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Immunopathology of Experimental Models of Syphilis, Influenza, and Asthma

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Abstract

The introduction of immunopathologic reaction classification in the 1960s led to a major advance in understanding immune effector mechanisms and how lesions of immunopathologic diseases developed. In this article, immunopathologic mechanisms are presented for experimental models of syphilis, influenza, and asthma. The chancre of syphilis is a delayed hypersensitivity skin reaction that is initiated by sensitized T cells that activate macrophages to phagocytose and kill the infecting organism, *Treponema pallidum*, in interstitial tissues. The primary immune effector mechanism in experimental influenza is T-cell-mediated cytotoxicity that kills infected epithelial cells, bronchial lining cells, and Type-II pneumocytes, in a manner similar to viral exanthema. The bronchial lesions of the experimental model of asthma in mice are preceded by an immune complex vasculitis and not an immunoglobulin E-mediated mast cell mechanism.

Keywords

asthma; delayed-type hypersensitivity; immune complex vasculitis; immunopathology; influenza; syphilis; T-cell cytotoxicity

I. INTRODUCTION

Classification of immunopathological reactions completely changed the way in which we understand and analyze immune-mediated diseases and lesions. To illustrate this approach, I use three experimental models of disease: syphilis, influenza, and asthma. When I first learned about immune-mediated tissue reactions in medical school and during residency, there was no useful classification of immune reactions. This led to a very long list of reactions that provided little in the way of mechanism (Table 1). About all that was known was that some were mediated by immunoglobulin antibodies and some by cells. At that time, cell-mediated reactions consisted essentially of delayed-type hypersensitivity (DTH) skin reactions. My first laboratory project with William O. Weigle and Frank J. Dixon as a freshman medical student at the University of Pittsburgh was to determine the relationship between DTH and antibody production. We found that DTH skin tests became positive

about 1 d before antibody production could be measured by immune elimination of radiolabeled circulating antigen.¹ My understanding of DTH reactions was greatly expanded by Byron Waksman during my residency at Massachusetts General Hospital and my knowledge of immunoglobulins by John Fahey (who eventually chaired the department of microbiology at the University of California at Los Angeles [UCLA]) at the National Institutes of Health.²⁻⁴ How lymphocytes respond to stimulation featured a year of study at the University of Birmingham in England with Philip Gell.⁵⁻⁷ When I returned to my first faculty position at the University of Pittsburgh in 1966, I found that I was expected to teach immunology to the first- and second-year medical students. Fortunately, it was at this time that Gell and Coombs published the first classification of immune-mediated reactions in their book *Clinical Aspects of Immunology*.⁸ They proposed four types of immune reactions: (1) atopic or anaphylactic, (2) cytotoxic, (3) immune complex, and (4) delayed hypersensitivity. This classification system provided the stimulus for expanding my understanding of immune reactions and eventually led to an expanded classification including seven types of immune reactions (Fig. 1).⁹

The first four reactions are mediated by antibodies, the next two by cells, and the last by either.

1. Neutralization or activation. These reactions occur when antibody modifies a biologically active molecule so that it is no longer active, or it blocks an activating ligand from reacting with a receptor. In some cases, an antibody can mimic an activating ligand to activate a cell-surface receptor. Examples include antitoxin neutralization, diabetes, myasthenia gravis, and hyperthyroidism (Graves' disease).
2. Cytolytic. In these reactions, antibody reacts with antigens on the surface of cells, activates the complement, and causes cell lysis. Examples of cytotoxic reactions include transfusion reactions, hemolytic anemias, erythroblastosis fetalis, and bacteriolysis.
3. Immune complex. In immune complex reactions, antibody reacts with soluble antigens, causing loss of solubility (precipitation) with deposits on vessel walls, fixation of the complement, attraction and activation of polymorphonuclear leukocytes, and acute inflammation. Some examples of this type of reaction are glomerulonephritis, vasculitis, Arthus reaction, and abscess formation.
4. Atopic or anaphylactic. Allergen reacts with the immunoglobulin E (IgE) antibody on the surface of mast cells, resulting in cross-linking of surface IgE, degranulation of mast cells, release of pharmacologically active agents (histamine, serotonin, prostaglandins, etc.), and constriction of bronchial smooth muscle or dilation of vascular smooth muscle. Examples include asthma, anaphylactic shock, hives, and intestinal parasite immunity.
5. T-cell cytotoxicity (T-cell-mediated cytotoxicity [CMT]). So-called "killer" T cells react with class I major histocompatibility markers and surface antigens on nucleated cells, causing activation of perforin and other mechanisms that cause cell death. Examples of CMT include autoimmune thyroiditis, poison ivy,

