



THE RELATION BETWEEN ARTHROPOD-INDUCED HYPERSENSITIVITY  
 AND VECTOR-BORNE PATHOGENS - A HYPOTHESIS

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I. INTRODUCTION

The feeding activities of certain insects and other arthropods are natural parasitic mechanisms basic to the phenomena of direct injury to a given host and of the transmission of some pathogenic organism to that host. Both of these biologic relationships, as is well known, have been the subject of research and observation during the modern period of parasitologic investigation dating from the early decades of this century. Due to socio-economic reasons, especially in the colonization of so-called tropical regions, major emphasis has been placed upon the role of arthropods as vectors of animal and human infection, whereas the direct injury to vertebrates resulting from the bites and stings of these invertebrates has received less attention. Historically, these two avenues of research have developed relatively independently and the field of medical entomology has long been preoccupied with arthropods acting as intermediate hosts of various pathogens ranging from viral and rickettsial agents to metazoan helminth parasites.

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Inevitably, the question must be raised: given two distinct biologic phenomena, associated with the same host-parasite relationship between a certain vertebrate and a certain arthropod, are these phenomena completely independent or are they related? Furthermore, if a relationship exists between the two mechanisms, does it result in a purely quantitative change or is the interaction expressed by some qualitative change? (Kartman, 1966).

The direct effects of arthropods on vertebrates, in terms of local and systemic reactions to bites and stings, are being given more attention in texts and review papers. For example, Horsfall (1962), in his treatise on medical entomology, has a chapter devoted to diseases caused by arthropods and described by the term "Arthropodiasis". A paper by Beard (1963) presents a comprehensive review of research on insect toxins and venoms. Generally, the field of sensitization to insect bites has expanded in comparatively recent years due to the contributions of West, McKiel and associates in Canada, Feingold, Benjamini and co-workers in the United States of America, and Gordon and Crewe in England. McKiel and West (1961) have reviewed studies on hypersensitivity to bites of various insects, and some of the studies with fleas are summarized by Feingold and Benjamini (1961).

In the present paper, suggestions are presented regarding a hypothesis that in nature there may be a relationship between the phenomenon of hypersensitivity to the bites of certain haematophagous arthropods and their efficiency as vectors of pathogenic agents. Such a relationship could be positive or negative; for example, a vector-induced hypersensitive response in the skin of the vertebrate host, characterized by a specific type of leukocytic invasion, might provide a milieu either favourable or unfavourable for the survival, transport, and ultimate propagation of a pathogen introduced by the vector.

## 2. SUGGESTIVE EVIDENCE

Many kinds of arthropods can elicit a sensitization mechanism in vertebrate hosts that are exposed repeatedly to their bites. A list of some of these arthropods is given in Table I which also indicates some of the important pathogenic agents that are transmitted by these vectors. With the exception of certain helminths such as tapeworms, the pathogenic organisms are introduced to the animal or human host either during the act of blood-sucking or by way of contamination of the skin with faeces carrying the pathogenic organism. Depending upon the method of feeding, the arthropod may take its meal directly from a capillary or from a pool of extravasated blood resulting from injury to a capillary. Some arthropods such as trombiculid mites, feed on lymph, and many blood-sucking arthropods ingest fluids other than blood from their hosts.

A series of extensive experiments by Gordon and Crewe (1948) showed that haematophagous insects generally are pool feeders. The insects studied included mosquitos, tsetse flies, horseflies, and bed-bugs. These workers pointed out that most of the parasites introduced by insects feeding on pools of extravasated blood will be deposited into the tissues in or surrounding the haemorrhage and not directly into the circulation. Thus such a changed environment may have a bearing on the immediate fate of, or upon the subsequent development of, these pathogens. The complexity of this local environmental ecology is complicated further by the fact that the bites of such insects also elicit in sensitized hosts a hypersensitive response that may be manifested either by a delayed or by an immediate skin reaction.

