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MOLECULAR MIMICRY: ANTIGEN SHARING BY PARASITE AND HOST AND ITS CONSEQUENCES*

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INTRODUCTION

Several recent papers have been concerned with a hitherto neglected aspect of the host-parasite relationship: the sharing of antigens between parasite and host. These reports have called attention to this phenomenon but generally little evidence, experimental or observational, was presented in support of its existence. Possible consequences of this sharing of antigenic determinants, or molecular mimicry as it may be called, were explored. These consequences fall into several categories: pathogenicity to the host due to autoimmune-like reactions (Rowley and Jenkin, 1962), host-parasite adaptation (Sprent, 1962), control of the size of parasitic burdens (Dineen, 1963), and cause and maintenance of host antigenic polymorphism (Livingstone, 1960; Mourant, 1961; Damian, 1962a; and Eichner, Finn and Krevans, 1963).

The main purposes of the present paper are to examine the evidence for molecular mimicry and to discuss its origin and consequences, including the possible relationship between molecular mimicry and host antigenic polymorphism, as well as convergent molecular evolution among parasites.

The experimental evidence for molecular mimicry which one usually encounters is the direct immunological demonstration of host antigen in parasite material, either by inhibition reactions or by the stimulation—through immunization or infection—of antibodies which cross-react with host antigens. The cross-reactivities discovered in this way have most often been due to blood group antigens or other well-known heterogenetic systems. Deliberate experiments designed to uncover other shared systems have been rare. Kabat (1956), in considering reports of blood group substances in animal parasites, warned against the possibility of contamination with host antigens when organisms are isolated from animal tissues or cultivated in

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media containing complex animal substances. His admonition applies to other antigens as well. The existence of contaminating antigens of host origin in parasites made it necessary to introduce and define a new term, "eclipsed antigen" for an antigenic determinant of parasite origin which resembles an antigenic determinant of its host (Damian, 1962a). Implicit in this definition is the idea that the host will not recognize an eclipsed antigen as being foreign and thus will not produce antibodies against it. This statement will be enlarged upon later. Most of the evidence herein for eclipsed antigens is taken from the literature of helminthology. A smaller number of important references to the bacteria will also be given. The picture with viruses is less clear, but some work suggesting the presence of eclipsed antigens in that heterogenous group will also be reviewed. It is important to bear in mind that much of this evidence is only suggestive since the possibility of host contamination often has not been eliminated. It is hoped that this presentation will have a stimulative effect in accelerating the search for eclipsed antigens and exploring attendant implications.

EVIDENCE FROM HELMINTHOLOGY

Numerous helminth parasites have been reported to contain one or more antigens which have a widespread occurrence in vertebrate host species and which are possibly eclipsed in certain hosts.

A. *Nematoda*

Among the nematodes, *Ascaris lumbricoides* and *A. lumbricoides* var. *suum* have been favorite subjects for immunological investigations and it is not surprising that studies on them have provided a good deal of evidence for molecular mimicry. Oliver-González (1944, 1946a, 1946b; Oliver-González and Torregrosa, 1944) found blood group A and B activity in a polysaccharide isolated from *A. lumbricoides* var. *suum*. The polysaccharide removed all anti-A and anti-B agglutinins from human A, B, and O sera. Ascaris cuticle also exhibited blood group activity, but to a lesser extent. Ascaris polysaccharide was shown to have Forssman activity by its ability to inhibit sheep cell hemolysis by rabbit anti-Forssman serum and guinea-pig serum (Oliver-González and Torregrosa, 1944). Later Oliver-González (1946a) decided that the blood group specificity of Ascaris was A-type, on the basis of finding enormous increases of anti-A_1 and anti-A_2 titers, but not of anti-B or anti-O, in rabbits infected with the worm. He (1952) further reported that pulverized adult worms absorbed sheep cell agglutinins which were present in 98 of 120 "normal" human sera tested. In 1953, he reported that Ascaris polysaccharide, when injected intravenously into monkeys and rabbits, resulted in a total loss of anti-A_2 and a partial anti-A_1 loss for a period of 24 hours. Graña (1945) was able to show that sheep cell hemolysins formed in humans but not in rabbits after injection of saline extracts of *A. lumbricoides* var. *suum*. Ota (1953) found that rabbit antisera to *A. lumbricoides* extract inhibited Forssman, C, and A_{IV} activities. Later, Ota and Tadokoro (1954) found, by the use of chicken antisera to partial B

