A CRITICAL REVIEW

BASIC MECHANISM OF HYPERSENSITIVITY REACTIONS

By

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1. INTRODUCTION

Life usually exists in harmony with its environments by making constant adjustments. However, there are times, when conditions are so altered that a physiological balance becomes impossible, and disease ensues. A peculiar state is when the biological system reacts violently in contact with certain substances which are usually inocuous. Such states, whether they exist in human or in animals have been grouped together under the term 'hypersensitivity' which in most instances is due to foreign proteins (96). Some people like Vaughan & Black (234) prefer to call this state only 'sensitivity'. It is important at the very outset that the various terms

may be clearly defined. As in other fields of medical science, there is lack of precise terms in this field as well. Allergy is a term which was coined by Von Pirquet (1906) to denote the altered reactivity produced typically by tuberculin. Anaphylaxis, both in laboratory and clinical practice is a specific phenomenon brought about in a sensitized person or animal by reinjection of the specific foreign protein.

Hypersensitivity reactions are broadly classified into two groups—immediate and delayed reactions. The immediate variety comprises of several types of anaphylactic reaction and the atopies, a term first used by Coca and Cooke (41) to indicate a group of human allergic disorders like hay fever, bronchial asthma, eczema, urticaria and gastrointestinal allergy.

In the delayed reactions, exposure to specific antigen results in an inflammatory response, reaching its maximum intensity in 24-48 hours, as exemplified by the tuberculin reaction. Contact dermatitis is an important form of delayed clinical reaction.

Both immediate and delayed types of reactions may occur as a result of infection or drug administration. The immediate type of allergic reactions may be produced in man by parasitic infestations like ascariasis, filariasis etc. or by drugs like penicillin. The delayed reaction to bacterial infection may lead to chronic inflammation in various organs. Similar chronic disease has also been produced by drugs. The mechanism of homograft rejection is due to an immunologic attack by the recipient on the antigenic component of the grafted tissue and has a strong resemblance to delayed hypersensitivity reactions.

Animal experimentation yields basic data about mechanism involved in various disease processes, and thus helps in evolution of specific therapy. The animal models are also useful in screening potential therapeutic agents. However, animal data has its limitations and the conclusions drawn can only be employed with due reservations in clinical practice. The purpose of the present review is to examine the animal data in this context, and compare it with similar data in man wherever available.

2. ANAPHYLACTIC REACTIONS

A. Systemic Anaphylactic Shock :

I. *General Properties* :

In 1902, Portier and Richet (186) reported that the first injection of an extract of actinaria failed to produce symptoms in the dog; but the second injection into the same animal after a few days resulted in death in a few minutes. They coined the term "anaphylaxis" to describe the peculiar attribute which certain poisons possess of increasing, instead of diminishing the sensitivity of an organism to their action. Later on, Arthus (3) showed that even non-toxic proteins produce hypersensitivity reactions; rabbits for example, were found to react anaphylactically to injections of horse serum. However, to be antigenic a substance had to be protein in nature and foreign to the species (192).

The fundamental properties of the anaphylactic reaction, established during the first thirty years, have been summarized by Sanyal (207) as follows :

(*i*) Anaphylactic shock results from the second injection of antigen provided a period of time is allowed to elapse between the sensitizing and the challenging doses (186).

(*ii*) Anaphylaxis is a specific phenomenon and shock is only possible on challenge with the specific protein to which the animal has been sensitized (205, 206, 52).

(*iii*) The state of sensitization can be passively transferred when the serum from a sensitized animal is injected into a recipient animal. The injection of the specific antigen to the recipient animal after a suitable interval of time produces symptoms which are similar to those of active anaphylactic shock (171).

(*iv*) The symptoms of anaphylactic shock vary in different species, the predominant one being asphyxia in the guinea-pig (6), right heart failure in the rabbit (40), and peripheral circulatory failure in the dog (181, 239).

(*v*) An isolated smooth muscle from a sensitized guinea-pig contracts in contact with the antigen but tachyphylaxis develops on repeated exposures (222, 47).

(*vi*) The smooth muscle can be passively sensitized when it is incubated with the sera from a sensitized animal (47, 97).

(*vii*) There is a close resemblance between the symptoms of anaphylactic shock and the toxic effect of histamine in the various species (54).

Exposure of the animal to antigen leads to the formation of antibodies mostly in the reticulo-endothelial system. On injection of the challenging dose, the combination of antigen with the cell-fixed antibodies leads to activation of proteolytic enzymes, cell stimulation and breakdown, and release of metabolites. The characteristic smooth muscle contraction, increase in capillary permeability and glandular secretions are usually attributed to the pharmacological actions of these released metabolites. The following scheme summarizes the main steps of the anaphylactic reaction (202) :—

SCHEME OF ANAPHYLACTIC REACTION

Exposure to Antigen → Formation of antibodies (Reticulo-endothelial System)

Re-exposure to antigen → Combination of antigen with Antibodies.
Activation of enzymes (Proteolytic). Resulting cell stimulation and breakdown.
↓
Release of metabolites
↓
Effects

(*i*) Smooth muscle contraction.

(*ii*) Stimulation of glandular secretion.