A rather simple relationship between this mechanism and the transmission of insect-borne parasites is based upon the well-known fact that intense irritation and itching may result after the bite. In the case of body lice and fleas the resultant scratching of the bite site may facilitate the entry and establishment of the rickettsiae causing epidemic and endemic typhus, respectively. In the case of "kissing bugs" a similar response to skin irritation may aid in the entry of the trypanosomes causing Chagas' disease. In the case of mite-borne rickettsial infection causing tsutsugamushi disease, Wolbach (1948) noted that the symptoms underlying the initial reaction, with its accompanying necrosis, should be interpreted as the effect of the salivary secretion of the vector. In the louse-borne relapsing fever the spirochaetes are released when the louse is crushed against the skin during the act of scratching by the host.

These instances illustrate the contention that the sensitized host and the host's behavioural reaction to the bite of the arthropod may be considered almost a necessary component in the life cycle of the parasite (Gordon, 1958). Considering the fact that only sensitized hosts will, upon challenge, react by scratching, rubbing, biting, or by other forms of self-attack, it seems probable that unsensitized, or desensitized, hosts quite often can avoid becoming infected by pathogenic organisms deposited on their skin in the vector's faeces or, as in the case of relapsing fever spirochaetes, being released from the arthropod's haemocoel by the host's crushing of the invertebrate.

### 3. TRIAMOMA BUGS

The species of triatomines that are associated with the transmission of Trypanosoma cruzi cause reactions in sensitized hosts that are characterized by large weals with erythema and oedema at the puncture site. In hypersensitive hosts on occasion there is a profound response characterized by prostration, severe pain, vomiting, and at times anaphylactic shock, fever, and severe systemic effects. The literature suggests that the usual type of reaction is of the delayed type, 24-48 hours after the bite, and that an immediate type reaction seldom appears (Lavoipierre, et al. 1959). On the other hand, the characteristic lesions produced may in many cases be clinically similar to, or even identical with, certain facets of the symptomatology seen in Chagas' disease. Lumbereras, Flores and Escallón (1959) carried out experiments in which the reaction in humans to the bites of triatomids was compared with the clinical picture in Chagas' disease. They found that the eyelid oedema experimentally produced was identical with the ophthalmo-lymphonodular complex, or Romaña's sign, characteristic of the trypanosome infection. These workers further suggested that the immediate reaction caused by the triatomid may be favourable for the penetration of Trypanosoma cruzi and its subsequent spread in the lymphatics. Although no definitive evidence is available on this problem, it is noteworthy that specialists have emphasized the view that the skin reaction following the bite of the vector may be directly or indirectly related to the acquisition of the trypanosome infection by the vertebrate host (Pick, 1954).

### 4. MOSQUITOS

By means of actual observation of the mosquito during the act of feeding, it has been determined that the insect obtains its meal most frequently from pools of extravasated blood and to a lesser extent directly from a capillary which has been penetrated by the flexible mouthparts (Gordon & Crewe, 1948). These workers also noted that salivary material was deposited in the host's skin during feeding activity.

The clinical reactions to mosquito bites have been described by many workers (Horsfall, 1962; Beard, 1963; McKiel, 1959). It is sufficient to describe briefly the histopathologic response of a sensitized host to the bites of mosquitos. Rockwell and Johnson (1952) have evaluated the reaction to mosquito bites on human subjects. A skin biopsy was taken from a subject 30 minutes after being bitten by Aedes aegypti. This subject was sensitized and responded with moderate immediate and delayed reactions. The skin section showed oedema of the corium and starting perivascular infiltration of neutrophils, eosinophils, lymphocytes, and plasma cells. Biopsies of skin at six hours, 24 hours, two days, and five days showed progressive increase in the proportion of lymphocytes and histiocytes with occasional neutrophils and eosinophils. In severe reactions, the main difference was an increase in the intensity of the infiltrate which contained a greater proportion of polymorpho-nuclear leukocytes and eosinophils.

Goldman, Rockwell and Richfield (1952) pointed out that severe reactions to mosquito bites showed a striking eosinophilic response accompanied by inflammation with marked epidermal and dermal oedema. In general, these authors indicated that a basic similarity was noted in the histopathology of immediate and late reactions. However, they stated that "the characteristic response of the hypersensitive individual is an increased inflammatory reaction with a greater predominance of eosinophils within the inflammatory infiltrate." (In the above quotation the term "hypersensitive" is interpreted as denoting a severe immediate type of reactivity.)

