Current data overwhelmingly document the existence of a worldwide asthma epidemic, although individual studies remain controversial. The epidemic is thought to involve primarily persons with allergic asthma, and many diverse theories, based on an immunopathologic understanding of disease, have recently emerged to explain this involvement. In the context of recent insights into the immune basis of experimental asthma, we discuss in this review the leading asthma epidemic theories, including a new theory based on inhaled environmental proteases. Although no single theory may yet be fully embraced, there exists substantial hope that a unifying mechanism for the epidemic will be revealed through additional research. Key words: adjuvant, air pollution, aspirin, asthma, costimulatory molecule, dust mite, helminth, immunoglobulin E, protease, T_{H}2 cell.

http://ehpnet1.niehs.nih.gov/docs/2002/suppl-4/553-556kheradmand/abstract.html

Evidence has accumulated over the past 30 years indicating that the allergic syndromes, especially asthma, have increased in prevalence and severity (1). These trends have, for perhaps the first time, transformed what was formerly a relatively inconspicuous ailment into an epidemic illness of significant public health concern. In addition to chronic disability and negative impact on quality of life, the economic burden of asthma is now substantial (2,3). Perhaps most disturbing, these alarming asthma statistics are not confined to the United States but are reflected throughout the industrialized world (4), creating an unprecedented medical conundrum. Legitimate doubt as to the existence of the asthma epidemic may be raised on the basis of supporting epidemiologic data. Many studies documenting a rise in disease prevalence are based on patient questionnaires, which are subject to considerable bias. Despite this and other methodologic objections, an increase in asthma prevalence has been consistently documented throughout the world—indeed, there appear to be no studies that refute this trend (4). Further, asthma mortality data, which provide a far more objective end point than prevalence statistics, are also increasing in the same countries where prevalence is rising (5). Thus, despite reasonable objections to the methodology of many supporting studies, current literature overwhelmingly supports the existence of a true asthma epidemic.

In this review we consider the potential role the environment in mediating the epidemic of asthma. We first consider the immune mechanisms that may underlie the causes of asthma and subsequently the major theories that have recently emerged to explain the epidemic.

The Immune Response and Asthma

Many of the asthma epidemic theories incorporate recent insights into the immunopathologic basis of allergic inflammation. Inflammatory responses are complex, involving numerous cells and secreted products that activate a diverse range of host-protective responses. However, partially compensating for this complexity is the redundancy of immune responses, in which the same immunomodulatory mechanisms are activated in response to many different inflammatory insults. This redundancy is such that much of immunity can be organized into two principal responses called T-helper type 1 (TH1) and type 2 (TH2) cells, which secrete interferon gamma and other cytokines, confer protection against pathogens such as bacteria. In contrast, TH2 cells, which secrete cytokines such as interleukin (IL) 4, IL-5, and IL-13, control other large pathogens such as parasitic worms. Both T-cell types are mutually antagonistic and are rarely found together at the same inflammatory site. T-helper cells are usually protective, of course, but they are also associated with maladaptive responses. TH2 cells especially are thought to contribute to allergic diseases including asthma and allergic rhinitis (6,7) by secreting cytokines such as IL-4 and IL-13 (8) or by promoting secretion of allergenic products such as immunoglobulin E (IgE) (9).

Theories of the Asthma Epidemic

The major theories regarding the asthma epidemic propose that environmental changes create a relative imbalance in TH1 and TH2 cells and/or an overall increase in allergenic products. Yet, despite what appears to be a unifying pathophysiologic framework, extremely diverse theories have emerged. Under the following subheadings, we discuss the evidence that supports and refutes these theories and indicate where future studies might be helpful in clarifying unresolved issues.

