Conclusions

It seems likely that, even allowing for the influences described, those who usually relight their cigarettes when smoking have a moderately greater rate (about 15%) of chronic bronchitis than those who do not adopt this method of smoking. It is, however, a matter for speculation whether this is because they are more likely to smoke to a shorter butt, consuming a little more tobacco but considerably more tar (Moore and Bock, 1968) than normal smokers, or whether the actual extinguishing and relighting of charred and possibly compressed tobacco leads to a greater production of those substances in tobacco smoke which are likely to be the cause of the type of lung damage seen in chronic bronchitis (Thurlbeck *et al.*, 1963).

In any event this investigation has shown that relighters have a higher risk of chronic bronchitis than those not relighting, and an earlier study (Dark *et al.*, 1963) has shown that they have greater risk of developing lung cancer. While cigarette smokers in general may be classed as a high-risk group in respect of chest disease it seems that relighters are even more at risk.

I wish to thank Professor M. R. Alderson, formerly Director of the Regional Cancer Registration Bureau, who helped plan the investigation, and the Manchester Regional Hospital Board for allowing the staff of the Mobile Chest *X*-ray Service to obtain the histories and the computer section to process the information. I am particularly grateful for the care and attention to detail given by the staff of these departments and for the help of Miss Hepple in the classification of occupation and social class.

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PRELIMINARY COMMUNICATIONS

Effects of Hyperthermia on Bladder Cancer

R. R. HALL, R. O. K. SCHADE, J. SWINNEY

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Summary

A study of the effect of bladder lavage with isotonic fluid at 45° C on proliferative transitional cell carcinoma has shown definite cancericidal changes. These early studies suggest that further investigation of hyperthermia on a larger scale would be worth while.

Introduction

The treatment of cancer by heat, either by raising the body temperature or applied locally, has been regarded with suspicion by most oncologists.

Introduced unwittingly by Busch (1866) it was perpetuated in the form of "Coley's toxin" (Coley, 1898; Nauts *et al.*, 1953). More recently the generation of high fever or the induction of total body hyperthermia in patients with advanced malignant disease has been investigated and advocated (Crile, 1962, 1963; von Ardenne and Krüger, 1966; Cavaliere *et al.*, 1967; Henderson and Petigrew, 1971), but such treatment is fraught with danger and followed by dubious success.

Experiments have shown, however, that tumour cells both in vitro and in vivo are more susceptible to heat than are normal tissues (Vidal, 1911; Johnson, 1940; Selawry *et al.*, 1957; Cavaliere *et al.*, 1967; Suzuki, 1967; Muckle and Dickson, 1971; Dickson and Muckle, 1972) and may be killed when subjected to temperatures over 40° C.

Heating most organs in vivo is technically impracticable, so that attempts to use local hyperthermia for treating cancer have been few (Westermark, 1898; Percy, 1912, 1914, 1916) and have passed unnoticed. The urinary bladder is exceptional in that it is particularly suitable for the application of local hyperthermia, as its wall may be heated by irrigation with hot isotonic fluid.

Conservative management of multiple superficial tumours of the bladder still presents difficulties despite advances in intracavitary chemotherapy (Jones and Swinney, 1961; Veenema, 1966; Riddle and Wallace, 1971) and the more recent innovation by Helmstein (1972) of prolonged bladder distension. Hyperthermic irrigation was thus considered worthy of trial for this form of bladder carcinoma.

Patients and Methods

Altogether 35 treatments were carried out in 32 patients. Thirty patients had multiple non-invasive superficial transitional cell carcinomata of the bladder unsuitable for endoscopic resection or diathermy. The two other patients had clinically invasive bladder cancer (U.I.C.C. class T3) and were included because their general condition precluded radical therapy.

In all the patients the nature and extent of the tumour was established by cystoscopy and bimanual examination under general anaesthesia and intravenous urography, and biopsy specimens of the tumour and intervening normal bladder mucosa were obtained.

The effectiveness of the treatment was assessed by cystoscopy and bimanual examination and by biopsy between one day and eight weeks after the completion of treatment.

The bladder was irrigated through a 20-gauge (French) three-way Foley catheter with normal saline prewarmed in a heating coil and hot-water bath. The flow of saline through the bladder of about 2 l. per hour was adjusted so that the optimal temperature of the outflow from the bladder was 45° C; but fluctuations may occur which can be corrected by modifying the rate of flow. This temperature was judged the most satisfactory after initial trial, being tolerated by all patients; higher temperautres tend to cause discomfort.

Newcastle University Hospitals
R. R. HALL, F.R.C.S., Senior Registrar in Urology
R. O. K. SCHADE, M.D., F.R.C.PATH., Consultant Pathologist
J. SWINNEY, M.S., F.R.C.S., Professor of Urological Surgery

The first patient was treated for one hour only, the second for three hours, and another received 12 treatments of one hour each. The remainder received 12 daily treatments of three hours, lying alternately supine and prone during treatment. Three of the latter patients received two separate courses of treatment.

