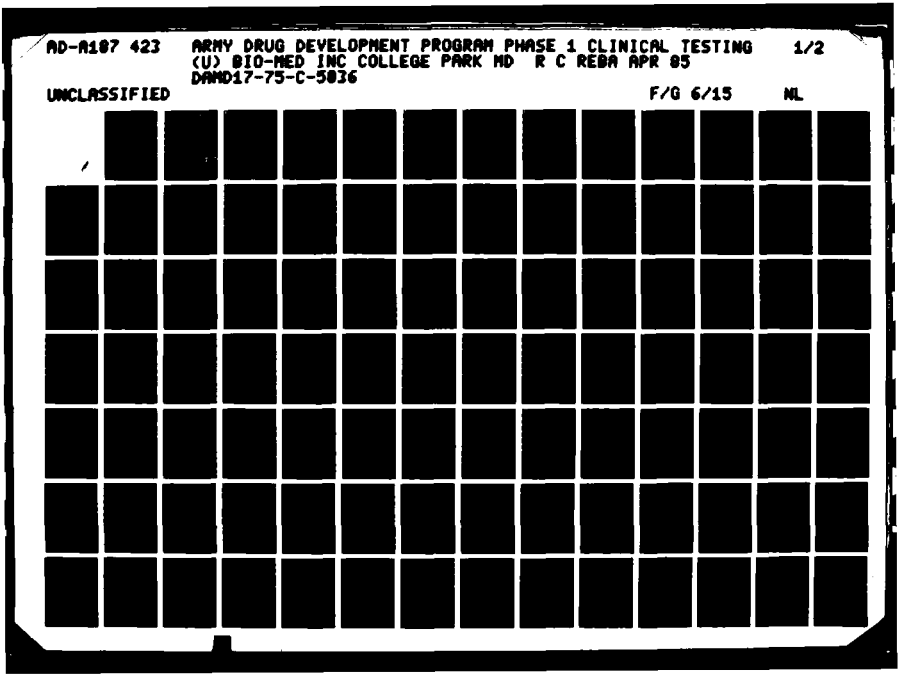
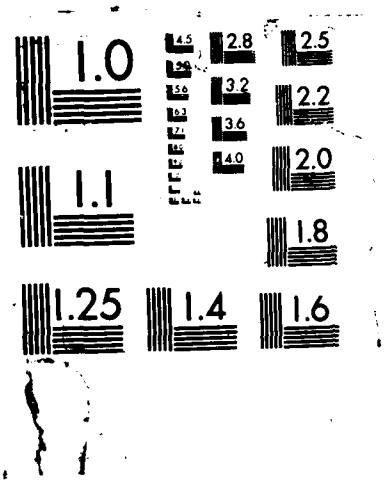
AD-A107 423 ARMY DRUG DEVELOPMENT PROGRAM PHASE 1 CLINICAL TESTING 1/2
(U) BIO-MED INC COLLEGE PARK MD R C REBA APR 85
DAMD17-75-C-5036

UNCLASSIFIED F/G 6/15 NL




1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
4.5
5.0

AD _____

Army Drug Development Program
Phase I
Clinical Testing

ANNUAL REPORT
January 1983 - August 1983

Richard C. Reba, M.D. Principal Investigator

April 1985

Supported by

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

Contract No. DAMD17-75-C-5036

BIO-MED, Inc.
4401 Hartwick
College Park, Maryland 20740

Approved for public release;
distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unlss 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-A187423	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Army Drug Development Program Phase I Clinical Testing	5. TYPE OF REPORT & PERIOD COVERED Annual Report Jan. 1983 - Aug. 1983
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Richard C. Reba, M.D.	8. CONTRACT OR GRANT NUMBER(s) DAMD17-75-C-5036
9. PERFORMING ORGANIZATION NAME AND ADDRESS 4401 Hartwick College Park, Maryland 20740	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 63764A.2M463764D995.AA.041
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Medical Research and Development Command Fort Detrick, Frederick, MD 21701-5012	12. REPORT DATE April 1985
	13. NUMBER OF PAGES 103
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)

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

Approved for public release; distribution unlimited

18. SUPPLEMENTARY NOTES

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

Antimalarials, Leishmaniasis, WR 6026 2HCl, Hepatic enzymes, Abate, Diet, Human Subjects, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT)

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

From January 1983 to August 19, 1983 research was continued at BIO-MED, Inc. under contract DAMD17-75-C-5036 "Phase I Clinical Studies: The Army Drug Development Program". Activities include Experiment # 21, WR 2HCl: Short Term Safety and Tolerance Study and Experiment # 22, The Effect of Low and High Caloric Diet upon the SGOT and SGPT of Normal Human Subjects.

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

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

SUMMARY

During this reporting period, BIO-MED, Inc. continued to design and implement Phase I clinical studies in support of the U.S. Army Drug Development Program.

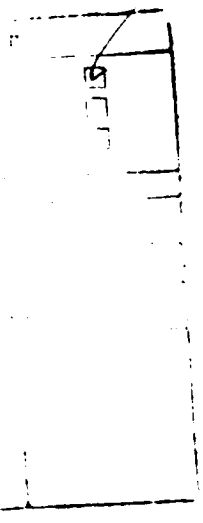
Experiment #21, WR 6026 2HCL: Short Term Dosage Safety and Tolerance Study: Single Oral Dose, Rising Dose Levels, was implemented and completed during the reporting period. The final clinical report is presented in this report. WR 6026, originally synthesized and tested as an antimalarial agent, was the first drug for the treatment of leishmaniasis to be proposed for clinical trials by the U.S. Army Drug Development Program. In this double-blind study of safety and tolerance, 1 mg to 60 mg of WR 6026 2HCL or a placebo was given to healthy, male volunteers in a single oral dose. The drug was well tolerated up to and including the 60 mg dose level. Abnormalities in laboratory blood tests of subjects were minimal or of doubtful significance. Methemoglobinemia was not detected.

Experiment #22, The Effect of Low and High Calorie Diets Upon the SGOT and SGPT of Normal Human Subjects was completed during the reporting period. Elevations in serum glutamic oxaloacetic transaminase (SGOT) and/or serum glutamic pyruvic transaminase (SGPT) had been observed in both placebo and drug recipients during the course of studies performed at BIO-MED, Inc. Because of the importance of the levels of these hepatic enzymes to Phase I clinical drug tests and because hyperphagia was suspected as a cause of SGOT and/or SGPT elevations, this study was implemented to determine if high caloric intake could be associated with elevations in SGOT or SGPT. In an approved crossover study of the effects of various high calorie diets upon the hepatic enzymes, 18 subjects were fed a basic balanced diet of 2500 calories supplemented with 2500 to 3500 carbohydrate calories given ad libitum for three days. On the fourth day, 10 of the 18 subjects had SGOT or SGPT elevations in the abnormal range. In the crossover leg of the study, subjects received only the basic balanced 2500 calorie diet. One subject had one borderline elevation of the SGOT (subject value 48, normal 47) in the low calorie period.

If these phenomena can be reproduced and clarified, the interpretation of all SGOT and SGT determinations may be affected. It is possible that a new avenue of investigation will be opened into the pathophysiology of liver damage.

During the reporting period, a protocol was developed for study of the pediculicide, ABATE. The protocol, "Phase I Safety and Tolerance Testing for the Pediculicide, ABATE: Cutaneous Toxicity and Sensitivity", is included in this report. It is the purpose of the study to provide an estimate

of the prevalence of cutaneous toxicity and hypersensitivity as a result of the dermal application of ABATE.



FOREWORD

Phase I clinical studies of drugs under development by the U.S. Army Research and Development Command (USAMRDC) were performed at the clinical facility of BIO-MED, Inc. under the terms of the contract DAMD17-75-C-5036. All protocols were jointly reviewed by BIO-MED, Inc. and the Division of Experimental Therapeutics of the Walter Reed Army Institute of Research, and approved by the Institutional Review Board of BIO-MED, Inc. and the Human Subjects Research Review Board, Office of the Surgeon General, Department of the Army prior to implementation at BIO-MED, Inc.

Special assurance for the conduct of these studies has been extended from the Headquarters of the USAMRDC to BIO-MED, Inc.

For the protection of human subjects the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

TABLE OF CONTENTS

A

BIO - MED, Inc.

4401 HARTWICK ROAD · COLLEGE PARK, MARYLAND 20740 · TELEPHONE (202) 882-0977

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 21

TITLE:	WR 6026 2HCL: SHORT TERM DOSAGE SAFETY AND TOLERANCE STUDY: SINGLE ORAL DOSE, RISING DOSE LEVELS
PRINCIPAL INVESTIGATOR:	RICHARD C. REBA, M.D.
CLINICAL DIRECTOR:	KEVIN G. BARRY, M.D.
ASSOCIATE DIRECTOR:	LESLIE B. ALTSTATT, M.D.
INSTITUTIONAL REVIEW BOARD MEMBERS:	GEORGE BANNING, JR., M.D., CHAIRMAN JAMES A. DUKE, Ph.D. JOSEPH J. D'ERASMO, LL.B. JUDY HANNAH ANGELO J. TROISI

FINAL CLINICAL REPORT

EXPERIMENT NUMBER 21

WR 6026 2HCl: Short Term Dosage, Safety and Tolerance Study Single Oral Dose, Rising Dose Levels

ABSTRACT

Forty-four healthy subjects were given increasing single oral doses of WR 6026 2HCl or placebo (1 mg - 60 mg, 11 dose levels) in a double blind study of safety and tolerance. There were no physical abnormalities, symptoms or laboratory abnormalities that could be attributed to drug administration. WR 6026 2HCl was safe and well tolerated under the conditions of this experiment.

INTRODUCTION

WR 6026 2HCl (WR6026) is a primaquine analog synthesized and tested for the treatment of vivax malaria during World War II. Other 8-aminoquinolines showed greater promise and the drug was not further developed as an antimalarial.

More recently, WR 6026 was found to be highly active in the antileishmanial drug screening program when it was found to effectively suppress the number of liver amastigotes of three-day infections with Leishmania donavani in hamsters. The drug has consistently shown significant suppression at 0.0508 mg/kg in divided oral doses administered twice daily for four days. This dose is 470 to 700 times less than the reference antimonial compound, meglumine antimoniate (Glucantime®). WR 6026 also shows promising activity in the hamster model against laboratory strains of L. donavani which are relatively resistant to another pentavalent antimony, Pentostam®.

