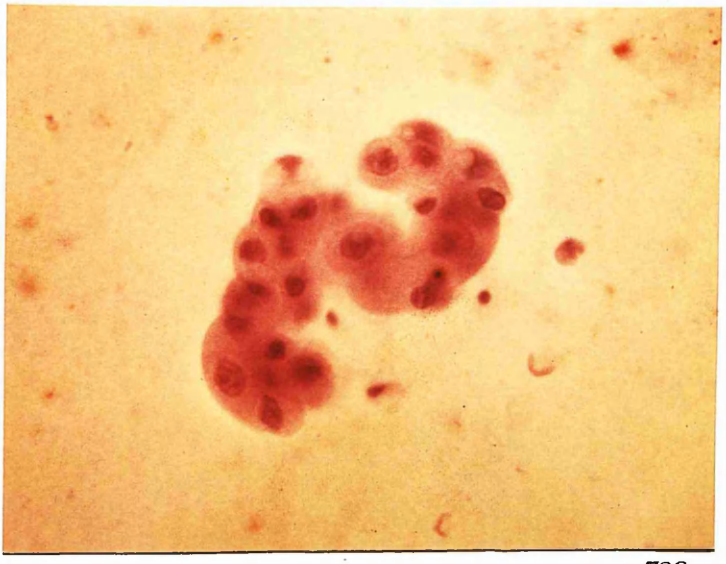
x 520

Fig. 10. Cells from Papillary Carcinoma of Renal Pelvis. (Case No. 127.)



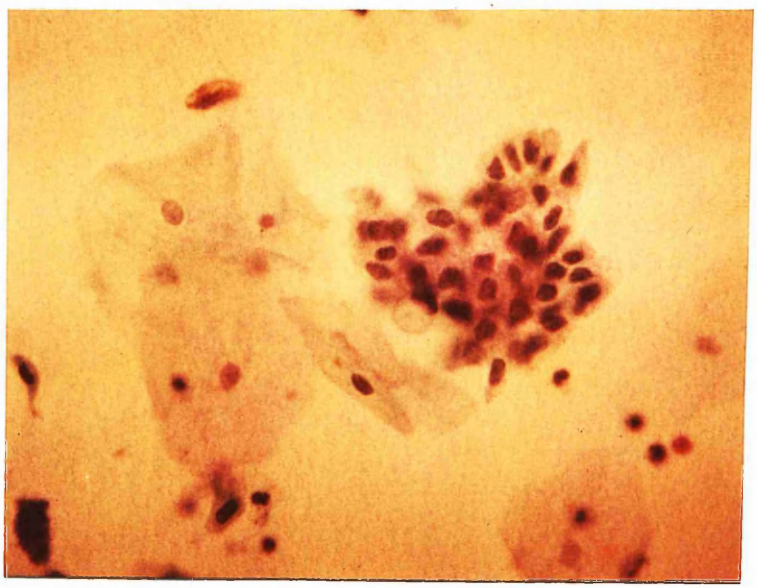
x 520

Fig. 11. Smear from Workman with Renal Calculus.



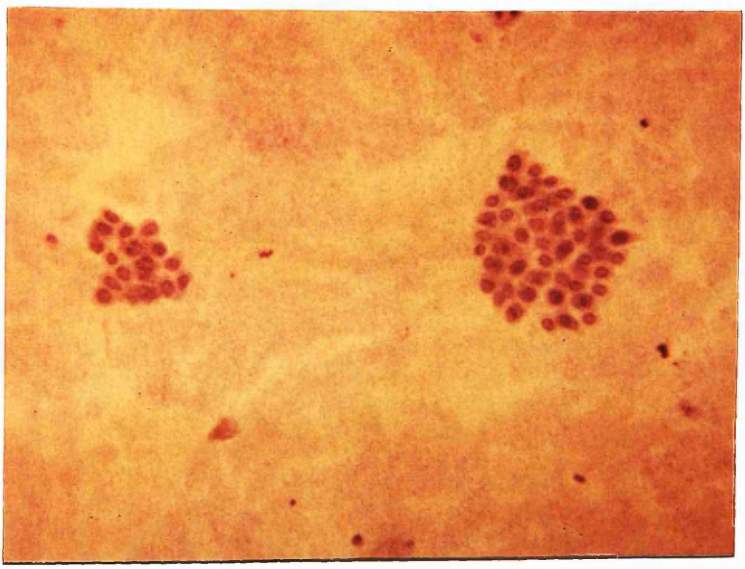
x 700

Fig. 12. Smear from Hospital Patient with Renal Calculus.



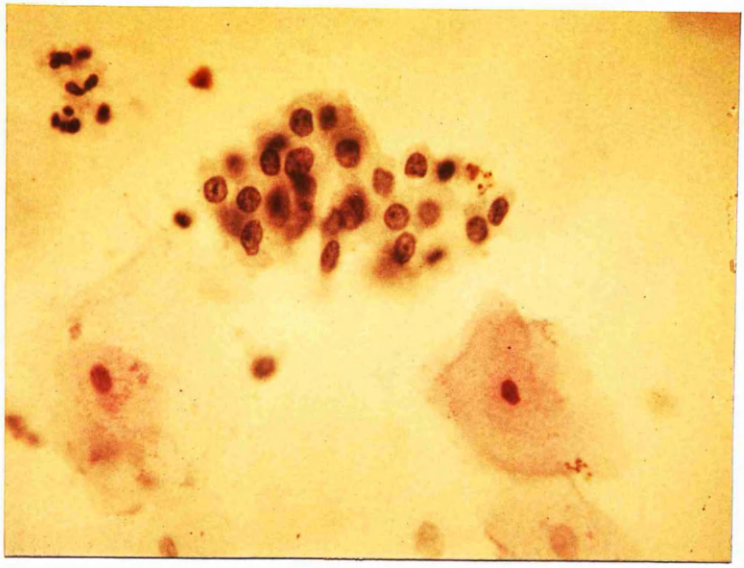
x 450

Fig. 13. Benign Papilloma Cells. (Case No. 51.)



x 280

Fig. 14. Benign Papilloma Cells. (Case No. 66.)



X 580

Fig. 15. Benign Papilloma Cells. (Case No. 51.)

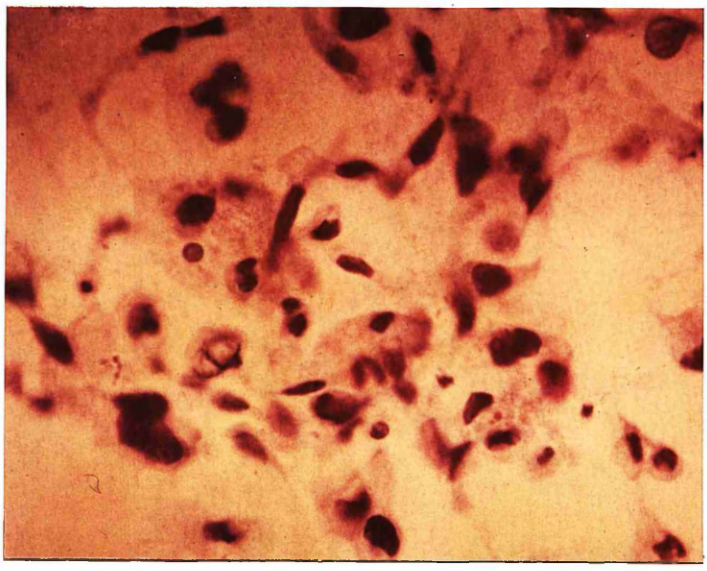
X 580

Fig. 16. Benign Papilloma Cells. (Case No. 66.)

x 140

Fig. 17. Particle of Tumour in Smear.

(Case No. 38.)



x 550

Fig. 18. Smear from an old case.

(Case No. 22.)

Fig. 19. Azo Plant built 1930.

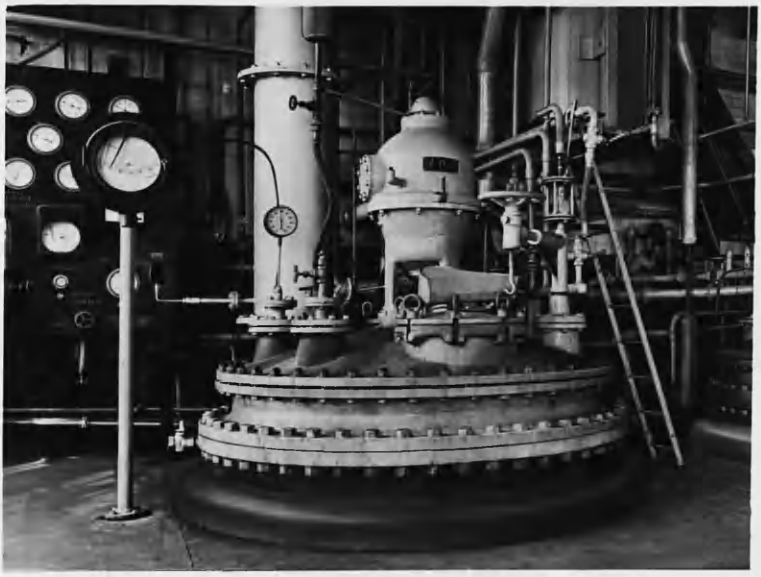


Fig. 20. Benzidine Plant built 1950.

APPENDIX A

Techniques for Routine Urine Testing

Wet smear

The men attend at the works surgery and pass urine into two jars, the first of which is discarded to exclude cells from the urethra and prepuce.

10 - 15 ml. of urine from each specimen is poured into 15 ml. conical tubes and 16 are centrifuged together at 2,000 r.p.m. for 10 minutes. The supernatant fluid is decanted into 6" x $\frac{5}{8}$" test tubes and tested for albumin by salicylsulphonic acid. Two 3" x 2" slides are divided into 8 sections by a diamond marker. One drop of each urine deposit is added to the slide and the eight specimens are examined at a time without coverslips under 16 mm. objective. The absence of coverslips saves time and gives a greater depth of deposit with more cells per field. The number of cells present are recorded using + to ++++ as an indication of quantity.

Original stained smear method (after Crabbe 1952)

An equal volume of 95% ethanol is added to the urine and 40 ml. are centrifuged for 15 minutes at 2,000 r.p.m. The supernatant fluid is removed. The smear is made by spreading a drop of the urine deposit on slides which have been smeared with glycerine albumen. When the smear begins to cloud round the edges or in its thinner parts, it is fixed in equal parts of 95% alcohol and ether. It must not be allowed to dry at any time.

The smears are then stained using Papanicolaou's technique (1954).

Concentration technique now in use

1 Adjust the urine to pH 6.0 with a few drops of 0.5NaOH or 0.5HCl. (This avoids the precipitation of phosphates).
2 Centrifuge at 2,000 r.p.m. for 10 minutes in a 50 ml. conical tube.
3 Slowly draw off the supernatant fluid by suction.
4 Add 10 to 15 ml. of absolute alcohol, shake and leave for 5 minutes.

5 Fill up with distilled water and shake gently.
6 Centrifuge as before for 10 minutes.
7 Slowly draw off the supernatant fluid.
8 Add 3 - 4 drops of glycerine albumen diluted with an equal volume of distilled water.
9 Centrifuge as before for 5 minutes.
10 Carefully draw off the few drops of supernatant fluid.
11 Mix the deposit by gentle shaking and with a clean capillary pipette of 0.5 mm. internal diameter remove the deposit and expel on to a clean marked slide. Spread the deposit on the slide with the tip of the pipette so that the resultant smear can be covered by a $\frac{7}{8}$" square coverslip. While the smear is still wet examine under a 16 mm. objective for even distribution of cells.
12 Allow the slide to dry (usually 1 to 5 minutes) and immediately place it in the ether/alcohol fixative. After 5 minutes the smear is ready for staining but it may be preserved in the fixative indefinitely.
13 The smear is stained by Papanicolaou's method (1954) but the E.A.65 counterstain is adjusted to pH 5.5.

THE INCIDENCE OF BLADDER TUMOURS IN A DYESTUFFS FACTORY

BY

T. S. SCOTT

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THE INCIDENCE OF BLADDER TUMOURS IN A DYESTUFFS FACTORY*

BY

T. S. SCOTT

From the Clayton Aniline Company Ltd., Manchester

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 Haser (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 who 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

*A summary of this paper was read at the Tenth International Congress of Industrial Medicine, Lisbon, September, 1951.

…ext was flaked without distillation. After …ation the amine was then sulphonated in …er building.

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

…pha Naphthylamine.—Alpha naphthylamine was …nufactured in this factory for four years only, …n 1926 to 1930, by the nitration of naphthalene …subsequent iron reduction of alpha-nitro-…thalene. The usual number of men employed …his process was three, and the total number who …ked on it for six months or more was four. None …ese men has developed bladder tumour.

…he case, which might be attributed to alpha …thylamine in the manufacture of intermediates, …eloped a tumour after being employed for 18 …rs in the manufacture of naphthionate of soda …m alpha naphthylamine. During this process a …illation residue containing about 17% of beta …thylamine (from the 4% beta impurity) was …overed as a molten product, set in trays, broken …by hand, and transferred to casks. It has …viously been suggested by other investigators …oldblatt, 1949; Müller, 1951) that the beta …thylamine impurity in alpha naphthylamine is …e causative factor in tumour production, and this …se was, owing to the nature of the process, more …ely exposed to the residue with a high beta …thylamine content than to technical alpha …thylamine.

…niline.—The manufacture of aniline by the iron …uction process started before 1900 and has always …en carried on in separate buildings. The total …mber exposed over six months since 1920 is 76. …evious records are not dependable. The normal …rking complement is 11. No cases of bladder …mour have been found among men in this process …though some men have worked since the early …ys of primitive plant and bad conditions, and …ese exposures up to 45 years are substantiated. In …rope tumours attributed to aniline have been …orted by Gross (1940) 33 cases, Goldblatt (1949) …ree cases, and Müller (1951) 22 cases, but Gehr-…nn and others (1949) reported that they had found …e tumours in men from an aniline plant with a …bstantial number of employees who had worked …s exposed up to 25 years.

Other Exposures.—One man was employed on …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

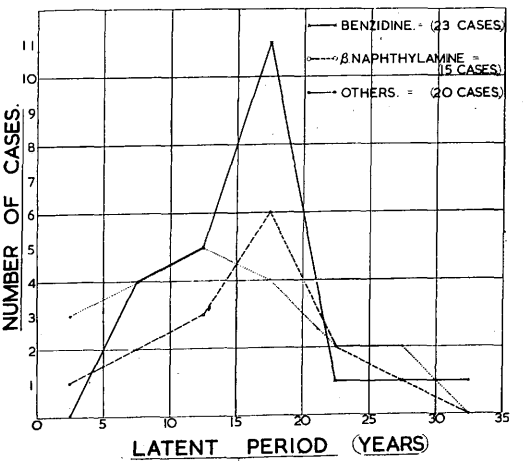

FIG. 3.—Graph of time from starting work to diagnosis of tumours.

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

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

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

xposure and Latent Periods.—All the men in factory who developed tumours were still ployed at the time of diagnosis and therefore the nt and exposure periods are the same. The short- was 15 years and the longest 27 years with an rage of 21 years. The cases among the men dling benzidine in the colour factory had a ger average exposure (21 years) than those ufacturing (16 years), and the first case among handlers arose seven years later. It is reasonable ssume, therefore, that the intensity or the nature the exposure in the manufacturing process was termining factor in producing tumours earlier n in handling.

Age at Diagnosis of Bladder Tumours

Of the 66 cases, 40 entered the industry before age of 30, 17 between the ages of 30 and 40, nine after the age of 40. It will be seen from ble 4 that of those under 30 the average age of set of tumour was 42 and of death was 44; of se between 30 and 40 the average age of onset s 51 and of death 54; and in those over 40 the rage age of onset was 58 and of death 66. From Registrar General's figures for 1947 the average e of death of 1,417 males in England and Wales o died of neoplasms of the bladder, urethra, and ter was 67·5 years. Stocks (1950) took records of es of cancer of the bladder and ureter from 275 pitals in England and Wales in 1945. He found t the average age of all cases at first attendance s 62·3 years and at death 66·3 years. These figures

TABLE 4

AT DIAGNOSIS OF BLADDER TUMOURS (ALL CASES)

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

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.

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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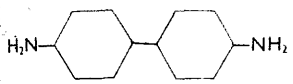
The Control of Occupational Cancer of the Bladder*

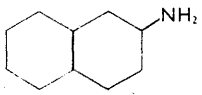
By T. S. SCOTT

From The Clayton Aniline Company, Ltd.

