PROTEIN STUDIES

No evidence of myelomatosis could be found—no bony involvement, no abnormal plasma cells, and no abnormalities in the serum immunoglobulins (IgG 710 mg/100 ml, normal 510–1600 mg/100 ml; IgA 315 mg/100 ml, normal 125–425 mg/100 ml; IgM 50 mg/100 ml, normal 47–170 mg/100 ml), nor were any Bence-Jones protein or other immunoglobulin fragments shown by immunoelectrophoresis of the urine concentrated 100 times.

The concentrated urine was remarkable in having a noticeably viscous consistency and in showing, after electrophoresis, three unique bands with β , γ^3 , and γ^4 , mobilities (fig. 3). These all stained clearly by a periodic acid-Schiff method, when identical bands were found in an extract of the tumour and in the ascitic fluid and were even faintly visible in serum stained by P.A.S. A rabbit antiserum raised against the urine concentrate of the patient and absorbed with normal urine concentrate reacted only with the patient's fluids, tumour extract, and the occasional cast in the urine deposit. Unfortunately the kidney obtained at necropsy, which had been stored unfixed at -70°C to permit fluorescent antibody studies, was lost by accident.

Discussion

The oliguric renal failure in this patient resulted from the cast formation obstructing the distal and collecting renal tubules. His carcinoma of the pancreas contained mucoproteins, and from the electrophoretic staining of the ascitic fluid, serum, and urine obviously these were being liberated to enter the circulation. There seems little doubt that it was these mucoproteins which, after filtration through the glomeruli, became concentrated in the collecting tubules with the resultant formation of casts. We do not know whether intrinsic proteins—such as

Tamm-Horsfall—needed in the formation of other renal casts were necessary in this case. Renal failure due to obstruction of the renal tubules by casts has long been recognized in patients with myelomatosis with heavy Bence-Jones proteinuria, the syndrome being called "myeloma-kidney." A similar sequence may contribute to renal failure in some cases of primary nephrotic syndrome, including that caused by minimal glomerular change (Connolly, *et al.*, 1968), where retention of a large filtration surface can result in the heaviest proteinuria.

The syndrome of "myeloma-kidney" can now therefore occur in three known clinical situations (1) with heavy proteinuria, (2) with pancreatic carcinoma, and (3) with paraproteinuria. As the morphological appearances in the kidney in the last two conditions are identical they can no longer be considered pathognomonic of myeloma. The earlier the diagnosis can be made in these situations the more chance there is of affecting the otherwise inevitable outcome, and electrophoretic examination of concentrated urine is an essential investigation. A high fluid throughput of 3 l. daily should be maintained and intravenous pyelography avoided, especially when it involves fluid-deprivation. In this way the incidence of renal tubular obstruction in myelomatosis has been kept to less than 10% in the current Medical Research Council trials.

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The Changing Face of Chronic Bronchitis with Airways Obstruction

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Summary

A total of 178 patients with obstructive airways disease were studied between 1966 and 1972, a period which followed a substantial fall in atmospheric pollution in Sheffield. Compared with patients from an earlier study of the same age and smoking habits they had less productive cough, fewer winter illnesses, less severe breathlessness, and only one-third of the rate of decline of forced expiratory volume (FEV). The analysis of the change in the annual loss of FEV was complicated. There were virtually no sudden steep falls of respiratory function, and patients with very low values of FEV survived for long periods. The predominant cause of death was cor pulmonale.

Chronic hypoxia may be more of a problem in the next few years than bronchial infection. I believe that the clean air policy has effected an improvement and that the nature of chronic bronchitis with severe obstructive airways disease is changing, but further studies will be needed to confirm this.

Introduction

Chronic bronchitis is defined by the production of sputum. Its incidence varies widely both between different countries and between different communities. At least 25% and sometimes 50% of heavy smokers in industrial communities in England were found to produce mucus excessively and were labelled chronic bronchitics (Higgins *et al.*, 1956; Higgins *et al.*, 1959; College of General Practitioners, 1961). The production of sputum, however, attracted less attention than its associated disabling complications—airways obstruction, with severe breathlessness, and pulmonary heart failure. Bronchial infection, cigarette smoking, and atmospheric pollution have been principally accused of causing progressive airways obstruction, though the causative mechanism has never been clearly defined. This paper describes an attempt to elucidate the aetiology of the disease by studying its evolution over a period of time. A prospective study was made of 178 patients with established airways obstruction, and special attention was paid to the progress of the obstruction and to the cause of death. The findings were compared with those from a previous group studied six years earlier in the same clinic.

