Current Practice

URINARY TRACT DISEASES

Management of Tumours of the Bladder

J. COSBIE ROSS,* CH.M., F.R.C.S.

British Medical Journal, 1970, 4, 661-663

Tumour of the bladder is a fairly common condition. No fewer than 3,764 deaths were recorded in England and Wales for the year 1969. The paramount symptom is haematuria, the blood being usually terminal and perhaps accompanied by small clots. Only in the final stages (and associated with extensive neoplasms) is the haematuria continuous, and it is well to remember the old description of the bleeding as profuse, painless, and periodic. Too often the patient experiences a few days' painless haematuria, and attributes it to a "cold in the bladder" when it clears up. Only when he has had a second or third attack some months later does he consult his doctor and thus valuable time is lost. The only safe and inflexible rule is to insist on a full investigation, especially a cystoscopy, in every patient with haematuria. If there is haematuria there is almost certainly a lesion of the urinary tract, as it is rare for systemic diseases and blood dyscrasias to manifest themselves initially by blood in the urine.

It is often said that in men a tumour is the most likely cause of haematuria, whereas in women this is more likely to be due to an inflammatory lesion. True though this generalization may prove to be, it does not exonerate us from the duty of insisting on a cystoscopy. Moreover, at the stage when treatment may be expected to be most effective there are usually no physical signs and the diagnosis depends largely on the cystoscopic findings. Such signs as a palpable, suprapubic swelling and induration felt on rectal examination above the prostate are late in development and ominous prognostically. Similarly, symptoms such as frequency, nocturia, dysuria, and strangury usually indicate a widespread lesion. Rarely a pedunculated tumour near the bladder neck may cause retention of urine. As time goes on, spread of the lesion to the pelvic lymph nodes leads to swelling and oedema of the leg.

Confusion has arisen as so many methods of treatment are advocated in this condition, but it must be remembered that tumours of the bladder vary from the benign, easily treated papilloma to the most malignant lesion. Many years ago Ewing pointed out that the villous character of most of these lesions is partly due to the muscular contractions of the bladder wall and partly to the fact that the tumour is constantly bathed in urine. More recently treatment has been based on the view that seedling implantation on intact uro-epithelium is unlikely and that the multiplicity and tendency to recurrence are due to a potentially malignant condition of the bladder lining. Consequently cystoscopic follow-up must be maintained for the rest of the patient's life. Equally, in some patients it may be necessary to consider either complete cystectomy or irradiation of the whole of the epithelium of the bladder. The management, therefore, is strongly influenced by two fundamental characteristics of the disease—that is, the tendency to recur and the tendency to multiple lesions.

It may well be said that "once a papilloma of the bladder, always a papilloma," and this is illustrated by one of my patients. This man had a fairly large papillary tumour treated by diathermy and subsequently attended regularly for cysto-

scopy—at first at six-monthly and later yearly intervals. The bladder remained clear for twelve years, but on the thirteenth a bun-shaped tumour, which proved to be malignant, was found.

Diagnosis

When cystoscopy is carried out the benign or malignant nature of the tumour is also assessed. This is based not only on the appearance of the bladder lesion and the degree of induration of the pedicle but also on the biopsy, which should be done in every case. In malignant cases palpation under anaesthesia is also important. A cystogram may show a filling defect and the intravenous pyelogram may show a hold-up at the lower end of the ureter, or even non-function of one kidney. If there is any back-pressure effect on the ureter and kidney then the bladder tumour is almost certainly malignant, as benign lesions, however large, do not cause a ureteric hold-up. A well-known diagnostic error lies in jumping to the conclusion that a non-functioning kidney on intravenous pyelography (combined with haematuria), indicates a tumour of the kidney. This mistake should not arise if the rule regarding carrying out a cystoscopy in every patient with haematuria is observed. Cytological methods are frequently used and have been especially useful in patients working in chemical processes involving carcinogenic substances. If the urine contains particles, these are sent to the laboratory; if no particles are present, the urine is centrifuged and the deposit stained. Clumps of neoplastic cells may be seen and identified by pathologists who have taken a special interest in this type of investigation. It cannot be sufficiently stressed, however, that a negative finding from cytological examination is of no significance, but the method is of value in following up chemical workers who have at one time been at risk. Occasionally in follow-up cystoscopy a blind biopsy of apparently normal bladder wall will reveal a carcinoma *in situ*.

