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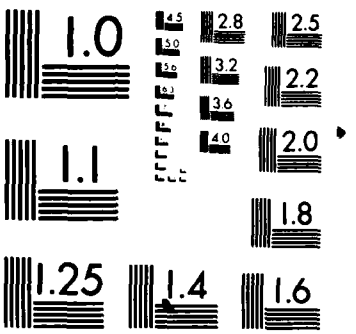

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CELL PHYSIOLOGY OF THE MALARIA PARASITE (U)

FINAL REPORT

by

Jerome Vanderberg

August 1984

(For the period 1 October 1972 to 31 August 1981
under Contract No. DADA 17-73-C-3027)

(And the period 31 December 1981 - 30 April 1984
under Contract No. DAMD 17-82-C-2045)

New York University Medical Center

New York , New York 10016

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serum		

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

During the period covered by this report, a series of studies was done on the cell physiology of the malaria parasite. The studies were outgrowths of previous studies that we had done on the basic physiology of the parasite, and focussed particular attention on problems with an "applied" approach. Studies were done on the in vitro culture of (a) the sporogonic stages, with the aim of culturing sporozoites in vitro, (b) the exoerythrocyticjstages, with the aim of testing potential prophylactic drugs in vitro, and (c) the

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erythrocytic stages, with the aim of testing potential suppressive antimalarials that act by inhibiting merozoite invasion of red cells.

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SUMMARY

During the period covered by this report, a series of studies was done on the cell physiology of the malaria parasite. The studies were outgrowths of previous studies that we had done on the basic physiology of the parasite, and focussed particular attention on problems with an "applied" approach. Studies were done on the in vitro culture of (a) the sporogonic stages, with the aim of culturing sporozoites in vitro, (b) the exoerythrocytic stages, with the aim of testing potential prophylactic drugs in vitro, and (c) the erythrocytic stages, with the aim of testing potential suppressive antimalarials that act by inhibiting merozoite invasion of red cells.

FOREWARD

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

BODY OF REPORT

Progress for the period 1 October 1972 - 31 August 1973
(as presented in Annual Report, January 1974).

This report represents the completion of one year's work on a series of research problems relating to the cell physiology of the malaria parasite. The study was an outgrowth of previous work that I had done on the basic physiology of the parasite, and focussed particular attention on problems with an "applied" approach.

Studies on the penetration mechanism of the invasive stages of the malaria parasite described the movement of the sporozoite through the salivary glands of the mosquito. Serum albumin was found to stimulate the motility and secretory capacity of sporozoites. Studies on the chromosomes of the malaria parasite were devoted largely to preparative techniques for ookinetes, which are essentially the focal point for chromosomal activity. A separation and concentration procedure was developed which should permit future progress in this area. Studies on nucleic acid synthesis by the exoerythrocytic form demonstrated that purine precursors of nucleic acids could be incorporated by the parasite. Studies on the mode of action of prophylactic drugs first focussed on the fine structure of the exoerythrocytic form mitochondrion. Cristae were discovered for the first time. Primaquine was found to have morphological effects on these mitochondria.

Papers Published During Contract Period

Nussenzweig, R., J. P. Vanderberg, G. Spitalny, I. Rivera-Ortiz, C. Orton and H. Most. 1972. Sporozoite-induced immunity in mammalian malaria - a review. Am. J. Trop. Med. Hyg. 21 (Suppl.): 712-728. (Supported by Army Research Program in Malaria).

Sterling, C., M. Aikawa and J. P. Vanderberg. 1973. The passage of Plasmodium berghei sporozoites through the salivary glands of Anopheles stephensi. J. Parasitol. 59: 593-605. (Supported by Army Research Program in Malaria).

Clyde, D., H. Most, V. McCarthy and J. P. Vanderberg. 1973. Immunization of man against sporozoite-induced falciparum malaria. Am. J. Med. Sci. 266: 169-177. (Supported by Army Research Program in Malaria, Paper No. 1168).

Terzakis, J., J. P. Vanderberg and R. Hutter. 1973. The mitochondria of pre-erythrocytic Plasmodium berghei. J. Protozool. 21: 251-253. (Supported by Army Research Program in Malaria).

Progress for the period 1 September 1973 - 31 August 1974
(as presented in Annual Report, January 1975)

Studies were done on various aspects of the cell physiology of the malaria parasite. It utilized previous findings of a "basic research approach" in order to focus particular attention on problems "applied approach."