(*iii*) Dilatation of capillaries and increase in the permeability.

II. *Symptoms* :

In dogs, the intravenous challenge of antigen results in immediate retching, vomiting and evacuation of bowels. This is followed by a profound fall in the blood pressure and severe

collapse with shallow and rapid breathing. Blood becomes incoagulable and remains so for several days (181, 239). At autopsy, the liver is seen to be engorged with blood (142, 239). There may be haemorrhagic patches in the intestines.

In the rabbit, the fall in blood pressure is associated with extreme slowing of respiration. There may be occasional preagonal clonic convulsions. At autopsy, lungs are usually partly collapsed and the right side of the heart is dilated (5). The spasm of the pulmonary blood vessels during anaphylaxis in rabbits leads to high pulmonary pressure which results in right-sided heart failure (40). Isolated strips of the pulmonary artery of sensitized rabbits react anaphylactically to *in vitro* challenge with the antigen (93).

In the guinea-pig, the primary cause of death is asphyxia brought about by contraction of the smooth muscles of the bronchioles (6). There is a spasmodic and rapid irregular breathing which is followed by violent tonic and clonic convulsions; finally, the respiration ceases but the heart continues to beat (204, 6). At autopsy, the lungs are seen to be emphysematous. The injection of the challenging dose in the rat is followed by laboured breathing, severe weakness and progressive hypothermia. The animal passes blood-stained stools. Intense congestion and haemorrhages in the intestines are seen at autopsy (212). Circulatory collapse also plays an important part in anaphylaxis in the mouse (147). There is a fall in the rectal temperature (127, 184) and dilatation of blood vessels. An increase in capillary permeability leads to oedema and haemo-concentration. Circulatory failure gives rise to anoxia and respiratory distress (165).

When it occurs in man, anaphylaxis resembles that seen in the guinea-pig (23,208). The symptoms less frequently resemble those seen in the rabbit (36) or the dog (58).

More recently, it has been reported that oedema of the upper respiratory tract involving the epiglottis, hypopharynx and larynx is the dominant symptom of anaphylaxis in man and the upper respiratory tract has been suggested to be the target organ (116, 224). The other symptoms of anaphylaxis are pruritus, urticaria, angioneurotic oedema, feeling of tightness in the chest, pulmonary insufficiency, nausea, vomiting, colic, diarrhoea, and hypotension. Obstruction of respiratory tract and general visceral engorgement have been seen at autopsy. No definite pathological changes are, however, demonstrable in patients who have died suddenly with profound and irreversible hypotension (224).

The various agents which have produced anaphylaxis in man are antisera, hormones, chymotrypsin, trypsin, penicillinase, bee venoms, protein antigens used for diagnosis and desensitisation, *polysaccharides like* dextran, acacia, decholin, thiamine, Sulphbromthalein, procaine, salicylates, iodinated compounds, *penicillin*, demethyl chlortertracycline, streptomycin, aminopyrine and furadantin (7,214).

Respiratory distress characterises anaphylactic shock in the horse and the calf (194, 43), the pigeon (84) and the chicken (133) whereas in the cat, the symptoms of circulatory collapse predominate (222). In the white monkey, there may be immediate collapse and cessation of respiration (130), but in the rheusus, there is progressive weakness, vomiting and haemorrhages

Anaphylaxis has been reported in the earthworm as well as in the paramecium (189, 190) but such studies have in the main been academic.

B. Anaphylactic Reaction of the Isolated Smooth Muscles :

The isolated smooth muscle of the sensitized animal contracts when exposed to a low concentration of the specific foreign protein to which the animal had been sensitized and this is followed by tachyphylaxis. This was first demonstrated with the guinea-pig ileum and later on with the guinea-pig uterus (222, 47), and is known as the "Dale-Schultz reaction".

It is also possible to sensitize fresh smooth muscle preparations by incubating them with high titre antisera. When these tissues are washed repeatedly to remove traces of free antisera and subsequently challenged with the specific antigen, an anaphylactic contraction is obtained. This reaction is known as "the passive Dale-Schultz reaction" (47, 97). Anaphylactic reaction of the Dale-Schultz type has also been shown to occur with the rat uterus (123).

C. In Vitro Reaction of the Tissue Particles :

The addition of specific antigen to uniformly minced particles of lung tissue from sensitized guinea-pigs leads to release of histamine. This reaction has been extensively used by Mongar and Schild (152, 153) for fundamental studies on the quantitative aspsects of the anaphylactic reaction.

D. Passive Anaphylaxis :

It is possible to sensitize animals passively by intravenous injections of antisera obtained from a previously sensitized animal (171). After a time period, injection of the antigen leads to anaphylactic shock. The isolated chopped guinea-pig lung has also been sensitized passively (154, 31).

E. Passive Cutaneous Anaphylaxis :

Antibody-containing sera may be injected into the skin of the rat of the guinea-pig. The antigen and a coloured colloidal dye are administered intravenously. The local reaction in the previously prepared site is unmasked by seepage of the colloidal dye from the blood to the prepared site (172, 173, 29). This type of reaction has also been used for quantitative studies.

