The Neglected saliva: medically important toxins in the saliva of human lice

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SUMMARY

Although there has been a great deal of research effort within the last two decades on identifying the active components of the saliva of blood-sucking ticks, mosquitoes, biting flies, fleas and bugs, essentially neglected have been the human lice. Despite initial reports in the early part of this century suggestive of vasodilatory, anticoagulant and immunosuppressive properties of the saliva, for the next 50 years there were no biochemical studies on the active principles. Very recently, anatomical and biochemical studies have begun to characterize the bioactive molecules in lice saliva. The louse stocks a salivary vasodilator in excess over what is needed for a single bite, and injects similar amounts at each successive bite. The vasodilator in lice saliva appears to have different pharmacological properties than peroxidative, oxidative and maxidilan types of vasodilators reported from other blood-sucking insects. Possible anticoagulant activities have also been characterized. This belated, but welcome, interest comes at a time of resurgence of lice-born disease in certain parts of Africa, and of resistance to chemical control in Europe and North America.

Key words: *Pediculus*, *Phthirus*, lice, saliva, salivary gland, wasp, parasite.

INTRODUCTION

While parasitic insects vary widely in their morphology, physiology and ecology, there exist convergent analogies in solutions to problems posed by their parasitic life style. For example, just as a parasitic wasp's venom is the chemical interface between the wasp and its host, so the saliva of the blood-sucking insect is its initial chemical contact with its (potential) host. In both cases, the success of the parasite in further utilization of that host hinges on whether the injected molecules can alter the normal biochemistry and physiology of the host sufficiently to permit access by the parasite. Access through action of toxins present in the venom or saliva may be accomplished by rendering the host into a condition favourable for physical entry of all or part of the metazoan parasite. Alternatively, access may be in the form of rendering part of the host into a condition suitable for its physical uptake into the parasite, or access may be effected by salivary modifications to the parasite itself. In this paper, I briefly review the state of knowledge, or, perhaps more properly, the state of neglect, about the salivary toxins of human blood-sucking lice from the perspective of their capacity as parasites. In view of the worldwide medical importance of blood-sucking lice in human history, I will take opportunities to consider the medical relevance of greater attention to the nature and actions of toxins in the saliva of these insects in their capacity as disease vectors. Finally, in view of the contributions to this volume of researchers on parasitic wasps, and of the symposium organizers' efforts to coax contributors into forging parasitological principles applicable beyond their own system, where the opportunity avails itself I pause to compare processes in the lice–human host interaction with those of parasitic wasp–host insect interaction.

SALIVARY COMPONENTS OF BLOOD-SUCKING INSECTS OTHER THAN LICE

Considerable effort has been made to identify the salivary molecules used by some blood-sucking insects to render host biochemical pathways under the control of the parasite, and there are a number of excellent reviews on them which I do not attempt to duplicate here (e.g. Ribeiro, 1995*a*, *b*; Champagne & Valenzuela, 1996). I briefly note here some of the reported aspects, to provide a framework for comparison to what is known from human lice. Erythrematous vasodilators, those that cause reddening at the bite site, have been isolated from a number of such parasites. A vasodilatory protein occurs in the sand fly saliva (Ribeiro *et al.* 1989; Lerner & Shoemaker, 1992), while a different peptide causing such effects occurs in the saliva of the blackfly (Cupp, Cupp & Ramberg, 1994). This effect is induced by a tachykinin in *Aedes aegypti* (Champagne & Ribeiro, 1994), and by a catechol oxidase/peroxidase activity in *Anopheles albimanus* (Ribeiro & Nussenzveig, 1993). The great variation in vasodilatory molecules found in the salivas of different blood-sucking insects is readily apparent. As Champagne & Ribeiro (1994) have noted, this variation strongly suggests that different blood-

sucking insects have each made use of a different 'domestic' protein for the particular specialized need to intercede in a particular host haemostatic pathway.