Based on animal studies in rats and dogs, the toxicologic profile of this drug is similar to primaquine. Administration of 0.3 mg/kg/day to dogs for 28 days produced little toxicity except for a slight elevation in methemoglobin values in one of six dogs. Doses of 1 and 3 mg/kg/day produced numerous dose related abnormalities in hematology and clinical chemistry studies with diffuse histologic abnormalities of the erythropoetic and reticuloendothelial systems. These studies suggested that elevated methemoglobin values should be useful as an early indicator of drug toxicity.

In studies conducted during WW II, multiple doses of WR 6026 combined with quinine were administered (5 mg base every 4 hours for 14 days). Some subjects complained of gastric, shoulder, back, neck and inguinal pain. Anorexia, nausea, vomiting, diarrhea, headache and generalized weakness occurred less frequently.

This report presents the results of a single dose study of the safety and tolerance of WR 6026 2HCl in man administered in increasing doses from 1 mg to 60 mg.

METHODS AND MATERIALS

STUDY DESIGN:

A double blind, 2x2 rising dose level design was used. A dose ranging from 1 to 60 mg of WR 6026 or placebo was administered as a single oral dose to 44 subjects.

SUBJECT SELECTION:

Forty-four non-smoking qualified subjects between the ages of 18 and 35 years participated in the study. The subjects were recruited from the Washington,D.C. metropolitan area by newspaper advertisement.

Candidates for participation had a complete evaluation including medical history and physical examination, chest x-ray, electrocardiogram (12 Leads) and a urinalysis. Blood examinations included the following: a CBC with differential count, platelet count, RBC indices and reticulocyte count, serum concentrations of glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphorous, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, and total bilirubin. Methemoglobin, G6PD and haptoglobin concentrations were measured.

Subjects were selected so that the risks of participation were slight and comparable for all subjects. Certain candidates were routinely excluded such as those with murmurs indicating organic heart disease or active lesions on chest x-ray. The presence of conditions which neither increased risk nor compromised the validity of the study did not result in exclusion from study. Laboratory values falling between 2 and 3 standard deviations from the mean were usually cause for rejection, but exceptions were made taking the other laboratory results, clinical findings and the purpose and design of the study into account. For instance, marginal elevations of the hematocrit, hemoglobin and red blood count were not, in the absence of other positive findings, a cause for rejection. Deficiency of G6PD was cause for exclusion.

To eliminate a known cause of methemoglobinemia, only non-smokers (defined as individuals who did not smoke every day and who had not smoked tobacco regularly for the past 30 days) were eligible for this study.

Candidates were given a concise written explanation of the study protocol. The investigator held a group discussion at which time the candidates had the opportunity to ask

questions. Each candidate was interviewed in private and permitted to sign the informed consent form in the presence of the investigator and a witness, only after the investigator had determined that the individual was fully capable of rendering free and informed consent.

PROCEDURES:

Drug administration:

The subjects were admitted to the controlled environment of the BIO-MED Clinical Research Facility at College Park, Maryland. Four subjects were tested at each dose level, two receiving drug 1 mg capsules (Control No. WRA-06-05182) or 5 mg capsules (Control No. WRA-07-05182) and the other two placebo (control No. WRA-08-05182). Assignments to the drug or placebo group were random through lottery with the sealed code available only for emergencies and end-of-study analysis. The test capsules were ingested in the presence of one of the investigators. For each group, the capsules were administered simultaneously.

Recording:

Individual records were maintained on each subject. The following data were recorded: vital signs, weight, laboratory test results, symptoms and pertinent physical findings. The following schematic depicts details of procedures and observations during the study period.

STUDY PLAN
SINGLE ORAL DOSE
SAFETY AND TOLERANCE OF WR 6026

Study Day	0*	1*	2*	3	7	14
Dose		X				
Physical Exam	X		X			X
Interview	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
ECG	X		X			X
Lab.Tests+	X		X	X	X	X

*Controlled environment
+Laboratory tests listed on page 4 are repeated.

Adverse Reactions:

Signs and symptoms of possible drug intolerance were carefully noted and evaluated. Standard BIO-MED procedures for management of medical emergencies and study suspension were in effect during the study.

Final Evaluation of Subjects:

On the last day of the study for each subject, final physical examinations and laboratory evaluations were performed. Subjects with abnormal findings were monitored until findings had returned to normal.

The schedule for the rising dose level study is presented below:

SCHEDULE
RISING DOSE LEVEL

Study Group	Dose	Subject #s	Date admitted to facility (1983)
1	1mg	583-586	1/11
2	5mg	587-590	1/18
3	15mg	591-594	1/25
4	20mg	595-598	2/8
5	25mg	599-602	3/1
6	30mg	603-606	3/8
7	35mg	607-610	3/29
8	40mg	611-614	4/5
9	45mg	615-618	4/26
10	50mg	619-622	5/10
11	60mg	623-626	5/17

The subjects of each group were observed through the 7th day of the study for evidence of intolerance before the next dose level was initiated.

RESULTS

Forty-four subjects were enrolled in the study. There were eleven dose levels. All subjects were dosed as scheduled. One subject (591, a placebo recipient) failed to return for evaluation and testing on study day 7 (7s) and was lost to follow-up.

Observations made in the various categories of the individual clinical summaries were tabulated as follows:

SYMPTOMS: Symptoms were uncommon and occurred with nearly equal frequency in drug and placebo groups as follows:

SYMPTOMS

	Drug Group		Placebo Group	
DOSE	SUBJECT NO.	SYMPTOM(S)	SUBJECT NO.	SYMPTOM(S)
1mg	585	1s(*)-gassiness 2s-headache 3s-muscle pain	583	1s-Muscle cramps, nausea 2s-stomach "cramps & and spasms"
15mg			591	1s-Diarrhea
25mg	600	1s-"not hungry"		
35mg	608	2s-"fatigue"		
40mg	612	2s-"slight sore throat"		
45mg	616	2s-"stomach felt upset"	617	2s-four semi-formed stools.
			618	2s-"appetite not up to par"
60mg			626	1s-vomited a few oz. of yellowish fluid 10 min. after taking capsules.

*s-Study day (eg, 1s is study day 1)

PHYSICAL FINDINGS: No abnormalities were found on physical examination in the drug or placebo groups during the study which could be attributed to study participation.

VITAL SIGNS: There were no significant abnormalities of the vital signs in either the drug or placebo groups.

LABORATORY DETERMINATIONS: Laboratory determinations were perfomed as scheduled except for: 1) Subject 591 who failed to return for sampling on 7s and 14s; 2) Group 11 had the samples scheduled for 14s drawn on 15s because of scheduling conflicts; 3) Subject 600 had the 7s sample obtained on 9s; and 4) Subject 608 had the 14s sample drawn on 15s. Subject 589 had a retic count of 2.3 on 14s; he returned on 4 Aug. when his retic. count was normal. Subject 622 had 1+ protein on 14s; he was unwilling to return for follow-up urinalysis.

In this study, each subject had blood obtained on study days 0, 2, 3, 7 and 14 for the scheduled array of laboratory tests. The detailed results of these tests are tabulated in the appendix. Each test result was judged to be high, low or normal according to whether it fell above, below or within the limits of the 95th percentile for that particular test as estimated from selected values from healthy subjects (appendices B, C and D).

In appendices B, C and D, the laboratory abnormalities are annotated (H=high, L=Low). The abnormal values are also recorded in the individual clinical summaries (appendix E).

Tables I and II show the number of subjects having at least one abnormally high or low laboratory value for the category of laboratory test listed after drug administration (tables of laboratory values in the appendix include pre-treatment values).

For each laboratory determination shown in Tables I and II, the Fisher's test statistic was calculated comparing the number of subjects with high or low values among the drug recipients with the corresponding numbers of subjects with abnormal values among the placebo recipients. The test statistic is shown if the P value is .05 or less.

TABLE I

NUMBERS OF SUBJECTS HAVING AT LEAST ONE ABNORMALITY OF THE BIOCHEMICAL MEASUREMENTS SHOWN IN DRUG AND PLACEBO STUDY GROUPS

TEST	DRUG		PLACEBO		FISHER'S TEST*	
	# High	# Low	# High	# Low	HIGH	LOW
GLUCOSE	2	1	2	1	NS+	NS
BUN	2	0	1	1	NS	NS
CREATININE	1	3	0	5	NS	NS
SODIUM	3	3	2	3	NS	NS
POTASS.	1	7	0	8	NS	NS
CHLORIDE	1	2	1	3	NS	NS
CO2	8	0	7	0	NS	NS
URIC ACID	2	6	0	4	NS	NS
T.PROTEIN	1	4	0	1	NS	NS
GLOBULIN	6	2	0	0	.01	NS
CALCIUM	0	5	0	5	NS	NS
PHOS.	3	1	5	0	NS	NS
CHOL.	2	1	2	1	NS	NS
TRIGLY.	1	0	3	2	NS	NS
ALK.PHOS.	0	0	0	0	NS	NS
SGOT	2	1	0	2	NS	NS
SGPT	3	0	3	1	NS	NS
LDH	0	3	0	4	NS	NS
T.BILI.	0	0	1	0	NS	NS

* Plot 50, Statistics, Vol 1, Tektronix, Inc. 1975,p 2-30. As employed here, 2x2 contingency tables for high and low values are constructed, e.g., URIC ACID

	# with High Abn.	# without	Totals	Fisher's Test
Drug Group	2	20	22	
Plac.Group	0	22	22	.24
Totals	2	42	44	

	# with Low Abn.	# without	Totals	Fisher's Test
Drug Group	6	16	22	
Plac.Group	4	18	22	.36
Totals	10	34	44	

+NS: P>.05

TABLE II

NUMBER OF SUBJECTS WITH HIGH OR LOW ABNORMALITIES OF BLOOD COUNTS, METHEMOGLOBIN AND HAPTOGLOBIN

TEST	DRUG		PLACEBO		FISHER'S TEST*	
	# High	# Low	# High	# Low	High	Low
HCT	3	2	2	2	NS+	NS
HGB	1	2	0	1	NS	NS
RBC	2	1	1	1	NS	NS
WBC	0	6	2	2	NS	NS
LYMPHS	6	0	8	1	NS	NS
SEGS	0	4	1	5	NS	NS
MONOS	0	0	2	0	NS	NS
EOS	2	0	4	1	NS	NS
MCV	2	1	1	0	NS	NS
MCH	1	2	0	0	NS	NS
MCHC	0	12	0	13	NS	NS
PLATELETS	0	0	3	0	NS	NS
RETIC.	4	0	1	0	NS	NS
HAPTOGL.	2	0	2	1	NS	NS
METHEMGL.	0	0	0	0	NS	NS

* as in Table I.
+NS:P>0.05

DISCUSSION

Phase I clinical studies of WR6026 2HCl were undertaken to identify safety and tolerance factors with a single oral dose. It was originally planned to start at a dose of 1 mg per subject, to increase the dose to 5 mg and then add 5 mg per dose level up to 30 mg. Symptoms of intolerance had been seen when the drug had been given at 30 mg/day (in the WWII studies) and animal studies had suggested the possibility of methemoglobinemia. In this extended study, the dose was raised to 60 mg/subject without encountering signs or symptoms of intolerance of a degree that would preclude administration of this drug to a patient for the treatment of Leishmaniasis.