Mosquitos often probe repeatedly in various places on the skin of man or animals preparatory to blood feeding. Quite often malaria infections can be produced in vertebrate hosts by interrupting this probing activity even before blood can be demonstrated in the mosquito's stomach. Thus it seems evident that saliva containing malaria sporozoites can be injected into the skin before or at commencement of actual withdrawal of blood. It is known, as already stated, that saliva is deposited in the skin during the act of blood-sucking (Gordon & Crewe, 1948).

When the sporozoites of the malaria parasite are injected by the mosquito along with its saliva into a host's skin many sporozoites apparently are quickly dispersed by the bloodstream as shown in experiments with Plasmodium gallinaceum (Coulston et al., 1945). In earlier studies Huff and Coulston (1944) have shown that sporozoites enter cells of the lymphoid-macrophage system and into heterophils and begin to develop as cryptozoites as early as 30 minutes after inoculation into the host's skin. The sporozoites in macrophages appeared to be trapped in cytoplasmic processes, while in lymphoid cells they appeared confined to vacuoles in the central portion of the cytoplasm. After six hours no sporozoites could be seen in the intracellular spaces and many of them were noted inside heterophil granulocytes. Since no growth and development of the parasite into later stages were noted in this type of cell, it was assumed that practically all sporozoites phagocytized by them were destroyed.

Huff and Coulston (1944) demonstrated the development of P. gallinaceum in macrophages from forms still recognizable as sporozoites to mature segmenters. Working with the same malaria species, Schulemann and Spies (1940) concluded that the pre-erythrocytic stages grow in histiocytes. The former workers also demonstrated the re-entry of macrophages and other mononuclear phagocytic connective tissue cells by cryptozoic merozoites in skin as early as 41 hours.

Kikuth and Mudrow (1939a, 1939b) described pre-erythrocytic stages of P. cathemarium from 16 hours to 64 hours after intramuscular inoculations of sporozoites taken from infected mosquitos. The parasites were found intracellularly at the site of inoculation and were undergoing schizogony in histiocytes of the reticulo-endothelial system. These authors considered their findings as proof that the sporozoite develops within cells after inoculation by the mosquito. Later work by several workers definitely showed that, with bird malaria parasites, the sporozoites did develop intracellularly to the pre-erythrocytic stages (for review see Bray, 1957).

The evidence bearing on mosquitos, malaria, and the host's hypersensitive skin reactions to the bites of mosquitos is, as in the other examples, primarily a recital of certain experimental findings that are completely independent both in terms of research design and in theoretical rationale. Nevertheless, in view of the relatively large amount of work that has been devoted to malaria and to the effects of mosquito bites, I feel strongly that these two fields, when united, should offer a fertile area for productive research.

## 5. TICKS

The so-called hard ticks of the family Ixodidae feed on the host by puncturing the skin and deepening the wound into a cavity with concomitant development of haemorrhage. After insertion of the mouthparts, they soon become encased in a wall that penetrates the dermis for about a millimetre (Arthur, 1953). This wall, which has a tube in its centre through which blood moves to the tick's mouth, has been described as a laminated eosinophilic zone or "cement substance" (Cowdry & Danks, 1933). A characteristic oedematous inflammatory reaction usually occurs. The capillary endothelium becomes swollen and is infiltrated by polymorphonuclear leukocytes, accompanied by a marked cytolysis of fibroblasts. The feeding of various species may cause a local necrosis or a lamellate or columnar necrosis of muscle tissue (Hoeppli & Feng, 1931).