Patients and Methods

All patients attending the bronchitis clinic in the first three months of 1966 were admitted to the study, which ended on

31 December 1972. The patients had been referred by their family doctors, who agreed to follow-up in the clinic. The Medical Research Council Short Questionnaire on Respiratory Symptoms (Medical Research Council, 1960) was answered. The forced expiratory volume in 0.75 seconds (FEV) and the forced vital capacity (FVC) were measured with a Poulton spirometer (McKerrow *et al.*, 1960) at the beginning of the study and thereafter at intervals of one to three months. Most patients had aerosol sprays of isoprenaline and oral bronchodilators such as choline theophyllinate and salbutamol. Acute exacerbations, with more copious purulent sputum, were treated with oxytetracycline and ampicillin. Some patients also received prednisolone for reversible airways obstruction and others frusemide or chlorothiazide for cor pulmonale. We continually urged patients to stop smoking.

The rates of change of FEV and FVC were calculated from a regression of measurements against time in years. The spirometric tests were available for a period before 1966 on a number of patients already attending the clinic. These were included in the calculation of regressions and the duration of follow-up was counted from the first spirometric measurement. The variance of individual measurements about the mean slope was also obtained. Regression equations were not calculated unless there were at least five measurements during a minimum period of one year. Patients with a history of ischaemic or rheumatic heart disease and severe physical deformity were excluded. Causes of death were ascertained from death certificates or from family doctors. More than half of the deaths occurred in hospital. Standard deviations and not standard error were used throughout on analysing results.

Results

A total of 178 patients (158 men and 20 women) were studied. Their mean age in 1966 was 59.6 ± 9.0 years. Only 29 (16.3%) denied producing sputum on most days at least three months of the year. Many of these admitted to previous habitual production of sputum, but this was not present when they were seen in 1966. A total of 121 (68.0%) complained of breathlessness when walking at a normal pace on the level, or more severe disability, and 34 (19.1%) had sudden exacerbations of wheezing and breathlessness which responded to aminophylline or intermittent or continuous prednisolone and which were considered to be due to bronchial asthma. A total of 92 patients (51.7%) had two or more acute chest illnesses which required at least a week in bed or hospital admission during the six-year period. A further 23 (12.9%) had only one such illness. Only 26 (14.6%) had never smoked cigarettes, 45 (25.3%) had stopped smoking cigarettes, and the remainder were smoking in some degree in 1966. In 34 patients (19.1%) right heart hypertrophy was evident on the electrocardiogram judged by dominant R waves in V_1 - V_3 , inverted T waves in V_1 - V_3 dominant R in aVR, and dominant S in V_5 . Of the 63 (35.4%) of patients who died during the study 41 (23.0%) died of cor pulmonale (one also had carcinoma of the lung), 11 (6.2%) of acute bronchopneumonia, two (1.1%) of status asthmaticus, four from other respiratory disease—chiefly carcinoma of the lung—and five from non-respiratory disease.

Regressions were calculated on 144 patients. The remaining 34 either died too early in the study or were irregular attenders, but there was nothing in their symptoms or spirometry to suggest that they were different from the other patients. The mean initial FEV for the whole group of 178 was 0.93 ± 0.55 l. (mode, 0.7 l.) and mean FVC 2.39 ± 0.75 l. The mean rate of deterioration of FEV was 0.023 ± 0.053 l./year and of FVC 0.069 ± 0.107 l./year (figs. 1, 2). No fewer than 46 (25.8%) showed an improvement in FEV, though this was mostly very small, and 29 (16.3%) an improvement in FVC. The mean variance about the regression for FVC was 0.171 l. and for FEV 0.088 l. The asthmatic patients were no

FIG. 1—Distribution of regressions of forced vital capacity (FVC).

FIG. 2—Distribution of regressions of forced expiratory volume (FEV 0.75). For reasons of clarity six patients have been omitted from graph.

FIG. 3—An FEV plateau. The FEV remains fairly constant over 10 years.

