is the form of research most likely to convince clinicians; secondly, we can specify the precision with which we wish to know the answer; thirdly, if future objections are raised to vitamin K we have a known population in which they can be investigated without bias; and, fourthly, prognostic factors can be recorded on entry rather than having to rely on medical records.

There are two problems: clinicians should only randomise infants for whom there is real doubt about the appropriateness of the treatment, and a trial to detect side effects similar in magnitude to the benefits in low haemorrhagic risk infants would need more than a million infants. The requirement for clinical doubt is perhaps not a problem. McNinch and Tripp showed that justifying a policy of treating all infants is of current clinical interest,¹⁰ and a trial with infants at low risk of haemorrhagic disease should be of interest to many clinicians. If risks of haemorrhage and side effects are not closely related such a trial would also answer the safety question for infants with higher risks of haemorrhage. The question of sample size is more difficult. I believe that we should decide what degree of safety is acceptable and achieve a sample sufficiently large to be able to show this. For a treatment intended for an entire population this is the least we can ethically do. For example, a trial to detect the increase in the cancer rates suggested by Golding *et al*¹ would require 40 000 infants and would also reveal differences in mortality from all causes of about 4/1000. An even larger trial would be required if we wished to test separately the intramuscular and oral routes of administration.

ORGANISING A TRIAL

Such a trial would be simpler to organise than trials of acutely ill patients since prospective parents could

be approached well before the start of the trial to allow time for careful explanation and informed consent. The treatment is available in all maternity units, and no placebo would be necessary since only major events, mortality and cancer, are of interest and these events are distant in time from the treatment. Although follow up of 40 000 children over several years would be difficult, substantial use of existing cancer and death registries could be made.

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Current Issues in Cancer

Superficial bladder cancer

R R Hall

This is the fourth in a series of articles examining recent developments in cancer and updating what we know about the disease

Freeman Hospital, High Heaton, Newcastle upon Tyne NE7 7DN
R R Hall, consultant urologist

Series editor: G M Mead.

G M Mead is consultant in medical oncology at the Cancer Research Campaign's Wessex Oncology Medical Unit

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Bladder cancer is almost certainly a product of the industrial revolution and the cigarette smoking that has accompanied it. Exposure to a chemical bladder carcinogen such as β naphthylamine, benzidine, or 4-diphenylaniline¹ can be proved in only a small proportion of patients and only a handful obtain industrial diseases benefit after developing "Prescribed Industrial Disease C23." None the less, the continued use of known carcinogenic substances in British industry for many years after their identification, the wide range of industries with a known or suspected increased risk of bladder cancer, and our ignorance of the carcinogenic potential of many materials used in current manufacturing should be a cause for continuing concern.

The association between bladder cancer and cigarette smoking, first considered more than 30 years ago,^{1,2} has been confirmed only recently.^{3,4} The incidence of this cancer among workers in "at risk" industries has been shown to be increased if they smoke as well,⁵ and first degree relatives of bladder cancer patients may increase their familial risk if they smoke.⁶ Whether the increased tobacco consumption by young women in recent years will alter the current 3:1 male to female preponderance of this disease and

whether young women can be persuaded to stop smoking for this reason remain to be seen.

Whatever environmental causes may exist, it has been the molecular aetiology of bladder cancer that has attracted most recent attention. As Jones *et al* have explained, "chemical and physical carcinogens leave footprints of their activities on DNA because of the patterns of base changes they induce."⁸ Chromosomes 1, 5, 9, 11, and 17 have shown non-random changes in bladder cancer, and allelic deletions of chromosomes 9 and 17 occur in over 60% of bladder tumours.⁹ Chromosome 9 aberrations have not been reported in any other solid tumour, the deletion of chromosome 17 with its tumour suppressor gene p53 occurs frequently in bladder cancer,¹⁰ and cigarette smoking increases mutagenic DNA changes in bladder tumours.¹¹ "Working from gene to carcinogen is likely to have a profound impact on our understanding of the origins of human [bladder] cancer."⁸

Presentation and diagnosis

Haematuria is well known as the main presenting symptom of bladder cancer but bladder tumours may present with any bladder symptom. Most patients are alarmed by blood in their urine and seek medical advice promptly. Few people suffer increasing fre-

quency, dysuria, or recurrent "cystitis" without at least one visit to their general practitioner. Many patients with advanced bladder cancer, however, are still diagnosed after a considerable delay that is not their fault.