The nature of the cutaneous reaction and the histopathology of tick bites would seem to suggest that this arthropod could provide a mechanism whereby pathogenic organisms could be introduced via skin lesions. Foggie (1959) obtained negative results, however, in attempts to inject lambs with the staphylococci of so-called tick pyaemia, by the intradermal injection of the bacteria together with salivary extracts from Ixodes ricinus or by feeding ticks on skin heavily contaminated with the organisms. As a matter of fact, sections of the tick-bite wound infected with staphylococci showed that the oedematous tissue had been replaced by pus cells and granulation tissue that had the effect of localizing the infection in a skin abscess. Furthermore, data gathered from farms in districts where a high incidence of pyaemia occurred showed a lower infestation with ticks than on farms with a low incidence of the infection. Thus the evidence can be taken either as a case of no correlation, or perhaps as suggesting a negative correlation.

It is of interest here to mention the phenomenon of resistance of the host to ticks. Trager (1939a) has observed that guinea-pigs, after infestation, can develop an immunity to Dermacentor variabilis which effectively prevents ticks from engorging during subsequent infestations. This immunity appeared to be generalized and lasted about three months. A similar type of acquired immunity was noted in rabbits and deer mice against larval D. variabilis, in guinea-pigs against larval D. andersoni, and by rabbits against larvae of Haemaphysalis leporis-palustris.

Trager (1939a) also demonstrated that the immunity to ticks could be produced by the inoculation of an extract of larval ticks and could be passively transferred. This immunity appeared to depend on the presence of a circulating antibody that accelerated local cellular invasion which had the effect of walling off the tick larvae from normal feeding. In further work on this problem, Trager (1939b) showed that guinea-pigs could be partially immunized against larvae of D. variabilis by intracutaneous inoculations of extracts of cephalic glands, salivary glands, the digestive tract of partly engorged adult female ticks, or of the salivary glands of unfed adult females.

Although the work of Trager is not specifically germane to the subject under discussion, it is related when viewed from an epidemiologic standpoint. It seems obvious that an acquired immunity to the feeding of an arthropod vector could prevent the initiation of a certain number of infections if the phenomenon occurred under natural conditions. The incidence and degree of immunity could influence the incidence of natural infections with a given arthropod-borne disease organism. Thus it is possible that host immunity to vector arthropods could account in part for such phenomena as discrepancies between the geographic distribution of the vector and of the infection (or disease).

## 6. HORSE-FLIES

In the category of related observations it is relevant to mention the studies of Crewe and Gordon (1959) who noted that reactions to the biting of an arthropod may be complicated by associated reactions to a pathogen released by that arthropod during blood-sucking. These authors, working with the horsefly Chrysops and the filaria parasite Loa loa, indicated that the human host showed two types of immediate reactions after the bite: (1) a reaction to some substance in the saliva of the fly, and (2) a reaction to the nematode parasite introduced into the host's skin by the feeding horsefly. A similar observation of the two types of immediate reaction was made in monkey hosts. No significant relationship was shown to occur between these independent, but closely associated mechanisms. However, the immediate reaction following the bites of Loa-infected Chrysops was more severe than the reaction elicited by the feeding of uninfected flies.

The observations with Loa loa and Chrysops suggested to Gordon (1958) that an immediate type reaction to a parasite, released into the arthropod bite site, may interfere with, or even prevent the subsequent survival and development of the parasite. Gordon speculated that the reaction in man, if actually found to be antagonistic to the parasite's development,

might help to explain why comparatively few of the infective nematode larvae apparently are able to reach the adult form in an indigenous African population exposed constantly to the bites of Chrysops and thus to superinfection with the filariid.

#### 7. TSETSE FLIES

The trauma produced by the feeding mechanism of tsetse flies causes haemorrhage and the insect thus feeds on pools of extravasated blood. The relation of "pool feeding" to the transmission of trypanosomes by species of Glossina may be of some importance since the metacyclic trypanosomes are inoculated into solid tissues and there is early development of lesions at the site of inoculation (Buxton, 1955). In an individual who is not sensitized to tsetse bites the histopathologic reaction is confined solely to haemorrhage. However, in a sensitized host, in addition to haemorrhage, there is dilation of blood vessels and extensive separation of collagen fibres, which forms the characteristic weal (Gordon & Crewe, 1948).