1) A technique was perfected for collection and concentration of large numbers of ookinetes from infected midguts. This procedure may be useful for future work on in vitro culture of the sporogonic stages of the parasite, ultimately leading to a sporozoite production system. 2) Improved techniques were developed for long term in vitro maintenance of sporozoites under refrigeration, while some progress was made on freeze-preservation. This may eventually lead to suitable storage techniques for a sporozoite vaccine. It also permits easy shipment of sporozoites between laboratories for drug testing. 3) Albumin was found to enhance the protective effect of irradiated sporozoties injected intramuscularly into mice. This may eventually lead towards practical vaccination of humans against malaria.

Papers Published During Contract Period

Vanderberg, J. P. 1974. Studies on the motility of Plasmodium sporozoites. J. Protozool. 21: 527-537. (Supported by Army Research Program in Malaria, Paper No. 1237).

Progress for the period 1 September 1974 - 31 August 1975
(as presented in Annual Report, January 1976)

Studies were done on various aspects of the cell physiology of the rodent malaria parasite, Plasmodium berghei. These studies utilized previous findings of a "basic research approach" in order to focus particular attention on problems with an "applied approach".

1) Progress was made on a system for separation of sporozoites from ground-up infected mosquitoes by means of a DEAE - cellulose column. It should thus be possible to more easily obtain sporozoites for immunological or pharmacological research. 2) Further progress was made on techniques for refrigeration maintenance, and for freeze-preservation of sporozoites. This may more readily permit shipment of sporozoites between laboratories for drug testing. 3) Studies were continued on factors which enhance sporozoite motility in the skin, and sporozoite penetration of subcutaneous blood vessels. This may lead to more effective vaccination by the intramuscular route. 4) A technique was developed for infecting rodents with in vitro-maintained EE forms. This may lead to an in vitro assay system for causally prophylactic antimalarials. 5) Work was completed on a project which sought to separate out ookinetes from infected mosquitoes. This is a helpful development in progress toward an in vitro system for sporogonic development.

Papers Published During Contract Period

Kramer, L. and J. P. Vanderberg. 1975. Intramuscular immunization of mice with irradiated Plasmodium berghei sporozoites. Enhancement of protection with albumin. Am. J. Trop. Med. Hyg. 24: 913-916. (Supported by Army Research Program in Malaria, Paper No. 1346).

Progress for the period 1 September 1975 - 31 August 1976
(as presented in Annual Report, January 1977)

Studies were done on various aspects of the cell physiology of the rodent malaria parasite, Plasmodium berghei. These studies utilized previous findings of a "basic research approach" in order to focus particular attention on problems with an "applied approach".

1) Progress was made on a procedure for infecting rodents with exoerythrocytic forms from the livers of sporozoite-infected animals. As it should be possible to maintain these EE forms in vitro, this procedure may lead to an in vitro assay system for causally prophylactic antimalarials. 2) Progress has continued on our previously reported system for separation of sporozoites from ground-up infected mosquitoes by means of a DEAE-cellulose column. It should thus be possible to more easily obtain sporozoites for immunological or pharmacological research. 3) Studies continued on factors which control sporozoite motility. Determinations of potential energy supplying substrates in the mosquitoes hemolymph gave some indications of sources of energy for sporozoite movement within the mosquito. Tests with specific inhibitors of energy metabolism demonstrated that the TCA cycle and oxidative phosphorylation play an important role in energy production of motility. 4) Further progress was made on techniques for cryopreservation of sporozoites for the possible use of such preserved sporozoites in vaccines against sporozoite-induced malaria. 5) A technique was perfected for the regular production of Plasmodium berghei ookinetes in a simple in vitro system.

Papers Published During Contract Period

Terzakis, J. A., J. P. Vanderberg and M. Weiss. 1976. Viruslike particles in malaria parasites. J. Parasitol. 62: 366-371. (Supported by Army Research Program in Malaria).

Weiss, M. and J. P. Vanderberg. 1976. Studies on Plasmodium ookinetes. 1. Isolation and concentration from mosquito midguts. J. Protozool. 23: 547-551. (Supported by Army Research Program in Malaria, Paper No. 1403).

Progress for the period 1 September 1976 - 31 December 1977
(as presented in Annual Report, January 1978)

Studies were done on various aspects of the cell physiology of the rodent parasite, Plasmodium berghei. These studies utilized previous findings of a "basic research approach" in order to focus particular attention on problems with an "applied approach".

