

## Effect of aspirin in "aspirin sensitive" patients

S I ASAD, D M KEMENY, L J F YOULTEN, A W FRANKLAND, M H LESSOF

### Abstract

**Eighteen patients with a history of urticaria or asthma, or both, induced by aspirin were studied before and after provocation of symptoms with aspirin. The plasma prostaglandin  $F_{2\alpha}$  concentration, which was characteristically raised before challenge, fell significantly at the time of adverse reactions. Repeated administration of aspirin up to a dose of 650 mg daily induced tolerance in most of the patients, and several developed bronchodilator responses to aspirin.**

**Although median total IgE concentrations may be raised in patients with aspirin sensitivity, it appears likely that pharmacological rather than immunological mechanisms are chiefly responsible for the phenomena of aspirin sensitivity and desensitisation.**

### Introduction

In patients with aspirin intolerance manifested by acute urticaria, angioedema, or bronchospasm within two hours of ingestion there is evidence that tolerance to aspirin may be induced by repeated administration over 24-48 hours of doses up to 650 mg a day.<sup>1,2</sup>

The time course for both the induction and the loss of tolerance to aspirin and the known effect of aspirin as a cyclo-oxygenase inhibitor suggest that the mechanisms may be pharmacological rather than allergic, acting through an effect on prostaglandin production. A purely pharmacological effect would not, however, explain the apparent association of aspirin intolerance with other allergic features. Although the occurrence

of urticaria or asthma does not always indicate an allergic origin, reports suggest that serum IgE concentrations may be increased in some cases of aspirin intolerance.<sup>3,4</sup> Allergic reactions may also be triggered via a prostaglandin pathway, at least in vitro,<sup>5</sup> and the presence of a pharmacological effect and an allergic triggering mechanism are not therefore mutually exclusive.

We have looked for evidence both of allergy and of disturbances of prostaglandin metabolism in 14 patients with aspirin induced urticaria and four with aspirin sensitive asthma. Serum total IgE concentrations were determined in 12 patients and plasma prostaglandin  $F_{2\alpha}$  and  $E_2$  ( $PGF_{2\alpha}$  and  $PGE_2$ ) concentrations measured before and after aspirin desensitisation in seven patients with aspirin sensitive urticaria. We also investigated the skin mast cell reactivity before and after induction of tolerance by skin prick test with codeine phosphate in dilutions known to provide a non-immunological stimulus to mediator release.

### Subjects and methods

Eighteen patients with a convincing history of aspirin induced urticaria or asthma or both were selected from the allergy clinic at Guy's Hospital. Their ages ranged from 18 to 63 years. We also selected 20 age and sex matched controls from among patients attending the skin clinic at Guy's Hospital. None of the controls had a personal or family history of atopy, and all gave negative responses in radioallergosorbent tests with three major inhalant allergens (cat dander, grass pollen, and house dust mite).

Total serum IgE concentrations were measured by a modified version of the liquid phase double antibody radioimmunoassay described by Nye *et al.*<sup>6</sup> A 50  $\mu$ l sample of test serum was incubated overnight at room temperature with 100  $\mu$ l <sup>125</sup>I-IgE (Pharmacia IgE test kit) and 100  $\mu$ l rabbit anti-IgE (Hoechst Ltd) diluted 1/60 000 in 0.05M phosphate buffered saline, pH 7.4, containing 0.2% human serum albumin (Kabi AB), 0.05% Tween 20 (Sigma Ltd), and 50  $\mu$ l horse serum (Sera-Lab Ltd). The following day 50  $\mu$ l normal rabbit serum (1/122) and 50  $\mu$ l donkey antirabbit antiserum (1/16; Wellcome) were added and the tubes incubated overnight. The precipitate was washed three times in 2 ml 0.05M phosphate buffered saline, pH 7.4, containing 0.05% Tween 20 and the radioactivity counted in an LKB 1280 Ultragamma. The results were expressed as IU/ml by reference to a standard curve constructed using IgE standards (Pharmacia IgE test kit).

