

The cellular basis for allergic rhinitis

Howarth PH. The cellular basis for allergic rhinitis.
Allergy 1995; 50: 6–10. © Munksgaard 1995.

In both seasonal and perennial rhinitis there is epithelial mast cell accumulation and tissue infiltration by eosinophils. Activation of these cells can be observed by electron microscopy and by elevated levels of tryptase and eosinophil cationic protein in nasal lavage fluid. Furthermore, seasonal increases in the antigen presenting cell (Langerhans' cell) are also evident. Investigations into the mechanisms involved in cell accumulation and activation reveals upregulation of leucocyte endothelial adhesion molecules and an increase in interleukin-4 (IL-4) in naturally occurring rhinitis, while mRNA for IL-4, IL-5 and granulocyte macrophage colony stimulating factor activity and lavage tumour necrosis factor- α (TNF α) levels are increased following local allergen challenge. These cytokines may be derived from a variety of sources, including mast cells, eosinophils and T-lymphocytes, and contribute to the underlying inflammatory process in rhinitis.

P. H. Howarth

University Medicine, Southampton General
Hospital, Southampton, UK

Key words: rhinitis; mast cells; eosinophils;
basophils; T-lymphocytes; Langerhans' cells;
inflammation; cytokines.

Peter Howarth, MD
University Medicine, Level D, Centre Block
Southampton General Hospital, Tremona Road
Southampton SO16 6YD, UK

Introduction

Allergic rhinitis is associated with mucosal inflammation. This is characterised by the presence of basophilic cells and eosinophils in nasal smears, an epithelial accumulation of mast cells and eosinophils, tissue eosinophilia, an increase in mucosal Langerhans' cells, T-lymphocyte accumulation and activation, and upregulation of the vascular endothelial expression of leucocyte adhesion molecules. The inflammatory cell changes are evident in relationship to clinical disease expression, and the symptoms of rhinitis – nasal pruritus, sneezing, rhinorrhoea, nasal obstruction and loss of sense of smell – can be explained on the basis of mediator release from mast cells, basophils and eosinophils (Fig. 1).

Mast cells

Immunohistochemical staining of nasal biopsies with monoclonal antibodies directed against mast cell tryptase shows an increase in mast cells within the airway epithelium in both seasonal and perennial rhinitis compared with biopsy findings in non-atopic non-rhinitic subjects (3–5). One study using less specific immunohistochemical staining has reported, in addition, an increase in submucosal mast cells in seasonal rhinitis (33), but this could not be substantiated in either the tryptase immunohistochemical studies or in a detailed transmission electron microscopic analysis (13).

The epithelial mast cells are in an activated state

in symptomatic rhinitis, with both ultrastructural evidence of degranulation on electron microscopy (13) and elevated levels of the mast cell mediators histamine and tryptase evident in nasal lavage fluid (34). The released mediators are considered to give rise to the classic nasal symptoms of rhinitis (itch, sneeze, discharge and blockage) through interactions with receptors present on both neural and vascular elements within the nasal mucosa (Fig. 1). Histamine is prominent in this respect. Nasal challenge with histamine induces nasal pruritus, sneezing, discharge and transient nasal blockage (27) and H₁-antihistamines alleviate all of these symptoms with the exception of nasal blockage (21). Nasal blockage can also be induced by lipid mediators, such as leukotrienes, prostaglandins and platelet activating factor (18), which may explain the lack of effect of H₁-antihistamines. Leukotrienes appear to be relatively more important than histamine, as the 5-lipoxygenase inhibitors have been shown to inhibit acute allergen-induced nasal obstruction (20, 23) and a leukotriene D₄ (LTD₄) receptor antagonist has been reported to prevent acute allergen-induced nasal obstruction in naturally occurring ragweed rhinitis (10).

