Section of Urology

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Occupational Tumours of the Bladder

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Introduction

It is now almost sixty-five years since Rehn of Frankfurt-on-Main (1895) first drew attention to the unusual incidence of bladder tumours amongst men employed in the dye-making industry. He described the occurrence of bladder tumours in 3 (and possibly in a fourth) out of 45 workmen, who had been engaged for many years in the manufacture of fuchsin. These men were employed in a workshop where crude fuchsin was produced by the heating together of toluidines, aniline, nitrobenzene and ferric chloride. The conditions of working at this time may be gathered from Rehn's description that "as regards the melting shop on hot days when there is much evaporation of nitrobenzol, aniline and so on, new workmen are often so affected by such urgency of micturition that urine passes involuntarily into their clothes". Rehn concluded that: (1) The fumes which develop during the manufacture of fuchsin lead to disturbances in the urinary system. (2) After years of working in the fuchsin industry tumours of the bladder may occur as a result of the continuous irritation. (3) The injurious effect is mainly due to the inhalation of aniline vapour.

Since that time a vast amount of work has been carried out in the industrial and experimental fields in an endeavour to elucidate the problem of causation and prevention. The clinical aspect of the tumours has been less fully surveyed and so far as I am aware has never been presented to this Section. The following review is based on those cases which have been under the care of Macalpine and myself in Manchester.

Historical Review

Although mauveine—the first coal tar dye—was synthesized by Perkin of London in 1856, the dye manufacturing industry did not flourish for long in England and later became established mainly in Germany and to a lesser extent in Switzerland. It is therefore not surprising that the early records of occupational bladder tumours are almost entirely from German and Swiss sources.

At first Rehn's views were severely criticized, but other similar cases soon appeared and by 1906 Rehn was able to report 33 additional cases collected from seven different factories. Further reports by Leuenberger of Basle (1912) and by Schewin (1920), Curshman (1920), Oppenheimer (1920) and others in Germany left no doubt that bladder tumours were an occupational hazard in the dye manufacturing industry. Many more reports have appeared from Germany culminating in that of Gross (1940). Since 1933 Müller has reviewed the incidence in the Swiss chemical industry and in 1951 published his treatise. He records 161 patients (139 cases of vesical tumour and 22 of hæmorrhagic cystitis).

During and after the First World War dye manufacturing plants were started in other countries and in due course so-called "aniline tumours" began to appear. In England Wignall (1929) and Macalpine (1929) drew attention to this occupational danger. Goldblatt (1947, 1949) reviewed his experiences from two British chemical factories and produced records of 99 cases. Scott (1952, 1959) has also contributed a valuable series of cases. During 1947 the Association of British Chemical Manufacturers instituted a research project, which resulted in the invaluable statistical reports of Case *et al.* (1954).

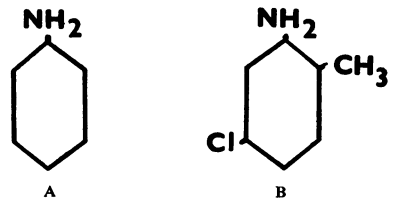
In the United States the first case was recorded by Anderson in 1931 and was quickly followed by the reviews of Ferguson (1934), Gehrman (1934), Gay (1934, 1937), Anderson (1934) and Evans (1937). Maguigan (1950) details nearly 200 cases which had occurred in America. Melick (1958) has recorded 16 cases amongst 71 men manufacturing 4-amino-diphenyl (xenylamine). Series of cases have also been reported from Italy (Di Maio, 1937, 1949), Barsotti and Vigliani (1949, 1952). In France Billiard-Duchesne has described his findings (1949, 1958).

Occupational tumours have also occurred in the manufacture and use of substitution products of alpha- and beta-naphthylamine, which have been used as antioxidants in the rubber industry (Case and Hosker, 1954). Benzidine has also been used in rubber manufacture.

Search for the Carcinogenic Agents

The dye-stuffs manufacturing industry is complex, involving many processes and the handling of many chemicals. This has rendered the search for the bladder carcinogen very difficult. In general all synthetic dyes are derived from coal tar products. Their manufacture may be divided into three main stages: firstly, the production of crude coal tar compounds such as benzene, toluene, xylene, naphthalene and anthracene; secondly the manufacture of intermediate compounds from these chemicals; and thirdly, the manufacture of the dyes from the intermediate products. Vesical tumours are found mainly amongst men employed in the second division and to a lesser extent in the third. There is little or no evidence that handling of the finished dyes induces tumours.

In the past in a dye-stuffs factory many men moved from process to process as occasion required and were seldom continuously on any one plant. This multiplicity of exposure made identification of the carcinogens difficult. The fact that a considerable period of exposure to the carcinogens may be required, and that even then a long latent period may elapse before a tumour appears, has led to further confusion. Many workers may also have left the industry before their tumours develop and their future course may remain unknown. Industrial chemicals may also contain considerable quantities of impurities and at times it is problematic as to which substance is the carcinogen. Furthermore a fair number of intermediate products in a dye-works, although apparently not carcinogenic, are capable of causing considerable vesical irritation and have added to the perplexity. Ortho-



A B

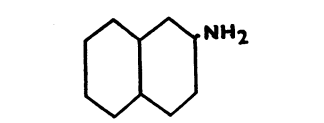
FIG. 1.—A, Aniline. B, 5-chlor-ortho-toluidine, a non-carcinogenic bladder irritant.

toluidine and 5-chlor-ortho-toluidine (Fig. 1B) are particularly irritating and may cause hæmaturia. From amidst all this confusion by the careful analysis of the known works histories of men developing tumours and by animal experiments with the suspected carcinogens the following facts appear to have been established:

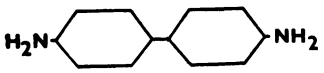
Aniline (Fig. 1A).—Although the lesions are still frequently referred to as "aniline tumours" this substance has now been exonerated as a bladder carcinogen. Over the past forty years in no factory manufacturing aniline have tumours been attributable to it. Animal experiments have also been entirely negative. The tumours arising in Rehn's and other early German and Swiss series were probably attributable to naphthylamines, 4-amino-diphenyl (xenylamine) or other closely related compounds arising as impurities during the manufacture of magenta (fuchsin) or to the actual manufacture of magenta itself.

The Carcinogens (Fig. 2)

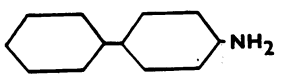
Beta-naphthylamine, benzidine and 4-amino-diphenyl (xenylamine) have all been shown to be carcinogens or the precursors of carcinogens in the urinary tract in man and animals.



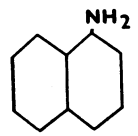
A, Beta-naphthylamine.



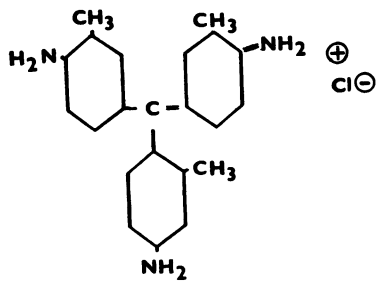
B, Benzidine.



