VASCULAR ALLERGY AND ITS SYSTEMIC MANIFESTATIONS

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To

MARY

My Wife

FOREWORD

Most textbooks on allergy concern themselves with a general review of the fundamentals, the preparation of allergens, together with skin tests and the description, as well as the treatment of the more common allergic diseases such as hay fever, asthma, atopic eczema and urticaria. The allergic manifestations in other organs receive but passing emphasis. With the increasing knowledge of hypersensitivity it becomes apparent that certain specific tissues may become involved in the allergic response, in conjunction with or to the exclusion of those of the respiratory tract. This is exemplified by individual publications and monographs dealing with allergy of the eye, skin, hematopoietic systems, and so on. Except in instances of damage by direct cellular contact with the antigen, the manifestations of these various shock organs can be attributed to reactions in the supplying blood vessels. The latter may be the primary target of the allergenic stimulation responsible for the secondary effects in special tissues. However, in addition to these there are the allergic responses in the cardiovascular system. Information already available has indicated that sensitization to exogenous factors, such as tobacco, foods, drugs, antibiotics, and infection may account not only for reversible, but also for irreversible reactions in the heart and blood vessels. These include the more generalized vascular syndromes such as some types of periarteritis nodosa (also referred to as hypersensitivity angiitis). It has likewise become increasingly evident that autoimmune processes may play an important role in conditions such as rheumatic heart disease, the vasculitis in rheumatoid arthritis, and the multifaceted symptoms of other so-called collagenous diseases such as lupus erythematosus disseminatus, dermatomyositis, and scleroderma, in which the connective tissue vascular system in its totality is implicated in the hypersensitivity response.

While there are various contributions dealing with the immunological mechanisms involved in these clinical entities, there is as yet no single book available in which a correlation of the immunological, pathological, and clinical aspects of

vascular allergy and its systemic manifestations has been presented. It is therefore the purpose of this monograph to coordinate the above-mentioned features and to emphasize that sensitization of the vascular structures may be responsible not only for disease in special organs and tissues, but also of the heart and blood vessels as such.

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June, 1963

JOSEPH HARKAVY

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CHAPTER 1

HYPERSENSITIVITY

INTRODUCTION—DEFINITIONS

THE STUDY of hypersensitivity has made increasing progress during the past fifty years. It deals with the phenomena of anaphylaxis, allergy, and atopy, conditions which may be regarded as various forms of hypersensitiveness to substances that in most instances are foreign proteins. The manifestations of hypersensitivity result from specific reactions between antigen and antibody, or by some operationally similar factor. Such interaction is followed by injury or irritation to the tissues of the sensitized host at the point of impact, either through the release of a toxic substance or from an as yet unknown mechanism. The damage to the tissue which may ensue can occur promptly, that is, minutes after the introduction of the antigen, in which case it is referred to as an immediate form of hypersensitivity. This is exemplified by the state of anaphylaxis. If the reaction is postponed from twenty-four to forty-eight hours, it is referred to as delayed hypersensitivity.

IMMEDIATE REACTION

The immediate reaction is mediated by humoral antibodies which may be either precipitating or non-precipitating. The circulating antibody is transferable by plasma or washed cells (Chase, 1951) and is associated with skin reactions which are immediate and transient, of urticarial character. The tissue responses are usually limited, involving smooth muscles, blood vessels, and collagen.

DELAYED REACTION

The delayed type of hypersensitivity is exemplified by the reaction to infection, and after contact with simple chemicals, poison ivy, and other substances. The reactivity may appear in a wide range of cells. There is no conclusive proof at the present that humoral antibodies are implicated in this delayed process. The hypersensitivity is transferable only by cells. The skin reactions are of the tuberculin type and persist for several days. They consist essentially of a proliferative mononuclear cellular response.

ALLERGY

The term *allergy*, introduced by von Pirquet in 1906, may be defined as a qualitatively altered capacity of living tissue to react specifically to antigenic stimulation. It implies previous exposure to the specific antigen

and connotes both the immediate and delayed forms of hypersensitiveness. It is gradually replacing the term *atopy* which was originally employed by Coca and Cooke to indicate an inherited form of sensitiveness. Later, Cooke regarded atopy as designating allergy of the wheal reacting type of spontaneous hypersensitiveness, rather than those with an hereditary factor. Variations in the term allergy, such as *anergy, hypoergy, hyperergy,* or *hyperergic reaction,* have been employed to indicate quantitative degrees of sensitivity. The hyperergic response with which we are mostly concerned implies a highly augmented state of hypersensitiveness to a given substance as compared with reactions in a control group. Although these variant terms do not greatly add to our understanding of the hypersensitive state, frequent usage makes their definition desirable.