F. Arthus Reaction :

A local inflammatory reaction is produced by repeated injections of the antigen in the rabbit and was first described by Arthus (3). The reaction may also be produced in guinea-pig, in rat (88), and in man.

G. Isolated Mast Cells :

Mast cells are obtained from peritoneal cavity of sensitized rats, or are passively sensitized after collection from normal animals with antisera. Addition of specific antigen leads to release of histamine and this has been taken to be the parameter of the anaphylactic reaction (232, 163, 182). The rabbit basophil leucocytes have also been used in a similar manner.

H. Human Leucocytes :

There is a release of histamine from human leucocytes obtained from allergic patients on exposure to the specific antigen (135, 136).

3. DELAYED HYPERSENSITIVITY REACTIONS

A. Tuberculin Reaction : It is the most extensively studied type of delayed hypersensitivity reactions. It is produced in tuberculous animals or in animals immunized with killed mycobacteria by injection of the protein of tubercle bacilli, or tuberculin. Delayed hypersensitivity reactions have been produced with protein components of other infective agents as well. This type of sensitivity is best seen in man, guinea-pig and the rabbit (15).

B. Contact Sensitivity : A form of delayed hypersensitivity can be produced by painting the skin with chemicals like picryl chloride or 2-4, dinitro fluorobenzene. The sensitivity can be passively transferred by cells of the donor animal but not by plasma (15).

4. THE ANTIGEN-ANTIBODY REACTION

Although the symptoms of systemic anaphylactic shock vary in different species in many respects, there may be a common fundamental mechanism involved. The differing manifestatoins may be explained on the basis of spasmodic contraction of strategically placed smooth muscles, which in the dog are situated around the hepatic veins, in the rabbit are located in the pulmonary blood vessels, and in the guinea-pig are found in the bronchioles (227).

However, this simplified hypothesis cannot explain the manifestations either in the rat or in the mouse and in many cases in man as well (212, 213, 62, 7, 224).

There is a general agreement that the phenomenon of anaphylaxis is due to a specific antigen-antibody reaction. The antigen, of necessity, has to be a foreign protein, but non-protein substances can also become antigenic by combining with the native proteins.

The anaphylactic antibodies were at first thought to be closely related to precipitins (66, 238, 48). The recent improvements in the technique of immuno-chemistry have led to a better understanding of the nature of the antibody. These belong to the family of immunoglobulins, and are capable of sensitizing the host tissues for systemic, local and under certain experimental circumstances, *in vitro* anaphylactic reactions. A study of the properties of these immunoglobulins has shown that they are characteristic of the species and can only transfer the reaction within the species or those closely related to it. The mammalian anaphylactic antibodies have been mainly classified into two types. The anaphylactic antibodies of the guinea-pig and the mouse are very similar and have been called γ_1-immunoglobulins (17, 243, 166). The anaphylactic antibodies in rat, rabbit, dog and man are similar and have been referred to as the reaginic type (16). The γ_1-anaphylactic antibodies and the reaginic antibodies have both similar electrophoretic mobilities, but differ in their molecular size and sensitivity to heat and reducing agents, the former being more resistant. The γ_1-immunoglobulins are synthesized in large amounts during the entire course of immunization, but reaginic antibodies are only produced in minute amounts during the early phase.

It is well-known that antibodies prepared in rabbit, duck or rat may passively sensitize guinea-pig and this fact would apparently question the specificity of the anaphylactic antibodies. Recent studies have, however, revealed that the foreign immunoglobulin which transferred the sensitivity was not the anaphylactic antibody of the donor species but one of its γ_2 or IgG immunoglobulins which do not mediate anaphylactic reaction in the donor species. The transfer of anaphylactic sensitivity is possible because of certain structural resemblances with the anaphylactic antibody of the guinea-pig (16).

It has been shown that non-antibody γ-globulins prevent the uptake of antibodies during passive sensitization and can even reverse a freshly established one, but not one which is well-established. The blocking action is more efficient if the non-antibody γ-globulins are obtained from a species capable of sensitizing tissues of the recipient species (174, 155).

The German workers at first believed that the antigen-antibody union occurred in the blood and the complex so formed incorporated complement and formed anaphylotoxin (82, 78, 79). The subsequent symptomatology was ascribed to the toxic effects of the newly formed anaphylotoxin which was shown to initiate proteolytic activity (118, 35). However, Dale conclusively demonstrated that the anaphylactic reaction occurs in the complete absence of blood whilst artificial saturation of the circulation with high titre antibody sera protects against the development of anaphylactic reaction (47, 49, 51).

In the *in vitro* studies, it has been shown that intact cells are required for the anaphylactic reaction, though basic histamine releaser can act on intracellular particles as well (151). This fact would suggest that the antigen-antibody reaction occurs on the cell surface. The mast cells, particularly in the dog and the guinea-pig show characteristic changes during anaphylaxis (117, 164, 213, 22). It is possible that these cells release their contents of pharmacologically active substances during the anaphylactic reaction.