measles (and other viral exanthemas), tissue graft rejection, graft-versus-host reactions, and influenza.

6. Delayed type hypersensitivity (DTH). Sensitized lymphocytes react with antigens to release lymphokines that attract and activate macrophages. Activated macrophages phagocytize and digest adjacent cells and tissue. The tuberculin skin test, autoallergic diseases, experimental allergic encephalomyelitis, tuberculosis, and chancre of syphilis are all examples of DTH.
7. Granulomatous reactions. Either antibodies or lymphocytes cause destruction of tissue that macrophages cannot digest. This leads to accumulation of macrophages in collections known as granuloma. Examples include tuberculosis, sarcoid, berylliosis, leprosy, and foreign body granulomas.

How does this classification fit with the widely used type-I and -II immune reactions based on participation of different T-helper-cell populations? Th1 reactions are defined by mediation of cytokines interferon (IFN)- γ and interleukin (IL)-2 and Th2 reactions by IL-4, IL-5, IL-10, and IL-13. Thus, the Th classification of an immune reaction can be identified by determining the cytokines involved. Unfortunately, the Th-classification system does not clearly define the immunopathologic mechanism, because Th1 cytokines are involved in complement-mediated reactions, such as lytic and immune complex reactions, as well as cell-mediated reactions including DTH and CMT. Only anaphylactic reactions are characterized by Th2 cytokines. Thus, identification of an immune reaction as a Th1 or Th2 may have importance for induction, but not for the immune effector mechanism. With this background, I now present our results with experimental models of syphilis, influenza, and asthma, as examples of how the immune mechanisms are active in these infections.

II. SYPHILIS (DTH)

Syphilis appeared suddenly in Europe shortly after the return of Columbus from the New World. The clinical manifestations are wonderfully described by poet Francisco Lopez de Villalobos in an English translation from the original, published in 1498.¹⁰

Yet oft the moon four monthly rounds shall shine
Before convincing symptoms shall appear.
Yet with uninvited heaviness is seized.
With drooping spirits his affairs pursues
And all his limbs their offices refuse.
The cheerful glories of his eyes decay
And from his cheeks the roses fade away.
It seems but just that it should have its
beginning Only in those parts that do the wicked sinning,
And they but suffer from a rightful punishment.

The latter quote refers to the syphilitic chancre that appears on the organ of sexual contact. It is remarkable that an explanation of this chancre was not known until our work with Jim Miller and his students on an experiment model in rabbits (see below).

From another historical document by Diaz de Isla, the cause of the rapid spread of the disease becomes apparent.¹¹ Columbus had with him six sailors and six Indians as he set out on foot for Barcelona via Seville, and they took part in sexual orgies between Palos and Barcelona. This was shortly followed by the siege of Naples by the army of Charles VIII of

France. Several hundred troops from all over Europe (Swiss, Spanish, French, English, Germans, and Russians) fought, Naples was overrun with “le mal Francais” (syphilis), and the troops were quickly infected. Because medical care for soldiers was essentially nonexistent at the time, Charles VIII sent the troops home to France. Within five years, medical observers throughout Europe were writing about this new disease. The Italians called it the Spanish or French disease, the French called it the Italian or Neapolitan disease, the English and Turks called it the French disease, the Russians called it the Polish disease, and the Spanish called it the disease of Espanola (Haiti).