In view of earlier studies studies of this drug using human subjects, symptoms were surprisingly mild. Muscle pain, a prominent feature of earlier studies, was seen in only one subject and that at the 1 mg dose level. Gastrointestinal symptoms were more prominent in the placebo subjects than in those receiving drug. None of the symptoms seen in the subjects receiving drug was debilitating nor considered to be a contraindication to the use of the drug at the respective dose level.

Physical examinations and recorded vital signs showed no signs of clinical problems in these subjects during the study.

In the absence of definitive signs or symptoms of drug intolerance in this study, the laboratory studies become critical in assessing the relative risk of drug administration. Laboratory studies were considered as follows.

In studies of this type, the convention has evolved that in order to place a minimal number of subjects at risk, only four subjects are enrolled at each dose level. Of these four, two receive drug and two receive placebo. In the event of ambiguity or uncertainty of the results, the drug level may be repeated. In the absence of untoward reactions, four more subjects are employed for study of the next dose level. This general type of experimental design has over the past ten years been demonstrated safe for human subjects in the context of the drugs studied at the doses given, and this design has produced useful data leading to further study and successful drug development.

However, the design--in statistical terms--is not robust. The number of independent observations at each dose level is

so small that no meaningful statistical statement can be made about the "significance" of any observed outcome at any single dose level. If formal statistical procedures are to be employed then certain constraints are imposed on the treatment of the data. Only observations about individual subjects can be treated as independent observations. It must be emphasized that multiple observations of the same variable in a given subject (such as multiple determinations of blood glucose) are not independent of one another and contribute little or nothing to statistical power.

These considerations led us 1) to combine all observations as either "Drug" or "Placebo", regardless of dose level since individual dose levels have prohibitively small numbers of independent observations and 2) to express observations in terms of numbers of subjects with and without abnormalities and whether the abnormalities that occur are high or low in regard to each specific laboratory test.

For the purposes of this study, we have re-defined our criteria for laboratory abnormalities. Previously, we have defined abnormal values as those values falling more than two standard deviations from the mean (derived from BIO-MED data) for any particular laboratory determination. It is clear that many of the test results do not follow a Gaussian distribution. We have elected to use the percentile method for establishing laboratory norms, which does not depend upon any assumptions about the distribution of the data from any particular test.

Using these criteria for characterization of data as "normal" or "abnormal", we can identify which individuals had abnormal laboratory tests (after administration of the drug) and whether these abnormalities were "high" or "low". Individuals with abnormal values may then be further classified according to whether they received drug or placebo. The differences in the occurrence of subjects with abnormalities in the drug and placebo groups may be compared statistically using Fisher's test for significant differences. This procedure was used with the laboratory data from this study. Outcomes and tests for the statistical significance of these results are shown in Tables I and II.

Of all the laboratory tests, only serum globulin was abnormally high in a significantly greater ($p<.05$) number of subjects receiving drug than in subjects receiving placebo (six receiving drug vs. none receiving placebo). Of the six subjects who received drug, three also had elevations of the

serum globulin before receiving the drug, thus casting doubt on the apparent drug effect. There was a trend toward lower white blood cell counts and higher reticulocyte counts in the drug recipients (Table II); the differences were not statistically significant, nor were they clinically significant in any individual case.

Blood specimens for ordinary laboratory measurements were also examined for methemoglobin. Methemoglobin was not detected in any subject over the course of the study. Positive controls used at the test facility assure us that clinically relevant levels of methemoglobin would have been detected.

Haptoglobin levels were measured assuming that with hemolysis, haptoglobin would combine with the resulting free hemoglobin and that complex would rapidly be removed from circulating blood by the liver, resulting in a lowered haptoglobin. Haptoglobin levels for all subjects over the course of the study are presented in appendix D. Abnormally low levels of haptoglobin were seen in only one subject, a placebo recipient.

In summary, the laboratory abnormalities seen were minimal or inconsistent or in the case of serum globulin, of doubtful significance. Nevertheless, in future clinical studies of this drug, subjects should be observed for changes in serum globulin. The white blood cell count and the reticulocyte count may also be carefully observed in future studies.

SUMMARY

WR 6026 2HCl or a placebo was given by mouth to 44 human subjects in a 2x2 double blind, rising dose level study. Doses began at 1 mg, the study was stopped after dose of 60 mg. No clinically significant symptoms were seen in subjects receiving the drug and no abnormal physical findings nor abnormalities of the vital signs were seen. Laboratory studies showed no clear evidence of clinically significant drug effect. Abnormalities in serum globulin were seen in six subjects receiving the drug. Marginal elevations in the reticulocyte count and reductions in the white blood cell count suggest to us that these variables be closely monitored in future studies. This drug is well tolerated in single oral doses up to 60 mg/dose.

It is concluded that single oral doses of up to and including 60 mg of the preparation of WR 6026 2HCl provided for this experiment may safely be given to healthy individuals. Subjects with Glucose-6-phosphate dehydrogenase deficiency were not observed in this study, but this drug must be presumed unsuitable for use in such subjects. Tolerance and acceptability of the drug may reasonably be expected in clinical use.

APPENDIX

TABLE OF CONTENTS

APPENDIX A

NORMAL LABORATORY VALUES AS DEFINED BY THE PERCENTILE METHOD

CHEMISTRIES

VARIABLE	LOWER-UPPER LIMITS OF NORMAL*	UNITS
GLUCOSE	72.3 - 109.5	mg/dl
BUN	6.9 - 20.4	mg/dl
CREATININE	0.82 - 1.50	mg/dl
SODIUM	135.6 - 143.6	mEq/L
POTASSIUM	3.64 - 5.43	mEq/L
CHLORIDE	97.9 - 107.4	mEq/L
CARBON DIOX.	24.5 - 32.1	mEq/L
URIC ACID	3.84 - 7.76	mg/dl
CALCIUM	8.99 - 10.74	mg/dl
PHOSPHATE	2.44 - 4.97	mg/dl
CHOLESTEROL	123.8 - 227.8	mg/dl
TRIGLYCERIDES	31.2 - 268.6	mg/dl
SGOT	11.6 - 37.1	U/L
SGPT	5.1 - 45.2	U/L
BILIRUBIN TOTAL	0.17 - 1.29	mg/dl
ALKALINE PHOS.	37.8 - 129.4	U/L
LDH	116.4 - 244.2	U/L
TOT. PROTEIN	6.02 - 8.13	g/dl
GLOBULIN	1.88 - 3.36	g/dl

*Derived from laboratory values of 200 normal subjects according to the method of Mainland +.

+ Mainland, D., Clinical Chemistry, Vol. 17, No. 4, 1971, p. 267-274.

APPENDIX A (cont)

NORMAL LABORATORY VALUES AS DEFINED BY THE PERCENTILE METHOD

HEMATOLOGY VALUES

VARIABLE	LOWER-UPPER LIMITS OF NORMAL*	UNITS
HEMATOCRIT	39.58 - 50.64	Vol%
HEMOGLOBIN	13.38 - 17.49	GMS%
RED CELL COUNT	4.34 - 5.73	$10^6/mm^3$
MCV	80.47 - 99.12	CuMicr.
MCH	27.04 - 33.86	mmgm
MCHC	32.57 - 35.46	%Hgb
WHITE BLOOD CELLS	4.16 - 9.89	$10^3/mm^3$
LYMPHOCYTES	18.64 - 46.74	%WBC
NEUTROPHILES	38.59 - 73.05	%WBC
MONOCYTES	1.36 - 12.08	%WBC
PLATELETS	147.78 - 346.13	$10^3/mm^3$
EOSINIPHILES	0.70 - 7.74	%WBC
RETICULOCYTES	0.28 - 1.92	%RBC
HAPTOGLOBIN	18.7 - 150.8	mg/dl

*derived from laboratory values of 200 normal subjects according to the method of Mainland +.

+ Ibid.

