CLINICAL RESEARCH

Bronchoalveolar mast cells in extrinsic asthma: a mechanism for the initiation of antigen specific bronchoconstriction

KEVIN C FLINT, K B PETER LEUNG, BARRY N HUDSPITH, JONATHON BROSTOFF, FREDERICK L PEARCE, NORMAN McI JOHNSON

Abstract

Bronchoalveolar lavage performed in 10 patients with extrinsic asthma and 14 controls yielded similar recoveries of fluid and cells. Mast cells and eosinphils, however, formed a greater proportion of the cells recovered from the asthmatic subjects ($p<0.001$ for mast cells; $p<0.01$ for eosinophils), the histamine content of the lavage cells being correspondingly increased ($p<0.01$). Both the percentage of mast cells and the histamine content of lavage cells were significantly inversely correlated with the forced expiratory volume in one second (FEV_1; expressed as percentage of predicted) and with the ratio of FEV_1 to forced vital capacity before lavage. There was also a significant inverse correlation between the concentration of histamine required to produce a 20% fall in FEV_1 and the percentage of mast cells recovered ($p<0.05$).

When incubated with antihuman IgE bronchoalveolar mast cells from asthmatic subjects released a significantly increased proportion of total cellular histamine than cells from control subjects at all effective doses of anti-IgE. By contrast, dose response curves for IgE dependent histamine release from peripheral blood leucocytes were similar in asthmatics and controls. Specific antigen led to release of histamine from bronchoalveolar cells and peripheral blood leucocytes of asthmatic subjects but not controls.

Lying superficially within the airways, bronchoalveolar mast cells would be readily exposed to inhaled antigen and would release mediators directly on to the airway surface. Their immunological response suggests that they are likely to be important in the pathogenesis of airflow obstruction in asthma.

Middlesex Hospital, London W1
KEVIN C FLINT, MA, MRCP, Sir Jules Thorn research fellow
BARRY N HUDSPITH, MIBIOL, senior medical laboratory scientific officer
JONATHON BROSTOFF, MB, FRCP, reader in clinical immunology
NORMAN McI JOHNSON, MD, MRCP, senior lecturer in medicine

Department of Chemistry, University College London, London WC1
K B PETER LEUNG, BSC, associate research assistant
FREDERICK L PEARCE, PHD, reader in chemistry

Correspondence to: Dr K C Flint, Medical Unit, The Middlesex Hospital, London W1N 8AA.

Introduction

The mucosal surface is the first site of contact for ingested or inhaled allergens. Of the various cells lining this surface of the nose, lungs, or gastrointestinal tract, the mast cell has assumed importance because of the immediacy of the reaction when this cell is triggered. Thus the cross linking of IgE (reaginic) antibody by antigen releases potent chemical mediators which are central to the pathogenesis of immediate hypersensitivity reactions.[1] There is now increasing evidence that mast cells form a heterogeneous population, and at least two morphological subpopulations have been identified—namely, mucosal mast cells and connective tissue mast cells.[2] More important, mast cells have been shown to be functionally heterogeneous, and cells from different species or even from given tissues within a single species differ in their functional properties.[3] Much of our knowledge of the role of the mast cell in human IgE mediated reactions comes indirectly from studies of rodent mast cells, blood basophils, chopped human lung, and more recently mast cells enzymatically dispersed from lung fragments.[4,5]

We have shown that mast cells recovered by bronchoalveolar lavage from non-asthmatic subjects differ from mast cells isolated from whole lung preparations in their ready response to anti-IgE without passive sensitisation and the degree of inhibition of this histamine release by sodium cromoglycate.[6] Lying superficially within the airway, such cells would be readily exposed to inhaled antigen, and mediators liberated as a result of such antigen contact would be released directly on to the airway surface. Bronchoalveolar mast cells may therefore have an important role in the generation of bronchoconstriction after antigen challenge.

We have now extended our early work in normal subjects to determine the numbers of mast cells recovered by bronchoalveolar lavage from patients with extrinsic asthma and the functional response of these cells to immunological challenge.

