PRINCIPLES OF IMMUNOLOGY—A BRIEF REVIEW

PART II. CLINICAL IMMUNOLOGY

By

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AntigenAntibody Reaction in vivo.

Antigen-antibody reaction in vitro have been enumerated in Part-I. The biological effects of antigen-antibody reaction will now be studied. These reactions occuring in body are usually of beneficial nature to the host. They either alter the biological activities of the antigen or neutralize its toxic products by exerting anti-enzymatic action and thus render the antigen harmless. These in vivo protection phenomena form one of the major factors in total defence of the host.

Sometimes, however, tissues of a host react toward a specific substance in a manner which is different from earlier experiences of the same individual or from those of other individuals of the same species. This altered reactivity of tissues toward specific substances is termed *Allergy.*

Allergy.

(Allos = other; Ergon = energy i.e. altered energy).

Conventionally, "allergy" is used synonymously with "hypersensitivity". Strictly speaking, however, the term allergy should also be inclusive of "hypoergy" (diminished reactivity) and "anergy" (absent reactivity). The study of allergy thus becomes the study of antigen and antibody of allergy and their reaction.

Allergens.

These substances are, usually like antigens in immunity, proteins or partial compounds like lipids, lipoid-soluble extracts of plants or foods. They can be microbial or non-microbial. Some of the latter ones are formaldehyde, metal salts, quinine, penicillin, etc.

Antibodies in Allergy.

As described previously, these are usually univalent, heat-labile, non-precipitating and cannot pass through placenta. Usually again they are beta-globulins. When they are gamma-globulins, the gamma-globulin molecule is physically changed as it combines with its allergen. Either the molecule is compressed or altered so that it can injure the tissues. Further, the optical rotation of this globulin complex with allergen is different from that of normal complex. Similarly, heat-denaturation of human gamma-globulin produces an effect on the gamma-globulin which is similar to that of the allergen-antibody complex, it increases the capillary permeability and binds complement.

The effectiveness of antigen-antibody complex is gauged by the property of the antibody and not by that of antigen molecule. Again, the antibody factor alone determines the complement-fixing and the tissue-fixing property.

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Antibodies in allergy are either circulating antibodies i.e. serum antibodies or cell-fixed i.e. cellular antibodies. The former ones differ from the circulating ones in immunity (vide infra) in that they are non-precipitating and hence non-observable in tubes. However, their presence is established by the fact that they produce "wheal and flare" type of skin test which appears in 30 minutes after intracutaneous injection and the response disappears after 60 minutes.

Cellular antibodies are fixed to cells; are not found in serum, and hence cannot be transferred passively by serum but can be demonstrated in their effects by transferring these living cells of allergy to a nonsensitive but homologous animal. The latter animal will show similar allergic effects following the transfer.

Mechanism of Tissues Injury in Hypersensitivity.

Development of hypersensitivity in a given individual depends upon (1) his opportunity for repeated contact with the allergen and (2) his capacity for sensitization. The latter is genetically determined.

Traditionally, the reactions of hypersensitivity are categorized into (a) the Immediate ones i.e. those beining within minutes of contact with allergens and (b) the Delayed ones, which begin within serveral hours of the contact. (Vide Table II). The immediate reactions are due to circulating antibodies and the delayed once are due to cell-fixed antibodies.

The injection of a soluble allergen into a sensitized animals results in the formation of soluble antigen-antibody complexes. These soluble circulating complexes are pathogenic and produce tissue injury by acting as trigger mechanism, activating the complement system and inducing the release of various tissue toxins like histamine etc. These result in profound effects of host tissues. The immediate tissue effects are different in different species. In human beings any single or combination thereof can occur. The effects are (1) contraction of smooth muscle of uterine and ileal strip as in the Schultz-Dale reaction, and in bronchial asthma; (2) endothelial proliferation in acute experimental glomerulonephritis or chronic glomerulonephritis of membraneous type in experimental serum sickness; (3) haemorrhagic vascular necrosis and polymorphonuclear and eosinophilic infiltration in the Arthus reaction; (4) fixation of complement and haemolysis.

