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A review of the immunology of parasitic nematodes

by

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The development of immunological studies in nematode infections has been reviewed during succeeding periods of its history by TALIAFERRO (152), CULBERTSON (24), SOULSBY (137, 139), URQUHART, JARRET and MULLIGAN (169) and TROMBA (166). SHIKABALOVA (126) has given a review of Soviet literature. Major research emphasis has been placed on acquired immunity, and the following discussion is oriented toward this aspect of immunology in nematodes and other helminths.

Thirty years ago the possibility that animals might acquire an immunity to helminth parasites comparable to bacterial and viral infections was almost unrecognized among helminthologists (155, 169). Aside from a preoccupation with taxonomy, life cycles and anthelmintics, a reason for this was the assumption that acquisition of immunity was unlikely as helminths frequently infected adult animals. But once it was known that infection with helminths prevented superinfection, and recovery from infection resulted in a greater or lesser acquired immunity to subsequent infections (1, 8, 16, 72, 73, 74, 75, 76, 123, 167), then a steadily increasing number of papers dealing with the immune reactions of hosts to helminth parasites has appeared. Although interest in this field is relatively recent, much of the current research can be traced to the original observations and hypotheses of Chandler, Sarles, Stoll and Taliaferro.

Because of the generally held concept that helminths, unlike protozoa, were incapable of stimulating immunity, much of the early work with helminths dealt with the development of diagnostic tests (166). However, a report by FUJINAMI (32) of acquired immunity to *Schistosoma japonicum* appeared in 1916 and was followed by demonstrations of acquired immunity to trichinosis (27), strongyloidiasis (113) and haemonchosis (147). As a logical outgrowth

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on initial studies on serological diagnosis, precipitin tests were employed by SCHWARTZ (122) and HEKTOEN (34) to study biological relationships and by CANNING (15) to demonstrate antigenic specificity of nematode tissue.

Succeeding years saw an amplification of experimental work along lines already established and the formulation of basic concepts and hypotheses. Metazoan parasites were recognized to be suitable for immunological studies, and at the same time to confirm established immunological principles (155). Differences in the immune response of helminths, in contrast to those occurring in most bacterial infections, soon became apparent. Antibodies in the sera of animals immunized by natural or experimental infections could be measured by conventional techniques, and in some cases the protective ability was demonstrable by passive immunization. Although comparable or identical antibodies could be demonstrated in the serum after parenteral administration of extracts, such injections gave only partial protection against subsequent challenge. It became evident that not only were living parasites necessary for the full expression of immunity, but that many antibodies were elicited, only some of which were protective (166).

ACQUIRED IMMUNITY

Immunity to the continuous accumulation of parasites, i. e., acquired immunity, or the resistance to reinfection as the consequence of pre-existing infection, has long been known to exist, e. g., the tapeworm, *Taenia saginata,* in humans (8). The presence of even a single parasite of this species protects against additional infection, although protection is lost when parasites already present have been expelled. Acquired immunity is a phenomenon of wide occurrence in mammals, although the bases for it are yet unknown. AFRICA (1) found that rats which had been infected with the rat nematode, *Nippostrongylus brasiliensis,* and in which the egg production had reached a low level or ceased, were either entirely or partially refractory to subsequent infection. His results were later corroborated by CHANDLER (16), and development of acquired immunity was conclusively demonstrated.

MECHANISMS AND MANIFESTATIONS

The mechanism of acquired immunity in infections with parasitic worms has been reviewed by TALIAFERRO (155) and TAYLOR (160). One of the first indications is the failure of the number of adult worms to increase as the result of continued reinfection, followed by a reduction in the number of established adult worms. Other manifestations of immunity are also apparent, namely: (i) inhibition of reproduction as shown by a decrease in egg output; (ii) a tendency toward growth retardation, indicated by an increase in time required to reach maturity and the smaller size of worms at maturity; (iii) a tendency toward complete inhibition of development beyond the fourth larval stage; (iv) the self-cure phenomenon; and (v) a spring-rise in fecal egg counts associated with a loss of immunity.