In addition to the effects of acute mast cell degranulation on immediate symptom generation, this cell may also contribute to the eosinophilic mucosal inflammation which is evident in rhinitis. Mast cells within the nose have been demonstrated to contain preformed cytokines, in particular interleukin-4 (IL-4), IL-5, IL-6 and tumour necrosis factor- α

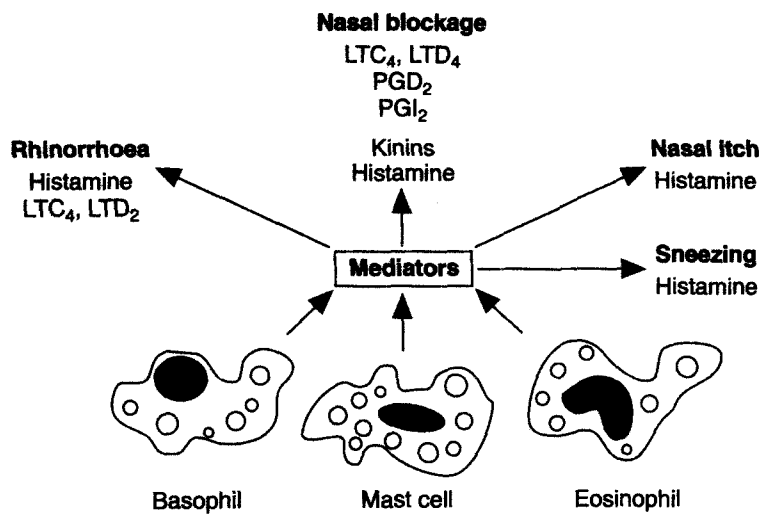


Fig. 1. Mediators and nasal symptom generation.

(TNF α) (4, 6). The immunoreactivity for IL-4 exists in two patterns with different antibodies recognising separate epitopes. One antibody, 49D, stains cytoplasmic IL-4 and this pattern is evident in both rhinitic and non-rhinitic biopsies, whereas the antibody 3H4 gives a peripheral ring staining to the cells and is considered to recognise a secretory form of IL-4. The 3H4 pattern of immunoreactivity is increased in seasonal and perennial rhinitis in comparison to findings in the normal nose (4, 5), and is thus indicative of ongoing cytokine secretion by mast cells in active disease.

Eosinophils

Eosinophils are evident in nasal mucosal biopsies within the submucosa and epithelium in active rhinitis (3–5) and their recovery is increased in nasal smear specimens. Transmission electron microscopy examination of nasal biopsies from patients with rhinitis reveals evidence of ultrastructural granular changes of eosinophil activation. The normal eosinophil has granules which on electron microscopy have an electron-dense core surrounded by a less dense matrix. The electron-dense core is due to the presence of crystals of major basic protein (MBP) (6) which comprise approximately 55% of the granular protein content. In addition to MBP, the eosinophil granules contain within the matrix, eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) and eosinophil peroxidase (EPX), as well as numerous enzymes such as ribonucleases and histaminase (1, 31). Eosinophils in nasal biopsies from rhinitic patients have also been demonstrated to contain IL-5 (4). Eosinophil activation is associated both with the release of the granule components and the *de novo* generation of arachidonic acid end products. The major lipoxygenase arachidonic-acid cleavage product is LTC₄. Eosinophils, primed by chemotactic factors and cytokines such as IL-3, IL-5 and granulocyte macrophage col-

only stimulating factor (GM-CSF), have an enhanced state of activation and exhibit exaggerated LTC₄ generation and release (24, 30, 32).

Elevation of immunoreactive LTC₄ is evident in nasal lavage fluid in seasonal allergic rhinitis (21). In addition to an eosinophil source, LTC₄ may also be derived from either mast cell or basophil activation (17). A marker which is more specific for eosinophil activation is ECP, and an increase in nasal lavage ECP is also evident in seasonal and perennial allergic rhinitis (Fig. 2).

Basophils

Basophils are evident in nasal smear samples in allergic rhinitis (28, 29) and can be demonstrated to increase in asymptomatic seasonal rhinitic patients following nasal allergen challenge (2). When activated, basophils release histamine and LTC₄, but unlike mast cells generate only very small quantities of tryptase and no detectable prostaglandin D₂ (17).

Basophils, which like mast cells possess high affinity IgE receptors, are also derived from CD34-positive progenitor cells in the bone marrow (22). An increase in circulating basophils is observed in rhinitis (9) consistent with stimulation of these progenitor cells. It is now also appreciated that basophils from peripheral blood are capable of synthesising the cytokines IL-4 and IL-8 (7, 12). The relevance of this cell population to cytokine synthesis within the tissue is, however, uncertain as IL-4 predominantly co-localises to mast cells in nasal biopsies (4, 5).