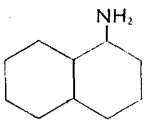
UPATIONAL tumours of the bladder were st described by Rehn in 1895, and many have accumulated since then. In this Goldblatt reported a notable series in nd *Table 1* shows my own cases reported ear. The heaviest incidence occurs in s engaged in both the manufacture and three aromatic amines, namely benzidine,



phthylamine



ha-naphthylamine

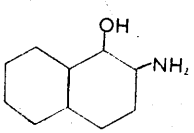


other compounds, such as auramine and ed naphthylamines come under suspicion in's original cases were in workers manu- fuchsin (or magenta). Aniline was at also blamed but recent evidence has completely exonerated it as an industrial en.

tablish the best methods of prevention een necessary to answer several questions. h processes and with what substances danger lie? Is the active carcinogen stance suspected or is it present as an ? Is the hazard present all the time or ome stage of the process? How is the attacked in the human?

phthylamine

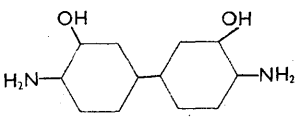
danger of manufacturing beta-naphthy- as recognised from industrial experience he production of experimental tumours (Heuper, Wiley, Wolfe, 1938). Bonser Leeds excluded impurities as the cause ng tumours in dogs with a highly puri- pound. In 1951 she and her co-workers that one of its metabolites, 2-amino-1-



was a local carcinogen by implanting it in the bladders of mice. In dogs given betanaphthylamine the concentration of 2-amino-1-naphthol in the urine was 200 times that in the blood plasma. It is important and significant that man excretes beta-naphthylamine as 2-amino-1-naphthol to a comparatively high degree. It is reasonable therefore to conclude that beta-naphthylamine and not an impurity is responsible for the industrial tumours attributed to it and that this metabolite of it is active in their production.

Benzidine

Benzidine as a cause of bladder tumours in workmen had been suggested in this country since the nineteen thirties but it was not until 1950 that Spitz (1950) and her co-workers induced tumours with it in animals. These were multiple, but no bladder tumours occurred. Baker, in my own department, showed that 3:3'dihydroxy-benzidine



Cases of Tumours of the Bladder

Type of exposure	Total	Alive	Dead
Benzidine	30	22	8
Beta-naphthylamine	15	9	6
Alpha-naphthylamin	1	1	0
Mixed. Bz., *p*n., ∝−n.,	17	12	5
Other	3	3	0
Total	66	47	19

Table 1

* Read at a meeting of the Association on 30th October, 1953.

was a metabolite in the human and with it we have induced tumours, similar to those of Spitz, in rats. Bladder and local tumours also appeared.

There is a striking resemblance between these tumours and those induced by 2-acetylamino-fluorene and the latest investigations were on acetyl benzidine, as acetylation is important in the metabolism and carcinogenic property of benzidine.

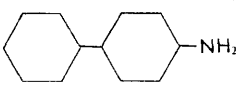
Alpha-naphthylamine

This has not been shown experimentally to be a carcinogen. Bladder tumours in workmen who have been exposed to it have been reported.

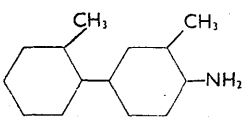
In its commercial form it always contains a small proportion of beta-naphthylamine as an impurity and larger amounts occur in residues but it might be premature to conclude that this is the only carcinogenic factor. It cannot be presumed that alpha-naphthylamine is not itself carcinogenic.

Aniline

Aniline is made from the same raw material as benzidine. Occupational bladder tumours were at one time known as "aniline cancers"—a misnomer which stuck for many years. No cases of tumour from aniline have arisen in any of our workmen who have been engaged in its manufacture, which has always been done in a separate building with no exposure to the other amines. Many of these men have had long exposure, some of well over 40 years, and in the earlier decades working conditions were bad and contact was heavy. Moreover, experimental tumours have not been induced with aniline. Last year Walpole, Williams and Roberts (1952) drew attention to the fact that naphthylamines and 4-aminodiphenyl



and 3:2'dimethyl 4:aminodiphenyl



were present as impurities in aniline in the early days of manufacture at the end of the last century, and they have induced tumours in rats with the two latter compounds. This goes a long way to explain the undoubted occurrence of the tumours in aniline workers in Europe which have been reported by earlier writers.

Description of Disease

Occupational tumours of the bladder occur as benign papilloma and carcinoma. Once they have arisen they do not differ from those of non-occupational origin. Recurrences or fresh tumours are frequent and are not always of the same ty as the original growth.

Exposure and Latent Periods

Tumours appear after a latent period, that the time between entry to the industry and ons of the disease ; this ranges in my own ser (*Figure 1*) between 4 and 32 years with an avera of 16 years and a mode between 15 and 20 yea but shorter and longer periods have been ported. This latent period is not necessarily same as the exposure period and tumours m develop years after a man has left the indust (*Table 2*). The average latent period is much same as in those who stay on, so that given su cient exposure, the process of tumour develo ment is not arrested by removal from contact.

Prevention

At first these three amines—benzidine, be naphthylamine and alpha-naphthylamine—peared to be harmless. No acute toxic effe resulted from heavy industrial exposure. Th did not cause cyanosis from methaemog binaemia as do aniline and many other amin and they were not even irritant to the skin. was not until after an unusually high incide of tumours of the bladder was recognised workmen that the hazard became evident.

The industry itself had to deal with this n problem. Although it may at first appear to a comparatively localized hazard confined to small section of only one industry, yet the pr ciples and methods of control are simply application of industrial medicine and hygi and they could be applied to the prevention many other hazards in other industries.

The measures which have been adopted c sist of medical, chemical and engineering. It also essential for a precise assessment of hazard that comprehensive technical reco should be kept as well as personal and medi ones. These must include the plants and p

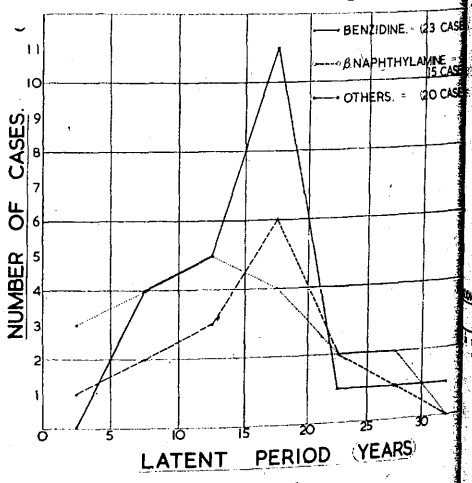


Figure 1

8 workmen who left before onset of tumour

	Average	Type of exposure							
		Bz	Bz	Bz	Bn	Bz	Bn	Bn	α + Bn
ure in years	7	5	11	9	4	7	6	8	8
t period in years	15	10	17	20	16	13	19	9	18
of Tumour		P	P	C	P	P	C	C	C

Table 2

worked in, and the type and chemical the compounds contacted.

on the technical side, which comprises e chemical and engineering aspects, that atest hope of effective control lies, and blem is primarily a technical one, in that, s can be found to prevent the exposure to carcinogens, it is solved. The most way to achieve this would be to cease nufacture altogether.

has been done voluntarily by the industry country in the case of beta-naphthylamine, on account of the hazard, and a much ficult and costly method now omits beta-naphthylamine in the manufacture of dyestuffs. A similar eradication is not technically possible with benzidinē or alpha-naphthylamine and they are still manufactured and used. All operations which carry the risk of absorption, which in industry is usually by inhalation or through the skin, must be made as safe as possible. Old plant, the design and layout of which cannot be adapted for safe working, should be scrapped. Our old benzidine plant originally built for T.N.T. manufacture in 1915 and changed over to benzidine in 1918 has been replaced by a new building basically planned and equipped for safe working under the strictest modern conditions.

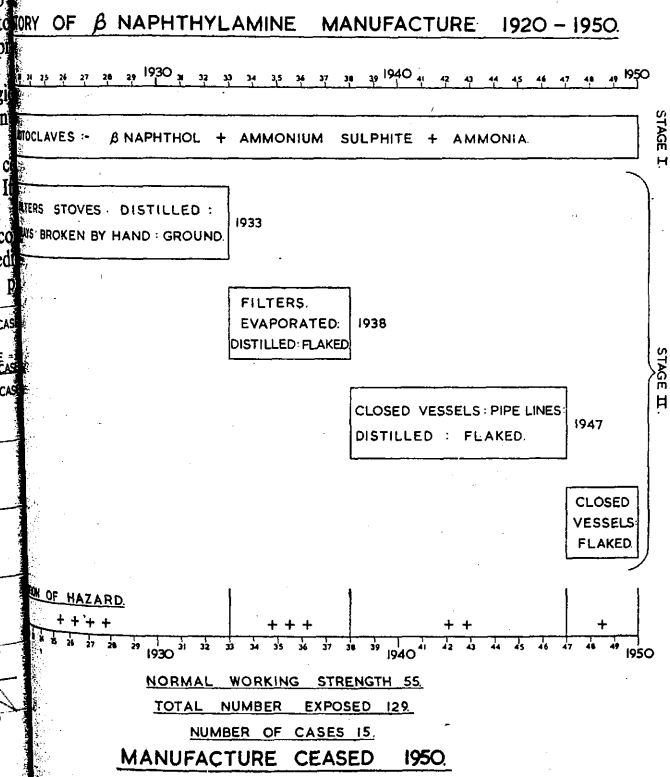


Figure 2

Other plant has been modified to keep the carcinogens contained in enclosed systems and, wherever their was exposure of the compounds as in open pans or filters, adequate arrangements were made for their complete enclosure and for safe maintenance. For distribution, handling has been replaced by mechanization, transmission through pipelines, or by using enclosed containers. Physical and chemical forms of the compounds have been modified to avoid those which would vaporize readily or get into the atmosphere as dust. Soluble salts have been made instead of the dusty bases; solutions or slurries are distributed through pipelines, or wet pastes are used to avoid dusting. Heat processes such as distilling, melting, stoving and heat drying which increase the risk from volatilization have been re-

vised and, where possible, cold methods of manufacture substituted, but sometimes the risk can be lessened by distributing molten amine by enclosed pipelines. Harmful impurities in the form of unreacted free amines in the finished colour are closely guarded against. Ventilation of working places and local draughting at points where exposure was likeliest to occur were carefully tested and improved. Tests for the determination of infinitesimal amounts of amines in the atmosphere, and on the clothing of workmen have been devised. Although safe or permissible concentrations cannot be laid down, a check can thus be kept on the efficiency of the precautions taken, and measures are taken to improve them if necessary.

The application of some of these principles can be seen in the history of the manufacture of beta-naphthylamine which started here in 1920 (*Figure 2*). From then until 1933 the charge was filtered in open filters, dried in hot stoves which men entered without precautions, distilled, set in open trays, broken up by hand and finally ground to a fine powder. Exposure was thus extremely heavy but the hazard was not realised then, although in 1933, when an odd case or so had arisen, stoving was omitted and the trays and grinding were replaced by a flaker. In 1938, when the hazard became 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, at the end of the war, further refinements became possible and distilling was omitted. Finally, manufacture of beta-naphthylamine ceased in 1950, and it was replaced by the safer alternative method of sulphonation of beta-naphthol and subsequent amidation in the synthesis of those intermediates for which beta-naphthylamine was used. These later developments would have been much earlier but for the war.

Medical

Despite the strictest technical precautions a medical officer, full time or part time, is indispensable in the control of this hazard. Selection of workers, supervision of their health, the early diagnosis of tumours, liaison with the family doctor, urologists and hospital, regular review, rehabilitation and replacement of those who have had tumours, are matters for the doctor alone. For maintenance and investigation of records, supervision of the general conditions and places of work, and of the measures taken to protect the workmen from exposure, he requires the appropriate technical help and advice but they come within his province and he is frequently the co-ordinator of the various specialists in these fields.

Selection

Men to be employed must have a high standard of personal hygiene to keep down absorption by the skin and mouth, and must be mentally capable of co-operating in the hygienic protective measures prescribed ; men with a history of exposure to other industrial carcinogens and those with previous or existing genito-urinary disease, or neoplasm in any organ or tissue, are excluded because of the risk of subsequent confusion in the assessment of the hazard. For the same reason all applicants have microscopic examination of urine and those with red blood cells or abnormal cells are rejected, even if otherwise healthy. Incidentally, I do not reject on a family history of cancer as there is no evidence that this predisposes to occupational bladder tumour.

Of the published industrial cases in this country where the age at death is given, about 60 per cent died before the age of 55 whereas from the Registrar General's figures of male deaths in 1949 the average age at death from neoplasm of the bladder and ureter in the United Kingdom was 67·5 years. My own series of cases (*Table 3*) shows how the age of onset of tumours in those who develop them is almost entirely dependent on the age at which they entered the industry, since tumours occur after a latent period usually 15 to 20 years. This results in a correspondingly earlier death. It will be seen that those who entered the industry below the age of 30, onset and death occurred at a much earlier age than in those who entered after the age of 40. It is not suggested that older people are less susceptible, but only that the older a man is on entry, the older he is likely to be at onset if he develops a tumour and that younger entrants may have their lives shortened if tumour develops. In selecting men for this type of work I therefore exclude those under 30 and where the physical effort required and the available labour allow accept men over 40 for preference. The average age at entry of the present labour force in the new benzidine factory is 41 years. None had worked in chemicals before, except the foreman who had to have previous experience.

Apart from these special considerations, the physical standard required will depend on the type of work to be done. Good health and strong physique have no relation to a man's resistance to bladder carcinogens.

Age at entry, onset, and death

Age at entry	Under 30	31-40	Over 40
Number of cases (Number of deaths)	40 (10)	17 (5)	9 (4)
Average age at onset of tumour	42	51	58
Average age at death	44	54	66
Average latent period	18	16	13

Table 3

tion and training may not be strictly a matter, but I think it is ethically right worker should be told what the hazard he should be taught how the safeguards for his protection can be used to the best ge. Work on these jobs is voluntary and fer men to other jobs without penalty if sh to come off. It is some indication of d relations and confidence existing that seldom asked to do this.

on of Risk

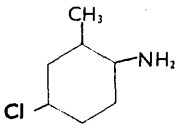
vent amines remaining on the skin and sorbed after work, full working clothing ied to each man and must be changed d of each shift and a bath must be taken. e applies on accidental contamination. e. clothing such as gloves, aprons, rs and other devices, are supplied g to the nature of the job.

der to keep down the time of possible to a minimum the hours of work are nd no overtime is permitted except in emergencies.

umbers who are exposed to risk are re- the minimum necessary to do the work casual or temporary workers are allowed plants; only men who have been passed medical officer are permitted, and selected are appointed to cover the absence of men; cross-transfers from one hazardous another are not allowed so that workmen exposed to more than one carcinogen. mall works I think it might be better to man or one small team to do all the e there is risk, rather than to increase bers exposed.

mployment of men for short periods has ocated on the ground that this would he duration of exposure and hence the umour induction. Comparatively short f exposure of a few months have, how- n reported as causing tumour and even ones may come to be accepted, so that he period of exposure does not obviate nd certainly increases greatly the num- risk. Therefore, as far as possible, we on the same jobs, if they are willing, han multiply the numbers at risk by replacements.

ve, so far, been discussing some of the prevention of the hazard, but however the measures we have applied may be, tumours are still likely to arise, for er entry, in those who have already been to offer real hope of successful treat- umours must be diagnosed as early as efore the growth is inoperable. Ordinary examination is useless in the early diag- bladder tumours; only advanced likely to be detected, and may at times by this means. Haematuria is some- ent in advanced malignant disease, although it may sometimes be severe in small benign papilloma; it may be a symptom of some other disease or injury or may, in workmen in this industry, result from a transient haemorrhagic cystitis caused by an apparently non-carcinogenic bladder irritant such as 5-chlor-orthotoluidine.



The diagnosis can be made with certainty only by cystoscopy. Workmen who have had no symptoms or complaints naturally do not relish the prospect of undergoing this operation and it cannot be applied as easily as some routine methods of screening, such as blood counts or X-rays, which are used for other occupational hazards.

In America and some continental countries all workmen are said to be cystoscoped at regular intervals of a year as a routine. In one clinic abroad, which I visited only this year, I was told that although most workmen accept it once a year, it could not be applied more often as they would certainly refuse. There are several other objections to routine annual cystoscopy. A tumour can arise and become inoperable in less than a year; its application might lead to refusal to undergo it at the very time when it has become most necessary; in this country many men would leave after one or two cystoscopies rather than continue in work where it was a condition of employment and the numbers exposed would be increased by their replacement; the psychological effect on men if cystoscopy were to be made a condition of employment, would almost certainly be bad. All investigators in Britain have agreed that routine cystoscopy would not be accepted by British workmen and attempts to institute it have had to be abandoned.

