Symposium

BASIC MECHANISMS IN ALLERGIC DISEASES

BRET RATNER, M.D., New York City, Chairman; T. N. HARRIS, M.D., Philadelphia; MILTON G. BOHROD, M.D., Rochester, N.Y.; ADOLPH ROSTENBERG, JR., M.D., Chicago

RECENT DEVELOPMENTS IN THE CELLULAR TRANSFER OF HYPERSENSITIVITY AND ANTIBODY FORMATION

T. N. HARRIS, M.D.

This review will describe certain developments which have appeared recently in the immunologic literature involving the transfer of viable cells from one animal to another. In 1940 Landsteiner and Chase showed that it was possible to remove cellular exudates from guinea pigs sensitized with simple chemical compounds, wash these cells and transfer them to fresh guinea pigs and then to demonstrate in the recipient guinea pigs dermal sensitivity to the original compound. More recently, Dr. Merrill Chase sensitized guinea pigs with o-chlorobenzoyl chloride: paraffin oil had been injected intraperitoneally into these animals 48 hours before, in order to induce the necessary cellular accumulation. These cells were collected, washed and injected into a recipient guinea pig, which thereupon developed a positive reaction to the allergen.

Similar experiments were done with cells secured from lymph nodes of sensitized guinea pigs and in the case of heat-killed tubercle bacilli suspended in hydrocarbon as antigen. The same phenomenon has been demonstrated by Metaxas with intradermally injected cells, and by Lawrence in the human species with leucocytes collected from blood and injected intradermally. Tissue reactions of the immediate type of hypersensitivity have also been demonstrated by Chase as a function of transferred cells by the use of the Schultz-Dale technic, as well as by an adaptation of the PK type of reaction to the measurement of classical antibodies.

It was felt in our laboratory that this type of approach might provide more direct information on the mechanism of antibody formation in the cells involved. Accordingly, a study of such cells was undertaken, using largely bacterial cells as antigens and measuring the agglutinins produced thereto. The hind foot pads of rabbits were injected with 0.2 cc. of a 0.5% suspension of Shigella paradysenteriae, previously killed by exposure to alcohol, and 4 days later—at a time when the popliteal lymph node is known to contain antibody—the animals were killed and the lymph nodes excised. The cells of the nodes were gently teased into salt solution with fine dissecting needles. The lymph nodes were generally large and swollen and as the teasing was begun streams of whitish material would pour out into the surrounding fluid. The cells were collected, washed and injected into recipient rabbits. The sera of the recipient animals showed some agglutinins on the first day after transfer, and an increase in titer on the 2nd day. The peak titer usually occurred on the 3rd or 4th day, after which there was a plateau for a few days, with a decline in titer beginning at about the 7th day. The serum titer had usually returned to its pre-injection level between the 28th to 40th day after transfer.

The effectiveness of such transferred cells in causing the appearance of antibody in the recipient animal could be prevented by any of the following treatments of the cells: freezing and thawing in a dry-ice-alcohol bath, incubation overnight at 37°C, ultraviolet irradiation, injection into species other than the rabbit (guinea pig, embryonated hen’s egg), and exposure to alcohol. It was felt that the appearance of antibody in the serum of the recipient rabbits was not due to active immunization or to passive immunization, but probably to some function of the transferred cells.

PATHOLOGY OF THE ALLERGIC AND COLLAGEN DISEASES

MILTON G. BOHROD, M.D.

The pathologic changes found in allergic disease are probably never pathognomonic. There are, however, characteristic findings which show varying degrees of necrosis, exudation with edema.
granuloma formation, or homogenizing change in collagen. If each of these changes is selected for classificatory purposes and the allergic and related diseases be assigned in the classification according to the predominant change, a classification such as that in table 1 may be constructed. This table shows also the experimentally produced states and the (probably) nonallergic conditions which show similar histologic findings. Table 2 indicates that each of these groups has important clinical and immunologic correlations.

### Table 1

<table>
<thead>
<tr>
<th>Examples in Human Pathology</th>
<th>Examples in Experimental Pathology</th>
<th>Nonallergic Mechanisms Which May Produce Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing Tissue selective</td>
<td>Cortical necrosis of kidney; acute pancreatic necrosis</td>
<td>Arthus and Schwartzman phenomenon</td>
</tr>
<tr>
<td>Necrotizing Cell selective</td>
<td>Thrombocytopenic purpura; granulocytopenia</td>
<td>Antiplatelet serum</td>
</tr>
<tr>
<td>Anaphylactoid</td>
<td>Serum sickness; asthma and hay fever; atopic dermatitis; glomerulonephritis; periarteritis nodosa</td>
<td>Experimental anaphylaxis; experimental nephritis, etc.</td>
</tr>
<tr>
<td>Granulomatous Tuberculoid</td>
<td>Tuberculosis; brucellosis; tularemia, etc.; beryllium granulomas</td>
<td>Experimental infections with same organisms?</td>
</tr>
<tr>
<td>Granulomatous Rheumatoid</td>
<td>Rheumatic fever; rheumatoid arthritis; “giant-cell” rheumatoid granulomas</td>
<td></td>
</tr>
<tr>
<td>Hyalinoid Collagen diseases</td>
<td>Disseminated lupus erythematosus; dermatomyositis; scleroderma</td>
<td>None known</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Amyloidosis</td>
<td>Parenteral injection proteins or nucleic acids</td>
</tr>
</tbody>
</table>

Necrotizing lesions resemble the Arthus and Schwartzman reactions. They may select specific tissues or pick out single specific cells in a tissue, as for instance in the bone marrow. One source of sensitizing substances responsible in the induction of this group of lesions is probably auto-antigens, which lead to auto-immunization.