APPENDIX B

SUBJ CODE NO	STUDY DAY	GLUC	BUN	CREAT	NA	K	CL	CO2	URIC ACID	CA	PO4	CHOL	TRIG	SGOT	SGPT	TOTAL BILI	ALKA PHOS	LDH	TOTAL PROT	GLOB	DRUG OR PLACEBO
583																					
	- 6	88	13	1.1	137	3.9	98	29	6.8	10.2	3.8	227	79	38H	25	1.2	69	231	8.2H	3.3	P
	0	85	11	1.1	140	4.8	99	31	5.7	10.3	3.8	202	71	41H	30	1.0	61	193	7.8	3.2	
	2	94	13	0.9	138	4.1	103	28	6.2	9.6	5.4H	188	83	28	27	0.5	63	148	7.2	3.0	
	3	96	14	1.2	139	4.8	101	31	6.4	10.2	5.4H	214	82	34	27	0.7	60	176	7.5	3.1	
	14	85	18	1.3	140	4.0	100	29	7.0	9.8	4.3	204	60	37	34	1.1	58	167	7.4	3.1	
584																					
	- 6	78	16	1.0	139	4.0	99	29	6.7	10.2	3.5	176	54	23	31	0.7	77	199	7.6	2.3	P
	0	81	20	1.1	140	4.3	99	31	6.2	10.3	3.9	189	62	29	33	0.8	75	174	7.2	2.2	
	2	93	16	1.0	139	4.7	102	32	6.1	9.7	4.5	190	80	20	34	0.5	78	134	6.8	2.2	
	3	96	15	1.2	141	4.2	101	30	6.2	10.3	4.3	203	95	23	52H	0.7	78	145	7.3	2.3	
	7	86	19	1.1	141	4.0	101	28	6.4	9.7	3.6	175	76	21	33	0.5	83	189	6.9	2.1	
	14	93	14	1.0	141	4.7	99	32	6.5	10.1	3.1	199	110	29	39	0.8	82	174	7.1	2.3	
585																					
	- 6	89	14	1.0	139	4.3	99	30	6.4	9.7	3.8	171	82	16	17	0.7	52	150	7.3	2.4	1 MG
	0	83	14	1.3	142	4.2	100	31	6.1	9.6	4.0	171	77	18	19	1.0	51	112L	6.9	2.3	
	2	84	14	1.0	138	4.1	100	31	6.0	9.7	4.3	176	79	20	26	0.8	55	118	7.0	2.4	
	3	82	17	1.2	143	4.4	102	31	6.3	9.6	4.8	170	82	17	38	0.7	52	129	7.0	2.4	
	7	87	13	1.1	143	4.1	99	31	6.3	10.2	4.1	176	77	16	18	0.9	53	147	7.4	2.5	
	14	91	10	1.2	141	4.4	99	33H	7.3	9.8	3.9	176	75	20	19	1.1	55	146	7.1	2.5	
586																					
	- 6	97	18	1.0	138	4.2	99	28	6.2	9.9	4.1	188	98	29	38	0.5	58	174	7.5	2.5	1 MG
	0	93	11	1.1	138	4.2	99	27	6.5	9.5	3.7	159	49	23	20	0.6	62	180	6.7	2.1	
	2	100	14	0.9	139	4.6	103	29	5.2	9.4	4.3	154	76	18	18	0.4	58	126	6.0L	2.0	
	3	98	15	1.1	142	4.9	102	32	5.4	9.5	4.5	162	89	17	41	0.4	53	130	6.2	2.1	
	7	87	13	1.1	144H	5.0	105	29	6.5	9.6	4.3	159	83	13	19	0.3	51	137	6.2	2.0	
	14	99	12	1.1	142	4.7	105	31	6.5	9.3	4.0	154	134	20	19	0.7	51	128	6.0L	1.9	
587																					
	- 13	94	10	1.1	137	3.7	99	29	6.0	9.9	4.2	142	42	16	6	1.0	96	134	7.9	3.1	P
	0	88	18	1.2	136	4.2	97L	28	6.0	9.4	4.5	128	44	12	11	0.7	98	126	7.3	3.0	
	2	93	12	1.2	138	4.1	99	29	4.8	9.5	5.1H	124	91	15	9	0.4	96	107L	7.2	2.9	
	3	92	13	1.2	139	4.2	98	31	5.5	9.6	5.7H	126	78	27	14	0.5	94	121	7.1	2.9	
	7	95	16	1.2	137	4.2	99	30	6.2	9.8	4.6	138	58	23	11	0.6	93	133	7.3	3.0	
	14	92	12	1.2	136	4.3	99	29	6.9	9.4	4.0	138	29L	13	11	1.2	97	101L	7.4	2.9	
588																					
	- 6	97	10	1.1	141	3.8	108H	30	6.1	9.3	3.7	140	70	[illegible]	17	0.3	56	140	6.7	2.7	P
	0	80	15	1.1	141	3.7	100	29	6.7	9.7	4.1	148	76	21	16	0.3	59	170	7.1	2.8	
	2	85	11	1.0	140	4.2	101	30	6.1	10.0	3.2	180	103	24	20	0.5	60	153	7.4	3.1	
	3	90	16	1.1	139	4.5	100	31	6.3	9.6	3.5	177	78	37	24	0.3	59	139	7.1	3.0	
	7	85	8	1.1	140	3.6L	101	29	6.9	8.8L	3.6	156	62	26	23	0.4	62	153	6.5	2.6	
	14	97	10	1.1	139	3.9	102	29	6.6	8.8L	3.3	164	158	18	16	0.3	61	123	6.7	2.6	
589																					
	- 5	92	13	0.9	139	3.5L	98	33H	7.1	9.0	5.4H	184	124	17	18	0.4	58	136	6.9	2.6	5 MG
	0	91	11	1.1	142	3.8	98	30	6.6	10.2	5.5H	200	113	16	18	0.4	60	171	7.6	2.8	
	2	90	16	1.2	140	3.6L	99	28	5.7	9.6	5.5H	206	169	20	24	0.3	58	160	7.0	2.6	
	3	89	18	1.1	144H	4.0	100	32	6.3	9.9	6.2H	219	231	37	34	0.4	57	165	7.5	3.0	
	7	93	17	1.2	145H	4.5	105	30	8.1H	9.5	4.9	196	85	32	42	0.4	61	183	7.0	2.6	
	14	94	7	1.2	141	4.6	102	31	7.1	9.1	4.2	198	103	17	22	0.7	62	154	7.0	2.4	
590																					
	- 6	91	7	1.1	140	3.7	103	30	6.2	10.0	4.3	234H	69	17	12	0.9	75	131	7.5	2.9	5 MG
	0	91	14	1.0	140	4.2	98	31	8.1H	9.5	4.1	228H	60	11L	11	0.8	66	137	7.0	2.5	
	2	98	9	0.9	138	4.2	99	31	5.4	9.6	3.9	230H	57	15	13	0.5	65	134	6.9	2.6	
	3	99	14	1.0	140	4.6	99	32	5.7	9.6	4.3	219	50	19	16	0.4	71	145	6.7	2.5	
	7	82	9	0.9	139	3.6L	98	30	6.7	9.3	3.8	235H	40	21	22	0.8	73	154	6.9	2.6	
	14	112H	8	1.0	139	4.2	102	29	5.8	8.7L	4.1	213	51	14	14	0.4	72	121	6.5	2.2	
591																					
	- 20	90	11	0.9	140	4.3	101	29	7.1	10.5	4.0	163	104	18	28	0.7	109	192	7.7	2.5	P
	0	87	13	1.0	142	4.5	105	29	10.5H	9.5	3.1	140	85	22	21	0.6	105	151	6.7	2.3	
	2	99	11	1.0	142	4.2	106	29	5.9	9.4	4.8	140	63	14	19	0.3	99	128	6.5	2.1	
	3	91	16	0.9	141	4.0	104	29	6.4	10.0	4.7	146	105	18	15	0.4	113	150	7.1	2.2	
592																					
	- 20	89	12	0.9	139	4.2	100	31	4.1	9.3	4.8	158	57	11L	7	0.3	67	140	6.9	2.2	15 MG
	0	88	13	1.1	139	3.9	96L	32	5.4	10.0	4.7	181	87	21	22	0.6	76	140	7.6	2.7	
	2	95	10	1.1	135L	3.5L	100	27	3.9	9.5	3.6	170	37	23	34	0.5	112	121	7.9	3.5H	
	3	90	15	1.0	141	4.3	102	32	4.5	9.6	4.6	168	79	15	11	0.4	58	119	6.9	2.1	
	7	94	11	1.0	139	4.0	98	31	4.6	9.6	4.4	186	90	15	19	0.7	69	121	7.3	2.3	
	14	91	11	1.1	139	3.9	99	30	4.7	9.9	4.7	184	117	13	20	0.6	74	126	7.1	2.3	

