Clinical and Therapeutic Significance of Patterns of Allergic Reactions of the Lungs to Extrinsic Agents

The 1977 J. Burns Amberson Lecture¹ ²

J. PEPYS

In the analysis of respiratory tract reactions, much emphasis is placed on possible allergic mechanisms. The term “allergy” was introduced by von Pirquet in 1906 (1) to describe the profound biologic transformation of the intact organism resulting from adequate exposure to viable and nonviable agents, so that re-exposure, often to small, indeed minute, and apparently innocuous amounts of extrinsic agents, elicits a different sort of reaction. This can be summarized as the “acquired,” “specific,” “altered capacity to react,” the nature of the reaction depending on the particular allergic mechanisms.

The traditional criteria for regarding a reaction as allergic, with or without supporting immunologic evidence, are as follows.

1. There is history of previous exposure—without symptoms, namely, the period of sensitization. This is influenced by factors such as the route, dosage, and duration of exposure.
2. The degree of specific sensitivity tends to increase with further exposure.
3. A proportion, usually low, of exposed subjects are affected. This concerns elicitation of reactions, usually by dosages far less than those capable of sensitization, which in turn are usually far less than those capable of irritation. The latter are likely to affect most exposed subjects, unrelated to previous exposure.

In the 1950s, attention was being paid to the fact that, whereas the various types of allergy have characteristic features, they may, and often do, coexist, depending for their elicitation on appropriate tests with the appropriate antigenic components. They may even be interdependent, as in the Type III reaction, in which a Type I immediate reaction plays an introductory role in the development of the later reaction (2–4). Hypersensitivity to Mycobacterium tuberculosis (5), to dermatophyte fungi (6), and to Candida albicans (7) are classic examples of the coexistence of different types of allergy.

Type I and Type III allergic reactions can be elicited by both polysaccharide and protein antigens. Type I reactions may be mediated by, mainly, long-term sensitizing heat-labile antibody, reagin, IgE, or by short-term sensitizing IgG antibody, or perhaps by both acting together. Type IV allergic reactions appear to be confined to protein antigens.

The presence of very high titers of precipitating antibodies to polysaccharide antigens, for example, of M. tuberculosis in infected guinea pigs, stimulated my interest in a search in man for precipitins to common environmental allergens. This was greatly facilitated by the introduction of agar-gel precipitation tests (8, 9). Most attention was being given to Type I and Type IV allergies in man at the time, with interest in Type III allergy waxing and waning with the use of heterologous antisera, later to be supplanted in many instances by chemotherapy and antimicrobial drug treatments. My clinical and research interests were thus broadened to include the study of Types I, III, and IV allergies.
and assessment of their role or roles, if any, in allergic respiratory disease. The working assumption was that if the antibodies were present for the mediation of the appropriate type or types of allergic reaction, such reactions might be expected wherever the allergen combined with the antibodies, this in turn being reflected in the nature of the clinical manifestations.

**Factors Influencing Allergic Respiratory Disease to Extrinsic Agents**

Three main factors, each complex and yet due to be unraveled in greater detail, are concerned in the production by extrinsic agents of different forms of allergic respiratory disease, such as asthma, pulmonary eosinophilia, and extrinsic allergic alveolitis, the latter two comprising “hypersensitivity pneumonitis” in North American terminology.

*Immunologic reactivity of the subject.* The genetic bases for the capacities of persons to be sensitized by comparable exposure, with the production of different types of antibodies and of allergic reactions, are only beginning to be determined. They are likely to play an important part in clinical management.

At present, the main example, highly relevant to allergic respiratory disease, is the classification into atopic and nonatopic. The characteristic immunologic feature of “atopy” is the genetically determined capacity to produce specific IgE antibodies readily in response to the immunologic challenge presented by the ordinary, usually limited, exposures in daily life to common environmental allergens (10).

Skin prick tests with a battery of 3 or 4 common allergens suffice to identify most atopic subjects in the United Kingdom (11). Approximately 30 per cent of the UK population give immediate reactions to one or more, irrespective of the presence or absence of clinical manifestations. Such information can be of use in practice; for example, atopic subjects so defined show a higher incidence and far more rapid Type I sensitization than nonatopic subjects to occupational agents, such as the enzymes of *Bacillus subtilis* (12, 13), and the complex salts of platinum (14, and Webster, L: Personal communication).

The probability of genetic factors in precipitin production is suggested by the different incidences of serum sickness after injection of increasing dosages of heterologous serum reported in the early years of this century. Genetic studies of subjects with precipitins after inhalation exposure are needed. Some suggestion of a genetic background possibly related to this is the report of a significantly higher incidence of HL-A 8 in subjects with farmer’s lung.

