

## Respiratory symptoms, lung function, and sensitisation to flour in a British bakery

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**ABSTRACT** A survey of dust exposure, respiratory symptoms, lung function, and response to skin prick tests was conducted in a modern British bakery. Of the 318 bakery employees, 279 (88%) took part. Jobs were ranked from 0 to 10 by perceived dustiness and this ranking correlated well with total dust concentration measured in 79 personal dust samples. Nine samples had concentrations greater than 10 mg/m<sup>3</sup>, the exposure limit for nuisance dust. All participants completed a self administered questionnaire on symptoms and their relation to work. FEV<sub>1</sub> and FVC were measured by a dry wedge spirometer and bronchial reactivity to methacholine was estimated. Skin prick tests were performed with three common allergens and with 11 allergens likely to be found in bakery dust, including mites and moulds. Of the participants in the main exposure group, 35% reported chest symptoms which in 13% were work related. The corresponding figures for nasal symptoms were 38% and 19%. Symptoms, lung function, bronchial reactivity, and response to skin prick tests were related to current or past exposure to dust using logistic or linear regression analysis as appropriate. Exposure rank was significantly associated with most of the response variables studied. The study shows that respiratory symptoms and sensitisation are common, even in a modern bakery.

Occupational asthma and rhinitis occur in bakers<sup>1</sup> and the environmental agents responsible appear to be components of the grain itself<sup>2-4</sup> or grain contaminants, such as mites, weevils, and moulds<sup>5-7</sup>. The relative importance of these potential allergens may vary according to the source of the flour, conditions of storage, and intensity of exposure. Recent papers describing grain components as important allergens have come from Australia,<sup>2-4</sup> where grain has a low moisture content. A higher moisture content, or storage of grain or flour for long periods, may promote the growth of contaminant micro-organisms, mites, and insects. Materials added to flour before baking, such as yeast and amylase, derived from *Aspergillus* species,<sup>8</sup> may also be allergenic.

As many as a third of bakers and grain workers may show evidence of sensitisation,<sup>9-11</sup> which appears to be related to intensity and duration of exposure in the industry as well as to host factors, such as atopy.<sup>11,12</sup> Mechanisms involving IgE and the mast cell have been implicated,<sup>12,13</sup> but precipitins to components of flour have also been identified<sup>5</sup> and non-immunological processes, such as direct activation of complement pathways, may be involved.<sup>14</sup>

Apart from case reports, there is little information about asthma and sensitisation in British bakers. This study was designed to (a) describe the levels of exposure to bakery dust in a modern British bakery, (b) estimate the prevalence of symptoms and sensitisation in the workforce of the bakery, and (c) explore relations between indices of exposure and response.

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### Methods

#### STUDY DESIGN AND SUBJECTS

The study was a cross sectional survey of current employees conducted over six consecutive days and nights. All current workers with the exception of

drivers and salesmen, whose contact with the bakery involved only the collection of goods for delivery, were invited to participate in the study.

#### DETERMINATION OF CURRENT EXPOSURE CONCENTRATIONS

Concentrations of airborne dust in the breathing zones of workers were determined with personal air samplers. Either open faced filter holders (Casella, London) housing preweighed 25 mm diameter glass microfibre filters (GF/A, Whatman, Maidstone; nominal pore size 1.6  $\mu\text{m}$ ), or closed face 37 mm diameter three piece polystyrene aerosol monitors (Millipore, Harrow) housing preweighed 0.8  $\mu\text{m}$  pore size polycarbonate membrane filters (Nuclepore; Sterilin; Hounslow) were used. These were connected to portable, battery operated vacuum pumps (AFC-123, Casella or L2SF, Rotheroe and Mitchell, Aylesbury) sampling at air flow rates of 2 l/min.

The bakery was divided into five main structurally separate areas: the main bread bakery; the confectionery bakery for producing buns, rolls, scones, and pastries; the hot plate bakery for producing pancakes and crumpets; the workshop area; and the administration offices and canteen. Within each area one or more employees wore sampling devices for periods of up to eight hours to provide gravimetric measurements of total airborne dust.