H - HIGH
L - LOW

SUBJ CODE NO	STUDY DAY	GLUC	BUN	CREAT	NA	K	CL	CO2	URIC ACID	CA	PO4	CHOL	TRIG	SGOT	SGPT	TOTAL BILI	ALKA PHOS	LDH	TOTAL PROT	GLOB	DRUG DOSE C PLACEBO (P)
593																					
	- 6	101	12	1.0	138	4.6	103	27	5.4	9.0	3.2	189	46	23	25	0.3	66	209	6.7	2.5	P
	0	83	11	1.0	140	4.8	102	29	6.3	9.5	3.1	206	66	26	23	0.4	84	183	7.0	2.5	
	2	101	11	1.0	139	4.2	103	29	4.7	9.3	3.9	219	123	20	24	0.4	65	154	7.0	2.6	
	3	102	18	1.1	141	4.7	103	29	4.9	10.0	4.3	232H	128	24	10	0.4	75	159	7.1	2.5	
	7	90	10	1.1	138	4.7	102	28	5.8	9.1	2.8	205	45	19	21	0.8	70	161	6.9	2.4	
	14	93	9	1.1	139	4.5	103	27	5.7	9.6	2.6	214	122	18	22	0.7	68	176	6.9	2.4	
594																					
	- 6	84	11	1.0	137	3.9	99	27	4.9	9.4	3.7	186	38	22	32	0.7	98	167	7.9	3.5H	15 MG
	0	97	9	1.0	139	4.3	102	30	4.5	9.6	3.3	166	43	22	27	0.8	110	117	7.7	3.4H	
	2	89	12	1.0	140	4.3	101	32	4.0	9.3	4.5	167	68	14	17	0.3	59	123	6.9	2.2	
	3	94	10	1.1	138	4.1	98	31	4.1	10.1	4.2	181	41	26	31	0.6	104	117	8.2H	3.6H	
	7	98	10	1.1	136	4.1	98	29	4.8	9.3	3.9	175	33	22	29	1.2	104	116L	7.9	3.3	
	14	90	10	1.1	139	3.6L	100	28	4.4	9.7	4.7	161	35	24	26	0.5	114	135	7.9	3.3	
595																					
	- 13	96	13	1.1	140	3.8	101	30	6.3	9.9	3.1	192	123	11L	16	1.3H	71	170	8.0	3.1	P
	0	107	13	1.1	144H	4.4	104	31	3.7L	9.9	3.4	134	51	18	24	0.3	75	139	7.2	2.7	
	2	98	14	1.0	143	3.6L	105	29	4.6	9.2	3.7	156	92	15	20	0.4	64	137	6.9	2.7	
	3	95	11	1.0	143	3.8	105	29	4.9	9.1	3.6	161	90	21	26	0.3	59	136	6.9	2.6	
	7	88	14	1.1	142	3.8	105	28	4.9	8.9L	3.5	159	73	16	20	0.4	70	153	6.8	2.6	
	14	94	19	0.8L	140	3.9	100	30	5.2	9.6	3.4	160	93	33	48H	0.8	62	159	7.1	2.7	
596																					
	- 6	92	10	1.0	143	4.1	101	30	5.7	9.9	3.2	171	80	14	17	0.6	73	139	7.2	2.4	P
	0	111H	16	1.1	141	4.2	104	29	6.2	9.7	3.3	145	106	17	15	1.1	71	141	6.8	2.1	
	2	97	14	1.1	144H	4.1	106	27	4.9	9.5	5.3H	147	93	12	11	0.5	69	133	6.7	2.2	
	3	98	11	1.1	140	3.9	105	26	5.1	9.6	4.2	145	81	15	15	0.5	64	126	6.9	2.2	
	7	97	16	1.1	141	3.9	105	26	5.5	9.3	3.4	144	72	16	13	0.6	69	146	6.8	2.2	
	14	89	15	0.8L	140	4.3	100	28	5.7	9.7	3.8	149	58	19	18	0.5	78	140	6.8	2.3	
597																					
	- 6	92	11	1.2	140	4.2	101	30	5.0	9.6	3.6	166	92	13	29	0.4	87	133	7.4	3.1	20 MG
	0	95	17	1.2	139	4.2	103	28	5.1	9.6	3.6	161	118	14	27	0.2	86	137	7.2	2.9	
	2	101	13	1.3	140	3.9	104	29	4.7	9.5	5.1H	177	102	16	34	0.2	83	120	7.0	3.0	
	3	105	10	1.3	138	4.0	100	27	5.2	9.4	5.2H	174	113	17	39	0.2	85	126	7.2	3.0	
	7	95	12	1.4	139	4.0	102	29	6.3	9.5	4.3	188	87	22	47H	0.5	92	150	7.3	3.0	
	14	85	12	1.1	139	4.3	99	29	5.4	9.7	3.7	177	106	22	41	0.4	84	141	7.2	3.0	
598																					
	- 6	90	13	1.0	140	4.2	101	28	7.6	9.8	4.5	179	331H	20	32	0.6	94	145	7.3	2.9	20 MG
	0	87	16	0.9	139	5.0	100	28	5.9	10.1	4.7	176	178	17	26	0.4	97	160	7.5	2.9	
	2	90	18	1.0	137	4.1	101	27	5.7	9.8	5.0H	202	387H	21	27	0.4	84	131	7.4	2.9	
	3	94	15	0.9	136	4.3	103	26	5.8	9.6	4.6	196	272H	29	38	0.3	84	132	7.3	2.8	
	7	80	15	1.1	139	3.9	101	25	7.9H	9.6	4.8	202	147	24	34	0.6	93	194	7.6	2.9	
	14	92	14	0.8L	138	4.0	101	26	7.4	9.4	4.3	182	302H	23	27	0.5	94	172	7.1	3.0	
599																					
	- 12	75	9	1.4	138	3.9	100	28	7.3	9.2	2.6	149	79	18	12	0.6	123	198	8.1	3.7H	25 MG
	0	82	12	1.2	136	4.1	98	30	6.6	9.4	3.3	136	76	19	15	0.5	124	184	7.9	3.5H	
	2	97	13	1.3	140	4.2	104	30	6.5	9.9	4.2	146	97	20	16	0.6	120	163	8.1	3.8H	
	3	92	11	1.4	137	4.1	102	29	5.6	9.3	4.2	150	84	17	18	0.4	116	184	8.0	3.7H	
	7	60L	14	1.3	138	4.0	102	30	6.2	9.4	2.7	136	95	20	21	0.6	113	184	7.9	3.6H	
	14	81	14	1.3	138	3.9	104	31	7.1	9.3	3.6	132	66	20	17	0.4	121	205	7.9	3.7H	
600																					
	- 6	84	14	1.1	140	4.7	104	29	5.0	9.4	4.4	142	45	37	28	0.4	61	175	7.1	2.7	25 MG
	0	82	14	1.1	142	5.0	100	29	5.7	10.3	4.1	143	49	22	24	0.6	76	212	7.8	2.9	
	2	91	11	1.1	148H	4.8	108H	30	4.9	10.2	4.7	148	54	21	21	0.9	68	158	7.3	2.8	
	3	92	12	1.3	139	4.0	104	29	3.9	9.2	4.9	142	47	12	20	0.5	66	143	7.0	2.7	
	9	90	12	1.0	138	4.5	101	29	4.0	9.4	3.6	154	68	14	10	0.5	67	168	7.3	2.9	
	14	95	13	0.9	141	4.1	103	31	3.7L	9.9	4.6	149	99	18	27	0.3	73	160	7.4	2.8	
601																					
	- 20	92	9	1.0	140	4.0	101	30	5.2	10.0	3.8	170	131	13	23	0.6	79	128	7.3	2.6	P
	0	87	8	0.9	137	4.1	98	30	5.2	9.3	3.9	155	111	15	18	0.7	75	151	6.6	2.4	
	2	102	11	1.0	142	4.1	106	29	4.9	10.2	5.6H	184	221	18	19	0.7	90	127	7.0	2.6	
	3	92	10	1.1	137	3.7	101	27	4.4	9.4	5.2H	176	110	17	23	0.5	84	137	7.0	2.6	
	7	88	13	1.1	138	3.9	101	28	5.4	9.7	3.9	186	67	15	20	1.5H	77	132	6.9	2.5	
	14	82	12	1.1	140	3.7	105	30	6.6	9.6	4.0	175	97	17	16	0.9	81	152	7.0	2.6	
602																					
	- 6	82	9	1.2	138	4.3	103	29	5.4	9.2	3.4	133	37	27	20	0.5	69	218	7.3	3.0	P
	0	83	12	1.1	139	3.9	101	28	5.1	9.4	3.7	139	42	35	27	0.5	75	243	7.3	2.8	

H - HIGH
L - LOW

SUBJ CODE NO	STUDY DAY	GLUC	BUN	CREAT	NA	K	CL	CO2	URIC ACID	CA	PO4	CHOL	TRIG	SGOT	SGPT	TOTAL BILI	ALKA PHOS	LDH	TOTAL PROT	GLOB	DRUG DOSE PLACEBO (S
	2	81	10	1.1	141	3.9	104	28	5.6	9.5	3.6	147	56	26	24	0.7	78	175	7.1	2.9	
	3	89	9	1.3	137	3.9	103	28	4.5	9.1	3.5	147	50	15	24	0.5	78	162	7.2	3.0	
	7	81	16	1.1	138	3.6L	104	28	5.0	9.1	3.4	138	36	31	26	0.8	83	227	6.9	2.8	
	14	89	10	1.0	139	4.1	106	31	4.8	9.3	3.7	141	42	19	24	0.2	78	173	7.3	3.1	
603																					
	- 6	88	15	1.2	138	3.9	99	31	6.1	9.4	3.9	151	75	23	35	0.7	55	129	6.5	1.8L	30 MG
	0	83	18	1.4	139	3.9	99	29	7.4	9.3	4.2	153	139	17	24	0.6	64	153	6.7	2.1	
	2	101	21H	1.6H	139	3.9	100	30	5.8	9.0	3.7	158	118	14	16	0.4	60	126	6.4	2.1	
	3	91	21H	1.1	139	4.1	95L	33H	5.8	9.0	3.8	163	140	15	29	0.5	50	127	6.0L	1.8L	
	7	98	21H	1.1	140	3.7	104	32	6.6	9.3	3.5	153	86	16	26	0.7	57	137	6.5	2.0	
	14	90	18	1.0	139	4.1	100	29	5.8	9.2	4.1	134	207	14	14	0.3	73	156	6.3	2.0	
604																					
	- 6	97	16	1.1	137	3.7	99	30	4.7	9.6	3.6	140	67	18	21	0.5	78	123	7.5	2.7	P
	0	94	16	1.0	136	3.5L	100	29	4.1	9.7	3.5	140	47	24	28	0.7	82	159	7.2	2.7	
	2	97	14	0.9	137	3.7	101	30	3.9	8.8L	4.1	133	51	15	13	0.4	80	141	6.9	2.7	
	3	86	15	1.0	139	4.4	95L	33H	4.0	9.4	4.1	139	60	13	24	0.4	72	144	6.9	2.5	
	7	104	15	1.1	139	3.5L	103	31	5.2	9.3	3.8	131	63	25	30	0.6	82	157	7.5	2.9	
	14	98	17	1.0	136	4.1	99	30	4.6	9.1	3.6	141	67	12	18	0.4	83	146	7.5	3.1	
605																					
	- 27	77	17	1.0	145H	4.3	101	33H	7.1	9.9	3.5	229H	201	25	53H	0.6	47	151	6.9	2.0	30 MG
	0	80	14	1.1	139	3.9	101	36H	6.8	9.2	3.5	139	121	21	31	0.6	57	175	6.3	2.0	
	2	84	11	1.3	141	4.0	102	32	5.0	9.4	4.0	164	257	20	35	0.4	56	169	6.4	2.1	
	3	84	13	1.1	140	4.5	95L	34H	5.6	9.9	4.1	174	158	26	60H	0.5	52	168	6.3	1.9	
	7	84	16	1.3	142	3.9	104	32	6.7	9.4	3.7	163	112	21	46H	0.7	61	173	6.4	2.0	
	14	85	15	1.1	139	4.0	102	29	6.3	9.1	3.9	155	121	11L	27	0.6	54	148	6.2	2.1	
606																					
	- 62	94	10	1.1	137	3.7	99	29	6.0	9.9	4.2	142	42	16	6	1.0	96	134	7.9	3.1	P
	0	88	14	1.1	136	3.8	100	29	5.3	9.1	3.7	120L	38	16	13	0.7	86	112L	6.5	2.5	
	2	96	11	1.1	136	4.1	98	31	4.3	9.0	4.3	121L	53	14	8	0.6	86	90L	6.8	2.8	
	3	87	12	1.2	139	4.3	94L	32	4.9	9.7	4.4	133	50	11L	14	0.7	84	121	6.9	2.6	
	7	97	17	1.3	141	3.6L	105	32	6.5	9.2	4.5	120L	25L	19	19	0.6	93	129	7.1	2.8	
	14	78	11	1.2	139	3.8	102	27	5.7	9.0	4.4	124	19L	15	9	0.9	93	123	6.6	2.7	
607																					
	- 6	89	10	1.0	136	4.0	101	30	5.9	9.5	3.5	229H	85	33	39	0.4	76	171	7.7	3.4H	35 MG
	0	72L	11	0.9	138	3.8	100	30	4.8	9.4	3.5	214	87	22	38	0.5	76	138	7.4	3.2	
	2	84	16	1.0	135L	3.6L	99	28	5.0	8.8L	3.7	217	87	21	33	0.5	73	144	7.1	3.0	
	3	92	12	0.9	139	3.9	105	27	4.5	9.2	3.1	220	86	21	35	0.4	70	109L	7.2	3.0	
	7	85	12	0.8L	140	3.8	103	31	6.3	9.1	3.6	197	143	24	30	0.4	72	154	7.2	3.2	
	14	95	9	1.0	138	3.9	101	31	4.9	9.3	3.4	241H	90	26	44	0.6	75	142	7.5	3.3	
608																					
	- 48	92	9	1.0	140	4.0	101	30	5.2	10.0	3.8	170	131	13	23	0.6	79	128	7.3	2.6	35 MG
	0	97	12	1.1	137	4.1	100	28	5.2	9.3	4.4	168	76	17	20	0.6	90	151	6.5	2.4	
	2	92	12	1.0	135L	3.8	102	26	4.3	8.6L	4.4	153	111	12	11	0.3	85	139	6.1	2.2	
	3	90	9	1.0	140	3.9	102	31	4.2	9.5	4.5	171	128	19	16	0.4	86	138	6.7	2.4	
	7	89	12	1.0	139	4.0	104	30	5.4	9.4	3.3	162	85	18	11	1.2	82	151	6.7	2.6	
	15	95	14	1.1	140	3.9	102	30	5.0	9.6	4.3	182	74	15	13	0.6	94	108L	6.9	2.4	
609																					
	- 86	97	10	1.1	141	3.8	108H	30	6.1	9.3	3.7	140	70	22	17	0.3	56	140	6.7	2.7	P
	0	65L	9	1.1	137	4.0	99	31	5.0	9.4	2.6	146	87	21	24	0.3	66	145	6.8	2.8	
	2	105	13	1.0	135L	4.3	98	29	4.9	8.9L	3.6	166	90	21	17	0.3	62	150	6.9	2.8	
	3	90	14	0.9	142	4.5	103	31	5.1	9.9	3.9	180	65	27	23	0.3	65	114L	7.5	2.9	
	7	91	10	1.0	141	3.9	105	31	6.0	9.2	3.6	143	77	28	23	0.5	67	148	6.8	2.9	
	14	89	10	1.0	136	3.6L	99	31	5.5	9.0	3.2	150	75	21	12	0.5	64	145	6.9	2.9	
610																					
	- 83	94	10	1.1	137	3.7	99	29	6.0	9.9	4.2	142	42	16	6	1.0	96	134	7.9	3.1	P
	0	97	13	1.3	138	4.2	100	30	6.0	9.4	4.4	129	64	8L	11	0.9	103	118	6.9	2.8	
	2	92	13	1.2	133L	4.1	96L	31	4.4	8.4L	4.7	125	78	10L	4L	0.7	91	103L	6.3	2.4	
	3	93	11	1.1	138	4.3	99	33H	4.7	9.4	4.6	134	52	17	9	0.8	90	71L	6.8	2.5	
	7	94	21H	1.4	137	4.3	102	30	5.5	9.4	4.5	132	78	16	16	1.0	97	112L	7.3	3.0	
	14	87	11	1.2	140	3.8	102	31	6.1	9.0	4.6	126	57	16	14	0.5	89	98L	6.6	2.6	
611																					
	- 6	91	13	0.9	139	4.0	101	32	5.2	9.1	3.3	143	54	16	17	0.4	92	125	5.6L	1.6L	40 MG
	0	107	13	0.8L	139	4.4	101	32	4.7	9.8	3.4	167	95	24	26	0.6	111	167	6.7	2.2	
	2	97	18	1.0	139	4.6	100	33H	4.2	9.2	4.4	183	143	19	25	0.3	103	133	5.8L	1.7L	
	3	100	14	1.1	145H	5.6H	99	33H	3.4L	9.5	4.4	175	101	16	27	0.3	95	117	5.8L	1.7L	
	7	87	13	1.0	139	3.9	102	32	4.8	9.2	3.7	135	96	22	34	0.4	100	154	5.8L	1.8L	
	14	96	15	0.9	142	4.2	102	33H	5.3	9.0	3.4	137	77	14	16	0.2	103	130	5.7L	1.8L	