Patients and methods

The study was approved by the hospital ethical committee. Ten patients with asthma (four women; mean age 31 years, range 19-42) with one or more positive reactions to skin prick tests with 10 common inhalent antigens gave informed consent to bronchoalveolar lavage. The mean serum IgE concentration was 77 (SE17) IU/ml and none of the group were smokers. Six patients used only a salbutamol inhaler, three used inhaled salbutamol in combination with sodium cromoglycate, and one salbutamol in combination with an oral theophylline preparation. Two of the patients receiving sodium cromoglycate also took an antihistamine (terfenadine) as required. Salbutamol was stopped for 12 hours before the study and sodium cromoglycate, antihistamine, and theophylline for two weeks.

The control group consisted of 14 subjects (six women) undergoing bronchoscopy as a routine diagnostic procedure and in whom no underlying disease was found (mean age 47 years, range 22-74; seven were smokers). In this group the mean serum IgE concentration was 53 (SE18) IU/ml and two subjects had positive reactions to skin prick tests.

Pulmonary function tests—Forced expiratory volume in one second and forced vital capacity (FEV_1 and FVC) were measured before bronchoalveolar lavage. Histamine bronchial provocation tests were performed using a French-Rosenthal dosimeter between one week and one month after lavage, following the guidelines of the American Thoracic Society.[7] For each patient the histamine concentration required to produce a 20% reduction in FEV_1 (PC_{20} histamine) was calculated.

Bronchoalveolar lavage—After intravenous premedication with atropine (0·6 mg), fentanyl (100 μg), and diazepam (10 mg) local anaesthesia of the upper airways was achieved with lignocaine (10%) spray. No bronchodilator premedication was used. The bronchoscope was then passed pernasally in the usual way, but isotonic 1·5% lignocaine (Xylocaine Epidural, Astra Pharmaceuticals, UK) prewarmed to 37°C was used for topical anaesthesia throughout. Bronchoalveolar lavage was performed in the medical segment of the right middle lobe using three 60 ml aliquots of buffered (pH 7·4) isotonic saline carefully prewarmed to 37°C. Fluid was recovered into siliconised glass containers at room temperature. Supplementary oxygen was given by nasal catheter (6 l/min), and after lavage all asthmatic subjects routinely received 5 mg nebulised salbutamol and 100 mg hydrocortisone intravenously. Oral prednisolone was given as follows: 20 mg at four hours, 10 mg at 24 hours, and 5 mg at 48 hours after lavage. All subjects were admitted overnight.

Total and differential cell counts—Lavage fluid was centrifuged (200 *g* for five minutes) and the cell pellet washed twice with Roswell Park Memorial Institute 1640 (Flow Laboratories). Total cell numbers were evaluated using acridine orange and ethidium bromide in a modified Neubauer chamber. Cytocentrifuge smears were made and dried in air. Routine differential cell counts were performed by counting a minimum of 200 cells on preparations fixed with methanol and stained with May-Grünwald-Giemsa. Differential counts of mast cells were performed on preparations fixed with Carnoy's fluid and stained in the alcian blue safranin reaction, as described.[6]

Immunological challenge—Functional studies were performed as described.[6] Briefly, recovered cells were resuspended at roughly 2×10^6 cells in 250 μl Tyrode's buffer. In asthmatics fewer total cells were required to give equivalent numbers of mast cells and measurable concentrations of histamine for release experiments. Cells were challenged at 37°C with anti-IgE (Dako, England) or specific antigen according to skin prick test result (grass pollen, n=1; house dust mite, n=7) and the reaction allowed to proceed for 10 minutes. Cells were then separated from supernatant by centrifugation (200 *g* for five minutes at room temperature), each made up to the same volume, and cells lysed with perchloric acid (2·4% final concentration) before estimation of histamine.

Histamine assay—Histamine was assayed by an automated fluorometric method (Technicon autoanalyser II fluoronephelometer) and expressed as a percentage of total cellular histamine. Hence histamine release was calculated as the ratio: [histamine supernatant/(histamine supernatant+histamine cell pellet)] ×100%. Results were corrected for spontaneous release by subtraction.

Peripheral blood leucocytes were prepared by dextran sedimentation from heparinised blood. After the final wash with Tyrode's buffer they were resuspended at a concentration of 10^7 leucocytes/ml and 250 μl incubated with anti-IgE or antigen for 30 minutes at 37°C. The reaction was stopped by the addition of two volumes of ice cold buffer followed by centrifugation (200 *g* at 4°C). The cell pellet was lysed with perchloric acid and histamine assayed as above.

Statistical analysis of results was by Student's *t* test for unpaired samples.