Infection

Through complex means, a variety of infections are believed to influence the expression of asthma. For example, a relative deficiency in TH1-inducing infections or inflammations involving the upper and lower airway may lead to excess TH2 activation in the airway (10,11). Presumably, low-grade infections with TH1-dependent pathogens such as Mycobacterium tuberculosis, the causative agent of human tuberculosis, and related organisms antagonize TH2 cells and thereby suppress diseases such as asthma. Experimental support for this theory exists, as shown by the ability of mycobacteria such as M. tuberculosis to suppress allergic lung inflammation (12,13). In addition, certain bacterial products such as DNA (unmethylated CpG motifs) are sufficient to block or reverse experimental allergic lung disease (14). However, the negative statistical association of tuberculin reactivity (a skin test–based index of exposure to M. tuberculosis) with subsequent atopic disease in Japanese schoolchildren (10) has not been confirmed in other populations (15). Further, although mycobacterial diseases such as tuberculosis have been declining in importance for a century or more (16), it is not clear why this has resulted in increased allergic disease only in the last 30 years. Thus, while mycobacteria and their products clearly antagonize allergic lung inflammation, the evidence that exposure to these organisms has changed sufficiently to account for the epidemic is inconclusive.

Other infections are proposed to contribute to allergic disease, including chronic infections with the bacterium Chlamydia pneumoniae, respiratory viruses, parasites such as Toxocara canis, and fungi, including Aspergillus species. In all respects, these organisms differ markedly from each other and probably contribute in very different ways to allergic disease. Parasites and fungi likely cause disease directly, as extracts from these organisms are powerful allergens (17,18). Despite their long associations with asthma, the mechanisms by which C. pneumoniae and viruses may mediate allergic disease are not clear. However, in an allergic setting, an inappropriate TH2 immune response may be generated against...
any respiratory tract pathogen, delaying clearance of the infection and effectively converting the organism into a self-replicating allergen (19). In accord with a recent study, eradication of the organism under these circumstances may not necessarily resolve the underlying asthma (20). Thus, some infections may exacerbate existing disease, but no studies yet demonstrate that infections are intrinsic causes of asthma, and they cannot currently be implicated in the asthma epidemic.

A related theory proposes an entirely different etiology for allergic disease—that lack of $T_{H2}$-dependent pathogens, especially intestinal helminths, creates an imbalance of polyclonal compared with specific IgE. Lack of exposure to parasites is proposed to lead to increased specific IgE, which, if not countered by the effects of polyclonal antibody, becomes extremely efficient at triggering allergic disease (21). Parasite infestations have clearly declined in Western societies, but like tuberculosis, this trend was all but complete long before the asthma epidemic began. Further, additional data suggest that asthma rates may not differ significantly between urban, parasite-free groups and rural, heavily parasitized populations, suggesting that factors other than parasites themselves may be more important (22).

Another serious obstacle with this hypothesis is the clinical evidence that elimination of virtually all IgE, using modified neutralizing antibodies, has little effect on clinically relevant physiologic end points in asthma patients (23).

The Hygiene Hypothesis

This theory also implicates a variety of infections or microbial products (or lack thereof) in mediating immune bias in favor of $T_{H2}$ reactivity and predisposition to asthma. An important additional tenet of this theory is that such exaggerated $T_{H2}$ conditioning occurs primarily in the perinatal period, involving the aberrant tendency of the neonate to preferentially mount $T_{H2}$ immunity. With maturity, the immune system adopts a more balanced activation profile characterized by both $T_{H1}$ and $T_{H2}$ responses (24). For unclear reasons, genetically predisposed individuals retain their $T_{H2}$ predisposition, potentially resulting in childhood asthma that carries over into adulthood (25). A critical assumption of this theory is that maternally acquired allergens are carried across the placenta and against which the fetus begins making $T_{H2}$ responses (26). Thus, the fetus is literally born allergic. Genetic factors are acknowledged to play a role, but these are presumably secondary to primary alterations in exposure to the various infectious agents or their products discussed earlier. In addition, hyperactive intrauterine mechanisms that attempt to limit the embryotoxic effects of $T_{H1}$ cytokines are also thought to play a role (25).