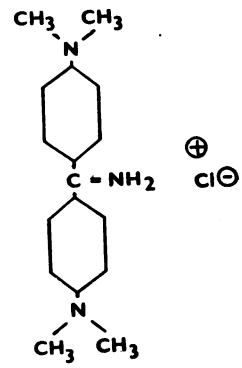
C, Xenylamine.



D, Alpha-naphthylamine.



E, Magenta.



F, Auramine.

FIG. 2.—The carcinogens.

Beta-naphthylamine.—Clinically Gross (1940), Di Maio (1949), Barsotti and Vigliani (1949, 1952), Scott (1952) and Goldblatt (1947) accepted beta-naphthylamine as a hazard. Experimentally Hueper and Wolfe (1937) and Bonser (1943) obtained bladder tumours in dogs; Bonser *et al.* (1958) have carried out an ingenious series of experiments to test the apparent species differences in the dog, rat, rabbit and mouse to the feeding of beta-naphthylamine. These experiments would appear to indicate that beta-naphthylamine is broken down in the body to metabolites, one of which, 2-amino-l-naphthol, is carcinogenic. It is only in those animals which are capable of breaking beta-naphthylamine down to this metabolite, that tumours can be induced.

Benzidine.—Factory statistics have usually shown a high incidence of vesical tumours amongst men employed in the manufacture and handling of benzidine. Doubts were, however, felt that these men might also have been exposed to beta-naphthylamine. Scott, however, in 1952 definitely established the carcinogenicity of benzidine by describing a series of 30 tumours occurring amongst men exposed to this compound only. Experimentally Spitz *et al.* (1950) obtained bladder tumours in dogs. This finding has been confirmed and many compounds related to amino-diphenyl and diamino-diphenyl have been proved carcinogenic in animals (Walpole *et al.*, 1954; Miller *et al.*, 1956).

Certain homologues and derivatives of benzidine such as tolidine, dichlorbenzidine and dianisidine are used for similar purposes to benzidine but to a much less degree. Their carcinogenicity is not known with certainty; they may be weak carcinogens.

4-*Amino-diphenyl* (*xenylamine*).—Xenylamine —a rubber antioxidant—has never been manufactured in this country. Its potential dangers were recognized and proof of its carcinogenicity in animals established by Walpole *et al.* (1952, 1954). In the U.S.A. the manufacture of xenylamine was begun in 1935. Melick (1958) has described 16 cases of bladder tumour occurring amongst 71 workers (22·5%).

Alpha-naphthylamine.—Workmen manufacturing or using alpha-naphthylamine undoubtedly develop bladder tumours. As manufactured it contains approximately 4% of beta-naphthylamine and this may be the active carcinogen. Evidence is, however, accumulating that alpha-naphthylamine may be a urinary tract carcinogen in its own right.

Magenta and auramine.—The statistical evidence of Case and Pearson (1954) suggests that men engaged in the manufacture of these dyes, and possibly in their handling, may develop vesical tumours. So far it has been impossible to determine whether the hazard can be attributed to the intermediates, impurities or the finished dye (Scott and Williams, 1957*b*).

The Early Diagnosis of Tumours

Occupational tumours of the bladder present no specific signs or symptoms: hæmaturia is the most common heralding sign but by the time of its appearance a tumour may already have reached a considerable size. The invasive and more malignant tumours tend to be relatively silent in their onset and may at first only declare themselves by mild cystitis and faint transient hæmaturia. By the time of investigation they may have extensively permeated or even have penetrated the bladder wall. Amongst a works population, who have been exposed to carcinogens and are thus known to be at risk, there is therefore a great need for a means of early tumour detection. Three methods have been tried as screening measures: (1) Microscopic examination of the urine for red blood cells. (2) Routine cystoscopy. (3) Cytological diagnosis.

Microscopic Examination of the Urine

Oppenheimer (1920) recommended regular microscopic examination of the urine for red blood cells as a means of detecting bladder tumours in men exposed to carcinogens. Since 1934 such regular examinations have been applied in several British dye-stuffs factories. The unstained centrifuged deposits of specimens of urine from men in hazardous processes are microscopically examined at monthly intervals for red and white blood cells. The presence of large numbers or the persistence of small numbers of red blood cells in the urine of a man who had a sufficient exposure to carcinogens is almost invariably regarded as an indication for cystoscopy.

Several factors, however, tend to render the test somewhat inaccurate. Hæmaturia is not specific for bladder tumours and gross or minute quantities of blood may appear in the urine as the result of many diseases. Acute hæmorrhagic cystitis may also be a manifestation of the absorption of certain chemicals such as toluidines or 5-chlor-2-toluidine, which are often made and used in dye-stuffs factories. Red blood cells may also be found in the urine of some apparently healthy individuals. Scott, examining candidates for employment in a dye-works, found that 6·2% of the applicants had microscopic hæmaturia of undetermined origin (more than 6–8 red blood cells per low power field on microscopy of a centrifuged deposit).

Despite the possible disadvantages many pre-symptomatic diagnoses have been made by the

wet smear technique. Scott (1959) has reported that during the eleven years from 1940 to 1950 at one factory 40 men were found to be suffering from bladder tumours. The urine of all had been regularly examined by the wet smear technique. In 16 the presence of red blood cells, observed only on microscopy of the urine, was the sole indication of a tumour. In 12 instances small numbers of red cells, considered to be insufficient in quantity to warrant advising cystoscopy, were present before gross hæmaturia or other symptoms appeared. In the remaining 12 no blood cells were seen before the onset of symptoms. The technique therefore detected an asymptomatic tumour in 16 instances but failed in the remaining 24.

Routine Cystoscopy

Annual routine cystoscopy of all exposed workers was first instituted in the United States (Gehrman, 1934; Wolfe, 1937; Evans, 1937) and was later adopted in other countries (Di Maio, 1949; Barsotti and Vigliani, 1949; Billiard-Duchesne, 1949; Müller, 1951). Many tumours, particularly at the first screening of a works population, have been discovered in this way and if accurately and regularly carried out the examination is undoubtedly an additional safeguard. It appears, however, to be extremely doubtful whether all workmen continue to submit to the examination. In Great Britain routine cystoscopy has never been practised. Even in the gentlest hands the examination is irksome and it has been felt that the many cystoscopies with negative findings may give a false sense of security and lead to refusal of examination at a time when it may be most necessary.

Cytodiagnosis

About 1945 Papanicolaou, who had achieved considerable success in the diagnosis of cancer of the vagina, cervix and uterus by the examination of vaginal smears, turned his attention to the possibility of diagnosing malignant neoplasms of the urinary tract by smears prepared from urinary sediments. The urine for the examination is mixed immediately after collection with an equal quantity of 95% industrial alcohol to prevent cellular disintegration and is then stained by a special technique.

The interpretation of the smears is difficult. The diagnosis is based on the appearance of isolated, or preferably groups of, exfoliated cells. Unfortunately there is no single criterion of malignancy. Papanicolaou bases his classification on structural modifications of the cells and their nuclei and on changes in the inter-relationship of cells as shown in cell clusters and tissue fragments. He records his findings in the following classes: (1) Absence of atypical or abnormal cells. (2) Atypical cytology but no evidence of malignancy. (3) Cytology suggestive but not conclusive of malignancy. (4) Cytology strongly suggestive of malignancy. (5) Cytology conclusive for malignancy.