If the chance of hitting upon an early tumour by a routine annual cystoscopy is not acceptable, then some other methods of deciding when cystoscopy should be done must be applied. In my works, microscopic examination of a wet smear of the urine of all workers is done at monthly intervals. The presence of large numbers or the persistence of small numbers of red blood cells in a man who has been sufficiently exposed is almost invariably regarded as an indication for cystoscopy. Examination of stained smears of urinary deposit for tumour cells by the Papanicolau technique has been done on our men for the past two years and we have been fortunate that Dr. Crabbe has examined and interpreted these for us. The appearance of tumour cells is obviously an indication for cystoscopy. If doubtful or suspicious cells are noted, frequent re-examination or cystoscopic investigation is called for depending on other factors such as the wet smear or the exposure history. A negative finding, as with the wet smear, is not

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BY

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Tumours of the urinary bladder occurring amongst the general population usually disclose their presence by the onset of symptoms such as haematuria, dysuria, frequency, or pain. In some cases haematuria may develop from a small benign papilloma which offers a good chance of successful treatment, whilst in others the tumour may have reached large proportions and even metastasized before its discovery.

In 1920 Oppenheimer in Germany recommended regular microscopical examination of the urine for the presence of red blood cells as a means for the earlier detection of occupational bladder tumours. For similar reasons in 1934, Cresdee, Guest, and Wignall (unpublished) instituted such regular examinations in two British dyestuffs factories and shortly afterwards Hope and Scott (unpublished) applied them in a third factory. They hoped that red blood cells or other abnormal constituents in the urine might give an indication for cystoscopy before the onset of symptoms due to a tumour so that earlier diagnosis might afford a chance of more effective treatment. During the next 15 years Cresdee, Goldblatt, Scott, and Williams (unpublished) in Great Britain extended these examinations of wet unstained smears of urinary sediments to include more men at more frequent intervals. Many cases diagnosed by this means were included amongst those described by Goldblatt (1949) and by Scott (1952) and all of them were included in the figures used by Case, Hosker, McDonald, and Pearson (1954), and Case and Pearson (1954) in their survey of the incidence of the disease in Great Britain. They confirmed statistically that there was a significantly higher incidence of bladder tumours amongst men exposed to α- and β-naphthylamine and benzidine than in the general population and revealed an occupational hazard of bladder tumours amongst men engaged in the manufacture of magenta and auramine.

Similar examinations of wet smears of urinary sediment have been used as an indication for cystoscopy in Germany for a number of years (Gross, 1940). In Switzerland, however, the urine was examined for occult blood in 1932 but by 1937, after consultation with American colleagues, routine cystoscopy was chosen as the most efficient method of achieving early diagnosis (Müller, 1951). Routine annual cystoscopy of exposed workers was first instituted in the United States of America in 1937 and has continued until recently with concurrent examinations of wet smears (Gehrmann, 1934; Gehrmann, Foulger, and Fleming, 1949). They even advocate the cystoscopy of all men before starting work. Similarly this procedure was adopted early in Italy and still continues to be applied (di Maio, 1937 and 1949). Many tumours have been diagnosed in this way, but there is no indication of what proportion of unaffected men have continued to undergo cystoscopy annually for up to 20 years. It is claimed by the above authors that regular annual cystoscopy can be achieved. In France Billiard-Duchesne (1949) published the results of his cystoscopies, but Aboulker, Gaultier, Benguigui, and Smagghe (1949) record the successful use of the wet smear technique which suggests that routine cystoscopy was not acceptable to them.

In Great Britain it is admitted that, although a substantial proportion of healthy men who have been at high risk might undergo cystoscopy on first demand, with repetition the numbers would quickly dwindle to levels which would invalidate any of the alleged advantages. Cystoscopy may be accompanied by some discomfort and is an operation which must be performed with great care if all sequelae are to be avoided. In Great Britain it has been the practice to restrict it to the necessary minimum. Furthermore, in practice, routine cystoscopy cannot be extended effectively to those persons with a relatively small exposure to carcinogens but

ill have a remote chance of developing a r tumour. Some tumours may grow to able proportions in a year, so that an annual copic examination does not afford complete even if there were no defaulters and no cations.

the reasons given above, routine cystoscopy nsidered to be quite unsuitable for intro- n into British factories. Since their inception 4, the examinations of wet unstained smears nary deposits have resulted in many pre- matic diagnoses, but despite these successes, ases were only discovered when inoperable. work of Papanicolaou and Marshall (1945) Papanicolaou (1947) suggested that a study exfoliated from the bladder epithelium into ne might offer another method of screening pulation at risk. Accordingly in 1951 the colaou smear technique of urine examination roduced into the three factories alongside ginal wet, unstained smear technique. A inary report on the results of the first year pplication has been given by Crabbe (1952). results were sufficiently encouraging to the continuation and extension of the colaou technique during subsequent years subject of this paper is the evaluation of the two techniques against the symptoms toscopic findings.

Methods

tion of Samples.—At first, urine samples were only from men working on suspect processes. however, some successes had been achieved, the ter examinations were extended to cover men left the hazardous processes and were employed work in the factory.

recently, in two of the factories, the working of all persons employed have been examined employment cards of all persons who have at had the possibility of contact with known or carcinogens are marked for the collection of mples. No difficulty has been experienced in samples and their regular collection is now as one of the routines of factory life. A large on of men exposed to carcinogens in the past employed in a multitude of unrelated jobs else- the factories, and must be specially sought out their regular samples. The bottles are delivered ton in the afternoon and collected full next

third factory it has been possible to examine the all the men. For geographical reasons it is for them to attend at the surgery to void their It is preferable to collect the urine in two jars the first containing contamination from the and prepuce, but this was only possible in the ey where the men attend at the surgery, or pecial sample is demanded.

Wet Smear Technique.—About 10 to 15 ml. of fresh urine is centrifuged at approximately 2,000 r.p.m. for 15 minutes. A drop of the sediment is placed on a microscope slide. A cover slip can be applied, but this is not necessary for low- or medium-power examination and much time can be saved by dispensing with it.

The presence of red blood cells, leucocytes, and epithelial cells is noted, and a rough count of red cells is made. An experienced technician very quickly develops the ability to assess the number of cells present at a glance.

The decision to advise cystoscopy on wet smear examination alone always rests on the results of repeated examinations unless the urine contains sufficient blood to be visible to the naked eye, when cystoscopy becomes imperative. One of us (T. S. S.) examined the urine of 2,000 consecutive male applicants for employment, none of whom had previously been exposed to chemicals, and 124 (6·2%) were rejected because of considerable numbers of red blood cells in the urine although there was no other factor which on physical examination would have been cause for rejection. Apart from this presence of red cells in the urine of a proportion of apparently healthy men, such cells may appear in the urine from other causes such as calculi, infection, or renal or prostatic disease; the problem is further intensified by the fact that certain aromatic amines, such as ortho-toluidine and 5-chlor-2-toluidine, can cause acute chemical cystitis with haematuria so that if a man with microscopic haematuria has a history of recent contact with such amines further urine examinations after his removal from exposure are necessary. Thus microscopic haematuria in a single sample cannot be taken as an absolute indication for cystoscopy.

The wet smear technique has diagnosed many tumours but is not specific. Where no tumour was detected other conditions of the urinary tract were occasionally found. Sometimes, however, a man with no detectable cause for the microscopic haematuria would undergo a negative cystoscopy on two or three occasions and then refuse at the very moment when cystoscopy was vital.

Although the presence of an abnormal number of red blood cells has been the usual criterion for cystoscopy, as pointed out by Nassauer (1920) the presence of pus cells in the urine of men previously exposed to carcinogens is also an indication for further investigation.

Each man's case has to be considered individually, taking into account the intensity and duration of exposure, the nature of the carcinogen and the time that has elapsed since first exposure, together with the severity and duration of the urinary abnormalities. For instance, inconclusive wet smears combined with a history of long and severe exposure would lead the medical officer to advise cystoscopy more readily than if the exposure had been moderate or negligible.

Papanicolaou Smear Technique.—About 40 ml. of urine is centrifuged at approximately 2,000 r.p.m. for 15 minutes and a portion of the sediment is smeared on to an albuminized slide. Without letting the smear dry, it is immediately placed in a fixative solution consisting of equal parts of 95% ethanol and ether for a minimum time of 10 minutes. It is then stained with haematoxylin,

counterstained, and mounted. The preparations are permanent and can be kept indefinitely. A detailed description of this technique has been given by Papanicolaou and Marshall (1945).

Although it is preferable to use freshly voided urine when possible, this is not absolutely necessary. It has been stated by Sawaya, Sandin, and de Almeida (1954) that specimens of urine must be processed within one hour of micturition as the cells may be so altered as to render interpretation impossible. We have found that even in unfixed urine, cellular degeneration does not proceed so rapidly and the addition of absolute alcohol serves to fix and preserve the cells for as long as 96 hours at room temperature. It was, therefore, possible to collect the specimens at convenient points in two of the factories and to deliver them to the laboratories for processing later.

Sediments from the majority of both fresh and fixed normal urines contain so few cells that they appear to be almost acellular, and in order to reduce the time spent on the examination of the slides various methods have been devised to concentrate more cells into each smear. Chute and Williams (1948) and Ruth Graham (1950) advocate making smears from the pooled deposit of the whole urine samples. Deden (1954), on the other hand, allows 200-400 ml. of urine to stand for six hours in a separating funnel and then centrifuges the sediment, while Rofe (1955) removes the non-cellular elements by differential centrifugation and the mucus by solution in water after fixation of the cells. Though these methods are too prolonged for a busy laboratory where many urines per day are being processed, a modified form of differential centrifugation is being used successfully in one of our laboratories.

The interpretation of the smears is difficult and requires a thorough knowledge not only of the criteria of malignancy as laid down by Papanicolaou in his atlas (1954) but also of the numerous variations from the normal due to non-neoplastic conditions. While anyone can be trained in a matter of weeks to identify and record blood and epithelial cells in wet smears, it takes many months of instruction and practice before a technician can make a reliable assessment of the cytological characteristics of exfoliated cells. The results are interpreted as follows:—

Class I ..... Normal Class II ..... Atypical	}	Negative
Class III		Suspicious
Class IV .....Probably malignant Class V .....Definitely malignant	}	Positive

A positive result is considered an indication for cystoscopy. Suspicious smears are regarded as positive if exposure has been heavy or if blood is also present, but in other cases repeated samples are examined until a decision can be reached. The cases presented below will serve to illustrate the application of the Papanicolaou technique:—

Case 1.—This man was aged 51 when the tumour was found. He had been exposed to the manufacture of benzidine for seven years from 1933.

Routine wet smears of urine had been done from 19[illegible] but had never suggested the presence of a tumour. Papanicolaou tests since 1951 were negative until May 1955, when a suspicious result (Class III) was noted. Early in June the smear was Class II but on June 30 it became positive (Class IV). Cystoscopy on July 1 revealed a papilloma and this was confirmed as a benign tumour on biopsy.

Case 2.—This workman was aged 49 when the tumour was found. He had been exposed to benzidine for [illegible] years, from 1931.

His urine had been tested for R.B.C.s from 19[illegible] onwards and showed no significant quantity of blood cells. Papanicolaou smears made on two separate occasions in December, 1953, were definitely positive. Because of this he was cystoscoped on January 25, 19[illegible] and a small area of malignant tumour was revealed which was confirmed as transitional cell carcinoma on biopsy.

Results

During the five years 1951 to 1956 the urines of approximately 1,800 men were screened by the Papanicolaou smear technique and also, except in three cases, by the wet smear technique.

Of these 1,800 men, 91 were cystoscoped as a result of the two tests or on account of developing symptoms and 62 new cases of bladder tumour were discovered. The results are shown in Table I. (The examination of the urines of those men with a previous history of treated bladder tumour will have been under regular cystoscopic review and is considered separately.)

Fifty-one men with positive Papanicolaou smears showed bladder tumours on first cystoscopy (three positives). (*a*) Twenty-six had symptoms and

TABLE 1

SMEAR RESULTS AND FINDINGS IN 91 MEN CYSTOSCOPED

Cystoscopic Findings	Smear Results and Findings in 91 Men Cystoscoped						
	True Positives	Probably True Positives	False Negatives	Total	False Positives	True Negatives	Total
Symptoms and/or R.B.C.s	26	4	6	36	4	18	22
No symptoms	26*	1	–	27*	6	–	6
Total	52	5	6	63*	10	18	28

* One case of carcinoma of the prostate.

R.B.C.s on microscopy sufficient in thembe an indication for cystoscopy. (*b*) Twentynot at any time had R.B.C.s or any other n that a tumour was present. One man had apanicolaou smears but no bladder tumour scopy, although a carcinoma of the prostate overed on clinical examination.

men with positive Papanicolaou smears, showing no tumours on first cystoscopy, d bladder tumours from five months to rs later (probably true positives). (*a*) Four mptoms or R.B.C.s sufficient to warrant y in any case. (*b*) One showed no R.B.C.s me.

men with negative Papanicolaou smears bladder tumours on first cystoscopy (false s). (*a*) Four were cystoscoped because of R.B.C.s. (*b*) Two showed only occasional nd had symptoms .

wo cases of bladder tumour and one case oma of the prostate were detected.

en had positive Papanicolaou smears, but er tumours have so far been discovered on y (false positives). (*a*) Three showed ufficient in themselves to be an indication scopy. (*b*) One had slight symptoms. howed only occasional R.B.C.s.

en men had negative Papanicolaou smears tumour on cystoscopy (true negatives). re cystoscoped because (*a*) 11 showed ufficient to be an indication for cystoscopy, ven had both R.B.C.s and symptoms. one men were cystoscoped.

Discussion

the five years under review, 51 (76·1%) l men with positive smears had bladder on first cystoscopy and the figure becomes out of 67 when the five " probably true " and the carcinoma of prostate are

ith negative Papanicolaou and wet smears med to be clear of tumours in the absence ms and were not submitted for cystoscopy. hat in the five years all the tumours found n early stage in their development on first on suggests that this view is reasonable. es it was found that a tumour was present apanicolaou smear was negative but all had an excess of red blood cells or had

and 3 show the results of the application d smear technique and the Papanicolaou to the urine of the 91 men who were ted.

and 3 show that in applying the wet smear technique to the urine of 88 of the men there were 25 (28·4%) false negatives and 20 (22·7%) false positive results whereas the Papanicolaou technique in 91 cases yielded only six (6·6%) false negative and 10 (11·0%) false positive results. From these data it can be concluded that the latter technique is superior as a diagnostic measure. In fact, as a result of the Papanicolaou technique 25 men were sent for investigation and a tumour detected before the onset of microscopic haematuria or any other indication that a tumour was present.

TABLE 2
WET SMEAR RESULTS

Cystoscopy	Red Blood Cells or Symptoms		Total
	Positive	Negative	
Tumour present	34	25	59
No tumour found	20	9	29
Total ..	54	34	88*

* In three cases no wet smear tests were done.

TABLE 3
PAPANICOLAOU SMEAR RESULTS

Cystoscopy	Papanicolaou Test		Total
	Positive	Negative	
Tumour present	57*	6	63
No tumour found	10	18	28
Total ..	67	24	91

* One case of carcinoma of prostate.

False Positive Results.—When cells with malignant characteristics are present in the urine and no growth is found anywhere in the urinary tract, the result is regarded as a false positive. At their first cystoscopy 15 men gave false positive results but five of them showed visible tumours on cystoscopic follow-up after five, 10, 11, 29, and 46 months respectively.

The following case is given as an example:—

Case 3.—This man was aged 58 when the tumour was found. He had been exposed to β-naphthylamine for eight years.

His urine was tested for R.B.C.s from 1936 onwards; occasional R.B.C.s had been apparent since 1950 but never of such significant number as to warrant cystoscopy. The Papanicolaou test showed malignant cells from March, 1953, onwards. He was investigated because of this in September, 1953, but no abnormality was seen except that on cystoscopy there was a little redness in a tiny area at the apex near the air bubble. Five weeks later, in October, 1953, the bladder looked more normal than previously and there was no change again in February, 1954. However, five months after this (July, 1954) and 10 months after the first cystoscopy a sessile tumour was found high up in the apex and a smaller tumour was seen near to the right ureteric orifice.

Clinically they appeared to be papillomata, but biopsy revealed them to be carcinomata.