Platelet aggregation inhibitors also occur in the saliva of many blood-sucking insects, such as tsetse flies (Mant & Parker, 1981), mosquitoes (Champagne *et al.* 1995), fleas (Ribeiro, Jefferson & Azad 1990), sucking bugs (Sarkis, Guimaraes & Ribeiro, 1986), blackflies (Abebe *et al.* 1996), and sandflies (Ribeiro, Rossignol & Spielman, 1986). Most platelet aggregation inhibitors reported to date are apyrases. Anticoagulants blocking various steps in the coagulation pathway *per se* have also been reported from the salivas of some blood-sucking Arthropods (Ribeiro, 1995*a*). Anticoagulants have been described that block at Factors V and VII (ticks, Gordon & Allen, 1991), at Factor Xa (ticks, Waxman *et al.* 1990; black flies, Jacobs *et al.* 1990) or at thrombin (tsetse flies, Mant & Parker, 1981; sucking bugs, Ribeiro & Sarkis, 1982). Anticoagulants that block this clotting cascade have not been widely reported from mosquitoes, as these parasites feed in small capillaries whose haemostasis is more effectively controlled at the level of platelet aggregation (Ribeiro, 1995*a*).

Blood-sucking arthropods must also contend with the potential immune response of the host against the salivary molecules injected during parasite feeding. Hence, it is not surprising that some components of the saliva are able to suppress various points in the pathways of the host immune response, just as the venom injected into hosts by some parasitic wasps affects the host immune reaction (see Beckage, this volume). The initial secretion of interleukin 2 (IL-2) or interferon-γ by T-helper cells for cell-mediated immunity may be suppressed by salivary components (Cross, Cupp & Enriquez, 1994*b*, Urioste *et al.* 1994), as may be secretion of IL-4 by T-helper cells that stimulates B-cells to produce antibodies (Cross *et al.* 1994*b*). Alternatively, the proliferative response of T-cells to IL-2, or of B-cells to IL-4, may be suppressed (Cross *et al.* 1994*a*). Arthropod salivary components have also been reported to suppress the proliferative response of these cells to subsequent *in vitro* stimulation with known mitogens (Cross *et al.* 1994*b*, Dusbabek *et al.* 1995) or with the original salivary antigen (Wikel & Osburn, 1982, Dusbabek *et al.* 1995). Further, some salivas have been demonstrated to suppress the cell-killing activities of, or the numbers of, neutrophils, eosinophils, macrophages, and N-K cells (Theodos & Titus, 1993, Kubes *et al.* 1994).

SALIVARY COMPONENTS OF HUMAN LICE

In comparison with the intensity of research on other blood-sucking insects, investigations on the salivary components of human lice have been nonexistent, despite the attention called to the problem for over two decades. Twenty years ago, Nelson *et al.* (1977) reviewed the interaction of ectoparasites (including lice) and their hosts and noted '[investigations] of chemical or antigenic compounds of arthropod oral secretions have been few...' and that 'although slow progress is being made, more chemical analysis of oral secretions are needed'. Wikel (1982) cautioned that '[i]nformation concerning the nature of the host immune response to the sucking lice, Anoplura, is surprisingly limited'. Subsequently, Ribeiro (1987) echoed that surmisal, noting 'suitably detailed information is available for only a few species of hematophagous arthropods', where lice were not among those for which such information was available. Subsequently, Law, Ribeiro & Wells (1992) were again unable to locate a single report on such investigation of lice saliva. Ribeiro (1995*a*) found that the anoplurans are the last remaining order containing blood-sucking insects for which vasodilators and anticoagulants have still not yet been identified.

Despite the fact that each year tens of millions of persons world-wide are injected with the saliva of human lice, there is essentially no information about the actual molecules injected by these insects into their human hosts. Lice (and several bugs) are unusual blood-sucking insects studied to date, in that they possess two independent pairs of salivary glands; in lice these are the 'reniform' glands and the 'U-shaped' glands. Each pair is located in the thorax, and traversing anteriorly from each gland is an apparent salivary duct (see Buxton, 1947).