In addition to the difficulties in understanding how infections may contribute to the asthma epidemic, several independent observations challenge the assumption that the neonatal immune response is $T_{H2}$ biased and therefore predisposed to asthma. The greater susceptibility of neonates to infections, rather than indicative of such an abnormality, more likely reflects simply a normal one that has yet to develop memory. Further, whereas some innate components of immunity such as neutrophils may be truly immature or only partially functional in the neonate (27), neonatal T cells actually produce both $T_{H1}$ and $T_{H2}$ cytokines comparable to their adult counterparts (28). Also, rather than inducing ineffective immune responses, as some reports have implied, immunization of newborns or even fetal baboons with common antigens produces normal, competent antibody responses (29). Thus, there are few data to support the existence of an intrinsic, neonatal T-cell defect that might underlie a predisposition to allergy. It is further difficult to understand how antigens would accumulate in the maternal blood in sufficient quantity to cross over to the fetus to induce sensitization. Neonatal T cells do react to a variety of foodborne and other environmental antigens, but this appears to be an extremely common and perhaps ubiquitous feature of pregnancy, and therefore one that is unlikely to participate in the asthma epidemic (30,31). However, other mechanisms by which the neonate might acquire an allergic predisposition have been suggested. One provocative concept is that maternal-derived amniotic cytokines bias the developing fetal immune system toward $T_{H2}$ reactivity (32).

The maternal–fetal relationship is clearly complex and one that may have important consequences for allergic reactivity and asthma in early and late life. Maternal intrauterine factors may ultimately be shown to be important in determining allergic reactivity of the newborn, but it is unclear how such mechanisms can account for the asthma epidemic. It seems more likely at this time that an environmental factor simultaneously affecting the mother and the newborn may largely account for concomitant maternal and neonatal allergic sensitization and asthma, and perhaps the asthma epidemic as well.

Air Pollution

Certain air pollutants are associated with respiratory allergy and have been shown experimentally to modify $T_{H2}$ function and IgE secretion. Tobacco smoke acts as an immunologic adjuvant, promoting antigen-specific IgE production in sensitized mice (33). More general air pollutants may also influence the severity of allergic disease. Diesel exhaust particles (DEP) augment nasal cytokine production and increase production of allergen-specific IgE in humans (34,35). In mice, DEP exacerbate antigen-induced experimental allergic airway disease but are incapable of inducing disease independent of antigen (36). Therefore, like certain infectious etiologies, diverse hydrocarbon-based air pollutants may exacerbate existing allergic disease, but there is no evidence yet that they give rise to new cases, and their role in the asthma epidemic consequently remains to be established.

Aspirin Use

The use of aspirin in pediatric patients began to decline about 20 years ago at approximately the time when the childhood asthma epidemic began. Aspirin, unlike its substitute acetaminophen, blocks prostaglandin E$_2$ (PGE$_2$) synthesis by inhibiting the enzyme cyclooxygenase-2. PGE$_2$ in turn promotes $T_{H2}$ development and $T_{H2}$-like effects. The switch away from aspirin to acetaminophen in children, the result of aspirin’s association with the devastating neurologic illness Reye’s syndrome, therefore, resulted in a population with higher average PGE$_2$ levels and potentially greater susceptibility to allergic diseases such as asthma (37). Arguing against this provocative theory is that the asthma epidemic also involves adults who use aspirin. Further, other cyclooxygenase inhibitors, including nonsteroidal anti-inflammatory drugs such as ibuprofen, are commonly used in children and do not induce Reye’s syndrome. Finally, no independent association of acetaminophen use with the asthma epidemic in children has yet been determined.

Exercise and Obesity

This theory postulates that decreased physical activity and increased obesity, increasingly common characteristics of American children, might partly be responsible for the epidemic (38). These same changes are associated with epidemic increases in other lifestyle-related illnesses such as type 2 diabetes mellitus, suggesting a possible common etiology between childhood asthma and diabetes (39). Although intriguing, no studies have yet provided insight into how asthma might arise with decreased activity, obesity, or diabetes. However, the evolving lifestyle of the Westernized child probably also includes greater amounts of time spent indoors, perhaps resulting in increased exposure to an indoor pollutant that induces asthma.
Environmental Proteases

