A GLANCE AT MODERN MEDICAL PROGRESS IN ALLERGY

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Hypersensitivity or allergy is often considered a relatively new medical phenomenon, and it is true that as in other branches of medicine, a great amount of progress in research, especially in immunology, has been made in the last two decades.

However allergy as a field of study has an ancient and interesting past. A great deal of description and nomenclature exists in the field of allergy, beginning from the time Lucretius called allergic phenomena *idiosyncrasies*, and Sextus Empiricus classified man as body, soul and idiosyncrasies. The word *idiosyncrasy* at that time had a wider meaning than it has today: good vision at night, chilliness under the sun, perspiring in shadow, and ability to eat beef although fish caused indigestion, were all *idiosyncrasies*. However, the relationship between allergy and idiosyncrasy was not emphasized until the 19th century when Hyde Salter, in 1868, described the role of food idiosyncrasies in asthma. At the same time, Charles Blackley developed a skin test which enabled him to discover which grasses caused his hay fever.

Animal experiments in this field also clarified many clinical observations. Magendie gave several albumin injections to animals. He observed that no harm was done at the first injection, but that after repeated injections the animals sickened and died. Von Behring made a similar observation which he called *paradoxical reaction*. The same type of reaction was observed by Charles Richet and Portier in 1909, who used the term *anaphylaxis*, meaning without protection. Not too long after, it was found that *idiosyncrasies*, *paradoxical reaction*, and *anaphylaxis* were all linked together by the same immunologic mechanism. About the same time a relationship between anaphylaxis and hay fever was suggested by Wolff-Eisner. And as asthma, vasomotor rhinitis and eczema were now linked together under the new concept of an *exudative diathesis*, the basis of modern allergy was fairly well established. Finally, in 1906, von Pirquet,

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called the father of allergy, coined the word *allergy*, meaning altered reaction. The word designated the altered response of an individual toward a specific material resulting from prior experience with that material.

The mechanism of hyposensitization, which he called *anti-anaphylaxis*, was described by Besredka in 1907. A few years later, Noon successfully used inoculation for hay fever, and about this time, Dale and Laidlow showed the similarity between anaphylaxis and histamine effect in experimental animals. These theoretical concepts, widely accepted until very recently, are embodied in the so-called "cellular histamine theory". This theory has enjoyed almost universal support for the past quarter century although in recent years some allergic manifestations could not be explained by the effect of histamine alone.[1] Further investigations have led to the discovery of some histamine-like substances and metabolites, called chemical mediators. These include acethlcholine,[2] bradykinin,[3] heparin,[4] 5- hydroxytryptamine,[5] slow-reacting substances,[6] and perhaps others. They produce contractions of the smooth muscles and changes in capillary permeability, and are thought to be released by the antigen-antibody reaction.

The present dominance of the cellular view, however, has not eliminated entirely another concept which received considerable mention in current discussions of hypersensitivity. This is the *humoral theory*, which gives primary importance to anaphylactogenic poisons. The anaphylatoxin is supposedly formed in the body fluids as a consequence of antigen-antibody union. The original anaphylatoxin theory of Friedemann and Friedberger in 1909, revived by Rocha e Silva,[8] was further investigated by Burdon with Schultz-Dale apparatus.[9]

A certain confusion resulted in the early twentieth century as clinical and experimental allergic study advanced rapidly together. To avoid misidentification, Coca used the term *atopy* for those allergic diseases of a hereditary nature which occurred spontaneously; and anaphylaxis for artificially induced hypersensitivity.

The demonstration of circulating antibody reagins in atopic sensitivities by Prausnitz-Küstner[10] in 1921 was the biggest allergic discovery of the century. Reagins (abnormal type antibodies) against pollens, fungi, animal danders, and foods have been detected in the allergic person. The type and severity of the symptoms are related to the antigen-antibody combination, and to the release of auto-pharmacologic mediators.

This great success in detecting antibody states brought out the inherent confusion between immunity and allergy. Immunity had been described

as protection or resistance against diseases because of the presence of antibodies. Now allergy was also discovered to be caused by the presence of antibodies. It remained to be discovered in the next decade that the essential difference between immunity and allergy lies in the amount and distribution of the specific immune bodies between body fluids and cells. Immunity and allergy can be thought of as two sides of a coin (Figure 1).

Figure 1.

