

eunuchs we studied, and there is no rationale for using a patented artificial ester of testosterone instead of the free hormone for oral therapy.

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MORTALITY FROM MALIGNANT DISEASE IN PATIENTS WITH ASTHMA

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Summary Case-control studies suggest that a lower proportion of people with malignant disease give histories of allergic disorders than patients with other diseases. Seven hundred and sixty-five men and one thousand one hundred and twenty-seven women with asthma were followed up over a 20-year period. As expected, mortality from respiratory disease was higher than in the general population. Deaths from all cancers excluding lung cancer were significantly reduced in both men and women with asthma; deaths from lung cancer among men were reduced but not significantly. These results are compatible with a mechanism which protects against death from cancer in people with asthma.

Introduction

FISHERMAN¹ reported that atopic disease was significantly less common in patients with malignant disease compared with age-matched controls. Four other case-control studies²⁻⁵ found that the proportion of patients with malignant disease reporting allergic disorders was significantly reduced; one of these studies was restricted to females,² whilst another³ reported a significant reduction among female patients but not among males. Other comparable investigations have produced equivocal or negative findings. Logan and Saker⁶ questioned a hundred and four patients with carcinoma of the cervix and a smaller sample with miscellaneous malignant conditions together with ninety-seven control patients (who had not been matched for age and sex); 27% of each of the groups with malignant disease and only 11% of the control group reported an allergy. Two groups of workers^{7,8} questioned patients before their diagnoses had been confirmed; subsequent analysis revealed no significant difference in reporting symptoms of allergy in those

found to have cancer compared with the other patients. Another study⁹ on patients with Hodgkin's disease did not collect any data from controls. Though the weight of this evidence seems to suggest some diminution in the risk of malignant disease developing in patients with allergic disorders, the findings are variable; and how much of this variation is due to (1) chance, (2) the method of data collection, (3) the categories of patients used, or (4) the biases inherent in case-control studies cannot immediately be determined. Fedullo¹⁰ criticised the use of the case-control approach; we report on a large sample of patients known to have asthma who have been followed over several years and examine the death-rates from malignant disease.

Method

From the late 1930s to the early 1950s a special asthma clinic was held at the Manchester Royal Infirmary; the records for the clinic were filed separately from other patients' histories and were subsequently transferred to microfilm. The microfilm records have been examined, and attention paid to the history, clinical findings, results of investigation, and response to treatment. Patients under the age of 25 were excluded, since their death-rate from malignant disease within 20 years would be too low to justify the cost of follow-up. Patients over 60 have been excluded because of overlap between asthma, other chronic respiratory disease, hypertension, and cardiac problems. Patients were included if they had a history of wheezing dyspnoea with intervening periods of complete symptomatic remission and a normal chest X-ray. Most patients had positive responses on skin testing to a range of antigens and eosinophilia; they had been recommended to have de-sensitisation or other conventional treatment for asthma. Patients with chronic bronchitis, tuberculosis, obvious heart-disease, hypertension, or sinus disease were excluded; one or two patients gave a history typical of byssinosis and these patients were also excluded.

A record card was sent to the National Health Service Central Register for each patient in the study. This record card contained the surname, forename (where provided), marital status for women, the (full) postal address, and the age of the patients on the date on which they attended the clinic. These identification particulars are somewhat limited, particularly as no full date of birth was available and for some patients initials were available rather than forenames. Whilst tracing these individuals on the N.H.S.C.R. the full date of birth was obtained; for those who had died, a copy of the entry of the cause of death was obtained.

Using the patient's date of birth, the date of first attendance at the clinic, and the last known date alive or the date of death, the number of years of life were calculated by sex, 5-year calendar periods, and 5-year age-groups. Applying the age and calendar period death-rates for England and Wales, it was possible to calculate the expected numbers of deaths from all causes, all cancer, lung cancer, leukaemia, and Hodgkin's disease. The expected number of deaths so derived was then corrected for area mortality using data published by the Registrar General¹¹ for the North-West region in 1936-55, while for 1956-70 the material has been corrected for the known mortality in the Manchester Regional Hospital Board area.