and O antigens, that Ascaris had B_{III} and O_{III} partial antigens. Soulsby (1958a), studying the sera of experimentally immunized rabbits, found increased heterophile antibody titers were stimulated by adult worm tissues, particularly intestine, and larval extracts and metabolic products. The sera of Ascaris-infected pigs showed a weakly hemolytic antibody which Soulsby (1958b) compared to the low molecular weight Forssman antibody discovered by Talmage, Freter and Taliaferro (1956). Soulsby and Coombs (1959) confirmed Oliver-González's findings that human anti-A and anti-B agglutinins were inhibited by Ascaris material. They were also able to show that infection of pigs with Ascaris stimulated anti-A agglutinins and that porcine anti-A was neutralized by Ascaris extracts. Furthermore, metabolic products of living Ascaris larvae were shown to contain the A substance since culture fluid inhibited the sensitization of pig type A red cells by A-isoantibody. Kagan, Norman and Allain (1959) were unable to find fucose in unhydrolyzed polysaccharide and crude saline extract antigens of Ascaris. This last observation seems to be at variance with the reports given above which suggest that Ascaris contains blood group antigens of the ABO system, since L-fucose is a component of the A, B, and H substances (Kabat, 1956). The work of Springer and collaborators has relevance here. They (1962) reported that polysaccharides of certain higher plants were blood group H active, even though they lacked sugars responsible for the activity of the human antigen. Oliver-González and Koppisch (1958) found that dogs which had anti-A_2 agglutinins in their sera underwent a fatal anaphylactoid reaction when injected with extracts prepared from various tissues of *A. lumbricoides* var. *suum*. Guinea pigs which had a "normal" titer of anti-A_2 agglutinins did not exhibit the anaphylactoid reaction subsequent to injection of Ascaris extracts. However, they did develop liver congestion similar to that shown by the dogs. This condition was absent in injected guinea pigs which had no or low titers of anti-A_2. Mice, previously injected with A_2 human erythrocytes, also gave the liver congestion reaction following Ascaris extract injection. Unsensitized mice did not develop this reaction. Koppisch and Oliver-González (1959) extended these experiments by pre-sensitizing mice with human O, B, A_1, and A_2 erythrocytes. The mice were subsequently injected with Ascaris cuticular extract. Since liver and kidney congestion appeared only in those mice presensitized with A_2 cells and followed by Ascaris extract, the authors concluded that the extracts had A_2 specificity. They speculated that the A_2 substance from the worms coats the erythrocytes and then reacts with the anti-A_2 in the serum, with resulting intravascular agglutination of erythrocytes and organ congestion.

Oliver-González and Torregrosa (1944) found that a polysaccharide fraction of *Necator americanus* inhibited human anti-A and anti-B and rabbit Forssman hemolysin. Later, Oliver-González (1952) reported that pulverized adult *N. americanus* removed sheep cell agglutinins which were present in human sera.

Ancylostoma duodenale has been reported to contain A_{IV} (Ota, 1953) and A_{IV}, B_{III}, and O_{III} by Ota et al. (1954).

Trichinella spiralis was first reported by Mauss (1941) to contain the Forssman antigen. She found that the sera of infected rabbits lysed sheep red cells, the hemolysin was absorbed by guinea pig kidney, and rabbit anti-trichina serum injected into two guinea pigs and a chicken produced allergic symptoms. Rose (1943) failed to find Forssman hemolysins in human cases and in rabbits experimentally infected with *T. spiralis*, and thought Mauss' findings may have resulted from use of rabbits previously infected with *Pasteurella lepiseptica*, a Forssman positive organism. Oliver-González and Torregrosa (1944) reported that *T. spiralis* polysaccharide inhibited the activity of human anti-A and anti-B and rabbit Forssman hemolysin. Later, Oliver-González (1946b) demonstrated inhibition of human anti-A_1 and anti-A_2 isoagglutinins by the polysaccharide. Oliver-González and González (1949) suggested that *T. spiralis* releases an A_2 isoagglutinogen-like substance into the blood stream of the host. Oliver-González (1952) also found that living mature larvae of Trichinella absorbed all normal sheep cell agglutinins from human sera. A polysaccharide isolated from the muscle stage of the parasite, when injected into monkeys and rabbits had the property of lowering the titers of "normal" agglutinins for human A_1 and A_2 erythrocytes present in these animals (Oliver-González, 1953).

Evidence suggests that the pig nematode *Oesophagostomum dentatum* contains the Forssman antigen. Soulsby (1958b) found that an extract of third stage larvae of this parasite almost completely absorbed the Forssman antibody (stimulated by infection with Ascaris) in pigs. He (1958c) also found that *O. dentatum* infection in the pig is associated with an increase in heterophile antibodies, being first of a Forssman type in early stages of the infection, then of a Buchbinder type following patency of the worm infection.