In one of his essays, D.H. Lawrence attributes the rise of puritanism to the arrival of syphilis in Europe, in particular, to the strict adherence of abstinence and monogamy associated with puritanism.¹² The symptoms and course of the disease was the subject of considerable clinical concern for many years, and the founder of American medicine, William Osler, is known for his statement, “He who knows syphilis knows medicine.”¹³

Syphilis is caused by a spirochete known as *Treponema pallidum*.¹⁴ The classic early sign is a raised, firm, ulcerated lesion called a chancre. The only practical experimental animal that can develop a similar lesion is the rabbit (Fig. 2B).¹⁵ Given the limitations on medical investigation that can be done with humans, our laboratory at University of California at San Diego (UCSD) contacted Jim Miller at UCLA to help us unravel the pathogenesis of the chancre in rabbits; this began when Sheila Lukehart and Steve Norris joined our lab. Working with *T. pallidum* is not an easy task, because it is still not possible to be cultivated *in vitro* and must be harvested from lesions induced in the testes of rabbits.

A comparison of the primary human chancre and those induced in rabbits is shown in Fig. 2A,B. With Sheila Lukehart, we undertook an immunopathologic investigation of what happened when *T. pallidum* grew in the rabbit testes.¹⁶ Using electron microscopy (EM), we found *T. pallidum* in the extra-cellular matrix (Fig. 2C). Using immunofluorescence to identify the organisms, we saw a marked increase in the number of *T. pallidum* in the interstitial tissue of the testes for ~13 d, a sudden decrease associated with fluorescent fragments in macrophages on days 14 and 15, and by day 17 the organisms were gone (Fig. 2D–H). With Professor Harry Powell at UCSD, fragments of organisms were identified with EM in the phagosomes of macrophages in the testes (Fig. 2I).¹⁷ This reaction is associated with marked hyperplasia of the diffuse cortex of the draining lymph nodes.¹⁸ In contrast to prevailing opinion at the time that syphilis was immunosuppressive, these findings demonstrated a rapid and powerful immune response to syphilis and that the chancre is a manifestation of a DTH. Using these facts as a basis, we proposed a recombinant *Bacillus Calmette–Guérin*–based vaccine for syphilis that would be effective in inducing DTH.¹⁹

Thus, when infection occurs, *T. pallidum* proliferates rapidly in the interstitial tissue. However, when DTH is established, sensitized cluster of differentiation 4 (CD4) T cells in the circulation will react with *T. pallidum* antigens in the infected tissue to become activated. Activated T cells proliferate locally and release cytokines that attract and activate macrophages. The activated macrophages phagocytize the organisms, eventually leading to their dismemberment in phagosomes. Normally, this reaction is extremely powerful and as seen in the rabbit models leads to rapid clearing of the infected tissues. However, if a rapid

and effective DTH response is absent or if the organisms are able to reach tissue sites that are not effectively patrolled by circulating cells such as brain, nerves, and thick vascular walls, prolonged disease may result, leading to secondary or tertiary disease. Chronic lesions occur when the DTH response is ineffective. Thus, we can compare the type of immune reaction in syphilis to that in leprosy.²⁰ A strong DTH reaction in leprosy leads to stabilization of the infection (tuberculoid leprosy), whereas strong antibody formation results in progressive disease (lepromatous leprosy). Similarly, a strong DTH reaction in syphilis leads to cure, whereas a dominant antibody response results in secondary or tertiary disease.¹⁵

III. INFLUENZA (T-CMT)

Influenza is caused by three types of viruses: types A, B, and C.²¹ During the 20th century, three influenza pandemics occurred: Spanish influenza in 1918 that affected more than 100 million people worldwide,²² Asian flu in 1958, and Hong Kong flu in 1968, each killing more than 1 million people.²³ The classic pathologic finding in the lungs of those who die from influenza is necrotizing bronchiolitis.²⁴ This necrosis occurs in the bronchiolar wall and is accompanied by submucosal edema and vascular congestion. The epithelial layer is desquamating, and necrotic epithelial cells are present in the lumen (Fig. 3A). A mixed inflammatory cell infiltrate is present throughout the involved bronchi.