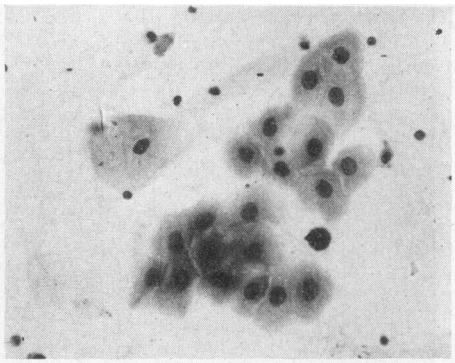
Classes 1 and 2 are regarded as negative, 3 as suspicious and 4 and 5 as positive.

In 1951 the Papanicolaou smear technique was introduced as a screening measure into three large British dye-stuffs factories. From two of these most of the author's patients are drawn. The smear results and the findings of any subsequent cystoscopic examinations were carefully correlated. Crabbe (1952) published a preliminary report. A more comprehensive survey was issued in 1956 by Crabbe *et al.* and a further report by Scott and Williams in 1957(*a*). Table I is produced by courtesy of Scott and Williams and shows the results over a period of seven years of screening approximately 2,000 men who had been engaged in the manufacture or use of bladder carcinogens and another 2,000 whose exposure had been indirect or small. The urine of the most heavily exposed men was examined monthly and of others at three- to four-monthly intervals. Wet smears and Papanicolaou stained smears were examined. As a result of these investigations 108 men were referred for cystoscopy—80 with positive cytological smears and 28, whose smears were negative, on account of erythrocytes in their urine or other symptoms. Cystoscopic investigation revealed 77 patients with bladder tumours. Of these men 70 had positive Papanicolaou smears before they were investigated—32 of these had sufficient erythrocytes in their urine (or in a few cases symptoms) to warrant cystoscopy but 38 had no indication other than the smear findings to show that a tumour was present.

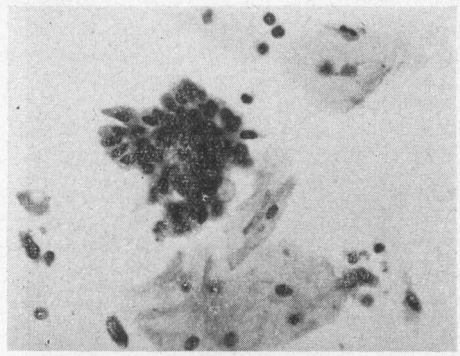
TABLE I.—PAPANICOLAOU TEST RESULTS
(Scott and Williams, 1957*a*)
The cystoscopic findings compared with the Papanicolaou smear results in 108 men sent for examination on account of positive Papanicolaou smears or the presence of blood cells in their urine

Cystoscopic finding	Papanicolaou test		Total
	Positive	Negative	
Tumour present ..	70	7	77
No tumour found	10	21	31
Total	80	28	108

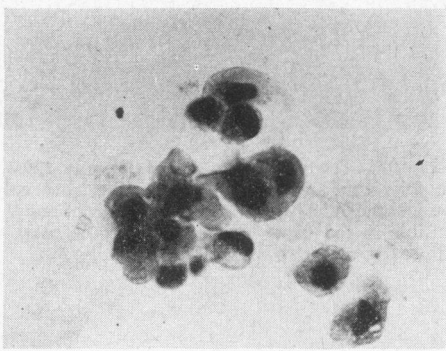
In 31 men no tumour was found on cystoscopy. Of these 21 had negative smears but were examined because they had symptoms or erythrocytes in their urine. 10 men had positive smears and were apparently false positive results —4 had renal calculi, 1 a stricture and another severe burns, 2 of the remaining 4 showed cystoscopic appearances suggestive of early



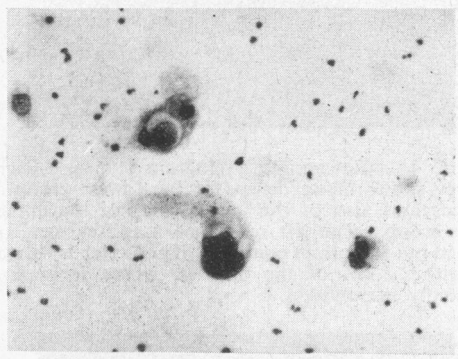
A, Normal epithelial cells and pus cells. ×270. The proportion of cytoplasm to nucleus is normal. The nuclei do not stain deeply.



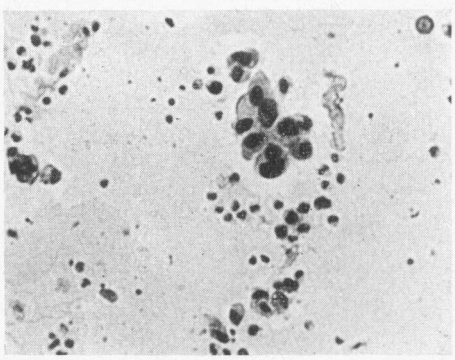
B, Transitional cell papilloma. Normal squamous cells and pus cells are also present. ×330. The cells are clustered. The cytoplasm is reduced. The nuclei are large and stain deeply.



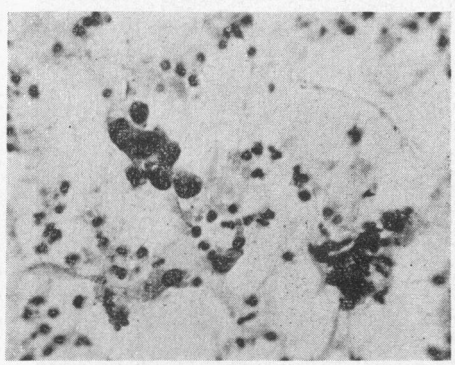
C, Malignant cells—class V. ×440. Cells irregular in shape and size. Vacuoles. Large nuclei, unequal in size and shape, stain deeply. The presence of a tumour was diagnosed on this film. Cystoscopy showed a papillary carcinoma. A biopsy confirmed the diagnosis.



D, Malignant cells—Class V. ×220. The film shows two curious cells with the characteristics of malignancy. Cystoscopy revealed a solid papilloma. Biopsy confirmed the diagnosis of carcinoma.



E



F

E, Malignant cells (Class IV). ×240. Investigation at this time failed to reveal a tumour. The smears continued to be positive. F, Made nine months later again showing tumour cells (Class IV) and pus cells. ×270. A further urinary investigation revealed a tumour in the left renal pelvis. A left nephro-ureterectomy was performed (15.1.57) and the presence of a transitional cell carcinoma confirmed. The patient died of phthisis eleven months later. A post-mortem showed no tumour in the bladder.

FIG. 3.—Papanicolaou smears.