Immunologic reactivity of the subject may also have a bearing on responses, such as the affinity or avidity of antibody produced and the capacity of complement to modify the solubilization and handling of immune complexes (15). These are also likely to influence the outcome of sensitization and could, for example, clarify questions such as the presence of antibodies associated with disease in some subjects and not in others.

*Nature of the extrinsic agent.* The physical, chemical, and biologic properties of the causal agents can all influence their capacity to sensitize and to elicit reactions. Some examples recognized at present are demonstrated by the influence of particle size on penetration into the respiratory tract; for example, the spores of *M. faeni*, which are 1 to 2 μm in diameter, can reach and be retained in the peripheral gas-exchanging tissues, as in extrinsic allergic alveolitis; chains of spores of *Aspergillus fumigatus* 10 to 12 μm in length are likely to lodge in the proximal bronchi, as in allergic bronchopulmonary aspergillosis. The size of the antigen molecules is important (many allergens have molecular weights of 20,000 to 40,000 daltons), as is the number of these molecules, as they usually represent minor quantitative constituents in the causal source. In mice, for example, repeated minute dosages are the most effective in eliciting persistent high avidity IgE responses, suggesting recognition of only one of the multiple antigen determinant sites in a mixture (16). The capacity of chemical agents of small molecular size to act as haptons and to combine with the appropriate proteins or perhaps other chemical carriers can also determine their allergenicity. For example, there is a direct relationship of allergenicity of the complex

<table>
<thead>
<tr>
<th>TABLE 1 IMMEDIATE ASTHMATIC REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of reaction (min)</td>
</tr>
<tr>
<td>Maximal reaction (10-15 min)</td>
</tr>
<tr>
<td>Duration of reaction (1-2 hours)</td>
</tr>
<tr>
<td>Immunochemistry</td>
</tr>
<tr>
<td>IgE</td>
</tr>
<tr>
<td>STS-IgG</td>
</tr>
<tr>
<td>Bronchodilator</td>
</tr>
<tr>
<td>+</td>
</tr>
<tr>
<td>Not known</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
</tr>
<tr>
<td>+</td>
</tr>
<tr>
<td>0 (?</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Not known</td>
</tr>
</tbody>
</table>
platinum salts to the number of leaving halide ligands, as demonstrated by prick tests in sensitized refinery workers (17). Biologic properties such as the capacity to grow in the respiratory tract of *A. fumigatus* and possibly *M. faeni* can have an important effect on the respiratory function. The capacity of fungi and organic dusts, and possibly also of other inhaled agents to activate the C3 component of complement by the alternative pathway (18, 19) may simulate immune complex reactions without the participation of antibodies. The macrophage activation that results from the C3 activation (20) could also enhance sensitization and antibody responses.

**Circumstances of exposure.** The way in which the subject meets the extrinsic agent is relevant to sensitization on the one hand and to elicitation of reactions on the other. Thus, ordinary environmental exposure suffices to induce production of specific IgE antibody in atopic subjects. More intensive exposure is needed to induce precipitin production both in nonatopic and atopic subjects, and it may also induce IgE production as well in subjects classified as nonatopic. Little is known about the amounts and duration of exposure required for sensitization by the many different allergens. In already sensitized subjects the manner in which the antigen is met can exert a profound influence on the initiation and clinical presentation of the disorder.

These three basic factors, namely immunologic reactivity, nature of the agent, and circumstances of exposure are the main themes of this presentation.

**Clinical Investigation in Allergic Respiratory Disease**

The respiratory tract is readily accessible for direct challenge and measurement of functional changes in provocation tests. These tests are of considerable value for precise etiologic diagnosis, often otherwise unattainable. The test results are furthermore most informative, revealing reactions in different parts of the respiratory tract and also different patterns of reaction, and provide an insight into the actions of therapeutic agents, such as the β-adrenergic stimulant bronchodilators, cromolyn sodium, and local and systemic corticosteroids.

**Features of Reactions**

The reactions can be classified in terms of speed of appearance and duration into immediate, nonimmediate, and combinations of these, sometimes with and often without evidence of specific antibodies (tables 1 and 2) (21).

**Bronchial Reactions (Asthma)**

The term “asthma” will be used in the present context in its most widely accepted form, as “airway obstruction reversible spontaneously or by treatment.” Examples will be given of provocation tests (1) with aerosols of allergens, (2) with gaseous chemical emanations, and (3) with chemical dusts, in relation to each of the forms of asthmatic reaction.