Yamaguchi (1952) reported A_{IV} partial antigen and the Forssman antigen in the larvae of *Gnathostoma spinigerum.*

Several of the filarial worms appear to have eclipsed antigens. The cotton rat parasite *Litomosoides carinii* was reported by Oliver-González and González (1949) to contain an isoagglutinogen-like substance. *Dirofilaria immitis* absorbed sheep cell agglutinins from human sera (Oliver-González, 1952). Ridges and Augustin (1961) reported that apparently normal cats had precipitins for two α-globulins of normal human serum and that infection of the cats with *Wuchereria malayi*, a human parasite, caused an increase in these precipitins. Dammin and Weller (1945) found 13 of 104 patients with filariasis bancrofti had heterophile agglutinin titers over 1 : 32 and Franks (1946) reported that the incidence of filaremia in Okinawa (due to *Wuchereria bancrofti*) was greater in persons lacking anti-A in their sera. This suggested to Oliver-González and González (1949) that *W. bancrofti* possesses a blood group-like substance. Oliver-González (1952) also reported that sera from only one of 26 people with *W. bancrofti* agglutinated sheep cells.

B. *Cestoda*

Hacig, Solomon and Weinbach (1959) found evidence for the Forssman antigen in *Hymenolepis diminuta* although Larsh (1943) could not demonstrate Forssman hemolysins in rabbits injected with ground *Hymenolepis nana* var. *fraterna.* Oliver-González and Torregrosa (1944) showed that a polysaccharide from *Taenia solium* cysticerci inhibited anti-A and anti-B agglutinins and Forssman hemolysins. Oliver-González (1946b) also gave evidence for A-substance in *Taeniarhynchus saginatus.* Ota (1953) reported that *T. saginatus* contained the A_{IV} antigen and later (Ota et al., 1954) extended this list to include B_I, B_{III}, O_I, O_{II}, and O_{III}.

Graña (1944) found that subcutaneous injection of hydatid fluid into patients previously infected with *Echinococcus granulosus* resulted in the appearance of high titered hemolysins and agglutinins for sheep erythrocytes. This antibody stimulation was not noted after injection of hydatid fluid into normal individuals. The presence of blood group P_1 substance in hydatid cyst fluid indicates what is probably a true eclipsed antigen in the case of hydatid infection of P_1-positive humans. That the P_1 antigen is not a host contaminant may be deduced from the following facts: (1) the antigen in cyst fluid was first sought because of the association of strong *anti-*P_1 with human hydatid infection (Cameron and Staveley, 1957); (2) these authors found that the presence of P_1 was correlated with an active germinal layer in the cyst wall, P_1 activity being nil when scoleces were absent; and (3) P_1 substance was found in cyst fluids from three host sources, sheep (Cameron and Staveley, 1957; Levine, Celano and Staveley, 1958), man (Levine et al., 1958), and pig (Prokop and Oesterle, 1958). Kagan et al. (1960) found that various hydatid materials cross-reacted with host liver antigens. Pursuing this further, Goodchild and Kagan (1961) compared, electrophoretically, hydatid fluids (*E. granulosus* and *E. multilocularis*) with sera of three host species. They found striking qualitative similarities in the patterns obtained, but the components were greatly reduced in quantity in the cyst fluids. Kagan and Norman (1961), using immunodiffusion techniques, demonstrated many host components in test antigens prepared from hydatid tissues. These results of Kagan and his collaborators suggest contamination of Echinococcus hydatid fluid with antigens of host origin, but the possibility of eclipsed antigens should not be overlooked.

C. *Trematoda*

A few trematode species have been reported to contain host-like antigens. Oliver-González (1946b) found that *Fasciola hepatica* polysaccharide inhibited the anti-A_1 and anti-A_2 isoagglutinins of human sera. Noronha-Pérez (1944) reported Forssman antibodies in cases of human schistosomiasis mansoni. Oliver-González and Torregrosa (1944) found that a *Schistosoma mansoni* polysaccharide fraction inhibited the anti-A and anti-B agglutinins of human sera and Forssman hemolysins in rabbit sera. Dammin and Weller (1945) could not detect heterophile agglutinins in rabbits previously ex-