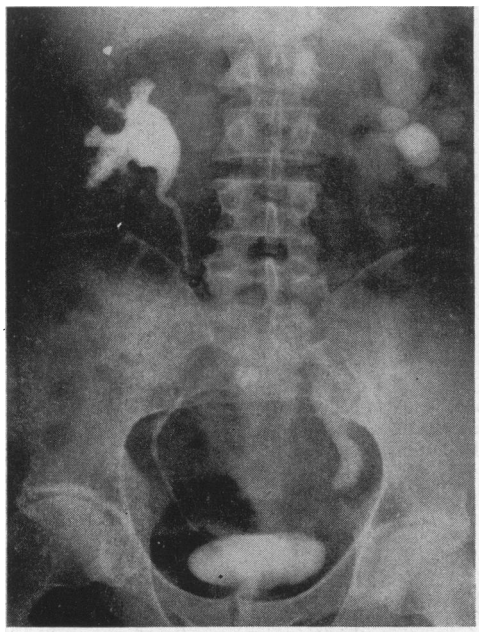


FIG. 4A.—Retrograde pyelogram (1954). Right kidney shows filling defects of the lowest group of calyces and also of the lowest calyx of the uppermost group. The left renal pelvis and calyces are dilated but smooth in contour. The ureter is dilated to within 3 cm of the bladder, where it appears markedly narrowed.

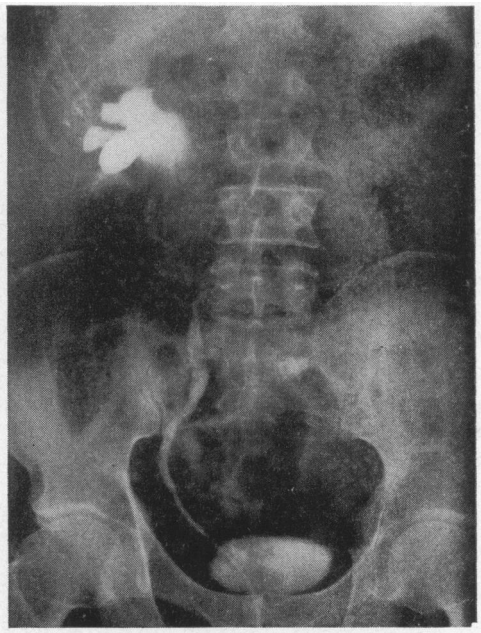


FIG. 4B.—Right retrograde pyelogram (29.4.55). The filling defects of the renal pelvis and calyces have advanced. The outline of an apparent papilloma is visible in the ureter at the level of the sacro-iliac joint. The ureter lower down is irregular.

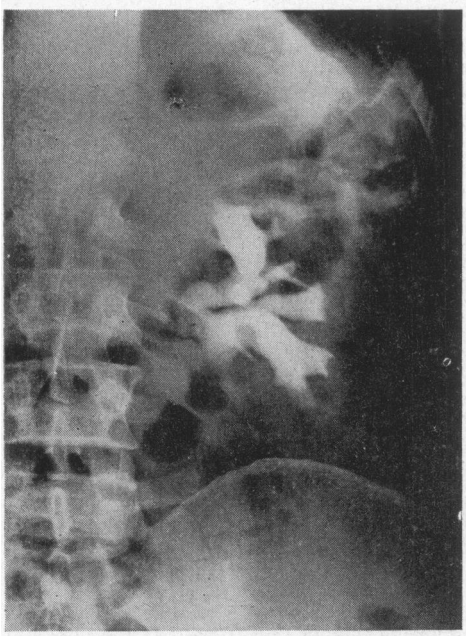


FIG. 4C.—Intravenous pyelogram showing the improvement in the left kidney following the resection of the lower end of the ureter.

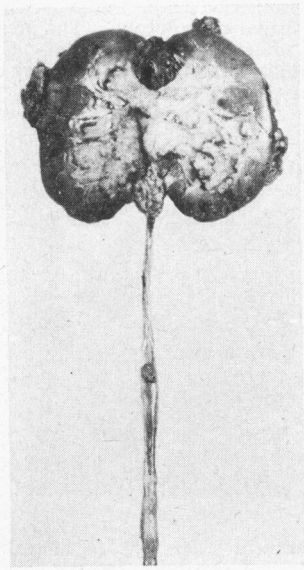


FIG. 5.—Specimen of right kidney and ureter removed at operatian showing papillomata of the renal pelvis and ureter.

FIGS. 4 and 5 (*Case I*).—Papillomata of the right renal pelvis and each ureter.

tumour formation and in 2 no abnormality has as yet been detected.

It was hoped that the Papanicolaou technique might provide a useful means of surveillance following treatment of a tumour. Table II

TABLE II
(Scott and Williams, 1957*a*)
A comparison of the Papanicolaou smear results with the findings of 225 review cystoscopies carried out on 47 men, who had been treated for bladder tumour

Papanicolaou smear result	Cystoscopy			Total
	Negative	Suspicious	Positive	
Negative ..	83	10	20	113
Suspicious ..	19	20	4	43
Positive ..	27	27	15	69
Total	129	57	39	225

shows a comparison of the Papanicolaou smear results with the findings of 225 review cystoscopies carried out on 47 men, who had been treated for bladder tumours. Of 129 review cystoscopies in which no tumour was found only 83 of the urines yielded a negative smear. Again of 39 cystoscopies at which a tumour was definitely recognized the urine of 20 gave negative smears. The explanation of these erratic findings is not clear. It must, however, be stressed that the Papanicolaou smear, whilst most useful as a primary screening measure, cannot be relied upon for post-treatment reviews.

The Present Series of Patients

The present series consists of 182 patients, who have been found to be suffering from occupational tumours of the urinary tract. Of these 180 suffered primarily from bladder tumours; in one case a renal and in another a ureteric lesion was unaccompanied by any bladder lesion.

The majority of these patients have been referred by the Medical Officers of two large factories engaged in the chemical and dye-making industry, but some who had left their former employment have been found in hospital practice and the occupational nature of their lesion has been established from their history and its subsequent confirmation at the factory concerned. 4 patients have been traced to a third small factory which is principally engaged in the manufacture of magenta.

Causative agents.—The exposures to the compounds accepted as industrial bladder carcinogens were: benzidine 43 cases, alpha-naphthylamine 19, beta-naphthylamine 20, mixed contacts (many in contact with beta-naphthylamine) 85, manufacture of magenta 4, and others (including some magenta cases) 11 cases.

Incidence.—The chief incidence has occurred amongst men actively engaged in the manufacture of the carcinogens and to a slightly less degree amongst those using them in the manufacture of dyes or other compounds. Their work classification is: staff men 9, foremen 2, manufacturers 89, users 59, others 23. Although their exposure is less, staff men and foremen have not escaped. There is also an incidence amongst men coming more indirectly into contact with the carcinogens—chemical engineers, plant cleaners, plumbers and even a laundryman, who had handled contaminated clothing.

Period of exposure and latent period.—The amount of contact with a carcinogen necessary to induce tumour formation is difficult to ascertain as it depends on the nature of the carcinogen as well as on the period and intensity of exposure. Estimates are usually based on the period of exposure, which is reckoned as the length of time during which a worker has been engaged on a hazardous process.

