Lung function, atopy, specific hypersensitivity, and smoking of workers in the enzyme detergent industry over 11 years

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ABSTRACT A study of 2800 workers employed in three factories of the two major manufacturers of enzymatic products in the United Kingdom covering 11 years of operation from 1969 to 1980 showed that 2344 workers had sufficient lung function data to meet the operational criteria and these were analysed in three separate groups by factory locations. Spirometry and prick tests for specific skin reactions to standardised enzyme were performed at six monthly intervals for the first six years of the study and then annually. Factory enzyme dust and total dust measurements were made to determine the degree of dust exposure of the subjects. The lung function of the factory groups was analysed for the effects of working in the detergent industry, the degree of exposure to enzymes, skin prick test positivity to enzymes, atopicity, and smoking. The 4.5% of workers who had experienced respiratory effects from enzymes were analysed separately. Exposure to the enzyme allergen has had no significant long term effect on the lung function of the detergent workers. A higher proportion of atopics than non-atopics became skin test positive to the allergen and more smokers than non-smokers were sensitised. The overall lung function of detergent workers showed 39 ml/year loss in FEV₁ on the 11 year longitudinal study and 51 ml/year loss on the lateral (cross sectional) analysis with better lung function in the south east than the north west of England. In the development of the methodology for the study several potential problems were discovered that could remain unrecognised in a cross sectional analysis performed in isolation.

Detergent products containing enzymes were first manufactured in the United Kingdom in 1968 and allergic reactions to them have been reported.¹⁻⁸ The Soap and Detergent Industry Association (SDIA) medical recommendations⁹ have been followed since 1969. SDIA and other studies have shown a pronounced reduction in enzyme related respiratory incidents corresponding to the environment improvements in the factories in the United Kingdom.^{7,9} There was no overall relationship between changes in lung function and the duration of contact of workers with atmospheric enzyme dust.

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concluded that enzymes used in detergents can produce an IgE mediated asthma that is dose related but respiratory disease other than asthma is unlikely to arise from the use of these enzymes.¹⁰ The risk of respiratory and skin test sensitisation to the enzyme detergents during their domestic use is most unlikely. Subsequent serological studies⁸ have substantiated these conclusions.

The purpose of this paper is to present the results of an epidemiological study covering 11 years of enzyme detergent production and its effects on 2344 workers in the detergent industry.

Methods of measurement and analysis

ENVIRONMENT ENZYME DUST MEASUREMENT
The high volume dust sampler (Galley sampler), developed within the industry in 1969, has been

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used regularly to measure enzyme dust levels, and full details of monitoring and analytical measurement have been published.¹¹ The dust levels were used to determine the degree of exposure of the subjects.

MEDICAL MONITORING

The SDIA Medical Programme⁹ was introduced in 1969. The initial examination consisted of:

- (a) a personal medical history and MRC based questionnaire,¹²
- (b) a full physical examination,
- (c) a chest radiograph,
- (d) spirometry using a standard technique for determining forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) corrected to BTPS,⁷ and
- (e) skin prick tests. A standardised test procedure^{9,13} using enzyme antigen and three common allergens: grass pollen, *Aspergillus fumigatus*, *Dermatophadoides culinae* (*pteronyssinus* or *farinae*). Weal size and flare were measured and compared with a saline control.

An atopic was defined as an employee having a history of atopy—for example, infantile eczema, asthma, or hay fever—or a positive skin prick test to one or more of the three common allergens, or a combination of these. Atopics already working were allowed to continue, but in 1969 all known atopics who had experienced symptoms of allergy to common allergens were removed from exposure and no new atopics or individuals with significant findings of established chest disease or poor lung function have been allowed to work in enzyme detergent production.

After this initial screening, employees were examined at six monthly intervals for six years from 1969 to 1975 and thereafter annually. A history was taken, followed by spirometry and skin testing with the enzyme antigen and control solutions. Chest radiographs were repeated annually or biannually and read by an independent consultant. Sickness absences were monitored and additional examinations carried out whenever necessary. Individuals who became skin test positive to the enzyme antigen were removed from exposure if they also developed respiratory symptoms.

Information obtained from the MRC based questionnaire, medical history, and physical examinations is not described in this paper.