The finding of apparently malignant cells in the urine before a tumour actually becomes visible is comparable to the finding by von Haam and Menzies (1953) of malignant cells in vaginal smears from laboratory animals some time before the gross appearance of experimentally induced carcinoma of the cervix uteri.

Chute and Williams (*loc. cit.*) in their series of cases were surprised at the number of carcinomata of the prostate that gave rise to positive smears in the sediment from ordinary voided urine, as distinct from that passed following prostatic massage. Amongst our cases one man with positive Papanicolaou smears was found to have a carcinoma of the prostate.

However, amongst our 10 false positive cases there are four men who have repeatedly shown malignant cells in the smear during the past two years and a further three who have shown similar findings recently. In none of these cases so far has a tumour been found on cystoscopy. The following case is a typical example:—

Case 4.—A man aged 44 had had slight exposure to bladder carcinogens, but had occasional attacks of cystitis with pain and dysuria.

He has had a few red blood cells persistently in the urine since 1949. The first Papanicolaou smears in April, 1952, were strongly positive, and all subsequent smears have remained so. He was cystoscoped in September, 1952, and again in February, 1954, but no abnormality was found either in the bladder or elsewhere in the urinary tract.

Masina (1952) in this country and Melicow (1952) and Melicow and Hollowell (1952) in America have noted that normal-looking epithelium taken from tumour-bearing bladders removed at total cystectomy when examined microscopically showed foci of cellular activity which closely resembled areas of tumour formation and other areas which they thought might in time develop into obvious growths. These observations may help to explain the continuous false positive smears from men with apparently normal bladders. It remains to be seen whether these men will develop tumours of the renal pelvis, ureter, bladder, or prostate later.

The remaining three false positive cases had renal calculus, urethral stricture, and haematuria following extensive burns. Ferguson (1949) points out that there are certain non-neoplastic conditions which produce cells almost identical to malignant ones and give rise to misinterpretation.

False Negative Results.—When a growth is found in the urinary tract of a man whose urinary sediment never shows the presence of tumour cells, the result is a false negative. There were six false negative results in our series, of which the following case is an example.

Case 5.—This man was aged 52 when the tumour was found. He had been exposed to α-naphthylamine for 19 years from 1935. His urine had been tested for R.B.C.s from 1936, and by the Papanicolaou technique from 1951. Although occasional R.B.C.s were noted they never reached sufficient numbers to warrant cystoscopy and the Papanicolaou results were always negative until he developed acute haematuria in September, 1954. Cystoscopy revealed a benign papilloma which was confirmed by biopsy.

In five of these cases the growth was clinically of a simple papillary type. On section, four were histologically benign, whilst in the fifth the biopsy material was unsatisfactory. In the sixth case a solid type of carcinoma covered with slough and calcareous deposit was present.

"Benign" Papillomata.—Benign papillomata appear to vary very much in the cells which they shed, and in some cases as Dean (1948) and Lea (1955) better point out, the exfoliated cells show no recognizable difference from the normal. Papanicolaou (*loc. cit.*) says such growths may be recognized by the presence of cuboidal and columnar cells often arranged in groups and clusters, sometimes showing a palisade formation, and he places them in the category of Class II, reporting them as atypical but suggestive of benign papilloma. However, he says, "their occasional presence in cases in which there is no evidence of such a growth limits their diagnostic significance", and also that "intermediate cell types from the prostate are also seen, some with a cuboidal or columnar form reminding one of cells exfoliated from a benign papillary growth". McDonald (1954) says that it is exceedingly difficult to distinguish benign papillomata unless fronds of tissue are exfoliated, while Osborn (1953) observes that such fragments of tissue show little cellular variation. Other authors (Chute and Williams *loc. cit.*; Schmidlapp and Marsh, 1950; Deden, *loc. cit.*) have come to the conclusion that cells from benign papillomata do not usually deviate from the normal sufficiently to permit a diagnosis and that amongst their cases their false negative results were mostly such tumours.

Our experience of these benign tumours is of considerable interest. Fifty-six men had bladder tumours in association with the exfoliation of abnormal cells. In 53 of them these cells showed apparently malignant characteristics and in the other three only clumps of "benign papilloma

ere seen. Yet, of these 56 men, 29 had benign papillomata; 15 of these were ed by biopsy, four proved to be malignant psy, and 10 were treated without biopsy. seven men had clinical carcinomata; 22 nfirmed by biopsy.

26 out of 29 men with clinically benign mata had apparently malignant cells in the only four out of 19 of these tumours were to be malignant on biopsy. Although it is to suggest that malignant changes were taking place in these tumours, such an ion would lead to an abnormally high e of malignancy amongst them. No satisexplanation is available to explain the of cells with apparently malignant character- the urine from such a high proportion of containing benign tumours. In our e it has not been possible to predict the ature of the tumours from the appearance afoliated cells. Nevertheless, these results at, contrary to many opinions, the Papanichnique is capable of detecting a significant ion of benign papillomata.

Papanicolaou Technique in Follow-up of Cases.—As there is a continuing liability er tumours to appear in persons who have ted for a bladder tumour, it is essential that pic reviews should be continued for life. nped, when the Papanicolaou technique was nd, that it could be substituted for at least hese review cystoscopies. We have applied o a group of 42 men who have had tumours Table 4).

TABLE 4

S OF 225 REVIEW CYSTOSCOPIES OF 42 MEN ED WITH RESULTS OF SMEARS BEFORE EACH CYSTOSCOPY

Cystoscopy			Total
Negative	Suspicious	Positive	
83	10	20	113
19	20	4	43
27	27	15	69
129	57	39	225

his it appears that dependence cannot be the result of Papanicolaou smears from a previous history of a treated tumour. viduals showed complete agreement all while others continually showed false or false negative results. At the present our investigation it can therefore only be the stained smear technique is unreliable ng established cases. It is too early yet whether these false positive smears have ostic significance.

Conclusions

Our experience over the past five years has shown that the Papanicolaou technique can be successfully used as a method of screening the urine of an industrial population. This confirms the suggestions of Case (unpublished, 1949) and of Cromwell and Papanicolaou (1952) that cytological examination of the urine would be of value in detecting industrial bladder tumours. The most important advantage of the method is its ability to indicate the presence of a tumour at a very early stage of its development, often before any presenting symptoms or other urinary abnormalities have given an indication of its presence. Poole-Wilson (1953) observes that on account of routine medical examination in industry occupational bladder tumours tend to be seen in an earlier stage than those arising spontaneously.

To obtain the best results both the Papanicolaou and the wet smear technique should be employed together. On the other hand, wet smears of concentrated deposit can be examined for epithelial cells, and a Papanicolaou smear only made and examined if such cells are seen. If the urine is acellular much time and trouble can be saved in this way without a significant loss of efficiency. By this means it is possible to maintain a much more comprehensive and frequent check on large industrial populations than can be achieved by the use of routine cystoscopy. It is also possible to include considerable groups of workers whose chance of tumour development may only be remote.

Routine annual cystoscopy of persons with high risk is claimed to be practicable abroad. If it had been used as a screening method on this population it would have involved at least 8,000 cystoscopies in five years compared with the 91 carried out for us. The fact that early diagnosis was achieved in our cases leads us to believe that the techniques we have described offer very considerable advantages. We consider that they are indispensable, if all necessary care is to be given to workers in any factory where a hazard of industrial bladder tumours exists.

Summary

A description is given of cytological methods of achieving early diagnosis of occupational bladder tumours. The results obtained by examining the urine of some 1,800 workers for the presence of microscopic haematuria and by the Papanicolaou technique are reported together with the cystoscopic findings amongst 91 men.

The advantages and disadvantages of the two techniques are discussed.

It is concluded that the Papanicolaou technique offers considerable advantages in the diagnosis of benign and malignant tumours of the bladder, and

that this, coupled with the examination of urine for red blood cells, is the method of choice for screening an industrial population with a high risk of such tumours.

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THE CONTROL OF INDUSTRIAL BLADDER TUMOURS

A Code of Working Practice Recommended by the British Dyestuffs Industry for the Manufacture and Use of Products Causing Tumours of the Bladder

BY

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T. S. SCOTT and M. H. C. WILLIAMS

From the Papilloma Committee of the Association of British Chemical Manufacturers

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Bladder tumours have been recognized as an occupational hazard amongst dyestuffs workers for over 60 years. The news of this hazard reached Great Britain in 1912 following the visit of Thomas Legge, then H.M. Senior Medical Inspector of Factories, to Frankfurt-am-Main in 1911 (Legge, 1912, 1913), but it was not until 1926 that the first cases in England were described by members of the factory medical inspectorate (Bridge, 1927). The first contribution from the industry itself came from Wignall in 1929. By 1933 Bridge, H.M. Senior Medical Inspector of Factories, reported that 28 deaths from occupational bladder tumours had come to his notice. Goldblatt (1949) described 101 cases from a group of British factories and Scott (1952) recorded 66 cases from yet another works.

In 1947 the Dyestuffs Group of the Association of British Chemical Manufacturers (A.B.C.M.) set up and financed a major research project on industrial papilloma of the bladder. This has been described in a booklet which was circulated to managements, trades unions, and workmen (1953). A scientific committee was appointed under the chairmanship of Professor A. Haddow to guide research work into the cause, consider diagnostic methods, and examine preventive techniques. A sub-committee was invited, under the chairmanship of Mr. N. Strafford, to provide accurate methods for the analysis of suspected compounds under industrial conditions (Butt and Strafford, 1956). In 1948 a research fellow, Dr. R. A. M. Case, was appointed at the Chester Beatty Institute to conduct an investigation into the industrial data. This enquiry covered the records of over 30 years of the manufacture of dyestuffs and their intermediates in Great Britain. The results and the statistical analysis were published in 1954 (Case, Hosker, McDonald, and Pearson, 1954).

Case and his co-workers were able to produce statistical proof that contact with alpha-naphthylamine, beta-naphthylamine and benzidine, three compounds which had previously been suspected, caused a significant incidence of bladder tumour amongst the men engaged in their manufacture or use. No evidence was found to inculpate aniline and it is now considered that under the conditions of its manufacture and use in this country it is not a significant cause of bladder tumour, and that the name aniline cancer of the bladder is an unfortunate misnomer. Suspicion, however, fell on the manufacture of magenta and auramine and further data collected and analysed confirmed that the risk also existed in connexion with their manufacture. The results of the study were at once given to the Ministry of Pensions and National Insurance, and in 1953 papilloma of the bladder was prescribed as an industrial disease in occupations involving contact with alpha-naphthylamine, beta-naphthylamine, or benzidine, and the manufacture of auramine or magenta.

Progress had already been made in many directions to improve the methods of protection from the compounds now proved to be carcinogenic, but it was obviously necessary not only to devise the safest possible method of working but also to be able to assess the efficacy of those measures in eradicating the tumours. We were, therefore, invited by the A.B.C.M. to draw up a " code of industrial practice" to cover the manufacture and use of known or suspected bladder carcinogens and the present paper is based on the recommendations made to the member firms of the Association in 1953 now brought up to date. Many of these recommendations have been made before but it is felt that repetition is not without virtue in this context.

This report is based on the following premises which are now generally accepted in Great Britain and which have been confirmed by the report on the

eld survey, by other published reports, and by the dustrial experience of the authors:—

(*a*) That the high incidence of bladder tumours has occurred in men working on the manufacture or handling of beta-naphthylamine, benzidine, and to a lesser extent, alpha-naphthylamine.

(*b*) That there is a widely variable latent period (or induction period) between entry to the industry and onset of the tumours. This may range from one to 45 years with an average of 18 years and the most common time of development is between 15 and 20 years. This does not necessarily coincide with the period of exposure, which also varies widely. Exposure periods of a few months are accepted as being sufficient to cause a tumour.

(*c*) That the process of tumour development, once initiated, is irreversible and is not arrested by cessation of exposure. Thus the exposure period may, in those who leave the industry and subsequently develop a tumour, be shorter than the latent period. During this time it is not possible to demonstrate any pre-tumour changes in the bladder, nor is any method of treatment known which would prevent the development of a tumour.

(*d*) That the onset of tumour and death occurs at much earlier ages in those who enter the industry before the age of 30 than in the general population or in entrants over 40. This may be applied as a rough test for occupational hazard, *i.e.*, death from bladder tumours in younger age groups would give rise to the suspicion that the tumours were of occupational origin. It is not thought that younger people are more susceptible to the disease but only that the younger the age at entry into the industry, the younger will be the victim at onset should a tumour develop. Older people are in fact more likely to develop spontaneous tumours of nearly every type including bladder tumours.

(*e*) That the proportion of exposed persons who will be affected is influenced by the intensity and duration of exposure. The higher the " dose " as determined by these two factors, the greater will be the number affected.

(*f*) That the mean latent period is influenced by the type of carcinogen. It had previously been thought that the severity or length of exposure might influence the latent period and this is the case in a number of recorded animal experiments. The statistical analysis, however, did not confirm this view.

(*g*) That the cancer-producing potency of these substances in industry varies, technical beta-naphthylamine being about twice as potent as benzidine and four times as potent as technical alpha-naphthylamine. It is strongly recommended that all compounds which are known or suspected to be cancer-producing should, where manufacture is necessary, be manufactured and handled with equally stringent precautions as far as is technically possible.

(*h*) That alpha-naphthylamine may be a carcinogen itself apart from its beta-isomer impurity. Therefore even if alpha-naphthylamine can be manufactured free of its beta-isomer impurity it should still be regarded as dangerous, unless overwhelming proof to the contrary could be adduced.

(*i*) That aniline does not cause occupational tumours of the bladder in men engaged in its manufacture or use.

(*j*) That there is an occupational hazard of bladder tumour in the manufacture of auramine and magenta with a latent period of the same order as the other occupational cases. This does not necessarily mean that the finished products, auramine and magenta, are themselves the causal agents and the statistical analysis could not elucidate this point.

Case and others (1954) give a statistical estimate of the number of cases that may be expected in the future from the people who have already been exposed. Case (1953) has also set out a method by which it is possible for a firm in Britain to estimate the number of deaths that might arise by the non-occupational risk of the disease. A comparison of this with the observed number can be used to detect dangers associated with unsuspected processes and eventually to test the efficacy of new precautions. Case and Lea (1955) have described a more general and simpler method of achieving this object, and, in conjunction with Case and Pearson's tables (Registrar General's office, in the press), the method can be applied to other forms of cancer as well.

Description of the Disease

Occupational tumours of the bladder present all clinical and histological stages between benign papillomata and infiltrating carcinomata. A papilloma may undergo malignant change. The tumours occasionally occur in the ureter or the pelvis of the kidney (Macalpine, 1947). There is no demonstrable difference between those contracted by chemical workers and those arising in the general population.

Recurrences are frequent and tumours may recur as papillomata or as carcinomata irrespective of the nature of the original lesion. It is thought that many of these so-called recurrences are fresh tumours arising in an already activated bladder mucosa. The usual complications, such as haemorrhage and infections, occur with either type of tumour.

The onset is insidious and the disease may be advanced or even incurable before any symptoms or signs appear, but, on the other hand, it is common for severe symptoms to occur in the early stages when treatment is likely to effect a cure. Usually, the first sign is haematuria, but bleeding may not be visible even in advanced disease. Another sign is pyuria caused by the tumour surface ulcerating or becoming infected. Other signs or symptoms such as dysuria or frequency may arise, depending on the stage to which the tumour or its complications has advanced. It will be obvious from this that any haematuria, even in microscopic amounts, must be regarded with suspicion and this is extremely important in early diagnosis.

Because of the tendency to recurrence, it follows that once a tumour has been treated it is necessary to have regular follow-up examinations and review of each case at suitable intervals. Even when apparent cure has been maintained over many years at least annual re-examination should be continued. In view of the long latent period, in some cases over 30 years, it also follows that once a man has been exposed for a sufficient time to chemicals which can cause bladder cancer he remains at risk for the rest of his life, whether he continues to work with them or not. We consider that a period of six months' exposure can be sufficiently long but even shorter periods may come to be accepted as sufficient to induce a tumour.

PART I

Medical Recommendations

This section deals with the medical control of the hazard, with selection and education of workers, the methods of protection, and the keeping of records. Our recommendations for ensuring the early diagnosis of tumours in industrial workers at risk are the subject of a separate paper (Crabbe, Cresdee, Scott, and Williams, 1956), which should be studied in conjunction with these recommendations.