Our knowledge of the effects and role of antigen-antibody complex is derived antirely from experimental work.

Antigen-antibody complexes produce tissue damage, in all probability, through (1) the mediation of serum factors, (2) liberation of pharmacologically active amines, and (3) activation of enzyme systems.

With the aid of the enzymatic action, A-A complexes cause degranulation of basophils and mast cells, liberating vasoactive amines. These amines increase the capillary permeability and spasm of smooth muscles. Local tissue involvment results in inflammatory changes in blood vessel walls, polymorphonuclear leukocyte infiltration, and finally there is catabolism of A-A complexes.

TABLE II

CLASSIFICATION OF HYPERSENSITIVITY REACTIONS (Criep, 1967)

I. Those Associated with Circulating antibodies. .....
(Immediate Response)

II. Those associated with Cellular sensitivity.
(Delayed Response).

- Microbial (see Table. III). Id Reactions.
- Non-microbial. e. g. 1. Eczematous allergic contact dermatitic
  2. Fixed eruption.
  3. Homologous graft rejection

III. Those resembling I and/or II

A. Autoimmune (see the text).

B. Homoimmune e. g. Rh-sensitization. Transfusion reactions.

C. Heteroimmune e. g. Nephrotoxic serum nephritis.

....Non-familal...

..(1)...Anaphylaxis. (A-A. Reaction in tissues) (One Reactant fixed in tissues)

Systemic	Cutaneous.
1. Direct	1. Direct
2. Passive	2. Passive
3. Reversed passive	3. Reversed passive

..(2)..Arthus Reaction (A-A. Reaction in b.vs.) (No reactant fixation)

..(3)..Serum Sickness (A-A Reaction protracted)

a. Experimental.

b. Clinical.

....Familial..Examples..Atopy, bronchial asthma, hay-fever' urticaria, allergic rhinitis, angio-oedema.

TABLE III

DIAGNOSTIC SKIN TESTS (Criep, 1967)

I. BACTERIA.	II. VIRAL.	III. PARASITIC.	IV. MYCOSES.	V. SARCOIDOSIS.
Diphtheria.....Shick	L. G. V.... Frei.	A. Protozoa	A. Superficial.	Kveim.
carlet fever.....Dick S-C* reaction.	Mumps.	1. Sleeping sickness.	Dermatophytoses.	
Brucellosis....Brucellin.		2. Leishmaniasis.	(Trichophytin)	
Tularemia.....Foshay.		3. Toxoplasmosis.	B. Deep.	
Glanders.....Mallein.		B. Metazoa.	1. Coccidiomycosis	
Tuberculosis..Tuberculin.		1. Filariasis	2. Blastomycosis	
Leprosy.....Lepromin.		2. Ascariasis.	3. Histoplasmosis.	
Chancroid....Ito-Reens-tierna.		3. Schistosomiasis.		
Whooping cough.... Pertussin.		4. Strongyloidiasis.		
		5. Trichinosis.		
		6. Hydatid dis.(Casoni)		

*Schultz-Charelton Reaction.

Vasoactive amines liberated in tissues are Histamine, Serotonin (5-hydroxy-tryptamine), Slow Reacting Substance (SRS), Bradykinin, Heparin, Acetylcholin, and Anaphylatoxin.

Anaphylaxis.

Immediate reactions may manifest clinically diversly depending on the rate and site of the reaction. Anaphylaxis may be systemic or cutaneous. The systemic reaction exhibits different clinical signs in different animal species, but is always the same in a given species of host regardless of the type of antigen involved.

Active. Anaphylactic shock characteristically occurs upon injection of a given antigen into a host which is hypersensitive to that allergen. *Clinically,* generalized urticaria, angioedema, pruritus, fall in blood pressure, asthma, circulatory collapse, laboured respiration, laryngial oedema, and death may occur within a few minutes or the patient may recover. The anaphylactic shock has not been reported in patients with agammaglobulinaemia.

