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IMMUNOLOGY OF OCCUPATIONAL LUNG DISEASES

Robert Burrell

Owing partly to their function and partly to their anatomical location, the lungs and skin are the organ systems most in contact with the external environment. Both the gas-exchanging regions of the lung and the airways are constantly bathed in large volumes of air containing great varieties of suspended mineral and organic dusts. Such particulates may be either antigenic in themselves or may, as a result of an immunological reaction, lead to pulmonary damage. Although most immunological reactions are beneficial, there is a growing realization that they can be two-edged swords and may occasionally be accompanied by harmful side effects. Four basic types of immune injury have been described, and here again the lung shares with the skin the distinction of being the only other organ system susceptible to all four.[1] Pulmonary immune injury is seen most often in subjects exposed to large amounts of dust as a result of either their occupation or their hobby.

Although the lung is usually thought of as an organ of respiration, it also has important immunological functions. The lung clears itself of inhaled foreign particles by means of cells lining the airways. It also cleanses the internal pulmonary environment of harmful agents that are carried to the lungs by the pulmonary circulation. This it does through a series of aggregates of lymphoid tissue. Since with many antigens phagocytosis is a necessary prelude to antibody production, the immunological importance of the pulmonary macrophage specifically and the lungs in general should be apparent.

Of first order of importance in the defense of the lungs are the immunological effectors known to be present in the pulmonary tissue. Of the five major classes of immunoglobulins, two, IgA and IgE, are characteristically produced in lymphoid tissues associated with external secre-

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tions such as those found lining the lamina propria of the bronchial mucosa. Secretory IgA, unlike its humoral counterpart, possesses an extra chain or secretory piece which is acquired as the molecule passes from the site of its synthesis in a plasma cell through the epithelial cells into the mucosa. Such antibody appears to be stimulated locally by antigenic contact and is not necessarily reflected in the antibody content of the peripheral circulation. Molecules of the IgE class are synthesized in plasma cells of bronchial lymph nodes and respiratory mucosa, but do not have a secretory piece.[2] Other classes of immunoglobulins may also be found in respiratory secretions,[3] particularly if the individual is IgA-deficient.[4]

Such secretory antibody is therefore the body's first line of specific humoral defense against respiratory pathogens, and protection against respiratory infection depends more on these antibodies than it does on the antibodies found in the serum. All immunoglobulins may be stimulated by antigenic contact with respiratory tissues, particularly if the stimulus is accompanied by irritation. This type of immunity is dependent on cells whose origin is the stem cells of the bone marrow, and is sometimes referred to as B cell-dependent.

Another form of immunity is associated with the presence of mature lymphocytes, the maturation of which is controlled by the thymus. This type of immunity is referred to as T cell-dependent and is responsible for resistance to many intracellular infections, delayed hypersensitivity, graft rejection, and certain other immunological responses. Such cellular immunity has been recognized to be of great importance in regard to the lymph nodes of respiratory tissue, but its protective role in regard to the air passages and alveoli is just beginning to be appreciated.

Both B and T cell systems of the lung are capable of being stimulated by direct antigenic contact with the respiratory tissues, but this is not necessarily so if antigenic contact is made via extrapulmonary routes.[5,6] Pulmonary T and B cell responses may occur with such extrapulmonary contact with antigen if the latter is accompanied by nonspecific pulmonary stimulation.[5] The immune responses of the lung to respiratory contact with antigens have not been studied extensively and present a fertile field for exploration.

TYPES OF IMMUNE INJURY

A practical system has been formulated for classifying the different modalities of immune injury.[1] The classification has proved useful, not only to the experimentalist, but also to the clinician who must take etiological pathophysiology into consideration for diagnostic and therapeutic purposes. Four distinct immunological responses have been described, all of which can play a role in the etiology of pulmonary

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Figure 6–1 Summation of the four types of immunologic injury. (Redrawn from Bellanti, J. A.: Immunology. Philadelphia, W. B. Saunders Co., 1971.)

disease (Fig. 6–1). In reviewing these different responses, it must be kept in mind that human pulmonary disease is often the result of a mixture of more than one type of response.