Our studies began in collaboration with a group of investigators then at the Trudeau Institute in Saranac Lake, New York, who were using genetically modified mice to study the immune reaction to experimental influenza infection; in particular, the role of CD4 and CD8 T-effector cells and T-regulatory cells (Tregs).^{25–28} The striking findings were the invasion of the infected bronchial epithelium by T cells and the killing of virus-infected epithelial cells (Fig. 3B–E).²⁹ Other prominent findings were the formation of bronchus-associated lymphoid tissue (BALT; Fig. 3F) and the proliferation of bronchial epithelium filling alveolar spaces later in surviving mice (Fig. 3G,H). Both CD4 and CD8 T cells could take part in the cytotoxicity of infected epithelium. Induced BALT (iBALT) formation and epithelial proliferation were seen in several models but more so in mice with severe combined immunodeficiency and depleted Tregs.

A summary of findings is as follows. Influenza virus infects pulmonary epithelium and type-II pneumocytes. With overwhelming infection or lack of a prompt immune response, the virus kills the infected cells, leading to necrosis of the bronchial epithelium and loss of fluid into the lungs, interalveolar hemorrhage, and death. Infection may be cleared by induction of T-cell cytotoxicity, with elimination of infected cells and regeneration of the epithelium and type-II pneumocytes. Failure to clear chronic infection may lead to hyperproliferation of pulmonary epithelial cells and/or type-II pneumocytes, which may be controlled by Tregs. Extensive proliferation has been reported in mice,^{30–34} swine,³⁵ and humans,^{36,37} who survive the acute infection. Winternitz et al. compared this proliferation to that of carcinoma of the lung.³⁶ In some reports, this may be interpreted to be fibrosis, although epithelial morphology is evident.³⁸ Production of immunoglobulin antibody will prevent new cells from being infected, a result accomplished by flu vaccination. iBALT formation results in a local site of antibody production in the lung. BALT is present normally in some mammalian

species, including rats and rabbits, but not in humans or mice.³⁹ iBALT in mice and humans is stimulated by inflammation or infection, reacts to antigen in the airways, and serves as a site for local immune responses.

The major finding of intraepithelial lymphocyte infiltration was originally seen in experimental models of swine³³ first and then mice.^{29–32} However, the similarity of this reaction to human viral exanthema was unappreciated. Thus, the main immunological defense mechanism against small pox, measles, and other viral exanthema is T-CMT.⁹ Similar to contact dermatitis, wherein antigen is present in epithelial cells with a prominent basement membrane, antibody-mediated immune reactions and other cellular reactions are ineffective. When infection of epithelial cells occurs, antigen diffuses across the basement membrane, is picked up by dendritic macrophages, and then taken to draining lymph nodes, where sensitization occurs. When sensitized cytotoxic T cells are eventually released into the circulation, CD4 or CD8 lymphocytes are attracted into the epidermis by an antigen gradient and attack epithelial cells containing antigen (poison ivy urushiol or viral antigens expressed on the cell surface). This leads to microabscesses and eventual loss of the affected epithelium. Repair is achieved by regeneration of the epithelium after the attacked infected cells have been destroyed. A recent study did not identify this reaction after infection in mice, although a figure in Bi et al. clearly shows intraepithelial lymphocyte infiltrations in infected sensitized mice.⁴⁰