posed to cercariae of *S. mansoni.* They also searched for heterophile agglutinins in human cases of schistosomiasis mansoni and recorded titers greater than 1:32 in only 5 of 123 cases. Oliver-González and González (1949) reported that adult *S. mansoni* incubated in human group B serum reduced the anti-A_2 titer to zero and concluded that *S. mansoni* secretes an A_2-like substance. An alternative explanation, namely that the antibody could have been absorbed to the surfaces of the worms rather than neutralized by a secretion was suggested by Damian (1962b), who therefore considered secretion of an A_2-like substance unproved for *S. mansoni.* Oliver-González (1952) found that sheep cell agglutinins, present in 82% of 120 "normal" human sera tested, were reduced to zero titer after incubation with living *S. mansoni* adults. Kagan (1958) found that infection of rabbits with *S. mansoni* cercariae stimulated no increase in Forssman antibodies (anamnestic response). In a deliberate search for common antigens between *S. mansoni* and its laboratory host, the albino mouse, Damian (1962b) found at least six cross-reacting systems. By Ouchterlony analysis it was discovered that five of seven rabbits immunized with an adult worm homogenate developed precipitins to components in uninfected mouse serum. At least four separate systems were indicated with one antiserum, two of which gave type I reactions (identity) with antigens in *S. mansoni* saline extract and two of which were unique to the mouse serum. Further evidence for common antigens of worm and mouse was his finding that three of seven rabbits showed increased titers for mouse erythrocyte agglutinins after immunization with *S. mansoni.* Finally, it was shown that *S. mansoni* antigen could stimulate the production of Forssman hemolysins in the rabbit. The suggestion of common antigens in schistosome and mouse is of interest and possibly of considerable significance in view of increasing numbers of reports of natural rodent infections in Africa and South America (Malek, 1961). The Forssman antigen is present in the organs of the mouse (Tanaka and Leduc, 1956; Stern and Davidsohn, 1956) but absent from the erythrocytes (Davidsohn and Stern, 1950). Damian (1962b) failed to find a Paul-Bunnell type of heterophile agglutinogen in *S. mansoni.* Neither could he demonstrate the blood group A antigen in the worm, an observation contrary to the findings of Oliver-González and co-workers (1944, 1949). He suggested that the anti-A activity of Forssman hemolytic sera (Schiff and Adelsberger, 1924) could explain this discrepancy. Ota et al. (1955) infected rabbits with *S. japonicum* and followed changes in titer in anti-A agglutinins and Forssman hemolysins. They found increases in both activities, after one or two months in some but not all of the rabbits. Matsuse (1956) reported that A_{IV}, B_{III}, and 0_{III} partial antigens were present in *S. japonicum.*

D. *Acanthocephala*

Apparently the only report concerning an acanthocephalan is that of Oliver-González (1946b) in which he reported that a polysaccharide from *Macracanthorhynchus hirudinaceus* did not inhibit the anti-A isoagglutinins in human sera.

In this same paper, it will be recalled, Oliver-González reported that similarly prepared polysaccharide fractions from other worms, that is *Ascaris lumbricoides, Trichinella spiralis, Fasciola hepatica,* and *Taeniarhynchus saginatus* all had the property of inhibiting anti-A agglutinins. Of these worms, *M. hirudinaceus* is the only one that lacks a vertebrate tissue-inhabiting stage in its life cycle. This fact could be used, of course, in an argument favoring either an eclipsed or contaminating Forssman antigen in the worms. The uncertainty here only serves to emphasize the need to examine the origins of antigens from infectious organisms.

EVIDENCE FROM BACTERIOLOGY

The bacteriological literature contains a good deal of evidence for eclipsed antigens, the earliest probably being that of Rothacker (1913), who reported that *Salmonella schottmuelleri* contains a heterogenetic antigen. Again, as with the helminths, much of the evidence is circumstantial and in many instances the possibility of contaminating host antigens has not been eliminated or even considered. However, some of the most convincing evidence for eclipsed antigens is encountered among the bacteria and the strongest cases are presented below.

Shorb and Bailey (1934) examined 187 strains of bacteria, representing 81 species, for the Forssman antigen. They found the antigen to be present in 15 species including at least 66 strains. Since they grew the bacteria on medium derived from beef, which lacks the Forssman antigen, it appears unlikely that the antigen was a culture contaminant.

Springer and his collaborators (1961) have recently summarized their important work showing the occurrence of A, B, and H (O) antigens in gram-negative bacteria grown on chemically defined media which were proved free of blood group antigens. They examined 282 strains (many isolated from the blood of patients) of which nearly half were blood group active. About ten per cent showed high blood group activity.

Markowitz, Armstrong and Kushner (1960) suggested a common antigen between nephritogenic streptococci and the rat glomerulus. Antisera prepared in rabbits to the streptococci had the ability to cause glomerular lesions when injected into rats.

Rowley and Jenkin (1962) showed antigenic similarity between *Salmonella typhimurium* and the mouse. They found a fraction of pig serum that had high mouse hemagglutinating activity and opsonic properties for *Salmonella typhimurium.* Furthermore, rabbit antiserum to mouse tissues greatly enhanced the clearance of *S. typhimurium* C5 from the circulation of the susceptible host strain of mice. When this serum was absorbed with mouse erythrocytes, both hemagglutinating and opsonic activities were reduced.

EVIDENCE FROM VIROLOGY

The picture with viruses is confused, mainly because, as Gorer (1961) stated, "It seems that viruses may 'borrow' antigenic material from their

hosts and thus their antigenic constitution may be altered by that of the host in which they have proliferated...."

A few reports are suggestive of eclipsed antigens in viruses. Simonsen and Harris (1956) found evidence of a shared antigen between the Rous-1 virus and its host, the chicken. More importantly, they have called attention to the use of a powerful experimental tool which eliminates the problem of host contamination in the search for eclipsed antigens: namely immunological tolerance. In their work, turkeys which are normally resistant to virus were made tolerant to chicken blood. The tolerant turkeys thereby became susceptible to the Rous-1 virus, the simplest explanation being that the virus and the chicken shared one or more antigens. Harris and Simons (1958) later concluded, from further tolerance experiments, that the antigen which was shared was similar to, or identical with, blood group A substance. Their attempts to show the antigen in purified virus were inconclusive. Springer and Tritel (1962) found blood group A active material in partially purified egg-grown influenza virus. They also found the antigen in chicken embryos and called attention to the fact that A active substance was not proved to be in the virus itself.