Each cause of death obtained from the general register office was classified according to the rules prevailing at the time of death, and the deaths were then grouped by cause. The basic hypothesis being tested was that the general mortality from all causes would be considerably

TABLE I—AGE-DISTRIBUTION OF PATIENTS ON ENTRY TO STUDY

Age (yr.)	Male (%)	Female (%)
25–	17.3	16.2
30–	18.0	18.4
35–	18.8	19.4
40–	14.6	17.0
45–	15.0	14.9
50–	9.9	8.4
55–59	6.4	5.7
Total	765	1127

increased in patients with severe asthma, but that there might be a reduced risk of mortality from all cancers, Hodgkin's disease, and leukaemia. If patients with asthma smoked less than the general population, this would reduce their death-rate from lung cancer, but the presence of chronic respiratory disease introduces a confounding effect, and the overall reduction in lung cancer was difficult to predict.

Results

Despite the limited information on each of the patients, the N.H.S.C.R. staff were able to trace 86.3 % of the subjects, including those known to have died. Table I shows the age and sex distribution of the patients who were traced, and table II indicates the periods during which they were first seen at the clinic. Seven hundred and sixty-five males aged 25–59 were followed up, and for those who remained alive to the end of 1970 the average follow-up time was 21.2 years; two hundred and seventy-five males died during follow-up. More women were included in the study (one thousand one hundred and twenty-seven); their follow-up time was similar. This provided over 13,000 man-years and 22,000 woman-years of follow-up experience.

Table III shows the numbers of deaths observed and expected by selected cause of death for males and females combined, together with the ratio of observed to expected deaths and the probability of each result. The data have been compared for lung cancer, all cancers excluding lung cancer, Hodgkin's disease, leukaemia, all these forms of malignant disease combined, and all causes of death.

The original material was examined for each of the sexes separately, but combined in table III for ease of presentation. Observed deaths from lung cancer were

reduced, but not significantly. There was a significant reduction in observed deaths from all other cancers. The results for either sex were consistent for the rest of the cancer group (male deaths observed (O)=11, deaths expected (E)=21.90, P=0.008; females O=32, E=43.94, P=0.037). There was also non-significant reduction in male deaths from lung cancer (O=11, E=15.71, P=0.14). There were fewer lung-cancer deaths in women, but they just exceeded the expected figure (O=5, E=4.29, P=0.43).

Discussion

Using microfilm records of patients seen at outpatient clinics some 20 or 30 years ago creates difficulty in ensuring that all the subjects who were followed up definitely had asthma with an allergic basis. Inclusion of late-onset asthma that was not directly related to allergy will reduce the chance of an "allergic" effect, and to a greater extent so will the addition of patients with other respiratory diseases. The available data had to be used to identify the presence of asthma; it is felt that the follow-up of these subjects, though possibly diluted by a proportion of patients without an allergic condition, provides a fair or conservative test of the hypothesis. 13 % of the subjects were not traced; this failure-rate is small considering the limited particulars for identification available from the microfilm records. It is unlikely that the failure-rate will have affected the results, because there is no evidence that those who could not be traced had a higher or lower death-rate from malignant disease.

The standard technique for analysing this kind of material has been used.^{12,13} It is felt that this approach is more valid than a study of cases and controls, which poses considerable problems in the selection of controls. Interpretation of these data hinges upon the reliance that can be placed upon the calculated expected figures. The subjects in this study were only included if they were thought to have asthma; it was anticipated that their mortality-rate from all causes would be higher than the expected figure because of an increased death-rate from respiratory diseases. The method of analysis used does not compare the relative proportions of deaths by cause but calculates, for the actual numbers of years lived by each individual in the study, the probability of death from malignant disease.