However, fatal anaphylactic shock is possible in animals like rats and mice in which the mast cells have been damaged and their contents washed away by chemical treatment (213, 62). Passive anaphylaxis is also possible in such animals (29). This apparent anomaly has been explained by Mota in terms of the two types of antibodies, one of which attaches to the mast cells and produces lysis in contact with the antigen, the other affecting different sites (158, 159, 160, 161). Humphrey and Mota (110) thought that the antigen-antibody reaction occurred on the mast cell surface. Labelled antigen may be recovered from the mitochondrial fraction within a few seconds of intravenous injection, as such, intracellular antigen-antibody reactions cannot be ruled out (98). Mota, Dias de Silva and Fernandes (162) observed the antigen-antibody reaction of mast cells under the microscope and characterized the changes as "bubbling of the cell cytoplasm". In the rabbit the reaction largely occurs in the blood with involvement of leucocytes and platelets which are stores of histamine and 5-HT in this species (108, 109). The problem is further complicated by the fact that antigen may combine with antibody to form soluble complexes *in vitro*, the injection of which may produce some of the manifestations of anaphylactic reaction. Two or more antibody molecules appear to be required for the formation of such active complexes. It has been suggested that the antibody molecules are brought into

apposition by the antigen and this initiates changes in the antibody molecules which lead to liberation of metabolites. It is possible that in the sensitized state, antibody molecules are fixed on certain tissue cells. Antibody molecules combining with the same antigen may interact with each other leading on to alterations in the heavy chains which bind these molecules to the cell surface. The damage to the cell membrane may then initiate the further steps of the anaphylactic reaction (114).

A second theory has also been proposed to explain anaphylactic sensitization. It has been postulated that anaphylactic sensitization occurs due to sequestration of antibodies. The antigen combines in solution with the sequestered antibody and thus forms a complex which is toxic to the cell (134). Broder (34) has supported this hypothesis.

The antibodies involved in delayed hypersensitivity are not present in plasma. The delayed reaction can be passively transferred by using cells of the sensitized donor. A principle present in lysed sensitized cells can transfer sensitivity and has been named 'transfer factor' (132).

5. ACTIVATION OF PROTEOLYTIC ENZYMES

The antigen-antibody reaction ultimately leads to release of histamine and other toxic substances. The humoral hypothesis postulated the formation of 'anaphylotoxin' by incorporation of complement with antigen-antibody complex and resultant proteolytic activity due to removal of a natural antitryptic ferment. The hypothesis fell into disfavour, but the importance of proteolytic activity was revived when it was shown that trypsin itself produced symptoms resembling anaphylactic shock (197). The importance of proteolysis was also emphasized by Herberts (103). The mechanism of histamine release during anaphylactic reaction has been studied in detail by employing a number of blocking agents and using isolated chopped guinea-pig lung or isolated smooth muscles. The present position has been reviewed by Mongar & Schild (156) and hence only the salient features are mentioned below.

(*i*) Several enzyme poisons, particularly those blocking SH radical, prodcue almost complete inhibition (150). Iodoacetates are particularly effective.

(*ii*) Histamine release from sensitized lung on addition of antigen requires the presence of oxygen, and the reaction stops in an atmosphere of nitrogen (152). This would indicate that either a functioning cell is essential, or that oxygen itself takes part in the reaction.

(*iii*) Phenol prevents histamine release and Dale-Schultz reaction, but when it is removed, the tissue is seen to be desensitized, as fresh addition of antigen fails to provoke a contraction. This would indicate that phenol does not prevent antigen-antibody union, but acts at a later stage (152).

(*iv*) Anaphylactic reaction cannot be produced, if the tissue is exposed to 45°C even for a short time. This would indicate the necessity of a heat labile factor. Exposure at 41°C aggravates the reaction and extremely low temperature (0°C) inhibits both desensitization and histamine release. Reactions at 17°C are more complex (153, 156).

(*v*) The shape of curve of histamine release due to anaphylactic reaction at various pH indicates an enzyme action. Maximum activity is observed at pH 7.8 and minimum at 6.2 (154).

(*vi*) Calcium is the only ion required for antigen-antibody reaction (154).

On the basis of the above data Mongar and Schild (156) have postulated the following scheme of reaction :

Cell-fixed antibody+antigen
Inhibition by raised temperature → Enzyme precursor+Ca^{++}
↓
Inactivated enzyme←Active enzyme
(Short lived)
+
Inhibition by phenol →

Bound histamine←Histamine releaser
(mast cell granules)
↓
Free Histamine
+
Plain muscle cell
↓
Anaphylactic contraction

Mongar and Schild did not attempt to identify the enzyme systems activated.

Activation of proteolytic enzymes by anaphylotoxin was visualized early. Complement fixation by antigen-antibody reaction leads to formation of anaphylotoxin. The importance of complement fixation has been emphasized in passive cutaneous anaphylaxis in the rat (170). Complement fixation reaction and anaphylactic reaction have certain common features, like the necessity of calcium. However, the heat labile factor for the former reaction is well-known to be inactivated at 56°C, whereas that for anaphylactic reaction is inhibited at 45°C. Chymotrypsin has been demonstrated to be present in mast cells (18) and may be the tryptic ferment involved.