Results

Table I shows the percentage recovery of lavage fluid and total and differential cell counts in the two groups. The proportion of eosinophils was significantly increased in asthmatic subjects ($p<0·01$).

TABLE I—*Percentage recovery of lavage fluid and total and differential cell counts in patients with extrinsic asthma (n=10) and controls (n=14). Values are means (SE in parentheses)*

	% Recovery	Total cell count (×10^6/l)	Differential count (%)			
			Macrophages	Lymphocytes	Neutrophils	Eosinophils
Asthmatics	38·0 (4·0)	12·2 (3·9)	80 (4·0)	9 (4·1)	3 (0·5)	8 (2·7)
Controls	39·5 (3·6)	11·7 (1·9)	86 (2·5)	8 (1·5)	4 (1·0)	2 (0·5)

Table II gives the individual data from asthmatic subjects relating to the histamine content of the recovered cell population, the percentage of this population made up by mast cells, and the spontaneous release of histamine by these cells during 10 minutes' incubation at 37°C. Table II also lists the spirometric indices (FEV_1 (% predicted) and FEV_1:FVC ratio) and results of histamine bronchial provocation testing (PC_{20} histamine) for each of these subjects. Both the percentage of mast cells (mean 1·41 (SE 0·3)% *v* 0·25 (0·07)%; $p<0·001$) and the histamine content of the lavage cells (mean 193 (SE 55) pmol/10^6 cells *v* 27 (5) pmol/10^6 cells (21·5 (SE 6·1) *ng*/10^6 cells *v* 3·0 (0·6) *ng*/10^6 cells); $p<0·01$) were significantly different between the asthmatic and control subjects. The spontaneous release of histamine was significantly greater in asthmatic subjects (mean 18·4 (SE 4·1)%) compared with controls (mean 8·1 (0·9)%; $p<0·05$).

TABLE II—*Histamine content of recovered cells, percentage recovery of mast cells, and spontaneous release of histamine during 10 minutes incubation at 37°C in asthmatic subjects compared with spirometric and PC_{20} histamine test results*

Case No	Histamine content (pmol/10^6 cells)	Recovery of mast cells %	Spontaneous release of histamine %	FEV_1:FVC ratio	FEV_1 (% of predicted)	PC_{20} histamine (mmol/l)
1	508	2·8	14·5	48	55	2·7
2	447	2·0	46·5	68	76	1·8
3	252	2·2	23·4	68	83	7·2
4	229	1·8	7·1	68	79	3·6
5	182	1·6	31·0	67	90	4·5
6	122	1·1	13·1	68	67	–
7	81	0·8	17·0	65	81	2·2
8	79	1·5	10·2	81	87	4·5
9	19	0·1	8·2	83	97	45·0
10	13	0·2	10·5	82	100	9·0

Conversion: SI to traditional units—Histamine: 1 pmol≈0·1 ng; 1 mmol/l≈0·1 mg/ml.

Table III shows the correlation coefficients for comparisons between the percentage of mast cells, histamine content of recovered cells, spontaneous release of histamine, and measured lung function parameters. There was a significant inverse correlation between the percentage of mast cells among recovered cells and both FEV_1 (% predicted) ($p<0·01$) and the FEV_1:FVC ratio ($p<0·005$). Similar inverse correlations were seen between histamine content and these parameters of pulmonary function. There was a significant inverse correlation between the percentage of mast cells and the PC_{20} histamine ($p<0·05$), although the correlation between PC_{20} histamine and the histamine content of lavage cells failed to reach significance.

TABLE III—*Correlation coefficients for comparisons between spirometric indices, PC_{20} histamine, histamine content of lavage cells, percentage of mast cells, and spontaneous release of histamine during 10 minutes' incubation*

	Histamine content	Percentage of mast cells	Spontaneous release of histamine
FEV_1 (% of predicted)	−0·74; $p<0·01$	−0·72; $p<0·01$	−0·12; NS
FEV_1:FVC ratio	−0·79; $p<0·005$	−0·76; $p<0·005$	−0·26; NS
PC_{20} histamine	−0·46; NS	−0·60; $p<0·05$	−0·35; NS
Histamine content		0·88; $p<0·001$	0·54; $0·05<p<0·1$
Percentage of mast cells	0·88; $p<0·001$		0·39; NS

FUNCTIONAL STUDIES

Dose response curves for anti-IgE induced histamine release from peripheral blood leucocytes were not significantly different between the asthmatic and control subjects. By contrast, there was an accentuation of response of broncoalveolar mast cells in the patients with extrinsic asthma, with a significantly increased percentage of total cellular histamine released at all effective doses of anti-IgE tested (figs 1 and 2). The percentage of histamine released in asthmatic subjects did not correlate with serum IgE at any dilution of anti-IgE.