ORIGIN OF ECLIPSED ANTIGENS

Buchbinder in 1935 suggested that micro-organisms may acquire heterogenetic antigens from the host; this conclusion being based upon his observation that most species of bacteria which contain the Forssman antigen are either human pathogens or animal parasites. The work of Holtman (1939a, 1939b) has been cited in support of an "implanted antigen" hypothesis by Carpenter (1956). Holtman (1939a) found that *Salmonella typhosa* and *Salmonella paratyphi*, both originally lacking the Forssman antigen, acquired this antigen after prolonged culture on horse serum agar containing the antigen. Washing did not remove the antigen and it was retained through 21 daily subcultures on beef extract agar which lacked the antigen. The activity disappeared after 50 transfers. Holtman (1939b) also repeated the experiment with the variation that the bacteria, originally free of the antigen, were placed in collodion sacs in the peritoneal cavities of guinea pigs, which have the antigen. Living, but not dead, cultures acquired the antigen after incubation for 21 days and retained it through 50 daily transfers on antigen-free medium; the antigen had disappeared after 77 transfers. The collodion sacs were permeable to macromolecules since the guinea pigs developed specific agglutinins to the bacteria used. This fact makes it impossible to categorically eliminate transduction or transformation as the process by which the hetero-specificity became acquired. Holtman himself considered two possible explanations: (1) the acquired antigen was absorbed after passing through the membrane or (2) it was "elaborated by the bacteria through the stimulation of hitherto dormant enzymes." Holtman considered the latter explanation more probable since the antigen persisted after 50 transfers. This induced enzyme idea of Holtman must be considered within the context of the times, that is instructions for induced en-

zymes were thought to originate exogenously. In his words (1939b), "it seems logical to conclude that the heterospecificity of many bacteria may be due to the environment in addition to the original constitution of the species."

Doubt must be cast upon the implanted antigen hypothesis. A more satisfactory explanation, consistent with current knowledge of the origins of biological specificities, is that there would be a positive selection of any antigenic determinants of a parasite resembling antigenic determinants of the host. The adaptive value would be, of course, an increased compatibility of the parasite with the host's immune mechanism. The original similarity would be fortuitous and probably an imperfect one, but mutation and selection could operate together to perfect the relationship.

Holtman's results may be brought within the bounds of the eclipsed antigen hypothesis if the antigens in question are, as he suggested, the final products of an inducible enzyme system. One can visualize certain microorganisms as containing a store of information on host antigens, the appropriate ones being evoked in the host environment. This mechanism could supplement, as a defense to the host immune response, the well-known antigenic variability of microorganisms (see Beale and Wilkinson, 1961), a joint consequence of mutation and their tremendous reproductive potential.

It seems appropriate to examine here the reasons for suggesting that any antigenic similarities could exist between phylogenetically unrelated organisms constituting a potential host-parasite association. On theoretical grounds, the pendulum has been swinging for some time now from the idea of a nearly infinite universe of antigens to a concept of a limited and even rather small one. Jerne (1960) has recently summarized estimates of the size of this universe. These range from Quastler's low estimate of 250 through Burnet's of 10,000 to Talmage's "almost infinite." Conversely, estimates of the number of different antibody specificities which may be made, range from 5000 (Talmage) through 50,000 (Haurowitz), 1,000,000 (Jerne) to potentially infinite (Monod). Either a limited antigen or antibody universe is compatible with the present argument, the main point being that the number of immunological specificities is finite. This point is well-supported by the evidence of immunology, where cross-reactions between antigens of organisms unrelated either phylogenetically or ecologically (hosts and parasites), are commonplace. A listing of such cross-reactivities may be found in Heidelberger's (1959) review of polysaccharide immunological specificity, which shows that polysaccharides from many plant gums are able to precipitate anti-pneumococcal sera. Springer, Williamson and Readler (1962) reported polysaccharides of higher plants which exhibit blood group activity. It is evident that the strongest case for fortuitous sharing can be made with polysaccharide antigens and this seems reasonable in view of the following points. Polysaccharides and polysaccharide moieties of proteins are strong determiners of antibody specificity (Carpenter, 1956). Fewer conformational channels are open to polysaccharides than to proteins (Landsteiner, 1945). Picken (1960) and Bell (1962) have

called attention to the ubiquity of mucoids as components of cell surfaces and polysaccharides are usually the main components of bacterial capsules and cell walls and of helminth cuticles. Finally, Jerne (1955) stressed the dominant role played by surface antigens in antibody production.