TYPE I

Type I reactions are those dependent upon reagin or antibody of the IgE class. Clinically such reactions are seen in the atopic patient with the classical forms of immediate hypersensitivity or allergy. IgE antibodies become fixed to certain receptor sites on mast cells by means of the nonantigen-reactive ends of the heavy chains of the globulin when specific antigen reacts with such cell-bound antibody. When two or more IgE molecules react with one molecule of antigen, it is postulated that the heavy chains are stressed in such a fashion that damage results to the attached cell, causing it to release various pharmacologically active mediators that result in the clinical manifestations.[7] Histamine, acetylcholine, heparin, 5-hydroxytryptamine, slow reactive substance A (SRS-A), and various plasma kinins are among those substances known to be released in Type I reactions.[8]

These mediators activate physiologically secondary target organs, e.g., smooth muscle and vascular tissue. If the inhaled particles are large (over 60 microns), the site of IgE activation is usually in the nasal turbinates resulting in the allergic rhinitis-hay fever diathesis. When smaller (6 to 20 microns) antigenic particles are inhaled, they lodge in the bronchi and bronchioles and if they react with specific IgE, bronchial asthma may result. Chronic stimulation of this kind may result in certain forms of cellular hyperplasia leading to the development of nasal polyps and bronchial smooth muscle hypertrophy as seen in hay fever and chronic bronchial asthma, respectively. Mucous metaplasia in which the ciliated cells are often replaced by goblet cells also occurs. The basement membrane may be often thickened or even ruptured, possibly owing to antigen-antibody complexes, but IgE may not be the only immunoglobulin involved in such basement membrane damage.[9, 10]

A few of the occupationally associated agents which are known to induce Type I sensitivity are listed below:

Agent	*Reference*
Isocyanates	11
Enzyme detergents	12
Platinum salts	13
Piperazine dihydrochloride	13
Aminoethyl–ethanolamine	13
Thermophilic actinomycetes	14
Wood dusts or resins	15, 16
Coffee bean dust	17
Wheat weevil	18

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The immunological methods for incriminating a Type I response rely on demonstrating the physiological effect of specific IgE present in the patient. This is more easily effected either by skin testing or by measuring the subject's ventilatory capacity following an aerosol challenge. Positive immediate skin tests (Type I) are characterized by the sudden appearance (within 1 to 2 minutes after challenge) of an edematous wheal and an erythematous flare. In subjects in whom extreme hypersensitivity is suspected or in whom there are contraindications to direct testing, the Prausnitz-Küstner or P-K test should be used. This is an indirect test in which the skin of a normal volunteer is first passively sensitized with an intracutaneous injection of a small amount of the patient's serum. Twenty-four hours later, the same site is injected with the antigen and a wheal and flare response sought.*

The Prausnitz-Küstner (P-K) test should not be confused with the passive cutaneous anaphylaxis (PCA) reaction which is occasionally used erroneously to diagnose human Type I allergy. In the latter reaction, guinea pig skin is first passively sensitized with serum, an incubation period is allowed to elapse, and then antigen and Evans blue are injected intravenously. The accumulation of the dye at the site of serum injection is regarded as a sensitive, positive reaction. This method will not detect human IgE unless the test is performed in monkeys or other nonhuman primates.[7]

Inhalation challenge tests are an excellent means of diagnosing Type I allergies and distinguishing them from other forms of immune injury. Although care is required for their performance, the response correlates well with clinical pulmonary disease. In such tests, the patient's forced expired volume in 1 second (FEV_1) is measured before and shortly after an aerosol challenge. If the subject is sensitive, his FEV_1 falls significantly within an hour, and slowly reverts to normal, usually in 2 to 4 hours. The fall likewise may be reversed by adrenergic drugs. After the initial reaction in some subjects, an additional decline in FEV_1 may occur after 3 to 4 hours; such a fall is usually an indication of the onset of a Type III response.

Type II

Type II reactions are those that result from antibody reacting with either an intrinsic antigenic constituent of the cell, an intrinsic antigen that is adherent to the cell, or an intrinsic antigenic specificity coincidentally similar to an extrinsic antigen. Several such antibodies have been associated with various forms of occupational respiratory disease.

Chief among the antibodies to intrinsic antigenic constituents of lung tissue are the humoral antibodies to an insoluble lung connective tissue component.[19] This antigen is collagen or reticulin and is also present in WI-38 human embryonic lung fibroblast cell cultures.[20] Circulating antibodies to this antigen are spontaneously produced in a variety

*A P-K test should not be done without first testing the patient's serum for Australia antigen.