Anaphylactoid lesions are predominantly exudative, sometimes almost exclusively edematous. They make up the bulk of the lesions which are treated by the practicing allergist. Eosinophilia is a common finding in the peripheral blood, in exudates and in the tissue lesions.

Granulomatous lesions may resemble those of tuberculosis (tuberculoid granulomas) or of the rheumatoid diseases (rheumatoid lesions). The similar histologic picture of tuberculoid lesions is the result of the similar allergic state which exists in all of them; a similar skin test for all of them, when appropriate antigen is used, is a clinical correlate of this fact. The purely histologic diagnosis of tuberculosis is no longer justified and the etiologic agent of tuberculoid granulomas must be sought by bacteriologic methods. Rheumatoid granulomas occur around joints, in skin, and in eyes and viscera. The lesions in the lining of joints is often nonspecific.

The collagen diseases are probably only in a minority of cases allergic, unless auto-antigens will be found to be responsible in this group. Periarteritis nodosa represents a disease which shows characteristics about equally divided between the collagen diseases and the anaphylactoid states. The lupus erythematosus cell is a distinct advance in the diagnosis of one of this group; lupus erythematosus. Plasmaclastyosis and hyperglobulinemia are frequent findings. When they reach their most marked degrees, amyloidosis is a possible end-result.

One of the characteristic features of all the foregoing groups is their tendency to be associated together. Typical periarteritis nodosa occurs with asthma and with rheumatoid arthritis; granulomas with periarteritis nodosa (Wegener’s granuloma); all of these with amyloidosis; and innumerable other combinations. Similarly, histologic lesions of one group may be found to some degree in any of the other groups. This frequent co-existence is evidence that they share mechanisms in common and that, in some fashion, they belong together in one classification.
<table>
<thead>
<tr>
<th>Type of Clinical Reaction</th>
<th>Clinical Course (Velocity)</th>
<th>Duration</th>
<th>Skin Reaction</th>
<th>Antibody in Serum</th>
<th>Increased Serum Globulin</th>
<th>Specific Infection</th>
<th>Eosinophilia</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing</td>
<td>Immediate</td>
<td>Rapid</td>
<td>Short</td>
<td>0 or + Necrosis</td>
<td>0</td>
<td>0 or +</td>
<td>0 or +</td>
<td>++++ (Diffuse)</td>
</tr>
<tr>
<td>Anaphylactoid</td>
<td>Immediate</td>
<td>Rapid</td>
<td>Short to moderate</td>
<td>Wheal type</td>
<td>Frequently +</td>
<td>Usually 0</td>
<td>+ to ++++</td>
<td>+ (Fibrinoid)</td>
</tr>
<tr>
<td>Granulomatous</td>
<td>Delayed</td>
<td>Variable</td>
<td>Short to long</td>
<td>Tuberculin type</td>
<td>0</td>
<td>0 to +++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Tuberculoid</td>
<td>Delayed</td>
<td>Slow</td>
<td>Long</td>
<td>0</td>
<td>0</td>
<td>0 to ++</td>
<td>0</td>
<td>0 or +</td>
</tr>
<tr>
<td>Rheumatoid</td>
<td>Delayed</td>
<td>Slow</td>
<td>Long</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0 or +</td>
</tr>
<tr>
<td>Hyalinoid</td>
<td>Delayed</td>
<td>Variable</td>
<td>Short to long</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0 or +</td>
</tr>
<tr>
<td>Collagen disease</td>
<td>Delayed</td>
<td>Slow</td>
<td>Long</td>
<td>0</td>
<td>0</td>
<td>+ to ++++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Delayed</td>
<td>Slow</td>
<td>Long</td>
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<td>0</td>
<td>+ to ++++</td>
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</tbody>
</table>
Allergy is a battle against the invasion into the body of foreign substances that are inhaled, ingested or injected. The body is so constructed that it continually impedes the invasion into the circulation of materials that cannot be utilized. When the organism fails to prevent the entrance of inimical agents, allergy may ensue.

The major role in allergy is played by the antigen-antibody tissue reaction. The union between antigen and fixed cellular antibody (sessile antibody) produces cellular irritation which results in physiologic disturbances of the affected tissues.

For example, in serum sickness the antigen must be present either in the circulation or within the cells in order to bring about the reactions with early formed antibodies.

We believe that histamine does not play a major role in the resultant physiologic pathology of the phenomenon under discussion but, if anything, a very minor one.