Gordon and Willett (1958) observed that in rabbits and man a local reaction in the form of a chancre developed at the site of the bite of tsetse flies infected with trypanosomes. Histologically, the reaction was characterized by oedema and infiltration with numerous mononuclear histiocytes, fewer eosinophils, and an association with trypanosomes throughout the reacting site. Such reactions did not occur in guinea-pigs, rats, and in two monkeys used in the experiments. The authors concluded that in rabbits, at least, the metacyclic trypanosomes developed locally into the usual blood forms.

#### 8. FLEAS AND BUBONIC PLAGUE

Perhaps one of the most promising combinations of circumstances that may be used to support the view presented here is suggested by the well known role of fleas both as vectors of Yersinia (Pasteurella) pestis and as the cause of skin reactions in sensitized animal and human hosts. It has been demonstrated that a definite sequence of cutaneous reactions occurs in guinea-pigs when these animals are exposed repeatedly to flea bites (Benjamini et al., 1961). Several stages of reactivity were observed and are listed briefly as follows:

- I. Induction period; no reactivity (four days).
- II. Predominantly delayed reactivity (on fifth day after initial exposure and lasting four days).
- III. Immediate and delayed reactivity (on ninth day and lasting 48 days).
- IV. Predominantly immediate reactivity (on fifty-seventh day and lasting 31 days).
- V. Non-reactivity (on eighty-eighth day and lasting 150 days).

Later studies were made to correlate the various stages of the above skin syndrome with histopathological responses and with the cellular picture characteristic of delayed and immediate reactivity (Larrivee et al., 1964). The results suggested a specific relationship between the delayed skin reaction and mononuclear leukocytic infiltration, and between the immediate type of skin reactivity and a massive infiltration of eosinophils. Thus the work showed that, in the guinea-pig, each stage of skin reactivity was accompanied by distinct histopathologic phenomena peculiar to a given stage.

A brief review of the histopathologic findings are presented as follows in conformity with the five stages listed above:

- I. Induction period: The fascicle of the flea penetrates the epidermis and dermis causing mild trauma characterized by an invasion of a few lymphocytes that virtually disappear in 24 hours. Direct microscopic observation of fleas during the act of feeding has shown that they feed mainly by penetrating the lumen of small blood vessels and less frequently from pools of extravasated blood resulting from the rupture of

capillaries. During the act of sucking blood from these vessels, droplets of salivary fluid were seen to be emitted near the puncture in the vessel wall but never into the vessel lumen (Lavoipierre & Hamachi, 1961).

- II. Delayed reactivity: There is an intense monocytic and lymphocytic infiltration of the dermis in conjunction with hyperplasia and mononuclear invasion of the epidermis.
- III. Immediate and delayed reactivity: There is evidence of both monocytic and eosinophilic cellular infiltration, the former appearing during the delayed phase and the latter showing an intensity during the immediate response 20 minutes after the challenging bite.
- IV. Immediate reactivity: There is an intense eosinophilic infiltration within 20 minutes and a mild mononuclear response within 24 hours.
- V. Non-reactivity: Histologic sections representing skin samples biopsied at 20 minutes and 24 hours after flea bites show a negligible cellular response comparable to samples taken from non-sensitized control animals.

It is of importance to note at this juncture that the guinea-pig, a rodent susceptible to and associated with sylvatic plague in South America, is the animal in which hypersensitivity to flea bites has been demonstrated. Thus the first assumption is that rodents in nature become sensitized to flea bites, probably quite early in life, and that they exhibit the clinical-histopathological sequence of reactivity comprising the hypersensitivity syndrome referred to above. Implicit in this assumption is the precept that different species of rodents, and even strains within species, may vary in the degree of reactivity and in the types of reactivity stages characterizing their response to flea bites.

This leads to the third factor in the epizootiologic triad, the pathogenic agent. Many years ago it was noted that plague bacteria from infected fleas were more susceptible to ingestion by mammalian phagocytes than were plague organisms taken from the tissues of infected animals (Bacot & Martin, 1914). This phenomenon was considered to be a change in virulence; that the plague bacillus had lost some of its invasiveness while residing in the gastrointestinal tract of fleas. Only quite recently has more exact information been obtained on the problem, and the data show that the plague organism does undergo significant changes during its sojourn in the flea, and that these changes are related intimately to the host's cellular defense.