In pioneer work SARLES (114) and TALIAFERRO and SARLES (158) found that larvae of *N. brasiliensis* administered to previously infected rats were trapped in the lungs and skin by *in vivo* precipitates similar to those formed *in vitro* when infective larvae were placed in serum of previously infected rats. Moreover, an apparent secondary cellular response was observed. They found both the precipitates and the characteristic cellular response to be manifest after challenge of passively immunized rats. Although the first *in vivo* precipitin tests were reported in *N. brasiliensis* by SARLES and TALIAFERRO (115), it was not until the work of SARLES (114) with the *in vitro* test with infections of this nematode in rats that the study of the serology of these infections was extensively pursued.

This test consisted in the formation of precipitates at the oral, anal and excretory pore openings of developmental forms of *N. brasiliensis* when they were placed in serum from previously infected animals, the precipitates apparently caused by the combination of antibodies formed to the secretions and excretions of the worms in the host animal reacting to infection. SARLES (114) set forth the hypothesis that "the formation of oral and intestinal precipitates precedes and appears responsible for the inhibition of the activity and development of the parasite". Using flourescent antibody techniques, JACKSON (36) later confirmed that these precipitates did contain antibody. Other workers who subsequently studied the *in vitro* reaction of nematode infections were OLIVER-GONZÁLEZ (89), ROTH (109) and MAUSS (69) with *Trichinella spiralis,* OTTO (98) with *Ancylostoma caninum,* LAWLER (60) with *Strongyloides ratti,* OTTO, SCHUGAM and GROOVER (99) with *Necator americanus,* OLIVER-GONZÁLEZ (91) with *Ascaris lumbricoides,* SMITH (131) with *Trichosomoides crassicauda,* SADUN (112) with *Ascaridia galli* and SMITH (130) with *Heterakis spumosa.* These workers accepted the view that the antibodies produced against the secretions and excretions of the worms were protective.

METABOLIC PRODUCTS AS FUNCTIONAL ANTIGENS

CHANDLER (17, 20), SARLES (114) and TALIAFERRO and SARLES (157) introduced the concept of metabolic products, i. e., secretion and excretion products, such as exsheathing fluid and excretory products, as functional antigens. Although the concept was new to nematode immunology, it was forecast by the significant work on *Trypanosoma lewisi* by TALIAFERRO (151, 153) who suggested that immunity resulted from the intereference with some metabolic system of the parasite. In recent years some degree of immunity has been obtained by vaccination with "metabolic products" collected from *Nippostrongylus* (163), *Trichinella* (11), *T. lewisi* (162) and *Ascaris* (135). Nematodes are not known to produce toxins which elicit the formation of antibodies comparable to those encountered in some bacterial diseases, but such antigenic substances as the exsheathing fluid described by ROGERS and SOMMERVILLE (106, 107) and SOMMERVILLE (133) and the proteolytic enzyme and lipase reported by THORSON (164, 165) may be important as specific antigens. BUEDING and co-workers (9, 35, 65, 66) have demonstrated specific immunological differences in

enzymes catalyzing identical reactions in both schistosomes and vertebrates, and vaccination with "metabolic products" may one day be possible. Actual work with antigens associated with tissue-dwelling stages from *in vitro* culture has been reported by DIAMOND and DOUVRES (25), DOUVRES (26), LOWER (62), POYNTER and SILVERMAN (102), SILVERMAN, POYNTER and PODGER (129) and WEINSTEIN and JONES (173, 174). Promising work has already been done by SOMMERVILLE and WEINSTEIN (134) with *in vitro* culturing of intestinal-dwelling fourth stage larvae of *N. brasiliensis.*

Although generally recognized that stage-specificity of antibodies is a logical corollary to the functional antigenicity of metabolic products, interpretations of the immune response to maturing and migrating helminths are controversial. Proposed mechanisms of local and parenteral immunity have been discussed extensively in papers by CHANDLER (18, 20, 21) and TALIAFERRO (154, 155). Opposing views have been presented by CAMPBELL (14) and OLIVER-GONZÁLEZ (90) who showed that stage-specific antibodies were not confined to specific sites but could be demonstrated in serum. These views, however, are reconciled when all manifestations of the immune response to helminths are considered as essentially local but dependent on the concentration of antibody, rather than on special antibody-producing mechanisms at the site (166).