#### EXPOSURE RANKING

Independently of the measurement of dust concentrations, each employment category was ranked on a scale of 0 to 10 for perceived dustiness by the bakery manager in consultation with an occupational physician from the baking industry (table 1). Office;

transport, and workshop staff who worked in physically separate accommodation and never entered production areas were graded 0, whereas subjects working in the flour room or in the manufacture of scones were graded 10.

#### WORKPLACE EXPOSURE MEASUREMENTS

Seventy nine personal dust samples were collected throughout the bakery (table 1). Nine of the samples had concentrations in excess of the exposure limit for nuisance dust (10  $\text{mg}/\text{m}^3$ ).<sup>15</sup> The geometric mean total dust concentrations were, in general, consistent with the rank of workplace exposure (table 1) but there was considerable variation within some exposure ranks, such as exposure rank 6.

#### RESPIRATORY QUESTIONNAIRE

All participants completed a self administered questionnaire on respiratory symptoms based on the Medical Research Council (MRC) Questionnaire (1976). Additional questions were added to indicate whether the respiratory symptoms experienced (breathlessness, wheeze, chest tightness, and sneezing or itchy, running nose) improved on days off work or on holidays (if they did they were considered to be work related). Further questions asked if the participant thought that work "affected" his or her chest or nose. Participants also completed questions on smoking habits and on occupational history. Smokers were defined as those who had smoked at least one cigarette a day or equivalent in other tobacco products for at least one year and ex-smokers had ceased smoking at least six months before the study.

Chronic bronchitis was defined as sputum production on most days for at least three months each year.

Table 1 Number of employees participating in the study and results of dust sampling by exposure rank

Rank	Employment	Total No of employees	Participants		No of samples tested	Dust sampling total dust ( $\text{mg}/\text{m}^3$ )	
			No	%		Range	Geometric mean
0	Office, transport, and vehicle-workshop staff	52	37	71	1	0.18	0.18
1	Despatch, traywashing, nursing, and canteen staff	23	23	(100)	2	0.00- 0.08	0.01
2	Slicers, wrappers, and packers	84	70	83	23	0.00- 3.65	0.34
3	Bakery manager, quality control staff	7	6	(86)	0	—	—
4	Production foremen, security staff	29	28	97	5	0.01- 0.99	0.24
5	Bakery maintenance staff	20	19	(95)	1	2.97	2.97
6	Staff attending ovens or in cooking areas	29	26	90	16 [3]	0.00-37.57	1.73
7	Bakery cleaning staff, doughmakers (main bread bakery)	57	54	95	12 [2]	0.01-16.80	2.13
8	Doughmakers (confectionery bakery), mixers (hot plate bakery)	9	9	—	10 [1]	0.59-14.10	2.69
9	Staff preparing ingredients in confectionery bakery	2	2	(94)	2 [1]	9.97-12.05	11.00
10	Flour room staff, scone production staff	6	5	—	7 [2]	1.84-13.03	6.59
	Total	318	279	88	79 [9]	—	—

Percentages in round parentheses are based on fewer than 25 subjects. Numbers in square parentheses refer to samples with levels above 10  $\text{mg}/\text{m}^3$  (the exposure limit for nuisance dust is 10  $\text{mg}/\text{m}^3$ ).

Dyspnoea was defined as being troubled by shortness of breath when hurrying on level ground or walking up a slight hill.

#### PULMONARY FUNCTION

Forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were measured with one of four dry wedge spirometers (Vitalograph, Buckingham). These were checked for leakages and calibration (using a one litre syringe) at least three times each day. Measurements were expressed at ATPS and a calibration factor for each spirometer was included. The best FEV<sub>1</sub> and the best FVC was taken from three technically satisfactory forced expiratory manoeuvres where the best two recordings were within 5% of each other.<sup>16</sup> All measurements were made at an ambient temperature within the range 18–23°C.

Each individual's FEV<sub>1</sub> and FVC was divided by the square of height and standardised to age 25 years using age regression coefficients calculated from the study participants. Separate linear regressions were used for subjects over or under 25.

#### NON-SPECIFIC BRONCHIAL REACTIVITY

Non-specific bronchial reactivity was measured by the method of Yan *et al*<sup>17</sup> using hand held De Vilbiss No 40 nebulisers to a total cumulative dose of methacholine of 120  $\mu$ mol. The provocative cumulative dose of methacholine producing a 20% fall relative to the postsaline FEV<sub>1</sub> (PD<sub>20</sub>) was calculated by linear interpolation of the final two points on a logarithmic scale.

