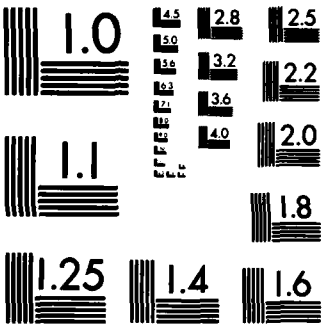
AD-A158 674 CHEMOTHERAPEUTIC STUDIES ON SCHISTOSOMIASIS AND CLINICAL EPIDEMIOLOGICAL A... (U) BRASILIA UNIV (BRAZIL) A R PRATA ET AL. SEP 82 DAMD17-82-G-9499 1/1

UNCLASSIFIED F/G 6/5 NL



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

AD_____

CHEMOTHERAPEUTIC STUDIES ON SCHISTOSOMIASIS AND CLINICAL, EPIDEMIOLOGICAL AND IMMUNOLOGICAL STUDIES ON MALARIA IN AMAZONAS, BRAZIL, ALONG THE ITUXI RIVER

Annual/Final
1 Oct 81-30 Sep 82

Prata, Aluzio R., M.D.
LTC Willis A. Reid, Jr.
MAJ Anthony B. Bosworth
Norman Peterson

September 1982

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Grant No. DAMD17-82-G-9499

University of Brasilia
Brasilia, D.F., Brazil

Approved for public release; distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER	2. GOVT ACCESSION NO. AD A158674 / 3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) CHEMOTHERAPEUTIC STUDIES ON SCHISTOSOMIASIS AND CLINICAL, EPIDEMIOLOGICAL AND IMMUNOLOGICAL STUDIES ON MALARIA IN AMAZONAS, BRAZIL, ALONG THE ITUXI RIVER	5. TYPE OF REPORT & PERIOD COVERED Annual/Final 1 Oct 81-30 Sep 82
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Prata, Aluzio R., M.D. Norman Peterson LTC Willis A. Reid, Jr. MAJ Anthony B. Bosworth	8. CONTRACT OR GRANT NUMBER(s) DAMD17-82-G-9499
9. PERFORMING ORGANIZATION NAME AND ADDRESS University of Brasilia Brasilia, D.F., Brazil	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 62770A.3M162770A871.AH.046
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research and Development Command Fort Detrick, Frederick, MD 21701-5012	12. REPORT DATE September 1982
	13. NUMBER OF PAGES 10
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)	15. SECURITY CLASS. (of this report) Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Brazil
Schistosomiasis
Malaria
Chemotherapy
Immunology
Epidemiology
Drug Resistance
Entomology

Accession For	
NTIS GRA&I	☒
DTIC TAB	☐
Unannounced	☐
Justification	
By	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A/1	

DTIC COPY INSPECTED 3

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

During the reporting period, 457 compounds were screened in the PCT and PMT. Of these 5 were designated confirmed or unconfirmed active and 23 were toxic. Nine compounds were tested in the SCT. Upgrading of research mouse colony facilities was begun. Mark and release studies of Anopheles darlingi at the Ituxi River Study Area are being conducted to determine dispersal patterns from possible larval breeding sites. Construction of an insectary is nearing completion at the University of Brasilia. Preliminary studies to Colonize An. darlingi have been initiated.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

PROBLEMS AND OBJECTIVES:

1. Schistosomiasis, malaria and leishmanisais continue to pose a threat to American military personnel who are or who might have to be stationed in the Middle East, Africa, the Far East, the Caribbean or Latin America. These diseases also inhibit development and cause great human misery, a potential source of political unrest, in many of the developing countries where they are found.

2. There currently is no single drug that is a totally satisfactory treatment for schistosomiasis. It also is highly desirable that, in addition to developing better therapeutic agents, we also develop prophylactic methods, either drugs, treatments for exposed skin or treatments for the uniform, which will reduce casualties resulting from exposure to schistosomiasis. The mode of transmission of this disease is such that troops moving through or stationed within an endemic area could be expected to experience a high level of exposure and infection. This would result in unaffordable and unnecessary loss of combat strength and would result in a burden on medical facilities. It should be possible, through sustained research effort, to avoid these problems. Research with the objective of identifying potential chemoprophylactic and chemotherapeutic agents for schistosomiasis is being conducted by the US Army Medical Research Unit/Brasilia (USAMRU/Brasilia), located at the Núcleo de Medicina Tropical (NMT) of the University of Brasilia (UnB). Standardized screening procedures in a mouse - Schistosoma mansoni - Biomphalaria glabrata system are being used.