IV. ASTHMA (IMMUNE COMPLEX REACTION)

Asthma is an inflammatory disease of the lung, characterized by variable symptoms related to reversible airflow obstruction and bronchoconstriction.⁴¹ The airways narrow, swell, and produce extra mucous, making breathing difficult. Approximately 25 million individuals in the United States have asthma, and, of these, ~60% have allergic asthma. Classic allergic asthma is attributed to degranulation and release of mediators from mast cells, activated by reaction of an allergen with IgE antibodies on the surface of the cell. These mediators include histamine and serotonin (acute bronchoconstriction, etc.) as well as various prostaglandins and leukotrienes (chronic inflammation). The pathologic features of human allergic asthma include thickening of the basement membrane, mucosal cell hyperplasia of the bronchial epithelium, hypertrophy of peribronchial smooth muscle, and peribronchial inflammation, including prominent increases in mast cells (Fig. 4A). Repeated exposure to allergen leads to a true adaptive response. As the number of mast cells increases, hyperplasia of the mucous cells increases, and, like a weight lifter, hypertrophy of the smooth muscle occurs, so that, unless treated, subsequent responses continue to increase in severity as a result of the increasing numbers of mast and mucous cells and smooth muscle mass.

Understanding classic allergic asthma has been hampered by the lack of a valid experimental model. In 1993, Hassel et al. reported a mouse model of increased airway responsiveness after sensitization to ovalbumin (OVA) and pulmonary challenge.⁴² This model, and variations thereof, have been the subject of more than 3000 publications.⁴³ Sensitization included six to seven intraperitoneal injections of 10–20 µg of OVA with or without alum during a 2–6-wk period, followed by 1 wk of rest. The mice were then challenged every 2–3 d intranasally or by aerosol inhalation for 6–9 d and euthanized for study 2–3 days after the

last challenge. After challenge, the effects of various drugs on airway resistance were tested, and bronchial lavage fluid was analyzed for inflammatory cells, IgG and IgE antibodies, cytokines (type I: IL-2, -9, and -17 and interferon [INF]- γ ; type II: IL-4, -5, and -10), and histology. The results were generally consistent with a type-II allergic response, including elevation of type-II cytokines, IgE antibody to OVA and thickened basement membrane, hyperplasia of mucous cells, and ill-defined inflammation around the bronchi.

A pathological principle holds that it is difficult to determine the origin of a lesion by the time that it is fully developed or has reached an end point. This is particularly true for human diseases, but animal models provide a means to study early development of a disease. Thus, we decided to investigate the development of the lesions of experimental asthma after one, two, and three challenges—not just the third challenge.⁴³ We found that after one challenge, necrotizing vasculitis with polymorphonuclear leukocyte infiltrate typical of an immune complex lesion occurs (Fig. 4B). After two challenges, necrosis of the vessel wall is still present, but the nature of the perivascular inflammation changes to include increasing eosinophilic, round-cell perivascular infiltrate, and early iBALT formation (Fig. 4C). After three challenges, mononuclear infiltrate and iBALT formation increase (Fig. 4D,E). Skin testing at the time of challenge elicited a firm, indurated, erythematous reaction 6 hr after challenge (Arthus reaction)⁴⁴ and double-diffusion-in-agar readily detected precipitating antibody. We did not see any immediate wheal and flare reactions.

To quantitate histologic changes in the bronchi, it is necessary to obtain a longitudinal section of the major bronchi, as shown in Fig. 4F. Changes in the bronchi, shown in Fig. 4G,H, were greatest 48 hr after challenge and then began to resolve. After one challenge, slight thickening of the basement membrane and hyperplasia occurred, with increased mucous blebs over the epithelial lining cells and a slight increase in peribronchial mononuclear cells (Fig. 4H). After two challenges, increased thickening of the basement membrane occurred, greatly increasing hyperplasia of the mucous lining cells, prominent hypertrophy of the peribronchial smooth muscle, and marked bronchial mononuclear inflammation (Fig. 4J). The number of nuclei in the bronchial lining increased from 17 (normal) to almost 30, thickness of the bronchial mucosa increased from 0.01 to 0.06 mm, and thickness of the bronchial smooth muscle increased from 0.01 to 0.03 mm. Type-II cytokines (IL-4, -5, and -17) in the bronchial fluid increased. IL-4 (B-cell stimulating factor-1) and IL-13 stimulate B cells (iBALT), attract eosinophils, increase mucous hyperplasia, and are active in classic allergic inflammation. IL-5 also stimulates B-cell proliferation and attracts eosinophils.^{45–47} Thus, it seems that the end result is consistent with classic allergic asthma.