**Immediate asthmatic reactions.** Immediate asthmatic reactions to provocation tests can be blocked by cromolyn sodium but not by corticosteroids and are effectively reversed and terminated by inhaled bronchodilators (21).

**Aerosol allergen test.** A recent example of reactions to aerosol allergens that illustrates the analytic etiologic value of provocation testing and its practical consequences is provided by our findings in asthma in workers handling rats and As shown in figure 1, the urine, particularly of the rat, may contain appreciable amounts of serum proteins; in addition, there are small proteins (molecular weight, 20,000 daltons), an α-2-globulin in the rat, and a prealbumin in the mouse, in the urine of male animals. These proteins appear to be the main allergens in our sensitized subjects, many of whom recognized for themselves this particular effect of male animals.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEATURES OF NONIMMEDIATE ASTHMATIC REACTIONS</td>
</tr>
<tr>
<td>Onset</td>
</tr>
<tr>
<td>Maximal reaction</td>
</tr>
<tr>
<td>Duration of reaction</td>
</tr>
<tr>
<td>Bronchodilator</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Immunology</td>
</tr>
</tbody>
</table>

---

575
or did so when their attention was drawn to it. The small urinary proteins give vigorous specific immediate reactions to prick tests, positive radioallergosorbent test (RAST) for specific IgE antibody, and positive inhalation tests (figure 2) with aerosol solutions. Most of the subjects gave negative or weak reactions to extracts of hair and, except for one (figure 3), to the animals’ serum proteins. The inhalation of dust from dried rodent urine may therefore be a source of sensitization to heterologous serum and other proteins. Care is needed to eliminate the urine, and perhaps female animals should be used preferentially, to try to decrease sensitization and/or to prevent reactions.

**Gaseous emanation occupational type test.** An indistinguishable example of an immediate asthmatic reaction to gaseous chemical emanations from simulated occupational type testing is shown in figure 4. There is, at present, little or no immunologic evidence. Exposure to the painting of a 2-part polyurethane varnish/toluene diisocyanate preparation (22) elicited an immediate asthmatic reaction that was blocked by cromolyn sodium, as is the case with immediate asthmatic reactions to common allergens for which immunologic evidence of IgE sensitivity is available. The atmospheric concentration of the toluene diisocyanate in the test chamber capable of eliciting immediate and nonimmediate asthmatic reactions can be less than 0.001 ppm, i.e., less than $10^{-6}$, far less than the irritant concentrations and illustrating the minuteness of eliciting dosages (23). Specific reactions have been elicited with various isocyanate preparations, and some subjects react to several different preparations to which they have been exposed. Comparable test procedures giving low concentrations adjusted for dose-response reactions have been effectively used by other workers.

Another example of an immediate asthmatic reaction to gaseous molecules running into a
nonimmediate one is provided in figure 5, which shows the response to a single natural breath of the emanations from the heating of 1 g of epoxy resin cured with phthalic acid anhydride (24). The presence of specific IgE antibody to a phthalic acid anhydride conjugate with serum protein in a patient giving an immediate asthmatic reaction has been reported (25).

Similar immediate asthmatic reactions have been elicited, some with succeeding nonimmediate reactions, by such tests with other epoxy resins cured with trimellitic acid and triethylene tetramine (24) and with emanations from natural pine resin (colophony), which is widely used as an adhesive and as a bonding agent for soldering materials used extensively in the electronics industry (26).

Chemical dust occupational type test. An example of an immediate asthmatic reaction to a chemical dust is shown in figure 6, in which the subject inhaled for 10 min the dust produced by pouring to and fro a mixture in 1 kg of lactose of 40 mg of a complex platinum salt, in this case ammonium hexachloroplatinate (29). The reaction was blocked by cromolyn sodium.

The exquisitely high allergenicity of some of these materials is shown by positive reactions elicited with an absolute skin prick test dose of $5 \times 10^{-15}$ g or less, i.e., a dose of the order of 100,000 molecules. The platinum salts provide an exceptional example of basic immunochromical information derived from clinical research. Prick tests made in sensitized refinery workers with a wide range of chemically characterized platinum compounds showed that the allergenicity is dependent on the number of chlorine or other halide leaving ligands in the molecule. Information of this sort is not otherwise obtainable at present, except from man, and is indeed rarely available for allergens in general (17).

Nonimmediate asthmatic reactions. Nonimmediate asthmatic reactions to provocation tests are blocked by corticosteroids, can be blocked

---

**Fig. 2.** Immediate asthmatic reaction demonstrated as change in airway resistance (Raw), to inhalation test with mouse prealbumin compared with negative reactions to mouse serum and a control solution.