Present evidence thus indicates that the mechanism of immunity depends on humoral factors, with secondary cellular co-operation. Precipitins formed by the host against various materials passing out of the mouth, anus and excretory pore of intestinal nematodes result *in vivo* in visible precipitates and are unquestionably of functional importance in allergic reactions of the host. It is probable, but not yet proven, that the precipitins are instrumental in effecting the immobilization, delay in development, stunting, prevention of food assimilation and inhibition of enzymatic activity of the parasite. CULBERTSON (24) suggested that the depression of egg production in female worms might be explained by the occlusion of the genital pore with precipitates, and ROGERS and SOMMERVILLE (107) showed that precipitates at the excretory pore of exsheathing larvae placed in antiserum against exsheathing fluid might inhibit moulting. It is more likely, however, that the active materials penetrate within the parasite to affect the tissues and organs, rather than the immune mechanism acting merely by affecting the outside environment (138). Support for this idea is provided by SCHWABE (121), who showed that oxygen consumption of *N. brasiliensis* larvae in immune serum was significantly reduced well before the appearance of precipitates at the natural orifices. The inhibition of egg production also appears to be the result of antibody effect upon oögenesis as such, rather than of mechanical interference (138). The effect may be comparable to the antibody ablastin, which develops during infections of *Trypanosoma lewisi* and inhibits protein and nucleic acid synthesis (156).

ACQUIRED IMMUNITY IN GASTROINTESTINAL NEMATODES

A significant reduction in the number of adult worms developing from

a standard infection in an immunized group of animals has been the most frequently recorded demonstration of acquired immunity. The reduction in number may be caused by the death of developing worms or by their inhibition as larval stages. The death of developing worms, at least in species whose developmental stages *in vivo* involve even a limited somatic migration during which antigen may be made available to the host, is comprehensible in terms of antibody operating against somatic or metabolic antigens (169). The acquisition of antigens and the means of action of the immune mechanism is less clear in such parasites as *Haemonchus* and *Trichostrongylus,* whose development is apparently completed with no or, at most, limited disruption of the epithelial lining of the abomasum of the intestine. Antibodies against a nematode *(T. spiralis)* have been shown only recently to be present in gastric or intestinal mucosa (23), but the mechanism of the immune response in almost all gastrointestinal species is unknown.

Although it is clear that specific antibody and local cellular response (hypersensitivity) are significant factors in acquired immunity, the types of antibody involved and the role of local tissue immunity or antibody production are still uncertain (59). The mechanism of resistance in haemonchosis is unknown. SILVERMAN and PATTERSON (128) found infective *Haemonchus* larvae to develop in resistant sheep to the fourth and fifth larval stages by the fifth to seventh day, after which the majority of worms became inhibited until they were eliminated, usually by the tenth to fifteenth day. This degree of immunity was accomplished after infecting sheep with 15,000 larvae.

Trichostrongylosis in sheep is characteristically a disease of young animals, and STEWART and GORDON (146) demonstrated experimentally that its absence in adults was due to immunity acquired from a previous infection resulting from the administration of 10,000-20,000 larvae. In rabbits LELAND and DRUDGE (61) showed that in initial *Trichostrongylus* infections, worm recoveries averaged 18.6 per cent, but after reinfection the average was only 4.6 per cent. SPRENT and CHEN (142), OLIVER-GONZÁLEZ (96) and SOULSBY (135) failed to protect small laboratory animals against *Ascaris* infection by immunization with tissue extracts, although Oliver-González and Soulsby did achieve a measure of success by the subcutaneous injection of embryonated *A. lumbricoides* eggs. Immunity to *Ancylostoma caninum* has been studied extensively by OTTO (98). A single subcutaneous dose of 50,000 larvae normally produced a lethal infection, whereas two to five times this number were harmless when administered over a five to seven month period. The same degree of protection was obtained when the immunizing doses were administered orally. A strong immunity to *Dictyocaulus viviparus,* the cause of bovine parasitic bronchitis, can be acquired under field conditions (159, 175), but a single experimental infection of adequate size (4,000 lavae) also results in resistance to reinfection (101, 110). These examples illustrate the marked

variation in the innate susceptibility of hosts to different nematode infectinos (Table 1).

TABLE 1

Innate susceptibility of animals to nematode infection. Numbers of parasites developing in previously uninfected hosts.