Peripheral venous blood for  $PGF_{2\alpha}$  and  $PGE_2$  assay was obtained

### Department of Medicine, Guy's Hospital Medical School, London

S I ASAD, MB, MPHIL, honorary lecturer in medicine

D M KEMENY, BSC, PHD, lecturer

L J F YOULTEN, MB, PHD, honorary consultant in applied pharmacology

A W FRANKLAND, MA, DM, consultant allergist

M H LESSOF, MD, FRCP, professor of medicine

Correspondence to: Dr S I Asad, Department of Medicine, Fourth Floor, Hunt's House, Guy's Hospital Medical School, London SE1 9RT.

from forearm veins immediately before aspirin desensitisation, at the onset of a positive reaction, and 30 and 90 minutes thereafter. Plasma concentrations of  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  were measured by radioimmunoassay.<sup>7</sup> Validation of the radioimmunoassay has been described.<sup>2</sup> (Anti- $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  bovine serum albumin were obtained from the Pasteur Institute, Paris; 5-6(n) H  $\text{PGF}_{2\alpha}$  and  $\text{E}_2$  from the Radiochemical Centre, Amersham; and  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  from Upjohn.) Skin prick testing was done on the forearm with two concentrations of codeine phosphate (0.6 and 6.0 g/l; Macarthy's Ltd). Weal diameter was measured at 10 minutes.

**Aspirin provocation test**—Capsules containing acetylsalicylic acid 30, 60, and 100 mg were prepared by the hospital's pharmacy; for the higher doses, one (325 mg) or two (650 mg) tablets of soluble aspirin were dissolved in water.<sup>1,2</sup> Patients were admitted to the metabolic ward for the aspirin provocation tests. Informed consent was obtained from the patients and the study approved by the ethical committee of Guy's Hospital Medical School. All challenges were started in the morning and performed by progressive, incremental oral administration of aspirin at two hour intervals.<sup>1,2</sup> An antecubital vein was cannulated with a 21 gauge butterfly catheter and kept patent by a slow infusion of sterile saline. The next day aspirin was readministered at the dose that had produced the earlier response and again increased at two hour intervals until a 650 mg dose was tolerated. This was taken as evidence of successful desensitisation.

## Results

Figure 1 shows the serum IgE concentrations. The range of serum IgE values in the control group was 2.3-145.0 IU/ml, with a median value of 25.0 IU/ml. In patients with aspirin sensitive urticaria the range was 34-800 IU/ml and the median value 105.5 IU/ml. This difference in IgE concentrations was significant (median test:  $\chi^2 = 6.6$ ;  $p < 0.02$ ).

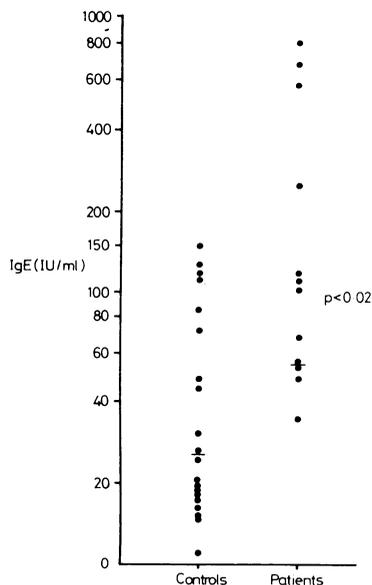


FIG 1—Serum IgE concentrations in controls and patients with aspirin induced urticaria. (Bars are median values.)

Eighteen aspirin sensitive patients were given aspirin and also a placebo challenge as part of an oral aspirin provocation test. Of the 18 patients challenged with aspirin who reacted with either urticaria or bronchospasm, 16 were subsequently desensitised (see table). Neither urticaria nor angioedema nor bronchospasm occurred after placebo challenge.