Medical Control.—Medical control is essential to ensure (1) proper selection and adequate medical supervision of workers; (2) early diagnosis of bladder tumours; (3) liaison with the family doctor, the urologist, and the hospital; (4) the follow-up of men with established tumours from the point of view of their treatment, regular reviews, and working capacity; (5) general supervision of the health of workers, supervision of plant hygiene, investigation of the records to determine the incidence of sickness due to bladder disease.

It is recommended, therefore, that where there is a hazard there should be a medical officer, either full-time or part-time, depending on the amount of work involved. It is desirable that all investigation and treatment should be undertaken with the cooperation of the workman's family doctor and that, if possible, all the cases in one area should be treated by the same surgeon or unit, who would thus gain valuable experience of industrial tumours. To this end the works doctor should approach the man's family doctor to arrange through him the necessary investigation or treatment by the surgeon with whom he would also be in touch.

It is an important part of the treatment and rehabilitation of these cases that they should be enabled to continue at work and not become chronic invalids; here again it is essential to have skilled medical advice on their capacity for work and placement in a job.

Records.—The following records should be maintained in relation to each suspected carcinogenic substance:

1. (*a*) Plant and processes. Chemical and physical form of products during process and isolation (*e.g.*, base, sulphate or hydrochloride, etc.)
   (*b*) Quantities manufactured and handled
   (*c*) Methods of manufacture and handling with dates of changes
   (*d*) Type and design of plant used with dates of changes
   (*e*) Plant hygiene precautions
   (*f*) Duration and types of shift worked

2. The following records should be maintained in relation to each man working with these compounds:—
   (*a*) Name and address
   (*b*) National Insurance number
   (*c*) Date of birth
   (*d*) Date of entry into the industry
   (*e*) Date of starting hazardous occupation

(*f*) Previous significant occupational history
(*g*) Works history
(*h*) Any significant accidental contamination
(*i*) Particulars of death certificate

The information compiled from these records is essential for a precise assessment of the hazard in the future. They need not necessarily be kept by the medical officer but should be available to him. Many of these particulars will already be recorded by the technical and labour departments.

Where no records have existed previously a register should be compiled with these particulars, as far as they can be ascertained, in respect of present and past workers. This is similar to the nominal rolls supplied by the member firms for the I.B.C.M. field survey. This register should be continued in the future and kept up to date. From it may be calculated, by the methods mentioned earlier, the number of cases of tumour likely to arise by the ordinary risk of the disease. The actual incidence may, now or in the future, be compared with this and hence may indicate the existence of a hazard and whether the measures applied for control have been effective. Arrangements have been made for the appropriate records to be maintained in the future by H.M. Senior Medical Inspector of Factories.

Selection.—New entrants to jobs which involve risk of tumour, either in manufacture or use of carcinogenic substances, should be selected by the works medical officer, bearing in mind the following considerations:—

Age.—The age of onset of bladder tumours in those who develop them is almost entirely dependent upon the age of entry into the industry, occurring after a latent period of usually 15 to 20 years. Men over the age of 30 should be chosen when practicable in order to reduce the likelihood of onset and mortality from these tumours at early ages. Men over 40 should be given preference.

Personal Hygiene.—A high standard of personal hygiene is essential to reduce the absorption of chemical by the skin and mouth to the minimum. Generally speaking, those whose standard of hygiene is poor will be unlikely to cooperate in the personal preventive measures such as clean working, bathing, and changing. The dirty should obviously be rejected; nail-biting increases the risk of ingestion; septic teeth and mouths suggest poor hygiene; the bearded should be excluded because of the possibility of the beard becoming contaminated and so increasing the risk of absorption by the mouth and nose; mouth breathers with nasal obstruction should also be excluded as they may tend to remove masks.

Intelligence.—A sufficient standard of intelligence is necessary to understand the hazard, to profit by training in methods of prevention, and to apply the self-discipline necessary to cooperate in the measures prescribed for personal hygiene and protection.

Previous Health.—Special attention must be paid to any previous disease of the genito-urinary system and to any previous history of cancer of any type or of any organ. An applicant with such a history must be rejected because of the risk of non-occupational disease which would confuse the assessment of the hazard and the diagnosis of industrial tumour. There is no evidence that a family history of cancer predisposes to bladder tumour and we do not recommend rejection merely on this ground.

Present Health.—Men selected should be free from gross disease, especially of the genito-urinary system, and from cancer or any pre-cancerous lesions of any organ or of the skin. The urine should be examined for albumin and blood and pus cells, partly to assist in excluding genito-urinary disease and partly to avoid confusion in the interpretation of urine tests after the applicant has started work.

Occupational History.—It is most important to ascertain whether there has been any previous exposure to carcinogens. Men who have previously worked in occupations in which they have been exposed to other carcinogens should be excluded from starting work with these compounds. This would also entail the rejection of men with a previous industrial history of work in tar products, gas works, rubber works, coke ovens, and in other chemical plants carrying a carcinogenic risk. On a plant where the hazard is suspected but not proved it is undesirable to employ men who have had previous exposure to carcinogens.

Apart from the above considerations, the standard of fitness required will be determined by the type of work to be done. The physique or strength of a man or the general state of his health is no indication of his resistance to bladder tumour.

Education and Training.—The worker selected should have explained to him clearly and simply (*a*) what the hazard is, (*b*) where and how it arises, (*c*) the measures which are taken on the plant to prevent risk, (*d*) how he should use the measures provided for his personal protection.

We consider that it is not possible to justify the concealment of such a risk from men who are being exposed to it. Better cooperation can be expected if they understand what is being done to attain safe working conditions and why it is being done. A simple explanation of the situation, including reference to medical care, engenders confidence in the

worker's mind. Particular care should be attached to supervision and training during the first few weeks of a man's employment on such a plant.

Protective Measures.—In industry these compounds enter the body by two main routes—inhalation and absorption through the skin—but it should be borne in mind that they can also be ingested. Thus the aim of all preventive measures must be to reduce to the minimum, and where possible to eliminate, all contacts between operator and carcinogens. The first and basic method of ensuring this end must be by plant design and operation. The second line of defence is the provision of personal protection for the workmen but the hygiene of the plant and of the working environment is more important than any measure which depends for its efficiency on the cooperation or discipline of the operator or on any measure which is under his control (Legge, 1934).

Working Clothing.—No man should wear any of his own clothing while exposed to carcinogens. A complete set of working clothing should be supplied and should include underwear, footwear, socks, and outer-wear. They should be changed immediately on accidental contamination, and should be changed and washed at regular intervals depending on the plant conditions and on the degree of exposure but not less than once a week in any circumstances. A daily change will avoid the absorption of amine which has impregnated the clothing on the previous day. For laundering a slightly acid synthetic detergent is preferable to alkaline soap as the latter leads to the formation of the insoluble base which may dry in the clothes. The clothing should be tested at frequent intervals for the presence of amines by the methods which have been described by Butt and Strafford (1956). This forms a useful check on the efficacy of the measures taken to prevent absorption of the noxious substances. The working clothing supplied should be taken off at the end of each shift and must be left at the factory. On no account should it be taken home. Separate lockers should be provided for home and working clothes so that no cross contamination takes place. A clean smock or coat can be worn during meals so that tables and food are not contaminated from working clothes.

Protective Clothing.—The protective clothing, which should be supplied and worn in addition to the working clothing described above, will vary according to the process and the type of plant and the resultant potential exposure, but will generally consist of overalls of closely woven cotton or wool (or blouse and trousers of similar material), rubber boots, rubber or plastic gloves with gauntlet fitting or long sleeves attached, and a cap which can be washed.

GLOVES.—PVC and rubber withstand the amine but if new carcinogens are discovered care must be taken to ensure that protective materials are resistant to them. Gloves contaminated on the inside must be destroyed. The outside of gloves should be washed by the operative during and after work but the laundering of gloves for re-issue is not recommended because of the danger of accidental re-use and incomplete decontamination. Cotton gloves are inadequate and may result in longer absorption than brief contact with bare hands followed by immediate washing. This latter practice may be necessary where delicate manual operations are carried out by fitters. Impervious armlets can be worn with gloves in dealing with molten carcinogens or solutions.

APRONS.—Light impervious aprons for handling molten carcinogens or solutions should extend up to the neck and below the tops of the rubber boots.

FOOTWEAR.—Rubber safety boots are preferable to clogs as they are more impervious and they can be worn to knee length if liquids are being handled. Turning down the tops of boots is wrong, particularly when aprons are worn, as liquid is apt to run inside the boots.

MASKS.—Should vapour or dust give rise to heavy atmospheric contamination, hoods with clean compressed air supplies should be used. Dust respirators are not always dependable because of the unreliability of individual fit and the risk of skin absorption from the face and neck. Cotton wool pads are not adequate protection against these dusts or vapours.

Baths.—Suitable changing and bathing facilities with adequate hot water, soap, and towels must be available at the factory. Shower baths are the most satisfactory and are usually preferred, but some workers, especially the older ones, prefer a slipper bath. The main objection to the slipper bath is that in cases of contamination some amine may remain on the skin from the bath water; there may also be some danger of inhaling amine volatilized by the hot water while lying in the bath.

(1) A bath or shower must be taken at the end of each shift so that small quantities of amine which may be present on the skin will be removed. This must be obligatory and the bathing time should be paid for. Twenty minutes is regarded as adequate time.

(2) These compounds can be absorbed directly through the skin in any physical form as salt or base, molten liquid or solution, or at any temperature, so that if there is accidental contamination

if contamination occurs during plant maintance or cleaning, it is essential that the workman bathed immediately and his clothing completely anged. If contamination is very heavy and a per bath is used, a second bath is advisable as water in the first becomes heavily charged with ine. A scrubbing brush will help to remove mical from rough skin or fissures and care uld be taken to ensure that the nails are cleaned. e hair should also be washed and it should be membered that spectacles, if worn, may be ntaminated.

Hours of Work.—Process operation should be so usted as to limit the time of exposure to a nimum. (*a*) No overtime should be worked cept in an emergency and an emergency should be garded as being an occasional isolated incident d not a continuous period. (*b*) If men work with se amines for part of a day or shift they should th and change before going on to other work to mplete their shift.

Limitation of Numbers Exposed.—The total mber of men exposed regularly to these carcinoens should be limited as far as conditions allow. (*a*) Only men who have been selected by the dical officer should be allowed to work on ocessing or handling operations.

(*b*) Temporary or casual process workers and ndlers should be kept to a minimum and avoided possible.

(*c*) Cross transfers from one hazardous plant to other should not normally be allowed so that fusion as to the relative risks of each plant or ocess may be avoided. But, in small factories, may be better to employ one man, or a small mber of men, to operate all the plants where there a risk rather than to increase the numbers exposed.

(*d*) Similarly, the handling of these substances in y plant should be confined if possible to one man if the scale of work is too large for this, to a ited number of men who would handle, weigh, d charge all the dangerous material where chanical methods cannot be installed.

(*e*) Selected deputies should be appointed to cover e absence of regular men. No other men should allowed to do the job.

All men engaged on these processes should be ployed on a voluntary basis and no industrial ctions should be applied to persuade men to dertake this work or to remain on it.

In plants where radical improvements have been ried out or in new plant which has been built th due regard to safe working, we recommend at men of suitable age who have not previously en exposed to carcinogens should be employed whenever possible, although it may be necessary to employ certain key men who have previous experience and possibly previous exposure.

Cases of tumour developing after a few months of heavy exposure to benzidine and beta-naphthylamine have been reported. Safe working should be achieved by appropriate plant design and methods of working and no reliance should be placed on the practice of employing men for short periods, as advocated by earlier writers, as this would only increase the numbers of men at risk.

PART II

Plant and Operating Precautions

This section will deal with the industrial and technical measures recommended in the manufacture and use of alpha-naphthylamine, beta-naphthylamine, benzidine and its homologues, and a number of other processes. Before discussing the details peculiar to each process it is proposed to lay down the basic principles which must lie behind all efforts to eradicate this hazard completely from the industry.

Buildings.—In the design of new plants the ceiling should be sufficiently high to allow adequate ventilation. Where possible, pressure vessels containing molten carcinogen should be isolated in the open air. The walls should be made of a material which cannot become impregnated with chemicals. The floors should have an adequate slope to drain and be constructed of a material which will withstand both physical and chemical damage. If wear and tear occurs so that pools form, these must be filled in since they can form a constant source of atmospheric contamination as well as a cause of splashes. Where a high level of exposure is liable to occur no wood should be used in the construction of stairs, platform floors, or hand-rails, all of which should be made of metal. Floor grids must be easily removable and drains should have a sufficient gradient to ensure quick flow. Although it may be difficult to alter old sheds, these recommendations represent the standard to be aimed at.

Ventilation.—Forced ventilation will be desirable for all buildings where carcinogens are regularly handled in a manner where there is any possibility, however remote, that the general atmosphere may become contaminated with vapour or dust. In order to achieve adequate air changes in the lower floors of some buildings, it may be necessary to provide air suction trunks from the roof to each floor in order to achieve the desired effect. It must be made clear that the need for forced ventilation of the general working space is much more necessary

where volatile hot carcinogens are being handled than where the hazard is in the form of dust. Likewise, forced ventilation is least necessary where there is no hot process and the final product is handled as a paste. All general airflow should be arranged so that the air current moves away from the man.

No plant item containing hot molten carcinogen should be vented within the working space and if a number of such vent pipes are necessary a common scrubber system should be provided so that contaminated air does not enter other sheds nearby or re-enter the shed from which the contamination originated. If no such scrubber system is installed the vent pipes must be carried well above any point where air is entering the working space, such as windows or ventilators.

Plant.—The object in all plant design must be to contain the carcinogens within an enclosed system wherever possible whether they are present as dust, vapour, or liquid. Every plant item should be considered with regard to its enclosure and ventilation outside the working space. Lagging liable to be contaminated should be encased in an impervious material, so that spillages can be effectively removed. Hot contaminated lagging is a danger and care should be taken during its repair. Catwalks should be provided where necessary to avoid damage to lagging. All operations involving manual handling of carcinogens whether in concentrated form or when they are present only as an impurity should be studied with a view to the establishment of automatic enclosed types of plant. All such plant should be designed so that decontamination can be carried out before it is handled by fitters. Sharp angles of pipes should be avoided to minimize the chance of blockages, and in pipe design special attention should be paid to ease of replacement.

When these improvements have been carried out there remains the risk of these carcinogens being in contact with the workroom atmosphere during final packaging in manufacture, or in charging if these intermediates are being used. Bulk handling of material in enclosed pipelines as molten liquid, slurry, or solution will often close this last loophole. If manual handling is inevitable in charging or isolating the material, adequate draughting and full protective clothing must be relied upon. It is realized that bulk handling will only be possible where considerable quantities of carcinogens are being handled. Evidence available suggests that by far the greatest risk exists on plants which handle carcinogens consistently every day. Where dust is likely to occur floors should be kept wet to prevent it from rising into the atmosphere. A pipe with multiple holes can be fitted so that the floor can be kept constantly wet.

Sampling of Product.—Where sampling of h carcinogens within an enclosed system is necessa for process control, a device can be installed carry out a melting point determination witho opening up the plant. Where samples have to withdrawn this should be done in a small vent cabinet. The use of dip pans for sampling is u satisfactory because hot amine is given off to t atmosphere during withdrawal and transport. T use of dip sticks to determine the depth of liquid vessels containing carcinogens is dangerous ar automatic depth recorders should be installed.

Batch Weighing.—Tumours have occurred among weighmen. Adequate draughting should be pr vided where any batch weights of intermediates a made up and suitable protective clothing should worn by the operator.

Isolation of Solids.—Filter presses and ope nutsches are unsatisfactory for the isolation carcinogens or of materials where the carcinoge are present as impurities, unless a completely im pervious one-piece suit with compressed air supp is worn by the operator. When the operation completed the clothing must be scrupulous decontaminated before the man emerges from th suit. Rotary filters, pressure filters, vacuu nutsches, and automatically discharging whizzer all totally enclosed, are more suitable. The emptyin of closed nutsches by shovel easily leads to co tamination of skin and clothes and re-slurrying the only satisfactory method of discharge. Attentio should be paid to the possibility of pastes drying ou and giving rise to dust hazards. Flakers should totally enclosed and their discharge points draughte

Disposal of Still Residues.—Tar or pitch must n be allowed to set hard on the inside of stills. On n account must a man enter a still to chip out suc pitch unless he is protected by a completely im pervious suit with a fresh-air feed hood. This latte practice should only be an emergency measure. Thi risk can be eliminated entirely if molten still residue are fed directly to a furnace which must destroy th carcinogen and not distil it to the outside atmosphere

Drying.—The hazard to workmen on driers in th dyestuffs industry is real and may arise in th drying either of concentrated carcinogens or o products derived from them which contain un reacted carcinogenic amines. It is recommende that where complete dryness is not essential, tra drying should be avoided and the materials shoul be isolated as pastes from enclosed filters or fro

closed high-speed automatically discharging izzers. Where possible no unreacted carcinogenic ine should remain in the products derived from cinogenic intermediates and routine analyses y be necessary to check this.