ALLERGEN

The agent responsible for an allergic reaction is referred to as an *allergen.* This term must be distinguished from the word *antigen,* a substance which, when injected into an animal, will stimulate the formation of antibodies. Antigens are complex biological substances of high molecular weight. They usually are proteins, but nonproteinaceous substances, especially polysaccharides, may also act as inciters of antibody formation. An allergen is generally a protein containing material which is also capable of behaving as a true antigen. Antigens are also able to act as allergens. For example, egg white when introduced into an animal body will cause the development of antibodies and an anaphylactic type of hypersensitiveness. When egg white is ingested by an individual who is allergic to it, it functions as an allergen and may induce reactions in the form of asthma, eczema, or other disorders.

Prominent among allergens are inhalants such as dust, pollen, mold spores, animal danders, feathers, insecticides, and foods such as eggs, milk, wheat, and so on.

ANTIBODIES

Antibodies are plasma globulin molecules, often the same as normal gamma globulin in all respects except for their capacity to react specifically with antigen. The group of gamma globulins includes a major component which consists of more than 90 per cent of the total, known as the 7S gamma globulin fraction, and two minor fractions known as 19S gamma globulin (*beta* 2M globulin), and *beta* 2A globulin, constituting less than 10 per cent of the gamma globulins. It has been suggested that these two minor components, because of their common antibody function be called gamma 1M and gamma 1A globulins. Gamma 1M has a sedimentation rate of 19S and a molecular weight of about one million, whereas that of 7S is approximately 160,000. The molecular weight of 1A globulin is not known but is probably similar to 7S gamma globulin.

SHOCK ORGANS

The tissues which react to an allergenic stimulus are referred to as *shock organs* or *shock tissues*. The symptoms which follow such stimulus depend upon the nature of the allergenic excitant and upon the character and function of the particular shock organ. Thus the common and generally well-known clinical manifestations resulting from allergic reactions in the respiratory tract may be exemplified by hay fever and asthma; those in the skin by various types of eczema; in the eyes by conjunctivitis and other disturbances; in the nervous system by migraine, headaches, and so on.

CARDIOVASCULAR DERANGEMENTS

Not as familiar as the above reactions are the allergic reactions in the cardiovascular system. This system may be the major shock tissue in certain experimental animals, such as rabbits, as well as in man. In order to have a clear understanding of the human responses to sensitization in the cardiovascular system it was therefore deemed advisable to consider the subject from the following points of view: (*a*) to survey the experimental reactions in the vascular system of the lower animals following sensitization, inasmuch as these may be regarded as the prototypes of the analogous disorders in the susceptible individual; (*b*) to review the different mechanisms and the abnormal alterations in tissues which follow sensitization by proteins as such, and bacterial and chemical agents; (*c*) to describe the clinical syndromes arising therefrom.

In textbooks dealing with diseases of the cardiovascular system, hypertension, arteriosclerosis, rheumatic fever, and certain specific infections are usually looked upon as precursors of many functional and organic disorders of the heart and blood vessels. Yet there are morbid processes in the cardiovascular system in which these predisposing factors are not demonstrable. Functional derangements in the heart and blood vessels have frequently been attributed to nervous disturbances, psychosomatic factors, or pharmacologic and toxic actions of substances such as tea, coffee, alcohol or tobacco, and various drugs. While this point of view may be valid to a certain extent, little attention has been paid to the fact that many of these ingestants, inhalants, and bacterial agents may be responsible for cardiovascular derangements because of their sensitizing, rather than toxic or pharmacologic, effects. If the latter were the only mechanisms at play, then everyone would be similarly affected to a varying extent. This is certainly not the case. Thus, for example, not everyone develops angina pectoris or coronary artery disease as a result of smoking. Nevertheless, the rising incidence of coronary artery disease and mortality in smokers raises the issue of whether tobacco is inherently toxic or whether it acts as a sensitizing agent in susceptible individuals. The same questions arise with respect to the newer therapeutic drugs and antibiotics, such as the sulfonamides, penicillin, as well as infection. These substances are increasingly responsible for sensitization resulting in the immediate, reversible, serum-sickness types of reaction,