**Fig. 3.** Comparable immediate asthmatic reactions, demonstrated by change in 1-sec forced expiratory volume (FEV$_1$), to inhalation tests with mouse and rat urine proteins and rat serum, and negative reaction to mouse urine to which the subject had not been exposed.
J. PEPYS
OCCUPATIONAL EXPOSURE TO ISOCYANATE

Fig. 4. Immediate asthmatic reaction demonstrated by change in 1-sec forced expiratory volume (FEV₁), to occupational type test with toluene diisocyanate used as activator for polyurethane varnish. Note inhibition of the reaction by pretreatment with cromolyn sodium (Intal®).

by cromolyn sodium, and are poorly and temporarily reversed by inhaled bronchodilators (21). “Late” asthmatic reactions and their inhibition by corticosteroids have been reported by other workers (28, 29).

Aerosol allergen test. We have now recognized at least three distinct patterns of nonimmediate reaction. Results of tests with an aerosol of pigeon serum in a nonatopic pigeon fancier with precipitins are shown in figure 7. This elicited a reaction starting after one hour and resolving by approximately 5 hours, followed by the more common nonimmediate reaction, which was maximal between 5 and 8 hours, and resolved within 24 hours (30). This reaction is compatible in speed of appearance and duration with a Type III reaction, and such patients give Type I and Type III cutaneous reactions, particularly to intracutaneous tests. The Type III cutaneous reaction and the nonimmediate bronchial reaction can be blocked by corticosteroids. Such nonimmediate asthmatic reactions may be accompanied by malaise, fever, and leukocytosis, simulating infective episodes.

It was suggested (31) that because IgE antibodies were seldom present in these subjects, short-term sensitizing IgG (STS-IgG) antibody (32) might be present and be responsible for the immediate skin test reaction and might act as an introductory mechanism for the Type III reaction and the nonimmediate asthmatic reaction. Supporting evidence has now been provided for this by passive transfer tests in man, showing that STS-IgG antibodies to avian anti-
 gens are present in such subjects (33). In non-
immediate asthmatic reactions due to western
red cedar, an immediate asthmatic reaction has
been shown by flow-volume measurements that
was not demonstrable by the 1-sec forced expira-
tory volume (FEV₁) (34), although so far, STS-
IgG antibody has not been reported. The STS-
IgG antibodies are less potent in eliciting im-
mediate reactions than IgE antibodies. Others
(35), however, have reported immediate asthma-
tic reactions to extracts of the Dermatopha-
goides sp. attributable to STS-IgG antibody.

It is suggested that the inhibition of the non-
immediate reaction shown in figure 7 by cromolyn
sodium could be attributable to its blocking
effect on an introductory immediate component,
thus preventing the evolution of the nonimmedi-
ate reaction.

Gasous emanation occupational type test.
An example of nonimmediate asthmatic reac-
tions to the gaseous emanations of toluene diiso-
cyanate, once again without immunologic evi-
dence, is provided in figure 8. This shows the
1- to 5-hour reaction followed by the 5- to 8-hour
reaction. This patient was sensitized by toluene
diisocyanate aspirated into the ventilation sys-
tem from the exhaust of a neighboring factory
(36).

Chemical dust occupational type test. Exam-
ples of nonimmediate asthmatic reactions to
chemical dusts are provided by workers with oc-
cupational asthma who are engaged in the man-
ufacture of antimicrobial drugs (37, 38). Sen-
sitivity was shown in different subjects to im-
purities in the materials or to particular anti-
genic determinants in the antimicrobial drug
preparations (figure 9), thus showing the highly
analytic value of these tests. Inhaled beclometha-
sone dipropionate can block this reaction (fig-
ure 10). Oral administration of the relevant an-
timicrobial drug elicited the same patterns of
asthmatic reaction as the inhalation test. Anoth-
er example is provided by a subject engaged in
the manufacture of salbutamol, who gave a non-
immediate asthmatic reaction, capable of being
blocked by pretreatment with inhaled beclo-
methasone dipropionate, to an intermediary
product, a "glycyl" compound, and not to its
precursors or the final product, salbutamol. The
patient had already suspected the "glycyl" com-
 pound, and our tests provided confirmation
(23).

Fig. 8. Nonimmediate asthmatic reactions, demon-
strated by change in 1-sec forced expiratory volume
(FEV₁) 1 to 5 hours and 5 to 24 hours after occupa-
tional type test with toluene diisocyanate as activator
of polyurethane varnish.