FIG. 4—Rapid fall of FVC when FEV remains fairly constant.

different from the group as a whole. The wide fluctuation of FEV and FVC often seen in these patients might have been expected to produce a double hump in the distribution curve, with emphysema and bronchitis patients being to the left with lower values and asthmatic patients to the right with a greater mean variance. This expectation was not fulfilled. The loss of FEV and FVC were related to the duration of follow-up. The longer the period of follow-up the less negative became the regression coefficients ($t=4.0$, $P<0.001$). This is hardly surprising, since some rapidly-deteriorating patients might be expected to die early in the follow-up period.

Though a mean regression was calculated of the change of FEV and FVC the decline of FEV was non-linear in some cases. Below 0.75 l. the fall of FEV flattened off to produce a plateau in 36 patients (fig. 3). A plateau was defined as an unchanged FEV over at least two years at values of less than 0.75 l. The length of the plateau varied from two to 10 years, thus patients may survive for long periods at low values of FEV. During the plateau period the FVC continued to decline and a combination of a low FEV and low FVC was a particularly common cause of death (fig. 4). Progressive arterial hypoxia was also seen during the plateau period. A more detailed study of this will appear elsewhere. As the long plateau period might influence the overall regression of FEV with time the mean rate of decline for 144 patients was recalculated without the plateau phases. The mean value was now 0.030 ± 0.060 l. per year, an insignificant difference ($t=1.11$, $P<0.1$). The FEV regression was positively related to initial FEV ($t=1.98$, $P<0.05$). Thus the presence of the plateau did not seem to alter the fact that patients with a lower FEV at the beginning of the study lost respiratory function at a greater rate.

There were 65 patients from the previous study included in the later group. Since these patients had been followed for a longer period any plateau phase would have had a greater chance of being established and might influence the findings for the decline of respiratory function in the whole group. The rate of decline of FEV for the 65 was 0.016 ± 0.032 and for FVC, 0.050 ± 0.11 . These values were not significantly different from the remainder ($P>0.1$) and probably did not exert an unduly large influence on the analysis of deterioration of respiratory function in the group as a whole.

COMPARISON OF FINDINGS

The findings from the previous study (Howard, 1967) have been compared with those of the present study (table). The patients were of identical age and sex and were studied for the same period. The number lost to follow-up or rejected for analysis and the number of deaths were calculated in different ways and were not comparable. The death rate in the earlier study was underestimated by inclusion of a number of early deaths among the "lapses." Nevertheless, the 125 patients in the 1966 study were selected and treated in exactly the same way as the present group. The later group had significantly less sputum, breathlessness, and chest illnesses and a threefold reduction in the rate of loss of FEV. Smoking habits overall were worse if anything, and a sharp smoking gradient was evident.

The lower initial FEV of the 1966 group and the plateau periods were unable to explain such a large fall in the rate of loss of respiratory function. The larger standard deviation of the initial FEV in the later group suggests a more inhomogeneous group of patients. Thus patients were selected from the 1966 series who had a regular sputum habit, who were not survivors of the earlier patients, who had an initial FEV of at least 0.75 l. (to avoid plateau problems), and who had had regular respiratory function tests for at least two years. There were 27 patients (23 men and 4 women) of mean age 58.7 ± 7.3 years who had been studied for 7.4 years on average. The mean initial FEV was 1.44 ± 0.050 l. and 15 (55.6%) were current smokers. None of these values were significantly different from the 1962 patients. The rate of decline of FEV was 0.042 ± 0.050 l. and for the FVC, 0.10 ± 0.14 l. Thus, in the most unfavourable terms the rate of decline of FEV was still only half that of the earlier group.

Discussion

The first studies of chronic bronchitis were concerned with the numbers of people in particular populations with symptoms of productive cough, chest illnesses, breathlessness, and