ERYTHEMATOUS, ANTICOAGULANT AND IMMUNOACTIVE FUNCTIONS IN LICE SALIVA

Early studies on lice salivary glands conducted before World War II detected certain biological activities in human body/head lice (*Pediculus humanus*), but over 50 years would pass before there was published any research toward the isolation of the active components. One early study of the erythematous and other skin reactions induced at the feeding site of *P. humanus* used the head of the insect as a tissue source for injection of extracts (Peck, Wright & Gant, 1943), when in fact, as mentioned, both pairs of salivary glands are located in the thorax. In studies on salivary anticoagulant activity in *P. humanus*, Nuttall (1918*a*) detected such activity, but could not distinguish the glandular source, since he combined the 2 kinds of salivary glands together before assay. In important initial biochemical studies, Mumcuoglu *et al.* (1996) characterized an anticoagulant activity in thoracic extracts containing the two kinds of glands, but as yet the specific glandular source of the activity has not been determined (Mumcuoglu, personal communication). Thus, the field of medical

parasitology still awaits even the determination of which lice salivary glands are producing which regulatory activities.

Similarly unattended have been the human crab lice, *Phthirus pubis*, ('papillion d'amour' in French). Feeding by these lice leaves blue-coloured marks ('*caeruleae maculae*') in the skin. Early in this century there was considerable debate over whether the *maculae* were consequent to an interaction of salivary components with haemoglobin or, instead, arose upon conversion of bilirubin to biliverdin (Nuttall, 1918*b*). Formation of this colour can be induced by intradermal injection of extracts from the reniform pair of glands, but not by the extracts from the U-shaped glands (Pavlosvski & Stein, 1925). Unfortunately, no biochemical studies to identify the responsible molecules have been reported during the past 75 years.

RECENT STUDIES ON LICE SALIVARY GLANDS

It is well known that structure can suggest function, such as that the array of hooks on a tick's haustellum positioned at the mouthparts accurately suggests its function to lodge the mouthparts into the host skin. However, while early anatomical studies described what overtly appears to be a duct running from each louse reniform and U-shaped gland toward to the mouthparts, it had never been published whether the morphological or histological structure of the interior of these glands and ducts actually suggest a salivary function. Recently, Jones & Wache (1998) reported presence of apparently chitin-lined ductworks in each gland type, but differences in other cellular structures between the two gland types. These histological differences were also reflected in distinct protein contents of the two kinds of glands, with the U-shaped gland having the apparently simpler composition, suggesting that each gland type contributes uniquely to the composition of the injected saliva.

Vasodilatory activity

As demonstrated previously with saliva from the sandfly (Ribeiro *et al.* 1986) and blackflies (Wirtz, 1988, Cupp *et al.* 1994), much information about the pharmacology of the salivary components can be gleaned from the nature of the erythematous lesion. In the former, the red spot appears at the sandfly feeding site within a minute of the bite, increases in size over the course of an hour, and persists up to 24 h, without itch or oedema, even in persons or rabbits not previously exposed (Ribeiro *et al.* 1986, 1989). The erythema of blackflies is also long lasting (Wirtz, 1988). In comparison, the red spot induced at lice bites can appear within a minute, matures within several minutes, and is gone 1–2 h later, also without itch or oedema and in previously unexposed persons (Jones & Wache, 1998). As with the sandfly, these results suggest a pharmacological action, distinct from the hypersensitive red-rashes that are systematically produced after multiple feeding sessions (Nuttall, 1918*a*, and personal experience of the present author). However, that the louse salivary agent does not cause so persistent an erythema as the sandfly and blackfly, and that its maturation to full size is much quicker than the sandfly, suggests different pharmacology and identity for the louse vasodilator.