ANALYSIS OF RESULTS

The workers have been analysed in three separate groups by factory locations A, B, and C. Factory A is in southern England and factories B and C in the

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north west (Manchester and Merseyside). Factories A and B manufactured enzyme detergents over the whole 11 year period of the study but factory C ceased incorporating enzymes into detergents in March 1975.

The lung function of factory groups was analysed for the following effects:

- (a) Working in the detergent industry,
- (b) Degree of exposure to enzyme dust,
- (c) Skin test positivity to enzymes,
- (d) Atopicity, and
- (e) Smoking.

Each of these effects was assessed by estimating the FEV₁ change in ml per year and the FEV₁/FVC ratio as a percentage change per year.

Exposure levels were defined as maximum exposure, medium exposure, minimum exposure, and no exposure, dependent on the enzyme dust levels. An assessment of the jobs done by each individual was used to determine his exposure level. As a general rule, workers in powder mixing and packing were in the maximum exposure group, those in shipping and warehousing the medium exposure group, and those who worked in these departments only part of the time (tradesmen, quality control technicians, and analysts, for instance) were in the minimum exposure group. The factory groups have been kept separate because of the geographical differences and differences in exposure.

To ensure that the main groups were not biased, the workers who had experienced respiratory hypersensitivity for enzymes (E cases) were analysed separately. A worker was defined as an E case if he or she was skin test positive to the detergent enzyme and had the relevant criteria such as shortness of breath, bronchospasm, or a drop in FEV₁ owing to exposure to enzymes. All E cases were removed from further exposure but not all E cases showed frank asthma.

STATISTICAL ANALYSIS

The results of the lung function tests have been analysed by two types of statistical analysis.

Longitudinal analysis

The FEV₁ change/year has been estimated as the common slope of regression lines of FEV₁ against age for each subject in the analysis group. The analysis thus follows each subject through time. To exclude unreasonable regression lines, subjects are eligible for this analysis only if they have at least four tests spanning more than 18 months. The FEV₁/FVC ratio has been analysed in the same way.

During the survey period it was recognised that there were specific test method variations during the evolution of the testing protocol. Analysis of the

FEV₁ results, making no assumptions about the nature of change in lung function, confirmed that the observations taken before 1972 were considerably more variable than those taken from 1972 onwards. For this reason, the longitudinal analysis has been performed twice: on data collected before 1972 and on data collected after 1972. These variations are discussed later.

Lateral analysis

This analysis takes the latest data for each subject in the analysis group and therefore is not a true cross sectional analysis, although it does complement the longitudinal analysis. It estimates FEV₁ change per year from a regression of FEV₁ against age (factories A and B) or age and height (factory C). Subjects are eligible for this analysis only if they are male and over 25, since the lung function for women and young men has been shown to differ.¹⁴ Our preliminary analysis confirmed this. There are 12% women in the study group, and less than 1% of the population are non-white.

Relationship between the analyses

The longitudinal analysis measures the actual changes in lung function with age of each individual over the 11 year period of the study. The lateral analysis plots a single lung function for each individual (men aged 25–65) against the age of that individual and the change of lung function with age is calculated from the line of best fit across all the ages in the study. Assuming that today's 50 year olds, when they themselves were 25, would have given similar results as today's 25 year olds, the lateral analysis may also be taken as a measure of the long term behaviour of the group.

Results

EFFECT OF WORKING IN THE DETERGENT INDUSTRY

FEV₁ change per year

Table 1 shows the estimated change per year in

Table 1 Effect of working in the detergent industry

	FEV ₁ change per year (ml/year)								
	Longitudinal analysis*						Lateral analysis†		
	Pre 1972			Post 1972					
	No	FEV ₁	SE	No	FEV ₁	SE	No	FEV ₁	SE
Factory A	267	-57	7	789	-22	3	658	-47	1
Factory B	154	+89	9	456	-41	3	511	-57	2
Factory C	300	+76	10	646	-53	1	1069	-50	2

*All subjects with at least four tests over 18 months.
†Men aged 25 and over.
SE = Standard error.

FEV₁ (ml/year) and the standard error for the groups of subjects.