as well as the delayed and irreversible forms implicating the connective tissue vascular system. The anatomical changes which follow such sensitization are characterized by fibrinoid degeneration of extravascular and intravascular collagenous tissue in arteries and veins, accompanied by eosinophilia. As a consequence of this involvement a variety of symptom complexes, depending upon the grouping of participating shock organs, make their appearance. The resulting syndromes represent clinical manifestations of vascular allergy. In cases in which sensitization of the vascular connective tissues becomes generalized, a picture of periarteritis nodosa may supervene. It is therefore important to recognize the early syndromes of vascular allergy before they progress to the stage of periarteritis nodosa, for the purpose of prevention if possible, and treatment.

Inasmuch as fibrinoid degeneration of collagenous tissue is also present in such diseases as disseminated lupus erythematosus, scleroderma and dermatomyositis and since, as pointed out by Baehr and Pollack in 1947, such alteration in the connective tissue, "is not a pathological process of sufficient specificity to serve as a common denominator for classification of disease," it was deemed advisable from the point of view of pathogenesis to explore to what extent allergy plays a role in the underlying mechanism of these maladies, and to review briefly their clinical and pathological manifestations.

CHAPTER 2

ANAPHYLAXIS

As indicated in the introductory chapter, anaphylaxis may be looked upon as the prototype of hypersensitiveness of the immediate type. The conditions necessary for establishing the anaphylactic state are as follows:

1. Introduction into a normal animal of an antigen-foreign protein, polysaccharide, or simple chemical which is capable of combining with tissue proteins that act as carriers

2. An incubation period of about ten days or less during which sensitization takes place with the development of antibodies in response to the antigenic stimulus. These antibodies are demonstrable by precipitin tests or by passive transfer to a normal recipient who becomes temporarily sensitized

3. Reinjection of the specific antigen into the sensitized subject, followed by union between it and the preformed antibodies in the blood or possibly on or within cells, which results in an immediate violent reaction that may be fatal. This is known as anaphylactic shock.

TISSUE REACTIONS

The tissues affected in the anaphylactic response are smooth muscles, blood vessels, and collagen, as well as other special cells. Reaction in smooth muscles is manifested by constriction of the bronchial musculature in the guinea pig, resulting in bronchial obstruction and asphyxia; by spasm of the pulmonary vessels and the presence of hyalin thrombi in the pulmonary capillaries in the rabbit, causing right-sided cardiac failure responsible for death; and by occlusion of the hepatic veins in the dog, producing distension of the liver and fall in blood pressure due to capillary dilation in the splanchnic area, leading to *exitus*. The implication of smooth muscle in anaphylactic response is also evident in the *in vitro* contraction of the guinea pig uterine strip after the application of the specific antigen (Schultz-Dale reaction).[27, 28]

CARDIOVASCULAR REACTIONS

EXPERIMENTAL

Systemic involvement of blood vessels in sensitized animals, such as rabbits, guinea pigs, and mice, may be visualized microscopically after parenteral introduction of antigen such as horse serum.[1] One may see arteriolar contraction with increased adherence of leukocytes to the vascular endothelium, emigration of leukocytes through the walls of capillaries and venules, and sticking of leukocytes to each other in clumps or emboli which block the circulation in many capillaries and venules. In addition

to the arteriolar constriction there is also increased capillary and venular permeability. The fact that these reactions occur in the absence of any nervous influence has been indicated by McMaster and Kruse [23] in mice, by Ovary [26] in the guinea pig, and by Szepsenwohl and Witebsky [29] in the three-day-old chick embryo which contains Forssman's antigen. The vascular network of the embryo goes into shock following the application of Forssman's antiserum. This is characterized by the shrinking of the embryo which sinks into the yolk, followed by a total standstill of the heart.

Anaphylactic reactions in the isolated heart have been studied in guinea pigs,[10, 20] rabbits,[13, 21] cats,[27] and rats.[22] These indicate severe disorganization of the heartbeat following challenge with an effective dose of antigen which varies qualitatively with the species tested and quantitatively with the degree of immunization of the host.

Electrocardiographic abnormalities during acute anaphylaxis, characterized by bradycardia and tachycardia and preceded by extrasystoles, depressions in the ST segments, QRS complexes and T waves, as well as heart block, have been described by Auer and Lewis,[7] Auer and Robinson,[6] Criep,[11] and Mikulicich [25] in guinea pigs, dogs, and rabbits. These responses were attributed to spasms of the muscles of the coronary vessels, anoxemia of the heart muscle due to contraction of the arterioles of the lung, and to permeability changes in the tissues. According to Bickel,[8] the ECG. pattern in the rabbit is similar to that produced by cor pulmonale.