Where these measures are technically impossible heat drying has to be used, the most dangerous undesirable of the methods of drying is that in ich a man has to enter the drying space where he y breathe or be in contact with any vapourized ine which is in the atmosphere. Hence tunnel ves are quite unsuitable. Stoves with forced air w must not be vented into the working space. st and sublimed material tend to blow from ill-ing doors and to collect in the flues, so that this thod of drying is not without hazard, apart from e detraying of a dusty product. Vacuum stoves e liable to produce high atmospheric contamina-on when the doors are first opened. All forms of y drying carry a heavy risk because of the dusting the material on discharge from the trays. If tray ying of small amounts of material containing cinogens is inevitable, special exhaust ventilation ould be provided and protective clothing with a sh-air hood should be worn. Drum driers which e totally enclosed produce a large amount of dust ich may contaminate the operator because of the ed for frequent blade adjustment and overhaul an enclosed draughted "venuleth" drier may be ed.

Enclosed self-discharging driers with the discharge nt adequately draughted are the best type avail-le at the moment. It must be remembered that if y unreacted bases are present, some will be atilized during drying and will be deposited in e ventilation system.

Grinding.—If possible grinding of carcinogens or aterials containing carcinogens should be avoided ogether since even the best enclosed draughted ll produces some dust. If it is possible to whizz e material down to a sufficiently low water content r subsequent use, this should be the method of olation preferred. Checks should be made to sure that aerosols are not produced by the hizzer and that maintenance is efficient.

Maintenance.—However effective plant design d operation can be made, it is eventually necessary o open up plant for inspection or repair. Unless ingent precautions are taken there is a high otential risk to maintenance and engineering ersonnel. All plant items should, therefore, be eared of carcinogen where possible before being smantled for maintenance. This may be achieved ther by steaming out an enclosed system ensuring at steam laden with amine is not sent to atmosphere, or by washing with cold water followed by chemical inactivation of any carcinogen remaining. Where the carcinogen is an amine, inactivation may be carried out with hypochlorite or formaldehyde or by diazotization and destruction of the amine. In the event of maintenance of a contaminated plant item being inevitable, as in the setting of flaker blades, complete impervious protective clothing is necessary together with the use of a fresh-air feed hood. Changes of clothing and washing facilities are as necessary for fitters on these processes as for processmen. Where contamination is likely to occur, protective clothing and plant decontamination must likewise be provided for other tradesmen, such as electricians, instrument fitters, and construction engineers.

Transport and Packaging.—Where dry flaked carcinogens are being packaged, drums with tight-fitting lids are advocated as the best method of transport. Damaged drums which do not fit standard draughted devices should not be used as dust may escape due to the setting up of uneven air currents.

Wooden casks must be avoided if possible. Where acid pastes are being handled, however, casks may have to be used but specially lined drums are preferred. Individual casks should have the lids fitted immediately after filling so that the paste does not have time to form a dust on the surface. The use of a handle in the centre of the lid may help to avoid contamination of the lid with the contents of the cask during heading up. If a cask used in the transfer of carcinogenic materials becomes unusable, it should be burned rather than sent for repair since it is impossible to remove dust from the cracks in a broken cask. Casks which have contained a carcinogen must be washed with cold water since tumours have occurred amongst cask washers who inhaled steam vaporized carcinogens from hot washing. Remote control hot water washing can be used if cold water fails to clean the vessel but care should be taken to ensure that the steam is adequately removed and does not drift towards the operator.

In the event of transfer of hot or molten material, special drums with indwelling dip legs can be used. In the event of such a drum containing a solid this will have to be melted in a draughted compartment before emptying. Drums requiring welding should be specially cleaned before repair so as to avoid vaporization of carcinogen during this work.

Where bulk handling is used special devices will be necessary to catch drips and ensure clean coupling of charging and discharging pipes. Local draughting will ensure that vapour does not arise

from the open ends of pipes after use. Bulk transport lorries should be supplied with warnings and full instructions for safe handling of material spilt after accidents, together with the necessary protective clothing. If such solid material sets on the road, its cold chipping with full protective clothing will be necessary after the police have been informed.

DETAILED CONSIDERATION OF MANUFACTURE AND USE

Having discussed the basic principles to be adopted in considering the elimination of this hazard from the dyestuffs industry, it is now proposed to devote a section to each relevant process. These sections may repeat some of the general principles but it is intended to point out to the manufacturer the main and also the subtle dangers associated with the operation of each process. Explanations based on experience of factory conditions are included where necessary as well as any relevant results of animal experiments.

Beta-naphthylamine

The manufacture of beta-naphthylamine has proved to be by far the most hazardous occupation in the dyestuffs industry. It was felt that no plant could be economically devised which could be operated with any degree of certainty that tumours would not occur. The cessation of its manufacture and use in 1952 in Great Britain is considered to be one of the most important measures in the prevention of industrial bladder tumours.

Its main use was in colour manufacture for which beta-naphthylamine was sulphonated. The sulphonated compounds, which are not considered to be carcinogenic, can be made effectively by the amination of the appropriate sulphonated beta-naphthols.

The use of beta-naphthylamine to make rubber chemicals and colours has also been abandoned in Great Britain. In the case of the rubber chemicals and small colour manufacturers, alternative products with similar or improved technical effects have been developed using non-carcinogenic intermediates.

Tobias Acid (2 Naphthylamine-1-Sulphonic Acid)

Since crude and technical Tobias acid contain a trace of beta-naphthylamine as an impurity, this compound must be treated with certain precautions. This impurity can be reduced to a minimum by appropriate control of process conditions. The beta-naphthylamine is present as the sulphate so that no free amine is volatilized during drying. However, the final dry powder may constitute a potential hazard, both in manufacture and use. Efficient draughting should be provided at the packaging point and a type of enclosed drier is recommended as opposed to any form of tray drying. The product is very apt to " fly " and it is doubtful if tray drying can be achieved with complete safety.

Full protective clothing for the workman with dust masks or fresh-air hoods should be adequate for charging this powder for use in subsequent processes, but pneumatic handling is preferable if large amounts are regularly used. Anti-dusting treatment of the powder should not be relied upon.

No tumours have been attributed to Tobias acid manufacture in any country to date, but in view of the vast increase in manufacture accompanying the cessation of beta-naphthylamine manufacture, exposure to it will certainly be increased greatly and the recommended precautions must be taken.

Benzidine

The findings of Case *et al.* (1954) removed any doubt previously held as to the hazard associated with the manufacture of this chemical. No alternative has been found, however, to the use of benzidine in colour manufacture as has been the case with beta-naphthylamine. The hazard is believed to exist after the conversion of hydrazobenzene to benzidine. In some factories, where the reduction of nitrobenzene to hydrazobenzene and the subsequent conversion to benzidine have been entirely separated, no tumours have been recorded amongst men carrying out the reduction process whilst many tumours have occurred amongst those working on the conversion and isolation of benzidine itself. However, in many cases reduction and conversion are carried on in the same building and therefore, full-scale precautions are recommended for both. Whether the reduction is effected by zinc dust, sodium amalgam, or electrolytic means enclosure of all plant items should be aimed at. If it is necessary to isolate the hydrazo compound enclosed types of filter should be used. The conversion vessel should be totally enclosed and dip pot sampling should be avoided. The material should be handled in an enclosed system as a slurry before isolation in an enclosed filter. The distillation of benzidine base and the isolation of the product in solid form as base is liable to result in contamination of the atmosphere with vapour which can be entirely avoided by final isolation as a salt. The final product must be packed with all necessary precautions against dust and skin contact. The salts of benzidine can be absorbed easily through the skin and no refuge must be sought in the suggestion that the salts are less dangerous. Tumours have occurred amongst men handling all the salts and the base in various factories in the world. Isolation of benzidine

salt, however, avoids almost completely the sibility of vapour contamination but a potential s and skin hazard still exists.

The isolation of this compound from an open s the filter press or any open filter device is gerous. In the event of the product being ufactured as base, the grinding of the final duct as opposed to flaking is strongly deprecated. e best conditions are most likely to be attained h the isolation of the final product as a salt paste the whizzing of base in an enclosed centrifuge be performed safely. Special attention must be l to the provision of protective clothing to the kman lidding drums in this manufacture. If mpts to isolate a very dry paste are made, a dust ard immediately arises and a user hazard is also ated as the packages are difficult to empty safely.

Benzidine Azo Colours

Tumours have occurred amongst a number of n manufacturing azo colours from benzidine. is interesting and important to note that these nzidine azo colours are the only ones using cinogenic intermediates made continuously ughout the year. The incidence of tumours ongst azo process men is largely confined to the nufacture of these large-scale benzidine colours. is would result in these particular workmen ing a considerably higher total dose of carcinogen an those employed for short and occasional periods other work using carcinogens as intermediates. If benzidine itself is manufactured in a user tory, then there is no doubt that bulk handling an amine slurry or tetrazo solution is to be erred to filling and emptying containers. In ptying a package with a shovel in azo manufacture re is no doubt that the clothing will become con-minated. In the case of smaller manufactures ere handling drums or casks is inevitable an tomatic device can be installed which will wash t the benzidine from the container by high ssure cold water. This can be operated quite ily and the water is used to make the solution r the subsequent tetrazo reaction. It may prove st effective to charge all the benzidine used in azo shed to one well-protected point using such device. Subsequently, slurry or tetrazo solution n be pumped to different units as is advocated the case of factories where benzidine is manu-tured within the same works. Great care will be essary in obtaining samples from such a central rce for assessment of the strength of the slurry. automatic enclosed device should be installed obtaining such samples without using a dip tin ch would drip on the surrounding floor and haps splash the man taking the sample. It is not recommended that batch weights of benzidine should be made up but if this has to be done, full-scale impervious clothing must be worn together with a fresh-air hood.

Tests for residual benzidine in the final product should be made to avoid atmospheric contamination during its drying or grinding.

o-Tolidine, Dianisidine, and Dichlorbenzidine

Although animal experiments on the rat suggest that the homologues and derivatives of benzidine are considerably less carcinogenic than the parent amine, it is felt that in industrial practice the homologues should be treated in a similar fashion to benzidine itself if large amounts are handled. Whereas there are records of men developing tumours who have been exposed to benzidine without its homologues, no population is known which has been exposed to the homologues of benzidine without the parent amine also being manufactured in the same plant.

Thus, in the manufacture of azo colours from o-tolidine, dianisidine, dichlorbenzidine, or benzidine disulphonic acid, an emptying device employing high-pressure water jets should be used for charging these intermediates to the azo vats. Benzidine disulphonic acid is not believed to be a carcinogen.

The final colour should be analyzed to ensure that no free amine is volatilized during drying.

Alpha-naphthylamine

The manufacture of alpha-naphthylamine has been associated with an incidence of tumours of the bladder amongst workers employed on it under poor conditions where very heavy exposure was encountered. Even under these conditions, exposure of five years or more was necessary for a tumour to develop. Statistical evidence suggests that it is of considerably lower potency than benzidine or beta-naphthylamine as a carcinogen in man. The commercial product usually contains about 4% beta-isomer but this level may be higher in some cases. Hazards exist during reduction of alphanitro-naphthalene and distillation and isolation of the final product. Completely enclosed plant should be used for the reduction with special attention paid to the gland of the agitator shaft. Any residue should be transferred through an enclosed system to a vessel where the amine can be completely destroyed. Special devices should be used for obtaining samples in order to ascertain the state of the reduction and the use of a dip pot for obtaining such samples is strongly deprecated. Where large quantities of material are to be handled by the user the final product should be transferred molten in tankers but some flaking will be necessary

for the smaller user. The flaker should be totally enclosed and draughted. Attention to the flaking conditions can increase the size of flake and reduce the amount of fine dust in the final product.

Alpha-naphthylamine Sulphate

This manufacture carries with it not only the risk in the charging of the initial amine, but also the risk of handling the final product. Thus, the charging point should be adequately ventilated to avoid contamination of the general atmosphere with dust or the material can be handled molten in an enclosed system to avoid this hazard completely. The hazard in the filtration and drying of this product is one of skin contact and inspiration of dust. During the drying, vapour will not be given off but dust will collect in the vents from the drying space. A continuous enclosed drier is recommended and the use of any form of tray drying is strongly deprecated.

Alpha-naphthol

Although this chemical is made from alpha-naphthylamine it is not believed to be carcinogenic. Bulk use of molten alpha-naphthylamine in a totally enclosed system to avoid atmospheric contamination is recommended. Analytical estimations of alpha-naphthylamine in the final product should be maintained to ensure its safety.

Naphthionic Acid

There is no evidence to suggest that naphthionic acid itself is carcinogenic but its manufacture involves the handling of alpha-naphthylamine. The amine charging point is the first hazard. In the event of a bulk supply of molten alpha-naphthylamine being available, heated enclosed measure vessels and weigh-scales can be used so that no problem of charging solid alpha-naphthylamine arises. If alpha-naphthylamine flake or alpha-naphthylamine sulphate is used efficient draughting and full protective clothing will be necessary. Alpha-naphthylamine flake packs in the drum on standing so that no automatic emptying device is suitable, and for the same reason it is not suitable for pneumatic handling.

The sulphonation is never quite complete so that the naphthionic acid dust is contaminated with amine. Further, the sulphonation is preferential to the alpha-isomer so that the unsulphonated amine will contain more of the beta-isomer than the original amine charged to the sulphonator. This high proportion of beta-isomer constitutes a very real hazard. During the washing of the acid these amines are present in the liquors together with tar. This tar, contaminated with beta-naphthylamine, should not be removed in an open vessel or filter press. An enclosed filter with automatic discharge is the most suitable means of purifying naphthionic acid liquors. The recovered amine must be collected in a drum or vessel and either destroyed chemically or disposed of at sea. It is unsafe to use regular amounts of this recovered amine for any other process in the industry.

If a solvent bake process is used, a major problem of distillation of the solvent for use again arises. The recovered amines have to be removed from the still as well as tar. Leakages will contaminate the atmosphere with beta-naphthylamine. A direct run of tar and amines from the still to a muffle furnace for destruction appears to be the most satisfactory method of disposal of these waste products. Full protective clothing is adequate for the subsequent use of naphthionic acid in the dyestuffs industry.

Sodium Naphthionate

This chemical is not thought to be carcinogenic but precautions must be taken to enclose all plant items which contain even a small trace of unsulphonated amine, particularly when they are hot. Equally, all residues from the plant should be handled molten in an enclosed system before disposal or destruction.

Phenyl-alpha-naphthylamine

This secondary amine can be made from alpha-naphthylamine but this involves charging a carcinogen to the phenylation vessel. Furthermore, the condensation with aniline is not complete and free carcinogen in the final product constitutes a hazard in isolation and its subsequent use. All these hazards can be easily eliminated by making phenyl-alpha-naphthylamine from alpha-naphthol. Attention should be paid to the purity of the alpha-naphthol used, as this is made from alpha-naphthylamine and can contain this carcinogen as an impurity. Phenyl-alpha-naphthylamine is not believed to be carcinogenic.

Ethyl-alpha-naphthylamine

This secondary amine can also be made from alpha-naphthylamine, but again this involves charging a carcinogen and also the removal of unreacted starting material. Complete safety can be ensured by making it from alpha-naphthol and monoethylamine. Ethyl-alpha-naphthylamine is not believed to be carcinogenic.

Rubber Chemical Manufacture from Alpha-naphthylamine

Condensates of alpha-naphthylamine and aldehydes have been made as rubber chemicals. The

densation is never quite complete and their nufacture has been discontinued in Great Britain ause of the hazard in manufacture and isolation the potential hazard of their use in the rubber stry due to the presence of uncondensed inogen (Case and Hosker, 1954). Only by the of a solvent process is it possible to reduce the acted amine to negligible quantities, but this olves the hazard of redistilling the solvent and oving the carcinogen therefrom.

Alpha-naphthylamine Condensation Colours

hese condensations do not go to completion so special measures must be taken to remove acted carcinogens from the final product. erwise these impurities may constitute a hazard olation, drying, and grinding of the final colour.

Phenyl-beta-naphthylamine

is appropriate here to mention phenyl-beta-hthylamine because it is sometimes suspected ng to its name. It is not made from beta-hthylamine and is not considered to be car-genic. No tumours have been reported amongst men engaged in its large-scale manufacture in mber of countries for many years.