However, there is something missing: mast cells. After reviewing special stains of many sections, we could not find mast cells in normal lung or after one and two challenges. Only after three challenges were a few (less than four) seen around the trachea, but essentially none were found in the main stem or peripheral bronchi, although they were readily identified in the skin. Gersch et al.⁴⁸ found mast cells to be abundant in the dermis, tongue, and skeletal muscle of mice, but rarely in the heart, lung, and bowel mucosa. In addition, few peribronchial mast cells are seen in the lungs of naïve mice or those challenged by acute

inhalation of OVA; repeated challenges with OVA for more than 6 mo is required to see a significant accumulation of mast cells and to find mast cell growth factor in mouse lung.⁴⁹

Thus, the mouse model of asthma classifies as nonallergic asthma but is initiated by an immune complex reaction. Apparently, the mouse lacks the means to unleash a human type of allergic reaction in the lung. However, it seems the mouse lung can alter an immune complex reaction to accomplish the same changes in the bronchi that are characteristic of human allergic asthma. Dr. Tara Strutt of the University of Central Florida has carried out a more extensive luminex analysis of bronchial fluids from our experiments, which showed elevation of both type-I (IL-2 and INF- γ) and type-II (IL-4, -5, -10, -13, and -17) cytokines. Again, the more one looks, the more one sees variability and flexibility in the immune systems of different species.

V. SUMMARY

The rabbit model of syphilis reveals the chancre to be a DHT reaction that effectively destroys infecting organisms by activating phagocytosis and digestion by macrophages. A vaccine for syphilis should induce DTH over antibody production. The mouse model of influenza shows that activated T cells kill virus-infected bronchial epithelial cells and type-II pneumocytes (T-cell cytotoxicity) and that memory CD4 T cells are directly cytotoxic. A vaccine against flu that induces T-cell cytotoxicity may be more effective in fighting infection than those now in use that produce circulating antibody. The mouse model of asthma demonstrates that the bronchial lesions of asthma are preceded by an immune complex vasculitis in the lung. Thus, the asthma-like lesions in this model are mediated by immune complex reactions and not an anaphylactic or atopic reaction. The immune system works in mysterious ways.

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ABBREVIATIONS

CD	Cluster of differentiation
CMT	cell-mediated cytotoxicity
DTH	delayed-type hypersensitivity
iBALT	induced bronchus-associated lymphoid tissue
IL	interleukin
IFN	interferon

OVA	ovalbumin
Th	T helper
UCLA	University of California at Los Angeles
UCSD	University of California at San Diego

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IMMUNE EFFECTOR MECHANISMS

FIG. 1.
Classification of immune effector mechanisms (for description, see text)

FIG. 2.

Immunopathology of experimental syphilis in the rabbit. (A) Gross lesion (chancre) on human penis; (B) gross lesion (chancre) in rabbit skin; (C) electron microscopic view of *T. pallidum* organism swimming in extracellular matrix in testes. (D)–(F) Immunofluorescence localization of *T. pallidum* in interstitial tissue of testes. (D) Day 3 after infection; (E) day 10; (F) day 13; (G) day 17 (for description, see text); (H) immunofluorescent fragments in macrophages on day 14; (I) electron microscopic identification of fragments on *T. pallidum* in phagosomes of macrophage on day 14. EAE, Experimental allergic encephalomyelitis; T-CTM, T-cell-mediated cytotoxicity; T-DTH, T-cell delayed-type hypersensitivity.