CONSEQUENCES TO HOST

One idea that has appeared from time to time, either explicitly or implicitly, is that antigen sharing by host and parasite could lead to pathological autoimmune-like reactions in the host (Oliver-González, 1946a; Oliver-González and Koppisch, 1958; Oliver-González and González, 1949; Rowley and Jenkin, 1962; Becker, 1953). This appears unlikely since, evolutionarily, it is extremely difficult to see how the serious consequences of autoimmunity could be of any benefit to a parasite. In fact, it is a parasitological axiom that early host death is usually inimical to effective parasite dispersal.

The concept of eclipsed antigens as herein presented is in direct opposition to autoimmunity as a consequence, since the essential feature of an eclipsed antigen is *non-reactivity* in the appropriate host, and non-reactivity alone is its adaptive significance. The position of Rowley and Jenkin (1962) on the function of common antigens seems to be unclear. After building their hypothesis on the non-reactivity of self-components, they then ask whether a self-component brought into the body by a micro-organism would not lead to formation of auto-antibodies.

Since the environments of parasites are living organisms which themselves are subject to the forces of evolution, we can expect to find that a host defense mechanism against parasite encroachment upon self has evolved. I suggest here that a plausible and effective defense mechanism would be host antigenic polymorphism, whereby eclipsing would be counteracted to a degree by a variety of alternative antigenic states within a population of hosts. Many systems of host antigenic polymorphisms are known; the blood groups are classical examples. In recent years, evidence has accumulated which indicates that many other antigenic polymorphisms exist. Some examples are platelet antigens (Stefanini et al., 1953), leukocyte antigens (Payne and Hackel, 1961), various serum proteins (Oudin, 1960; Blumberg, Dray and Robinson, 1962), and tissue antigens (Hoecker, Counce and Smith, 1954).

E. B. Ford predicted years ago (1945) that the blood group genes were subject to natural selection and, although blood group frequency differences among human races were long explained as the result of non-selective forces such as genetic drift, the current consensus favors selection as the important mechanism (Brues, 1954; Allison, 1955; Sheppard, 1959; Livingstone, 1960; Mourant, 1961). Except in the case of the Rh system the nature of these selective forces is still being debated. Ford (1945) suggested that individuals of different blood types would vary in susceptibility to different diseases. In accordance with Ford's early predictions the association found between blood groups and degenerative diseases (see

Roberts, 1959) placed disease at the forefront; Livingstone (1960), and Chung and Morton (1961) noted that the selective effects of degenerative diseases, because of late appearance after major reproduction age was passed, would be slight. Chung and Morton hypothesized that the principle mechanisms of selection maintaining the ABO polymorphism acted during fetal and early postnatal stages. Both Livingstone (1960) and Mourant (1961) put forth arguments favoring infectious diseases as the selective force, and they cited blood-group-like antigens in infectious organisms as evidence for the hypothesis. Mechanisms were not postulated by either author.

Eichner et al. (1963), after presenting some rather indirect evidence for selective action on the ABO polymorphism, hypothesize that "random mutations on the red cell envelope" could result in a dictionary, as it were, of antigens similar to non-pathogenic foreign substances. This dictionary is, according to them, supposed to enable the antibody-producing mechanism to react more strongly to antigens dissimilar to those on the erythrocytic surface. This is an involved way of saying that an animal would have difficulty producing antibodies against self components. Their implication that a large variety of antigens in a host population would be advantageous is a view with which I concur (see below). However, they offer no explanation for the origin and maintenance of the ABO polymorphism other than the occurrence of random mutations.

The problem now lies in finding a mechanism which could maintain host antigens in a state of balanced polymorphism. An important influence on thinking in this area has been the demonstration by Allison (1954) that individuals heterozygous for the abnormal hemoglobin S gene (those having sickle-cell trait) are more resistant to falciparum malaria than the normal homozygote. The selective advantage of the heterozygote over either homozygote leads to a balanced polymorphism of the Hb^a and Hb^s genes.

Mourant (1961) stated, "...for a true equilibrium to occur, heterozygotes must have some advantage over homozygotes...." Morton and Chung (1959) seem also to be bound by this idea of heterosis in their consideration of selection in the MN system. They stated, "There are two hypotheses for heterozygote advantage: (1) independent action of alleles, the product of one being adaptive at some stage of development and the product of the second at another stage; (2) allelic interaction to produce effects that are quantitatively or qualitatively different from the sum of the homozygous effects.... Both hypotheses require that the MN locus have other and more important physiological effects than the production of erythrocyte antigens."

It can be seen that the advantageous heterozygote model has resulted in some difficulty in the case of antigenic polymorphisms. Mourant failed to see another applicable mechanism and Morton and Chung were forced to postulate unknown pleiotropic effects for certain blood group genes.