Passive. Passive sensitization of a normal animal is brought about by transfer of serum of sensitized animal to that normal. Now, an injection of allergen gives rise to anaphylaxis.

Reversed Passive Anaphylaxis. The antigen is injected intraperitonially into an animals and after an incubation period, the related antiserum (and not again the antigen) is injected. This leads to the anaphylactic shock. Example-Guinea pig normally contain Frossman antigen. When a guinea pig is injected with a serum containing anti-Frosemen-Antibody, the animal goes into shock.

In cutaneous anaphylaxis dye is employed to visualize the skin reaction.

Anaphylactoid Reaction. They resemble anaphylactic shock clinically. But they occur in a nonsensitized animal when injected with such substances as histamine, bee or snake venom, peptone or following injection of finely suspended or colloidal material. They have no connection with antigen-antibody reaction. The above injected materials may be causing liberation of vasopressive amines.

Arthus Reaction.

This is an immediate type of reaction which results in localized tissue damage. Inoculating into rabbit in the same subcutaneous region with repeated doses of horse serum, it is noted that the initial injections are without any detectable effects; but as one injection suceeds another, the local reactions become more intense and more persistent. The lesion is always characterized first by redness and oedema, induration appears later, and finally haemorrhage and necrosis, The essential lesion in this reaction is an inflammatory lesion of blood vessels following deposition of antigen-antibody complex in the vessel wall, and the damage is done largely by polymorpho-nuclear leukocytes.

Serum Sickness.

This usually appears after a few days of injection of serum. It is marked by urticaria predominantly. Nowadays because of fewer injections of sera this reaction

has diminished in frequency. This reaction and Arthus reaction are considered by some workers to be Intermediate reactions rather than Immediate ones

Atopy.

The suseptibility for sensitization appears to be inherited, but the individual must have effective contact with the respective allergen before hypersesitivity can become established. Inherited nature of atopy has been doubted by Kabat on statisiss tical grounds. He recommends further study of large number of families of patient-with atopy. *Prausnitz-Kustner Reaction.* The serum of allergic patients contain no precipitating antibodies but a skin-sensitizing antibody, an IgA, 'Reagin' (which is different reagin from that of syphilis). This is transferred to a nonallergic individual on one hand and the other arm is kept as a control. Now when the allergen is inoculated in both the sides, the test-side shows allergic phenomenon.

Autoallergic Phenomena.

Normally the body 'recognizes' its own proteins, and does not produce any antibody or a reaction against them. Under some less known conditions or in some individuals the body reacts towards these proteins or antigens as if they are 'foreign' to the body. This reaction is called autoimmunity or better termed autoallergy. Some of the conditions supposed to be due to autoallergy are :—

Tissues or Organ	*Diseases or conditions*
Blood-RBCs.	Acquired haemolytic anaemia.
WBCs.	Leucopenia.
Platelets.	Idiopathic tnrombocytopenic purpura.
Endocrines-Adrenals.	Idiopathic Addison's disease.
Thyroid.	Hashimoto's disease.
Connective tissues.	Systemic Lupus erythematosus.
	Rheumatoid disease.
Kidneys.	Acute glomerulonephritis.
Others.	Idiopathic ulceratitive colitis.
	Multiple sclerosis.
	(After Boyd).

Criteria to be considered when calling a condition autoallergic :—

(1) Circulating or cell-fixed antibodies to be demonstrated.

(2) Antigen should be known.

(3) Specific antibodies should be produced in experimental animals.

Common features of Autoallergic diseases ;—

(a) Often familial; (b) Follows an infection usually; (c) Hypergammaglobuliemia. (d) false positive serological STS of syphilis. (e) relief by corticosteroids.

For classificiation of hypersensitivity reactions see Table II.

For Delayed reactions see Table III.

For Hyposensitization see Pillsbury's "Dermatology".

For inability to form antibodies and "Dysproteinaemias" refer to Criep's "Dermatologic Immunology".

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