The median prechallenge plasma  $\text{PGF}_{2\alpha}$  concentration in patients with a history of aspirin induced urticaria was 24.6 ng/l (range 8.3-38.8 ng/l) compared with 5.9 ng/l in the controls (range 3.4-14.2 ng/l); furthermore, the three patients with the highest  $\text{PGF}_{2\alpha}$  concentrations were those in whom there was evidence of bronchospasm as well as urticaria in the subsequent response to aspirin. The

## Aspirin desensitisation in aspirin sensitive patients

Group	No of patients	No in whom desensitisation achieved	No experiencing one reaction before desensitisation
Aspirin sensitive urticaria	14	13	11
Aspirin sensitive asthma	4	3	2
Total	18	16	13

two patients with the lowest values were those in whom provocation with aspirin caused no adverse response. There was no similar clear cut difference in  $\text{PGE}_2$  concentrations: median control value 10.6 (range 7.9-20.6) ng/l; median value in the patients 12.2 (range 7.1-27.7) ng/l.

Some patients were not asked to have an indwelling catheter for prostaglandin measurements and four refused. Plasma  $\text{PGF}_{2\alpha}$  and  $\text{E}_2$  concentrations were measured in seven of the patients with aspirin sensitive urticaria before and two hours after the threshold dose. Figure 2 gives the results. The mean plasma  $\text{PGF}_{2\alpha}$  concentration fell from 25.41 (SEM 4.0) to 12.6 (3.6) ng/l in two hours ( $p < 0.01$ ; Wilcoxon test), and the mean  $\text{PGE}_2$  concentration from 16.8 (SEM 3.7) to 14.6 (3.6) ng/l (NS).

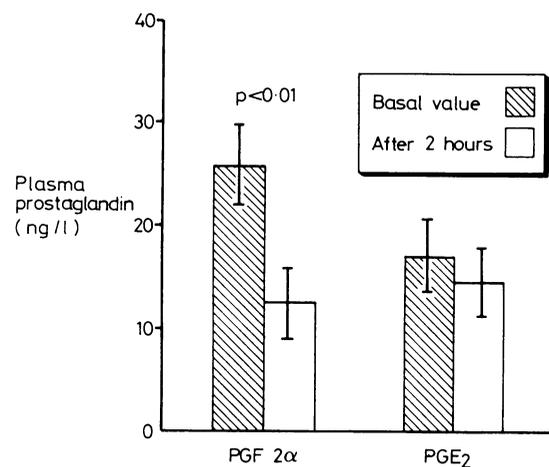


FIG 2—Plasma prostaglandin concentrations in seven patients with aspirin sensitive urticaria before and during provocation test with aspirin. (Bars are means and SEM.)

**Peak flow measurements**—These were determined with a Wright peak flow meter (Clement Clarke International Ltd). One of the patients with a history of aspirin sensitive asthma had two attacks of bronchospasm before clinical tolerance was achieved (fig 3). Two other patients with aspirin sensitive urticaria but no previous history of bronchospasm also had significant drops in peak expiratory flow rate (PEFR) after challenge with aspirin (fig 4). In each case the PEFR before the initial challenge was substantially less than the maximum subsequently achieved, and patients with aspirin sensitive urticaria sometimes appeared to develop a bronchodilator response to

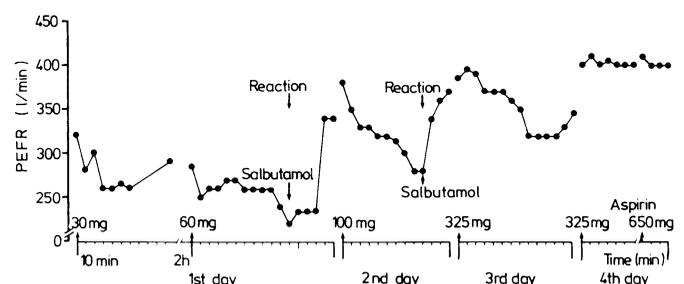


FIG 3—Peak expiratory flow rate (PEFR) measured on successive days before and after aspirin administration in patient with aspirin induced asthma.