Fig. 10. Inhibition of nonimmediate asthmatic reac-
tion, demonstrated by change in 1-sec forced expira-
tory volume (FEV₁), to occupational type test with
6-amino-penicillanic acid (6 APA) by inhalation of
beclomethasone dipropionate.
Fig. 11. Dual asthmatic reactions, demonstrated by changes in 1-sec forced expiratory volume (FEV\textsubscript{1}), to occupational type test with wheat flour. Note inhibition of both reactions by cromolyn sodium (---) and of only the nonimmediate reaction by beclomethasone dipropionate (•••). Results shown are for lactose (---), wheat flour (-----), 40 mg of cromolyn sodium before challenge (-----), placebo before challenge (-----), and 200 μg of beclomethasone dipropionate before challenge (•••).

Recurrent nocturnal reactions to tests with aerosol gaseous emanations and chemical dusts provide yet another form of nonimmediate asthmatic reaction. This comes on in the early hours of the morning after the test and is preceded in most cases by other reactions during the test day. It recurs to a gradually decreasing degree in some cases for many nights after a single test, with apparent normality during the daytime (39, and Unpublished observations). Such reactions have been elicited in tests with aerosols, e.g., of avian antigens; with gaseous emanations, e.g., formalin fumes (40); and with chemical dusts, such as ampicillin powder (37). This reaction is of importance in assessment of causal exposures, because it may recur for days, thus confusing the interpretation of cessation of work during weekends or holidays, and care is needed to see that it is no longer present when provocation tests are made.

Combined reactions. Dual reactions in which Type I and Type III mechanisms are present and are interdependent, and reactions with the same characteristics but without immunologic evidence, are common and are probably more common than is appreciated at present. In figure 11, such reactions are shown for an occupational test with baker’s flour in which cromolyn sodium blocked both reactions and beclomethasone dipropionate blocked only the nonimmediate reaction (41). Different combinations of immediate and various forms of nonimmediate reactions are not uncommon and tend to be reproducible on repetition of the test.

Clinical Interpretation of Patterns of Asthmatic Reaction

The causal relationships in immediate asthmatic reactions are usually readily evident, and until recently, these have formed the main basis for classification of asthma into extrinsic and implying atopic asthma. Nonimmediate asthmatic reactions are more difficult to relate to causal exposure, but when this is identified, they could be termed extrinsic nonatopic asthma. Such reactions develop more gradually and tend to be less obvious clinically, even when quite severe, than the immediate reactions. Subjects with this form of reaction, whether accompanied by immediate reactions or not, tend to develop increasingly “fixed” and poorly reversible airway obstruction, as in avian asthma (31) and allergic bronchopulmonary aspergillosis (42).

It is quite common in occupational asthma to get a history of asthma coming on several hours after exposure; in some persons whose reactions start in this way, immediate reactions on exposure may become evident at a later date.

The pattern of recurrent nocturnal reactions to provocation tests is similar to that observed in clinical and hazardous asthma (43). It may be that extrinsic causes as yet to be identified could be responsible, their effect being enhanced by repeated and more prolonged exposures.

Closer correlation of the patterns of asthmatic reactions to provocation tests with those of clinical asthma is likely to give a reciprocal and improved understanding of the disorder and its therapeutic management. Thus, a good and maintained response to an inhaled bronchodilator is suggestive of an immediate asthmatic reaction. A poor and temporary response is suggestive of a nonimmediate reaction. In patients giving both patterns of response, the bronchodilator may be effective at one time and poorly effective at another, depending on the pattern of asthma.

The effective blocking by corticosteroids of the 5- to 8-hour nonimmediate asthmatic reaction in contrast to their ineffectiveness on immediate reactions suggests that this is at least one, and probably an important, way in which they achieve their clinical effects.

The observation that cromolyn sodium may block not only immediate but also nonimmediate reactions, even without a preceding immediate reaction, as measured by the FEV\textsubscript{1} or by the clinical response, makes it difficult to assess what
patterns of asthma are present when it is effective in clinical usage. Such an effect on nonimmediate asthmatic reactions may explain its clinical efficacy in patients regarded as intrinsic (cryptogenic), because causal agents have not been identified.

It is not known whether the differences between the immediate and different forms of nonimmediate reaction are due to different forms of tissue reaction or to reactions in different parts of the bronchial tree or to both. Pulmonary physiologic studies may, it is hoped, provide some answers to these important questions.

In some cases, it is already possible to work backwards to causal mechanisms, by using the criteria described, and from these to the appropriate immunologic tests and etiologic factors. This clearly needs to be considerably extended, rather than to be confined, as at present, to using the term "asthma" only in its physiologic context of reversible airway obstruction, without reference to the different patterns in which this may be manifest.