Difference between time periods for longitudinal analysis—The results show that the longitudinal analysis of FEV₁ in ml/year is more variable before 1972 and not comparable with the lateral analysis. Factory A has a longitudinal loss of 57 ml/year compared with the lateral loss of 47 ml/year, factory B has a gain of 89 ml/year compared with a loss of 57 ml/year, and factory C a gain of 76 ml/year compared with a loss of 50 ml/year. In the post 1972 analysis there is a more reasonable relationship between the longitudinal and the lateral, and factory C has similar value for the analyses. Factories A and B have lower values on longitudinal than on lateral analysis. For this reason conclusion on the lung function effects studied in this paper are based on the post 1972 data. The explanation for the difference between pre and post 1972 data is discussed below.

Factory differences—Factory A, located in south eastern England, differs significantly from the two factories in the industrial north on the longitudinal analysis. The lateral analysis for all three factories is similar, but the factory in the south shows a loss of 47 ml/year compared with a loss of 50 and 57 ml/year for the two northern factories.

FEV₁/FVC as % change per year

In all analyses the FEV₁/FVC ratio confirmed the FEV₁ results. For this reason the FEV₁/FVC ratio data have not been included.

Survivors

During the 11 year study from 1969 to 1980, there was no abnormal turnover in the working population. Those who were still being tested in 1979 and 1980 are defined as survivors and those not tested in 1979 and 1980 because they had left the factory workforce are defined as leavers. It has not been possible to follow leavers and their last lung function measurement was taken while they were still in employment. The leavers in the study were 28% of the

Table 2 *Effect of degree of exposure to enzymes*

FEV ₁ change per year (ml/year)						
Longitudinal analysis				Lateral analysis		
Post 1972						
	No	FEV ₁	SE	No	FEV ₁	SE
Factory A						
Maximum	96	-51	7	85	-46	4
Medium	147	-22	6	140	-43	4
Minimum	496	-17	4	395	-47	2
No Exposure	12	(Small base)		0	-	-
Factory B						
Maximum	99	-42	7	115	-58	3
Medium	77	-34	5	81	-49	3
Minimum	202	-39	5	216	-59	3
No Exposure	57	-54	7	77	-65	5
Factory C						
Maximum	301	-54	2	395	-52	2
Medium	220	-57	3	374	-48	1
Minimum	125	-46	4	299	-50	2
No Exposure	0	-	-	0	-	-

total. There was no significant difference in lung function between leavers and survivors.

EFFECT OF THE DEGREE OF EXPOSURE TO ENZYMES

Table 2 shows the effect on FEV₁ of the three levels of exposure to enzymes for both the longitudinal and lateral analysis. The pre 1972 analysis is excluded from this, and subsequent tables for reasons explained already and the post 1972 analysis only is used for comparisons.

The low values on the longitudinal analysis for the medium and minimum exposure groups at factory A differ significantly from the maximum exposure group at this location. The FEV₁ of the maximum exposure group at factory A is the same as the two other maximum exposure groups. On the lateral analysis, factory B shows a larger loss for the max-

imum and minimum exposure groups compared with the other factories. The base sizes on the unexposed employees are too small to allow their use as a control group.

EFFECT OF SENSITIVITY TO ENZYMES

The comparison of FEV₁ between subjects who are skin test positive (PT+ve) to the detergent enzyme, subjects who are skin test negative (PT-ve), and subjects who were skin test positive (PT+ve) to the detergent enzyme at any time but who had reverted to skin test negative (PT-ve) is shown in table 3.

In the longitudinal analysis (post 1972) there is no significant difference between the PT+ves and PT-ves but FEV₁ loss per year is consistently less for PT+ves. PT-ves at factory C differ widely from those at factories A and B.

In the lateral analysis the northern factories give a

Table 3 *Effect of skin prick test sensitivity to enzymes*

FEV ₁ change per year (ml/year)						
Longitudinal analysis				Lateral analysis		
Post 1972						
	No	FEV ₁	SE	No	FEV ₁	SE
PT+ve subjects						
Factory A	52	-24	10	47	-41	5
Factory B	43	-34	8	48	-76	6
Factory C	103	-42	3	126	-54	2
PT-ve subjects						
Factory A	664	-23	3	544	-46	2
Factory B	334	-39	4	386	-55	2
Factory C	486	-55	2	886	-49	1
Subjects reverting from PT+ve to PT-ve						
Factory A	35	-6	11	35	-41	10
Factory B	18 (small base)			18 (small base)		
Factory C	57	-66	8	56	-53	4

higher FEV₁ loss for PT+ves than PT-ves. The total number of PT+ves reverting to PT-ves are too small for statistical comparison but the FEV₁ loss is relatively similar to that of the other two main groups.