1) Progress has continued on our previously reported system for separation of sporozoites from groundup infected mosquitoes by means of a DEAE-cellulose column. As the system has now been stabilized it should be possible for any laboratory to more easily obtain sporozoites for immunological or pharmacological research. 2) Further progress was made on techniques for cryopreservation of sporozoites for the possible use of such preserved sporozoites in vaccines against sporozoites-induced malaria. 3) Studies continued on factors which control sporozoite motality and penetration of blood vessels. Determinations of potential energy supplying substrates in the mosquito hemolymph (free amino acids, and carbohydrates) gave some indications of sources of energy available for sporozoite motility. Substrate deficiency studies showed that sporozoites could use sugars and some amino acids for energy metabolism. Tests continued with the action of specific inhibitors of energy metabolism on sporozoite motility. The various vasodilators which were tested did not appear to enhance the infectivity of sporozoites injected subcutaneously and intramuscularly into rodents. 4) Progress was made on in vitro development of exoerythrocytic forms removed from the liver of already infected animals. This approach may lead to an in vitro assay system for causally prophylactic antimalarials.

Papers Published During Contract Period

Weiss, M. and J. P. Vanderberg. 1977. Studies on Plasmodium ookinetes. 2. In vitro formation. J. Parasitol. 63: 932-934. (Supported by Army Research Program in Malaria, Paper No. 1443).

Vanderberg, J. P. 1977. Plasmodium berghei: Quantitation of sporozoites injected by mosquitoes feeding on a rodent host. Exp. Parasitol. 42: 169-181. (Supported by Army Research Program in Malaria, Paper No. 1404).

Foley, D. A. and J. P. Vanderberg. 1977. Plasmodium berghei: Transmission by intraperitoneal inoculation of immature exoerythrocytic schizonts from rats to rats, mice, and hamsters. Exp. Parasitol. 43: 69-91. (Supported by Army Research Program in Malaria, Paper No. 1442).

Foley, D. A. and J. P. Vanderberg. 1977. Transmission of mammalian malaria using immature exoerythrocytic schizonts. Experientia 33: 911-912. (Supported by Army Research Program in Malaria).

Vanderberg, J. P., M. Weiss and S. Mack. 1977. In vitro culture of the sporogonic stages of Plasmodium - A review. Bull. W.H.O. 55: 375-390. (Supported by Army Research Program in Malaria, Paper No. 1464).

Progress for the period 1 January 1978 - 31 December 1978
(as presented in Annual Report, January 1979)

Studies were done on various aspects of the cell physiology of the rodent malaria parasite, Plasmodium berghei. 1) Progress has been made on in vitro cultivation of exoerythrocytic stages of the parasite. When sporozoites are injected intravenously into susceptible rats, it is possible to enzymatically dissociate the liver and to obtain suspensions of hepatocytes that include parasitized ones. These infected hepatocytes are infective to other animals, and may be cultured in vitro for various lengths of time. This system may eventually be useful for screening causally prophylactic antimalarial drugs. 2) Progress was made on separation and purification of sporozoites on an agarose-lectin affinity column. 3) The research project on chemical components of mosquito hemolymph from malaria-infected and non-infected mosquitoes was concluded. Measurements of hemolymph volume gave a mean volume of 336 nanoliters per recently emerged mosquito, with lower yields for older mosquitoes.

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Mack, S. R., J. P. Vanderberg and R. Nawrot. 1978. Column separation of Plasmodium berghei sporozoites. J. Parasitol. 64: 166-168. (Supported by Army Research Program in Malaria, Paper No. 1471).

Mack, S. R. and J. P. Vanderberg. 1978a. Plasmodium berghei: Energy metabolism of sporozoites. Exp. Parasitol. 46: 317-322. (Supported by Army Research Program in Malaria, Paper No. 1519)

Mack, S. R. and J. P. Vanderberg. 1978b. Hemolymph of Anopheles stephensi from non-infected and Plasmodium berghei-infected mosquitoes. 1. Collection procedure and physical characteristics. J. Parasitol. 64: 918-923. (Supported by Army Research Program in Malaria, Paper No. 1498)

Foley, D. A., J. Kennard and J. P. Vanderberg. 1978. Plasmodium berghei: Infective exoerythrocytic schizonts in primary monolayer cultures of rat liver cells. Exp. Parasitol. 46: 166-178. (Supported by Army Research Program in Malaria, Paper No. 1525)