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of chronic pulmonary disease,[19] are of the IgA class,[21] and are demonstrable by the antiglobulin consumption test.[19] The role of these antibodies in the pathogenesis of pulmonary disease has been well studied. They are cytotoxic for lung fibroblast cell cultures,[22] induce increased production of serum LDH_2 and LDH_3,[23] localize in focal patches of certain alveolar septa,[23] cause increased localization in the lung of bacteria cleared from the blood stream,[23] induce an increase of interstitial alveolar connective tissue leading to a distention of the terminal airways,[23] and predispose the host to a more invasive form of tuberculous infection.[24-26] They seem to arise as a result of any chronic lung disease in which there is appreciable tissue damage and may in turn contribute to further injury.

Another important lung antigen is a glycoprotein associated with capillary basement membranes.[20, 27] It is found in these membranes in kidney, lung, placenta, and other organs. Caution is necessary in working with this antigen prepared from glomerular basement membrane preparations since such preparations are often contaminated with collagen fibrils with similar antigenicity to the antigen described above.[20] True capillary membrane glycoprotein antigen induces complement-fixing antibodies (IgG or IgM), thereby distinguishing it from the connective tissue antigen. The former antigen seems to be the target for antibodies and is associated with the injury seen in Goodpasture's syndrome.[28] How these antibodies arise is unknown, but they may well be due to coincidental specificity with an extrinsic antigen.

Another antigen reported from lung tissue in association with disease states includes a material which is probably reticulin, but no information is available about the nature of its antibody or its relation to pathological changes.[29]

Rheumatoid factor (RF) and antinuclear factor (ANF), primarily IgM and IgA antibodies, respectively, have been reported to occur in association with a variety of chronic occupational respiratory diseases. RF is found in both human[30] and experimental silicosis,[31] asbestosis,[32] and coal workers' pneumoconiosis (CWP)[33, 34] significantly more often than in the normal population. The antibody may develop owing to the adjuvant effect of materials such as silica[35] and be a reflection of chronic tissue damage, but some experimental evidence indicates that RF also contributes to the development of the lesion. Passively administered RF was found to result in more intensive vasculitis when granulomata were induced with Freund's adjuvant.[36]

ANF seems to be a better indicator of the prevalence and severity of disease in CWP[33] and asbestosis[32, 37] in that its presence correlates well with the extent of radiographic abnormality and its prevalence in subjects with these diseases is greater than that of RF. Little is known about the function, if any, of ANF in vivo. The suggestion has been made that the Type II antibody may form immune complexes with nucleoproteins

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and lead to interstitial pulmonary fibrosis, idiopathic forms of which are associated with an increased prevalence of ANF.[38] Should this hypothesis prove correct, the reaction resembles more closely a Type III response (see below). Finally, evidence has been obtained that passively administered human ANF increased the polymorphonuclear counts and mean volume of pleural effusion in artificially induced pleurisy in experimental animals.[39] None of these antibodies appears to be primarily pathogenic, but rather intensify pre-existing pulmonary insults from other causes.

Little evidence is available to incriminate Type II antibodies to extrinsic antigens adsorbed to normal lung tissue, although the suggestion has been made that fungal antigens associated with farmer's lung may do so and that subsequent antibody reaction with these leads to injury.[40]

Type III

An explanation of Type III or soluble immune complex reactions requires an understanding of some of the fundamentals of antigen-antibody reactions. Serum antibodies to many soluble antigens may be demonstrated by the precipitin reaction, but visible reactions will only be seen if certain conditions are met. The formation of a visible precipitate depends on the development of a lattice structure between bivalent IgG antibodies and multivalent antigens. Since the ratio of valence between antigen and antibody is so great, the two reactants are able to combine in different proportions depending on the relative concentrations of each. A range of such reactions through various concentrations is depicted in Figure 6–2.[41]

In regions of antigen excess, the number of antigen valences so outnumbers antibody valences that there are not enough antibody molecules to act as bridges between the antigen-antibody complexes (represented by the tube on the right in the figure); hence, no lattice of visible precipitate develops even though an antigen-antibody reaction has taken place. These complexes remain soluble and are capable of fixing complement.

Once the complement cascade has been activated through the C3 component, small peptide cleavage products become chemotactic for neutrophils. These cells are drawn to the area of immune complex deposition and may release their lysosomal enzymes which injure the adjacent tissue. Whether exposure to an antigen develops into such an injury reaction depends on many things. The concentration of antigen is very critical; if it is too high, apparently the complexes are too small or possess only one antibody molecule per complex so that complement is not fixed. If the complexes form at equivalence, i.e., relatively lower concentrations of antigen, they are precipitated and phagocytized in the circulation without incident.