3. Since 1975, reported cases of malaria in Brazil have quadrupled, according to Ministry of Health statistics. The vast

majority of these cases occur within that portion of the Amazon River basin lying within Brazil. Almost 200,000 cases were reported in 1981, and it is possible that several times that many occurred. In urban areas of the Amazon, malaria control is practiced and there is little malaria. However, in the rural areas where most of these cases originated, malaria control is inadequate and the system of reporting cases likely reflects a very conservative estimate. Drug resistance in falciparum malaria in the Amazon has necessitated a concentration on vector control by use of traditional residual spraying of houses with DDT in an attempt to ameliorate the serious effect malaria has on the rural population. However, residual insecticide usage has had a limited beneficial effect, because many houses are only partially enclosed and because DDT has been demonstrated to have a marked repellent effect on the primary malaria vector in the region, Anopheles darlingi. Vector biology studies by USAMRU/Brasilia have as their objective the development of sufficient knowledge about An. darlingi to permit the formulation of a practicable vector control strategy for this species under the above conditions.

4. Cutaneous and mucocutaneous leishmaniasis are zoonoses with many wild mammal reservoirs. It is widespread in Brazil. This vector borne disease is difficult to diagnose. Culture of some strains of the etiologic agent can not be done reliably. Treatment is extended, involves the use of toxic drugs and often has to be repeated because of ineffectiveness and/or relapse. It is difficult to confirm cure. The disease is potentially hideously disfiguring and may have a fatal outcome. The many days required for therapy and the detailed follow-up required to confirm cure would constitute an extreme burden on medical facilities. The grossly disfiguring effects of advanced mucocutaneous leishmaniasis would horrify and have a negative psychological affect on troops, unless they could be given genuine assurances. It is very important that we learn to prevent this disease. It is highly relevant to the development of locally effective control strategies that the animal reservoirs for the disease be identified. Leishmaniasis research at USAMRU/Brasilia has the objective of determining the reservoirs for leishmaniasis at a study site where the scope of transmission appears to have been extended to women and children, concomitant with habitat modification in government encouraged agricultural development.

PROGRESS:

1. Schistosomiasis: Following a period of interrupted testing activity due to inavailability of adequate numbers of mice of

desired quality, antischistosomiasis drug testing was resumed in October, 1981. In the Primary Mortality Test (PMT) system, designed to detect chemoprophylactic activity against Schistosoma mansoni, 604 compounds were given initial tests. Toxicity was noted in 161 of these compounds. Three compounds demonstrated significant antischistosomal activity. Retesting in the PMT was done on an additional 82 compounds. Of these, 21 were toxic. No significant antischistosomal activity was detected in retested compounds. In the Primary Curative Test (PCT) system, designed to detect therapeutic potential, 296 compounds were given initial testing. Toxicity was noted in 59 of these compounds. Sixteen compounds demonstrated significant antischistosomal activity. Retesting was done on 38 compounds in the PCT. Of these, 12 were toxic. Significant antischistosomal activity was detected in 3 of the retested compounds. Two compounds were tested in the Secondary Curative Test, designed to provide information on dose, time-to-action, and preferred route of administration of new compounds which demonstrate markedly significant antischistosomal activity. Many of the compounds tested are proprietary, and it is part of our agreement with the supplier that information regarding these specific compounds will not be generally distributed.

Reinitiation of testing was made possible by the establishment of a mouse colony in the Núcleo de Medicina Tropical, while the Central Bioterio was being partially renovated. This renovation is completed. Although it does not conform strictly to the high standard practiced in the United States for colonies producing animals for toxicological and drug testing, it is much improved. Breeding stock from the mouse colony at the Núcleo has been delivered to the Bioterio to reinitiate a colony there. We hope that mice of the quantity and quality needed can be produced there. Our snail colony remains capable of supporting our testing programs at full operational level.

2. Malaria: Successful mark, release and recapture studies of An. darlingi showed that this species could fly long distances (1 to 2 km) in less than a day and that it has strong human host seeking behavior. High percentages of marked mosquitoes (18.5%, 4.0%, 3.5% and 0.5%) from 4 release sites at about 1 km distances from the study area were recaptured at the study site within 8 days. Marked mosquitoes released from 4 additional release sites at 1.5-2 km distances from the study area were also recaptured at high percentages (6.0%, 1.0%, 0.5% and 0.5%). Larval surveys for Anopheles mosquitoes were made in conjunction with these studies in an effort to find breeding grounds. No An. darlingi immatures were found. Two separate tests for two different rates of fenitrothion application (1g/m^2 and 2g/m^2) showed that