Pulmonary aspergillosis and pulmonary eosinophilia. Lung diseases caused by A. fumigatus provide examples of the general relevance of the factors determining the form of disease due to inhaled agents. Thus, immunologic reactivity determines whether, in atopic subjects, (1) the fungus acts as an allergen, mediating Type I reactions and causing only asthma; or (2) precipitins are present, mediating Type III allergy as well, and because A. fumigatus can grow in the respiratory tract, causing asthma and pulmonary eosinophilia. In nonatopic subjects, the spores can act as an inhaled organic dust, stimulating the production of precipitins and causing extrinsic allergic alveolitis; or it can grow as a saprophyte, causing an aspergilloma accompanied by the production of abundant precipitins and with only limited evidence of allergy, or it may become invasive in subjects who are immunologically suppressed by disease or drugs.

Allergic bronchopulmonary aspergillosis. Allergic bronchopulmonary aspergillosis is a classic form of pulmonary eosinophilia almost invariably accompanied by asthma, and it is responsible for more than 80 per cent of cases in the United Kingdom (44, 45). The clinical features consist of episodes of recurrent, transitory, and scattered peribronchial shadows and varying degrees of collapse. These are often associated with fever and malaise and aggravation of asthma, occurring mainly in the winter in the United Kingdom, when A. fumigatus spores are most common in the air. Sputum and/or nasal plugs containing eosinophils and growing hyphae of A. fumigatus are present at some time or other in 74 per cent of cases (44, 46, 47). The bronchial plugs are formed in the proximal bronchi, where chains of spores could be trapped; the peribronchial shadows occur in these regions. A characteristic proximal bronchiectasis with normal peripheral filling develops at the sites of the shadows and is attributable to the tissue-damaging Type III reaction to antigens diffusing from the growing hyphae in the plug (figure 12). Evidence for deposition of immunoglobulins and activated complement has been found in resected specimens (48, 49).

Dual skin test and inhalation test reactions can be elicited with the appropriate allergens. Corticosteroids effectively block the Type III but not the Type I cutaneous and bronchial reactions. Cromolyn sodium blocks the immediate asthmatic reaction and may block both. Bronchodilators effectively and virtually completely reverse the immediate reaction, with only a partial and short reversibility of the nonimmediate reaction (21). These patients tend to develop poorly reversible or fixed airway obstruction (42), but it is remarkable how well they can cope with life, with peak flows during very long periods as low as 80 to 120 liter per min. They have specific IgE antibody to A. fumigatus that increases together with very high concentrations of total IgE during the episodes of pulmonary eosinophilia.

In the presence of asthma and pulmonary eosinophilia, the skin prick test with a reliable A. fumigatus allergen extract giving an immediate reaction is strong diagnostic evidence of the disease, the other features usually being found in most cases. Many asthmatic patients have past histories of "pneumonia" or "bronchopneumonia" before the diagnosis is made. Approximately 90 per cent of cases give weak to moderate precipitin reactions. Using a quantitative method for estimating antigen uptake and, by inference, antibody concentrations to protein antigens of A. fumigatus, very high titers of IgG antibody are found in sera from patients with aspergilloma, and increased titers are found in allergic bronchopulmonary aspergillosis, with negative reactions in uncomplicated asthma and healthy control subjects (50). This corresponds
with our previous semiquantitative precipitin test findings and contrasts sharply with the reports of little or poor discrimination between the various groups in quantitative Farr primary binding tests with mucopolysaccharide antigens (51).

There is also evidence suggesting that allergy to *C. albicans* may contribute to the clinicopathologic picture in allergic bronchopulmonary aspergillosis. Intracutaneous test with the *C. albicans* cell wall polysaccharide, mannan, gave dual Types I and III reactions in all 17 subjects tested. The *C. albicans* antigens can also give dual asthmatic reactions on inhalation testing (7). Serologic tests show a higher incidence of precipitins and the presence of specific IgE to the *C. albicans* mannan in patients with allergic aspergillosis than in those with uncomplicated asthma, who, in turn, had a higher incidence than healthy control subjects (7, 52). Thus, immunologic and biologic mechanisms for pulmonary eosinophilia, resembling those in allergic bronchopulmonary aspergillosis, are present for *C. albicans*, and therefore, it is also possible that in certain cases, such as the report of a patient with no evidence of allergy to *A. fumigatus* (53), that the cause may be allergy to *C. albicans*, for which the description, if proved, of allergic bronchopulmonary candidiasis would be appropriate.