When challenged with specific antigen both bronchoalveolar mast cells and peripheral blood basophils from asthmatic subjects showed a dose dependent release of histamine (grass pollen, n=1; house dust mite, n=7) (fig 3). We could not induce antigen to cause significant release of histamine from lavage mast cells recovered from non-atopic controls.

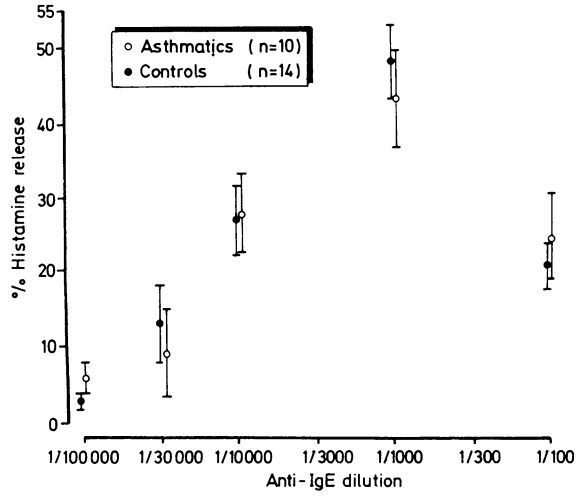

FIG 1—Anti-IgE induced histamine release from peripheral blood leucocytes of 10 patients with extrinsic asthma and 14 controls ($2{\cdot}5\times10^6$ leucocytes challenged in Tyrode's buffer and reaction allowed to proceed for 30 minutes). Points are means. Bars are SE. All values corrected for spontaneous release by subtraction.

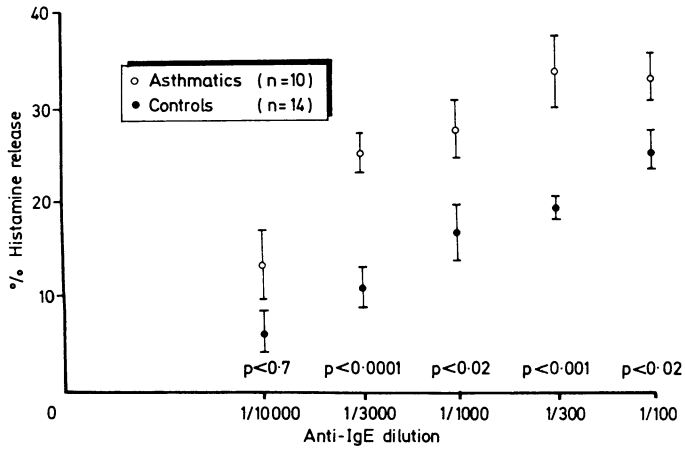

FIG 2—Anti-IgE induced histamine release from bronchoalveolar cells of 10 patients with extrinsic asthma and 14 controls (2×10^6 cells incubated with anti-IgE in 250 µl Tyrode's buffer and reaction terminated by centrifugation after 10 minutes). Points are means. Bars are SE. All values corrected for spontaneous release by subtraction.

Discussion

Bronchoalveolar lavage has now been performed in asthmatic subjects in several centres.[8-10] In our subjects the asthma ranged from mild to moderately severe. Nevertheless, with the use of prewarmed isotonic solutions, endoscopically visible bronchoconstriction was confined to the segment lavaged. There were no adverse effects in any subject and all were discharged the morning after bronchoalveolar lavage. Great care was taken to give routine bronchodilators and steroids after lavage.

Our controls tended to be older than the asthmatic group and in addition half of them were smokers. Ideally the controls should be normal subjects matched for age, sex, and smoking habit but we did not have ethical approval to study such a group. We did not, however, observe any significant effects due to age in the cell distribution in bronchoalveolar lavage either in the controls or in the asthmatic subjects, nor have we done so in any other of the many lavages that we have performed. Smoking is known to increase the total cell yield from bronchoalveolar lavage—in particular the numbers of macrophages; there were, however, no significant differences between our non-smoking and smoking controls as far as cell distribution was concerned. It is therefore unlikely that any of the findings we describe in asthma were due to the lack of matched controls.