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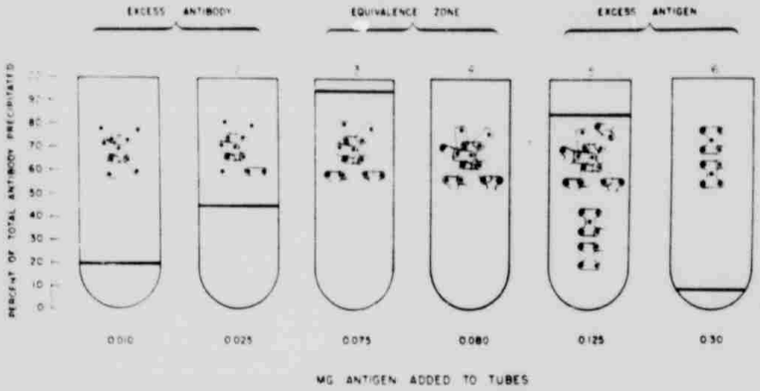


Figure 6–2 Schematic representation of a precipitin curve showing the composition of soluble immune complexes in ratios of antigen excess (Tube 6). Not enough antibody is available to build a lattice among the complexes, but such complexes are still capable of fixing complement. (From Raffel, S.: Immunity. 2nd Ed., 1953. Courtesy of Appleton-Century-Crofts, Publishing Division of Prentice-Hall, Inc., Englewood Cliffs, N.J.)

Type III reactions are responsible for the dermal Arthus reaction, part of the serum sickness syndrome, and the most common form of glomerulonephritis.[42] These conditions differ mainly in the site of deposition of the soluble complexes. Should the site be the lung, the ensuing reaction is thought by many to be the principal pathophysiologic mechanism of the disease variously known as hypersensitivity pneumonitis, vegetable pneumoconiosis, or extrinsic allergic alveolitis. An extensive literature has been amassed implicating the association of precipitins to various extrinsic antigens with these diseases. Most of these reports have dealt with farmer's lung[43, 44] or other forms of what collectively are called the vegetable pneumoconioses[45, 46] even though the inciting agent is sometimes of animal origin.[47, 48] A few of the occupationally associated agents known to produce precipitins and pulmonary disease are listed below.

Agent	*Reference*
Aspergillus spp.	14
Thermophilic actinomycetes	14, 45, 49
Pigeon excreta	48
Graphium spp.	50
Sisal fibers	51
Maple bark fungus	52
Alternaria	53

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It will be observed that some of these agents also induce Type I sensitivity.

Immunologic tests for incrimination of Type III reactions include skin testing, the demonstration of serum precipitins, and measurements of pulmonary function following inhalation challenge. Skin testing is performed by intracutaneous injection of antigen, but positive reactions do not appear until 3 to 4 hours after the test, are usually maximal at 7 to 8 hours, and resolve within 24 hours. In humans, a positive reaction consists of a markedly edematous, pruritic erythematous area with little or no central induration. The reaction in rabbits is more extensive and the inflammation often leads to a central necrosis.

The presence of precipitins against extracts of appropriate fungi is often demonstrated by the Ouchterlony method of immunodiffusion.[54, 55] Better and quicker results may be obtained by electrophoretically forcing the antigen to migrate to the anode against the cathodally migrating globulins of the patient's serum[56] (Fig. 6–3). With Aspergillus antigens, the presence of more than two lines is usually indicative of aspergilloma or invasive aspergillosis.[55]