**Peripheral gas-exchanging bronchioloalveolar tissue reactions—extrinsic allergic alveolitis.** In reactions to extrinsic agents in the peripheral gas-exchanging tissues of the lung, all three factors determining the respiratory response play a part in the pattern of the disease. (1) Immunologic capacity to react is reflected in the fact that this is a disease mainly of nonatopic subjects. (2) The role of the nature of the causal agent is reflected in their particle sizes, which permit penetration to and retention in the al-
veolar regions. (3) The influence of the circumstances of exposure is reflected in the need for intensive antigenic stimulation to induce precipitin production and possibly some aspects of Type IV allergy as well; in the influence seen in some cases on initiation of disease by re-exposure after a period of cessation of exposure, most noticeable in bird fanciers; and in the profound effects of regular or intermittent exposure on the clinical presentation of the disease.

Our identification by the precipitin test of the spores of the thermophilic actinomycete, *M. faeni*, which are 1 to 2 μm in diameter, as the major antigenic cause of Farmer’s lung due to moldy hay (54), confirmed by specific inhalation testing, opened the door through which many more and very different causes of extrinsic allergic alveolitis are now pouring. Among these are a wide variety of agents in a form capable of inhalation, including heterologous serum proteins in avian droppings, rodent urine, and therapeutic materials (pituitary snuff); spores of thermophilic and other actinomycetes and of many different fungi, including Aspergillus spp.; organic dusts, such as fish meal and wood dusts; mite antigens, such as *Acarus siro*; insect antigens from *Sitophilus granarius*, the wheat weevil, and free-living amoebae in contaminated water aerosols. Chemical agents such as toluene diisocyanate must also be considered (55).

Precipitins against the various agents are evidence of exposure and sensitization, and whereas they correlate on the whole with clinical disease, their significance in the individual subject must be determined by the associated clinical features and may need to be confirmed by provocation tests. This is very much the case with bird breeders or fanciers, in whom precipitins can be present without disease, for example, in poultry breeders (56); this is less common among pigeon fanciers (57), and seldom occurs in budgerigar and parrot fanciers (58). The precise nature of the clinically relevant antigen or antigens, in this case of avian origin, must be determined and may be important. Thus, we have found that it is the avian immunoglobulins that show greater specificity as antigens for the particular bird species to which the sensitized bird fancier was exposed or which was established as the cause of the disease, rather than the other avian serum proteins. This finds some support from a test that we have recently introduced in which the patient’s serum is tested against avian erythrocytes. In positive tests, the cells agglutinate and settle rapidly, because they are nucleated. This provides a rapid quantitative test that correlates well with the precipitin test (59). We have found that the main antigen on the erythrocyte surface is the light chain of avian immunoglobulin. It has also been shown that avian immunoglobulins are more effective in sensitizing laboratory animals.

Avian exposures also illustrate the importance of intermittent exposure, as in the sensitive pigeon fancier cleaning the loft at intervals, resulting in acute episodes coming on after several hours, so that identification of the causal exposure is not difficult, compared with regular exposure, as in the budgerigar or parrot fancier, with perhaps a single bird, in whom the disease develops gradually and insidiously and more dangerously, the patients often presenting with severe advanced pulmonary fibrosis. On radiography, nodular and micronodular shadowing may be seen (figure 13). On provocation testing, both groups of subjects give the acute form of reaction, thus confirming the relevance of the circumstances of exposure to the manner in which the disease presents. These observations mean that in affected subjects, there should be a relentless pursuit of possible sources of inhaled antigen, with detailed attention to past exposures.

The reactions elicited by inhalation testing and by skin tests, when appropriate, are compatible with Type III reactions in speed of appearance, duration, and response to corticosteroids, suggesting that the precipitins are playing an immunopathologic role. There is now some limited direct evidence for this (60, 61). This does not, however, exclude other allergic or nonallergic mechanisms. Among the latter is the activation of C3 component of complement by the alternative pathway by *M. faeni* and other organic dusts together with activation of macrophages (20). This may also be the explanation for the nonspecific inflammatory reactions elicited by intracutaneous tests with *M. faeni* extracts. Other causes of extrinsic allergic alveolitis, such as avian and other heterologous proteins that are suitable for skin testing, have given specific Type I and Type III, but not Type IV, reactions (51).

The production of reactions in the peripheral lung tissues is likely to result in some similarity of clinical manifestations, whatever the mechanism. It is likely, however, although not yet established, that there will be quantitative dif-
ferences between the amounts of allergen capable of eliciting immune complex C3 activation reactions and those needed for C3 activation without participation of antibodies. The enhancing effects of macrophage activation by activated C3 and its effect on immunologic responses may explain why some antigens are more potent causes of disease than others.