H - HIGH
L - LOW

SUBJ CODE NO	STUDY DAY	GLUC	BUN	CREAT	NA	K	CL	CO2	URIC ACID	CA	PO4	CHOL	TRIG	SGOT	SGPT	TOTAL BILI	ALKA PHOS	LDH	TOTAL PROT	GLOB	DRUG DOSE OR PLACEBO (P)
612																					
	- 6	83	12	0.8L	140	4.0	101	33H	5.0	9.4	4.1	164	81	16	19	0.5	117	131	6.4	1.9	P
	0	89	13	0.8L	141	4.9	103	33H	4.6	9.6	4.8	151	132	18	14	0.2	119	139	6.8	2.5	
	2	90	17	0.8L	141	5.1	101	33H	4.3	9.1	5.3H	157	82	19	26	0.2	112	140	6.3	2.1	
	3	101	12	0.9	147H	5.4	99	33H	3.3L	9.5	5.0H	161	71	17	22	0.3	109	139	6.4	2.1	
	7	86	11	0.8L	142	4.4	102	33H	5.4	9.4	3.9	160	99	23	29	0.5	122	160	6.7	2.4	
	14	91	14	0.8L	142	4.7	100	32	5.9	9.6	3.8	166	89	20	22	0.5	122	156	6.8	2.4	
613																					
	- 6	88	12	1.0	138	4.1	100	31	6.1	9.2	3.9	172	48	17	11	0.8	80	169	6.9	2.7	P
	0	100	18	1.2	140	4.2	105	31	6.8	9.4	4.1	167	73	18	8	0.8	69	170	6.9	2.8	
	2	95	12	1.0	138	4.6	100	33H	4.6	8.9L	4.2	175	172	20	14	0.3	69	171	6.5	2.6	
	3	95	9	1.0	142	4.5	100	30	3.6L	9.2	4.4	174	114	18	17	0.4	67	161	6.5	2.5	
	7	90	12	1.0	137	4.1	100	31	6.3	9.1	3.6	179	71	23	23	0.7	70	153	6.6	2.7	
	14	86	13	1.0	138	4.1	100	30	6.7	9.1	3.9	183	67	20	10	0.5	77	179	6.8	2.7	
614																					
	- 6	86	10	1.0	139	4.1	100	32	3.4L	9.5	3.7	186	74	18	27	0.9	65	154	7.3	3.0	40 MG
	0	91	9	0.9	139	3.7	103	32	3.6L	9.7	3.7	188	71	21	35	1.0	65	149	7.8	3.6H	
	2	89	12	0.8L	137	4.2	99	33H	3.8L	9.4	4.9	203	131	22	35	0.7	66	143	7.4	3.3	
	3	95	9	0.9	142	4.3	99	31	2.8L	9.7	4.4	185	87	18	32	0.8	61	144	7.2	3.0	
	7	89	8	0.9	137	4.1	100	32	3.9	9.4	4.0	178	96	16	30	0.9	67	149	7.2	3.2	
	14	88	13	0.9	139	3.9	99	31	4.6	9.6	4.1	196	80	17	24	1.0	74	146	7.7	3.4H	
615																					
	- 60	97	10	1.1	141	3.8	108H	30	6.1	9.3	3.7	140	70	22	17	0.3	56	140	6.7	2.7	45 MG
	0	86	8	-1.0	140	4.1	104	31	5.4	9.1	2.6	146	82	26	13	0.2	57	113L	6.8	2.8	
	2	93	10	1.1	139	4.3	100	32	7.7	9.7	3.0	165	67	22	20	0.5	66	132	7.4	3.1	
	3	93	12	1.3	140	4.2	100	31	5.6	9.7	3.7	178	81	28	28	0.4	73	169	7.9	3.6H	
	7	86	9	1.1	139	3.4L	103	32	6.4	8.8L	2.4L	130	62	23	21	0.3	64	157	6.7	2.8	
	14	93	10	1.1	140	3.8	102	32	6.1	9.3	3.1	150	77	39H	18	0.3	61	146	6.9	2.9	
616																					
	- 30	81	17	1.1	141	4.3	98	34H	4.8	9.4	4.2	138	51	22	22	0.4	67	144	6.4	2.1	45 MG
	0	84	7	1.0	138	3.8	101	31	4.5	8.9L	3.6	146	51	21	16	0.2	67	128	6.1	2.1	
	2	101	9	1.1	139	4.0	101	34H	4.1	9.3	3.6	154	50	16	19	0.3	65	133	6.5	2.4	
	3	91	9	1.2	140	3.7	100	34H	3.5L	9.1	4.1	158	71	20	34	0.3	66	170	6.5	2.5	
	7	100	11	1.1	141	3.5L	104	34H	5.3	8.9L	3.4	142	45	36	24	0.4	60	195	6.0L	2.1	
	14	89	7	1.1	138	3.7	98	34H	5.1	9.1	4.3	149	40	24	26	0.4	66	174	6.3	2.2	
617																					
	- 6	84	10	0.9	138	4.3	96L	32	3.3L	10.0	3.7	155	32	24	19	0.9	65	212	7.2	2.6	P
	0	87	6L	0.9	139	4.4	103	32	2.7L	9.2	3.9	135	31L	25	15	0.4	57	173	6.0L	2.2	
	2	95	7	0.9	141	3.9	105	33H	3.8L	9.1	4.0	128	42	20	22	0.4	61	167	6.2	2.5	
	3	84	8	1.1	142	3.7	107	31	3.1L	9.2	4.3	139	49	34	43	0.3	62	185	6.3	2.6	
	14	96	13	0.9	138	4.1	102	30	4.0	9.3	3.7	151	26L	26	34	0.5	64	191	6.7	2.7	
618																					
	- 6	82	15	1.2	142	5.0	99	33H	4.3	10.4	3.5	174	46	20	11	0.5	67	150	7.4	2.5	P
	0	84	15	1.2	142	3.5L	105	29	3.8L	9.7	3.4	171	52	26	6	0.4	79	148	7.3	2.5	
	2	88	9	1.1	139	4.0	102	30	3.3L	9.4	4.3	161	79	16	9	0.3	77	135	6.9	2.6	
	3	93	8	1.3	141	3.9	104	32	2.8L	9.6	4.0	166	85	18	20	0.3	76	153	7.0	2.7	
	7	58L	13	1.2	141	3.9	108H	29	4.8	9.9	3.5	162	40	29	14	0.5	74	229	7.3	2.4	
	14	89	12	1.1	141	3.9	101	32	4.2	9.4	3.5	180	110	21	23	0.2	73	156	6.7	2.4	
619																					
	- 6	85	11	0.9	141	3.9	103	31	6.0	9.1	3.9	148	34	22	25	0.5	62	147	6.7	2.3	P
	0	89	10	0.9	139	3.7	101	31	6.4	9.4	3.2	160	29L	24	27	0.8	70	137	7.0	2.4	
	2	96	9	0.9	141	4.0	104	33H	5.2	9.3	4.8	149	83	21	18	0.3	66	122	6.6	2.4	
	3	92	12	0.8L	141	4.3	103	33H	4.7	9.2	4.7	146	119	16	26	0.3	65	121	6.4	2.4	
	7	86	12	0.8L	143	4.2	102	31	6.0	9.1	3.7	143	59	36	41	0.6	67	136	6.6	2.4	
	14	91	12	0.8L	140	4.1	103	30	6.1	9.2	4.2	151	54	26	39	0.4	71	138	6.4	2.1	
620																					
	- 90	82	9	1.2	138	4.3	103	29	5.4	9.2	3.4	133	37	27	20	0.5	69	218	7.3	3.0	50 MG
	0	96	14	1.1	138	4.0	102	30	4.5	9.3	3.5	151	54	22	20	0.4	89	158	7.2	3.0	
	2	93	9	1.0	136	4.2	102	31	3.7L	9.3	3.8	147	88	22	16	0.3	87	145	6.8	2.9	
	3	85	11	1.0	138	4.0	101	32	3.9	9.2	4.0	148	84	19	16	0.3	84	145	7.1	3.1	
	7	74	9	0.9	140	4.6	100	32	4.8	9.5	3.3	145	62	35	31	0.6	88	169	7.2	3.1	
	14	93	17	1.1	138	4.4	103	30	5.1	9.0	3.7	158	76	20	22	0.3	77	169	7.0	2.9	
621																					
	- 6	88	10	1.0	140	3.8	100	33H	5.5	9.5	3.5	225	91	15	12	0.4	78	166	7.1	2.6	P
	0	103	9	1.0	138	4.1	97L	33H	5.0	10.1	3.9	265H	112	21	24	0.4	90	158	7.8	2.8	
	2	92	9	1.0	140	3.9	100	33H	4.4	10.2	4.7	255H	173	22	14	0.3	81	151	7.5	2.9	
	3	89	13	0.9	138	4.3	101	32	4.1	9.7	4.8	239H	276H	26	18	0.2	78	155	7.1	2.7	