T-lymphocytes

The T-lymphocyte represents a significant non-structural cell within the nasal mucosa. An increase in this cell population has been described in both

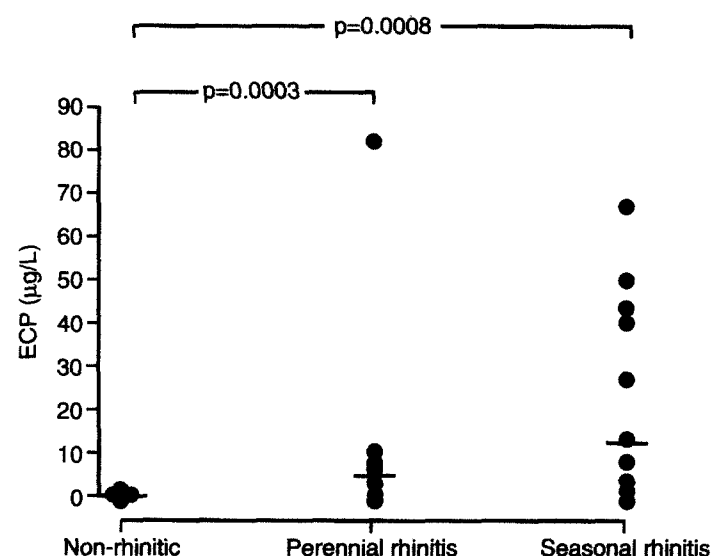


Fig. 2. Measurement of ECP in recovered nasal lavage fluid from healthy volunteers (n = 12) and patients with perennial (n = 11) and seasonal (n = 13) rhinitis.

seasonal (8) and perennial (8) rhinitic patients. These cells are activated with an increase in IL-2 receptor expression in perennial rhinitis in comparison with normal controls, but there is no seasonal change within grass pollen sensitive subjects when symptomatic and non-symptomatic periods are compared (8). The increase appears to be largely related to the CD₄ cell population which has the potential to generate pro-inflammatory cytokines. T-lymphocytes of the TH₂ subpopulation can generate IL-3, IL-4, IL-5, GM-CSF and TNF α (26). Following nasal allergen challenge, an increase in IL-4, IL-5 and GM-CSF mRNA positive cells has been described in association with a mucosal eosinophilia (11), consistent with T-lymphocyte activation, cytokine secretion and cell recruitment. Less information is available about T-cell cytokine synthesis in naturally occurring disease.

Langerhans' cells

For T-cell activation there has to be an interaction with antigen presenting cells. Within the airways the antigen presenting cell appears to be the dendritic or Langerhans' cell, as this function is poorly served by macrophages. These cells form a dendritic network within the mucosa and studies by Fokkens and colleagues have demonstrated a naturally occurring increase in mucosal Langerhans' cells in seasonal rhinitis (14) which can be mimicked by repeated allergen challenge.

Inflammatory model of rhinitis

In addition to mediator release from activated cells within the nasal mucosa, there will also be cytokine secretion which upregulates the expression of adhesion molecules on the vascular endothelium and their corresponding ligands on circulating cells. Secretion of cytokines also primes cells to respond to chemotactic stimuli, enhances the state of cell activation, and prolongs the survival of eosinophils within the nasal mucosal tissue (19). These processes may involve IL-3, IL-4, IL-5, IL-8, GM-CSF and TNF α (Fig. 3) which may have a variety of cell sources (19).

In the initial phase, allergen interacts with sensitised mast cells to release mediators, which induce the symptoms of rhinitis. The release of histamine also mobilises P-selectin on to the vascular endothelium and initiates leucocyte rolling margination (16). The release of TNF α from mast cells, as has been demonstrated during the immediate allergic reaction within the nose (6), promotes upregulation of the leucocyte endothelial adhesion molecules E-selectin, ICAM-1 and VCAM-1, which will result eventually in firmer leucocyte-endothelial adherence