EFFECT OF ATOPY

After the SDIA recommendations in 1969,⁹ no new atopic employees (as defined) were placed in enzyme detergent manufacturing areas, but this policy did not come into operation until two years after enzyme production had started. Atopics with symptoms were removed, and so the number of atopics was fewer than would be expected. There was no difference in lung function between the groups.

In a population that includes subjects excluded from the lung function analysis (because of insufficient lung function data) the effects of atopy and level of exposure on conversion to skin test positivity have been analysed; the results are shown in table 4. A significantly higher percentage of atopics (particularly in factory A where initial dust exposure levels were high) became sensitised compared with non-atopics, but the average time taken to become positive was similar, except at Factory A, where non-atopics took significantly longer to become PT+. Between factories A, B, and C there is a substantial difference in the overall time taken to reach positivity, with Factory C workers being sensitised in half the time taken at factories A and B.

In factory C significantly more subjects in the maximum exposure areas converted to PT+ve, and did so in a significantly shorter time. These trends are also present in factory B atopics. There are, however, anomalies between the maximum and medium groupings in factories A and B. This may result from the low enzyme dust levels from 1972 onwards which gave similar exposures to these groups.

EFFECT OF SMOKING

Smokers were classified by the MRC questionnaire, but in practice it was found that the most important factor was whether an employee smoked or not during the period covered by the lung function measurements. Smokers have a greater FEV₁ loss than non-smokers and the differences are statistically significant for factory C (table 5).

At the three factories the smoking habits of 2714 subjects were known. The relative conversion rates to skin test positivity to enzymes were determined for the smokers and non-smokers and a higher percentage of smokers than non-smokers became skin test positive to the enzyme.

EFFECT ON WORKERS WHO HAVE EXPERIENCED RESPIRATORY HYPERSENSITIVITY (E CASES)

A total of 126 E cases was recognised and sufficient lung function data were collected on 106; the results of the statistical analyses are shown in table 6. In the post 1972 analysis the loss of FEV₁ is not significantly different from the results given in table 1. The base sizes, however, are small and it could be argued, on the basis of the large error terms, that workers with good FEV₁ were balancing workers with poor FEV₁. For this reason it became necessary to investigate the individual rather than the group average since the concern is for workers with a large decrease in lung function.

The clinical data on the post 1972 group of 78 individuals have been carefully studied. None had chest radiograph changes suggestive of lung disease or damage due to their occupation and all appeared to make a satisfactory clinical recovery from their respiratory symptoms after their removal from enzyme exposure. Forty seven are smokers and 23 non-smokers; six stopped smoking during the survey period and the smoking habits of two are unknown.

Of the 27 subjects who had a substantially greater

Table 4 Effect of atopicity and exposure levels on conversion to PT+ve

Exposure level	Factory A			Factory B			Factory C		
	No	% PT+	Av time (years)	No	% PT+	Av time (years)	No	% PT+	Av time (years)
<i>Non-atopics</i>									
Exposure level:									
Maximum	80	18	6.3	118	24	2.8	503	29	1.5
Medium	111	23	3.6	65	14	1.9	405	3	3.0
Minimum	317	6	4.4	186	12	4.0	451	3	2.9
Totals	508	13	4.4	369	18	2.9	1359	13	1.7
<i>Atopics</i>									
Exposure level:									
Maximum	14	57	2.1	12	42	1.7	70	63	1.3
Medium	40	73	2.6	27	37	4.7	71	11	2.2
Minimum	78	22	3.8	51	16	3.0	114	8	2.9
Totals	132	43	3.0	90	26	2.9	255	24	1.7