Diisopropyl fluorophosphate (DFP) is a specific chymotrypsin inhibitor and it inhibits the anaphylactic reaction only when it is present at the time of addition of the antigen. If the tissue after incubation with DFP is washed to remove the inhibitor, addition of antigen is followed by anaphylactic release of histamine from the guinea-pig lung. It was concluded that DFP acts on a chymotrypsin like enzyme which is activated by antigen-antibody union (8). DFP also inhibits anaphylactic histamine release from human leucocytes (136); however, the histamine release from the isolated sensitized rat mast cells on addition of antigen was not affected by DFP though chymotrypsin like activity of the tissue was blocked (183). Thus it is seen that not only there is heterogenicity in the nature of antibodies but also there is a difference in the nature of enzyme systems which are activated.

Ungar (229) postulated an enzyme called serum profibrinokinase which is activated by

antigen-antibody action. This enzyme converts profibrinolysin to fibrinolysin; ultimate result being proteolysis. The theory has been contested by McIntire, Roth and Sproule (145, 146) on the basis of the fact that there is no evidence of fibrinolysin activity in the rabbit, and the activation cannot be blocked by Soyabean trypsin inhibitor.

Hayashi, Tokuda and Udaka (101) found that when tissue cultures of monocytes from sensitized animals were exposed to antigen, a protease appeared in the surrounding fluid. protease may be an endopeptidase related to cathepsin.

Hogberg and Uvnas (107) showed that lecithinase—A caused mast cell disruption. Snake venoms may contain lecithinase—A, which is known to be histamine releaser. Calcium, so important for anaphylactic reaction, is a co-factor of lecithinase—A *in-vitro*. However, SH blocking agents which block antigen-antibody reactions do not affect lecithinase action on lecithin.

Several other enzyme systems have also been suggested (230) but at present their identification is not unequivocal in any case.

6. THE CHEMICAL MEDIATORS OF HYPERSENSITIVITY

A. ACUTE REACTIONS

The chemical mediators which are involved in anaphylaxis include histamine, 5-HT, slow reacting substance (SRS) and bradykinin. As early as 1910, Dale and Laidlaw (54) noticed resemblance of the symptoms of anaphylactic shock in the various species with those produced by injections of histamine. The authors were, however, careful to point out that there are a few symptoms of anaphylaxis such as the incoagulability of the blood in the dog which cannot be produced by injections of histamine. Later on, it was shown that histamine is a physiological constitutent of many tissues but the critical evidence of release of histamine in anaphylactic shock came in 1932 from two different sets of workers (10, 68). The inability of antihistaminics to ameliorate the symptoms of anaphylactic shock has stimulated the search for other mediators. It seems that there is a considerable amount of species variation in the importance of different mediators in various hypersensitivity reactions. These evidences have been reviewed below with the main emphasis being on systemic anaphylactic shock.

A. *Role of histamine and 5-HT in various species* :

(*i*) DOG : Manwaring, Hosepian, O'Neil and Moy (143) first demonstrated the release of a hypotensive, smooth muscle-stimulating principle from a sensitized liver when in contact with the antigen. Clear-cut release was obtained in 1932 by Dragstedt and Gebauer-Fuelnegg (68) when they isolated histamine in a relatively pure state from the thoracic lymph of a dog subjected to anaphylactic shock. These findings have been confirmed (42, 167). It has been reported that antihistaminic drugs prevent the effects of anaphylactic shock in the dog (94). The role of histamine in dog anaphylaxis is now well-established. The substance has been demonstrated to be released during the process from sensitized liver (213) and the spasm of the smooth muscles of the hepatic vein by the released histamine explains nicely the symptomatology of anaphylactic shock in this species.

5-HT is released from dog platelets during antigen-antibody reaction (109) but critical evidence of release of 5-HT from the liver of the dog has not been obtained (213).

(*ii*) RABBIT : There is a decrease in the total blood histamine during anaphylaxis in the rabbit (203). This proved in the beginning a difficult factor to explain in as much as release of histamine from the organs should have produced a rise in blood histamine level. The first evidence of histamine release in anaphylactic shock from rabbit tissues was produced by Schachter (215) who showed definite release from skin and liver and to a lesser extent from small intestines. In contrast to other species the blood elements take part in anaphylactic shock in the rabbit (1,120). Simultaneously with the lowering of blood histamine, a sharp drop in leucocytes and platelets has also been observed (203, 131, 200). The platelets and the leucocytes are rich sources of histamine and 5-HT in this species (108) and release of histamine and 5-HT have been demonstrated from leucocytes and platelets during antigen-antibody reaction (109). Sanyal and West (213) reported that there was actually a rise in lung histamine and 5-HT contents during anaphylaxis and they attributed this to trapping of leucocytes and platelets in the pulmonary field. Thus not only rise in lung histamine and 5-HT content but also the fall in blood histamine and 5-HT levels was satisfactorily explained. When formation of platelet and leucocyte thrombi was inhibited by the use of heparin, the rise in lung histamine and 5-HT content was prevented and in some cases actually there was a fall (61). There are certain differences between the actions of histamine on blood pressure and changes during anaphylaxis, but overall similarities have been shown to be present by Rocha e Silva (196). Constriction of the pulmonary artery is a well-known effect of both histamine and anaphylaxis (92, 93, 80). However, anti-histamines have not been able to prevent the symptoms of anaphylactic shock in the rabbit (37, 195).

