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FINAL SCIENTIFIC REPORT

PERIOD COVERED: 1 AUGUST 1962 THROUGH 31 MARCH 1963

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INSTITUTION: THE ARMY MEDICAL RESEARCH UNIT OF THE UNIVERSITY OF CHICAGO (STATEVILLE PENITENTIARY)

SUBJECT: STUDIES ON CHEMOTHERAPY OF VIVAX MALARIA, FALCIPARUM MALARIA, AND PRIMAQUINE HEMOLYSIS

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CONTRACT NO. DA-49-007-MD-566

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Since the last interim report was submitted, several strains of chloroquine-resistant *P. falciparum* have been investigated at Stateville on inmate volunteers. One strain of *P. falciparum* which originated in Thailand has been found resistant to all modern synthetic antimalarial drugs except quinine. It is resistant to the new depot antimalarial drug developed by Parke-Davis which will protect against the Chesson strain of vivax for six months to one year. Two more strains of falciparum malaria which have proved chloroquine-resistant in American military personnel are stored in deep freeze but have not been studied.

A strain of *P. falciparum* obtained from a Marine, Captain Snell, who was flown from South Viet Nam to Great Lakes Naval Hospital, has been studied in him and also in inmate volunteers to whom this strain was transmitted. The Snell strain of *P. falciparum* from South Viet Nam is resistant to all drugs except pyrimethamine and quinine. The doses of quinine that are necessary to cure this strain appear to be larger than is usually the case in falciparum infections. The Parke-Davis depot drug, C1-501, does not protect against the South Viet Nam strain.

A new potential antimalarial drug obtained from the Cancer Chemotherapy Program, which has been studied extensively in malignancies in humans, has also received therapeutic trial. This compound
is of interest because its action is known. It blocks the incorporation
of valine into protein modities. Previous to therapeutic trial at State-
ville this compound was studied in *P. berghei* infections in mice by Dr.
Ralph Jones, Jr. and his group at the University of Miami. It was
effective in berghei infections. When tested in volunteers at Stateville
Penitentiary it could be demonstrated that the compound had partial
effect in vivax malaria, but when given intravenously its toxicity was
too great to warrant extensive testing. Toxicity consisted of a marked
fall in blood pressure in one of the two patients studied. It would be
worthwhile to study the effectiveness of similar compounds that could
be given by mouth.

The hypothesis that primaquine sensitivity may be beneficial
to the individual who has the characteristic enzyme deficiency in his
blood (G-6-PD deficiency) is being tested. Preliminary results indic-
ate that in all probability the enzyme deficiency does modify the sever-
ity of falciparum malaria, thus rendering individuals who possess this
genetically transmitted characteristic at a biological advantage. Add-
tional studies must be performed before final interpretations can be
made, but thus far it appears that this enzyme deficiency is an example
of balanced polymorphism.

Several additional biochemical characterizations have been
made of the red blood cells of individuals who lack G-6-PD. These studies concern the glyoxalase, adenine triphosphate and hexokinase of the cells. These enzymes do not appear to be involved in the initial stages of the hemolytic processes when drugs are administered to sensitive individuals. Likewise, the enzyme GA-3-PD does not change during primaquine administration and, therefore, is probably not directly involved in the mechanism of hemolysis.

Several genetic studies in heterozygous females who are primaquine sensitive are in progress but results were not available at the time the contract closed on 31 March 1963.
Alving, A.S., Powell, R.D., Brewer, G.J., and Arnold, J. D.:
Malaria, 8-Aminoquinolines and Haemolysis. Biol. Council
Symp. on Drugs, Parasites and Hosts, 1962, pp. 83-97.
(no reprints available)

Brewer, G.J., Powell, R.D. (by invitation) and Alving, A.S.: Studies
on the Mechanism of the Primaquine-type Hemolysis:
Erythrocyte ATP Content and Hexokinase Activity. J. Lab. &
ABSTRACT

(Final Scientific Report)

1. University of Chicago - Army Medical Research Unit, Stateville Penitentiary, Joliet, Illinois


3. Dr. Alf S. Alving, Principal Investigator

4. Report: 4 Pages long including abstract

5. Contract number: DA-49-007-MD-566, Army Medical Research #14

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Since the last interim report of investigations at the University of Chicago-Stateville Medical Research Unit the therapeutic response of several strains of *P. falciparum* from Southeast Asia have been studied. One strain obtained from Malaya, one from Thailand and one from South Viet Nam have proved resistant to chloroquine. They are all sensitive to quinine. The Thailand and Viet Nam strains are resistant to the Parke-Davis depot drug CI-501.

Investigations of drugs developed on the Cancer Chemotherapy Program and tested in berghei infections of mice by Dr. Ralph Jones, Jr. of Miami have been initiated at Stateville Penitentiary in volunteers infected with Chessor vivax malaria.

Genetic and biochemical studies of primaquine sensitivity (G-6-PD deficiency) have continued.