Burrows (1955) and Burrows and Bacon (1956) have demonstrated that virulent strains of Y. pestis, in comparison with avirulent strains, occur as three types: (1) a non-encapsulated, phagocytosis-sensitive or S-type; (2) a non-encapsulated, phagocytosis-resistant or R-type; and (3) a well-encapsulated, phagocytosis-resistant or M-type, rich in Fraction I antigen that has been correlated with virulence of the organism (Englesberg et al., 1954).

Cavanaugh and Randall (1959) confirmed the finding that the R- and M-types were resistant to phagocytosis by polymorphonuclear leukocytes, and that polymorphs readily ingested and destroyed the S-type bacilli both of virulent and avirulent strains of Y. pestis. Going beyond these findings, Cavanaugh and Randall (*ibid.*) showed that the phagocytosis-sensitive S-type of virulent Y. pestis was phagocytized by mononuclear leukocytes of mice and guinea-pigs, that the bacilli were not destroyed in these free macrophages, but actually multiplied within them. Finally, when released from the damaged monocytes the plague bacilli had changed to the encapsulated M-type and were highly resistant to phagocytosis either by neutrophils or monocytes.

In the above studies, Cavanaugh and Randall discussed the changes occurring in the plague organism while it developed and finally caused proventricular blockage in the flea vector. The evidence revealed that the blocked flea inoculates its host with the

phagocytosis-susceptible S-type of virulent Y. pestis which is phagocytized readily and destroyed in large numbers by neutrophils. On the other hand, a proportion of the invading bacilli are ingested by monocytes within which they multiply and finally break free as phagocytosis-resistant M-type organisms. This mechanism was considered to be the pre-condition for the initiation of widespread infection resulting in clinical bubonic plague in a susceptible vertebrate host.

More recent work on this problem has shown that avirulent strains of Y. pestis, which produce the capsular antigen Fraction I, also can be rendered phagocytosis-resistant when grown under specific conditions, and that virulent strains are phagocytosis-susceptible if they fail to elaborate Fraction I. It was concluded that resistance to phagocytosis is not necessarily the sole factor determining virulence of Y. pestis to the vertebrate host, but that the most critical factor is the intracellular survival and multiplication of the bacilli after phagocytosis (Janssen et al., 1963).

The above investigations provide the basis for a second assumption, namely, that under natural conditions the plague bacillus in the flea vector undergoes antigenic changes that convert it from an M-type to an S-type organism. In the latter state it is phagocytosis-susceptible when inoculated into a rodent or other host by a blocked flea. (A possible exception to this would occur during mass mechanical transmission of Y. pestis by fleas. It is known that some species of fleas seldom, if ever, block with plague organisms. They transmit the infection during interrupted feeding by transfer of the bacilli on contaminated mouthparts from one host to another. Thus, in such a case, it would be expected that phagocytosis-resistant M-type organisms are involved).

The hypothesis can be stated at this point, using the flea Y. pestis-host hypersensitivity complex as an example. Assuming that rodents are sensitized by, and react to, the feeding of fleas according to the sequence of hypersensitivity stages outlined above, it seems probable that the introduction of Y. pestis by a flea during the stage of delayed reactivity in the skin of the vertebrate host would present an environment favourable to the rapid phagocytosis of a majority of the bacilli by monocytic cellular elements within which the organisms would multiply and ultimately produce a fulminating infection in a susceptible host. On the other hand, during the state of immediate reactivity in the host skin, the flea-inoculated plague bacilli would be phagocytized in great numbers by polymorphonuclear cells and destroyed. Thus in hosts of equal susceptibility to Y. pestis the course taken by the infection would be modified according to the stage of reactivity, as in the two cases outlined above. Vertebrate hosts exhibiting other stages of the sensitization syndrome might not be expected to show well-defined correlations with the course of infection.