#### SKIN PRICK TESTS

Skin prick tests were performed on the flexor surface of the forearm using the following allergen extracts: B2 grass pollen (4100, Bencard), *Dermatophagoides pteronyssinus* (2801, Bencard), cat fur (3204, Bencard), wheat grain (5101, Bencard), *Aspergillus fumigatus* (2000, Bencard) bakers yeast (7902, Bencard), mould mix (*Alternaria alternata*, *A. fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, Dome/Hollister Stier), *Tribolium confusum* (5 mg/ml, Health and Safety Executive, London), mixed flour (5105, Bencard), *Tyrophagus longior* (5 mg/ml, Health and Safety Executive, London), *Acarus siro* (5 mg/ml, Health and Safety Executive, London), *Glycyphagus destructor* (5 mg/ml, Health and Safety Executive, London), *Tyrophagus putrescentiae* (5 mg/ml, 78/517 National Institute of Biological Standards and Control), and *G. domesticus* (5 mg/ml, Brompton Hospital). Positive control was histamine dihydrogen chloride and negative control was Coca's solution. All tests were read at 10 minutes. The mean of the greatest dimension of the weal and the dimension at right angles to this was calculated. A mean weal diameter of 2 mm or

more greater than the negative control was considered positive. Subjects were classified as atopic if they had one of more positive responses to common allergens (grass pollen, *D. pteronyssinus*, or cat fur). They were considered "grain mite positive" if they had a positive response to *T. longior*, *A. siro*, *G. destructor*, *T. putrescentiae*, or *G. domesticus*. Additionally, if *T. confusum*, baker's yeast, mixed flour, wheat grain, mould mix, *A. fumigatus*, or any of the grain mites were positive subjects were classified as "bakery antigen positive."

#### STATISTICAL PROCEDURES

The statistical significance of the relation of potential explanatory variables to symptoms, bronchial reactivity, and skin response was examined by using logistic regression analysis; the relation to FEV<sub>1</sub>/FVC ratio was analysed using linear regression.<sup>18</sup> The independent explanatory variables included in the analyses were age, sex, current smoker, ever smoked, atopic status, years worked in the bakery, current exposure rank, whether currently working at exposure rank 6 or more, and whether ever worked at exposure rank 6 or more.

## Results

#### CHARACTERISTICS OF THE SUBJECTS

A total of 279 (88%) of the 318 bakery employees took part in the survey (table 1), 92% of the men and 82% of the women. Two men and three women were unavailable because of illness and two men and one woman were on holiday. Twelve men and 19 women refused to take part in the study. Of the 39 workers who did not take part, 15 were from rank 0 (with the lowest exposure), six from rank 2, and one from rank 3. In all other exposure categories at least 90% of work force took part.

Twenty six male workers (a subset of exposure rank 7) were employed only on Saturdays to clean the bakery during its non-production day. They were much younger than the other workers (all were 20 or under compared with the remainder of the male work force of whom 77% were 25 or more) and all but two had been employed for less than two years. In addition 19 male maintenance workers (all those in exposure rank 5) had intermittent exposure. These two groups were therefore considered separately from the main group and are referred to as the intermittent exposure group in all subsequent analyses. The multivariate analyses identified a history of exposure rank 6 or more (past or present) to be the measure of exposure most frequently associated with response variables. Therefore the results in tables 2–4 are presented according to this categorisation of exposure.

In all, 55% of the workers in the main group were men (table 2) but the proportion varied in the different exposure categories. About half the workers had been

Table 2 Characteristics of study population by exposure rank. (Percentages in parentheses are based on fewer than 25 subjects)

	Percentage in given exposure rank				Intermittent exposure group	
	Main group			Total	5	7*
	Never ≥6	Past ≥6 only	Current ≥6			
Sex: Male	39	72	73	55	(100)	100
Age (y): <25	24	13	34	25	(16)	100
25-44	36	56	31	38	(53)	0
≥45	40	31	34	37	(32)	0
Years employed in bakery:						
<2	28	0	23	22	(5)	92
2-10	47	59	56	52	(63)	8
>10	25	41	21	26	(32)	0
Smoking status:						
Current smoker	47	59	54	51	(63)	23
Ex-smoker	17	26	11	17	(21)	0
Never smoked	36	15	34	32	(16)	77
Atopic	41	38	30	37	(50)	62
Total assessed	125	39	234	19	26	

\*A subset of exposure rank 7.