This inferred difference of the louse vasodilator from those reported from other blood-sucking insects is supported by recent biochemical analyses of the louse salivary gland proteins (Jones, unpublished data). In contrast to species that employ a haeme-containing protein to deliver nitric oxide (e.g. *Rhodnius*), the louse glands do not contain an abundant haeme protein. Distinct from species that contain salivary peroxidases or catechol oxidases that degrade biogenic amines, the louse gland does not contain such abundant enzymatic activities of this type. Nor does the active component of the louse glands react with antiserum generated against the sandfly maxidilan. The prospects for discovery in lice of yet another new salivary vasodilator seem quite high.

Of interest in this regard is that a major protein from the U-shaped gland has marked size and N-terminal sequence similarity to insect glutathione transferases. When formulating hypotheses on why this typically low abundance enzyme might be so abundant in this salivary gland, it is noteworthy that in vertebrates the enzyme acts in the terminal steps of synthesis of vertebrate peptidoleukotrienes. While these peptidoleukotrienes are more commonly known for their bronchoconstriction activity, when they are applied to or injected intradermally into the skin they cause vasodilation with erythema (Soter *et al.* 1983; Brain *et al.* 1985; Chan & Ford-Hutchinson 1985; Bisgaard, 1987). These data urge an inquiry into whether lice glands produce peptidoleukotriene (analogues) or, by way injection of glutathione *S*-transferase, facilitate peptidoleukotriene synthesis at the bite site.

The proportion of stored vasodilator injected during each louse bite has been estimated by observing the number of successive times a louse can induce an erythematous spot when it is repeatedly moved to a new feeding site just as host blood was beginning to enter the louse (Jones, unpublished data). Less than 10% of the stored vasodilator was injected at each attempt. Further, there is no detectable difference in salivary gland protein content (by SDS–PAGE) before and after a single louse bite (Jones & Wache, 1998). By comparison, *Ae. aegypti* appears to be able to exude 20% of the saliva contained in a pair of glands during 60 minutes

(Ribeiro, 1992). During a single bite, *Anopheles albimanus* injects 40% of the total salivary gland proteins (Ribeiro & Nussenzveig, 1993), and essentially all of the vasodilator activity in the saliva of *Culicoides variipennis* is injected at a single bite (Perez de Leon *et al.* 1977). These data, brief as they are, suggest that lice inject a much smaller fraction of their salivary gland contents during a single bite than do mosquitoes.

In its natural environment, the human body louse will be subjected to perhaps repeated dislodgement from a feeding site by the moving or scratching host, thus necessitating multiple feeding re-engagements of the host. Each new louse feeding site must be 'prepared' *de novo* into the necessary vasodilated state, and so the parasite must have both sufficient salivary stock, and sufficient salivation control, to be able to inject each time the requisite amount of saliva needed to induce the vasodilated state. In the experimental case where the same skin condition (e.g. forearm) is presented to the louse, the same amount of saliva would be needed to prepare the area at each bite, which is what the lice did perform at each successive site. In comparison, a solitary egg or egg-larval parasitic wasp must likewise successively engage multiple hosts. In the case of the wasp, stocked as it is with dozens of eggs ready for oviposition, a consistent amount of venom is required to 'prepare' each successive host for successful parasitism, and the parasite in fact does inject a similar amount of venom at each successive oviposition (Jones & Wozniak, 1991). Thus, despite the differences in ecology of the louse and the wasp, the similar pressures for repeated delivery of the requisite amount of their respective chemical interface with the host has convergently resulted in this similar level of physiological precision. This apparent importance for some ecological contexts of the parasite's ability to repeatedly deliver in perhaps rapid fashion the chemical interfacing the parasite with the host may indicate that important parameters for successful parasitism by blood-sucking insects include (1) the amount/potency of a single bite's saliva (Ribeiro, Rossignol & Spielman, 1985; Cupp *et al.* 1994); (2) the amount of salivary stock maintained relative to the average frequency of dislodgment during feeding, and (3) the physiological control to deliver the same or requisite amount of saliva at each successive bite.