There exists a consistent biochemical connection between the allergens associated with asthma and other organisms that activate Th2 cells and allergic mechanisms. The larvae of intestinal parasites secrete many products, but of particular interest are proteases, which they require presumably to burrow through host connective tissue that otherwise impedes their visceral migrations (40). As secreted products common to virtually all intestinal helminths, proteases are therefore logical triggers for immune, and especially Th2, activation. Other organisms associated with allergic reactivity and asthma also possess protease activity. The pollen of many plant species contains proteases required for fertilization. Because they cannot take food internally, fungi, which are strongly associated with asthmalike diseases such as allergic bronchopulmonary aspergillosis (41), must secrete proteases to digest organic matter. Further, the house dust mite, the organism serologically most commonly linked with asthma, is thought to shed a variety of asthmagenic proteins, but the most important of these are also proteases (42). Finally, the major cat allergen identified from the serum of asthma patients, Fel d I, is, or is associated with, a protease (43).

The strong association of proteases and clinically relevant allergens suggests a testable hypothesis regarding the role of these enzymes in asthma. This theory predicts that proteases act as immunologic adjuvants or costimulatory molecules, directing Th2 activation without necessarily serving as antigens themselves. Such a nonimmunogenic, adjuvant role of proteases would be required to explain the lack of serologically identifiable protease in other major human allergens. Even if shown, a Th2 adjuvant role for proteases does not by itself explain the asthma epidemic. Among other tasks, a change in overall accumulation and exposure to environmental proteases would have to be documented around the time at which the epidemic began. Surprisingly, such potential sources were originally identified many years ago and include laundry detergent proteases that proved to be risk factors for asthma in detergent factory workers (44,45). It is also striking that the first documentation of these epidemics occurred immediately before the global asthma epidemic, at a time when worldwide distribution of enzyme-containing cleaning products was just beginning. What remains unclear, however, is whether industrially derived proteases have accumulated worldwide within the populations experiencing the asthma epidemic. Mechanistic insight into how proteases activate Th2 cells is also lacking, although recent studies have begun to address this issue. For example, proteases may facilitate antigen presentation through the airway by disrupting airway tight junctions (46) and may exacerbate existing disease by disrupting IgE receptors (42).

Conclusions

A summary of the major theories deployed recently to account for the asthma epidemic, including the major arguments supporting and refuting them, is presented in Table 1. What most clearly emerges from this summary is a lack of experimental evidence that strongly supports any of the proposed hypotheses. Several environmental perturbations have the potential to modify immune function, particularly regarding Th2 activation, in ways that may exacerbate preexisting asthma. Thus, the adjuvant-like effects of air pollution–based hydrocarbons and the relative lack of PGE2 due to decreased aspirin use may similarly increase production of IgE and Th1 cytokines, thereby aggravating preexisting asthma. However, such agonist effects on disease are undocumented for any actual population of asthmatics. The other mechanisms are less clearly associated with immune function but are intriguing, primarily because of their statistical/epidemiologic associations with asthma and/or the asthma epidemic. The several epidemiologic links between environmental proteases and asthma are particularly interesting, but available data only weakly link proteases to immune function. Maternal–fetal interactions that may influence neonatal immune function also have intriguing connections to allergic disease, but the hygiene hypothesis is significantly undermined by conflicting data. Finally, environmental perturbations must be shown to induce new cases of disease before they can account for the asthma epidemic. Strikingly, none of the proposed mechanisms has yet been shown to be etiologic in this most important regard.

Future studies on the causes of the asthma epidemic will require new experimental and epidemiologic approaches and the expertise of diverse scientists. The results of these investigations are difficult to predict. None of the current epidemic theories can be dismissed on the basis of available data, but it is unlikely that all will be found to have merit after further study. A likely outcome of future research is that a more inclusive epidemic theory will emerge, one that incorporates features of some of the current hypotheses as well as wholly new concepts. A multifactorial etiology of the epidemic appears likely at this time, but a single major environmental factor, perhaps one of those considered above, may ultimately be shown to be most important. Future investigations will be valued not merely as academic exercises but as a means for resolving the asthma epidemic and improving respiratory health worldwide.