The period elapsing between the first exposure and the appearance of a tumour is known as the latent or induction period. When a tumour arises during the period of exposure to the carcinogens, the period of exposure and the latent period are the same. The appearance of the tumour may, however, be delayed and occur long after the man has left the industry. In such instances the latent period is much longer than the period of exposure. Table III shows the latent periods in this series.

TABLE III.—The Latent Period

Average age on entry to the industry ..	29 years
Average age at onset of tumour ..	50 years
Average latent period	20½ years
Longest latent period	41 years
Shortest latent period	3 years

The clinical investigation.—When a man is referred to the Urological Clinic, a full clinical examination, X-ray investigations and cystoscopy are first carried out in the outpatient department. If cystoscopy reveals a vesical tumour the patient is admitted to hospital for a further cystoscopy under general anæsthesia, biopsy of the tumour and a careful bimanual pelvic examination. When the tumour appears suitable for perurethral resection or diathermy the treatment is carried out at this examination. Otherwise the biopsy findings are obtained and the appropriate treatment then determined. It must be remembered that these men, having lived in contact with workmates who have suffered and died from bladder tumours, are fully aware of the implications of a positive finding and therefore require very careful and gentle handling. The following history of a man who worked alongside his mates for the greater part of the eleven years during which he was under treatment, illustrates the possible future envisaged by these men when a tumour is diagnosed:

Case I.—J. E. B., maintenance engineer foreman. Joined the company in 1928 at 25 years of age

From 1928 to 1945 was exposed to alpha-naphthylamine. In 1945 he developed hæmaturia, and cystoscopy revealed a papilloma in his bladder. In addition he occasionally passed small calculi. At this time he refused treatment.

In 1947 he was again reviewed. Large multiple papillomata were present in the bladder. For these he was given a course of deep X-ray therapy. A calculus was also present in his right kidney. The papillomata regressed but during the following year mossy papillomata in the region of the left ureteric orifice were diathermized. The calculus was also removed from his right kidney.

From 1948 to 1954 recurrent papillomata formed in his bladder and prostatic urethra and were diathermized. The renal tract was also kept under review. Towards the end of 1954 it became evident that papilloma formation was present in the right renal pelvis and ureter and that dilatation of the left renal pelvis and ureter was occurring owing to obstruction of the lower end of the ureter by a papilloma (Fig. 4). The patient was at first reluctant to have any further operative treatment but finally wished that everything possible should be done to prolong his life. After much consideration a right nephro-ureterectomy was performed on 18.5.55 (Fig. 5). 28.9.55: The lower 5 cm of the left ureter were resected and the ureter re-anastomosed to the bladder. Section of tissue from the right kidney and ureter and from the left ureter showed transitional cell papillomata. The patient made a good recovery. Cystoscopy (14.11.55) showed a very scarred and somewhat contracted bladder but no positive evidence of tumour. His frequency gradually increased and he subsequently started to wear a urinal. During August 1956 he had a convulsion whilst at work and was again admitted to hospital. He finally died on 5.9.56. Post-mortem examination revealed a diffuse carcinomatous infiltration of the bladder wall. Secondary deposits were present in the para-aortic glands. Tumour cells were found in the suprarenal glands and their pericapsular lymphatics. Gross pyelonephritis was present in the remaining left kidney.

Cystoscopic findings.—Occupational tumours of the bladder show no special characteristics to distinguish them from spontaneous tumours. In character they may range from the delicately fronded papilloma to the deeply infiltrating carcinoma. There does, however, appear to be a tendency to increased multiplicity and to an unusual incidence of accompanying tumours in the renal pelvis, calyces and ureter (*see* Renal and Ureteric Tumours, p. 810). The appearance of further tumours at new sites is perhaps also more troublesome than in the case of tumours of spontaneous origin. On account of the careful screening of workmen and especially since the advent of the Papanicolaou technique, the tumours tend to be seen at an earlier stage of development than amongst the general population; indeed amongst men still employed in the industry it is now rare to find an advanced tumour at the first cystoscopy.

Gay (1934, 1937) has described congestive lesions consisting of punctate ecchymoses or fine telangiectasia, which are thought to be precursors of tumour formation. Epithelial hyperplasia has also been noted. In the past I have been sceptical of these findings (Poole-Wilson, 1953). Amongst these men there does, however, seem to be an increased incidence of localized congestive lesions or areas of epithelial hyperplasia, but these areas do not necessarily develop into tumours and may appear and disappear. Biopsy of such areas has shown erosion of epithelium with inflammatory cell infiltration and some fibrosis. Their significance is not really understood but they do appear to indicate an unstable mucosa and possible future trouble. Somewhat similar lesions have been seen in experimental animals; McDonald and Lund (1954) noted equivalent findings in their experiments with the implantation of beta-naphthylamine induced tumours.

Primary diagnosis.—At the completion of the initial investigations of 180 bladder tumours, 102 (56·6%) were regarded as simple papillomata. 78 (43·3%) were classified as carcinomata.

The incidence of papillomata appears higher than might have been expected, but a good many papillomata were diagnosed in the days before cystoscopic biopsy examinations were carried out, and some early carcinomata may have been included in this group. Over recent years it has been our aim to carry out a biopsy in every patient. From the pathological aspect, however, there is often difficulty in deciding which tumours are true simple papillomata and which should be regarded as early carcinomata. In this series we have included amongst the benign or transitional cell papillomata those tumours which show a minor degree of cellular polymorphism yet insufficient to warrant regarding them as definite carcinomata. (These tumours are now placed in a special category of simple benign transitional cell papillomata marked "suspect".) The result of this grading is perhaps shown in the fact that of the 102 cases of papillomata, 22 have shown malignant changes either at the same site or elsewhere in the bladder, at a later date.

Treatment

The primary treatment carried out on these patients has varied a little over the years but in general conforms to the following pattern. The benign papillomata and some early papillary carcinomata have been treated by perurethral diathermy or resection. Localized carcinomata which were of suitable size have been treated by open diathermy destruction and interstitial irradiation. The more extensive carcinomata have been subjected to deep X-ray therapy.

Open diathermy destruction of multiple papillomata, partial cystectomy and total cystectomy had been carried out in a few cases. The numbers treated by each method are shown in Table IV.

TABLE IV.—THE PRIMARY TREATMENT OF BLADDER TUMOURS

Perurethral diathermy	108
Interstitial irradiation	31
Deep X-ray therapy	21
Open diathermy, partial and total cystectomy	17
No treatment	3
	180

Perurethral Diathermy Destruction

Cystodiathermy was used in 108 patients as a primary form of treatment.

TABLE V.—PERURETHRAL DIATHERMY

Total number of cases	108
Five-year survival: 65 out of 74 possible survivors	88%

The 88% five-year survival rate appears fairly satisfactory but by no means indicates the full story. Of the 65 survivors 13 died later from vesical tumour; in 5 the tumour reappeared in the bladder over thirteen years after the original onset. 5 other patients later died from natural causes and were apparently tumour free. There are 45 patients, who have survived periods ranging from five to twenty-one years, and who still remain tumour free. 2 further survivors are known to have vesical recurrences.