Sheppard (1959) has pointed out that there are other mechanisms which can maintain a balanced polymorphism besides heterosis. The advantageous heterozygote model is inconsistent with the eclipsed antigen hypothe-

sis. As can be seen in figure 1, the heterozygote (antigenic phenotype XY) will provide an environment in which two types of parasites, one antigenically X; the other Y; will be eclipsed and would thus be presumably more susceptible to the two types of parasites. The homozygotes X and Y are more susceptible to but one of the two antigenic types of parasite. Thus the heterozygote cannot be advantageous over the homozygotes.

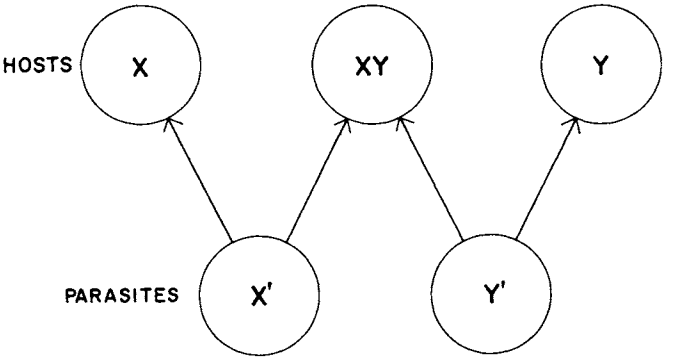

FIGURE 1

As Haldane (1955) said, "some polymorphisms are stabilized by heterosis, but it is always worth looking for a stabilizing agency in Darwinian natural selection." Such a selective mechanism, applicable to antigenic polymorphism and based upon eclipsed antigens, was suggested to the author by one put forth by Cain and Sheppard (1954) and Haldane (1955) as a possible explanation for the color and pattern polymorphisms of the snail, Cepaea. Their suggestion was that these Cepaea genes could be maintained as a balanced polymorphism by changes in selection pressure and direction dependent upon gene frequency. Thus, in the present context, when a blood group allele is at a low frequency in a population, it would be advantageous and have a positive selective value. As its frequency increases, the initial advantage would become disadvantageous. Figure 2 represents such a situation in its simplest form. "X" is a blood group gene in very high frequency; its allele "Y" is represented at first by mutation pressure alone—a monomorphic condition. According to the eclipsed antigen hypothesis, parasites bearing X or X-like antigens would have an increased opportunity to become established and the defenses of the X-bearing hosts would be circumvented with respect to that one antigen. Hosts with the mutation to "Y" would be selected, until such time as the Y-allele reaches a point of high frequency and allows an eclipsing environment for Y-bearing infectious organisms. Such an oscillation between high X and high Y frequencies could keep the XY system in a balanced state.

Mourant (1961) felt that since host-parasite antigen sharing would be detrimental to the host, "it would be best to have as few blood group antigens as possible, and man's rich variety would be a disadvantage." In

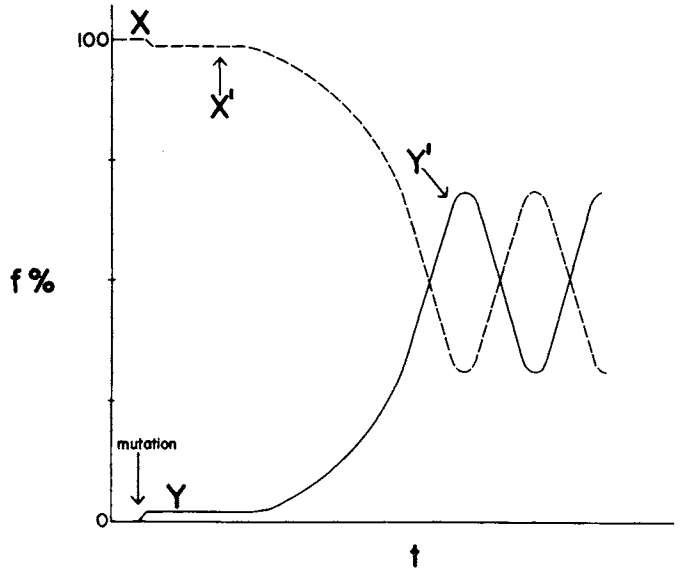

FIGURE 2

contrast, the theory here presented suggests that it is the monomorphic antigenic state, that is the condition of invarient antigens within a host population, which can lead to increased susceptibility to parasitism because a static antigenic environment would favor eclipsing of parasite antigens. Host antigenic polymorphism, the condition of alternative antigenic states within a host population, would be the advantageous condition.

The vexing problem of differences in blood group frequencies among different races might be explained within the framework of this theory as the result of different parasite environments in the various centers of racial development. This interpretation is quite distinct from that forming the recent controversy between Springer and Weiner (1962) on the one hand, and Pettenkofer et al. (1962) on the other. The latter group maintained that the world distribution of ABO blood group genes could have been influenced by certain specific epidemics in former times, that is by a selective elimination of group A and group 0 individuals by the epidemics; a view opposed by Springer and Weiner. The present theory is concerned with *origins* of the blood group systems, not with changes superimposed upon already existent ones. A search for positive correlations between blood group (or other antigen) frequencies of certain ethnic groups and the geographical ranges of infectious organisms having similar antigens should be made to test this hypothesis of racial antigenic differences. For this purpose, certain helminth and protozoan parasites would be uniquely suited because of their circumscribed distributions dependent upon the distribution of intermediate hosts. In a study of this kind, however, it would be wise to keep Darlington's (1957) words in mind, "Plants and animals in nature tend to

form communities of more or less interdependent species, and the communities can move as wholes, but the species that compose them often have had separate, very different geographical histories of their own. Animals (including man) and their parasites and diseases can have different geographical histories."