Predisposing Factors

For many years several predisposing factors have been recognized, including encrusting cystitis, vesical calculus, leucoplakia, squamous metaplasia, untreated ectopia vesicae, bilharzia, and cystitis granulosa. A high residual volume of urine may be a predisposing factor, as it permits any urinary carcinogens to remain in contact with the uro-epithelium. Possibly this explains why carcinoma of the bladder has a higher incidence in the neurogenic bladder. A virus has also been suspected, as the "Shope rabbit papilloma" is thought to be of viral origin. The most important recent development, however, has been the discovery that certain chemical substances (often associated with certain occupations) are carcinogens. Apart from chemical workers, those involved in such industries as those using synthetic rubber are also prone to this condition. Some years' exposure to carcinogens is necessary before the danger point is reached, and since the danger has been realized industry has taken steps to eliminate the risk. At

*Honorary Consultant Urologist, Liverpool Regional Urological Centre, Liverpool 1.

one time described as "aniline workers' cancer, it is now thought that the aniline itself is not carcinogenic, but that aromatic amines and certain intermediary substances in the manufacture of aniline are responsible; 2-naphthylamine, benzidine, and para-xenylamine—all aromatic amines—have been implicated. Endogenous carcinogens, resulting from disturbances of tryptophan metabolism have also been cited, and this probably explains the fact that cigarette smokers have a two to five times greater incidence of carcinoma of the bladder than non-smokers. Smoking appears to have a profound effect on tryptophan metabolism.

Classification

In view of the malignant change potentially present in all papillary tumours of the bladder it might be well to discard the term "papilloma" but it is always difficult to eliminate a well-established term in medicine. A wide classification is obviously necessary in a condition which presents such a variable degree of malignancy, the usual method being as follows:

- Stage 1a mucosal only.
- Stage 1b muscular wall involved.
- Stage 2 perivesical space invaded.
- Stage 3 paravesical lymph nodes involved.
- Stage 4 distant metastases.

The International Union Against Cancer (U.I.C.C.) has recently suggested that the "T.N.M." system should be used in an attempt to achieve uniformity of classification in clinics throughout the world.

T—The primary tumour in certain sub-groups:

- T.1. infiltration of subepithelial connective tissue.
- T.2. infiltration of superficial muscle.
- T.3. infiltration of deep muscle.
- T.4. infiltration of adjacent organs, e.g. bony pelvis.

N—Regional lymph nodes

Involvement of any lymph nodes below the pelvic brim.

M—Distant metastases

Para-aortic nodes are included in this category.

Treatment

I believe that there are two fundamental rules of treatment (though the following opinions stem directly from personal experience and would not necessarily be acceptable to all urologists, some of whom lay greater stress on earlier surgery). The first rule is that cystoscopic diathermy is the best and most effective treatment, provided the case is suitable. Secondly, unless it is intended to carry out a complete cystectomy it is inadvisable to open the bladder by the suprapubic route. This rule discourages partial cystectomy and also suprapubic diathermy, as the risk of implantation of malignant cells is too serious to be lightly undertaken. I have never seen a patient with malignant deposits in the suprapubic scar survive. Sometimes it is necessary to make a suprapubic incision to implant gold grains but then the utmost precautions must be observed, including the use of the cutting diathermy current for incision of the skin and fascia and for opening the bladder (after careful aspiration).

There are five principal methods of treatment available, as follows.

Cystoscopic Diathermy

Cystoscopic diathermy is the method of choice and should be carried out even in large tumours provided there is no detectable induration—either bimanually or by cystoscopy—and no deep penetration of the bladder wall. It is surprising

how often a successful result is obtained in a borderline tumour, though the procedure may be tedious and time-consuming. In bulky tumours resection using diathermy is also effective.