The general hypothesis being examined was that allergic disease reduces the risk of developing and dying from malignant disease. Lung cancer was the one category of malignant disease which could have been differently affected. Patients with asthma probably smoke less than the general population, and this should reduce their death-rate from lung cancer. Several sources suggest that chronic bronchitis increases the risk of lung cancer, independently of the amount smoked.^{14–17} If the presence of chronic bronchitis (rather than the aetiological factors causing bronchitis) is associated with the tendency to develop lung cancer, it is possible that the risk of lung cancer in patients with longstanding asthma and associated bronchitis and emphysema might be increased. Thus, there are three rather different mechanisms that might be involved in the development of lung cancer: (1) the general protective effect from allergic disease, (2) the

TABLE II—DISTRIBUTION OF PATIENTS BY YEAR OF ENTRY TO STUDY

Year of entry	Male (%)	Female (%)
1936–	0.7	0.6
1941–	11.9	10.6
1946–	53.0	57.0
1951–56	34.4	31.8

TABLE III—OBSERVED AND EXPECTED DEATHS BY CAUSE IN PATIENTS WITH ASTHMA

Cause	Observed deaths (O)	Expected deaths (E)	O/E	P
Lung cancer	16	20.00	0.80	0.22
All other cancers ..	43	65.84	0.65	<0.005
Hodgkin's disease ..	2	0.78	2.56	0.19
Leukaemia	2	1.83	1.09	0.54
All malignant disease ..	63	88.45	0.71	<0.01
All causes	554	351.22	1.58	<0.0001

lower risk from reduced smoking, (3) the increased risk due to the frequency of chronic bronchitis in the asthma patients. Before the current material was analysed, it was suggested that the combination of these factors might reduce mortality from lung cancer to a level intermediate between the expected mortality and the overall reduction in other malignancies.

The data presented are compatible with a reduced risk of mortality from cancer amongst asthmatic patients. The data by sex for lung cancer are less easy to interpret; a combination of the factors mentioned above seems to be associated with a moderate reduction in deaths from lung-cancer among males, but no reduction among females. Leukæmia and Hodgkin's disease have been presented, partly because the national mortality data gave death-rates for these diseases separately from all cancers.¹⁸ The site of the primary tumour was noted in most deaths from malignant disease (a few are recorded as "carcinomatosis, site of primary unknown"). No specific suggestions of variation in the ratio of observed to expected deaths by site were made before the analysis of the data; this, together with the small numbers involved in specific sites, suggests that further analyses of the present material will be unprofitable. The reduced risk of death from cancer (if not an artefact of the method) could be due to a difference in environmental exposure to carcinogens, a reduced liability to develop malignant disease, or a mechanism which protects against the development or progression of malignant disease. It seems unlikely that conventional treatment of asthma plays a part.

Several workers reviewed the relation between immunological surveillance and cancer.¹⁹⁻²² If the present findings are accepted as evidence for a mechanism protecting allergic patients against malignant disease, no light can be thrown on this mechanism by the approach used in this study. The aim of the study was to see whether prospective collection of mortality data supported the general hypothesis; such material can only throw light on this general issue, and more detailed specific studies are required to elucidate the operation of any underlying protective mechanism in allergic subjects.

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SCLEROSING PERITONITIS, AN UNUSUAL REACTION TO A β -ADRENERGIC-BLOCKING DRUG (PRACTOLOL)

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Summary Peritoneal disease, apart from the post-operative variety, is rare, but three female patients, who presented with abdominal symptoms and in whom an unusual peritoneal lesion was found at operation, had one factor common to their medical histories—namely, previous treatment with the β -adrenergic-blocking drug practolol. The main finding at laparotomy was a pattern of massive peritoneal adhesions, but one patient had no history of abdominal surgery, and the findings at laparotomy were unusual. Other possible causes of this sclerosing peritonitis can be excluded, and the possible involvement of practolol in these cases is supported by the identification, via the Committee on Safety of Medicines, of four similar cases.

Introduction

THOUGH reactions to drugs are increasing in number and variety, reactions affecting the peritoneal cavity are rare. Involvement of the retroperitoneal tissues in patients treated with serotonin antagonists is well recognised,¹ but this process is not complicated by involvement of the visceral and/or parietal peritoneum. Peritoneal fibrosis and adhesions are common after infections or operations involving the peritoneal cavity, but such reactions are usually not distinctive, so it is sometimes very difficult to be sure that peritoneal disease is an expression of toxicity to a drug. However, the following three case histories and the radiological and pathological features point strongly in that direction.

Case-reports

FIRST CASE

A 54-year-old housewife with a 5-month history of abdominal distension, vomiting, and weight loss was found to have a lower abdominal mass and was referred to a

PROFESSOR ALDERSON: REFERENCES—continued

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