CONVERGENT MOLECULAR EVOLUTION AMONG PARASITES

It is conceivable that antigenic convergence may develop among phylogenetically diverse parasites of the same host species if eclipsing of antigens is, as suggested above, a common phenomenon. There is in fact evidence that antigenic convergence does exist. Weiner and Price (1956) reported antigenic relationships between *Trichinella spiralis* and *Salmonella typhi.* There are many reports of cross-reactions between the trematode *Schistosoma mansoni* and the nematode *Trichinella spiralis* (Liu and Bang, 1950; Senterfit, 1958; Anderson, 1960; Jachowski and Bingham, 1961). Besides finding a common antigen between *S. mansoni* and *T. spiralis*, Biguet, Capron and Tran Van Ky, (1962) found that the cestodes *Taenia saginata* and *Echinococcus granulosus* and the nematodes *Onchocerca volvulus* and *Ascaris lumbricoides* also shared an antigen with *S. mansoni.* Oliver-González and Kent (1961) found similar antigens in Ascaris and Clostridium. Konopka, Goble and Lewis (1961) found that a primary infection with *Leishmania donovani* conferred resistance in mice to a superinfection with *Mycobacterium tuberculosis.* Louch (1962) found that infection with *Nippostrongylus muris* protected rats to some extent against subsequent infection with *T. spiralis* (though both nematodes, these worms are not closely related). Although, as mentioned above, it is commonplace to find antigenic similarities among unrelated organisms, the fact of immunological cross-reactivity takes on added significance when the organisms concerned parasitize a common host. Although some of these cases may be fortuitous, others may prove to be examples of convergent evolution on a molecular level. The possibility of antigenic convergence should not be overlooked by those engaged in serological taxonomy of parasitic groups.

SUMMARY AND CONCLUSIONS

Eclipsed antigens are defined as antigenic determinants of parasite origin which resemble antigenic determinants of their hosts to such a degree that they do not elicit the formation of antibodies. This phenomenon is termed molecular mimicry. The danger of confusing eclipsed antigens with contaminating antigens of host origin is stressed.

Well-authenicated cases of eclipsed antigens in helminths, bacteria, and viruses were reviewed, and equivocal evidence suggesting the widespread occurrence of eclipsed antigens in helminths, bacteria, and viruses was presented with the hope of stimulating further research. Reports of well-known heterogenetic antigens like the Forssman antigen and blood group antigens in infectious organisms should be accompanied by rigorous proof that they are not host contaminants. In the field of bacteriology, the work

of Springer stands as a model. The problem is more difficult with those parasites which cannot be cultivated *in vitro*. New approaches such as the use of immunological tolerance are needed.

The origin of eclipsed antigens was considered and it was concluded that they arose as the result of selection and mutation operating upon fortuitously similar antigens of the partners of an incipient host-parasite relationship. It is possible that some microorganisms have evolved inducible systems for the synthesis of eclipsed antigens.

Consequences of eclipsed antigens to the host were discussed and the popular concept implicating shared antigens in autoimmunity was rejected on evolutionary and immunological grounds. It was suggested that host antigenic polymorphism could have evolved as an effective defense mechanism against the eclipsing phenomenon. The blood groups and other cell antigen systems are the best-known examples of host antigenic polymorphisms but many others appear to exist. Although infectious diseases have been suggested by several authors as the primary selective agent in maintaining the blood group polymorphisms, no acceptable mechanism has heretofore been postulated. The heterosis model, so successfully applied to a hemoglobin polymorphism by Allison, seems to have formed a stumbling block to the polymorphic antigens problem. An alternative explanation, based on eclipsed antigens, was presented; namely, that the blood group genes could be maintained in a balanced polymorphic state by changes in selection pressure and direction dependent upon gene frequency. The selective agents would be parasites with antigens eclipsed by the blood groups. This mechanism was suggested by a similar one postulated by British workers to explain color and pattern polymorphisms in the snail, Cepaea.

Differences in blood group frequencies among different races could be the result of different parasite environments in the various centers of racial development. It was suggested that correlations be sought between blood group frequencies of certain ethnic groups and infectious organisms bearing eclipsed antigens and having intermediate hosts of circumscribed distributions.

Finally, it was suggested that convergent molecular evolution among parasites adapted to the same hosts could occur and evidence supporting this conclusion was given.

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