Details of the Two Groups with Regard to Symptoms and Respiratory Function

	1960-5 (125 Patients)	1966-72 (178 Patients)	Significance
No. (%) of Men	112 (89.6)	158 (88.8)	N.S.
No. (%) of Women .. .	23 (10.4)	20 (11.2)	N.S.
Mean age (years) $\pm$ S.D. ..	60.7 ± 9.9	59.6 ± 9.0	N.S.
No. (%) of lapses* .. .	31	34	Not comparable
No. (%) of deaths .. .	10 (10.4)	63 (35.5)	Not comparable
No. (%) with sputum .. .	123 (98.4)	149 (83.7)	χ^2 17.3; $P<0.01$
No. (%) with breathlessness ..	100 (80.0)	121 (68.0)	χ^2 5.36; $P<0.05$
No. (%) with chest illnesses ..	106 (84.8)	115 (64.6)	χ^2 15.2; $P<0.01$
Mean initial FEV (l.) $\pm$ S.D. ..	1.2 ± 0.165	0.93 ± 0.55	$t = 5.32$; $P<0.001$
Mean loss of FEV (l./year) $\pm$ S.D. ..	0.0834 ± 0.067	0.023 ± 0.053	$t = 8.747$; $P<0.001$
No. (%) of non-smokers .. .	11 (8.8)	26 (14.6)	N.S.
No. (%) of ex-smokers .. .	46 (36.8)	45 (25.3)	χ^2 4.64; $P<0.05$
No. (%) of smokers .. .	68 (54.4)	107 (60.1)	N.S.
Mean change in FEV (l.)			
Non-smokers .. .		$+ 0.009$ (n. = 20)	
Ex-smokers .. .		$- 0.020$ (n. = 40)	
Smokers:			
1-14 cigarettes daily ..		$- 0.017$ (n. = 51)	
15 or more .. .		$- 0.046$ (n. = 30)	
Pipe .. .		$- 0.012$ (n. = 3)	

N.S. = Not significant.

*In the 1960 group patients not included in the study (31) because of poor attendance or early death do not form part of the total number (125).

impairment of respiratory function as measured by simple spirometric tests. The proportion affected varied from about 8% to 60% of the population. All clinical features increased sharply with age, were greater in men than women, in urban dwellers than rural workers, and particularly in those living and working in dusty industries and who smoked cigarettes (Higgins *et al.*, 1956; Higgins, 1957; Stuart-Harris *et al.*, 1957; Fletcher *et al.*, 1959; Higgins *et al.*, 1959; College of General Practitioners' Report 1961; Fletcher *et al.*, 1961.) American studies confirmed the importance of cigarette smoking and atmospheric pollution to chronic bronchitis and the impairment of respiratory function (Balchum *et al.*, 1962; Brinkman *et al.*, 1962; Cocker *et al.*, 1962; Holland *et al.*, 1965) but age seemed to be of less importance (Payne *et al.*, 1964). Bronchial infection has been difficult to relate to the evolution of chronic bronchitis with airways obstruction and there have been opposing views of its importance (Francis *et al.*, 1961; Medical Research Council Report, 1966; Howard, 1967.)

The decline of FEV in normal people is 0.020 to 0.030 l./year (Kory *et al.*, 1961; Ferris *et al.*, 1965; Fletcher, 1968; Howard, 1970). Patients with bronchitis and established airways obstruction have an increased rate of deterioration of FEV (Higgins *et al.*, 1962; Medical Research Council, 1966; Howard, 1967; Burrows and Earle, 1969) and values between 0.040 and 0.083 l./year were recorded. The present study follows on from the previous work (Howard, 1967). The mean age of 59 years is unchanged and is similar to that found by Burrows and Earle (1959) and Renzetti *et al.* (1966). The sex ratio and death rate, are also unchanged. The mortality of 35% is similar to that recorded by Reid and Fairbairn (1958) and Medvei and Oswald (1962). Nevertheless, there are signs of change. Symptoms of sputum production, severe breathlessness, and chest illnesses were less common and the loss of FEV was much less. The distribution of regression coefficients for FEV has moved to the right (fig. 5). A small number of patients even improve at a rate of 0.050 l./year or more. The analysis of the change in respiratory function is complicated. Sudden, step-like changes in FEV which were a feature of the earlier study were hardly in evidence. Patients with very low FEV survived for long periods. But even when the problems of survivors from the earlier study, plateau periods in the FEV curve, and the loss of symptoms of bronchitis are taken into account, the large change in annual loss of FEV still could not be explained.

FIG. 5—Comparison of regression coefficients for decline of FEV in both groups.