Suprapubic Diathermy

Suprapubic diathermy for reasons given above should if possible be avoided. Almost the only indication for its use is the tumour with profuse and persistent bleeding uncontrollable by other means.

Irradiation

Interstitial irradiation, using gold grains, is a valuable and effective method of treatment in the selected patient. Implantation of gold grains is indicated for a single carcinoma not over 4 cm. in diameter which has not reached the muscle coat of the bladder wall. The method is unsuitable for tumours arising adjacent to the edge of a diverticulum, where accurate implantation is difficult.

About 60% of patients thus treated survive for five years. One small complication is that sometimes the phosphatic cap (which is present for some months after treatment) becomes detached and forms a vesical calculus, requiring perurethral lithotomy.

Intracavitary irradiation is not so frequently advised now as there are associated technical difficulties, and the bladder tends to become fibrotic and contracted.

External irradiation.—Megavoltage has proved a great improvement on the conventional method in that the beams are sharp-cut and such complications as proctitis are considerably diminished. The group of patients treated with megavoltage irradiation include those with the most malignant tumours—infiltrating and generally inoperable ones. Hence it is remarkable that in some series a quarter of these patients have been alive after five years. Megavoltage irradiation also has an excellent palliative effect, and frequently the bladder remains clear of growth and micturition normal, even when metastases are present elsewhere. This palliative action is very valuable in view of the extreme distress experienced by the patient during the terminal stages of an inoperable carcinoma of the bladder involving the trigone and internal urinary meatus. A disadvantage is that the uro-epithelium of the bladder remains vulnerable and may bleed at the touch of the cystoscope. Contrary to the usual teaching, however, I have found it possible to use cystoscopic diathermy with small recurrent tumours. A possible disadvantage is that occasionally persistent and intractable haematuria due to telangiectasia may necessitate cystectomy.

Cystectomy

Partial cystectomy has the disadvantage that it is difficult to remove sufficient bladder wall around the tumour to make the operation satisfactory without at the same time leaving only an inadequate tube in lieu of the normal bladder cavity. What looks like a medium-sized tumour on cystoscopy is often found to be much more extensive when the bladder is opened, usually because of unsuspected surrounding induration. For these and other reasons I rarely carry out partial cystectomy, and there appear to be few indications for this operation. The position is, however, different when considering complete or total cystectomy, which has several clear indications—namely, recurrent tumour after megavoltage; failure to respond to megavoltage; in certain cases of multiple tumours, too extensive for cystoscopic diathermy; and intractable bleeding due to telangiectasia following megavoltage.

If possible cystectomy should be postponed for a year after megavoltage irradiation, as healing is defective and slow within a few months of treatment. For example, the mortality of complete cystectomy in one series of figures was 45% when performed within nine months, whereas it was 15% if the operation was not carried out until at least nine months had elapsed.

The overall three-year survival rate after complete cystectomy has been quoted as 30%. The operation presents some difficulties when carried out after a previous irradiation owing to fibrosis, but I have the impression that the survival rate for the operation after megavoltage is better than when performed *de novo*, possibly because of the "frozen pelvis" and the effect of the irradiation on lymph nodes, etc. It is necessary to remove the prostate and the posterior urethra in men and the whole of the urethra in women. Because metastases may appear in the uro-epithelium of the urethra some authorities advocate removing the whole length of the male urethra together with the bladder.

The safest and most satisfactory method of dealing with the ureters is to implant them in the pelvic colon (after having first divided the bowel), the lower end being closed and the upper end being brought out as a terminal colostomy. The rectal bladder functions well and most patients find that a colostomy is less troublesome than an intestinal urinary conduit.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Immunosuppressive Drugs—I

British Medical Journal, 1970, 4, 663-665

Immune responses in man may be divided into two categories: the antibody-mediated and the cell-mediated. The antibody is thought to be produced by the germinal centres of lymph nodes, intestinal lymphoid tissue, and spleen. These lymphoid cells proliferate and produce antibody after antigenic stimulation. The cell-mediated system probably develops from the embryonic thymus. It comprises cells surrounding the germinal centres of lymph nodes and the paracortical cords of lymphocytes in those nodes. These cells are known as "immunologically competent." Rejection of grafts and delayed hypersensitivity reactions depend on cell-mediated immunity, while passive transfer of sensitivity requires immunologically competent cells or their products. Antibody itself cannot transfer this form of sensitivity, though antibody may well be implicated in the final destruction of cells.