Alpha-naphthylamine Azo Colours

here large amounts of alpha-naphthylamine are g used for azo manufacture the bulk handling of en amine is recommended. With the use of osed heated measure vessels, contact with the erial is entirely avoided. Where small amounts handled, efficient exhaust ventilation must be vided at the point where batch weighings are ied out and adequate ventilation provided at the ging point to the azo vat. Some azo reactions not complete and analytical tests should be ied out to ensure that no free amine is left in the l product. Tumours have occurred amongst a ber of persons carrying out colour drying and is attributed to the vaporization of uncoupled ine during drying. Such a hazard will be passed to the grinding and standardizing of these colours reacted amine is not controlled.

Auramine Manufacture

Although Müller (1933) attributed two cases of ladder tumour to auramine, it was not recognized at an occupational hazard was associated with the nufacture of this substance until the statistical stigations of Case and Pearson (1954) were blished. As yet it is impossible to indict any ticular part of the process but it is recommended at a review should be made of the handling of all rmediates and the final product in this process; a generally higher standard of housekeeping and working practice should be instituted. The object should be to cut down contact with all chemicals in the process to a minimum until more specific data on the exact cause of these tumours are available. The possibility must not be overlooked that these tumours may have been due to other chemicals handled in the auramine sheds in the factories where tumours have occurred. Further examination of this possibility would seem to be necessary before carrying out any drastic alterations.

Magenta Manufacture

The finding by Case and Pearson (1954) that a hazard has existed in Great Britain in magenta manufacture falls into line with the German experience in the early days of the chemical industry in that country.

In considering the appropriate protective measures to be taken it must be remembered that no tumours have been attributed to magenta in Germany amongst men starting work later than 1910. A general improvement of working conditions, together with a high standard of chemical handling, have apparently completely eliminated the hazard of this process in German factories without the installation of special totally enclosed plant such as is recommended for the manufacture of benzidine and alpha-naphthylamine. It is not possible to say at this moment whether the cause of the tumours in England is due to intermediates, to impurities in the magenta process, or to the final product itself. It would appear that a general review of working conditions in the manufacture of magenta, with special care to avoid atmospheric contamination and skin contact with chemicals employed in the processes, should result in the complete elimination of this hazard. In view of German experience it is not suggested that the building of special totally enclosed plant is necessary. A high standard of handling of chemicals should be sufficient to produce a result similar to that prevailing in Germany to-day.

Xenylamine (4-Aminodiphenyl)

4-Aminodiphenyl (referred to as xenylamine in the U.S.A.) has never been manufactured in Great Britain because experiments in rats and dogs demonstrated its carcinogenicity before its proposed manufacture (Walpole, Williams, and Roberts, 1952, 1954). Subsequently, Melick Escue, Naryka, Mezera, and Wheeler (1955) confirmed the existence of an industrial hazard in a report of tumours in men engaged in its manufacture in the U.S.A. Its manufacture has been discontinued there and it is recommended that manufacture should not be started in Great Britain. There is also the possibility that a

hazard may also have been associated with the manufacture of 4-nitrodiphenyl due to the reduction in the body of the nitro compound to the corresponding amine.

ASSESSMENT OF RESULTS ACHIEVED BY IMPROVEMENTS

It is most important to ensure that the improvements in plant and working which have been introduced are effective. It must be borne in mind that the chemical industry is always changing and some so-called improvements may open up new sources of contamination.

Butt and Strafford (*loc. cit.*) have established methods of analysis of air, clothing, and liquors for the presence of benzidine and beta-naphthylamine. By their method routine sampling of atmosphere can be achieved at specific points by the use of 24-hour bubblers and spot samples can also be taken where an unusual practice carrying a risk of atmospheric contamination is being carried out. Similarly, atmospheric sampling is recommended for any other compounds which are thought to be suspect in any of the processes considered in this report. Analysis of clothing for contamination with carcinogens can also be used as an additional check on safe working as well as a means of ensuring the efficacy of laundering. The maximum concentration of carcinogen allowable in the air or on clothing which can be regarded as completely safe is not known and these tests are recommended as a means of assessing the efficiency of preventive measures or of giving warning of a process defect which is not otherwise obvious.

An additional check is afforded by the examination of the urine of workers for the presence of excess amines. Methods have been described by Kuchenbecker (1920) and by Glassman and Meigs (1951). High amine content in urine may indicate absorption due to unsatisfactory operating technique, accidental contamination, or dirty working.

CONCLUSIONS

The above recommendations have been made in the belief that if they are implemented the incidence of bladder tumours in workers in these processes will be reduced to a level no greater than that which prevails in the general population. Although this report incorporates the precautions which are thought to be necessary in the light of present-day knowledge, it must be realized that, as our knowledge of this hazard increases, further amendments and additions may become necessary as, for instance, when new chemicals or processes come into use or when other sources of hazard hitherto undetected become apparent.

It is hoped that the recommendations contained in this report will be carried out by the industry as soon as is practicable, but it must be remembered that the benefits to be reaped will not necessarily be visible for many years to come.

SUMMARY

Safe methods of working practice recommended to the Association of British Chemical Manufacturers for the manufacture and use of chemical compounds likely to induce tumours of the bladder are described. The present position of knowledge of industrial bladder tumours in Great Britain is given and the data from which the recommendations have been derived are detailed.

Medical supervision is essential to ensure proper control of the hazard. Desiderata for selection and education of the workers and for their personal protection are laid down. The need for maintaining accurate medical and industrial records is stressed. Limitation of exposure and of the number of men at risk should lessen the possible incidence. The early diagnosis, treatment, and follow-up of established cases of tumour are imperative.

Design and ventilation of buildings and plant are of primary importance. Completely enclosed plant with the carcinogens totally contained in the system is the ideal. The isolation, sampling, weighing, distilling, drying, grinding, or packaging of products and the disposal of residues can all be dangerous and measures to prevent contamination of the operators are recommended. Maintenance and cleaning of buildings, plant, and plant items can lead to serious exposure and men engaged in these operations must also be protected.

Detailed consideration of the manufacture and use of each relevant compound is presented. The dangers associated with each are pointed out and specific precautionary measures are given in detail in each case.

Beta - naphthylamine and 4 - aminodiphenyl (xenylamine) should not be manufactured as no safe economical method can be devised. Safer alternatives which have been developed should be applied.

Benzidine should be manufactured in a closed system. The base and the salts are all dangerous and bulk handling as a slurry or as tetrazo solution is preferred in user factories.

The homologues and derivatives of benzidine are considered to be less carcinogenic than the parent amine but if large amounts are involved, they should be treated with equal care.

Alpha-naphthylamine should be manufactured in a closed system and bulk handling of molten amine in enclosed containers or tankers is the safest method for the large user.

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sources of risk in the future.

We are deeply indebted to all our technical and medical
agues, too numerous to mention individually,
se advice, criticism, and help have contributed so
ally to the preparation of this paper.

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MORAL RESPONSIBILITY and DANGEROUS CHEMICALS

Wyers Memorial Lecture

By

T. S. Scott

Delivered to The Association of
Industrial Medical Officers
on 31st October, 1958.

Now in print for The Transactions
of The Association of Industrial
Medical Officers.

Hubert Wyers practised for many years in the chemical industry. This has also been my own special field of work. In honouring his memory today I wish particularly to discuss the moral attitude of the employer and the doctor in industry towards the manufacture and use of dangerous substances. I shall examine the responsibility of each in the recognition, control and prevention of industrial diseases and serious toxic hazards, from the administrative, technical and ethical aspects.

I am grateful for many reasons for the invitation to deliver this lecture. Hubert Wyers and I were life-long friends. We were fellow students in the same year in medicine at Glasgow University. After graduating we spent some years as hospital residents and then we both entered general practice, he in Essex and I in Manchester. Neither of us had had any particular bent for, or training in, industrial medicine or organic chemistry, yet after a period as appointed factory surgeon and part time factory doctors, each of us eventually became a full time industrial medical officer, and each of us was engaged in the chemical industry. Thus a friendship which had started in the days of our youth matured and deepened throughout the years, cemented by common interests and problems, by a great mutual liking and by a lively sense of pleasure and enjoyment in each other's company.

Wyers had serious problems to concern and to challenge him in his industrial practice - problems as serious as asbestosis and berylliosis. On my side my greatest preoccupation was with an equally grave industrial disease - cancer of the bladder. Again our work, our interests and our problems ran on parallel lines. How then did we, who had entered these highly technical industries from general practice, come to command and use the esoteric skills for which we had no special training but which were so vital to the solution of our problems?

Difficulties to be resolved by the doctor.

Much of the chemistry and engineering in the industry is incomprehensible to those outside it or to those entering it and it would be idle to pretend that even after many years' experience the industrial medical officer can be expected to have expert knowledge or skill in any of the many difficult sciences and technologies which comprise the daily working of this modern industry.

As doctors we are concerned with human beings, with the preservation of their lives and with the protection and promotion of their bodily health and mental happiness. The fact that we work in industry makes no difference to the fundamental principles of our vocation.

Some of us often speak of ourselves as simple doctors, meaning that we have an art and science of our own, but it may also imply that we disclaim any skill or responsibility outside that narrow field. How can the doctor in industry approach a serious toxic hazard and advise on adequate prevention measures if he is going to disclaim such skill and responsibility? It is true that he cannot by himself lay down and implement all the necessary chemical and engineering precautions which are inseparable from the complete control of dangerous substances in modern industry. It is true that he must depend on others for much technical advice and supervision, but at the same time he must shoulder a great deal of responsibility for matters usually outside the orbit of a simple doctor.

Recognition of industrial disease.

In last year's memorial lecture Andrew Meiklejohn reminded us of two important tenets propounded by Hubert Wyers, first that experience in general practice is a valuable training for industrial medical officers and secondly, and this might well be my text today, that medical work in the factory should be based on the sound practice of clinical medicine directed to the care of the individual workman. This is as essential to the doctor in industry as it is to the doctor in general or consultant practice.

It is the individual who suffers from industrial diseases and intoxications and it is in him or her that their manifestations are to be found even when statistics or elaborate investigations are necessary to prove that the origin of these diseases is occupational. In many cases considerable clinical acumen is needed to detect them at stages sufficiently early for treatment to be effective. Their recognition as industrial diseases depends on their being identified with specific occupations. In some cases strange or unusual diseases can readily be proved to be of occupational origin. In other instances it has not been easy to detect the connection of an apparently ordinary disease, such as occurs in the general population, with a particular industrial operation or group of workpeople. When the same occupational disease subsequently appears elsewhere it should usually be easily recognized but unfortunately this is not always the case and in some instances the whole sorry experience has been repeated.

This is not an original observation - in 1832 Thackrah wrote "to repeat and urge what is forgotten is sometimes as important as to state what is unknown."

This happened in the chemical industry in the case of occupational cancer of the bladder. It was first recognized in

Switzerland at the end of last century. It was not until the 1914-18 war that the allied countries started to make the chemicals which were responsible for it but the experience of the earlier manufacturers was forgotten if, indeed, it had ever been heard of or seriously believed and so the chain of events was repeated. It is for us one of the more gratifying features of this sad story that in Britain the existence of the hazard was urged by a medical officer inside the industry and that from him came the impetus which was the driving force in the post-war efforts towards its control here and abroad. I refer to the work of Maurice Goldblatt which is so well-known to us in this Association.

RESPONSIBILITY OF EMPLOYER

It has often been inferred that employers in many instances remained indifferent to the existence of a hazard or to its effects until forced to do something by the pressure of public opinion or by a heroic medical officer. That public opinion or the enactment of legislation forced many backward employers to take action is a matter of history, but the role of the heroic medical officer is less authentic. At first only those employers with advanced ideas and a reasonable degree of altruism employed medical officers and these were the very

employers who would be most conscious of their duty to their employees and most ready to take action to protect them. Where no doctor was voluntarily employed the Inspectors of Factories could take action to mitigate bad conditions but this was rendered possible only by the legislation which had resulted largely from the campaigns of the social reformers and the lead given by the good employers. It was not from any concern on the part of the less progressive employers, nor from any heroics on the part of the doctors.

Until about fifty years ago factory owners with advanced and liberal ideas like those of Robert Owen were rare, if not unique. A great change of sentiment and opinion has since occurred. In this century the duty of the employer to his employees has increasingly become directed towards their well-being, welfare and safety until now the employer, in this country at any rate, must take the ultimate responsibility for safeguarding his workpeople.

There can be little doubt that it was the employers' growing realisation of their responsibility which paved the way for the entry of the doctor into industry. It is not difficult to imagine the hostile reception the industrial physician would have had a hundred years ago before industry was ready for him.

When industry did begin to accept him, it was merely because in the early days the gravity of a hazard had produced a real need for his services or because some degree of medical supervision was required by statute. Moreover we cannot blink the fact that many factory doctors were originally engaged to protect the employer against compensation claims.

Industrial medicine has come a long way since then. Its standing has been established and it has now become indispensable in many industries not only because of the high potential risks attached to them, but also because of the improvements in health, morale and production which result from the pursuit of good industrial health programmes. The increase in the number of our members in recent years to a total surely undreamed of by the handful of men who founded this Association is itself evidence of the change in industrial philosophy, which the development of public opinion and the enlightenment of society has made possible.

At the same time we must remember that, whether in private enterprise or nationalised industry, the employer has to pay for the medical and ancillary services in his industry. Even a nationalised industrial health service would have to be paid for, by the State or by whatever form of corporation might

be set up to administer it. Therefore, apart from statutory requirements, the standard of the industrial medical services may largely be dictated by how much the employer can afford, or is willing, to pay. This may be a decisive factor in determining and limiting the scope and value of the work of the doctor in industry both now and in the future.

Difficult problems have to be resolved by the employer as the awareness of a serious hazard dawns and as its extent and gravity is realised. The effect of a hazard as serious as, for example, cancer of the bladder - of which men and management began to be aware simultaneously - can be disastrous on the men's morale unless there is mutual good faith and trust.

To keep faith the employers have to show not only that they are willing to institute investigations into the cause of the disease and support the efforts to attain early diagnosis and effective treatment but also that they are prepared to go to any necessary lengths to protect the men from the danger. This entails the safe control of the physical environment, which is obviously of supreme importance.

Chemists and engineers.

Nothing has yet been said of those who have made the greatest contribution to the medical officer's understanding of

the environmental factors in the hazard and their control. The chemists and chemical engineers have literally taught me, as I have no doubt they taught Wyers, the little I know of chemistry and of the workings of the chemical industry. In turn I have endeavoured, and I hope I have succeeded, to give them some appreciation of the medical side of the problem. The intimate knowledge and experience of their own works which they possess are of inestimable value in the investigation, administration and solution of many difficult industrial medical problems.

Safety Officers and industrial hygienists.

The place of the safety officer or safety engineer will depend on his training, qualification and experience. If he has attained a high standard of knowledge and skill he will obviously be of the greatest value in assisting to supervise dangerous toxic processes. While some of us have been fortunate to have had as associates safety officers of the highest calibre, it must be admitted that until a minimum standard of qualification is imposed some will be inadequately fitted for the duties they should be able to perform. It is only fair to say that in the chemical industry, their standards have usually been high and that many of them are widely experienced specialists in their own right.

Industrial hygienists have not so far become a feature of industry in this country. As with safety officers, a sufficient standard of attainment is essential for them to function satisfactorily. If the medical officer and the safety officer, with all the technical advice available to them, function as they should, the introduction of industrial hygienists into any but the largest of our organisations would result in much overlapping. It is difficult to see how it could be justified or useful as a working part of any but a few of our factories. On the other hand the creation of industrial hygiene or toxicological institutes in Britain is widely canvassed and the need for them is widely agreed. While separate industrial organisations may have insufficient work for highly trained and qualified hygienists there will be a need for them in these institutes not only for teaching and research but also for the provision of a service to supply facilities to firms which are not equipped or staffed to carry out the necessary procedures for themselves.

RESPONSIBILITY OF THE DOCTOR

So far I have not mentioned the part played by the two parties who, in the context we are discussing are the most concerned, the workman and the doctor. The problem of the effects of toxic substances in industry is not primarily a

problem of statistics, test-tubes, animal experiments or even of toxicology. It is a human problem, but while we in industry are primarily concerned with the preservation of the workman's health we have also to look beyond the individual human being.