Nematode	Host	Infective dose	Adults recovered: After time in days	Adults recovered: Number	Adults recovered: Per Cent
*Dictyocaulus viviparus**	Calves	500	35	88	11.6
*Haemonchus contortus**	Lambs	10,000	31	3,524	35.2
*Trichostrongylus colubriformis**	Lambs	30,000	70	10,551	35.2
*Nippostrongylus brasiliensis***	Rats	4,000	12	1,873	31.8

* Data from URQUHART, JARRETT and MULLIGAN (169)
** Data from VALDIVIESO (171)

Decrease in size or biotic potential of mature worms in immune hosts is well documented (169). When previously infected rats were challenged with *N. brasiliensis,* the number of worms maturing in the small intestine was reduced, their size decreased, fewer eggs were laid, and they were eliminated sooner than in previously uninfected rats (158). SADUN (112) found that when passively immunized chickens were challenged with *Ascaridia galli,* the resulting worms were significantly smaller than in controls. Stunted adult worms have also been observed at necropsies of calves repeatedly infected with *Dictyocaulus viviparus* (39) and with *Haemonchus contortus* (105).

Inhibition of larval stages of helminths has been observed in both immune and non-immune hosts (Table 2). In previously uninfected sheep, inhibition has been recorded after the administration of a single large dose of *Ostertagia* larvae (132). ROBERTS (105) found numerous fourth stage larvae in calves for many weeks after a single, large dose of *Haemonchus placei,* and SHORB and SHALKOP (127) found third and fourth stage larvae in pigs several months after infection with *Oesophagostomum quadrispinulatum.* Inhibition may be associated with the absolute numbers of developing parasites present, i.e., a few worms administered in a single dose will mature, whereas huge numbers given in a single dose in general will be retarded (28, 161). The actual cause of inhibition is unknown. BREMNER (7) suggested that it may be associated with substances produced by developing larvae which inhibit the growth of less developed larvae, or with a host reaction stimulated by the more developed larvae. READ (104) suggested that oxygen deficiency may be the factor involved.

Inhibition associated with acquired immunity has been recorded by

TABLE 2

Inhibition of larval development

Parasite	Host	Infective Dose	Stage	Time in Days	Reference
Non-Immune Host					
Ostertagia circumcincta	Sheep	20,000	4	92	132
Haemonchus placei	Calves	50,000	4	98 – 119	105
H. contortus	Sheep	10,000 – 50,000	3,4	30	38
Oesophagostomum quadrispinulatum	Pigs	150,000 – 209,000	3,4	65	127
Nippostrongylus brasiliensis	Rats	300	–	9	18
Immune Host					
Ostertagia circumcincta	Sheep	100,000	4	56	28
Dictyocaulus filaria	Sheep	–	5 (early)	100	161
D. viviparus	Cattle	–	5	150	161
Trichostrongylus retortaeformis	Rabbits	100,000	3	98	70
Haemonchus contortus	Sheep	5,000 – 100,000	3,4	10 – 12	128
Ancylostoma caninum	Dogs (young)	4,600	3	42	124
N. brasiliensis	Rats	300	3	9	18

several workers. MÖNNIG (80) found the developing stages of *Oesophagostomum columbianum* to remain viable for several months within the mucosa or in nodules in the mucosa of the intestine of a previously infected sheep. MICHEL (70) reported that when a massive number of *Trichostrongylus retortaeformis* was administered to a previously infected rabbit, a large proportion remained in the intestinal mucosa as late as the third larval stage and then recommenced development, either together or in relays in decreasing numbers to 98 days. SILVERMAN and PATTERSON (128) found that in resistant sheep *Hæmonchus contortus* larvae became inhibited at the fourth and fifth larval stages and were usually eliminated by the tenth to twelfth day. SCOTT (124) found that in dogs previously infected with *Ancylostoma caninum* inhibited larvae could be recovered from the small intestine to six weeks after challenge.

The fate of inhibited larvae is variable. They may be eliminated after a few days, as in *Haemonchus contortus* (128); they may persist for a year or be walled off and destroyed as in *Oesophagostomum* infections (127); or they may mature as in *Haemonchus placei* infections (105). The mechanism of retardation is unknown, but in the latter infections it is associated with the coexistence of an adult worm population. When the adults are removed by an anthelmintic, a proportion of the larval stages will mature.