Table 1. Theories of the asthma epidemic.

| Theory          | Arguments for                                                                 | Arguments against                                                      |
|-----------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Infection       | Decrease in T1-1-inducing infections facilitates Th2 activation               | Conflicting epidemiologic data; lack of supporting experimental data   |
|                 | Respiratory tract pathogens directly activate Th2 cells                      | Lack of supporting experimental data                                   |
|                 | Decline in helminth infestations results in more antigen-specific IgE        | Recent data do not support a major role for IgE in asthma; conflicting |
|                 |                                                                               | association of parasites with asthma                                    |
| Hygiene         | Decrease in T1-1-inducing microbial products worldwide leads to excess Th2  | Epidemiologic data are conflicting; lack of supporting experimental   |
|                 | activation                                                                     | data; Conflicting data about the true predisposition of the neonatal   |
|                 | Neonates intrinsically predisposed to Th2 responses                           | immune system                                                          |
| Air pollution   | Hydrocarbons in air pollution can act as Th2 adjuvants and trigger asthma     | Air pollution has declined during the asthma epidemic; lack of evidence  |
| Aspirin         |                                                               | that hydrocarbons actually cause allergic disease                       |
| Diet/exercise   | Decreased exercise, obesity, and diabetes are statistically associated with   | The asthma epidemic also involves adults who use aspirin; children take |
|                 | symptoms of asthma                                                            | other cyclooxygenase inhibitors                                       |
| Protease        | Protease activity a consistent feature of many allergens                     | No epidemic associations with noncyclooxygenase-blocking aspirin        |
|                 | Proteases linked to occupational asthma                                       | substitutes (acetaminophen)                                            |
|                 | Environmental sources of protease have increased during the asthma epidemic   | Experimental data supporting these associations are lacking             |

Asthma Occurrence • Contributions to the allergic asthma epidemic

Environmental Health Perspectives • VOLUME 110 | SUPPLEMENT 4 | AUGUST 2002 555
REFERENCES AND NOTES

1. Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, Ball LB, Jack E, Kang DS. Surveillance for asthma—United States, 1960-1995. Morb Mortal Wkly Rep Surveill Summ 47:1–7 (1998).
2. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. N Engl J Med 326:662–666 (1992).
3. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. J Allergy Clin Immunol 104:3–9 (2000).
4. Grant EN, Wagner R, Weiss KB. Observations on emerging patterns of asthma in our society. J Allergy Clin Immunol 104:51–59 (1999).
5. Beasley R, Pearce N, Crane J. International trends in asthma mortality. In: The Rising Trends In Asthma. Ciba Foundation Symposium 206 (Chadwick D, Cardow G, eds). Chichester:John Wiley & Sons Ltd., 1997;140–156.
6. Robinson DS, Hamid Q, Ying S, Tsicopoulos A, Barkans J, Bentley AM, Corrigan C, Durham SR, Kay AB. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 329:283–290 (1992).
7. Del Prete G, De Carlo M, D’Ellios MM, Maestrelli P, Ricci M, Fabbri L, Romagnani S. Allergen exposure induces the activation of allergen-specific Tc2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol 23:1445–1449 (1993).
8. Corry DB. L13 in asthma: home at last. Curr Opin Immunol 19:1484–1495 (2001).
9. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature 383:787–793 (1996).
10. Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The reverse association between tuberculin responses and atopic disease. Science 275:77–79 (1997).
11. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. Clin Exp Allergy 30:201–208 (2000).
12. Koh YI, Choi IS, Kim YW. BCG infection in allergen-presensitized rats suppresses Tc2 immune response and prevents the development of allergic asthmatic reaction. J Clin Immunol 21:51–59 (2001).
13. Nahori MA, Lagranderie M, Lefort J, Waldschmidt TJ, Businga TR, Thourou C, Joseph D, Lefort J, Thourou C, Joseph D, Koh YI, Choi IS, Kim YW. BCG infection in allergen-presensitized rats suppresses Tc2 immune response and prevents the development of allergic asthmatic reaction. J Clin Immunol 21:51–59 (2001).
14. Levy O, Martin S, Eichenwald E, Ganz T, Valore E, Carroll D, Corrigan C, Durham SR, Kay AB. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 329:283–290 (1992).
15. Del Prete G, De Carlo M, D’Ellios MM, Maestrelli P, Ricci M, Fabbri L, Romagnani S. Allergen exposure induces the activation of allergen-specific Tc2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol 23:1445–1449 (1993).
16. Corry DB. L13 in asthma: home at last. Curr Opin Immunol 19:1484–1495 (2001).
17. Koh YI, Choi IS, Kim YW. BCG infection in allergen-presensitized rats suppresses Tc2 immune response and prevents the development of allergic asthmatic reaction. J Clin Immunol 21:51–59 (2001).
18. Nahori MA, Lagranderie M, Lefort J, Waldschmidt TJ, Businga TR, Thourou C, Joseph D, Koh YI, Choi IS, Kim YW. BCG infection in allergen-presensitized rats suppresses Tc2 immune response and prevents the development of allergic asthmatic reaction. J Clin Immunol 21:51–59 (2001).
19. Levy O, Martin S, Eichenwald E, Ganz T, Valore E, Carroll D, Corrigan C, Durham SR, Kay AB. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 329:283–290 (1992).
20. Del Prete G, De Carlo M, D’Ellios MM, Maestrelli P, Ricci M, Fabbri L, Romagnani S. Allergen exposure induces the activation of allergen-specific Tc2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol 23:1445–1449 (1993).
21. Corry DB. L13 in asthma: home at last. Curr Opin Immunol 19:1484–1495 (2001).
22. Koh YI, Choi IS, Kim YW. BCG infection in allergen-presensitized rats suppresses Tc2 immune response and prevents the development of allergic asthmatic reaction. J Clin Immunol 21:51–59 (2001).
23. Levy O, Martin S, Eichenwald E, Ganz T, Valore E, Carroll D, Corrigan C, Durham SR, Kay AB. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 329:283–290 (1992).
24. Del Prete G, De Carlo M, D’Ellios MM, Maestrelli P, Ricci M, Fabbri L, Romagnani S. Allergen exposure induces the activation of allergen-specific Tc2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol 23:1445–1449 (1993).
25. Corry DB. L13 in asthma: home at last. Curr Opin Immunol 19:1484–1495 (2001).
26. Koh YI, Choi IS, Kim YW. BCG infection in allergen-presensitized rats suppresses Tc2 immune response and prevents the development of allergic asthmatic reaction. J Clin Immunol 21:51–59 (2001).
27. Levy O, Martin S, Eichenwald E, Ganz T, Valore E, Carroll D, Corrigan C, Durham SR, Kay AB. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 329:283–290 (1992).
28. Del Prete G, De Carlo M, D’Ellios MM, Maestrelli P, Ricci M, Fabbri L, Romagnani S. Allergen exposure induces the activation of allergen-specific Tc2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol 23:1445–1449 (1993).
29. Corry DB. L13 in asthma: home at last. Curr Opin Immunol 19:1484–1495 (2001).
30. Koh YI, Choi IS, Kim YW. BCG infection in allergen-presensitized rats suppresses Tc2 immune response and prevents the development of allergic asthmatic reaction. J Clin Immunol 21:51–59 (2001).
31. Levy O, Martin S, Eichenwald E, Ganz T, Valore E, Carroll D, Corrigan C, Durham SR, Kay AB. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med 329:283–290 (1992).
32. Del Prete G, De Carlo M, D’Ellios MM, Maestrelli P, Ricci M, Fabbri L, Romagnani S. Allergen exposure induces the activation of allergen-specific Tc2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol 23:1445–1449 (1993).
33. Corry DB. L13 in asthma: home at last. Curr Opin Immunol 19:1484–1495 (2001).