

dioxide while psychomotor function and blood pressure were unchanged. Thus the antagonist effect of naloxone could be expected only in the former values. Naloxone was effective in producing a large degree of reversal of the miosis, analgesia, and respiratory depression produced by the morphine. It also consistently produced complete reversal of the subjective effects of morphine. Previously it has been suggested that naloxone may selectively antagonize the respiratory depressant effect of morphine but allow the other effects to persist (Hasbrouck, 1971; Heisterkamp, 1972). The measurements of pain threshold made in this study showed clearly that naloxone antagonizes both the analgesic and respiratory effects of morphine.

Immediately after the injection of naloxone the subjects were unaware of any residual effects of the morphine though in the first measurements made after the injection miosis and respiratory depression were still present. These measurements were made at about six and 12 minutes after naloxone had been given. It is possible, therefore, that complete reversal might have occurred shortly after the injection, and that by the time the particular measurements were made the antagonist action was already declining. Thus these measurements might have represented an underestimate of the degree of reversal produced by naloxone.

The return of respiratory depression after the administration of naloxone has been described in clinical practice (Hasbrouck, 1971; Kersh, 1973; Fink *et al.*, 1968). These reports suggested that the duration of action of naloxone may be relatively short, but they contrast with the findings of Jasinski *et al.* (1968), who found evidence of antagonist activity three to five hours later. The doses of naloxone used in these studies were variable and did not permit a direct comparison to be made. Our results indicated that the duration of action of an intravenous dose of 0.4 mg/70 kg was limited, and little if any effect persisted after 45 minutes. *In vitro* studies of receptor occupancy by Kosterlitz and Watt (1969) and Kosterlitz *et al.* (1972) have shown the half time of the action of naloxone to range from 12-20 minutes. The half time of recovery cannot be determined accurately from the results of the present study, but it can be roughly estimated in the case of ventilatory response to be between 15 and 20 minutes. In clinical practice the duration of action of naloxone will be influenced by many factors such as the type and amount of narcotic and non-narcotic drugs received by the patient and by the general condition of the patient.

The cause of the evanescent action is unexplained; metabolism or redistribution are both possible explanations. Fujimoto (1969) and Weinstein *et al.* (1971) have shown that naloxone can be metabolised and that after large doses metabolites appear in the urine of animals and man. The rate of metabolism is unknown,

and its measurement awaits the development of a suitable method of assay.

Clearly naloxone is an effective morphine antagonist able to produce almost complete and simultaneous reversal of the principal effects of morphine. Other reports indicate that naloxone antagonizes the action of a wide range of narcotic drugs including pentazocine, for which there is no other effective antagonist (Evans *et al.*, 1973; Kallos and Smith, 1968). The absence of any demonstrable agonist side effects makes naloxone substantially superior to its predecessors, and it would seem to have considerable therapeutic potential (Evans *et al.*, 1974). The possibility that its antagonist action may wear off too soon is a hazard; agonist effects could then appear after a latent period. The action of naloxone could be prolonged by the administration of larger doses either intravenously or intramuscularly or by the use of an intravenous infusion. These problems, and the rate of metabolism, are currently under investigation.

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# Cigarette Smoker's Bronchitis: The Effect of Relighting

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## Summary

Male volunteers for mass radiography examination aged 40 or more were questioned about their sputum production, smoking habits, and, when applicable, their method of smoking cigarettes.

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Of 5,438 cigarette smokers 1,051 (19%) claimed that when smoking a cigarette they usually extinguished it at some stage and later relit it to smoke again. Anyone who admitted to producing sputum from his chest on most days of the year or on most days for a minimum of three months of the year for at least the last two years was classed, in the absence of other causative disease, as a chronic bronchitic. Such chronic bronchitics totalled 1,864 (34%).

The rate of chronic bronchitis among relighters (39.7%) was higher than the rate (32.9%) among the remaining cigarette smokers. The difference was of high statistical significance ( $P < 0.001$ ), and the same pattern was maintained when age and consumption were standar-

dized. After allowing for a trend towards lower social class and a preference for plain as opposed to filter cigarettes the rate of chronic bronchitis among relighters was about 15% greater than that of the remaining cigarette smokers.

## Introduction

A variation of the normal method of cigarette smoking is one in which the cigarette is extinguished at some stage and is later relit to smoke again. This practice, known as "dimping" in the Manchester area, may be repeated before the cigarette is finally discarded.

Others (Dark *et al.*, 1963) have shown that the practice of relighting seems to carry a greater risk of lung cancer than the normal method of smoking, and this paper presents the results of an investigation into the chronic bronchitis status of relighters.

## Subjects and Methods

The data were obtained during 1970 by questioning men from industry and the general public who volunteered for mass radiography and who were aged at least 40. Most of the volunteers lived or worked in towns within the South-east Lancashire conurbation.