A general practitioner will see one patient with bladder cancer every three or four years, out of many others with urinary symptoms that may not need hospital investigation. To avoid overlooking this single patient it cannot be emphasised too strongly that anybody with painless haematuria, any man with a urinary tract infection or frequency, urgency, and dysuria, and any woman with a urinary tract infection that fails to respond to appropriate antibiotics or with persistent, unexplained bladder symptoms should be referred for cystoscopy and either intravenous urography or plain abdominal radiography with ultrasound scanning. Open access for radiology and ultrasonography is an asset in this setting but cystoscopy is also essential. Urinary cytology may supplement these investigations but the absence of malignant cells by itself does not exclude urothelial cancer. Special haematuria clinics run by some hospitals should be encouraged, provided that they facilitate speedy investigation.

For the patient the advent of the flexible cystoscope has been a boon. Performed comfortably as an outpatient procedure, without a general anaesthetic, cystoscopy provides an immediate diagnosis or reassurance that a sinister bladder problem is not present.

At the time of initial diagnosis roughly 70% of tumours are confined to the bladder mucosa or submucosa and are designated "superficial" (TNM category Tis, Ta, Ti; see box). The remainder are more advanced, have invaded the detrusor muscle, perivesical tissues, the prostate, or other organs, and may well have metastasised to regional pelvic lymph nodes or beyond. For years the treatment of bladder cancer has been determined largely by this simple division into "superficial" and "invasive."

Most patients with muscle invasive bladder cancer die of local progression or metastases within three to five years. The main problem for these patients is how to achieve tumour control and prevent or treat metastasis. The behaviour of the rest of the bladder urothelium is of little importance.

By contrast, if managed properly most patients with superficial bladder cancer do not die of the disease but the whole of their remaining life is influenced by the tendency of the urothelium to develop new tumours at other sites in the bladder or urinary tract. It is these recurrences that necessitate lifelong cystoscopic follow up and continue to pose the principal problem of management.

Intravesical chemotherapy

First used more than 30 years ago,¹² the intravesical instillation of cytotoxic agents including thiopeta, mitomycin, doxorubicin, and epirubicin is now known to be a useful adjunct to endoscopic resection, as these agents reduce the multiplicity and frequency of superficial recurrence. Instilled every six to eight weeks and retained in the bladder for at least one hour on each occasion, these four drugs seem to be equally efficacious in reducing the recurrence rate of new and recurrent Ta and T1 bladder tumours by about half when compared with transurethral resection alone in randomised clinical trials.¹³

Toxicity is not a major problem, though chemical cystitis delays or stops treatment in around 5% of patients, depending on the frequency of instillation of the drug concentration in the bladder. This combined with the need for repeated catheterisation, the inconvenience of frequent hospital attendance, and the cost

TNM classification of bladder cancer

- Ta—Non-invasive papillary carcinoma
- Tis—Carcinoma in situ: "flat tumour"
- T1—Tumour invades subepithelial connective tissue
- T2—Tumour invades superficial muscle (inner half)
- T3—Tumour invades deep muscle or perivesical fat
 - T3a—Tumour invades deep muscle (outer half)
 - T3b—Tumour invades perivesical fat (T3bI, microscopically; T3bII, macroscopically (extra-vesical mass))
- T4—Tumour invades any of prostate, uterus, vagina, pelvic wall, abdominal wall
 - T4a—Tumour invades prostate, uterus, vagina
 - T4b—Tumour invades pelvic wall, abdominal wall

has tended to limit intravesical chemotherapy to those patients considered to be at greatest risk of recurrence. Indeed, in its guidelines for the clinical evaluation of new drugs, the United States Food and Drug Administration excludes good risk superficial bladder tumours from chemoprevention trials.¹⁴ This position, however, has now been challenged by the findings of two large multicentre randomised clinical trials conducted by the Medical Research Council Urological Cancer Working Party and the EORTC (European Organisation for Research and Treatment of Cancer) Genitourinary Group.

The MRC trial compared transurethral resection alone with transurethral resection plus a single post-operative instillation of mitomycin, or this treatment plus four more doses of mitomycin instilled at the time of each three monthly follow up cystoscopy for a year, in 502 patients with newly diagnosed Ta or T1 transitional cell carcinoma.¹⁵ After a minimum follow up of three years analysis confirmed that one dose of mitomycin reduced recurrence rates significantly.¹⁶ The EORTC trial (protocol 30863) compared the instillation of 80 mg epirubicin with an instillation of sterile water immediately after transurethral resection in 432 patients with new or recurrent solitary Ta and T1 bladder tumours. After a mean follow up of two years it was clear that epirubicin was beneficial, reducing the recurrence rate by 50% compared with water in newly diagnosed patients.¹⁷ The toxicity of single drug instillations is minimal.