It might be stated that the weal is the ultimate unit of the allergic reaction. The basic mechanism and genesis of weal formation, however, is not fully understood.

We postulated that weal formation would be a sudden constriction of the arteriole resulting in a fall in arteriolar pressure—the stoppage of blood to the venules with its sudden back flow—increased pressure on the endothelial lining of the venules and lymph structures with a transudate into the surrounding tissue and weal formation.

When unstriated muscle is stimulated or irritated by any means, whether it be chemical, hormonal, neural, physical or by the union of antigen and specific antibody, the only response that such smooth muscle can have is to contract.

The type of syndrome that is evoked depends upon the characteristics of the tissue affected. Thus, if the involuntary muscle of the arteriole contracts, if bronchioles become spastic, if the hepatic venules become stenosed, if perineural vessels are affected, if the unstriated muscle of the gastrointestinal tract is involved, one can readily see how different must be the resultant physiologic and pathologic disturbances. It enables us to conceive how the varied gamut of syndromes such as serum sickness, eczema, urticaria, hay fever, asthma, disturbances of the gastrointestinal tract, central nervous system involvement and the profound liver changes and changes in other organs may transpire. All these apparently diversified manifestations therefore come about from a single basic phenomenon, namely, a spasm of one or another of the many involuntary muscle structures in the various tissues. All this bears witness to the widespread distribution of sensitized tissue cells.

Although many tissues are affected, the major reaction dominates and overshadows all others, for it is the vital organ that contains the most strategically located smooth muscles that produces the major reaction in a given allergic episode.

With our present knowledge, were we to accept the histamine concept of the allergic phenomena, or the newer endocrine concept inherent in the use of ACTH and cortisone, or the dominant role of the psyche as the primary modus operandi of the allergic reaction and put aside the antigen-antibody mechanism, I believe there would be little hope for more than symptomatic relief of the allergies.

It is the study of the many ways and means that antigens have of invading the body and producing interactions with tissue-fixed antibodies which offers the greatest hope for a thorough understanding of the basic mechanism of the allergic phenomena. The contributions based solely on the antigen-antibody concept have given us a profound insight into the fundamental nature of allergy.

SOME OF THE MECHANISMS BY WHICH DRUGS AND ANTIBIOTICS PRODUCE REACTIONS

Adolph Rostenberg, Jr., M.D.

Too often when a patient takes a drug and some reaction develops, it is alleged that the patient is allergic to the drug in question without any evidence being offered to support that designation. Actually, there are many mechanisms by which drugs can produce reactions other than via an allergic sensitization. The accompanying table lists some of the known mechanisms.
AMERICAN ACADEMY OF PEDIATRICS

Mechanism

I. Pharmacologic
   a. acute
   b. chronic and cumulative

II. Enzymic Interference
   a. vitamin deficiency-like states
   b. photosensitization

III. Idiosyncratic

IV. Allergic

V. Shwartzman

VI. Herxheimer-like effect

VII. Ecologic

VIII. Biotropic

Example

Ergot gangrene
Argyria
Pellagra
Acrodynia
Sulfa light eruptions
Pellagra
Arsenical keratoses
Iododerma
Bromoderma
Penicillin "serum sickness"

"Penicillids"
Monilial eruptions
Erythema nodosum

By pharmacologic is meant an effect that is known to be a property of the drug in question and would develop in anyone who took the drug in adequate dosage and for an adequate length of time.

By enzymic interference is meant that a drug either "poisons" a given enzyme system or that the drug competes with the system for a necessary component so that its proper functioning is impaired. Probably the pharmacologic effect of a drug is often arrived at by this means, but, in the present case, the enzymic interference is one that is neither anticipated nor desired.

By idiosyncrasy is meant an inborn deviation in the way that the individual will respond to a given stimulus. Both qualitative and quantitative aberrations are included, although these are sometimes separated.

By allergy is meant a specifically acquired alteration in the capacity to react brought about by means of an antibody mechanism.

By the Shwartzman phenomenon in this connection is meant the production of cutaneous lesions where the skin has been prepared by either the lodgement of bacterial toxins or the organisms themselves; subsequently the intravenous circulation of the same or other bacterial toxins or the occurrence of an antigen-antibody union causes the development of a hemorrhagic necrotic reaction in the prepared skin site.

A Herxheimer effect is defined as an accentuation of pre-existing lesions or the development of new ones, based on a too vigorous destruction of organisms so that either allergens to which the individual is sensitive or toxic materials are released.

By ecologic interference is meant that the drug, by virtue of destroying competitors of a given micro-organism, renders conditions more favorable for the propagation of the organism in question.

By biotropism is meant that the drug has a stimulating effect on certain micro-organisms latent within the individual.

It should, of course, be realized that there are probably other mechanisms by which drugs produce reactions and also that many of the mechanisms discussed are not mutually exclusive. Consequently, the same clinical manifestation might be brought about by more than one of the processes considered. Many of the definitions given require further amplification for the sake of clarity and precision, but in the space of this abstract this was not possible.
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