A smoking history was taken which included the amount, type, duration, and method of smoking, and, in particular, each cigarette smoker was asked if he usually relit his cigarette. A cigarette smoker was defined as one who had smoked at least one cigarette each day for as long as a year (Doll and Hill, 1950), and those who had stopped smoking at least two weeks before attending for examination were classed as ex-smokers. Smokers of hand-rolled cigarettes were counted as cigarette smokers, and the amount of tobacco used was converted to cigarette equivalents (1 oz (28 g) a week=four cigarettes a day). Mixed smokers—that is, those smoking at least one cigar a week or 1 oz (28 g) of pipe tobacco a month in addition to their cigarettes—were excluded from the study.

Each volunteer was asked if he brought up or coughed up phlegm from his chest, and if so whether this was on most days of the year or on most days for at least three months of the year, and for how many years he had done this. Any person who had had this symptom for at least the past two years was classified as a chronic bronchitic.

All volunteers with incomplete or invalid records (2.4%) were excluded from this study, as were 68 persons whose subsequent chest x-ray films showed disease or abnormality (other than changes sometimes seen in chronic bronchitis) which was thought likely to be the cause of their sputum—for example, certain tuberculous disease, lung cancer, bronchiectasis, etc.

## Smoking Habits

Previous articles (Rimington, 1972, 1973) dealing with the effect on the prevalence of chronic bronchitis of the type of cigarette smoked and the method of smoking were based on the same sample of men and they showed that the smoking habits and type of cigarette smoked (filter or plain) were identical with those found in a nationwide sample of men of similar age (Todd, 1969).

### CHRONIC BRONCHITIS PREVALENCE

It is well known that the prevalence of chronic bronchitis increases with age and with increase in consumption of cigarettes. The results of this study showed no exception, and the table gives, in three consumption categories, not only the actual rates of chronic bronchitis for those who did and those who did not

usually relight their cigarettes but also the age-standardized rates based on a population equally divided into five-year age groups. The main point of interest in the table is that smokers who usually relit their cigarettes had a higher rate of chronic bronchitis than those who did not usually relight. For cigarette smokers as a whole the difference was highly significant ( $P < 0.001$ ). This statistical significance was maintained in the age standardized figures and was present irrespective of the amount smoked.

*Number, Percentage, and Age-standardized Percentage of Chronic Bronchitics among 5,438 Male Cigarette Smokers aged 40 or more by Amount and Method of Smoking*

	Cigarette Smokers							
	1-9 a day		10-19 a day		≥20 a day		All	
	R.	N.R.	R.	N.R.	R.	N.R.	R.	N.R.
No. of volunteers ..	122	519	482	1,491	447	2,377	1,051	4,387
No. of chronic bronchitics ..	41	131	183	425	193	891	417	1,447
Percentage of chronic bronchitics ..	33.6	25.2	37.9	28.5	43.1	37.4	39.7*	32.9*
Age-standardized percentage of chronic bronchitics	30.3	25.4	36.5	30.2	47.5	40.0	40.7	34.8

R. = Smokers who usually relight their cigarettes.

N.R. = Smokers who do not usually relight their cigarettes.

\* $P < 0.001$ .

## Discussion

Earlier articles (Rimington, 1972, 1973) considered the possibility of bias in the selection of this sample of men, but it was thought to be unlikely because the men were volunteers from the general public and industry, and specially selected groups such as doctor's cases were specifically excluded. The smoking habits of the sample corresponded with those of a nationwide sample (Todd, 1969) of men of similar age, and their rates of chronic bronchitis conformed with patterns found in other investigations of men of similar age (Higgins, 1959; Reid *et al.*, 1964; Lowe, 1969).

Other factors that influence chronic bronchitis rates must be considered. While age and consumption have been allowed for social class has not. A 10% sample showed, however, that for relighters the percentages in three social class groups (I and II, III, IV and V) were 8.5, 58.5, and 33 respectively, whereas the corresponding percentages for those not relighting were 14, 65, and 21. There is, therefore, a trend towards a lower social class in relighters, and since the same sample gave chronic bronchitis percentages of 27, 32, and 39 in the three social class groups the overall effect of the lower social class structure would account for about 3.5% of the 20.7% excess of chronic bronchitis among the relighters as compared with those not relighting. The proportions smoking plain cigarettes in the two groups must also be taken into account because an earlier study (Rimington, 1972) showed a 16.6% excess of chronic bronchitis among plain-cigarette smokers compared with filter smokers. The ratio of smokers of filter cigarettes to smokers of plain cigarettes among relighters was 42.5:57.5 but among non-relighters it was 59.2:40.8. These proportions, taken into account with the chronic bronchitis percentages found in plain and filter smokers, would account for about 2.5% of the 20.7% bronchitic excess of relighters. Thus, a lower social class and a preference for plain as compared with filter cigarettes could account for almost 30% of the excess of bronchitics among relighters. Against this there is the fact that relighters rarely keep their cigarettes in the mouth between puffs—less than 2% compared with 10% among non-relighters—and persons who adopt this method of smoking have a much greater prevalence of chronic bronchitis (Rimington, 1973). Furthermore, the definition of relighters used in this study—those "usually" relighting their cigarettes—must tend to reduce the difference in the rates of chronic bronchitis between relighters and those smoking normally.

## 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

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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 Dick-

son, 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 (Westermarck, 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 temperatures tend to cause discomfort.

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