Though these patients with good prognosis bladder tumours face only a 40% chance of superficial tumour recurrence, the opportunity to reduce the recurrence rate even further by a single instillation of mitomycin or epirubicin should not be ignored.

Prognostic factors

Factors determining the likelihood of tumour recurrence have been examined by many workers and it has become increasingly clear that the depth of invasion (Ta versus T1) is by no means the only determinant of prognosis. Tumour multiplicity, size, and histological grade, cytological findings in the urine, and dysplastic changes in the normal looking bladder epithelium have all been shown to be relevant. Nevertheless, the subjective nature of most of these factors and the need to combine multiple pieces of information have until recently limited our ability to define clear cut prognostic groups in everyday practice. Fortunately, the problem has been solved by an important multivariate analysis reported by Parmar *et al.* If, instead of relying on biopsy findings and measurement of size, the urologist simply counts the number of tumours at presentation and observes the presence or absence of tumour at the first follow up cystoscopy, patients can be divided into three separate groups whose follow up may be rationalised accordingly.

As discussed elsewhere,¹⁹ if, in addition, the use of intravesical chemotherapy is tailored to these simple prognostic groupings the lifelong management of patients with Ta or T1 bladder cancer may be improved considerably and savings achieved in health care services. Not only is this a welcome advance in urological care but it is a very gratifying outcome of years of clinical trial collaboration by urologists, pathologists, data managers, and statisticians in the United Kingdom and the rest of Europe.

Carcinoma in situ and pT1G3 tumours

The histological examination of resected bladder tumours cannot be dispensed with, however, because within the generality of superficial tumours are two small subgroups of patients with particularly poor prognoses who need special care.

CARCINOMA IN SITU

Urologists were slow to appreciate the sinister nature of carcinoma in situ but now the truly malignant potential of the "velvet patch" in the bladder is well known and considerable advances have been made in its treatment. Small localised areas of carcinoma in situ may be resected successfully like Ta and T1 tumours. But if the carcinoma in situ is diffuse or accompanied by severe dysplastic change in the normal looking urothelium intensive intravesical treatment with BCG (bacille Calmette-Guérin), doxorubicin, or epirubicin is mandatory if cystectomy is to be avoided or disease progression prevented.

Intravesical treatment yields up to 80% complete remission after one or two six week courses of instillations.²⁰ The short term results are good and fewer patients have needed cystectomy for carcinoma in situ in recent years. Whether the number of patients actually dying of cancer has been reduced, however, is not certain. Intravesical BCG is the treatment of choice at present, but because of its systemic toxicity possibly intravesical chemotherapy (which is usually free of systemic complications) should be used first and BCG reserved for chemotherapy failures. An EORTC phase III trial (protocol 30906) is investigating this issue.

pT1G3 TUMOURS

Despite their relatively innocent cystoscopic appearance, tumours that extend through the basement membrane into the submucosa (TNM category pT1) and are poorly differentiated (WHO grade 3) often prove fatal. One fifth to half of these tumours progress to muscle invasion with little or no warning and almost one third metastasise within two to five years.^{21,22} Hence immediate cystectomy is often recommended at the time of initial diagnosis. The possibility of replacing the bladder by orthotopic reconstruction makes cystectomy a less mutilating option, but given that half of pT1G3 tumours do not progress, that a survival advantage from immediate cystectomy has not been proved by clinical trial, and that radiotherapy may be curative, the optimal treatment for these uncommon tumours remains unclear. The current MRC trial comparing transurethral resection plus BCG with transurethral resection and radiotherapy is thus of considerable importance.

Immunotherapy with intravesical BCG

Many non-urologists have been unaware that intravesical instillation of BCG has been used in treating bladder cancer for 17 years²³ and are surprised at its likely benefit as immunotherapy. That instilling BCG into the bladder once a week for six to 12 weeks destroys carcinoma in situ and papillary superficial

Superficial bladder tumours. Some 70% of bladder tumours are confined to mucosa or submucosa at initial diagnosis

tumours²⁴ and causes measurable changes in the general immune system is beyond doubt.²⁵