Table 3 Symptoms reported by exposure rank. (Percentages in parentheses are based on fewer than 25 subjects)

Symptoms	Percentage in exposure rank				Intermittent exposure group	
	Main group			Total	5	7*
	Never ≥6	Past ≥6 only	Current ≥6			
Chronic bronchitis	6	23	21	13	(5)	0
Dyspnoea	17	28	19	19	(0)	8
Wheeze:						
Any	19	36	26	24	(21)	23
Work related	6	10	13	9	(5)	0
Chest tightness:						
Any	14	33	21	20	(16)	8
Work related	5	8	7	7	(5)	0
Difficulty in breathing:						
Any	12	23	17	16	(12)	8
Work related	4	8	9	6	(0)	0
Any chest symptoms:						
Any	31	51	35	35	(28)	23
Work related	9	6	17	13	(11)	0
Nasal symptoms:						
Any	27	46	54	38	(32)	46
Work related	13	20	30	19	(21)	8
Any chest or nasal symptoms:						
Any	46	72	57	54	(37)	62
Work related	17	33	36	25	(26)	8
"Work affects chest"	2	18	15	8	(0)	6
"Work affects nose"	7	27	30	17	(11)	12
"Work affects chest or nose"	8	40	32	21	(11)	12
Total assessed	125	39	70	234	19	26

Symptoms are defined in the text.

\*A subset of exposure rank 7.

Table 4 Standardised FEV<sub>1</sub>/FVC ratio, PD<sub>20</sub>, and results of skin prick test to any bakery antigen by exposure rank. (Percentages in parentheses are based on fewer than 25 subjects)

	Percentage in exposure rank				Intermittent exposure group	
	Main group			Total	5	7*
	Never ≥6	Past ≥6 only	Current ≥6			
Standardised (FEV <sub>1</sub> /FVC) × 100:						
<70	6	11	14	9	(19)	5
70-	28	42	39	33	(38)	32
80-	58	42	42	51	(44)	50
90-	8	6	5	7	(0)	14
Total assessed	108	36	57	201	16	22
PD <sub>20</sub> (mcmol):						
>120	74	64	58	68	(53)	71
30-120	15	11	24	17	(6)	29
<30	11	25	19	15	(41)	0
Total assessed	113	36	59	208	17	24
Skin prick test positive, any bakery antigen	28	54	35	35	(50)	58
Total assessed	118	39	60	217	18	24

\*A subset of exposure rank 7.

employed in the bakery for between two and 10 years and further 26% for more than 10 years. About one third of the workers in the main group had never smoked, 42% of the women and 23% of the men. By contrast, 77% of the Saturday part time workers had never smoked.

#### RESPIRATORY SYMPTOMS

For each of the exposure ranks within the main group the prevalence of most symptoms was similar for men and women, therefore the results for both sexes have been tabulated together (table 3). Chronic bronchitis was reported by 13% of the main group, the proportion increased with increasing exposure category. Dyspnoea was more common among women (25%) than among men (14%) and was not associated with increasing exposure.

Thirty five per cent of the workers in the main group reported one or more chest symptoms (wheeze, chest tightness, or difficulty in breathing), 13% had work related symptoms—that is, their symptoms were better when they were away from work—and 8% considered that working in the bakery affected their chest. Nasal symptoms (sneezing or an itchy or runny nose) were common; they were reported by 38% of the main group and about half were work related. In all, 25% of those in the main group reported work related chest or nasal symptoms, the proportion being highest among those currently (36%) or previously (33%) in exposure rank 6 or above.