Anticoagulants

Nutall (1918*a*) reported that the combined extract of five pairs of each of the reniform and U-shaped glands increased the clotting time of an unstated volume of blood from 20 to 60 min. Very recently Mumcuoglu *et al.* (1996) have partly characterized activities from a tissue extract containing both the two kinds of salivary glands. Those authors detected an apyrase activity, a 7 kDa antithrombin activity and an antifactor Xa activity, but the molecular identity and the precise location of each of these activities is unknown.

Immunoreactive components

Likewise warranting further investigation is the identity of components of the lice saliva that interact with the human immune system. As initially summarized by Mellanby (1946) and then Feingold, Behjamani & Michaeli, (1968), the change over time in human immune response to subsequent insect bites is progression through no initial response (first stage), to a second stage, delayed initial response (by monocytes, lymphocytes), then an immediate (neutrophils, eosinophils) plus a delayed response, then next a fourth stage immediate response only, and finally no response (fifth stage). Hoffman (1995) noted that prior to his review the only reported data in 25 years on allergenic response to insect saliva was a single paper on high IgE and IgG4 antibody titres in children exposed to mosquitoes (Reunala *et al.* 1994). He tentatively inferred that response to insect bites is generally different from the response to insect stings, and that hypersensitive reactions to the latter are typically IgE-mediated. However, very recently additional evidence for IgE-mediated hypersensitivity to mosquito salivary antigens has been presented (Brummer-Korvenkontio *et al.* 1997; Peng & Simmons, 1997; Shan *et al.* 1995).

While there has yet to be a single published study on immune response to specifically human lice saliva, a few hints of immunological effects of human lice saliva have lain in reports made earlier in this century. Stein (1931) inferred from microscopic analysis of feeding sites that the saliva at lice bites had 'incapacitated... local mechanisms in the skin' that would otherwise prevent typical wound-colonizing microorganisms from infecting that site. He did not describe just what cellular changes he had observed. Peck, Wright & Gant (1943) reported that some persons, while exhibiting erythematous vasodilation at the bite site, appeared otherwise insensitive to lice saliva. Other persons, after showing no initial response, then showed a delayed response when subsequently bitten. Then, bites occurring after the 'delayed only' phase induced an immediate and also then a delayed response. However, additional exposure to bites after the persons reached this stage did not yield the final 4th and 5th stage responses described (above) by Mellanby (1946). Progression of response to the immediate-type only (i.e. 4th stage response) has been documented in persons bitten by mosquitoes, fleas, bedbugs and sandflies, but not lice (Hoffman, 1995). It is unclear why in Peck's studies bite victims never reached the immediate-only stage of response. Identification of the components of lice saliva that cause the delayed and immediate

responses, as well as those that may block further progression through the classical stages of response, is an obvious next step.

With respect to humoral (circulating antibody) immune response, Balbi (1933) was able to transfer the immediate hypersensitive reaction from louse-infested to uninfested persons by injecting the latter with serum from the heavily louse-infested persons. However, he could not detect in the serum of louse-infested persons a titre of precipitating antibodies toward lice saliva. Nelson *et al.* (1977) interpreted these and other observations as indicative of IgE-based immediate hypersensitivity to lice. If this anticipation is borne out, it would be an interesting property of lice saliva as compared with other biting insects, since evidence of IgE involvement in the progressive response to bites of other insects is only now being hinted at for mosquitoes.

There is a tantalizing report by Abdel Fattah *et al.* (1994) suggestive of possible IgE induction by lice infestation. Those authors observed a 'marked correlation' between the presence of swollen cervical lymph nodes of lice-infested children and high serum titres of IgE. There is also the interesting report by Morsy *et al.* (1996) of an 'abnormal distribution of histocompatability antigens' in louse-infested patients. Those investigators detected a 'significant increase' in HLA-A11 and HLA-B5 in lice-infested persons. Human lice are apparently the only blood-sucking insects thus far potentially implicated with shifts in the distribution of histocompatability antigens. While these studies did not address whether the responsible antigens are salivary components, the results raise this hypothesis as a target of future experiments. Very recently, Jones & Wache (1977) detected in the serum of lice hosts antibodies that reacted more strongly with native epitopes, than with denatured components, of combined extracts of the reniform and U-shaped glands.