Release of protective antigens responsible for the stimulation of host immunity may occur during a specific stage of the parasitic life cycle of some nematodes (97, 108, 128, 136). Earlier work by CHANDLER (19) and SARLES and TALIAFERRO (115) with *N. brasiliensis* suggested that the parasitic larval stages were the primary source of protective antigens. OGILVIE (85), however, claimed that immunity to *N. brasiliensis* can be stimulated by adult worms and may not be stage specific. She found that immunity stimulated by adult worms acts not only on adult stages to inhibit reproduction but also to inhibit the development to maturity of larvae in a challenge infection. Furthermore, rats infected solely with females are more resistant to reinfection than those infected only with male worms (85). The actual role played in the production of protective antibodies by the sexes and life stages of nematodes and other helminths obviously needs clarification.

SELF-CURE REACTION

Many helminth infections can be terminated rapidly by an immune response. A curative mechanism known as the "self-cure reaction" has been demonstrated in several nematodes but is best known in *N. brasiliensis* and the abomasal nematode, *Haemonchus contortus*. This reaction, manifest by the rather dramatic elimination of adult worms, was first observed by STOLL (147) in lambs exposed to *H. contortus*. Subsequent work by STEWART (143, 144, 145) showed that the self-cure reaction in sheep was provoked by the intake of a further dose of infective larvae, and SOULSBY, SOMMERVILLE and STEWART (140) and SOULSBY and STEWART (141) determined that the moulting of *H. contortus* larvae from the third to the fourth stage was the essential stimulus to the self-cure mechanism. The reaction is basically a violent hypersensitive reaction on the part of the host during which the parasites are eliminated "mechanically" rather than directly affected by the immune response (139).

Rats infected with *N. brasiliensis* larvae undergo toward the end of the second week of infection a self-cure reaction which is manifest by a sudden drop in egg production by the worms, followed over the next few days by the expulsion of the latter from the intestine (1, 83). Unlike *H. contortus,* no challenge infection of *N. brasiliensis* larvae is necessary to initiate the reaction, and the phenomenon is associated with the acquisition of a degree of immunity by the host to re-infection with either larvae or adults. If adults are surgically introduced into the small intestine of rats which have recently undergone self-cure, they are rapidly expelled (5). MULLIGAN, URQUHART, JENNINGS and NEILSON (83) showed that immunity can be passively transferred by serum from animals which have recently undergone the reaction. In the self-cure reaction there is local intestinal edema and a transitory rise in blood histamine correlated with an increased titer of circulating antibody (145); this reaction can be suppressed by antihistamines and by heterologous anti-lymphocytic serum (48). Moreover, by cortisone and reserpine therapy, self-cure may be retarded

and the active infection prolonged (22, 125, 172). When cortisone is discontinued, the immune rejection occurs.

Several theories have been advanced to explain the mechanism of self-cure in *N. brasiliensis,* and these have been reviewed by BARTH, JARRETT and URQUHART (5). The first of these is that the action of immune serum is directed solely against the worms, i.e., an antiworm-antibody effect (144). A second is that the importance of antibody is not by direct action on the parasite but in the production of a state of hypersensitivity in the intestine (83). Reaction between fixed antibody and antigenic material from the worm may give rise to a local anaphylactic lesion which might render the environment unsuitable for the parasite. The anaphylactic theory is supported by the fact that rats which have undergone self-cure can be shocked with an intravenous injection of *N. brasiliensis* antigen (170). Such shock is mainly intestinal in location, and the gross lesion resembles that resulting from experimental infections. Although the upper intestinal diameter is doubled due to extensive hyperplasia of the mucosa and hypertrophy of the muscularis externa (149), the increase in size is largely due to an increase in the water content of both the lumen and the tissues (148).

The third and most probable possibility, proposed by BARTH, JARRETT and URQUHART (5), combines these ideas. They suggest that the increased capillary permeability associated with the local anaphylactic reaction may be important to permit a significant extra-vascular leak of plasma into the sub-epithelial spaces of the villi or into the intestinal lumen, thus permitting the antibody to act directly on the worms. Self-cure is preceded by a dramatic rise in mast cell numbers (37). The discharge of biogenic amines by mast cells, and the local permeability changes mediated by them, are apparently concerned in the mechanism by which antibodies are translocated from the lamina propria of the mucous membranes to their site of action in the lumen (125).