The allergic phenomenon can occur in any human organ as a result of the interaction of antigens and antibodies, causing a series of disturbances in the cell. Every practicing physician, whatever his branch of medicine, will be confronted with various allergic problems.[11] (Figure 2). The great variety of allergic type diseases is shown in Table 1.

The scope of allergy has enlarged as the presence of antibodies has been demonstrated in a variety of so-called idiopathic diseases. New immunological techniques are also being discovered which demonstrate the characteristics of these antibodies. Among these techniques are the hemagglutination test,[12] gel diffusion test,[13] improved Schultz-Dale test[14], immune electrophoresis,[15] ultra centrifugation,[16] the electron microscope, radioisotope techniques,[17] immune histochemical method (Coon's fluorescein labelling technique),[18] and autoradiography.

Body cells themselves may become antigenic in response to drugs or infection. Thus a group of *auto-immune* diseases, defined as immune response directed against the body's own tissues or organs, is formed. Organs known to respond in this way include the thyroid, central nervous system, peripheral nervous system, testes, eye, kidneys, adrenal skin, articular tissue, lung and the formed element of the blood.[19]

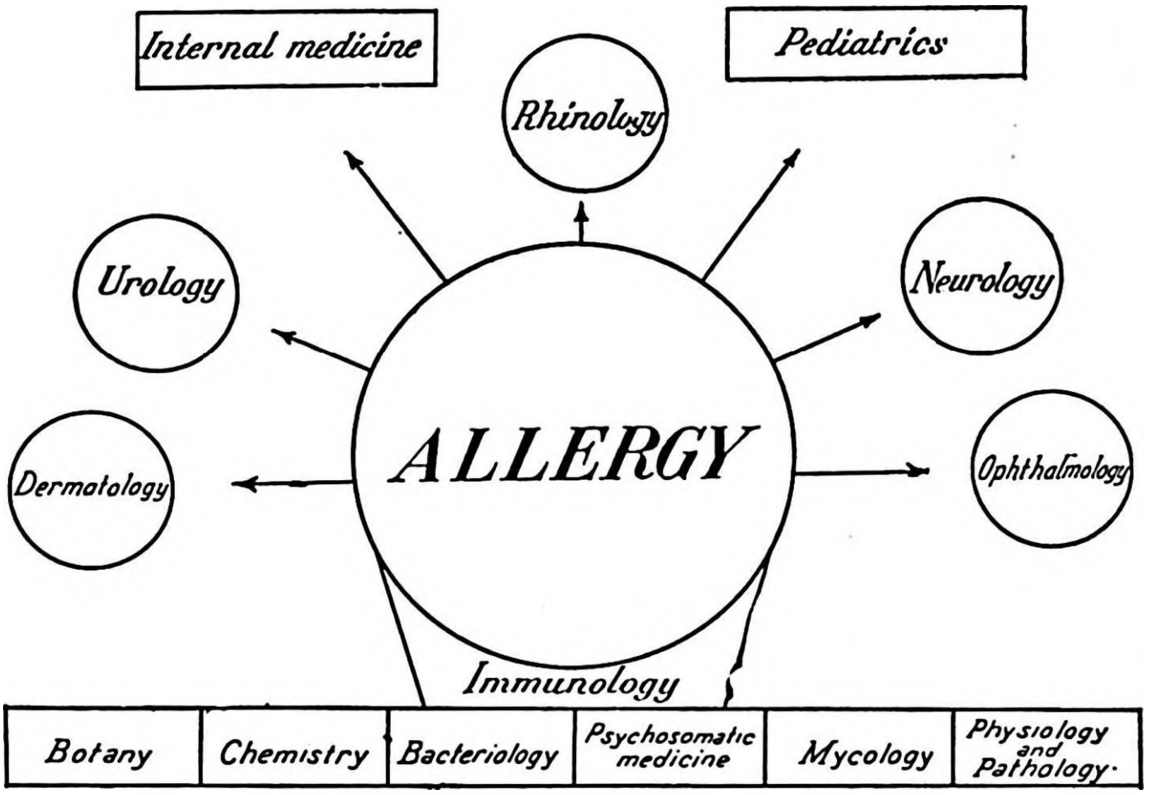

Figure 2. The relationship of allergy to other branches of medicine.