H - HIGH
L - LOW

SUBJ CODE NO	STUDY DAY	GLUC	BUN	CREAT	NA	K	CL	CO2	URIC ACID	CA	PO4	CHOL	TRIG	SGOT	SGPT	TOTAL BILI	ALKA PHOS	LDH	TOTAL PROT	GLOB	DRUG DOSE PLACEBO
	7	89	16	0.9	142	4.1	99	32	5.7	9.6	4.0	231H	104	20	15	0.3	74	153	7.0	2.6	
	14	97	14	1.0	140	4.8	102	31	5.2	9.8	4.2	251H	151	16	15	0.4	76	189	7.2	2.6	
622																					
	- 6	86	11	1.1	139	3.8	101	30	4.5	9.4	3.9	183	55	25	36	0.6	76	186	7.3	2.8	50 MG
	0	97	12	1.1	138	3.8	101	30	4.5	9.1	4.6	155	54	28	36	0.4	85	157	7.0	2.7	
	2	102	8	1.1	137	4.2	98	33H	4.3	9.8	4.8	195	91	36	38	0.5	88	169	7.6	3.2	
	3	92	11	0.8L	137	4.0	98	33H	4.0	9.8	4.4	196	76	33	41	0.6	79	177	7.5	3.1	
	7	94	7	1.0	142	4.6	101	32	4.2	9.0	3.8	152	66	42H	46H	0.4	86	173	6.6	2.6	
	14	96	13	1.2	139	4.0	101	28	5.4	9.5	4.2	207	44	28	39	0.5	72	175	7.6	3.0	
623																					
	- 13	85	10	1.3	141	4.0	103	31	5.1	9.3	3.4	145	46	19	13	0.4	50	131	6.8	2.5	60 MG
	0	84	10	1.2	140	4.6	99	32	5.5	9.6	3.4	143	66	2L	18	0.5	52	119	6.9	2.6	
	2	109	13	1.3	141	4.0	105	30	4.8	9.2	4.2	146	44	14	15	0.4	44	122	6.5	2.4	
	3	110H	16	1.5	139	4.2	107	32	4.7	9.4	3.8	149	55	17	10	0.3	43	126	6.7	2.6	
	7	115H	17	1.4	139	4.4	103	31	5.1	9.2	3.6	146	41	24	23	0.4	47	130	6.7	2.4	
	15	92	16	1.3	140	4.1	101	32	5.9	9.5	3.3	146	147	24	20	0.3	57	122	7.2	2.7	
624																					
	- 6	95	20	1.0	139	4.0	103	30	4.7	9.0	3.4	127	56	24	34	0.6	71	218	7.5	3.3	60 MG
	0	92	18	0.8L	140	4.4	101	31	4.0	8.9L	3.3	125	68	42H	42	0.4	67	172	6.8	2.8	
	2	95	14	1.0	039L	3.7	101	34H	3.8L	9.3	4.2	142	77	22	33	0.6	60	176	7.3	3.0	
	3	96	20	1.1	138	4.5	105	32	3.8L	9.2	4.6	135	78	22	29	0.4	65	167	7.3	3.1	
	7	94	24H	0.9	138	4.0	104	29	3.6L	9.0	3.7	131	68	32	45	0.4	70	199	7.0	2.8	
	14	96	16	1.0	139	3.9	99	32	4.6	9.5	3.6	122L	71	24	32	0.5	77	197	8.0	3.5H	
625																					
	- 6	102	15	1.1	139	3.8	109H	30	5.7	9.5	3.5	169	70	11L	17	0.7	104	182	7.0	2.7	P
	0	106	14	0.8L	142	4.6	100	32	5.4	9.3	3.4	163	81	29	27	0.7	104	143	6.8	2.5	
	2	113H	11	1.0	140	4.1	101	32	5.1	9.3	3.2	178	178	20	34	0.4	100	145	6.6	2.3	
	3	110H	14	1.1	137	3.8	103	30	5.2	9.2	3.6	192	343H	34	61H	0.3	113	167	6.9	2.5	
	7	77	12	1.0	140	3.7	100	31	5.8	9.2	3.0	195	136	20	71H	0.6	105	155	6.9	2.4	
	15	113H	11	1.0	141	4.3	101	32	6.3	9.6	3.0	182	131	19	33	0.3	114	171	7.4	2.7	
626																					
	- 6	102	8	1.2	136	3.8	106	31	6.6	10.0	2.8	151	91	18	21	0.8	117	170	7.5	3.0	P
	0	70L	9	0.9	142	4.4	101	31	6.9	9.8	3.9	128	61	28	23	0.5	97	168	6.7	2.4	
	2	83	7	1.1	139	3.8	102	30	5.8	10.1	3.5	162	61	23	24	1.1	116	178	7.4	2.6	
	3	113H	9	1.2	135L	4.2	101	29	6.4	9.9	3.1	159	72	21	20	1.2	112	166	7.3	2.7	
	7	89	7	1.0	139	3.5L	103	30	5.6	9.4	2.8	131	103	20	18	0.3	98	157	6.6	2.1	
	15	87	13	1.0	140	4.2	102	31	6.6	9.9	3.4	142	103	21	17	0.4	97	155	7.1	2.5	