It should be mentioned that little or nothing seems to be known regarding the relation of eosinophils to plague organisms. Since eosinophilia predominates during the immediate type hypersensitive reaction in the skin, the relation of these leukocytes to Y. pestis deposited in the skin is a significant problem. The ability of eosinophils to phagocytize micro-organisms was reported many years ago (Mesnil, 1895, Weinberg & Séguin, 1914). In recent work Litt (1964) has presented evidence that eosinophils are attracted by antigen-antibody complexes which they phagocytize. In the skin an antigen, in the form of an invading parasite, or a micro-organism, remains available over a relatively long period to form complexes with antibodies. Thus in a plague-resistant rodent such as Microtus californicus, populations of which have been shown by serologic tests to have high percentages of Y. pestis haemagglutinating antibody titres (Hudson et al., 1964), eosinophilia might be elicited both by the formation of antigen-antibody complexes and by an immediate skin reaction following the bite of an infective flea.

In nature, the relation of immunity to Y. pestis and hypersensitive reactions in the rodent undoubtedly constitutes a complex mechanism. Nevertheless, it is important to note that plague workers generally agree that immunity to plague bacilli appears to be primarily cellular rather than humoral. The hypersensitivity syndrome elicited by the flea bite and the immune response to invading Y. pestis are both characterized by a prominent cellular response.

In its simplest form, the hypothesis rests upon the assumption that the predominant cellular components responding to a particular type of sensitivity reaction at the cutaneous site of a flea bite may determine the fate of plague bacilli inoculated into a rodent host by the flea vector. Thus the bite site may be characterized as the cutaneous locus in which sensitivity-induced histopathogenic processes react with pathogens inoculated by arthropods.

It remains to be seen, of course, whether or not this hypothesis has a basis in fact. In view of the current rapid expansion of knowledge in the field of sensitization phenomena, especially in relation to disease processes, parasitologists and medical entomologists should pay some attention to the possible relationship between these phenomena in the vertebrate host and the fate of pathogenic organisms inoculated by arthropod vectors that are themselves the cause of the host's hypersensitivity. Such studies, if promising on an experimental basis, could be extended to epidemiologic and ecologic investigations.

#### SUMMARY

A hypothesis is suggested that in nature there may be a relationship between the phenomenon of hypersensitivity to the bites of certain haematophagous arthropods and the fate of pathogenic organisms inoculated into the vertebrate host by the same arthropods. Thus in a situation where the cellular defenses of the host are modified by cutaneous reactivity, the changed cellular environment either would be more favourable or more unfavourable to a pathogenic agent inoculated by the arthropod vector whose repeated feeding had elicited the hypersensitive state in that host.

Some notes are presented to suggest that these relationships may occur in the transmission of rickettsial, protozoan, bacterial, or other infections by vectors such as ticks, horse-flies, tsetse flies, lice, and mosquitos.

The main evidence presented as a basis for the hypothesis is taken from the ecologic complex comprising the relationship between plague vectors and vertebrate hosts. The flea is at once the agent that induces a well-defined hypersensitivity syndrome in its rodent host and also is the vector that inoculates virulent plague bacilli into the rodent.

Studies have shown that delayed and immediate types of skin reactivity to flea bites in sensitized guinea-pigs are characterized histopathologically by monocytic and eosinophilic cellular infiltration, respectively, at flea bite sites.

The plague organism, multiplying and finally blocking the proventriculus during its sojourn in the flea, undergoes antigenic mutation so that it changes from a phagocytosis-resistant to a phagocytosis-susceptible type. The latter type is destroyed by polymorphonuclear leukocytes, but it survives in monocytes, multiplies in them, and finally breaks out as an antigenically changed organism capable of resisting phagocytosis.

The above two considerations give some weight to the hypothesis that the predominant cellular components responding to a particular type of sensitivity at the cutaneous site of a flea bite may determine the fate of plague bacilli inoculated into a rodent host by the flea vector. Thus the bite site may be characterized as the cutaneous locus in which sensitivity-induced histopathogenic processes react with pathogens inoculated by arthropods. Whether or not these relationships actually exist remains to be determined by laboratory studies in which a number of well known arthropod-borne pathogenic agents may be employed.