Of those in the intermittent exposure group, the

Table 5 Results of logistic regression analyses\*

Dependent variable	Significant independent variable(s)	Regression coefficient (SE)	Constant term (SE)	Interpretation	
				Change	Increase in odds ratio
Chronic bronchitis	Ever $\geq 6$ exposure	1.66 (0.48)	-2.92 (0.42)	Ever v never $\geq 6$ exposure	4.1
Dyspnoea	Female sex†	1.03 (0.37)	-3.78 (0.76)	Female v male	2.8
	Ever smoked	1.08 (0.44)		Ever v never smoked	2.9
Work related chest symptoms	Current exposure rank	0.14 (0.07)	-2.38 (0.35)	Increase of one exposure rank	1.2
Work related nasal symptoms	Current exposure rank	0.25 (0.06)	-1.01 (0.57)	Increase of one exposure rank	1.3
	Age	-0.04 (0.01)		Increase of 10 years	0.7
Work related chest or nasal symptoms	Current exposure rank	0.22 (0.06)	-1.79 (0.06)	Increase of one exposure rank	1.2
PD <sub>20</sub> < 30 mcmol	Ever $\geq 6$ exposure	0.84 (0.40)	-2.13 (0.30)	Ever v never $\geq 6$ exposure	2.3
Positive skin test to one or more bakery antigens	Atopic	2.79 (0.39)	-2.89 (0.42)	Atopic v non-atopic	16.3
	Ever $\geq 6$ exposure	1.10 (0.38)		Ever v never $\geq 6$ exposure	3.0
	Years worked in bakery	0.06 (0.022)		Additional 10 years in the bakery	1.8

\*Based on workers in the main exposure group.

†Male = 1, female = 2.

proportion reporting symptoms was generally lower than for those in the main group. This was particularly true for the subset of exposure group 7 (the Saturday cleaning workers), none of whom had chronic bronchitis or work related chest symptoms, although 23% had wheeze which was not work related. Nevertheless, 12% considered that work affected their nose or chest.

The stepwise multiple logistic regression analysis identified a measure of exposure as the most significant independent factor associated with symptoms with the exception of dyspnoea which was most common in women and was also associated with a history of smoking (table 5).

#### PULMONARY FUNCTION TESTS

The regression coefficients for FEV<sub>1</sub> against age for men and women aged 25 or more combined were approximately 0.03 l/year both for smokers and non-smokers. The standardised FEV<sub>1</sub> for men was not related to any measure of exposure whereas women who had worked at some time in exposure rank 6 or more had significantly lower FEV<sub>1</sub> than those who had not.

The standardised FEV<sub>1</sub>/FVC ratio tended to decrease with increasing exposure rank (table 4), the proportion of workers with a ratio less than 80% increasing from 34% in those never exposed at rank 6 or more to 53% in those currently in exposure rank 6-10. One third of the workers had measurable bronchial reactivity (PD<sub>20</sub>  $\leq$  120 mcmol) (table 4), the proportion within the main group increasing from 26% in those never exposed at rank 6 or more to 42% of those currently in exposure rank 6-10.

The stepwise linear regression analysis of the age standardised FEV<sub>1</sub>/FVC ratio isolated sex and current smoking as the only two significant factors. The ratio was lower in men (average 4.3% less than women) and current smokers (average 2.4% less than current non-

smokers). A PD<sub>20</sub> of 30 mcmol or less was significantly associated with ever having been exposed at rank 6 or higher (table 5).

#### SKIN TESTS

Forty per cent of the workers (44% of the men and 34% of the women) had a positive skin test to one or more common allergens, the commonest being *D pteronyssinus* (30%) (table 6). A third had a positive test to one or more grain mites and there was a high degree of concordance in the results for the five grain mites. Of the 77 workers with a positive skin test to *D pteronyssinus*, 77% were positive to one or more grain mites compared with only 14% of those with a negative skin test to *D pteronyssinus* ( $p < 0.001$ ). Positive skin tests to one or more of the other bakery allergens occurred in 9%, reactions to *A fumigatus*,

Table 6 Results of skin prick tests

Positive to	No positive	%		
Common allergens:				
<i>Dermatophagoides pteronyssinus</i>	77	30	} 40	
Cat fur	67	26		
B2 grass pollen	48	18		
Grain mites:				
<i>Tyrophagus longior</i>	62	24	} 33	
<i>Glycyphagus destructor</i>	59	23		
<i>Acarus siro</i>	58	22		
<i>Glycyphagus domesticus</i>	46	18		
<i>Tyrophagus putrescentiae</i>	45	17		
<i>Tribolium confusum</i> (flour beetle)	28	11	} 38	
Other bakery allergens:				
Mixed flour	14	5		
Wheat grain	9	4		
Mould mix	6	2		
Bakers' yeasts	3	1		
<i>Aspergillus fumigatus</i>	1	<1		
Total assessed	259	100		

bakers yeast, and mould mix being uncommon (2% or less).