PARASITES AS TARGETS OF THEIR OWN SALIVAS AND VENOMS

As reflected in the above review, the target of salivary solutions is popularly envisioned as the host. However, this assumption may not necessarily be the case. With respect to blood-sucking insects, it has been proposed that mosquito saliva functions in part to lubricate the moving stylets of the mouthparts (Lehane, 1991), as well as to hold the stylets together by surface tension (Lee, 1974), and to this extent the mosquito itself is one target of its saliva. Whether the saliva of lice, or other blood-sucking insects, has a similar function is unclear, and the identity of any molecular components of the saliva of any blood-sucking insect that is necessary for a lubrication effect is wholely unknown. Further, even to the extent that this lubricant action of the saliva acts on the parasitic insect as a target, its action appears directed at the physical properties of the insect (frictional coefficient of the sliding stylets), and not with changing the physiology or biochemistry of the parasite itself. However, blood ingested by *Rhodnius prolixus* remains unclotted for days in the digestive tract of the parasite, on account of ingestion of its own saliva containing the inhibitor of platelet aggregation (Ribeiro & Garcia, 1980, 1981). Experiments have also indicated that mosquitoes imbibe their own anti-pyrase activity (Ribeiro, personal communication).

The parasitic wasp ovipositor, formed by appressed, moving stylets for penetration into the host and injection of material into tissues or blood, may be likened in that respect to the moving stylets of the mouthparts of blood sucking insects. Studies on how parasitic wasps have dealt with the problem appear to be even more sparse than with the blood-sucking insects. The parasite is exposed to the secretions that pass through the ovipositor, since it has been shown that the parasite egg may be coated with wasp ovarial secretions (including polydnavirus particles) that may 'alter' otherwise immunoreactive topology on the egg surface (see Beckage, this volume). However, the wasp venom *sensu stricto* (Jones & Coudron, 1993) enters the wasp ovipositor via a gland distinct from the ovary, and there are no published data on the effect of, or reach of wasp venom *sensu stricto* on the endoparasite.

MICROBIAL ALTERATION OF BLOOD-SUCKING BEHAVIOUR

There is the controversial proposition that the parasitic microbes vectored by blood-sucking insects may actually alter the feeding habits of the insect vector so as to increase the probability of entry of the microbe into the human host. For example, mosquitoes infected with the *Plasmodium* sporozoites have less coagulation-preventing apyrase in their saliva than do their uninfected counterparts (Rossigno, Ribeiro & Spielman, 1984). The infected mosquitoes thus spend more time probing the host with their mouthparts, and may thereby deposit greater numbers of these microbes. The applicability of this scenario to *Plasmodium*-infected *Anopheles stephensi* has been questioned, although data obtained for infested *An. gambia* were consistent with the proposition (Cupp *et al.* 1994). Evidence for decreased anticoagulant activity in the saliva of *Trypanosome*-infected *R. prolixus* was presented by Garcia *et al.* (1994).

Lice harbour typhus-causing rickettsial microbes in their digestive tract and faeces, which from the faeces gain entry into the human host through abrasions or other such openings in the skin. A feeding entry site through the skin created by the piercing stylets of the louse mouthparts may be a potential entry site for the pathogen it carries, as also

seems to be a plausible route of entry of *Trypanosoma cruzi* hosted by triatomid bugs (Titus & Ribeiro, 1990). One can envision that a louse induced to create a larger site or more sites would provide greater opportunity for the typhus-causing microbes in the faeces to be scratched into an opening. Although there do not appear to be any published investigations on the quality of the wound at the feeding site, or on the number of such feeding sites created by infected vs. uninfected lice, the situation reported for microbial suppression of mosquito salivary apyrase begs for such considerations of any microbial effect on the quality or quantity of lice feeding.