Specific reactions in the coronary arteries of guinea pigs sensitized with horse serum, following exposure to a small amount of homologous antigen, have been shown to be present by Wilcox and Andrus.[2, 32] These reactions, recorded electrocardiographically by direct leads applied to the isolated heart, were characterized by acceleration of the heart rate and alterations in the amplitude of contraction. The P–R interval was prolonged and deviations in the form of R, S, and T complexes were also evident. The authors concluded that the changes were the results of actual modification in the caliber of the coronary vessels and not due to an augmentation in the heart rate or muscle tonus.

The fact that the cardiac muscle *per se* participates in the process of sensitization, and that this muscle is capable of responding directly to antigenic impact independently of any alteration in coronary blood flow, has been demonstrated by Kellner, Penna, and Schweid,[18] Harkavy,[16] and Feigen and colleagues.[15] Kellner and his colleagues showed that perfusion with homologous antigen of the isolated hearts of guinea pigs which had been previously sensitized to proteinase and other agents caused disturbances in impulse formation and conduction in the form of ectopic beats and A.V. block of varying degree. Similar changes were obtained when isolated auricular muscle, devoid of blood supply, was exposed to the specific sensitizing agent. Feigen and his co-workers have also demonstrated that the response of the sensitized guinea pig heart to perfusion with an effective dose of homologous antigen (ovalbumin) was found

to consist of an acceleration of the rate of the heartbeat, an increase in amplitude of contraction, and a decrease in coronary flow. The characteristic mechanical reaction of the isolated atria was an increase in amplitude and frequency of contraction, the most intense effect of which resulted in fibrillation. These reactions were brought about by a release in the perfusate of physiologically active material elaborated during the anaphylactic reaction. This substance was identified as histamine by pharmacological methods as well as by paper chromatography of butanolic extracts. All of the mechanical and electrical events noted in the Langendorff [19] heart and in the isolated atria could also be reproduced precisely by an appropriate dose of histamine. Brockelhurst [9] has found in three experiments that the sensitized guinea pig heart liberated S.R.A. (slow-reacting substance), as well as histamine.

Tissue injury due to hypersensitivity.—The hyperergic reaction in the connective tissue vascular structures is exemplified by the Arthus [3, 4, 5] phenomenon. The latter manifestation follows the repeated intracutaneous or subcutaneous introduction of the specific antigen into the rabbit or other susceptible animal at intervals of several days. The initial application is without effect. Following the second injection there may appear a moderate degree of edema which remains for several hours. With successive injections the edema becomes more marked and prolonged, and after the fifth or sixth injection is followed by hemorrhage and necrosis. The necrotic lesion is characterized by increased permeability of the capillaries, by outpouring of fibrinogen into the tissue spaces with deposition of fibrin, and by thrombosis of the lymphatics, capillaries, and small veins, all of these being conditions which insure the local fixation of antigen.[24] Swelling and degeneration of collagenous fibers and eosinophilia also occur.

MECHANISMS OF THE ANAPHYLACTIC REACTION

The mechanisms responsible for the tissue reactions in anaphylaxis are as follows:

1. The interaction between a sufficiently high concentration of reactive antibody and the injected antigen results in a precipitate which in itself is capable of damaging blood vessel walls. This antigen–antibody interaction is probably the case in the Arthus phenomenon

2. According to Weiser [31] the severe tissue injury may be due to mediators liberated into the surrounding tissue fluids and blood from sensitized cells by the interaction of antigen and antibody. These agents act in turn upon other cells. The best documented of these mediators is histamine. Histamine is generally regarded as the principal mediator of anaphylaxis in the guinea pig and dog. In the rabbit however, both histamine and serotonin are released into the plasma during anaphylaxis. *In vitro* studies have also shown that following antigen–antibody reaction, serotonin is liberated mainly from the blood platelets. Histamine appears to be released from platelets as well as the tissues. Both amines contribute to the toxicity noted in this animal during anaphylaxis (Waalkes and Coburn).[30]

HISTAMINE

According to Farmer,[14] repeated intraperitoneal injections of histamine acid phosphate into rabbits, guinea pigs, and rats produce an inflammatory reaction in the vascular systems of the lung, heart, and endomyocardium. The lesions which are observed bear a marked resemblance to those seen in rheumatic carditis, rheumatic pneumonitis, and periarteritis nodosa.