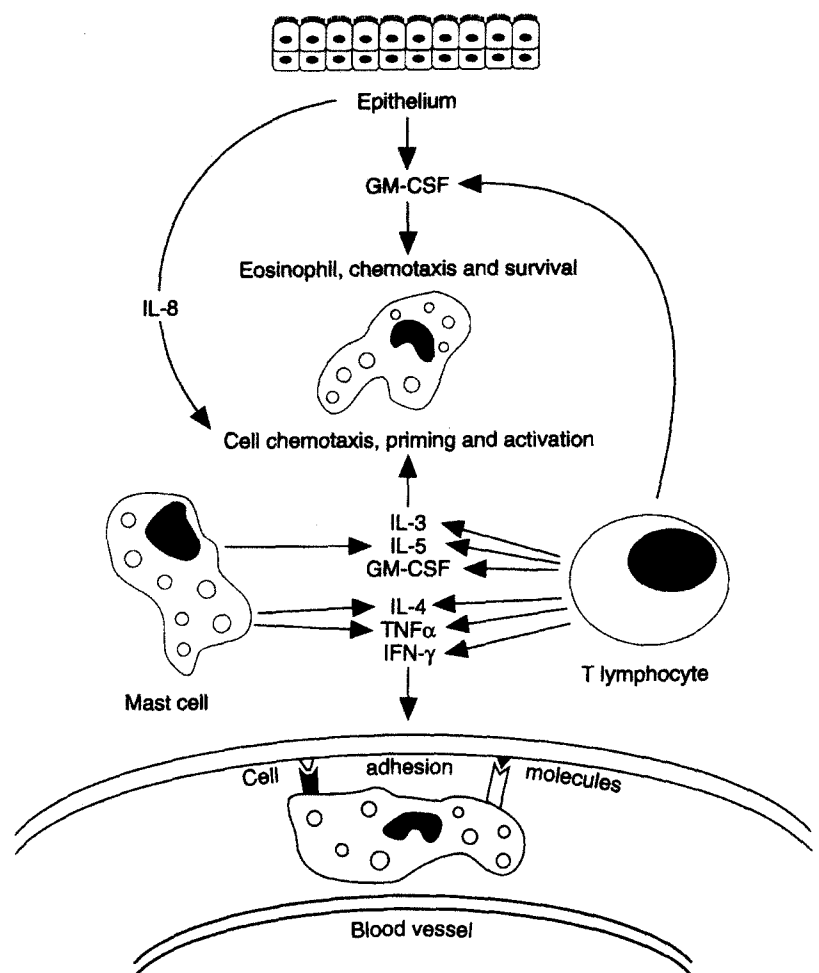


Fig. 3. Cytokines and tissue eosinophilia.

and allow leucocyte transendothelial migration under chemotactic stimuli (25). The release of mast cell IL-4 enhances VCAM-1 upregulation, an adhesion molecule whose expression is evident in both perennial and seasonal rhinitis (4, 5). The co-release of IL-5 will promote eosinophil priming and chemotaxis (19).

The interaction between antigen and high affinity IgE receptors on airway Langerhans' cells leads to antigen processing and the presentation of antigen to T-lymphocytes with their consequent activation and elaboration of cytokines (11). This will take a finite period due to the requirement for gene transcription and protein synthesis. Cytokine release from T-lymphocytes thus contributes to the amplification and maintenance of airway inflammation with mast cell mediator cytokine release initiating the process. The identification of active IL-4 secretion by mast cells in both seasonal and perennial rhinitis shows that this cell population also contributes to the persistence of inflammation in the presence of allergen exposure. In addition to a mast cell and T-lymphocyte source for pro-inflammatory cytokines, eosinophils themselves may serve an autoregulatory function through IL-5 generation and release, and the generation of cytokines such as IL-8 by the airway epithelium in rhinitis (4) will also contribute to the tissue leucocyte recruitment and prolong eosinophil survival in the epithelium. The recent report that IL-8 is chemotactic for mast cells may explain, in

part, the epithelial accumulation of this cell population in rhinitis (15).

The inflammatory cell influx into the airways in rhinitis, involving effector cells such as eosinophils and basophils, will thus expand the potential mediator secretory cell population and, in particular, increase the potential for leukotriene generation within the nose, which will contribute to nasal obstruction and rhinorrhoea. This cell accumulation and mediator elaboration contributes to the lesser benefit of H_1 -antihistamines in more severe disease. The airway inflammation along with the recruitment of mast cells onto the epithelial surface accounts for the clinical observation of 'priming', the situation where patients experience more symptoms for equivalent or lower pollen counts after a period of exposure to allergen, as in seasonal allergic rhinitis. It is thus apparent from an understanding of the inflammatory processes which underlie rhinitis that prevention of airway inflammation, with prophylactic therapy, is the optimal approach to control disease expression and that, while having some efficacy, inhibition of individual mediator release or end organ receptor antagonism will not give complete disease control.