MEDICAL RELEVANCE OF LICE SALIVARY ACTIVITIES

The practical urgency of greater attention to biochemistry of lice saliva is underscored by both historical and recent developments. As the natural vector to humans of microorganisms causing typhus and relapsing fever, the historical importance of *P. humanus* to human health has long been appreciated. The recent outbreaks of lice-transmitted relapsing fever in Sudan and Ethiopia demonstrate this role is still of current import (de Jong *et al.* 1995; Rahlenbeck & Gebre-Yohannes, 1995; Seboxa & Rahlenbeck, 1995; Mekasha & Mehaire, 1996). Rwandan refugee camps are also reported to be at risk to louse-transmitted epidemic typhus (Anonymous, 1994). There has even been a report of apparent exposure of United States residents to the typhus-group of rickettsial organisms (White *et al.* 1990). Clinical reactions such as erythema can arise during the process of sucking human blood itself, and even more severe symptoms may present themselves in sensitive individuals or in heavy infestations (Moore, 1918; Peck *et al.* 1943).

All the more ominous is the appearance of lice resistance to insecticides in many parts of the world. In progression, body lice resistance to carbaryl (Clark & Cole 1967) and then to malathion (Miller *et al.* 1972; Silverton, 1972) have been reported. The use of carbaryl for head lice in Great Britain has now been restricted (Scowen, 1995; Boulton, 1995) and lice resistance to malathion is now reported to be widespread in Europe (Izri & Briere, 1995). In rapid succession have appeared reports of lice resistance to permethrin in Israel (Mumcuoglu *et al.* 1995), Czechoslovakia (Rupes *et al.* 1995) and England (Burgess *et al.* 1995), as hundreds of millions of persons worldwide are being infested with lice each year (Mumcuoglu, 1996). North America is not exempt from this concern, as lice resistance to insecticides heralds 'a serious public health problem' in Canada (Robert & Nguyen 1995). In the United States itself 6–12 million persons are infested each year (Clore & Longyear, 1990; Sokoloff, 1994), and by its annual affliction of several million US school children, it is more prevalent among US children than all other childhood communicable diseases combined (Donnelly *et al.* 1991). Against this backdrop, numerous recent field reports from nurses attending to US school children describe resistance of lice to the currently approved control chemicals. (R. Todd, Insect Control Inc., personal communication).

PHARMACEUTICAL INTEREST IN BIOACTIVE SALIVARY COMPONENTS

While the above circumstances draw our concern to the lice saliva that serves as the point of interface between lice and human hosts, they also draw our interest to the prospects that the active components may be turned to the benefit of mankind. The wide variety of bioactive molecules apparently contained in the saliva of blood-sucking arthropods is of general clinical therapeutic interest. A recent commercial product developed for clinical use is based on the anticoagulant of the blood-sucking medicinal leech (Hiralog, Biogen, Inc.; Maraganorre & Adelman, 1996). An anticoagulant from tick saliva is being used to determine the nature of blood afflictions in clinical settings (McKenzie, Abbendscein & Eisenberg, 1996). A tick salivary anticoagulant has also been explored as a model agent to prevent undesired blood clotting during open heart surgery (Edmunds, 1995). Law *et al.* (1992) report that there also appears to be pharmaceutical interest in insect-derived anticoagulants as part of antithrombotic therapies, as alternatives to heparin. Mumcuoglu *et al.* (1996) anticipate that 'because the human body louse has a long-term parasite/host relationship [with only human natural hosts] we expect lice thrombin inhibitors to be specific yet less immunogenic to man than those of other arthropods'. These examples, along with that the FBI can identify an attacker from the DNA of the attacker contained in lice excreta transmitted during the attack (Replogle *et al.* 1994), show that medical and other applications of lice products are limited only by our imaginations.

ACKNOWLEDGEMENTS

This review was supported in part by the programme in Research and Graduate Studies of the University of Kentucky and by a grant from the National Institutes of Health (GM 33995).

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