Features of the disease are illustrated by two examples of more recently observed causal agents. The first is a young female scientific worker handling Wistar rats, which may lose as much as 3 g per day of serum proteins in the urine (62). After previous innocuous exposures, she developed episodes of dyspnea, fever, malaise, myalgia, and loss of weight. Radiographs demonstrated widespread nodular and micronodular shadowing like that in figure 13, mainly of the upper lobes, that cleared on cessation of exposure. Clinical exposure caused a decrease in the CO gas transfer factor of prolonged duration (figure 14). A provocation test with rat serum proteins provoked a febrile and systemic reaction with a decrease in gas transfer. Precipitins were present against rat serum proteins. This is a classic example of the immunopathologic basis of this disease, namely, that it has the characteristics of serum sickness with the reactions and disease influenced by the inhaled route of exposure.

The second example concerns the effects of inhaled aerosols of contaminated water. This was reported (63) to elicit reactions to extracts of the contaminated water, but not to extracts of the filtered water. We have investigated three and reported two factory episodes of febrile respiratory illness with features mainly of extrinsic allergic alveolitis, caused by aerosols of contaminated recirculating water (64, 65). The clinical features were worse on Monday or on resuming work after an interval away from it, and consisted of systemic manifestations such as fever, shivering, and malaise, and respiratory tract manifestations consisting of sneezing, dyspnea, cough, mucoid sputum, with crepitant rales in a number of cases. Febrile episodes clearing rapidly on cessation of exposure and recurring on its resumption can be a pointer to the diagnosis, occurring in some subjects with little complaint of respiratory disorder.

Strong precipitin reactions to extracts of the contaminated water were present in exposed
Immunopathologic Mechanisms in Extrinsic Allergic Alveolitis

There is much controversy about immunopathologic mechanisms in extrinsic allergic alveolitis. Different workers have provided evidence of Types I, III, and IV allergins, and even Type II allergy has been postulated. Whatever the case, the precipitin test has so far been the means of identifying most causes. The pathologic features consist of patchy alveolar infiltration with lymphoid, plasma, and histiocytic cells, and with epithelioid granulomas and characteristic giant cells with cytoplasmic clefts. These features were first reported in farmer's lung as hypersensitivity granulomatous interstitial pneumonitis (67).

Possible mechanisms for the granulomas without exclusion of others, are (1) insoluble immune complexes of antigen and precipitating antibody (68); (2) antigen-coated particles, such as the various spores, in which sensitized lymphoid cells may be concerned (69); (3) C3 activation by the alternative pathway, with macrophage activation (20). One or more of these factors and perhaps with different emphasis in individual subjects may be responsible for the granulomas (70). A markedly greater effect of inhaled spore particles as against antigen solutions in eliciting granulomatous pneumonitis in animals has also been shown (67). One point that needs emphasis, however, is that despite lymphoid cell sensitization, the full picture of Type IV allergy in terms of delayed skin test reactions has not been seen with antigens suitable for skin testing.

Conclusions

A panorama has been presented of patterns of lung disease and the types of allergic and nonallergic reaction on which they could be based. Occupational respiratory allergy presents itself as a field of great promise in all respects, and can be expected to flourish mightily. It provides in a sense the "justification" of proponents of a scientific holiday, for it is abundantly evident that "discoveries cause diseases," as shown by the increasing recognition of the disorders described here.

At certain points in clinical investigation, and even irrespective of any immunologic findings, pragmatic proof of the relationship of the suspected causal agent to the disease is required. Clinical exposures may serve, but more often, carefully controlled provocation tests are required; when these are simple, safe, reproducible, and made with doses far less than those ordinarily encountered, the ethics and importance of etiologic diagnosis make them obligatory. Among the fruits of meeting such clinical obligations have been the writing of a fresh "language" of allergic respiratory disease affecting the bronchi with its heterogeneity of patterns of asthmatic reaction, the peribronchial tissues with
pulmonary eosinophilia, and the peripheral lung tissues with extrinsic allergic alveolitis.

References

31. Hargrave, F. E., and Pepys, J.: Allergic respiratory reactions in bird fanciers provoked by at-


Bardana, E. J., Jr., McClatchy, J. K., Farr, R. S., and Minden, P.: The primary interaction of antibody to components of aspergilli. II. Antibodies in sera from normal persons and from patients with aspergillosis, J Allergy Clin Immunol, 1972, 50, 222.