the rates of application were not significantly different with regards to total numbers of mosquitoes which exited treated chambers. However, mosquito movement from chambers with treated paper was markedly higher than movement from the untreated control chambers. Mortality of mosquitoes was 72.6% and 78.8% of the total number tested in the chamber with $1g/m^2$ and $2g/m^2$, respectively. A field technician from Labrea was trained at UnB in Brasilia. During one month, he learned mosquito larval and adult surveillance techniques, data card records procedures, proper storage techniques and other entomological procedures. He was also trained to operate a radio station which is anticipated to be placed in the entomology laboratory in Labrea during the coming fiscal year. Over 500 female An. darlingi mosquitoes were collected near the city of Labrea and returned to UnB. These were used to produce mosquitoes for colonization attempts. This species has rarely been successfully colonized. Mating studies using 1,000 males and 1,000 females were conducted in a newly constructed insectary. Each day for 15 days, mating was checked by dissecting and examining 10 spermathecae; 30 mosquitoes were also blood fed and left for oviposition. The spermathecae were negative for spermatozoon, and no viable eggs were deposited. Force mating techniques were tried on over 100 females with over 300 males. These were also unsuccessful, even though force copulated pairs appeared to secure and clasp well. A 30 hour course entitled "Arthropods and Mollusks of Medical Importance" was given to 10 physicians at the Núcleo de Medicina Tropical. Introductory lectures were given in medical entomology, insect physiology and morphology, insect toxicology and biological control. Support for malaria serology studies was continued at only a low level because of the inavailability of an investigator to direct the effort. However, 858 examinations of sera by fluorescein labeled anti-humans IgG and anti-human IgM in indirect fluorescent antibody tests demonstrated the high level of malaria seropositivity we have previously seen in the Amazon River basin. Additionally, 40 sera from the Ituxi River area, examined at WRAIR to confirm locally acquired results, were 100% positive for the presence of IgG antimalaria antibodies.

3. Leishmaniasis: Arrangements were made for necessary space at the field laboratory maintained by the Núcleo de Medicina Tropical (NMT) in Três Braços for processing the potential mammalian reservoirs of leishmaniasis collected there and for storage of traps and other equipment. The hamster breeding and housing facilities were expanded to provide animals to use for inoculations in isolation, identification and diagnosis. A field vehicle has also been made available. Close coordination is being maintained between the epidemiological, clinical and parasitological studies being conducted by the NMT and the

present study to avoid duplication of effort and to reap the benefits of a multidisciplinary approach to research on this disease. From June through September, 1982, 24 nights of trapping produced 79 mammals. The secondary scrub habitat produced 76 mammals of 12 species (1 Metachirus nudicaudatus*, 1 Marmosa parvidens, 2 Marmosa murina*, 6 Didelphis albiventris, 9 Oryzomys capito*, 1 Oryzomys concolor*, 1 Oryzomys fulvescens, 2 Nectomys squamipes*, 39 Zygodontomys lasiurus, 8 Oxymycterus sp., 1 Holochilus brasiliensis and 5 Rattus rattus*), during 742 trap nights. Capture rate was one mammal per 9.8 trap nights. Two rodents (1 Zygodontomys lasiurus and 1 Oxymycterus sp.) were collected in the bananna and cacao plantation during 93 trap nights. One marsupial (Metachirus nudicatudatus) was captured in the tall humid forest during 141 trap nights. The species denoted by(*) have been identified as reservoir hosts for neotropical leishmaniasis elsewhere. Tissue specimens (skin, spleen and liver) from all mammals captured were inoculated intraperitoneally and into the feet of hamsters. These hamsters are being observed, but have not yet demonstrated signs of leishmaniasis infection. In only a small proportion of tests has sufficient time lapsed to suspect a negative determination. Domesticated dogs have previously been demonstrated to be infected in the study area.

RECOMMENDATIONS:

1. Increase emphasis on screening of compounds in the Primary Mortality Test, which provides an index of prophylactic potential.

2. Add to our screening system the anti-cercarial penetration screening protocol recently discontinued at WRAIR.

3. Continue studies of the dynamics of An. darlingi populations and movements in the study area on the Ituxi River.

4. Continue attempts to locate the larval breeding sites of An. darlingi in the study area.

5. Establish an Anopheles surveillance program in the town of Labrea near our study area on the Ituxi River.

6. Attempt to document natural malaria infections of An. darlingi and other species of Anopheles in our study area.

7. Continue efforts to colonize An. darlingi at the Núcleo de Medicina Tropical.

8. Continue the extensive program to capture mammals from all available habitats (e.g. tall forest, secondary forest, secondary scrub, cropland, pastureland and domiciliary) in the vicinity of Três Braços.

9. Conduct an intensive trapping program to capture mammals in and around houses where current leishmaniasis transmission in humans has been documented.