Hypersensitivity resulting from *N. brasiliensis* infections has been demonstrated by inducing intestinal anaphylaxis with *N. brasiliensis* antigen in immune rats (83) and by the appearance of reaginic antibodies in the serum of rats which have undergone self-cure (43, 84, 86, 87). Although it may be concerned with leak production, the function of the hypersensitive reaction remains to be demonstrated (5).

A response associated with the self-cure is known as the "spring rise" phenomenon. MORGAN and SLOAN (82) and MORGAN, PARNELL and RAYSKI (81) found egg counts of *Trichostrongylus retortaeformis* in feces of ewes to follow an annual cyclical pattern, with a marked, regular rise each year during the spring shortly after lambing. The major cause of the spring egg rise is due to maturation of latent overwintering larvae (30). In time the number of these larvae, in late stages, decreases in the mucosa, and larval development resumes when the immunity of the host declines. Development occurs in relays, the fecal egg count rising rapidly and, after a short time, falling to zero. After remaining at zero for about two weeks, these series of events are repeated. The periodic appearance and disappearance of eggs in the feces may continue for

months as successive groups of worms develop to maturity, and in so doing evoke the self-cure reaction, which leads to the expulsion of adults but does not seem to affect the dormant larvae.

Phenomena similar to self-cure in *H. contortus* infections have been described in *Ascaridia galli* infections of chickens (111), *Trichostrongylus retortaeformis* infections in rabbits and *Dictyocaulus viviparus* infections in calves (70, 71). Moreover, the reaction may not be limited to helminth infections, since McCULLOUGH and EISELE (63) observed that carriers of *Salmonella* ceased to excrete organisms when reinfection occurred. Immunological and other aspects of the self-cure reaction are reviewed by BARTH, JARRETT and URQUHART (5), SOULSBY (138, 139) and URQUHART, JARRETT and MULLIGAN (169).

ARTIFICIAL IMMUNITY

Most studies of immunity against nematodes of domestic animals have been directed toward an appreciation and understanding of naturally acquired immunity (160). Artificial immunization has received little attention in either the medical or veterinary fields, presumably because of discouraging results with small laboratory animals. TYZZER and HONEIJ (168) first showed with *Trichinella spiralis* that helminth larvae suitably treated with ionizing radiation do not develop normally in the host animal, and the effect of larval irradiation has now been investigated in a number of different host-parasite systems (169). Promising work has been done by ASHLEY (3, 4), KATIYAR, MUKHERJI and SEN (49), KEELING (50), JENNINGS, MULLIGAN and URQUHART (41), PROCHAZKA and MULLIGAN (103) and OGILVIE (87) with *N. brasiliensis,* by MATOFF and TERZIJSKI (68) with *Ascaris suum, A. lumbricoides* and *Trichinella spiralis* and by MILLER (77, 78, 79) with *Ancylostoma caninum,* but at present the only practical demonstration of immunological control of a nematode disease is an orally administered X-irradiated larval vaccine developed by JARRETT and co-workers (40) against the cattle lungworm, *Dictyocaulus viviparus.* Vaccines for other nematode diseases are still in the experimental stage, and anthelmintic techniques currently practiced against parasitized domestic animals are limited.

FUTURE OUTLOOK

Classical antigen-antibody interactions, as observed in bacterial and viral diseases, have been amply demonstrated in nematode and other helminthic infections (54), and the presence of protective circulation antibodies in natural helminth infections has suggested the presence of specific antigens responsible for their stimulation (57, 115). Even so, the complicated nature of the antigens used has impeded the development of a proper immunologic diagnosis of these infections. The complexity of the helminths and lack of knowledge of the many biochemical and physiological changes occurring during their develop-

ment make the antigenic mosaic difficult to study. Artificial immunity against natural infections has not been successfully induced, probably because of modifications occurring during the process of extraction or preparation of antigens.