The major aetiological factor which has changed in the past decade is atmospheric pollution. Sheffield has vigorously applied the provisions of the Clean Air Act and controlled effluent from factories and domestic premises. Pollution has been greatly reduced (fig. 6). This improvement has been coupled with a rehousing policy which moved city-dwellers to cleaner housing estates on the periphery. Since the environment was the only factor that changed substantially during the period of follow-up of the two groups it is reasonable to suggest that it was the major cause of the improvement seen in these patients with chronic bronchitis. The urban factor in chronic bronchitis was not taken seriously until the London smog of 1952, when over 4,000 people died in four days. Most of them already had chronic bronchitis. The association of peak mortality from bronchitis and smogs was seen in subsequent studies (Logan, 1956; Martin *et al.*, 1960; Scott, 1963). Atmospheric particulate and sulphur dioxide concentrations were related to bronchitis mortality in different areas of England and Wales (Pemberton *et al.*, 1954). Morbidity from bronchitis with airways obstruction follows the mortality data. Regional differences in sickness returns from England and Wales show area variations and rural urban gradients which correlate with levels of atmospheric pollution (Fairbairn *et al.*, 1958). International comparisons support these conclusions (Mork, 1962). It seems that improvement in pollution resulting from the clean air policy is having a beneficial effect that is not simply limited to those in the early phases of the diseases.

FIG. 6—Decline of atmospheric smoke ●—● and sulphur dioxide ×—× over Sheffield.

The nature of the fall of FEV confirms a prediction that there should be three phases in the process (Cayton and Howard, 1972)—firstly, small airway disease with no change of FEV; secondly, a declining phase when the FEV is a sensitive index of further airway disorder until the value falls below 0.75 l., when a third or plateau phase is to be expected in which substantial disease occurs with little effect on the FEV. It is of interest that patients may survive for long periods at very low levels of FEV—perhaps as long as a decade. A major complication of chronic airways obstruction is hypoxia. Prolonged survival of patients with severe obstruction might be expected to be associated with chronic hypoxia and hypercapnia. There was much evidence to support this and in particular the mode of death. Cor pulmonale was by far the commonest single cause of death—commoner in fact than chest infections, which occurred less often than might be expected. The problems of chronic hypoxia may become more evident in the next few years as patients with severe airways obstruction survive longer. A further follow-up study will be

gin shortly, which it is hoped will confirm the trends established by the present study.

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Inhibition of Experimental Asthma in Man by a New Drug (AH 7725) Active When Given by Mouth

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Summary

A new drug, AH 7725, with properties similar to those of disodium cromoglycate (Intal) has the additional feature of being effective when taken by mouth. Six patients with allergic asthma were studied by bronchial challenge tests with antigen. In every one the drug was found to inhibit (either partially or completely) the immediate-type asthmatic response. Late responses were not influenced. The results were significant at the 0.5% level.

These findings suggest that AH 7725 given by mouth may be able to inhibit naturally occurring asthmatic attacks in allergic patients. In this case its particular advantage as a prophylactic drug would lie in the treatment of very young asthmatic children and other patients who cannot take drugs by inhalation.

Introduction

In clinical practice disodium cromoglycate (Intal) has proved to be a useful prophylactic drug in asthma. Experimental studies show that it inhibits immediate-type hypersensitivity

reactions to antigen both in vitro and in vivo (Cox, 1967; Altounyan, 1967). Disodium cromoglycate can also inhibit the immediate-type bronchial reaction after challenge with antigen, but as a single dose it does not consistently alter the late component in dual bronchial reactions (Pepys *et al.*, 1968). One of its limitations is that since it is poorly absorbed by the gut it is inactive when taken by mouth.

A new compound, AH 7725, has been shown to have similar properties to those of disodium cromoglycate both in laboratory models (Assem, 1973; Fullarton *et al.*, 1973) and when given by inhalation in experimental asthma (Gayard, 1974). This new drug has the additional property of being relatively well absorbed from the gut and can therefore be taken by mouth.

We here report experiments testing the protective effect of AH 7725 given by mouth to asthmatic patients subjected to bronchial challenge with antigen.

Materials and Methods

The structural formula of AH 7725 is shown in the fig. Blood levels after the administration of single doses by mouth to normal volunteers have been measured by Woodings (1974). After doses of 200 to 500 mg in solution peak levels ranging from 2.7 µg/ml of plasma were reached in one and a half to two and a half hours.

BRONCHIAL TESTING PROCEDURE

Tests were carried out by the closed-circuit method (Herxheimer, 1951; McAllen, 1961), in which antigenic material is nebulized into the circuit and measured amounts of antigen can be inhaled by the patient. Asthmatic attacks

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