Routine intravenous pyelography and urine culture were performed before beginning treatment. Vesicoureteric reflux was not considered to be a contraindication to therapy but if the urine was infected appropriate antibiotics were prescribed for the duration of treatment. The patients' temperature, pulse, blood pressure, and urine output were recorded throughout irrigation. Full blood count, blood urea, creatinine, and electrolytes were estimated daily.

Results

Tumour Necrosis.—The results of treatment are summarized in the table. After the 35 courses of treatment four patients showed no tumour in the bladder when cystoscoped 3, 13, 14, and 18 days respectively after finishing treatment. Twenty-six courses of treatment produced partial regression of tumours but in five patients there was no visible change in the carcinoma up to eight weeks afterwards. Both patients with invasive carcinoma underwent necrosis of the visible tumour mass within the bladder. The first patient treated was clinically tumour free nine months later but subsequently redeveloped an invasive tumour. The second had a normal bladder three days after completing 12 treatments of one hour each and 13 months later had only a few superficial papillary tumours at a different site in the bladder.

Incidence and Extent of Tumour Regression (Size or Number of Tumours or Both) of Transitional Cell Carcinoma after Hyperthermic Irrigation of Bladder

Extent of regression	Nil	<50%	>50%	100%	Total
No. of courses of Treatment	5	7	19	4	35

Cystoscopic Appearance.—Cystoscopy the day after completion of the treatment showed changes ranging from moderate congestion of the mucosa to an angry oedematous sterile cystitis. Some tumours had disappeared, some were white and necrotic, and others remained apparently healthy. Some of the papillary tumours were swollen, so that it was difficult to distinguish tumour from oedematous, but previously normal, bladder mucosa. After an interval of two weeks the mucosa generally looked normal on cystoscopy. The site of the previous tumour usually appeared normal but sometimes was marked by reddening of the mucosa with fluffy superficial necrosis. Some larger necrotic tumours remained adherent for as long as one month.

Cytology.—Serial cytological examination of the urine during treatment showed numerous malignant cells at the beginning of treatment but subsequent specimens became progressively acellular.

Histopathology.—Histological examination confirmed that all patients had transitional cell carcinomata. In one patient with clinically superficial disease the tumour was moderately well differentiated and invaded the submucosa. This patient's tumour regressed by more than 50%. In a second patient the tumour was well differentiated but invading submucosa. Complete necrosis occurred as a result of hyperthermia. In all the other patients the multiple superficial tumours were well differentiated and non-invasive. The two patients with clinically invasive disease had carcinoma that was also well differentiated. The depth of infiltration could not be assessed from the biopsy specimens. Specimens taken from the tumours persisting after hyperthermia showed the same morphological pattern as those obtained before treatment. Biopsy of normal bladder mucosa showed varying degrees of hyperplasia before and after therapy. There was no evidence to suggest that the hyperthermia treatment caused any change in the degree of differentiation of the bladder tumours or that it gave rise to significant atypia of the bladder mucosa.

Subsequent Treatment.—The four patients with total tumour necrosis were given no additional active therapy. Those who had residual tumour were treated by transurethral resection (5), endoscopic diathermy with Kidd's cystoscope (20), and intravesical ethoglucid (1). Of the five patients showing no response to hyperthermia one was treated by cystectomy, one by intravesical thiotepa, and three by extensive endoscopic resection and diathermy.

Long-term Follow-up.—Because this study began in 1972 follow-up data were available for only 18 patients, and ranged from three to 20 months. Six patients were tumour free three to eight months after treatment, eight had superficially recurrent tumour amenable to endoscopic therapy, one was receiving intravesical thiotepa, two required cystectomy, and one received radiotherapy. Three died of intercurrent disease.

Discussion

It is evident that hyperthermic irrigation of the urinary bladder with isotonic saline is capable of producing necrosis of superficial transitional cell carcinoma without damaging the normal bladder mucosa. That raising the temperature to 41° C for one hour should result in extensive necrosis is difficult to understand but was observed in one patient. Despite this initial success it was decided to expose subsequent patients to longer periods of hyperthermia, though this may not have been necessary. Hyperthermic irrigation of the bladder at 41° to 45° C causes no discomfort, no systemic disturbance, and no electrolyte imbalance. The incidence of subsequent tumour recurrence did not prove excessive, so there is no reason to believe that hyperthermia is itself carcinogenic or that it stimulates later tumour formation.

Our purpose is not to discuss the pathophysiology of hyperthermic cancer cells but to draw attention to rather surprising observations of the effect of local hyperthermia on bladder tumours in clinical practice.

At present the use of intravesical hyperthermia is empirical and the temperature, frequency, and duration of treatment are arbitrary. Further experience with modified hyperthermic regimens will be required before the true clinical potential of this phenomenon can be assessed.

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