Foley, D. A., J. Kennard and J. P. Vanderberg. 1978. Plasmodium berghei: Preparation of rat hepatic cell suspensions that include infective exoerythrocytic schizonts. Exp. Parasitol. 46: 179-188. (Supported by Army Research Program in Malaria, Paper No. 1526)

Progress for the period 1 January 1979 - 31 December 1979
(as presented in Annual Report, January 1980)

Studies were done on various aspects of the cell physiology of the malaria parasite. 1) Progress has been made on a study of invasion of hamster peritoneal macrophages by the Plasmodium berghei sporozoite. It is possible that normal in vivo invasion by sporozoites may take place initially into the liver macrophages (Kupffer cells). Thus, our in vitro invasion system may be helpful in ultimately attaining complete exoerythrocytic development in vitro. This could be helpful in developing an in vitro drug screening system. (2) Studies on the surface characteristics of the P. berghei sporozoite have shown that sporozoites can bind a serum glycoprotein to their surface. This glycoprotein, which has terminal mannose and galactose groups associated with it, may interact with liver receptors in the liver of susceptible hosts. It may be possible to interfere with malarial sporozoite invasion by interfering with this receptor/recognition process. 3) An assay system has been developed for testing in vitro invasion of human erythrocytes by P. falciparum merozoites. A red blood cell surface glycoprotein or glycolipid may be active as a receptor for the parasite. This hypothetical receptor appears to contain . acetylglucosamine as an important component.

Papers Published During Contract Period

Mack, S. R., S. Samuels and J. P. Vanderberg. 1979. Hemolymph of Anopheles stephensi from non-infected and Plasmodium berghei-infected mosquitoes. 3. Carbohydrates. J. Parasitol. 65: 217-221. (Supported by Army Research Program in Malaria, Paper No. 1520)

Mack, S. R., D. A. Foley and J. P. Vanderberg. 1979. Hemolymph volume of non-infected and Plasmodium berghei-infected Anopheles stephensi mosquitoes. J Invert. Path. 34: 105-109. (Supported by Army Research Program in Malaria)

Vanderberg, J. P. 1979. Isolation and purification of sporozoites of the malaria parasites. In "The In Vitro Cultivation of the Pathogens of Tropical Diseases", Trop. Dis. Res. Ser. No. 3, pp. 77-89. Schwabe and Co., Basel. (Supported by Army Research Program in Malaria, Paper No. 1536)

Progress for the period 1 January 1980 - 31 December 1980
(as presented in Annual Report, January 1981)

Studies were done on various aspects of the cell physiology of the malaria parasite. 1) Attempts were made to initiate a system for *in vitro* culture of *Plasmodium falciparum* exoerythrocytic forms. Progress was made in the development of a system for laboratory production of *P. falciparum* sporozoites, and for culture of human hepatocytes. Our *in vitro* invasion system may be helpful in ultimately attaining complete exoerythrocytic development *in vitro*. This could be helpful in developing an *in vitro* drug screening system for *P. falciparum*. 2) Previous studies on the surface characteristics of the *P. berghei* sporozoite had shown that sporozoites can bind a serum glycoprotein to their surface. This glycoprotein, which has terminal mannose and galactose groups associated with it, may interact with liver receptors in the liver of susceptible hosts. It may be possible to interfere with malarial sporozoite invasion by interfering with this receptor/recognition process. Efforts have been directed towards further purification and characterization of the serum glycoprotein involved. 3) A new radioisotope assay system has been developed for testing *in vitro* invasion of human erythrocytes by *P. falciparum* merozoites. A red blood cell surface glycoprotein or glycolipid may be active as a receptor for the parasite. This hypothetical receptor appears to contain N-acetylglucosamine as an important component, but the prime receptor does not appear to be band III or receptors for C_3. Studies on fractionation of erythrocyte glycoprotein components have continued.

Papers Published During Contract Period

Schulman, S., J. D. Oppenheim and J. P. Vanderberg. 1980. *Plasmodium berghei* and *Plasmodium knowlesi*: Serum binding to sporozoites. *Exp. Parasitol.* 49 420-429. (Supported by Army Research Program in Malaria, Paper No. 1570)

Progress for the period 1 January 1981 - 31 August 1981 and
1 January 1982 - 31 August 1983
(as presented in Annual Report, August 1983)