References

1. BAINTON DF, FARQUHAR MG. Segregation and packaging of granule enzymes in eosinophilic leucocytes. *J Cell Biol* 1970; 45: 54-73.
2. BASROM R, WACHE M, NACLERIO RM, PIPKORN U, GALLI SJ, LICHTENSTEIN LM. Basophil influx occurs after nasal allergen challenge: effects of topical corticosteroid pretreatment. *J Allergy Clin Immunol* 1988; 81: 580-9.
3. BENTLEY AM, JACOBSON MR, CUMBERWORTH B, et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol* 1992; 89: 821-9.
4. BRADDING P, FEATHER IH, WILSON S, BARDIN P, HOLGATE ST, HOWARTH PH. Immunolocalisation of cytokines in the nasal mucosa of normal and perennial rhinitis subjects: the mast cell as a source of IL-4, IL-5 and IL-6 in human allergic inflammation. *J Immunol* 1993; 151: 3853-65.
5. BRADDING P, FEATHER IH, WILSON S, HOLGATE ST, HOWARTH PH. The effects of seasonal exposure to allergic nasal cytokine immunoreactivity and its modulation by fluticasone propionate. *Thorax* 1993; 48: 1059.
6. BRADDING P, MEDIWAKE R, FEATHER IH, et al. $TNF\alpha$ is localised to nasal mucosal mast cells and is released in acute allergic rhinitis. *Clin Exp Allergy* 1995 (in press).
7. BRUNNER T, HEUSSER CH, DAHINDEM CA. Human peripheral blood basophils primed by interleukin-3 (IL-3) produce IL-4 in response to immunoglobulin E receptor stimulation. *J Exp Med* 1993; 177: 605-11.
8. CALDERON MA, LOZEWICZ S, PRIOR A, JORDAN S, TRIGG CJ, DAVIES RJ. Lymphocyte infiltration and thickness of the nasal mucus membrane in perennial and seasonal allergic rhinitis. *J Allergy Clin Immunol* 1994; 93: 635-43.
9. CHARANCE M, HERBETH B, KAUFFMAN F. Seasonal patterns of circulating basophils. *Int Arch Allergy Appl Immunol* 1988; 86: 462-4.
10. DONNELLY A, GLASS M, MULLER B, et al. Leukotriene D_4 (LTD_4) antagonist ICI 204,219 relieves ragweed allergic rhinitis symptoms. *J Allergy Clin Immunol* 1993; 91: 259.
11. DURHAM SR, YING S, VARNEY VA, et al. Cytokine messenger RNA expression of IL-3, IL-4, IL-5 and granulocyte/macrophage colony-stimulating factor in the nasal mucosa after local allergen provocation: relationship to tissue eosinophilia. *J Immunol* 1992; 148: 2390-4.
12. ELMEDAL B, BJERKE T, RENDIGER N, MARKVARDSEN P, NIELSEN S, SCHIOTZ PO. IL-8 is produced and prestored in human blood basophils. *Allergy* 1993; 16: 2861.
13. ENERBACK L, PIPKORN U, OLAFSSON A. Intraepithelial migration of nasal mucosal mast cells in hay fever. Ultrastructural observations. *Int Arch Allergy Appl Immunol* 1986; 88: 289-97.
14. FOKKENS WJ, RIJNTES E, BROOM TLM, MULDER PGH. Fluctuation of the number of CD-1 (T6)-positive dendritic cells, presumably Langerhans cells, in the nasal mucosa of patients with an isolated grass-pollen allergy before, during and after the grass pollen season. *J Allergy Clin Immunol* 1989; 84: 39-43.
15. HARTMAN K, ZUBERBIER T, LIPPERT U, CZURNELAKI BM. In-vitro migratory response of human mast cells towards zymosan-activated serum and interleukins. *J Inv Derm* 1994; 718: 618A.
16. HATTORI R, HAMILTON RK, FRIGATES RD, McEVER RP, SIMS PJ. Stimulated secretion of endothelial von Willebrand factor is accompanied by rapid redistribution to the cell surface of intracellular granule membrane protein GMP-140. *J Biol Chem* 1989; 264: 7768-71.