We found increased numbers of mast cells within the bronchoalveolar cell population in asthmatic subjects with a corresponding increase in total cellular histamine. It is of particular interest that the increase in recovered bronchoalveolar mast cells from asthmatic subjects and the total histamine content of the lavage cell population

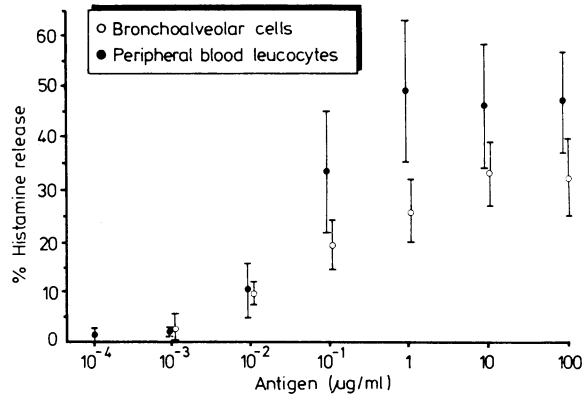

FIG 3—Antigen induced histamine release from bronchoalveolar cells and peripheral blood leucocytes of eight patients with asthma. Points are means. Bars are SE. All values corrected for spontaneous release by subtraction. Antigen failed to induce significant release of histamine from either peripheral blood leucocytes or bronchoalveolar cells of four non-atopic controls (<5% release at all concentrations of antigen).

correlated with the measured indices of airflow obstruction. This association between the recovery of bronchoalveolar mast cells and the severity of asthma in any particular subject strengthens the hypothesis that these cells may act as an antigen specific trigger for subsequent bronchoconstriction.

These cells are morphologically indistinguishable from bronchoalveolar mast cells in normal subjects. Our studies, however, have disclosed several functional differences. Asthmatic bronchoalveolar mast cells appeared to be less stable than those of normal people, with increased spontaneous release of histamine during 10 minutes' incubation at 37°C. This spontaneous release was widely variable, from 7·1% in one subject with mild asthma to 46·5% in a subject with asthma of greater clinical severity (table II). This high spontaneous release may be related to the trauma implicit in the way in which these cells are obtained. Spontaneous release from cells recovered from control subjects was much lower, however, suggesting an inherent instability of bronchoalveolar mast cells from asthmatic subjects. It has been proposed that the release of mediators from superficial cells through cooling of the airways may be concerned in the pathogenesis of excercise induced asthma.[11] Another factor which may therefore increase spontaneous release of histamine from these cells is cooling from 37°C to 20°C during recovery from the airways.

Immunological activation of bronchoalveolar mast cells of asthmatics by anti-IgE or antigen results in the release of cellular histamine. In the case of anti-IgE, this was accentuated in asthmatic subjects compared with controls with an increased proportion of cellular histamine being released at all dilutions of anti-IgE. This accentuation of release appeared to be confined to the lung as, despite differences in serum IgE values between the two groups, histamine release from peripheral blood basophils was similar in asthmatics and controls. Findlay and Lichtenstein also reported finding no difference in anti-IgE induced histamine release from

blood basophils between asthmatic and normal subjects.[12] This accentuation in bronchoalveolar lavage may reflect increased local concentrations of IgE, an increase in IgE Fc receptors on bronchoalveolar mast cells, or an alteration in the sensitivity of receptor response coupling. It is possible that the binding of IgE by bronchoalveolar mast cells differs from classical models. Unlike connective tissue mast cells, mucosal mast cells in rat gastrointestinal tract have been shown to contain intracellular IgE,[13] and bronchoalveolar mast cells resemble mucosal mast cells in many respects.[6]

Challenge with specific antigen (grass pollen or house dust mite) leads to histamine release in a dose dependent fashion from bronchoalveolar mast cells and peripheral blood basophils of asthmatic subjects. Inhaled antigen therefore has the capacity to cause similar release from sensitised mast cells in vivo. By contrast, antigen did not cause release of histamine from bronchoalveolar mast cells or peripheral blood basophils of non-atopic controls.