Studies were done on inhibition of invasion of human erythrocytes by merozoites of Plasmodium falciparum. 1) Progress was made in identifying receptors for the parasite found on the red blood cell surface. Three red blood cell membrane fractions (Band 3, macromolecules exhibiting I antigenic determinants, and a delipidated glycoprotein fraction) were separated from red blood cell membranes and tested for their ability to inhibit penetration of red blood cells by Plasmodium falciparum merozoites in an in vitro inhibition assay. The delipidated glycoprotein fraction (containing the major sialoglycoproteins and devoid of Band 3) was the only fraction that inhibited merozoite invasion. This fraction showed 73% and 70% inhibition of 1 mg/ml and 500 ug/ml, respectively, and slight inhibition below these levels. 2) Progress was also made on inhibiting the parasite - erythrocyte interaction by means of specifically synthesized agents. Sugars conjugated to bovine serum albumin (neoglycoproteins) were tested for their ability to inhibit Plasmodium falciparum merozoite invasion of red blood cells in an in vitro inhibition assay. The inhibitory effects of the neoglycoproteins on merozoite invasion of erythrocytes were determined by assessing ^{3}H-hpoxanthine incorporation into the cultures. The only neoglycoprotein that caused signficant inhibition was N-acetylglycosamine-bovine serum albumin. A comparison of the inhibitory effects of N-acetylglucosamine and N-acetylglucosamine bovine serum albumin was about 80 fold more effective than the free sugar in causing 50% inhibition of ^{3}H-hypoxanthine incorporation.

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Weiss, M. M., J. D.Oppenheim and J. P. Vanderberg. 1981. Plasmodium falciparum: Assay in vitro for inhibitors of merozoite penetration of erythrocytes. Exp. Parasitol. 51: 400-407. (Supported by Army Research Program in Malaria, Paper No. 1571)

Holmberg, S., S. Schulman and J. P. Vanderberg. 1981. Role of a serum factor in enhancement of in vitro interactions between Plasmodium berghei sporozoites and hamster peritoneal macrophages. J. Parasitol. 67: 893-897. (Supported by Army Research Program in Malaria, Paper No. 1579)

Shin, S. C., J. P. Vanderberg and J. A. Terzakis. 1982. Direct infection of hepatocytes by sporozoites of Plasmodium berghei. J. Protozool. 29: 448-454. (Supported by Army Research Program in Malaria, Paper No. 1621)

Progress for the period 1 September 1983 - 30 April 1984
(as presented in Annual Report, August 1984)

Solubilized preparations of purified glycophorins and specific domains of these molecules were assessed for their effects as inhibitors of Plasmodium falciparum invasion of human erythrocytes in vitro. The ability of newly invaded merozoites to continue developing and incorporating ^{3}H-hypoxanthine during a 24 h period after their invasion was used as an assay for merozoite invasion. Glycophorins A, B, and C were found to be equally effective as inhibitors. Previous studies had shown N-acetylglucosamine, a sugar component of glycophorins A and C, but not B, to be an effective inhibitor. Accordingly, molecular domains common to all of the glycophorins were further assessed. Sialic acid was shown to act almost as effectively as N-acetylglucosamine, presumably because of the structural similarities between these sugars. The inhibitory ability of sialic acid is considerably enhanced when presented to the parasite in a "clustered" form, as in an oligosaccharide. The acetyl group of these sugars does not appear to play an essential role in this inhibition. How the P. falciparum merozoite recognizes and interacts with the sugar domains of the glycophorin molecule remains to be determined.

Papers Published During Contract Period

Schulman, S., J. D. Oppenheim and J. P. Vanderberg. 1983. Assay of erythrocyte components as inhibitors of Plasmodium falciparum merozoite invasion of erythrocytes. Am. J. Trop. Med. Hyg. 32: 666-670. (Supported by Army Research Program in Malaria, Paper No. 1659)

Schulman, S., Y. C. Lee and J. P. Vanderberg, 1984. Effects of neoglycoproteins on penetration of Plasmodium falciparum merozoites into erythrocytes in vitro. J. Parasitol. 70: 213-216. (Supported by Army Research Program in Malaria, Paper No. 1688)

Gupta, S. K., S. Schulman, and J. P. Vanderberg. 1984. Stage-dependent toxicity of N-acetylglucosamine to Plasmodium falciparum. J. Protozool. (in press). (Supported by Army Research Program in Malaria, Paper No. 1710)

Vanderberg, J. P., S. K. Gupta, S. Schulman, J. D. Oppenheim and H. Furthmayr. 1984. Role of the carbohydrate domains of glycophorins as erythrocyte receptors for invasion by Plasmodium falciparum merozoites. Infection and Immunity (in press). (Supported by Army Research Program in Malaria, Paper No.)

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