It must be pointed out however, that histamine is not the only substance involved in the reactions of experimental or human hypersensitiveness. Neither does histamine explain all of the phenomena observed, such as incoagulability of the blood in the dog, change in sedimentation rate, and others. There is evidence that heparin, serotonin, as well as a slow-reacting substance,[17] and perhaps proteolytic ferments, may also be released during anaphylactic reactions. Serotonin is present in the mast cells of various animals, especially rats and mice, as well as in man. In man this substance is also to be found in blood platelets. Serotonin and histamine are inflammatory agents, which may be released not only by antigen–antibody interaction but also by other so-called liberating substances, such as peptone, anaphylotoxin, and Compound 48/80.

Irrespective of the nature of the mediator liberated as a result of antigen–antibody interaction, whether it be histamine, serotonin, other agents, or a combination of these, the vascular reactions which follow suggest that the primary point of contact between the specific antigen and antibody in the experimental animal and in the hypersensitive individual may be either on or within the cells of the vascular endothelium or the tissue immediately adjacent.

REFERENCES

1. Abell, R. G. and Schenk, H. P. (1938). *J. Immunol.*, **34,** 195.
2. Andrus, E. C. and Wilcox, H. B. (1939). *J. exp. Med.*, **69,** 545.
3. Arthus, M. (1903). *C. R. Soc. biol.*, **55,** 817.
4. — (1908). *Arch. int. Physiol.*, **7,** 471.
5. — (1909). *Arch. int. Physiol.*, **9,** 179.
6. Auer, J. and Robinson, C. C. (1913). *J. exp. Med.*, **18,** 450.
7. — and Lewis, P. A. (1910). *J. exp. Med.*, **12,** 151.
8. Bickel, G. (1960). *Schweiz. Med. Wschr.*, **90,** 912.
9. Brockelhurst, W. E. (1960). *J. Physiol.*, **150** (No. 4), 713.
10. Cesaris-Demel, A. (1910). *Arch. ital. Biol.*, **54,** 141.
11. Criep, L. H. (1931). *Arch. intern. Med.*, **48,** 1098.
12. Dale, H. H. (1913). *J. Pharmacol.* **4,** 167.
13. Demoor, J. (1921). *Arch. int. Physiol.*, **18,** 369.
14. Farmer, L. (1950). *J. Allergy,* **21,** 120.
15. Feigen, G. A. *et al.* (1960). *Circulation Research,* 713.
16. Harkavy, Joseph and Perlman, E. (1960). *Ann. N.Y. Acad. Sci.*, **63,** 327.
17. Kellaway, C. H. and Trethewic, E. R. (1940). *Quart. J. Exp. Physiol.*, **30,** 121.
18. Kellner, A., Penna, M. and Schweid, A. J. (1955). "Cardiac Anaphylaxis." *Circulation,* **12,** 670.
19. Langendorff, O. (1895). *Arch. ges. Physiol.*, **61,** 291.
20. Launoy, L. (1911). *Ann. Inst. Pasteur,* **25,** 561.
21. Leyton, A. S. (1916). *J. Physiol.*, **50,** 265.
22. McElroy, W. T. (1956). *Stanford Univ. Ph.D. Diss.*

23. McMaster, P. D. and Kruse, H. (1949). *J. exp. Med.*, **89,** 583.
24. Menkin, V. (1931). *Arch. Path.*, **12,** 802.
25. Mikulicich, G. (1951). *J. Allergy*, **22,** 249.
26. Ovary, Z. (1951). *Boll. Soc. ital. Biol. sper.*, **27,** 386.
27. Schultz, W. H. (1912). *J. Pharmacol.* **3,** 299.
28. — (1910). *J. Pharmacol.*, **1,** 549.
29. Szepsenwohl, J. and Witebsky, E. (1934). *C. R. Soc. biol.*, **115,** 1019.
30. Waalkes, T. P. and Coburn, H. (1960). *J. Allergy*, **31** (No. 2), 151.
31. Weiser, R. S. (1957). *J. Allergy*, **28,** 6, 475.
32. Wilcox, H. B. and Andrus, E. C. (1938). *J. exp. Med.*, **67,** 169.