Provocation tests by means of aerosol challenge are also useful in

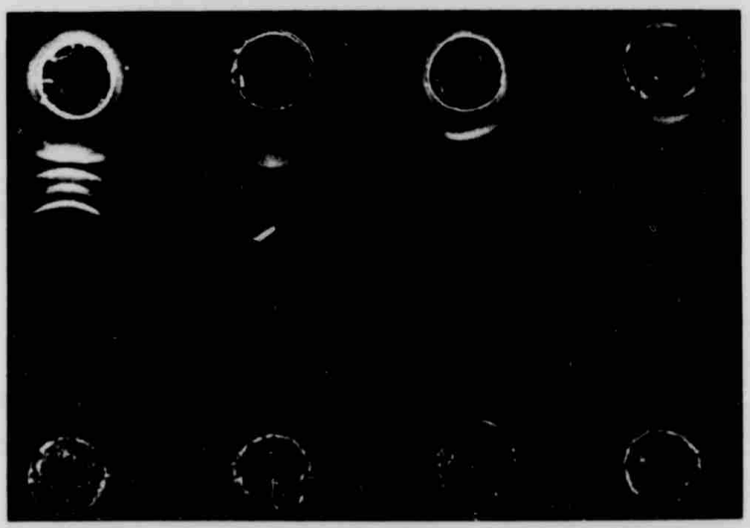


Figure 6–3 Counter-immunoelectrophoresis pattern between patients' sera (top row) and Aspergillus antigens (bottom row). Electrophoretically, the anode is at the top and the cathode is at the bottom. The patient on the left demonstrates a pattern indicating intimate antigenic contact with the fungus. Precipitation shown by the other sera is regarded as nonspecific.

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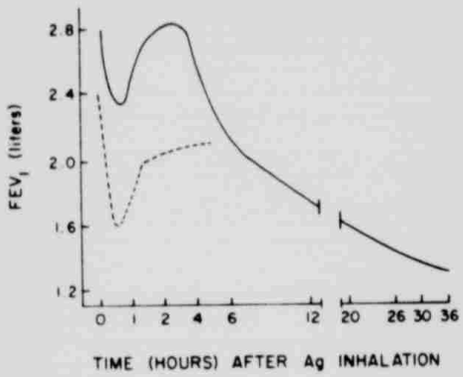


Figure 6–4 FEV_1 results obtained from two patients after aerosol challenge with fungal antigen. The dotted line was obtained from a patient who exhibited only a Type I atopic response. The solid line was from a patient who exhibited a dual response: an initial Type I reaction which resolved by 2 hours was followed by an additional Type III reaction between 4 and 6 hours. (Redrawn from Pepys, J.: Hypersensitivity diseases of the lungs due to fungi and organic dusts. Monogr. Allergy 4. 1, 1969.)

differentiating Type I from Type III reactions. A restrictive response is indicated when there are significant falls in both FEV_1 and forced vital capacity (FVC) about 4 to 6 hours after challenge. The ratio of FEV_1/FVC remains unchanged in such a response, but the decline in lung volumes may be accompanied by a reduction of the carbon monoxide-diffusing capacity. An obstructive response is also seen in which only the FEV_1 decreases, thereby leading to a change in the FEV_1:FVC ratio. Type III responses are more prolonged than Type I responses, are often accompanied by fever, and can be reversed by the administration of steroids. Often a patient will show a dual response (Fig. 6–4), indicating the coexistence of Type I and Type III reactions. In such instances, the time of appearance and resolution of such changes is important in differentiating them.

Type IV

Type IV reactions differ from the previous three in that humoral immunoglobulins are not involved. Rather, this form of reaction is due to cell-mediated immunity or delayed-type hypersensitivity. The prototype of this kind of reaction is the delayed skin reaction to tuberculin seen in persons who have been exposed to tubercle bacilli.

The principal cells responsible for this type of reaction are the thymus-dependent lymphocytes. When antigen reacts with specifically sensitized lymphocytes, a variety of effectors are released that account for such manifestations as migration inhibition of macrophages, target cell cytotoxicity, mitogenesis, chemotaxis, and transfer of specific sensitivity.[37] These factors all participate in vivo in producing the gross and histological appearances of the lesions of delayed hypersensitivity. As

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with humoral mechanisms of defense, such a line of immunity is ordinarily beneficial, but may also be injurious.

In addition to the well known injurious inflammatory reaction that accompanies tuberculin hypersensitivity, Type IV reactions are also largely responsible for the injurious reactions seen in berylliosis.[58] Several soluble mediators are demonstrable in vitro following incubation of patient's lymphocytes with beryllium salts and in turn correlate well with skin reactivity. However, skin or patch testing with beryllium salts is contraindicated because such testing may indeed induce primary sensitization or cause an exacerbation of pre-existing lesions in diseased subjects.[59]

Experimental evidence suggests that, in animals exhibiting Type IV skin sensitivity, severe pulmonary changes are produced if the animals are challenged with aerosolized antigen.[60–63] These changes consist of peribronchial and perivascular infiltrates of lymphocytes, some interstitial infiltrates, interalveolar septal thickening, dilatation of capillaries and increased respiratory frequency with no change in airways resistance.