Our findings are, in part, in agreement with the study of Tamioka *et al*, who also found an increase in the recovery of mast cells from asthmatic subjects.[14] In their subjects, however, the percentage of total cells made up by mast cells was lower with no correlation between this and the recovery of histamine and, in consequence, no difference in the latter respect between asthmatic and control subjects. There may be several reasons for this discrepancy. In the first instance, the technique of bronchoalveolar lavage and subsequent processing of lung lavage fluid varies considerably and minor differences may lead to large variations in results.[15] In particular we find the practice of filtering lavage fluid through gauze difficult to justify. Bronchoaveolar mast cells in asthmatic subjects have high spontaneous rates of histamine release, and delay in processing the cells for morphological evaluation may lead to degranulated mast cells being missed. This group's finding of cells which stain with fluorescein labelled anti-IgE but not with toluidine blue would be compatible with this, as plasma cells producing IgE form a very small percentage of bronchoalveolar cells.[16] Similarly, any delay would lead to the increasing loss of histamine spontaneously into the supernatant culture medium or buffer, where it would not be assayed as cellular histamine. No data on pulmonary function or information about the severity of asthma in their subjects was given, but it seems likely that the range of severity of asthma in our subjects was greater.

Contact with inhaled antigen would lead to local release of mediators within the airways, which may be sufficient in themselves to generate the pathophysiological events associated with acute asthma. Little is known as yet about the spectrum of mediators released from bronchoalveolar mast cells, but it seems likely that mast cells obtained from different sites will vary in this respect. An alternative possibility is that mast cells lying superficially may recruit secondary cells such as alveolar macrophages or submucosal mast cells with amplification of the response.

An alternative explanation for the demonstrated association between the severity of airflow obstruction and the recovery of cells would be that the site of recovery of cells by lavage fluid may be different in asthmatics and controls. Although the total number of cells recovered by bronchoalveolar lavage was similar in our two groups (table II), fewer total cells were recovered from the most severely affected asthmatics. Thus even in remission peripheral mucous plugging in patients with moderately severe asthma may lead to the recovery of cells predominantly from airways with a smaller component from the alveoli. We think that this provides a less likely explanation. Except for mast cells and eosinophils, the differential cell counts in the two groups, and in patients with asthma of differing severity, were indistinguishable. In particular, there was no increased contribution from neutrophils, which one might expect with predominantly airways lavage. In addition, the total number of mast cells and the total recovery of cellular histamine from a single segment were much greater in all but the most mildly affected asthmatics than controls. As 180 ml lavage fluid would be expected to reach most if not all of the airway surface of the lavaged segment in controls and asthmatics, this suggests an increase in the total number of mast cells within the segment in asthmatics.

Increased numbers of sensitised mast cells within the airways of asthmatic subjects may explain their rapid response to inhaled antigen. An inherent instability of this population of cells as shown by high spontaneous rates of histamine release after recovery may also explain the bronchoconstrictor response to non-immunological stimuli such as exercise and airway cooling, water mist, and sulphur dioxide. This latter possibility would be in keeping with the finding that sodium cromoglycate protects against such non-specific stimuli without effect on histamine or methacholine reactivity.[17]

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100 YEARS AGO

In cases of illness, the point that probably most affects the welfare of the patient is the qualifications of the nurse in attendance. So much of the treatment is necessarily carried out through her instrumentality, and the success of the treatment employed may be so favoured or impeded by her proceedings, that the modern idea of nursing is that it should only be undertaken by those who have been carefully taught and trained. Especially is this felt to be the case when dealing with a number of sick and helpless patients, such as are met with in our large infirmaries. This being so, we regret to see that the authorities of the Govan Parochial Board of Glasgow have decided, on the score of expense, not to adopt, in connection with their hospitals, the system of having trained nurses, as urged on them by the Board of Supervision, and for the adoption of which the Government now holds out special inducements. At their last meeting, the Board decided to continue their present system of utilising pauper inmates to do the nursing, under supervision from the superintendents. We think that this is an unfortunate decision to have come to. When it is considered that nursing includes careful watching and intelligent observation of the patient, with the view of noting changes and symptoms of importance in his condition, and that it aims at carrying out practically towards individual patients, or collections of patients, those sanitary rules which we know are necessary for those in health, and are of still greater consequence to the sick, we feel that uninstructed and untrained nurses should no more be placed in charge of a single patient, or of a hospital-ward, than that an unqualified man should be appointed medical officer to a parochial infirmary. (*British Medical Journal* 1885;ii:267.)