Numerous phase II studies of different strains of BCG have shown its efficacy, and a recent review has summarised its unwanted side effects, based on data from 2602 patients.²⁶ The most serious of these is systemic "BCG-osis," with lung granulomas, disturbed liver function, fever, and malaise. Prompt treatment with antituberculous chemotherapy is required, as a few deaths have occurred. The incidence of such severe toxicity is less than 1% but many more patients experience flu-like symptoms after each treatment, and irritative bladder symptoms are as common as the chemical cystitis caused by cytotoxic instillations. Animal and in vitro studies suggest that simultaneous treatment with isoniazid may reduce toxicity without affecting therapeutic benefit, but clinical proof is lacking.²⁷

Because of the systemic toxicity caused by BCG, and as European randomised trials comparing BCG with cytotoxic drugs have failed to show any superiority for BCG, it is usually reserved for treating carcinoma in situ, pT1G3 tumours, and those Ta and T1 tumours that fail to respond to other agents. In North America, however, practice is different. Two clinical trials conducted by the Southwest Oncology Group have shown BCG to be superior to doxorubicin and mitomycin²⁸; and a small study by Herr *et al* that BCG may reduce the subsequent incidence of muscle invasion in high risk patients.²⁹ Two ongoing EORTC trials should resolve some of the remaining uncertainty generated by this conflicting evidence.

Does intravesical therapy prevent death from bladder cancer?

The undoubted benefits of intravesical chemotherapy and BCG have been limited to the short term control of carcinoma in situ and multiple Ta and T1 tumours, reducing the incidence of superficial tumour recurrence, and avoiding cystectomy in some patients. Of equal concern should be the role of intravesical treatment in reducing tumour progression and cancer death, but despite the tens of thousands of patients who have received this treatment its contribution to long term survival is unclear.

Trials have concentrated on short term tumour control, comparing different agents and doses, toxicity, the timing of optimal treatment schedules, and the advantages of repeated courses of treatment or maintenance instillations. In addition, randomised trials tend to attract patients with a good prognosis, so that

the incidence of tumour progression has been very small. In the EORTC trial of epirubicin 1.4% of patients progressed to muscle invasion after two years, and in the MRC trial of mitomycin 5.3% progressed after a median follow up of four years.

No randomised trial comparing adjuvant intravesical therapy with transurethral resection alone has recruited more than a few hundred patients and with such a low progression rate worthwhile differences in survival will not have been detectable. Thousands, not hundreds, of patients will be needed.

If a meta-analysis of previous trials proves inconclusive priorities for future trials must be considered very carefully and death from bladder cancer included as a planned end point. Recruitment must aim at including as many "ordinary" patients as possible rather than insisting on selected groups that fit preconceived expectations. Data collection on the scale necessary for such prospective audit will have to become part of routine clinical work and not be an extra task for a few enthusiasts.

Conclusion

As a result of the precision and safety of modern transurethral endoscopic surgery (made possible by the technological advances of the past two decades) and the therapeutic activity of intravesical chemotherapy and immunotherapy, most patients who develop superficial bladder cancer will not die of the disease and most will retain normal bladder function. None the less, their quality of life will undoubtedly be diminished by the need for regular examinations, anxiety concerning possible tumour recurrence, and the inconvenience and toxicity of treatments necessary to deal with such recurrence.

Our clearer understanding of tumour prognostic factors and the application of the results of recent clinical trials should improve the prospects of many patients in the future. For those with a poor prognosis whose tumours cannot be controlled by endoscopic means the modern surgical techniques of bladder reconstruction and continent urinary diversion will be welcome, but the temptation to recommend immediate cystectomy for this reason should be resisted. Multi-centre randomised trials have played a major part in improving the treatment of superficial bladder cancer. They are the key to future progress.

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Correction

Consensus on diagnosis and management of primary antibody deficiencies

A typesetting error occurred in this fortnightly review by H M Chapel for the Consensus Panel for the Diagnosis and Management of Primary Antibody Deficiencies (26 February, p 581). In the appendix, an asterisk—indicating a home treatment centre—should have been inserted for Southmead Hospital, Bristol.

ANY QUESTIONS

Why do radiologists now call the thoracic spine the dorsal spine when the whole of the spine is dorsal but only the thoracic spine is thoracic?

Like the questioner I also dislike this use of the term because it is sloppy where the antithesis dorsal-ventral is paramount. Nevertheless, a distinction between upper and lower back is useful and respectable. The

Latin word *dorsum* has undertones of arch, ridge—that is, a convex shape for the upper back—in contrast to *tergum*=rear. And to pat someone on the back or place a burden on your back is, in English, a dorsal image in the thoracic sense only. So dorsal for thoracic has everyday as well as clinical usage in its defence.—THOMAS SHERWOOD, *professor of radiology, Cambridge*