FIG. 3.

Immunopathology of experimental influenza in mice. (A) The classic pathology of acute human influenza, necrotizing bronchiolitis,²³ involves necrosis of bronchial walls and exudate in lumen, sometimes called pseudomembranous inflammation. (B) Infiltration of lymphocytes into bronchial epithelium 8 d after infection of IL-10 knockout mice. (C) Immunoperoxidase staining of infecting virus in bronchial epithelium and type-II pneumocytes in wild-type mice. (D) CD3⁺ memory CD4 T cells in bronchial epithelium. (E) Memory CD4 T cells in bronchial epithelium and underlying tissue. (F) PAX 5 (B-cell marker) staining of BALT tissue 5 d after secondary infection of Treg-depleted mice. (G) Hematoxylin and eosin (H&E) staining of epithelial cells in alveoli of Treg-depleted mice 4 wk after infection. (I) Thyroid transcription factor-1 (epithelial cells) staining of proliferating epithelial cells.

FIG. 4.

Immunopathology of experimental asthma in mice. (A) H&E staining of human bronchial asthma, showing mucous hyperplasia with a bronchial plug, thickening of the basement membrane, hyperplasia of bronchial smooth muscle, and peribronchial infiltrate. (B)–(J). Mouse model of asthma. (B) Twenty-four hours after one challenge shows fibrinoid necrosis of vascular wall, with perivascular polymorphonuclear infiltrate. (C) Twenty-four hours after second challenge shows vascular necrosis, with increased perivascular infiltrate containing greater numbers of monocytes and eosinophils. (D) H&E staining. (E) PAX 5 (B-cell staining) 48 hr after the third challenge. Image shows marked perivascular and peribronchial inflammation, with iBALT formation and marked mucosal hyperplasia. (F) Longitudinal section of main stem bronchus of lung, which was required to obtain quantitation of microscopic changes. (G)–(J) High-power magnification of bronchial wall shows increasing basement membrane thickening, mucous hyperplasia of bronchial epithelium, smooth muscle hyperplasia, and peribronchial inflammation.

TABLE 1

Partial list of immune-mediated phenomena – circa 1960

Anaphylaxis	Asthma	Arthus reaction
Autoimmune thyroiditis	Poison ivy	Glomerulonephritis
Myasthenia gravis	Diabetes	Serum sickness
Tuberculin test	GVH reaction	Rheumatoid arthritis
Transfusion reaction	EAE	Schultz Dale phenomenon
Erythroblastosis fetalis	Myopathy	Cold hemaglobinuria
Multiple sclerosis	Scleroderma	Wheal and flare reaction
Pemphigus	Schick test	Erythema multiforme
Dermatomyositis	Hay fever	Schwartzman reaction
Giant urticaria	Shock	Psoriasis
Wegner granulomatosis	Polymyositis	Pernicious anemia
Mastocytosis	Hepatitis	Lupus erythematosus
Amyloidosis	Myeloma	Lymphocytic choriomeningitis
Tumor immunity	Orchitis	Jones Mote reaction
Sialoadenitis	Neuritis	Sialoadenitis
Phacoanaphylaxis	Endophthalmitis	Allergic uveitis
Hashimoto's thyroiditis	Angioedema	Hypothyroidism
Idiopathic thrombocytopenic purpura	Hereditary angioedema	
Hypercomplementemia	Glomerulonephritis	Hyperthyroidism
Hypocomplementemic vasculitis	Urticarial syndrome	Palpable purpura
Hypogammaglobulinemia of infancy		IgA nephritis
Epidermolysis bullosa acquisita		Regional enteritis
Erythema chronic migrans	Celiac disease	Extrinsic allergic alveolitis
Cold agglutinin disease	Berylliosis	Churg Strauss syndrome
Ankylosing spondylitis angioedema		Ankylosing spondylitis

EAE, Experimental allergic encephalomyelitis; GVH, graft versus host; IgA, immunoglobulin A.