Table 1 SOME ARTHROPOD VECTORS OF HUMAN AND ANIMAL PATHOGENS THAT ALSO CAUSE ALLERGIC RESPONSES IN THE VERTEBRATE HOST (based in part on HORSFALL, 1962)

ARTHROPOD VECTORS	PATHOGEN TRANSMITTED				CUTANEOUS RESPONSE OF HOST TO INJECTED SALIVA																	
	Virus	Rickettsia	Protozoa	Bacteria	Helminth	Hemorrhage	Edema	Vasodilation	Polymorphs	Lymphocytes	Histocytes	Necrosis	Wheal	Papule	Erythema	Bulla	Lymphadenitis	Fever, local	Fever, general	Anaphylaxis	Paralysis	
Culicidae	+				+	+	+	+	+	+			+	+	+	+	+	+				
Phlebotomus	+			+		+	+	+	+				+	+	+	+	+	+			+	
Simulidae			+		+	+	+	+	+				+	+	+	+	+	+				
Tabanidae			+	+	+	+	+	+	+				+	+	+	+	+	+				
Glossina			+			+	+	+			+		+	+	+	+	+	+			+	
Pediculus				+		+	+	+					+	+	+	+	+	+			+	
Triatominae		+	+			+	+	+	+				+	+	+	+	+	+			+	
Siphonaptera		+	+	+	+	+	+	+	+				+	+	+	+	+	+			+	
Acarina	+					+	+	+	+				+	+	+	+	+	+			+	+

## RESUME

A titre d'hypothèse, nous suggérons qu'il existe peut-être un rapport entre le phénomène de l'hypersensibilité aux morsures de certains arthropodes hématophages et leur efficacité en tant que vecteurs d'agents pathogènes. Dans le cas où les défenses cellulaires de l'hôte sont modifiées par une réaction cutanée d'origine allergique, le milieu cellulaire ainsi modifié deviendrait plus ou moins favorable à un agent pathogène inoculé par un arthropode vecteur dont les repas répétés sur l'hôte ont provoqué chez ce dernier un état d'hypersensibilité.

Les observations que nous rapportons tendent à montrer l'existence possible de tels rapports dans la transmission d'infections à rickettsies, protozoaires, bactéries, etc., par des arthropodes vecteurs tels que tiques, taons, glossines, punaises et moustiques.

Les principaux arguments en faveur de cette hypothèse sont tirés du complexe écologique qui relie les vecteurs et les hôtes vertébrés du bacille de la peste. La puce est à la fois agent d'un syndrome d'hypersensibilité bien défini chez le rongeur hôte, et vecteur, chez le même rongeur, de bacilles pesteux virulents.

Des travaux sur le cobaye sensibilisé ont montré que les réactions cutanées, retardées ou immédiates, aux morsures de puce sont caractérisées, sur le plan histopathologique, par une infiltration cellulaire de monocytes et d'éosinophiles au niveau des morsures.

Au cours de leur séjour chez la puce où ils se multiplient pour finalement bloquer le proventricule, les bacilles de la peste subissent une mutation antigénique. Du type résistant à la phagocytose, ils se transforment en type sensible à la phagocytose, type qui est détruit par les leucocytes polymorphonucléaires mais qui survit à l'intérieur des monocytes où il se multiplie et d'où il émerge finalement sous la forme d'un organisme capable de résister à la phagocytose.

Ces deux séries d'observations viennent étayer l'hypothèse selon laquelle l'évolution du bacille de la peste inoculé dans un hôte rongeur par une puce vectrice dépend des éléments cellulaires qui prédominent en réponse à la sensibilisation provoquée par la morsure. Ainsi, le siège de la morsure peut être défini comme le locus cutané de la réaction entre les processus histopathogènes induits par la sensibilité et les pathogènes inoculés par les arthropodes. Il reste à démontrer si de tels rapports existent ou non. A cet effet, des études de laboratoire devront être effectuées sur un certain nombre d'agents pathogènes bien connus transmis par des arthropodes.

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