The survey of these patients leaves no doubt that many benign papillomata and early papillary carcinomata may be controlled by perurethral diathermy. The figures, however, give no indication of the amount of cystoscopic investigation and treatment entailed. The course of the patient may be extremely variable. In some, after primary destruction of the tumour a trouble-free course ensues. In others there may be a period during which recurrent papillomata appear and require regular diathermy treatment. Eventually after a year or two recurrences may cease and the patient have many years of freedom. It is, however, never safe to regard these patients as cured and to dismiss them from care. In a considerable number recurrences or new tumours have appeared after five or more years of complete freedom. Such tumours may once more respond to perurethral treatment. In others these late tumours may gradually get out of control and apparently undergo carcinomatous changes.

In another group of cases recurrent papillomata will continue to appear at varying sites in the bladder and repeated diathermy treatment may be required to hold them in check. In such men it is, of course, essential to make absolutely certain that no renal or ureteric lesion is present.

In other instances, although the amount of tumour on inspection may not appear great, the bladder mucosa may show indefinitely outlined areas of red and apparently thickened mucosa. The appearances suggest that epithelial hyperplasia is present and that the mucosa is in an unstable state. Biopsy examination of these areas may fail to show tumour. These cases present a very dangerous problem because transition to an extensive invasive carcinoma may occur and progress at an extremely rapid pace. In some of these patients the subsequent course has shown that, despite control by biopsy, treatment has persistently lagged behind the progress of the disease. In such instances a decision to use more radical treatment such as deep X-ray therapy should not be too long delayed.

Although treatment may be started by perurethral diathermy the subsequent progress of the case may determine a change of treatment. In the present series, of the 108 cases who were started initially on this line of treatment 18 subsequently required treatment by other means.

Interstitial Irradiation

When the whole bladder mucosa must be regarded as a potential tumour site, interstitial irradiation may appear to be an unsatisfactory form of treatment. It must also be remembered that once a tumour-lethal dose of irradiation has been given to any part of the bladder it is not possible at a later date to carry out any further irradiation. The selection of patients for interstitial irradiation therefore requires great care. As has been previously mentioned, in a proportion of these occupational bladder tumours a localized carcinoma develops and the remainder of the bladder appears to remain free of tumour formation. In 31 such patients interstitial irradiation has been carried out as a primary treatment, with a five-year survival rate of 63% (17 out of 27 possible survivors).

This treatment has been reserved for definite carcinomatous lesions usually of Stage A or B. In some of the earlier cases Stage C lesions were implanted. The 63% five-year survival rate would seem to show that this method of treatment has proved its usefulness. I would, however, reiterate that if there is any suggestion of multiplicity of tumours it should not be used.

Interstitial irradiation has also been used as a secondary method of treatment for localized carcinomata that were primarily treated by perurethral diathermy. There have been 5 cases in this series with a five-year survival rate of 80%.

Deep X-ray Therapy

Deep X-ray therapy has been used as an initial form of treatment on 18 patients (2 palliation only). Of these 16 were suffering from

extensive or multiple carcinomata and 2 from severe multiple papillomatosis. Of the 18 patients 14 qualified for a five-year survival review and 6 or 43% were found to be living. Three of these survivors died at a later date from recurrent bladder tumour. In 4 of the patients who died, the bladder at the time of death appeared to be free from tumour but pelvic secondaries were present.

Deep X-ray was used as a secondary form of treatment in 10 instances. There were only 2 five-year survivals of 7 possible (28%).

Other Forms of Irradiation Therapy

Contact therapy was used on one of the earlier patients. He survived seven years but ultimately died of his tumour. In 2 patients the bladder has been irradiated by a central cobalt source—1 died at three years, the other is a four-year survival.

Radiation from a central source of cobalt has been employed once as a secondary form of treatment.

Renal and Ureteric Tumours

Amongst this series of occupational bladder tumours there has been a considerable incidence of accompanying tumours arising in the renal pelvis and ureter. The first 2 cases were recognized and described by Macalpine (1947). In 1 of these patients the lesion was unilateral, in the other bilateral renal tumours were present. Since then 14 further cases have been identified including 1 in which the tumours were again bilateral. Thus amongst 180 patients suffering from occupational bladder tumours 8·8% also developed renal or ureteric lesions (Table VI).

Table VI.—Renal and Ureteric Tumours

(Total number of patients with occupational tumours of the urinary tract—182)

Renal or ureteric tumour preceded by bladder lesions (2 bilateral)	16 (8·8%)
Renal or ureteric tumour without bladder lesions	2
Total	18 (9·9%)

2 patients have also been found, in 1 of whom a renal and in the other a ureteric lesion were unaccompanied by any bladder manifestation. An attack of painless hæmaturia led to a full investigation in the one instance, whilst the finding of tumour cells in routine Papanicolaou smears was the only indicative sign in the other.

From these findings it is evident that an investigation of men who have been exposed to urinary tract carcinogens must always include a full survey of the upper urinary tract. If intravenous pyelography fails to yield detailed pictures of the renal pelves, calyces and ureters, retrograde pyelograms and ureterograms should be made. The renal or ureteric lesion, however, commonly appears long after a bladder lesion has been found and treated. In fact it is probable that the lengthening of life resulting from early and adequate treatment of the vesical lesion may be the reason for the apparently increasing incidence of renal and ureteric tumours. Persistent recurrent vesical papillomatosis, hæmaturia which cannot be accounted for by a bladder lesion, and renal discomfort are symptoms which indicate the need for a further review of the upper urinary tract.

In 17 of these 18 men the upper urinary tract lesion was identified during life; the remaining renal tumour was found at post-mortem in a patient who had died from an advanced carcinoma of the bladder.

The tumour was confined to the renal pelvis in 13 patients (in 1 a tumour was also present on the other side); in 3 the renal pelvis and ureter were affected (in 1 of these a tumour was present in the other ureter); 2 patients presented ureteric lesions only. No patients presented any certain evidence of previous renal or ureteric stasis. 13 of the 20 lesions were on the left side and 7 on the right. Pathological examination showed that 10 were simple transitional cell papillomata; the remaining 10 showed carcinomatous changes.

The bladder tumours present in 16 of these patients varied considerably in type. In 4 an invasive carcinoma was present. In the remainder the lesion was primarily of a papillomatous nature.

In some this papilloma formation has been a pronounced feature and scattered groups of apparently small benign papillomata have been diathermized on many occasions. If such a state of affairs exists a search should immediately be made for a renal lesion. In this respect the following 2 cases are of interest. In the first the persistent appearance of small benign vesical papillomata ceased following the removal of a kidney containing a simple transitional cell papilloma and would support the view that the vesical papillomata were seedlings. In the second case the removal of a renal lesion made no alteration to the periodic appearance of bladder papillomata.

Case II.—E. M.