(*iii*) GUINEA-PIG : The symptoms of anaphylactic shock in the guinea-pig closely resemble those produced by histamine as well as by 5-HT (54, 104). Release of histamine in anaphylactic shock was demonstrated by Bartosch, Feldberg and Nagel (10). Histamine release from various tissues of guinea-pig was reported by Schild (216) and as a matter of fact, release of histamine from a sensitized guinea-pig lung has been used as a quantitative test for anaphylactic shock by Mongar and Schild (154). Critical release of 5-HT during anaphylactic shock has been demonstrated by Sanyal and West (213). Antihistamines prevent the effect of anaphylaxis in the guinea-pig (137, 81, 72), and anti 5-HT drug, LSD-25 has also a similar effect (175). However, the concentration of antihistaminics required to reduce anaphylaxis is considerably higher than that required to prevent histamine action (219). Dale (50) has explained that extrinsic histamine which is carried by blood, can be easily antagonized but intrinsic histamine which is liberated in the immediate neighbourhood of the reacting cell cannot be so easily countered. However, when a tissue has been desensitized to the action of histamine by extremely high doses of the same substance, it can still react anaphylactically (217). Thus though histamine and 5-HT may both be involved in anaphylactic shock in guinea-pig, there are definitely other factors involved as well.

(*iv*) *RAT AND MOUSE* : Rats and mice are well known to be resistant to histamine

(236, 144, 185) and anaphylaxis in these species is difficult to induce (85). The production of anaphylactic shock is facilitated by hypophysectomy (149), suprarenalectomy (77, 247, 60, 240), or by injections of insulin before challenge (211, 209). The injection of *B. pertussis* vaccine along with the sensitizing dose of antigen has a similar effect in the rat (140, 212) and also in the mouse (176, 139, 138). This procedure renders the rat and the mouse sensitive to histamine and 5-HT (130, 140, 177, 119, 128). Sanyal and West (212) showed that the period of sensitivity to anaphylactic shock in animals pretreated with *B. Pertussis* vaccine coincided with the period of sensitivity to both histamine and 5-HT. However, they did not find any evidence of increased histamine or 5-HT release in anaphylaxis, and also noted that depletion or blockade of histamine or 5-HT did not prevent the development of fatal anaphylactic shock in the rat (213).

Mota (158) however, considered histamine to be important in anaphylaxis in the rat. He opined that during systemic anaphylactic shock in the rat, there is mast cell disruption and histamine release (160, 161). The different results have been attempted to be explained by the presence of different types of antibodies. A rat mast cell sensitising antibody has been distinguished from rat γ_{-2}=antibody (161, 162).

However, both active (9) and passive (160) systemic anaphylaxis may occur without mast cell damage, and antihistaminics afford little protection (87, 161). Further, the passive cutaneous anaphylactic shock in the rat is unaffected by depletion of histamine or 5-HT (29) and is not affected by anti-histamines (29, 30). Cody, Code and Kennedy (45) also produced evidence to show that release of histamine was not important in the development of anaphylactic shock. Thus there is a considerable body of evidence to now support the hypothesis originally propounded by Sanyal and West (213) that histamine and 5-HT are not important mediators of anaphylactic shock in the rat.

In the mouse, Dhar and Sanyal (63) detected a slight lowering of skin histamine during anaphylactic shock, but again neither tissue depletors nor use of antagonists of either histamine or 5-HT could prevent development of fatal response. Mast cells have been reported to be damaged during anaphylactic shock (169). Vaz, Iff and Peixoto (235) reported that there was a release of histamine *in vitro* during anaphylactic shock in this species. Though separately histamine and 5-HT antagonists are not of much effect, a combination of the two antagonists has been found to be quite effective against systemic anaphylactic shock (112) and also against passive cutaneous anaphylaxis in mice (96). Iff and Vaz (112) further reported that a mixture of low doses of histamine and 5-HT produce symptoms similar to those noted in anaphylaxis. These authors have postulated that anaphylactic death may be due to peripheral plasma leakage and production of haemoconcentration due to combined effects of released histamine and 5-HT.

(*v*) MAN : Katz and Cohen (123) and Katz (122) produced experimental evidence for release of histamine in cases of human allergy. Cerqua (39) found that there was a rise in blood histamine during the asthmatic attack but Reisser (193) and Rose (201) found no consistent change. Beall (11) found that the plasma of patients during asthmatic attack contained histamine only in slightly greater amount than in controls, and explained it on the basis of rapid

catabolism (13). By employing an improved assay method, Beall (12) detected increased histamine excretion in urine during artificially induced asthmatic attacks. Histamine has been shown to be released from human asthmatic lung on contact with the specific antigen (218). A chain of bronchial rings obtained from asthmatic patients contract on exposure to the pollens to which the patient was sensitive and this is followed by desensitization (100). Mepyramine in a very high concentrations only produced a slight reduction in the contraction, though it was 10,000 times more effective against histamine. Rosa and McDowall (199) reported similarly. Duner and Pernow (71) reported that in some cases, a substance having antihistaminic activity was found in the urine of asthmatic patients. There was also decrease in the histamine excretion in a patient who had flushing and collapse after ingestion of lobster. Choudhury and Sen (39*a*) working in our laboratory showed that there was an increase in histamine content of sputum during asthmatic attack and there was a reduction as relief set in. They also showed that there is a rise in blood histamine levels, and attributed the above changes to antigen-antibody reaction. It has been postulated that histamine trapped in the tough and tenacious sputum prolongs the asthmatic spasm and may produce status asthmaticus.