In an immunological response antigen is taken up by the macrophage system. The antigen is altered, and its contact with small lymphocytes induces a proliferative response resulting in the formation of antibody and cells with the capacity to transfer cell-mediated immunity.

Immunosuppression can affect any of the above processes (see opposite). Methods of suppressing immune reactions, particularly those in clinical use, usually entail an attack on the lymphocyte. Irradiation, splenectomy, thymectomy, lymphocyte depletion by thoracic duct drainage, cytotoxic drugs, corticosteroids, and antilymphocyte globulin all seem to act mainly by interfering with lymphocyte function. There is no evidence that, in adults, splenectomy, irradiation to the spleen, or thymectomy potentiate other immunosuppressive agents. Immunosuppression by interfering with the activity of

Palliative Measures

Sometimes progressive and intractable pain, dysuria, and strangury with the frequent painful passage of clots through the urethra necessitate active palliative measures. One method is to carry out a simple ureterocolonic implantation of the ureters, thus eliminating troubles relating to micturition. In view of the limited expectation of life in such patients there is no need to be unduly concerned about the dangers of hyperchloraemic acidosis and ascending infection. Severe and persistent bleeding from an inoperable malignant growth may be controlled by bladder instillations of silver nitrate, starting with a 1/5,000 solution and working up to 1/1,000 if necessary. Similarly, thiotepa 60-90 mg. instilled into the bladder on alternate days (retained for three hours) may stop the haematuria. Thiotepa is also useful in cases where there are multiple, small velvety tumours present. The tiny lesions may disappear completely but a careful watch is necessary on the white blood count during the course of treatment.

To sum up, therefore, the principles of management are cystoscopic diathermy where possible; interstitial irradiation for circumscribed non-infiltrating malignant tumours; megavoltage irradiation for large, inoperable infiltrating lesions; for multiple papillary tumours either megavoltage or primary complete cystectomy; and for recurrent tumours after megavoltage—or for lesions failing to respond to megavoltage—complete cystectomy.

the macrophages is possible, but methods with a clinical application are not yet known.

At present three forms of immunosuppression form the basis of effective treatment in man—namely, antilymphocyte globulin, corticosteroids, and cytotoxic agents or antimetabolites. Nevertheless, the dosage, time of administration, and type of agent required for optimum effect are all largely unknown. Corticosteroids, purine analogues, folic acid antagonists, and alkylating agents can all suppress both humoral and

	IMMUNOSUPPRESSION
(1) Drug-induced	{ Corticosteroids { Folic acid antagonists { Purine analogues { Alkylating agents { Antilymphocyte globulin
(2) Surgical procedures	{ Neonatal thymectomy { Splenectomy { Thoracic duct drainage
(3) Irradiation to lymphoid tissue and bone marrow	
(4) Immunological procedures	{ Enhancing antibody { Reticuloendothelial blockade with particulate antigen
(5) Diseases	{ Malignant disease { Autoimmune disease (e.g. rheumatoid arthritis, Sjögren's syndrome, primary biliary cirrhosis) { Malnutrition and vitamin deficiencies { Infections (e.g. measles, leprosy) { Congenital immunological deficiencies { Granulomatous conditions (e.g. sarcoidosis, Crohn's disease)

cellular immunity. Unfortunately they are much less effective in suppressing established immunity than in preventing the induction of an immune response.¹⁻³ A definite species variation exists, and in different animals one drug may depress antibody synthesis and delayed hypersensitivity responses to different degrees.