aspirin as the dose was increased (figs 4 and 5). This was seen in three patients. In the other patients no significant changes in PEFR were seen either during aspirin provocation or on subsequent desensitisation, and there were no significant changes in PEFR after placebo challenge.<sup>1</sup>

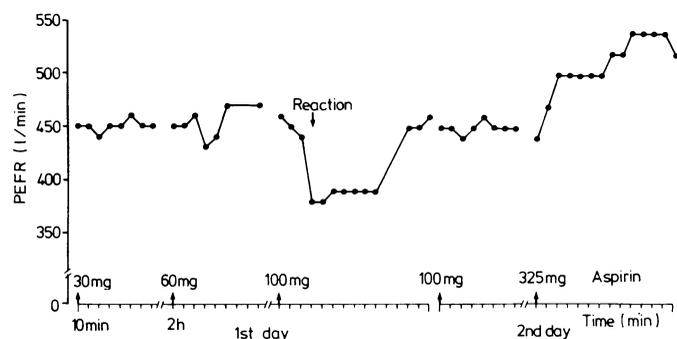


FIG 4—Peak expiratory flow rate (PEFR) measurements in patient with history of aspirin induced urticaria.

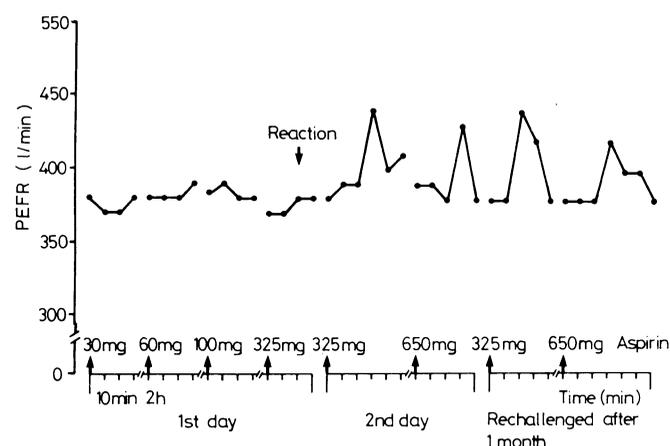


FIG 5—Peak expiratory flow rate (PEFR) measurements during provocation test with aspirin in patient with aspirin induced urticaria and asthma.

Results of skin prick tests to histamine (1 g/l) and codeine phosphate (6 g/l) were positive (weal  $\geq 5$  mm diameter) both before and after aspirin desensitisation in four patients with aspirin sensitive urticaria. Weal sizes were similar to those produced in four control subjects. There was thus no evidence of any change in mediator release or skin histamine reactivity.

## Discussion

There is no direct evidence of an immunological abnormality in most patients sensitive to aspirin,<sup>8</sup> and the cross sensitivity of these patients to a wide range of cyclo-oxygenase inhibiting drugs suggests a pharmacological rather than an allergic mechanism. Nevertheless, a high IgE concentration is not uncommon in these subjects, and two of our four patients with raised IgE values also had other evidence of atopy. Atopy and aspirin intolerance may therefore coexist and it is possible that the same abnormal metabolic pathway may be triggered by more than one mechanism.

In order to study skin reactivity to a non-immunological stimulus we studied the response to skin prick tests with codeine phosphate before and after the induction of tolerance. The response was not affected by aspirin and there was no difference between patients—either before or after aspirin administration—

and control subjects. This study therefore provided no evidence of abnormal skin reactivity to account for our findings.