10. Study the ecology of the reservoir species and determine which control methods are practicable.

11. Collect ectoparasites and endoparasites, and preserve pathological specimens from the captured animals.

PRESENTATIONS:

1. Bosworth, A., 1982. Entomological hazards in tropical medicine. VII Curso de Aperfeiçoamento em Medicina, 1 Sept - 23 Oct 81. Faculty of Medicine, University of Brasilia.

2. Bosworth, A. 1982. Entomology laboratory for physicians. IBID.

3. Peterson, N. 1982. Introduction to mammalogy and the role of mammals in tropical medicine. IBID.

BIBLIOGRAPHY:

1. Bosworth, A. and Marsden, P. Injurious Arthropods. In: T. Strickland ed., Hunters Tropical Medicine, 6th ed., W.B. Saunders Co. (In press).

2. Dixon, K.E., Llewellyn, C.H., Travassos da Rosa, A.P.A. y Travassos da Rosa, J.F. 1981. Programa multidisciplinario de vigilancia de las enfermedades infecciosas en zonas colindantes con la Carretera Transamazonica en Brasil. II. Epidemiologia de las infecciones por arbovirus. Bol. Of. Sanit. Panam. 91(3): 200-218.

3. Dixon, K.E., Travassos da Rosa, A.P.A., Travassos da Rosa, J.F. and Llewellyn, C.H. 1981. Oropouche virus. II. Epidemiological observations during an epidemic in Santarem, Para, Brazil in 1975. Am. J. Trop. Med. Hyg. 30(1): 161-164.

4. Hoch, A.L., Peterson, N.E., LeDuc, J.W. and Pinheiro, F.D. 1981. An outbreak of Mayaro virus disease in Belterra, Brazil. III. Entomological and ecological studies. Am. J. Trop. Med.

Hyg. 30(3): 689-698.

5. LeDuc, J.W., Pinheiro, F.P. and Travassos da Rosa, A.L.A. 1981. An outbreak of Mayaro virus disease in Belterra, Brazil. II. Epidemiology. Am. J. Trop. Med. Hyg. 30(3): 682-688.

6. Peterson, N.E. Changes in mammal species composition after burning a tract of land in the Amazon forest. (Submitted for publication to Journal of Mammalogy).

7. Peterson, N.E. and Pine, R.H. Chave para identificação de mamíferos da Região Amazônica Brasileira com exceção dos quiropteros e primatas. Acta Amazonica (In press).

8. Peterson, N.E., Roberts, D.R. y Pinheiro, F.P. 1981. Programa multidisciplinario de vigilancia de las enfermedades infecciosas en zonas colindantes con la Carretera Transamazonica en Brasil. III. Estudio de los mamiferos. Bol. Of. Sanit. Panam. 91(4): 324-338.

9. Pinheiro, F.P., Freitas, R.B., Travassos da Rosa, J.F., Gabbay, Y.B., Mello, W.A., and LeDuc, J.W. 1981. An outbreak of Mayaro virus disease in Belterra, Brazil. I. Clinical and virological findings. Am. J. Trop. Med. Hyg. 30(3): 674-681.

10. Pinheiro, F.P., Hoch, A.L., Gomes, M. de L.C. and Roberts, D.R. 1981. Oropouche virus. IV. Laboratory transmission by Culicoides paraensis. Am. J. Trop. Med. Hyg. 30(1): 172-176.

11. Pinheiro, F.P., Travassos da Rosa, A.P.A., Travassos da Rosa, J.F.S., Ishak, R., Freitas, R.B., Gomes, M.L.C., LeDuc, J.W. and Oliva, O.F.P. 1981. Oropouche virus. I. A review of clinical, epidemiological, and ecological findings. Am. J. Trop. Med. Hyg. 30(1): 149-160.

12. Roberts, D.R., Hoch, A.L., Peterson, N.E. y Pinheiro, F.P. 1981. Programa multidisciplinario de vigilancia de las enfermedades infecciosas en zonas colindantes con la Carretera Transamazonica en Brazil. IV. Estudio entomologico. Bol. Of. Sanit. Panam. 91(5): 379-399.

This bibliography includes work done by the Transamazon Project previously stationed in Belém, Brazil.

DISTRIBUTION LIST

Director
Walter Reed Army Institute of Research
Walter Reed Army Medical Center
ATTN: SGRD-UWZ-C
Washington, DC 20307-5100

Commander
US Army Medical Research and Development Command
ATTN: SGRD-RMS
Fort Detrick, Frederick, Maryland 21701-5012

Defense Technical Information Center (DTIC)
ATTN: DTIC-DDAC
Cameron Station
Alexandria, VA 22304-6145

END

FILMED

10-85

DTIC