Just as there is a humoral aggressive response against lung antigens in certain forms of chronic pulmonary disease (Type II), so there is also a Type IV counterpart. Such a mechanism has been described that reacts against a soluble connective tissue antigen of lungs.[64] Evidence of Type IV reactivity to this antigen has been found in a variety of experimental pulmonary diseases, e.g., experimental berylliosis and coal workers' pneumoconiosis, but also in a limited number of patients with chronic respiratory disease. Under these circumstances, the pathological change initiated by an extrinsic agent apparently leads to a Type IV reaction against an intrinsic antigen.

There are reports of Type IV responses to certain extrinsic antigens, notably bagasse, *Micropolyspora faeni*, and pigeon excreta, all of which antigens are usually associated with Type III reactions.[65, 66] The varied clinical picture seen in hypersensitivity pneumonitis appears to depend not only on variation in the host response, but also on the site of the antigen antibody reaction.[67]

Methods for detection of Type IV sensitivity are limited to intracutaneous skin testing and demonstration of mediators following in vitro incubation of patient's lymphocytes with test antigen. Positive delayed-type skin tests consist of erythema and 10 mm. or more of induration 48 hours after injection. The induration may proceed to necrosis; hence, the lesion does not resolve quickly. In very sensitive individuals, initial signs of reactivity may appear as early as 6 to 8 hours following injection.

One of the more popular methods of demonstrating in vitro correlates of Type IV reactivity is by the technique of macrophage migration inhibition. If macrophages and sensitized lymphocytes are incubated in tissue culture media within a capillary tube, the macrophages will begin

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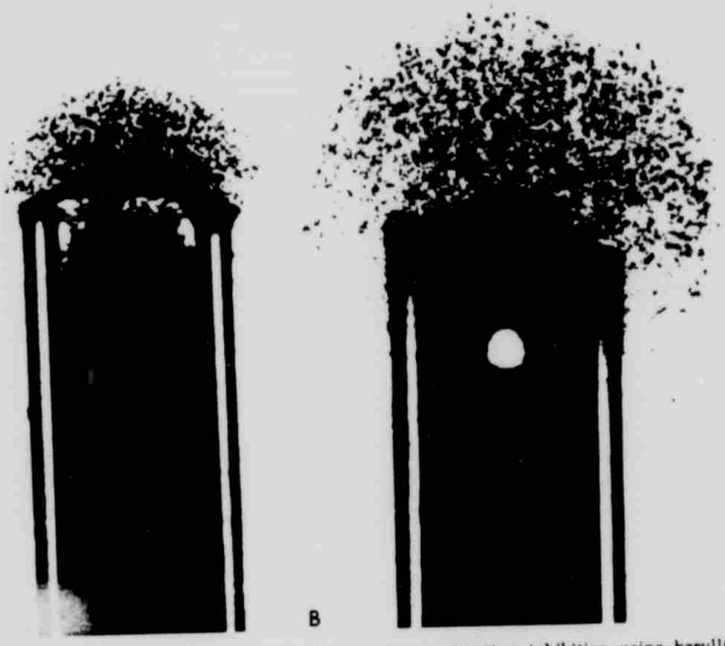


Figure 6-5 Enlarged views of macrophage migration inhibition using beryllium fluoride as antigen. A shows the macrophage migration from a patient with clinical beryllosis; B was obtained from a normal control. The beryllium salt markedly inhibited the normal migration of macrophages from the capillary tube only when the patient's cells were used. (Reproduced through the courtesy of Dr. J. J. Marx.)

to migrate out of the tube within 24 hours. If the cells are incubated with specific antigen, this migration pattern is greatly inhibited. The difference between normal migration and specific inhibition due to beryllium in a berylliotic patient's lymphocytes may be seen in Figure 6–5.[68] Another Type IV mediator commonly sought following incubation of lymphocytes with test antigen is lymphocytotoxin. In this procedure, the supernatant fluid from the lymphocyte-antigen mixture is placed on selected target cell cultures, e.g., fibroblasts. The cultures are either examined directly for cytopathogenic effects or, if the cells have been labeled with a radiochemical, release of the label into the medium is detected instrumentally.[70] One final method involves stimulating blast formation in patient's lymphocytes with antigen.[70] Sensitized cells will begin to divide, as evidenced by uptake of radioactively labeled thymidine following antigenic stimulation.

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