Numerous chemical mediators are released during an urticarial or asthmatic reaction. Stevenson *et al* detected increased plasma concentrations of histamine during aspirin induced asthmatic reactions,<sup>9</sup> and it seems likely that additional mediators such as leukotrienes, chemotactic factors, and prostaglandins may have a pathological role in early and late adverse reactions to aspirin. Antigen challenge of human lung fragments *in vitro* generates a great variety of arachidonic acid metabolites (PGF<sub>2α</sub>, E, D<sub>2</sub>, I and thromboxane A<sub>2</sub>) in parallel with histamine release.<sup>5</sup>

We have recently reported finding significantly higher plasma concentrations of PGF<sub>2α</sub> and a higher PGF<sub>2α</sub>:PGE<sub>2</sub> ratio in patients with aspirin sensitive urticaria than in control subjects,<sup>2</sup> suggesting that the abnormality in mediator release is not confined to histamine.<sup>9</sup> In this study we measured the PGF<sub>2α</sub> and E<sub>2</sub> response to challenge during the onset of clinical reactions to aspirin. PGD<sub>2</sub> metabolites were not measured, but aspirin significantly reduced concentrations of PGF<sub>2α</sub> though not those of PGE<sub>2</sub>. This fits with the observations of Ong *et al*, who noted that aspirin suppressed PGF production significantly more than PGE in the monocytes of both asthmatics and controls,<sup>10</sup> although asthmatics appeared to produce more PGF than non-asthmatics.

Despite the contrary view held by Settupane *et al*<sup>11</sup> and Stevenson *et al*,<sup>12</sup> our findings suggest that the respiratory and cutaneous reactions in patients with aspirin intolerance overlap to some extent. Two of our patients with urticaria, who had not previously complained of asthmatic symptoms, had a significant drop in PEFR after an aspirin provocation test. A third patient had asthma and urticaria, both induced by aspirin. In all three patients with a reduced PEFR there was an improvement in both urticaria and PEFR after the induction of tolerance to aspirin. Thus respiratory and cutaneous symptoms sometimes occurred in the same patient.

Stevenson and his colleagues noted a refractory period after the desensitisation of patients with a history of aspirin sensitive asthma, but this refractory period ended within two to five days in all but one of 16 patients.<sup>12-13</sup> In aspirin sensitive urticaria we too have noted a refractory period. All 14 patients were still refractory to an aspirin challenge seven days after maintenance doses of aspirin had been stopped, and in four, who agreed to be retested after two months, this refractory state persisted. While these limited observations do not allow firm conclusions to be drawn, it is notable that Pleskow and his colleagues found that when 28 patients with aspirin sensitive asthma were rechallenged after an interval of four months to two years, 11 showed variations between an asthmatic and a nasal response; these included four who lost their aspirin reactivity, of whom two became reactive again after a further interval.<sup>14</sup> This tendency to relapse was also seen in one of our patients with aspirin sensitive asthma, who was receiving corticosteroids. This patient enjoyed a remission in her asthma and an improvement in her PEFR (fig 3) for two weeks after aspirin treatment was initiated, only to suffer a relapse (after a viral respiratory tract infection) which was associated with a fall in PEFR from 400 l/min to 250 l/min and necessitated an increased dose of prednisolone. Our other two aspirin sensitive patients with latent asthma continued with 650 mg of aspirin daily for three weeks without any adverse effect.

The main abnormal finding in our study was that blood prostaglandin concentrations were abnormal in aspirin intolerance. This suggests the possibility of a defect of prostaglandin metabolism that is not dependent on immunological mechanisms but could well be triggered by allergic reactions in those patients who are also atopic.

The role of prostaglandins as a modulating system appears to receive further support from these observations. The rapid induction of tolerance to aspirin might be explicable if the defect in these patients is an aspirin induced disturbance in the homeostatic balance between arachidonic acid metabolites,

and the raised  $\text{PGF}_{2\alpha}$  concentrations in the unchallenged subjects are consistent with this.<sup>2</sup> As judged by the further change in  $\text{PGF}_{2\alpha}$  which we observed after challenge, the effect of oral doses of aspirin may be to reduce the disparity between aspirin sensitive and normal subjects in respect of some arachidonic acid metabolites. The surprising rise in PEF<sub>R</sub> during maintenance treatment with aspirin suggests that homeostatic adjustments may continue when incremental doses are given and that aspirin may in some circumstances act as a bronchodilator, as others have noted.<sup>15 16</sup> These findings will be the subject of further study.