Thackrah wrote "A study of medicine which disregards the prevention of disease limits its utility and its honour. It would strip the profession of its noblest attribute....." In industry we have a greater duty, and a greater opportunity, in the field of prevention than is possible in most other branches of medicine. This duty naturally devolves on the industrial medical officer. He has had a basic training in the essentials of science as well as in the art of medicine so that he can undertake the task of co-ordinating the work of all the experts necessary to the control of serious hazards. He is the best possible link in co-ordinating many specialties - as diverse as, for example, as chemistry, engineering, ventilation, or work study.

It is the doctor to whom managements and men naturally turn when the health and safety of workmen are at risk and they have the right to expect from him a balanced, and discrete judgment given without fear, favour, or sectional interest. One essential requisite must be stressed - men and management must

have complete confidence in his integrity and honesty as an industrial physician and these can only be preserved by the observance of a strict standard of professional and industrial ethics.

ETHICS OF PROHIBITION OF DANGEROUS MANUFACTURES

In the preventive field if the doctor in industry, faced with a serious toxic hazard, is to live up to the highest standard of ethics it might be held that he should advise that the manufacture and use of any very dangerous substance or the continuation of any very dangerous process be banned altogether. At first sight this seems a simple and attractive solution and for the doctor it would certainly be an easy way out. It is, however, not always so easy, or even so reasonable, as it appears on the surface.

Hazards vary in their degree of severity so that there is the obvious difficulty of knowing where to draw the line between manufactures carrying unacceptable toxic hazards and those with a permissible degree of risk. While the doctor can point out the existence of a hazard and indicate its extent and gravity, it may not be possible to define its exact cause or even to determine if the cause is chemical, physical or psychological. No specific substance or precise physical agent

can be blamed for the rheumatism, bronchitis or nystagmus of coal miners; should we seriously suggest that the correct prophylactic measure is to close the mines? Should we have shut down the cottom industry before the long and patient research of Richard Schilling and his co-workers demonstrated the cause of byssinosis and before its control was made possible by the system of draughting designed at the Shirley Institute? Such policies would be stupid; but even when the exact cause of a grave hazard is clear, the consequences of abandoning manufacture may give pause to those who would advocate prohibition of the compounds or cessation of the process. In some of the cases with the highest potential danger, it would be morally as well as materially wrong to use prohibition as a prophylactic measure.

Principles of allowing or prohibiting dangerous manufactures.

The industry carrying the highest potential danger to its workmen is the atomic industry. Much political and emotional controversy rages over the question of giving up atomic weapons because of the danger to humanity at large - not because of the hazard to the workmen engaged in the industry. The prospective benefits of nuclear power for peaceful purposes are too great for us to contemplate prohibition. Instead brilliantly designed plant and meticulous prophylactic measures

have been devised and have rendered this industry safer than many with much less potential risk.

This may be an extreme example but the same precepts apply on a more mundane plane. We do not forego the facilities afforded us by having lead batteries in our cars because lead is dangerously toxic nor do we deprive the farmer and the consumer of the advantages of certain insecticides because organic phosphorus compounds are highly poisonous. In these and many other instances prohibition has never been effected. The work of Ronald Lane showed that the lead worker can be protected and the incidence of lead poisoning in a vigorous growing industry is now virtually absent. Similarly in many other industries it has been shown that the assault on the health of the workmen can be prevented by the application of adequate prophylactic measures.

Nevertheless, some dangerous compounds have been banned from our factories and from our environment. Why some and not others? It is significant that those which were first prohibited were those for which safer and economically feasible substitutes were available. The first to be banned, and it was by international agreement, was yellow phosphorus in 1906. It is invariably claimed, and with considerable unction, that

this was done because of the dreadful disease of the jaw it caused and one is left to infer that this altruistic action was taken by the manufacturers regardless of any other consideration. There was another consideration and it was a decisive one - it was the fact that a safe alternative could be used to replace it.

That this contention is true can be illustrated by considering the two major uses of benzene in industry. This insidious poison was widely used both as a solvent and as a chemical without much concern, except for the high fire risk it carried, until it was realised that its chronic effects on the bone marrow were likely to be fatal. Many less toxic solvents can be used in its stead and benzene as a solvent has virtually disappeared from our factories, due largely to the efforts of the medical branch of H.M.Factory Inspectorate and especially to the work of Dr. Ethel Browning.

Benzene would almost certainly be used as a solvent today if we did not have less toxic compounds as satisfactory alternatives. The rubber industry alone could hardly have survived without it, and undoubtedly would have used it on a large scale. Extensive precautions and strict supervision would, in view of our present knowledge and enlightened sentiment, have

been attached to its use, but it would still have been used.

On the other hand, there is no substitute and no alternative to benzene as a chemical. It is one of the most important basic raw materials in the organic chemical industry and it is the starting point in the synthesis of many substances which we rightly regard as indispensable in our modern civilisation. Without it we would not be able to obtain many pharmaceuticals, dyestuffs, organic pigments, paints, insecticides and rubber chemicals. For these reasons, it is still used in large amounts and it has never been seriously suggested that benzene should be given up except as a solvent. Because the danger is known, modern chemical engineering methods are utilized to make its use as a chemical safe.

From this it may be thought that virtually anything, however dangerous, can be made safely, provided the danger is known but two important considerations limit this optimistic generalisation. In some instances, the cost would be prohibitive. In others, and herein lies a very special and important principle of industrial medicine in the chemical industry, users of dangerous compounds even in very small quantities may undergo much greater risks than those manufacturing them on a large scale. The users may be working in small factories sometimes under primitive

conditions, and may have little idea of the danger they are running, and even less idea of preventive techniques, unless specific warnings and clear instructions are communicated to them. When the toxicity of an industrial product and the prophylactic measures which have to be prescribed are being considered, its ultimate distribution may be the decisive factor in determining whether or not it should be made.

When highly toxic substances are to be made and when potentially dangerous processes are to be carried on, the medical officer has a heavy responsibility in that he has to advise on the degree of danger to be anticipated and the extent of the precautions which have to be applied to satisfy the required standard of safe working.

It is important for us to remember that, except where complete prohibition has to be effected, the primary function of industry is to produce and it is no part of our function to impede production by overloading it with precautions or strangling it by regulations which are not necessary.

This does not mean that we cannot resolve the difficulty in which we may find ourselves in having to choose between the rival claims of economics and safety. It may seem that we have

conflicting loyalties to reconcile if we are to retain our ethical integrity and satisfy our professional conscience in the industrial setting but certain principles can be formulated by which we may regulate our actions and reach our decisions.

If they are to be made, substances or processes which promote grave industrial diseases such as radiation sickness or occupational cancer call for the maximum necessary precautions at whatever cost may be involved. If the achievement of the required standard is not practicable, complete prohibition must be insisted upon and industrial or public opinion would surely make this effective. Lesser hazards require less drastic measures. It would not be necessary to apply the same sanctions to work where the possible danger is slight and its effects trivial.

Between such extremes there are all gradations so that we, the industrial physicians, have to determine how far the well-being of the workpeople is being prejudiced or is likely to be prejudiced and we have a responsibility to state the nature and extent of danger to health. Chemists, engineers, safety officers and production managers will co-operate with us to circumvent that danger with the lease possible interference with production.

But we as doctors must be satisfied that the men and women who may be at risk are adequately protected and we must insist that no person is wittingly or wilfully exposed to danger which can be avoided.

Application of the principles in chemical industry.

The principles I have discussed are applicable throughout the chemical industry and the way in which they have been applied can be illustrated by considering the industrial bladder carcinogens. Here is yet another instance in which the simplest solution would appear to be an absolute prohibition of the manufacture and use of all the carcinogenic agents. The gravity of the malady can leave no room for doubt that unless safe methods can be adopted this extreme measure would have to be applied.

By 1950 betanaphthylamine appeared to be so highly dangerous that its manufacture was voluntarily given up because it was impossible to devise and operate, at an economic cost, plant which could afford any degree of certainty that tumours would not occur. Its proposed abandonment was going to leave a serious gap in the dyestuffs and rubber industry. There was a subtle change of attitude and sentiment here.

In the past it is probable that, as we have seen, the manufacture would have been continued in the absence of a safer alternative but now the climate of industrial, commercial and public opinion made prohibition inevitable. This stimulated the chemists to contrive alternative methods of synthesizing the dyestuffs for which it had been used and to develop alternative non-carcinogenic products for the rubber industry. If no such alternatives had been developed the British industry could hardly have avoided giving up betanaphthylamine as the high cost of making and using it safely would have resulted in a prohibitively fantastic price for the ultimate products.

Benzidine and alphanaphthylamine are the other two most common and most widely used of the known bladder carcinogens; but they are less potent than betanaphthylamine, and so afford the prospect that safe methods of manufacture can be applied to them. No alternatives to them have been devised for the purposes for which they are so widely used. They are, however, essential intermediate compounds for the manufacture of a very large range of the colours for wool, cotton, paper and many other fabrics. Banning of their manufacture would cause a widespread slump and unemployment not only in the chemical industry but in the textile, paper, paint, rubber and many other industries. Without

international agreement, and this would be more difficult to obtain than it was in the case of yellow phosphorus in 1906, the adverse effect on these industries and on our economic position would be serious. As we have seen, other compounds and processes more dangerous are accepted as necessary manufactures.

For these reasons manufacture and handling of the products therefore continue. They are carefully safeguarded and close medical supervision of plant and personnel is maintained. Careful instructions as to their toxicity and methods of prevention are communicated to users in other factories and a code of safe working practice in their manufacture and handling has been issued to them.

Much has been said of giving up compounds because safer alternatives could be used or because they were found to be too dangerous after their toxicity to workmen had been proved by tragic experience. A few have been found to be so dangerous that their contemplated manufacture was not started. The insecticidal properties of 2-acetylaminofluorene made it an attractive social and industrial proposition until toxicological studies fortunately revealed its high potential as a carcinogen before it was made on a commercial scale.

Walpole, Williams and Roberts, (one of them, Michael Williams, is an industrial medical officer), working with experimental animals, demonstrated in 1952 that xenylamine was at least as potent a carcinogen as betanaphthylamine. It was being made and used in the U.S.A. as a rubber chemical. They warned of the danger of tumours arising in men exposed to it and recommended that its manufacture should not be contemplated in this country. Three years later in 1955, they were dramatically justified when a report was published of a series of cases of bladder tumour which had arisen in the men who had worked with it in the U.S.A. where it had been manufactured since 1938. It has now been given up there but many years must elapse before the final toll of tumours in these workmen is known. We are fortunate that it has never been manufactured industrially in this country.

Standards of safety.

Even with modern safe plant and processes assurance must be made doubly sure and a high margin of safety must be sought to make absolutely certain that the plant and operating precautions are completely safe. Contamination can still occur during maintenance operations and through accidental breakage or failure of equipment. The human element may fail if supervision allows men to relax from the strict standards laid down in operating the plant and handling the material. The minimum dose

of a carcinogen required to produce a tumour in man under industrial conditions is not known and it is not always possible to measure the amount of a toxic agent in the atmosphere or in body fluids. In such cases standards far more stringent than are usually required must be imposed.

Monitoring of the atmosphere is desirable but is not always possible. Keith Moore at the last meeting of this Association described the effects of hexoestrol in men working with it. He pointed out that it was impossible to find satisfactory methods of estimating it in the atmosphere or in the body. In this instance the effects of contamination appear in a relatively short time, days or weeks. With carcinogens many years may elapse before they are manifest.

Again we must not lose our sense of proportion. Moore found that simple local draughting, general ventilation and enclosure of the process have stopped the occurrence of the hexoestrol syndrome in his men. The work of A.J.Amor has already reduced the incidence of carcinoma of the lung and nasal sinuses in workers in the Mond nickel process to the level of that in the ordinary population. This has been achieved by non-specific prevention consisting of suppression of dust and other similar empirical measures put in 20 years ago.

Scope of the doctor in the chemical industry.

In the case of the carcinogens removal from exposure does not eliminate the possibility of developing the disease. In several industries many men have in the past been exposed to conditions we now know to be capable of causing tumours of lung, skin, or bladder after latent periods of up to 40 years. Some of these men have already developed tumours, a proportion of the other will eventually develop them and some will escape.

To ensure the adequacy and the effectiveness of any prophylactic programme, medical supervision must, therefore, be continued indefinitely in the case of the carcinogens and many serious toxic hazards. The industrial medical officer must do more than figure simply as a general practitioner inside the factory. He must be able to utilize and co-ordinate the skill and experience of scientists and technologists in many different specialties and he must continue to function as a doctor in his own right.

After the Windscale incident, the Fleck report this year recommended that codes of practice for dangerous processes should be compiled by experts. This is not a new idea. It was done for the chemical industry in 1953 to cover the manufacture and use of certain carcinogens and two industrial medical officers

were called upon to do it.

These two doctors were invited by the Association of British Chemical Manufacturers to recommend a code of working practice for the manufacture and use of products causing tumours of the bladder. They drew up a document which was accepted by the industry in 1953 as the recommended standard and a shortened version was published in 1957. Their recommendations first deal with the selection of workers, the general supervision of their health and working conditions, and much more work of a predominantly medical nature.

The second part of the report, however, is devoted entirely to questions of plant hygiene, operating methods and the precautions recommended therein. In this section they lay down principles for the construction and design of buildings, general and local ventilation of the working place, the design of plant and its working, the sampling, weighing, handling, isolation and drying of products, the maintenance of plant and even packaging and transport of materials. They then proceed to a detailed consideration of the methods of manufacture and handling of some twenty compounds known or suspected to be carcinogenic and the chemical and engineering precautions necessary for each one. None of these subjects appears in the

curriculum of the medical student and the doctor does not start in industry with any knowledge of them. He can hardly expect to be expert even after years of experience.

It is not surprising, therefore, that at the end these two doctors thank their technical and medical colleagues "too numerous to mention individually" whose advice, criticism and help had contributed so greatly to their work. In fact it was not only their own knowledge and experience but also the ability it gave them to utilize the knowledge and experience of colleagues with a different professional and technical training and a different expertise that enabled them to produce a comprehensive document of work in such a difficult sphere.

THE FUTURE

So much for the past and the present, but what of the future? Countless new compounds will certainly be synthesized and many will be produced commercially. Even with the largest toxicological laboratories, big enough and numerous enough to satisfy the dreams of the most optimistic planners, it will still be impossible to test every new chemical for chronic toxicity and carcinogenicity even if in vitro and animal experiments could be extrapolated to assess the vulnerability of the human industrial worker. Until we can be certain that it is harmless we must regard each new

compound as potentially toxic. We shall, therefore, still have to be ready to detect in our workpeople the first signs of any adverse effects of the new compounds which will be introduced into our factories. Some compounds which already have been in use on a comparatively small scale and which now appear safe may be in greater demand in the future. Their manufacture and use on a large scale may reveal long term noxious properties hitherto unsuspected. In the future, too, we must not forget the lessons of the past and allow substances we already know to be dangerous to cause a repetition of previous trouble. Nor must we allow precautions which may be inadequate to lull us into a false sense of security by any short term success that they may yield.

Conclusions.

In view of all the considerations I have examined, it will surely be conceded that while the value of our work depends on our being doctors we must use other sciences as well. Let us cease, therefore, to think of ourselves as simple doctors. We have to acquire something from many other specialities, professions and technologies, we have to have some understanding of difficult and sometimes abstruse technical matters and we have to be able to co-ordinate work which does not usually lie within the compass of the simple doctor.

I have chosen these lines of thought because Hubert Wyers was so closely concerned with toxic substances and hazards, because he applied himself so successfully to the solution of many of the most serious problems they presented and because I am in the same industry and have similar problems. He stood for the very best of what we mean to convey when we describe ourselves in terms of pride and humility as simple doctors. He was, if you like, a simple doctor but he was more that that. He was a man of many talents and many interests and he had a burning compulsion to do his work to the best of his not inconsiderable ability. He also had such a depth of learning - in the arts as well as in medicine - such a knowledge and experience of industry and such a wide sympathetic understanding of human nature as to make the word 'simple' a paradox where he was concerned.

Thackrah, Legge and the more recent pioneers of industrial medicine, some of them here today, laid the foundations and started the development of the situation he inherited. His gift to posterity was to foster this growth and to make easier the path of the men who came after him. Industrial medicine like other social advances can but reflect the philosophy of the hour. It is given to some few to influence that philosophy and the

doctor in industry is in a specially favourable position to do so, to lead those who manage it and those who work in it to a more acute realisation of their responsibilities and to a more effective discharge of their material and moral duties.

At the same time, we must never forget that we are doctors and that we have the ultimate responsibility for the lives, bodily health and mental happiness of the men and women who make our industry so prosperous and our standard of living so abundant.

Like Hubert Wyers we will keep faith.