Brocklehurst (25) reported that spasm of smooth muscles during anaphylactic shock is satisfactorily explained by release of histamine but that neither histamine nor 5-HT will produce symptoms analogous to anaphylaxis. The human bronchi do not seem to be very sensitive to 5-HT; and 5-HT aerosol which produced bronchospasm in the guinea-pig did not elicit asthmatic responses in susceptible individuals (106). There are qualitative differences in the actions of histamine and 5-HT on the human skin. Histamine injections produce a typical triple response, but 5-HT applied directly to the skin produces the flare but not the wheal (210). It may be noted that both anti-histamines and anti-5-HT substances have not been very efficacious in the treatment of human allergic disorders.

A functional alteration in the adrenergic system has been recently thought to be responsible for aggravating the toxic reactions to histamine in sensitised animals. Fischel, Szentivanyi and Talmage (76) have corroborated the earlier findings that dibenzyline reduces the toxicity of histamine in *Bordetella Pertussis* treated animals (126), whereas dichloroisopropylnoradrenaline (DCI) injected immediately before, increased the sensitivity to histamine. It has been thought that there is a state of β-blockade in rats and mice rendered hypersensitive to histamine by injection of the above vaccine. In such animals adrenaline failed to produce hyperglycaemia (76, 2). Histamine released as a result of antigen-antibody reaction may in its turn release adrenaline. In presence of a β-blockade adrenaline fails to produce hyperglycaemia and may actually produce hypoglycaemia. It has been shown that hyperglycaemia is associated with resistance to anaphylactic shock and hypoglycaemia has the opposite effect (64). It is thus possible that hypoglycaemia and the imbalance between α and β-adrenergic mechanism may contribute to the production of hypersensitivity to histamine in animals treated with *B. pertussis* vaccine (76, 2). However, this cannot completely explain the mechanism of sensitisation of such animals to anaphylactic shock, as specific α-blocking drugs do not ameliorate anaphylactic shock nor do β-blocking agents aggravate the same (2). It is possible that the β-blocking agents are too rapidly metabolized to affect the process of sensitization and as such studies are

in progress to determine the effect of repeated administration of these agents in the anaphylactic sensitization.

It has been speculated that β-adrenergic blockade may be a contributing factor in development of clinical bronchial asthma. It was seen that the partial β-blockade increases the bronchial response to allergens (188). Further, intravenous injection of isoprenaline produces a reduced blood pressure response in asthmatics as compared to normal individuals (46). However, propranolol, a powerful β-adrenergic blocking agent fails to alter bronchial sensitivity of normal subjects to either histamine or methacholine (248) and further, exercise induced bronchospasm in asthmatic children is not affected by β-adrenergic or α-adrenergic blockade (148).

(*b*) *Role of Slow Reacting-substance* :

Feldberg and Kellaway (74) obtained a substance from the perfused guinea-pig lung during perfusion with cobra venom which produces a slow and sustained contraction of the guinea-pig ileum. This substance was called 'Slow-Reacting substance'. Kellaway and Trethewie (124) obtained a similar substacne from the effluent of an organ subjected to anaphylactic shock. This substance is usually referred to as 'SRS-A' and has been intensively studied by Brocklehurst (24, 26, 27) and Boreus and Chakravarty (22).

It seems possible that both histamine and SRS-A may originate from mast cells (232, 22, 231). Release of SRS-A has been obtained with rabbit, monkey and human lung but not with that of horse or goat (22,26). Release of SRS-A- has been obtained *in vivo* in the rat (191).

SRS-A produces contraction of guinea-pig ileum, rabbit jejunum, hen rectal caecum and human bronchiole, but not of rat colon, rat uterus or bronchiole of rabbit, dog or cat (24, 26, 27).

SRS-A produces broncho-constriction when given intravenously in the guinea-pig but not after aerosol administration (20). It is interesting to note that SRS-A may produce broncho-constriction in asthmatic individuals (106). Compound 48/80 has also been shown to release SRS-A from rat mast cells (233).

However, recent studies have shown that SRS-A release in rats can occur in absence of mast cells, but not after leucopenia induced by nitrogen mustard. It seems that polymorphonuclear cells are the main sources of SRS-A (169-a). SRS-A has been demonstrated in the whole blood extract of the anaphylactic mouse (168).

(*c*) *Role of Acetylcholine* :

Acetylcholine was shown to be present in rabbit blood during anaphylactic shock (241). Went and Lissak (242) detected a substance during anaphylactic shock from the guinea-pig which was found to be identical with acetylcholine. However, atropine does not modify systemic anaphylactic shock nor does it affect the Dale-Schultz reactions (75).