In May 1943, when aged 43, seven years after his first exposure to beta-naphthylamine this workman developed hæmaturia. There had been no previous symptoms and routine tests at the factory for blood cells had been negative. Cystoscopy (J. B. Macalpine, 31.5.43) revealed a small bunch of sessile papillomata well above the right ureteric orifice. There was no evidence of infiltration. The papillomata were destroyed by perurethral diathermy. Intravenous pyelography revealed no abnormalities.

From 1943 regular cystoscopic reviews revealed no sign of recurrence until March 1948, when two small

papillomata were noted above the left ureteric orifice, another at the internal meatus and one within the prostatic urethra. Despite careful perurethral diathermy treatment recurrent crops of papillomata kept appearing over the next nine years. During the summer of 1957 he noticed a trace of blood in his urine on one occasion and during the following month complained of some pain in his left loin. Intravenous pyelography revealed a normal right renal pelvis, calyces and ureter. The left kidney was silent. Cystoscopy (3.9.57) showed no papillomata in the bladder or urethra; a faint trace of blood was noted coming from the left ureter. A ureteric catheter ran up this ureter easily for 15 cm and was then obstructed. Pyelogram fluid also failed to run further up the ureter.

10.9.57: Left nephro-ureterectomy. The renal pelvis appeared distended and the ureter dilated to 1 cm in diameter down to a point at the pelvic brim where it became normal in calibre.

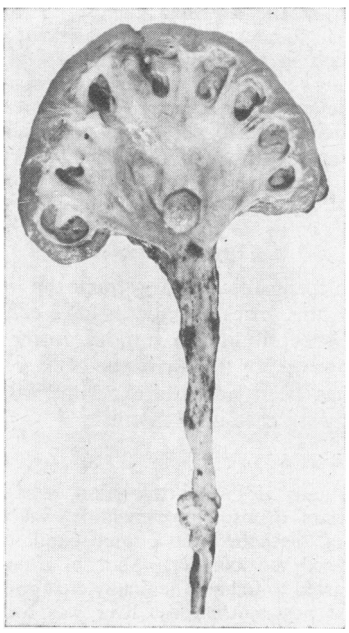


FIG. 6 (*Case II*).—Benign papillomata of the renal pelvis and ureter.

Examination of the removed specimen showed some pelvic and calyceal hydronephrosis. In the renal pelvis just above the pelvi-ureteric junction there was a benign type papilloma measuring 2·5 cm in diameter. Half-way down the ureter there was an occluding mass of papillomata about 2 cm in length. Above this mass the ureter was dilated but normal below it (Fig. 6).

Since his operation regular cystoscopic reviews have shown no further recurrences in the bladder. This man is at present apparently free of tumour sixteen years after the original onset of his trouble.

Case III.—J. T. S.

In March 1926, when aged 20, this man entered the dye manufacturing industry. He worked on the manufacture of alpha- and beta-naphthylamine until 1944, when he was referred to hospital on account of cystitis and hæmaturia. Previous routine urine tests for red blood cells had been negative.

Cystoscopy (J. B. Macalpine, 26.6.44) revealed an apparently simple papilloma in the vault of the bladder with a few smaller papillomata just below it. There was no evidence of infiltration. The tumours were destroyed by perurethral diathermy.

Regular review cystoscopies revealed from time to time recurrent papillomata in the bladder and posterior urethra (16.11.46, 17.11.48, 9.4.49, 3.1.51, 24.4.51 and 9.7.51). Occasional hæmaturia was noted during the autumn of 1952. Cystoscopy (27.10.52) revealed no vesical tumour. Intravenous pyelography showed a small calculus in the lowest calyx of the left kidney.

Cystoscopy (27.1.53) showed fronds just median to the left ureteric orifice. These were destroyed with diathermy and bilateral retrograde pyelograms were made. The right kidney and ureter appeared normal. The left pyelogram confirmed the presence of a small calculus in the lowest calyx. The pelvis and upper calyces appeared incompletely filled and deformed. The appearance suggested a tumour of the renal pelvis.

2.2.53: Left nephro-ureterectomy. The mucosa of the upper half of the renal pelvis and of the uppermost calyces was covered with transitional cell papillomata.

Review cystoscopies (25.1.54, 4.10.54) showed recurrent papillomata. During February 1956 some tiny clots were noticed in the urine. Cystoscopy (27.2.56 and 17.9.56) revealed no recurrences in the bladder. A right pyelogram and ureterogram were normal. May 1957: A small papilloma was destroyed at the site of the removed left ureteric orifice. Biopsy showed a simple transitional cell papilloma. During 1958 no recurrences were noted but cystoscopy on 20.2.59 revealed a papilloma (1·5 cm diameter) in the vault of the bladder. A biopsy of this tumour showed a transitional cell papilloma with moderate cellular polymorphism and fairly numerous mitotic divisions.

Treatment

12 patients were treated by nephro-ureterectomy. In one the lower end of the other ureter was later excised on account of papilloma formation. A nephrectomy alone was carried out on one patient. In another a proposed nephro-ureterectomy had to be abandoned on account of the extent of the tumour. 3 patients were too ill for any operative treatment—1 patient suffered from uræmia due to extensive bilateral renal tumours; 2 patients were dying from extensive vesical tumours. In one of these patients post-mortem examination confirmed the presence of a papillary carcinoma in the left renal pelvis but also revealed that a suspected chest secondary was a primary oat cell carcinoma of the right lung.

Urethral Lesions

Vesical papillomata may be accompanied by small and apparently subsidiary lesions arising in the posterior urethra and more rarely in the anterior urethra (Ashworth, 1956). These growths are frequently regarded as seedlings and it has been suggested that urethral instrumentation facilitates their implantation. In the present series a considerable number of such papillomata have been noted in the posterior urethra and to a much lesser extent in the anterior urethra. They have usually responded to perurethral diathermy.

In the following patient malignant changes supervened:

Case IV.—C. B.

During January 1936, when aged 28, this man commenced working in contact with alpha- and beta-naphthylamine. Twelve years later he was referred to Salford Royal Hospital as microscopic hæmaturia had been detected on routine urine investigation. Cystoscopy (18.7.48) revealed a solid papilloma above the right ureteric orifice and a small flat papilloma at 11.0 o'clock on the urethral margin. The papillomata were destroyed with diathermy.

Over the next two years further rather solid papillomata, occurring at various sites in the bladder, were destroyed by perurethral diathermy. Cystoscopy (28.11.50) showed a rather solid tumour on the trigone. Biopsy revealed a poorly differentiated transitional cell carcinoma. A course of deep X-ray therapy was given at the Christie Hospital (25.6.51–27.7.51, 6,000 rads on the 4 MV linear accelerator). The patient subsequently remained clear of tumour until July 1954 when cystoscopy revealed papillomata in the prostatic urethra and at intervals along the bulbous urethra. Biopsy showed a transitional cell tumour with a moderate number of dividing cells. The tumours were treated with diathermy but were proved recurrent and were never completely eradicated. During January 1955 further tumour formation appeared in the bladder. Total removal of the bladder and urethra was advised but refused. The urethra subsequently became grossly thickened from the base of the prostate to the distal portion of the bulb. The patient was finally admitted to hospital with acute retention and early peri-urethral extravasation and died shortly afterwards. Post-mortem examination revealed a carcinoma of the bladder invading the left pelvic wall. Carcinomatous deposits were present in the urethra and had produced a peri-urethral abscess.