17. HOWARTH PH. Allergic rhinitis: a rational choice of treatment. *Resp Med* 1989; 83: 179-88.
18. HOWARTH PH. Lipid mediators and allergic rhinitis. In: ROBINSON C (ed.). *Lipid Mediators in Allergic Diseases of the Respiratory Tract*. CRC Press 1993, 109-19.
19. HOWARTH PH, BRADDING P, QUINT D, REDINGTON AE, HOLGATE ST. Cytokines and airway inflammation. In: CHIGNARD M, PRETOLANI M, PRENESTO P, VARGAFTIG B (eds). *Cells and cytokines in lung inflammation 1993*. Ann New York Acad Sci 1994; 725: 69-82.
20. HOWARTH PH, HARRISON K, LAU LCK, DUBE L, COHN J. The influence of the 5-lipoxygenase inhibitor A-78773 on the nasal response to allergen in rhinitis. *J Allergy Clin Immunol* 1993; 93: 297A.
21. HOWARTH PH, HOLGATE ST. Comparative trial of two non-sedative H_1 -antihistamines terfenadine and astemizole for hay fever. *Thorax* 1984; 39: 668-72.
22. KIRSCHENBAUM AS, KESSLER SW, GOTT JP, METCALFE DD. Demonstration of the origin of human mast cells from CD34 + bone marrow progenitor cells. *J Immunol* 1991; 146: 1410-5.
23. KNAPP HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990; 327: 1745.
24. LOPEZ AF, SANDERSON CJ, GAMBLE JF, CAMPBELL HD, YOUNG IS, VADAS MA. Recombinant human interleukin 5 is a selective activator of human eosinophil function. *J Exp Med* 1988; 167: 219-24.
25. MONTEFORT S, HOLGATE ST, HOWARTH PH. Leucocyte-endothelial adhesion molecules and their role in bronchial asthma and allergic rhinitis. *Eur Resp J* 1993; 6: 1044-54.
26. MOSSMAN TR, COFFMAN RL. TH_1 and TH_2 cells: different patterns of lymphokine secretion lead to different functional properties. *Ann Rev Immunol* 1989; 7: 145-64.
27. MYGIND N, SECLER C, KIRKEGAARD J. Role of histamine and antihistamines in the nose. *Eur J Respir Dis* 1993; 64(Suppl. 128): 16-20.
28. OKUDA M, OTSUKA H, KAWABORI S. Studies on nasal surface basophilic cells. *Ann Allergy* 1985; 54: 69.
29. OTSUKA H, DENBURG JA, DOLOVITVH J, et al. Heterogeneity of instachromatic cells in human nose: significance of

- mucosal mast cells. *J Allergy Clin Immunol* 1985; 76: 695.
30. OWEN JR WF, ROTHENBERG ME, SILBERSTEIN DS, et al. Regulation of human eosinophil viability, density and function by granulocyte/macrophage colony-stimulating factor in the presence of 3T3 fibroblasts. *J Exp Med* 1987; 186: 129-41.
31. PETERS MS, RODRIGUEZ M, GLEICH GJ. Localisation of human eosinophil granules major basic protein, eosinophil cationic protein and eosinophil derived neurotoxin by immunoelectron microscopy. *Lab Invest* 1986; 54: 656-62.
32. ROTHENBERG ME, OWEN JR WF, SILBERSTEIN DS, et al. Human eosinophils have prolonged survival, enhanced functional properties and become hypodense when exposed to interleukin-3. *J Clin Invest* 1988; 81: 1986-92.
33. VIEGAS M, GOMEZ E, BROOKS J, DAVIES RJ. The effect of the pollen season on nasal mast cell numbers. *Br Med J* 1987; 294: 414.
34. WILSON SJ, LAU LCK, HOWARTH PH. Mediator and cellular events in naturally occurring seasonal allergic rhinitis. *Clin Exp Allergy* 1994; 24: 977A.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.