(*d*) *Role of Bradykinin* :

Bradykinin is a polypeptide which is formed in the tissue from inactive precursor as a

result of certain enzyme actions (198). Recently it has been postulated that bradykinin may be an important mediator of anaphylactic reaction (73). Pharmacological actions of bradykinin resemble the symptoms of anaphylactic shock (71). Bradykinin has been found to be present in blood during anaphylaxis in the dog (19), and the guinea-pig (32, 33). It is capable of producing broncho-constriction the in guinea-pig (45,21). Intravenous injection of bradykinin produces symptoms closely resembling anaphylactic shock in the rat (57). A rise in bradykinin content in plasma has also been demonstrated in the same species (56). Bradykininogen levels were found to be lowered during anaphylactic shock in the mouse (168). Animals exhibit hypersensitivity to bradykinin when pretreated with either *B. pertussis* vaccine or β-adrenergic blocking agents (141).

The inhibitors of kinin formation and a potent anti-kinin substance 'rheopyrin' have been shown to reduce anaphylactic sensitivity in the rat. A combination of antibradykinin substance with anti-histamines or anti-5-HT drugs was found to be even more effective (46a).

Dave (55) studied the antibradykinin activities of known antianaphylactic suubstances, and came to the conclusion that there is no positive correlation. She also failed to obtain critical evidence of bradykinin release from isolated sensitized tissues and found that substances with antibradykinin action, like imipramine or chlorpromazine do not significantly suppress anaphylactic shock in the rat or the mouse. It has been reported that bradykinin and related substances may be responsible for some of the symptoms in human allergic disorders, particularly bronchial asthma (226).

B. DELAYED REACTIONS

Fundamental studies relating to delayed hypersensitivity reactions are of comparatively recent origin. Inderbitzin (112) found that there is an increase in skin histamine content during the delayed reactions which attains its peak value in 48 hours. However, Graham and Schild (91) detected a diminution in histamine content in the rat skin but a transient increase in histamine forming capacity in the early stage of the reaction.

Hayashi, Yoshinaga, Koòno, Miyoshi, and Matsumura (102) detected a factor from pseudoglobulin fraction from arthus skin lesions during the delayed response, and termed it as "the arthus permeability factor". This factor has been shown to be specific in enhancing vascular permeability but not in inducing haemorrhagic change or leucocytic immigration. Hayashi (100) thought that arthus permeability factor is the natural mediator. The factor is locally available to initiate and maintain the effect and its activity parallels the time course of the response.

Ribonucleic acid produced increased vascular permeability to protein and increased leucocytic immigration following intradermal injection (113), and it has been thought that there may be a causal relationship between delayed hypersensitivity and RNA (221).

However, by far the most important mediator of the delayed hypersensitivity reaction seems to be a substance obtained from the lymph nodes. This factor which has been extensively studied by Willoughby and his coworkers has been called the "lymph node permeability factor"

or LNPF (246). The preparation of this factor and its characterization has been described earlier (245). This factor causes leucocytic immigration, increased vascular permeability to plasma proteins and also deposition of material resembling connective tissue fibrinoid. The LNPF is associated with a variety of delayed hypersensitivity reactions including tuberculin reaction, dinitrochlorobenzene contact-dermatitis etc. It has been detected in synovial fluid of patients having rheumatoid arthritis. It has been thought that LNPF may be a factor which determines the chronicity of inflammation (244). LNPF may possibly own its properties to its RNA content (220).

8. CONCLUDING REMARKS

Thus it is seen that a number of substances have been implicated in the hypersensitivity reactions in various species, and it is possible that others may join the list. In the human being histamine and kinins may be involved in nasal allergy producing increased vascular permeability and secretions. In the skin the same factors may be involved which may also be responsible for pain and itching. In gastrointestinal allergy the increase in motility may be produced by histamine, 5-HT, kinins and SRS-A; the increased secretions being produced by histamine and kinnins. The same factors may also be responsible for respiratory allergy (28).

It is suggested that certain criteria as follows must be laid down for assessment of the role of various mediators in anaphylactic shock :

(*i*) There should be a resemblance between the symptoms of anaphylactic shock and the actions of the mediators. Actually the entire work on mediators originated because of the classical observation on resemblance of anaphylactic shock with symptoms of histamine poisoning (54).

(*ii*) The substance under consideration should be present in the tissues, either in active or in a precursor form, and it should be released during anaphylactic shock. Study of the tissue levels before and after anaphylactic shock would help in obtaining evidence of release.

(*iii*) A critical evidence of release can be obtained by exposing isolated tissues of sensitized animals to antigen and noting the response of sensitive smooth muscle preparation to the released substance (38). Such an evidence can also be obtained by estimating the release from chopped particles of sensitized tissues similarly (152), or by estimating the mediator in the effluent from shocked organs (68).

(*iv*) There should be a protection against anaphylactic shock if the tissue levels are altered by suitable depleting agents or if specific antagonists of the mediator are used. The above line of approach has been successfully followed in the case of histamine and 5-HT.

It may not be possible to satisfy all criteria with a particular substance, but experiments performed on above lines will leave little doubt as to their precise role in experimental hypersensitivity reactions.

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