In some subjects aspirin may cause an improvement in asthma,<sup>16</sup> but this observation has received little attention in comparison with the relatively frequent reports of adverse reactions. The change from bronchoconstriction to bronchodilatation which we observed suggests that the balance between different prostanoid effects may differ not only from one subject to another but also in the same subject on different occasions.

We thank Miss W Proctor for drawing the graphs and Miss H Gaunt for typing the manuscript.

## References

- <sup>1</sup> Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J Allergy Clin Immunol* 1980;**66**:82-8.
- <sup>2</sup> Asad SI, Youlten LJF, Lessof MH. Specific desensitization in "aspirin-sensitive" urticaria; plasma prostaglandin levels and clinical manifestations. *Clin Allergy* 1983;**13**:459-66.
- <sup>3</sup> De Weck AL. Immunologic effects of aspirin anhydride, a contaminant of commercial acetylsalicylic acid preparations. *Int Arch Allergy Appl Immunol* 1971;**41**:393-418.
- <sup>4</sup> Phills JA, Perelmutter L. IgE mediated and non-IgE mediated allergic-type reactions to aspirin. *Acta Allergologica* 1974;**29**:474-90.
- <sup>5</sup> Schulman ES, Newball HH, Demers LM, Fitzpatrick FA, Adkinson NF Jr. Anaphylactic release of thromboxane  $A_2$ , prostaglandin  $D_2$ , and prostacyclin from human lung parenchyma. *Am Rev Respir Dis* 1981;**124**:402-6.
- <sup>6</sup> Nye L, Merrett TG, Landon J, White RJ. A detailed investigation of circulating IgE levels in a normal population. *Clin Allergy* 1975;**1**:13-24.
- <sup>7</sup> Dray F, Charbonnel B, Maclouf J. Radioimmunoassay of prostaglandin  $F_2$ ,  $E_1$  and  $E_2$  in human plasma. *Eur J Clin Invest* 1975;**5**:311-8.
- <sup>8</sup> Spector SL, Farr RS. Aspirin idiosyncrasy, asthma and urticaria. In: Middleton E, Reed CE, Ellis EF, eds. *Allergy: principles and practice*. 2nd ed. St Louis: CV Mosby, 1983:1249-73.
- <sup>9</sup> Stevenson DD, Arroyave CM, Bhat KN, Tan EM. Oral aspirin challenges in asthmatic patients: a study of plasma histamine. *Clin Allergy* 1976;**6**:493-505.
- <sup>10</sup> Ong KS, Del Duca C, Weaser JL, Wells ID, Novey HS. In vitro prostaglandins (PGs) production by monocytes of asthmatics and normal subjects. *J Allergy Clin Immunol* 1981;suppl:10. (Abstract.)
- <sup>11</sup> Settignano GA, Chafee FH, Klein DE. Aspirin intolerance. II. A prospective study in an atopic and normal population. *J Allergy Clin Immunol* 1974;**53**:200-4.
- <sup>12</sup> Stevenson DD, Pleskow WW, Curd JG, Simon RA, Mathison DA. Desensitization to acetylsalicylic acid (ASA) in ASA-sensitive patients with rhinosinusitis/asthma. In: *PAR: pseudo-allergic reactions*. Vol 3. Basle: S Karger, 1982:133-56.
- <sup>13</sup> Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. *J Allergy Clin Immunol* 1982;**69**:11-9.
- <sup>14</sup> Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin-sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin. *J Allergy Clin Immunol* 1983;**71**:574-9.
- <sup>15</sup> Kordansky D, Adkinson NF, Norman PS, Rosenthal RR. Asthma improved by nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1978;**88**:508-11.
- <sup>16</sup> Szczeklik A, Nizankowska E. Asthma improved by aspirin-like drugs. *Br J Dis Chest* 1983;**77**:153-85.