Table 5 *Effect of smoking*

FEV ₁ change per year (ml/year)						
Longitudinal analysis				Lateral analysis		
Post 1972						
	No	FEV ₁	SE	No	FEV ₁	SE
Non-smokers						
Factory A	257	-28	4	200	-48	3
Factory B	125	-34	5	129	-65	4
Factory C	202	-47	3	432	-48	1
Smokers						
Factory A	353	-35	5	302	-50	3
Factory B	302	-43	4	352	-56	3
Factory C	444	-56	2	637	-51	1

fall in FEV₁ than their group average, 20 are smokers, six non-smokers, and the smoking habit of one is unknown. In this group of 27 there are 16 who experienced further respiratory symptoms (cough, wheeze, tightness of chest). These include seven who suffered bronchitis or asthma before exposure to enzymes. Those with further symptoms could be related to episodes of bronchitis, contact with other irritants (nail varnish, smoke, cold, some powders), and further accidental or at the time unrecognised exposure to enzyme. Three subjects had no other apparent clinical cause than enzymes to associate with their loss of lung function.

Discussion

In this study of the effect on lung function of working in the detergent industry those at the factory located in south eastern England have significantly better lung function values than those at the two factories in the industrial north on the longitudinal analysis and were numerically better in the lateral analysis. This result supports other data. Within the United Kingdom the prevalence and mortality rates from chronic obstructive pulmonary disease tend to be higher in the north and west compared with the south and east even when allowance is made for the

effects of urbanisation.¹⁵ This study appears to confirm that average lung function is better in the south east than in the north west of England.

Measurements of FEV₁ loss by other investigators give values from 20 to 60 ml/year.^{14 16-22} If the whole population at the three factories in this study is combined, on the lateral survey a value of 51 ml/year loss is obtained, on the longitudinal survey, 39 ml/year.

There is no universally accepted standard for the change in FEV₁ with age for urban industrial populations. The subject has recently been reviewed by Glindmeyer, who compares the figures given in 16 different surveys, the FEV₁ change varying in these from 23 to 36 ml/year loss.²³ Examination of the circumstances of these surveys shows several factors that could give conflicting results—small survey numbers, ill-defined populations, and ethnic differences. These surveys were all cross sectional (lateral).

The survey groups that comprise populations most nearly like that under discussion (men living in industrialised areas of the United Kingdom and France) are those of Lowe²¹ and Kauffmann²² (neither was cited by Glindmeyer). Lowe studied two groups of south Wales steelworkers, only men with normal chests being admitted, and gives figures

Table 6 *Effect on E cases*

Total pre and post 1972		FEV ₁ change per year (ml/year)					
		Longitudinal analysis			Lateral analysis		
		Post 1972					
		No	FEV ₁	SE	No	FEV ₁	SE
<i>E cases</i>							
Factory A	38	38	-25	13	36	-66	12
Factory B	26	21	-43	7	22	-69	14
Factory C	42	19	-38	12	32	-43	11

of 41 ml and 42 ml for the loss in FEV₁/year. Kauffmann studied Parisian factory workers between the ages of 30 to 54 and found the loss of FEV₁ per year to be in the range of 44 to 60 ml. This estimate was based on measurements made between 1960 and 1972 and this survey and the results are closest to ours.

One explanation for the large differences between our study and other surveys (except the very recent study by Kauffmann) concerns the inclusion of young men. Many cross sectional surveys include men under 25 in the analysis of FEV₁ against age and height. Cotes states that the decline in male lung function is not properly established until after the age of 25.¹⁴ We also find that men younger than 25 exhibit variable behaviour, usually a rise in FEV₁ followed by a plateau before the final decline. The inclusion of young men in the analysis will therefore reduce the calculated FEV₁ loss. For example, in the case of factory C the inclusion of 228 men younger than 25 into the lateral analysis reduced the FEV₁ loss from 50 ml to 45 ml/year, bringing the results closer to Lowe, who includes men under 25.

The large differences between the results from the lateral survey compared with the results from other workers must also be viewed in the light of the industry's experience in taking lung function measurements over 11 years. The observations of subjects' lung function have been made on regularly calibrated Vitalographs and the testing procedures are affected by many types of variation. Experience has shown that obtaining consistent results is difficult. Analysis of our early results indicated a need for a standardised test procedure. This was adopted throughout the industry and the effect has been to reduce variation to the point where two longitudinal analyses are appropriate, one covering the early part of the data and the other the data since 1972 (when the procedure became fully effective). The measurement error, with a standard deviation of about 200 ml, will usually be higher than the yearly change in FEV₁ that is being estimated.