One patient in whom the bladder lesion is quiescent has recently developed a carcinoma of the anterior urethra, which appears to be a primary growth:

Case V.—J. C.

This man entered the dye manufacturing industry when 26 years of age and came into contact with alpha- and beta-naphthylamine. After a latent period of twenty-nine year he was investigated on account of an attack of hæmaturia. Cystoscopy (8.1.52) revealed a papilliferous tumour in the vault of the bladder. It measured 2–3 cm in diameter and had a broad base. Biopsy revealed a transitional cell tumour showing nuclear gigantism, hyperchromatism and frequent mitoses. It was classified as a papillary carcinoma. The tumour was destroyed by perurethral diathermy.

During November 1954 and again during August 1955 and April 1956 small papillomata were observed at cystoscopy and destroyed by diathermy. The original tumour site remained free from trouble.

The bladder subsequently remained free from tumour. At cystoscopy (10.2.59) it was noted that the urethra close to the external meatus was a little narrow but no tumour was found in the bladder or urethra. During July 1959 this man complained of difficulty in passing urine and noticed a swelling in his left groin. Examination revealed a carcinoma of the penile urethra with secondary deposits in the left inguinal glands.

28.7.59: Partial amputation of the penis and block dissection of the left iliac glands. The specimen showed a tumour apparently arising from the urethra and invading the corpora cavernosa penis. Microscopy revealed an anaplastic carcinoma, which was squamous in parts and in several areas had an adeno-carcinomatous pattern. Comparison of the histology with the vesical tumour removed in 1952 did not suggest that this urethral tumour was metastatic. The glands contained secondary deposits.

Liver Lesions

Apart from the urinary tract the remaining tissues in this series of patients have exhibited no special susceptibility to tumour formation. In view, however, of the incidence of liver tumours, which has been noted in experimental animals, the following case is of interest:

Case VI.—J. W. L.

On January 1, 1948, this man, who had had twenty years' exposure to benzidine, was treated by perurethral diathermy for a small papilloma on the left side of the bladder. Shortly afterwards his health started to fail and he finally died on March 19, 1948. At post-mortem the liver was found to be enlarged and many carcinomatous nodules were present in it. The bladder, renal pelves and ureters appeared entirely clear of tumour. No primary carcinoma was found elsewhere in the body. It was thought that the carcinomata in the liver might be primary lesions. Unfortunately no ultimate decision could be made as no sections were prepared by the pathologist concerned.

The Mode of Action of the Carcinogens

The mode of action of the urinary carcinogens is an intriguing problem but one which could not be adequately discussed in this paper. For reviews of the work which has been carried out and extensive bibliographies the writings of Bonser *et al.* (1958), Boyland (1958), McDonald and Lund (1954), McDonald and Thorson (1956),

Scott and Boyd (1953), and Walpole and Williams (1958) may be consulted.

Prevention

In this paper the recognition of occupational bladder tumours as an industrial hazard, the methods of early diagnosis, their clinical features and response to treatment are discussed. Whilst these subjects are of great importance the ultimate objective of medicine and industry must be the complete removal of the causative factors. The ethics of the manufacture of urinary and other carcinogens has been admirably discussed by Scott (1958). Absolute prohibition of their manufacture and use would appear to be the ideal method of prevention. Such a course, however, represents an over-simplification of the problem and fails to take account of the varying severity of different hazards, of possible means of rendering manufacture safe and of the industrial importance of the product. Scott concludes: "If they are to be made, substances or processes which promote grave industrial diseases such as radiation sickness, occupational cancer or aplastic anæmia 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."

By 1950 beta-naphthylamine was universally recognized as a highly dangerous industrial chemical. It was also found impossible to devise plant for its production and use which afforded adequate protection and yet could be operated at an economic rate. In the United Kingdom it was voluntarily decided to abandon its manufacture. The loss would have been a serious one as beta-naphthylamine is extensively used for the manufacture of Tobias acid and similar beta-naphthylamine sulphonic acids, which are employed in the synthesis of many azo dyes. Chemists, however, found it possible, but at considerable extra cost, to alter the mode of manufacture so as to produce the Tobias acid by the sulphonation of beta-naphthol followed by amidation. The production of the carcinogen was thus avoided. Beta-naphthylamine is now no longer made in Great Britain, Germany and Switzerland. The manufacture of rubber antioxidants derived from alpha- and beta-naphthylamine has also been abandoned in this country.

Owing to the recognition of its potential dangers by Walpole *et al.* (1952 and 1954) 4-amino-diphenyl (xenylamine) has never been manufactured in this country.

Benzidine and alpha-naphthylamine are unfortunately essential intermediate compounds for the manufacture of large ranges of colours used in many industries. No substitutes or alternative methods of making the dyes have yet been devised. Manufacture therefore still continues but is carried out in specially designed plant and under strict medical supervision. Users of these compounds are also warned of their toxicity. Benzidine has also been employed in the rubber industry but its use is now discontinued.

During 1957, in order to try and ensure safe working conditions, Scott and Williams (1957*b*) drew up for the Association of British Chemical Manufacturers a "Code of Working Practice Recommended by the British Dyestuffs Industry for the Manufacture and Use of Products Causing Tumours of the Bladder". This is now accepted as the standard of practice.

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Meeting
May 28, 1960

MEETING AT THE CHRISTIE HOSPITAL AND HOLT RADIUM INSTITUTE, MANCHESTER

The following papers were read:

The Papanicolaou Technique for the Diagnosis of Vesical Tumours.—Dr. T. S. SCOTT.

Carcinoma of the Urethra: the Technique and Results of Treatment by Irradiation and Surgery.—Professor RALSTON PATERSON and Mr. D. S. POOLE-WILSON.

Grading of Bladder Tumours.—Mr. D. S. POOLE-WILSON.

Experimental Tumours.—Dr. A. L. WALPOLE.

Sarcoma of the Bladder.—Mr. M. HALL.

Multiple Papillomatosis of the Bladder.—Mr. A. ASHWORTH.

The Treatment of Multiple Papillomatosis of the Bladder by Intracavitary Irradiation and X-ray Therapy.—Dr. R. C. S. POINTON.

The following demonstrations were given:

Linear Accelerator and Betatron.

Cytodiagnosis of Bladder Tumours.

Irradiation Treatment of Carcinoma of the Glans Penis.

Localization of Bladder Tumours for X-ray Therapy.

The Use of the Image Intensifier for Control of Interstitial Irradiation of Bladder Tumours.

The following cases were shown:

Carcinoma of the Bladder Treated by X-ray Therapy.

Melanoma of the Urethra.

Carcinoma of the Urethra.

Total Removal of the Bladder and Urethra for Vesical and Urethral Tumours.

Sarcoma of the Bladder Treated by X-ray Therapy.

Diverticulum Following Interstitial Irradiation of a Tumour of the Bladder.

Total Cystectomy for Multiple Papillomatosis.