TABLE 1

CLASSIFICATION OF ALLERGY ACCORDING TO INVOLVEMENT

1. Respiratory tract allergy
   - a. asthma
   - b. hay fever (seasonal allergic rhinitis)
   - c. perennial allergic rhinitis
2. Skin allergy
   - a. atopic dermatitis (eczema)
   - b. urticaria, angioneurotic edema
   - c. contact dermititis, cosmetic allergy
3. Central nervous system allergies
   - a. allergic headache
   - b. migraine
   - c. histamine cephalalgia
4. Ocular allergy
   - a. vernal conjunctivitis
   - b. Stevens–Johnson syndrome
   - c. Reiter's syndrome
   - d. allergic karatitis

5. Ear allergy
   a. allergic vertigo
   b. serous otitis
6. Gastro–intestinal allergy
   a. allergic gastritis, enterocolitis
   b. stomatitis, glossitis, pharyngitis
   c. esophageal allergy
   d. hepatocellular allergy
   e. painful epigastric syndrome, allergic pancreatitis
   f. Heiner's syndrome
7. Cardiovascular allergic reactions
   a. isolated myocarditis
   b. allergic vasculitis
   c. hypersensitivity angiitis
8. Diffuse connective tissue diseases (Collegen diseases)
   a. polyarteritis nodosa
   b. systemic hypererytheriatosus
   c. acute rheumatic fever
   d. rheumatoid arthritis
   e. scleroderma
   f. dermatomyositis
9. Genito–urinary tract allergy
10. Articular allergy
11. Allergy and hematology
   a. iso–immune or homo–immune reactions, red blood cell–erythroblastosis fetalis transfusion reactions
   b. purpura (allergy involving blood vessels)
      purpura simplex
      vascular purpura
      purpura due to drugs
      Henoch–Schoenlien purpura
12. Auto–immune (homo–immune) reactions
   a. thyroid
      experimental thyroiditis
      "Hashimoto" disease
   b. central nervous system
      experimental allergic encephalomyelitis
      demyelinating disease in man
      post–Pasteur rabies vaccine paralysis
   c. eye

allergic uveitis
sympathetic ophthalmia
phako–anaphylactic endophthalmitis

d. auto–immunity involving the formed elements of the blood
hemolytic anemia
agranulocytosis
thrombocytopenic purpura

13. Physical allergy
a. allergy
b. solar sensitivity

14. Drug allergy

In 1942 Klemperer popularized the term *collegen disease* as a diagnostic clinical concept. Collegen diseases seem to be related to allergy in that hypersensitivity appears to offer the only available clue, meager though it may be, as to the possible etiology of these diseases. The auto-immune reaction may be a cause of the characteristic inflammatory response seen in collegen diseases. It is also speculated that tissue injury in collegen disease may result primarily from the release of pathogenic enzyme products by cell lysosomes. Allergists have recently begun to investigate the thymus gland, which is believed by some to produce antibodies. Patients with dysgammaglobulinemia have been noted to have thymomas. The main function of the thymus seems to be to produce an immunologically competent cell.

Landerman[20] and other researchers believe that an enzyme defect produces angio–edema in cases of hereditary angioneurotic edema.

Landsteiner[21] proved that a non–protein substance after entering the body becomes allergenic by attaching itself to a tissue protein. This concept provides a basis for understanding simple chemical idiosyncrasies, or drug allergies.

Since Landsteiner's work, various allergic manifestations, myocarditis, skin lesions, from erythema to exfoliative dermatitis, are reported to have resulted from various drugs. Although in most instances skin-testing for drug allergies is unreliable, tests with penicilenic acid for penicilin allergy seem promising. After detecting the offending allergens, elimination or hyposensitization is the only solution for keeping the reaction under control. Since the elimination of the offending allergen is not possible in all allergic disorders, hyposensitization becomes the necessary therapy.

Hyposensitization has progressed a great deal since the time of Noon. The old multiple-injection hyposensitization technique has recently given way to the repository method, which involves new techniques of preparing and standardizing extracts of pollen and of emulsifying and administering them in repository form. [22]

Certain allergic manifestations have been relieved by surgical intervention. The removal of the carotid body (glomectomy) for the surgical treatment of bronchial asthma has been reported by Nakayama in Japan. [23] Overholt published his favorable results in 1961. [24] However recent studies have raised questions about the effectiveness of these procedures. [25]

Allergists are currently concerned with auto-immune diseases. The list of these diseases becomes longer day by day, and many so-called idiopathic diseases are being investigated jointly by immunologists and allergists. Investigations in the field of enzymology indicate that allergic syndromes may be caused by enzyme defects, in that enzyme deficiency, or lack of a given enzyme may result in an altered reactivity (allergy) of the body cells.

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