(Accepted 13 January 1984)

ONE HUNDRED YEARS AGO There has been of late a considerable popular outcry in favour of the provision of seats for assistants in shops. This movement is a laudable one, with which no fault can be found; but the advocates of the movement have now gone a step further, and propose to limit compulsorily the hours of shop-workers in the same manner as those of factory-people are now limited. A bill has been introduced into the House of Commons, under the title of the Shop-Hours Regulation (Liverpool) Bill, which, did it not bear on its back the highly respectable names of all three members for Liverpool, might provoke some sarcasm. It will undoubtedly send the Vigilance Association into hysterics. The Bill proposes that on and after the first day of October next it shall not be lawful for any premises, *i.e.*, shops and warehouses, to be open on Sundays for any period whatever, nor shall it be lawful for them to be open on any of the first five days of the week beyond the hour of eight o'clock in the evening, or on Saturdays beyond two o'clock in the afternoon. Section 5 imposes a penalty not exceeding £10 for each offence, and the schedule exempts the following from the operation of the Act: milk-sellers; tobacconists' shops where tobacco and smoking utensils alone are sold; shops licensed for the sale of refreshments; and apothecaries' shops for the sale of drugs only. We shall not be accused of any lack of sympathy with the objects which this Bill proposes to forcibly carry into effect, if we say that it introduces local option of a very dangerous and undesirable description. That a majority of people who approve this Bill should be able to dictate absolutely to their fellows at what hours they shall do their shopping, is a somewhat risky innovation from the politico-economical point of view. Hence we fear that any direct prohibitive legislation of this sort will fail of its effect. The most practical way of limiting shop-hours of work is to educate and enlighten local opinion upon the hardships and physical discomforts which long hours entail upon the persons employed. Abundant medical evidence has been adduced to prove these points; but any limitation of hours will have, we feel

assured, to be made voluntary if it is to succeed at all. What is bad for shop-assistants cannot, of course, fail to be bad also for factory-workers as well; and it is with the object of strengthening, as far as possible, the hands of those who are agitating for seats in shops and workplaces that we draw attention to some recent remarks of Mr. Redgrave, the Chief Inspector of Factories and Workshops. Mr. Redgrave observes in his last report, that in some factories the hands, when not actually occupied, as "doffers" of spinning-frames, for instance, are permitted to sit until called upon by the overlooker to doff a frame. A great deal of the time of weavers is occupied in watching the work, which can be done as well by a person sitting as standing; but it is rare to see any means provided for the rest of the weavers. On the contrary, the looms are placed so closely together, side by side, front to front, and back to back, that no seat could be placed. It is gratifying to learn, therefore, that an attempt has been made at several places to give the weavers and operatives an opportunity for rest during their hours of work. At Stourport an entire seat has been constructed for 1s. 9d., which can be fitted to any factory or shop. The seats cannot be damaged, and will not wear out. They may be thrown upon the floor without injury, and as the socket into which they fit does not project more than one inch from the surface to which it may be attached, the seat-fixture cannot infringe materially upon the narrow space behind any shop-counter. Similar seats have also been provided to several factories in Kidderminster, and are gratefully appreciated. At any odd moment when the weaver is not engaged at another part of the loom, he or she can sit down, and thus obtain rest for the legs during the lengthened period of daily labour that ten hours of work entail upon the life and limbs of a factory-weaver. The circumstances of a shop-hand and of a weaver doubtless differ in many respects, but in both cases the injury brought about by constant standing is the same; and what is necessary for the one is undoubtedly necessary for the other. (*British Medical Journal* 1884;i:962.)