CAMPBELL (11, 12, 13), KAGAN and colleagues (44, 45, 46, 47), OLIVER-GONZÁLEZ (91, 92, 93, 94, 95) and others have employed homogenates, saline-extracts, metabolic products and polysaccharides of helminths in a variety of serological and immunological reactions. But because of the undefined chemical characteristics of total homogenates or crude extracts of worms used in these tests, the results obtained have often been difficult to interpret and of doubtful specificity (2, 31). Moreover, most of the extracts or antigenic materials used have been obtained by methods not conforming to basic biochemical concepts for labile substances, e.g. proteins and polysaccharides. Detrimental physiochemical changes in polysaccharides and rearrangements and denaturation phenomena for proteins have been amply demonstrated (6, 10, 58, 64, 100). Unrelated parasites which cross-react may do so because of possible actual similarity in antigenic structure, or because of molecular rearrangement resulting from harsh treatment during the extraction process (55). Proteins possess high antigenic potential, and if the concept of immunological specificity is related to the intricate structure and chemical nature of protein antigens (33), specific interaction is possible only when antigens or their fractions retain native configurations.

Except for the work of CAMPBELL (12), DYMOWSKA (29), JESKA (42), KENT (51, 52, 53, 54, 55), OLIVER-GONZÁLEZ (94), SAWADA and colleagues (88, 116, 117, 118, 119, 120, 150), VALDIVIESO (171) and others, investigations of proteins and polysaccharides of parasitic helminths have been limited. These substances undoubtedly have functions related to phenomena observed as immunological manifestations of the host-parasite interaction, but information about their biochemistry and biological functions in terms of immunity is fragmentary (31, 56). Unsolved is the problem of acquired immunity related to the specific antigenic potential of substances present in or secreted by parasitic worms. A careful isolation of specific antigens undertaken with the necessary biochemical precautions, as has been done by KENT (54) and SAWADA, TAKEI, KATAMINE and YOSHIMURA (119), may lead to valuable information which can unravel the immune mechanisms and have practical value from the immunodiagnostic standpoint. In addition to the currently active and speculative lines of research already mentioned, work by COKER (22), MATHIES (67) and WEINSTEIN (172) on the effects of hormones on the immune response will undoubtedly receive future attention.

Because of the complexity of the parasites and a lack of knowledge of the relative immunological importance of different developmental stages and phases in the path for those parasites which migrate in the host, elucidation of the mechanisms of helminth immunity is difficult (103). SOULSBY (139) stated that there is an urgency for clarification of immune phenomena occurring in helminth infections. Such a clarification would allow for a greater understanding of the immunological mechanisms involved and for a more rational ap-

proach to the application of the phenomena for control measures. To date the basic immunological mechanisms of acquired immunity in nematode infections has occasioned only speculation, whereas the development of a test system equating protective immunity with a demonstrable immunoglobulin would allow for a resolution of this urgent problem.

SUMMARY

The immunology of nematode infections is reviewed. Most of the research has dealt with the immune responses which result in the inhibition of development and subsequent loss of adult infections associated with the administration of infective larvae to a resistant host, i. e., the effect of acquired immunity on the migration, development and establishment of the challange infection. The mechanisms by which the immunity of the host affects the parasites, however, is still not clear, but present evidence indicates that these mechanisms depend on humoral factors, with a secondary cellular cooperation. Acquired immunity, metabolic products as functional antigens, the "self-cure" phenomenon, and artificial immunity are discussed, and current research trends are reviewed. The need for studies yielding basic information on the mechanism of nematode immunity is emphasized.

RESUMEN

Se revisa la inmunología de infecciones causadas por nemátodos. La mayoría de las investigaciones realizadas hasta el presente han tratado con los mecanismos inmunológicos que resultan en la inhibición del desarrollo y en la pérdida subsecuente de parásitos adultos asociados con la administración de larvas infecciosas en un huésped resistente, p. ej., el efecto de la inmunidad adquirida sobre la migración, desarrollo y establecimiento de la infección de desafío. Los mecanismos por medio de los cuáles la inmunidad del huésped afecta a los parásitos, sinembargo, son aún casi desconocidos; pero la evidencia actual indica que estos mecanismos dependen de factores humorales con una cooperación celular secundaria. Se revisan la inmunidad adquirida, los productos metabólicos usados como antígenos funcionales, el fenómeno de *self-cure* y la inmunidad artificial, lo mismo que las tendencias actuales de investigación. Se destaca la gran necesidad de estudios que produzcan información básica sobre el mecanismo de inmunidad contra nemátodos.

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