Careful quality control of the data is therefore essential; this is particularly important for lateral (cross sectional) surveys, where transient sources of bias can have a pronounced effect on the calculated results.

The possibility that the lung function of the surviving population at the factories could have been affected by the normal turnover of workers was investigated. The analyses of survivors versus leavers show that leavers tended to have a better lung function than survivors but the difference was small. There was a significant number of workers with poor lung function as a result of dust exposure among

those who left the industry.

The effect on lung function of the degree of exposure to enzymes and sensitivity to enzymes as determined by a positive result to the skin test shows no adverse trends. In our study the lung function of atopics is no different from non-atopics but a much higher percentage of atopics became prick test positive to enzymes. The increased susceptibility of atopics to the enzymes used in detergent powders would be expected but this did not appear to have a measurable effect on their lung function.

The large reduction in enzyme dust levels coincided with a drop in the rate of conversion of those atopics still exposed post 1969 to a percentage equivalent to the post 1969 non-atopics. The time taken to become skin test positive to enzymes did not differ between atopics and non-atopics. With the lowering of enzyme dust levels through the 1970s, by enzyme encapsulation, and better industrial hygiene measures, the percentage rate of conversion to skin test positive of newly employed non-atopics was reduced significantly but, for those who became sensitised, the time taken was still about the same. These results are supported by conversion versus exposure levels.

The adverse effect on sensitisation and lung function of smoking confirms the findings of other investigations.^{24, 25} An FEV₁ loss of 50 to 100 ml/year has been shown for smokers²⁶ and a higher percentage of smokers became skin test positive to the enzyme than non-smokers.²⁵

The lung function of the 20 E cases who are also smokers has not returned to its expected level. It is not possible to determine if the loss is caused by enzymes or smoking. Smoking status could account for their relative rate of loss and this could be due to respiratory obstruction which does not (initially) produce symptoms.²⁷ Only three E cases (one at factory A and two at factory C) were identified whose lung function had not returned to its previous level for no other reason than enzymes.

The total percentage of E cases was 4.5% but this slightly overestimates occupational asthma caused by detergent enzymes. The percentage rates of occupational asthma caused by other prescribed allergenic agents²⁸ were investigated. Published reports give widely variable figures for the percentage of the population affected by these industrial allergens. Some well known allergens such as epoxy resin curing agents and isocyanates appear to have no well documented figures for the percentage of workers affected. Other allergens with firm documentation are those affecting flour and grain handlers (43% of workers),²⁹ animal laboratory workers (14%),³⁰ solder makers (22%),³¹ and platinum workers (60%).³² Detergent enzyme

appears a less potent allergen by comparison with these other prescribed industrial allergens.