There was no relation between positive reactions to common allergens and exposure to dust. The highest proportion of positive responses to bakery antigen was in those with a history of exposure in rank 6 or more (table 4). A high proportion of reactions to common allergens in the intermittent exposure subset of group 7 was associated with a high proportion of positive responses to grain mites and other bakery antigens.

In the logistic regression analysis positive skin test to one or more bakery antigens was associated with atopy, a history of exposure in rank 6 or higher, and the number of years worked in the bakery (table 5).

## Discussion

Total dust concentrations were measured in the production areas of this bakery and several samples exceeded the exposure limit for nuisance dust in the ingredients preparation and manufacturing areas. They were much lower in the wrapping and despatch areas. These objective measurements supported the independently derived ranking system used to classify the workforce for exposure according to job category. The measurements in cleaning and maintenance workers who were intermittently exposed showed great variability and much larger numbers of samples over longer periods would have been necessary to produce a useful profile of exposure in these subjects.

Work related symptoms were reported frequently by this workforce and sensitivity to components of flour was shown by skin prick tests in over a third of the subjects. Both were found to be more common in subjects with higher levels of bakery dust exposure. There was also evidence of exposure related respiratory effects from measurements of non-specific bronchial reactivity. By contrast, FEV<sub>1</sub>/FVC ratio was significantly related to sex and smoking but not to exposure, being lowest in men and current smokers.

Probably one or more allergens in wheat flour are responsible for the skin test responses and at least some of the respiratory effects observed in this population. Some symptoms, however, particularly nasal, are likely to be due to simple non-specific irritation. Other studies have implicated IgE in the asthma of bakers<sup>12,13</sup> but other immunological<sup>5</sup> and non-immunological<sup>14</sup> responses may also operate. Further work dissecting the nature of the response is required.

This bakery has a selection policy of excluding subjects with current symptomatic asthma from employment. This selection may have been expected to reduce the numbers of atopic subjects in the study, since atopic status and bronchial hyperreactivity are associated in the general population.<sup>19</sup> The prevalence of atopy, however, was similar to that of the general

population.<sup>20</sup> It was thought that the high prevalence of grain mite skin positivity might have resulted from cross reactivity with house dust mite but recent studies have found no such cross reactivity.<sup>21-23</sup> In the present study a positive skin test response to grain mites was related to exposure variables whereas a response to *D pteronyssinus* was not. This finding is being explored further. The relation of skin test responsiveness to bakery antigens with duration of exposure is consistent with the previous finding in an Australian bakery<sup>23</sup> and with a prospective study of skin test responses conducted over five years.<sup>10</sup> It indicates that continued exposure results in development of sensitisation to bakery dust components.

The present study has shown that even in a modern bakery control of dust exposure presents a continuing problem. Bakery dust concentrations exceeded the exposure limit for nuisance dust at some times in some areas and sensitisation of workers had occurred as measured by skin test responses to bakery antigens. Respiratory symptoms, non-specific bronchial reactivity, and skin responses were related to exposure to bakery dust.

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## Vancouver style

All manuscripts submitted to the *Br J Ind Med* should conform to the uniform requirements for manuscripts submitted to biomedical journals (known as the Vancouver style).

The *Br J Ind Med* together with many other international biomedical journals, has agreed to accept articles prepared in accordance with the Vancouver style. The style (described in full in *Br Med J*, 24 February 1979, p 532) is intended to standardise requirements for authors.

References should be numbered consecutively in the order in which they are first mentioned in the text by Arabic numerals above the line on each occasion the reference is cited (Manson<sup>1</sup> confirmed other reports<sup>2-5</sup> . . .). In future references to papers submitted to the *Br J Ind Med* should include: the names of all authors if there

are six or less or, if there are more, the first three followed by *et al*; the title of journal articles or book chapters; the titles of journals abbreviated according to the style of *Index Medicus*; and the first and final page numbers of the article or chapter.

Examples of common forms of references are:

- 1 International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979;1:532-5.
- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosino-phil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- 3 Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.