References

- ¹ Flindt MLH. Pulmonary diseases due to the inhalation of derivatives of *Bacillus subtilis* containing proteolytic enzymes. *Lancet* 1969;i:1177-81.
- ² Pepys J, Hargreave FE, Longbottom JL, Faux JA. Allergic reactions of the lungs to enzymes of *Bacillus subtilis*. *Lancet* 1969;i:1181-4.
- ³ Newhouse ML, Tagg B, Pocock SJ, McEwan AC. An epidemiological study of workers producing enzyme washing products. *Lancet* 1970;i:689-93.
- ⁴ Greenberg M, Milne JE, Watt J. Survey of workers exposed to dust containing derivatives of *Bacillus subtilis*. *Br Med J* 1970;ii:629-33.
- ⁵ Pepys J, Wells ID, D'Souza MF, Greenberg M. Clinical and immunological responses to enzymes of *Bacillus subtilis* in factory workers and consumers. *Clin Allergy* 1973;3:143-60.
- ⁶ Watt A, Morley R, Greenberg M, Fox AJ. Follow up of a group of workers exposed to dust containing derivatives of *Bacillus subtilis*. *Clin Allergy* 1973;3:133-41.
- ⁷ Juniper CP, How MJ, Goodwin BFJ, Kinshott AK. *Bacillus subtilis* enzymes: a 7 year clinical epidemiological and immunological study of an industrial allergen. *J Soc Occup Med* 1977;27:3-12.
- ⁸ How MJ, Goodwin BFJ, Juniper CP, Kinshott AK. Comparative serological and clinical findings in subjects exposed to environmental allergens. *Clin Allergy* 1978;8:347-60.
- ⁹ Soap and Detergent Industry Association. *Medical supervision of employees engaged in manufacture of enzymatic products*. London: SDIA, 1973.
- ¹⁰ Medical Research Council. Symposium on biological effects of proteolytic enzyme detergents. *Thorax* 1976;31:621-34.
- ¹¹ Bruce CF, Dunn E, Brotherton R, Davies DR, Hall F, Potts SCM. Methods of measuring biologically active enzyme dust in environmental air of detergent factories. *Ann Occup Hyg* 1976;21:1-20.
- ¹² Medical Research Council. Respiratory questionnaire (modified version). In: *SDIA 3rd report*. London: SDIA, 1970.
- ¹³ How MJ, Cambridge GW. Prick tests and serological tests in the diagnosis of allergic reactivity to enzymes used in washing products. *Br J Ind Med* 1971;28:303-7.
- ¹⁴ Cotes JE. *Lung function assessment and application in medicine*. 3rd ed. London: Blackwell Scientific Publications, 1979:375.
- ¹⁵ Brewis RAL. *Lecture notes on respiratory disease*. 2nd ed. London: Blackwell Scientific Publications, 1975:134-5, 175-6.
- ¹⁶ Higgins MW, Keller JB. Seven measures of ventilatory lung function. *Am Rev Respir Dis* 1973;108:258-72.
- ¹⁷ Cotes JE, Anderson HR, Patrick JM. Lung function and the response to exercise in New Guinea: role of genetic and environmental factors. *Philos Trans Soc Lond (Biol)* 1974;268:349-61.
- ¹⁸ Rossiter CE, Weill H. Ethnic differences in lung function: evidence for proportional differences. *Int J Epidemiol* 1974;3:55-61.
- ¹⁹ Miller GJ, Cotes JE, Hall AM, *et al*. Lung function and exercise performance of healthy Caribbean men and women of African ethnic origin. *Q J Exp Physiol* 1972;57:325-41.
- ²⁰ Kory RC, Callahan R, Boren HG. The veteran administration—army cooperative study of pulmonary function. *Am J Med* 1961;30:243-58.
- ²¹ Lowe CR, Pelemear PL, Campbell H, Hitchens RAN, Khosla T, King TC. Bronchitis in two integrated steel works. *Br J Prev Soc Med* 1968;22:1-11.
- ²² Kauffmann F, Drouet D, Lellouch J, Brille D. Occupational exposure and 12 year spirometric changes among Paris area workers. *Br J Ind Med* 1982;39:221-32.
- ²³ Glindmeyer HW. Predictable confusion. *JOM* 1981;23:845-84.
- ²⁴ Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;i:645-8.
- ²⁵ Zetterstrom O, Osterman K, Machads L, Johanson SGO. Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. *Br Med J* 1981;283:1215-7.
- ²⁶ Parkes WR. *Occupational lung disorders*. 2nd ed. London: Butterworth & Co, 1982:10.
- ²⁷ Franklin W, Lowell FC. Unrecognised airway obstruction associated with smoking—a possible forerunner of obstructive pulmonary emphysema. *Ann Intern Med* 1961;54:379-86.
- ²⁸ *Social Security Act 1975*. Occupational asthma. London: HMSO, 1981:10-2.
- ²⁹ Tse KS, Warren T, Janusz DS, Cherniak RM. Respiratory abnormalities in workers exposed to grain dust. *Arch Environ Health* 1973;27:74-7.
- ³⁰ Cockcroft A, Edwards J, McCarthy P, Anderson N. Allergy in laboratory animal workers. *Lancet* 1981;i:827-30.
- ³¹ Burge TS, Hedge G, Hawkins R, White V, Newman-Taylor AJ. Occupational asthma in a factory making flux cord solder containing colophony. *Thorax* 1981;36:828-34.
- ³² Roberts AE. Platinosis—a 5 year study of the effects of soluble platinum salts on employees in a platinum laboratory and refinery. *Archives of Industrial Hygiene* 1951;4:549-59.