H -HIGH
L - LOW

SUBJ CODE NO	STUDY DAY	HCT	HGB	RBC	MCV	MCH	MCHC	WBC	LYMPHS	SEGS	MONOS	PLTS	ATL	EOSIN	COMMENTS	DRUG DOSE OR PLACEBO (P)
583																
	- 6	48.3	15.5	5.4	89.4	28.7	32.1L	4.7	44	44	9	256	0	2	Retic 1.0	P
	0	44.5	14.6	5.0	89.0	29.2	32.8	4.9	49H	41	7	279	0	2	Retic 0.7	
	2	43.7	14.3	4.9	89.2	29.2	32.7	5.3	51H	38L	7	278	0	3	Retic 0.9	
	3	46.6	15.2	5.3	87.9	28.7	32.6	5.5	49H	39	8	276	0	3	Retic 1.3	
	7	44.7	14.5	5.0	89.4	29.0	32.4L	5.1	42	42	13H	300	0	2	Retic 1.5	
	14	41.8	14.2	4.9	85.3	29.0	34.0	4.3	46	44	6	275	0	3	Retic 1.4	
584																
	- 6	48.6	16.7	5.4	90.0	30.9	34.4	9.4	20	68	10	184	0	1	Retic 0.2L	P
	0	47.1	16.3	5.3	88.9	30.8	34.6	6.0	34	55	9	234	0	1	Retic 1.4	
	2	47.9	16.4	5.4	88.7	30.4	34.2	7.2	26	64	8	226	0	1	Retic 0.5	
	3	49.1	17.0	5.5	89.3	30.9	34.6	7.0	37	52	9	228	0	1	Retic 0.9	
	7	45.9	15.6	5.0	91.8	31.2	34.0	4.6	32	56	8	181	0	2	Retic 0.8	
	14	45.6	16.1	5.1	89.4	31.6	35.3	5.3	29	59	8	192	0	3	Retic 1.1	
585																
	- 6	45.3	15.1	4.9	92.4	30.8	33.3	5.7	24	66	9	294	0	1	Retic 1.5	1 MG
	0	41.7	14.4	4.6	90.7	31.3	34.5	5.0	32	57	8	245	0	2	Retic 1.3	
	2	44.7	14.8	4.9	91.2	30.2	33.1	7.2	32	59	7	272	0	2	Retic 0.8	
	3	42.4	14.5	4.7	90.2	30.9	34.2	6.6	32	58	7	256	0	2	Retic 0.6	
	7	43.1	14.6	4.7	91.7	31.1	33.9	5.5	26	65	6	293	0	1	Retic 0.8	
	14	41.6	14.5	4.6	90.4	31.5	34.9	4.9	27	63	7	270	0	2	Retic 1.3	
586																
	- 6	47.7	15.9	5.3	90.0	30.0	33.3	7.4	25	67	7	258	0	0L	Retic 0.8	1 MG
	0	47.3	16.1	5.3	89.2	30.4	34.0	9.4	20	73	6	304	0	0L	Retic 0.9	
	2	45.6	15.4	5.2	87.7	29.6	33.8	7.0	41	49	7	293	0	2	Retic 0.7	
	3	45.9	15.6	5.2	88.3	30.0	34.0	7.3	42	48	6	286	0	2	Retic 1.1	
	7	45.0	15.0	5.0	90.0	30.0	33.3	6.1	33	56	6	253	0	2	Retic 0.9	
	14	44.5	15.3	5.1	87.3	30.0	34.4	5.9	39	50	7	275	0	3	Retic 0.8	
587																
	- 13	49.0	16.0	5.6	87.5	28.6	32.7	6.2	36	51	9	230	0	3	Retic 0.3	P
	0	47.9	15.6	5.5	87.1	28.4	32.6	6.7	35	55	4	225	0	4	Retic 0.7	
	2	48.0	15.2	5.4	88.9	28.1	31.7L	7.4	46	45	4	221	0	4	Retic 0.8	
	3	45.5	15.1	5.3	85.8	28.5	33.2	7.9	37	52	5	219	0	4	Retic 0.7	
	7	44.4	14.9	5.2	85.4	28.7	33.6	7.9	32	60	4	256	0	3	Retic 1.3	
	14	47.0	15.5	5.6	83.9	27.7	33.0	5.7	31	60	3	254	0	4	Retic 0.7	
588																
	- 6	44.1	14.2	4.7	93.8	30.2	32.2L	6.0	41	47	5	242	0	6	Retic 1.0	P
	0	46.7	15.2	4.9	95.3	31.0	32.5L	5.7	38	54	4	270	0	4	Retic 1.0	
	2	47.2	15.5	5.0	94.4	31.0	32.8	6.0	56H	30L	5	264	0	7	Retic 1.4	
	3	44.5	14.9	4.8	92.7	31.0	33.5	5.5	45	42	5	252	0	6	Retic 0.8	
	7	40.9	13.8	4.4	93.0	31.4	33.7	5.6	37	49	5	243	0	8H	Retic 1.3	
	14	44.4	14.9	4.9	90.6	30.4	33.6	5.3	41	43	5	274	0	9H	Retic 1.0	
589																
	- 5	47.8	16.4	5.7	83.9	28.8	34.3	7.2	39	51	6	282	0	3	Retic 1.8	5 MG
	0	49.2	16.7	5.8H	84.8	28.8	33.9	6.9	40	48	5	292	0	5	Retic 1.5	
	2	48.2	16.4	5.7	84.6	28.8	34.0	8.1	37	52	6	293	0	4	Retic 1.7	
	3	48.6	17.1	5.8H	83.8	29.5	35.2	7.8	37	52	5	298	0	4	Retic1.4	
	7	43.7	15.5	5.3	82.5	29.2	35.5	7.2	37	51	7	301	0	4	Retic 1.8	
	14	48.0	16.6	5.8H	82.8	28.6	34.6	7.4	35	55	6	303	0	3	Retic 2.3H	
590																
	- 6	51.1H	16.9	5.3	96.4	31.9	33.1	5.3	28	64	5	250	0	1	Retic 1.0	5 MG
	0	48.5	16.2	5.1	95.1	31.8	33.4	4.0L	37	53	5	208	0	2	Retic 1.0	
	2	49.3	16.4	5.2	94.8	31.5	33.3	4.4	41	44	8	225	0	3	Retic 1.2	
	3	46.3	15.8	5.0	92.6	31.6	34.1	4.3	37	52	6	226	0	2	Retic 1.0	
	7	43.7	15.3	4.8	91.0	31.9	35.0	4.6	29	64	5	245	0	1	Retic 1.2	
	14	44.8	15.2	4.8	93.3	31.7	33.9	4.0L	34	53	7	283	0	3	Retic 1.7	
591																
	- 20	51.1H	17.2	5.5	92.9	31.3	33.7	5.9	45	45	8	283	0	2	Retic 0.6	P
	0	43.3	15.2	4.8	90.2	31.7	35.1	4.8	38	48	10	260	0	3	Retic 1.4	
	2	46.6	15.6	5.1	91.4	30.6	33.5	6.0	39	50	8	235	0	3	Retic 0.9	
	3	48.8	16.5	5.4	90.4	30.6	33.8	7.1	40	48	8	251	0	3	Retic 1.1	
592																
	- 20	44.0	14.6	4.2L	104.H	34.8H	33.2	4.6	33	53	10	350H	0	3	Retic 0.6	15 MG
	0	45.6	15.7	4.8	95.0	32.7	34.4	5.3	40	44	10	355H	0	5	Retic 1.0	
	2	44.1	14.2	5.3	83.2	26.8L	32.2L	5.5	38	53	7	188	0	1	Retic 0.9	
	3	42.7	14.4	4.5	94.9	32.0	33.7	5.5	45	41	9	305	0	3	Retic 0.7	
	7	45.9	15.7	4.9	93.7	32.0	34.2	5.4	39	46	9	356H	0	4	Retic 0.9	
	14	47.0	15.6	4.8	97.9	32.5	33.2	5.6	40	48	8	376H	0	2	Retic 0.9	

H - HIGH
L - LOW

APPENDIX C

HEMATOLOGY

SUBJ CODE NO	STUDY DAY	HCT	HGB	RBC	MCV	MCH	MCHC	WBC	LYMPHS	SEGS	MONOS	PLTS	ATL	EOSIN	COMMENTS	DRUG DOSE OR PLACEBO (P)
593																
	- 6	42.7	14.1	4.5	94.9	31.3	33.0	5.3	36	53	8	273	0	2	Retic 1.3	P
	0	42.5	14.9	4.7	90.4	31.7	35.1	6.0	42	47	8	299	0	2	Retic 1.5	
	2	44.9	15.5	4.8	93.5	32.3	34.5	7.2	39	51	7	272	0	2	Retic 1.3	
	3	47.4	15.6	5.1	92.9	30.6	32.9	7.9	38	51	8	313	0	2	Retic 1.3	
	7	43.2	14.8	4.7	91.9	31.5	34.3	6.1	37	50	9	290	0	2	Retic 1.4	
	14	43.2	14.8	4.6	93.9	32.2	34.3	6.1	37	54	6	294	0	2	Retic 1.7	
594																
	- 6	46.3	14.5	5.3	87.4	27.4	31.3L	4.2	49H	43	5	203	0	2	Retic 0.6	15 MG
	0	44.2	14.0	5.0	88.4	28.0	31.7L	4.7	40	54	5	173	0	1	Retic 0.7	
	2	43.2	14.5	4.6	93.9	31.5	33.6	5.6	41	47	8	306	0	3	Retic 1.0	
	3	46.3	15.2	5.6	82.7	27.1	32.8	6.7	46	47	4	199	0	2	Retic 0.6	
	7	43.2	14.5	5.2	83.1	27.9	33.6	4.5	50H	40	6	189	0	2	Retic 0.4	
	14	42.8	14.1	5.1	83.9	27.6	32.9	4.6	54H	38L	5	177	0	2	Retic 0.7	
595																
	- 13	48.8	16.5	5.3	92.1	31.3	34.0	4.9	33	55	8	126L	0	3	Retic 1.2	P
	0	45.2	15.1	4.8	94.2	31.5	33.4	4.0L	34	53	6	162	0	5	Retic 1.4	
	2	47.3	15.2	4.9	96.5	31.0	32.1L	5.7	39	50	7	169	0	3	Retic 1.3	
	3	44.8	15.0	4.9	91.4	30.6	33.5	5.5	37	50	9	180	0	3	Retic 1.5	
	7	42.6	14.4	4.6	92.6	31.3	33.8	4.6	31	60	6	157	0	2	Retic 0.8	
	14	44.0	15.0	4.7	93.6	31.9	34.1	5.3	30	58	7	169	0	4	Retic 1.8	
596																
	- 6	47.8	16.6	5.2	91.9	31.9	34.7	5.1	26	66	6	208	0	1	Retic 1.4	P
	0	48.1	16.1	5.2	92.5	31.0	33.5	5.9	29	64	4	224	0	2	Retic 1.4	
	2	48.8	16.2	5.0	97.6	32.4	33.2	6.3	44	43	7	189	0	3	Retic 1.5	
	3	49.4	16.4	5.4	91.5	30.4	33.2	5.6	43	46	6	157	0	3	Retic 1.1	
	7	46.4	15.5	5.0	92.8	31.0	33.4	5.7	31	60	6	212	0	2	Retic 1.1	
	14	46.5	15.9	5.0	93.0	31.8	34.2	5.6	28	65	5	237	0	1	Retic 1.2	
597																
	- 6	42.5	14.6	5.4	78.7L	27.0	34.4	3.7L	52H	39	7	190	0	1	Retic 1.5	20 MG
	0	42.9	14.1	5.3	80.9	26.6L	32.9	4.2	48H	43	6	180	0	2	Retic 0.8	
	2	41.8	14.6	5.5	79.6L	26.5L	33.3	5.6	52H	39	6	208	0	2	Retic 0.9	
	3	44.5	14.8	5.7	78.1L	26.0L	33.3	5.4	52H	38L	7	212	0	2	Retic 1.2	
	7	41.8	13.8	5.3	78.9L	26.0L	33.0	4.8	50H	41	6	211	0	2	Retic 1.2	
	14	42.6	14.1	5.3	80.4L	26.6L	33.1	4.0L	50H	42	5	197	0	2	Retic 1.3	
598																
	- 6	46.1	16.3	4.9	94.1	33.3	35.4	5.9	36	47	11	277	0	5	Retic 1.1	20 MG
	0	48.9	16.5	5.1	95.9	32.4	33.7	8.9	28	62	6	283	0	3	Retic 1.4	
	2	52.3H	17.0	5.2	100.H	32.7	32.5L	6.8	37	47	8	265	0	5	Retic 0.8	
	3	47.7	16.5	5.0	95.4	33.0	34.6	6.7	39	47	8	243	0	4	Retic 1.0	
	7	45.4	15.5	4.9	92.7	31.6	34.1	8.9	23	65	10	289	0	2	Retic 1.0	
	14	43.2	15.2	4.6	93.9	33.0	35.2	8.3	26	60	9	285	0	4	Retic 2.0H	
599																
	- 12	47.4	15.6	5.5	86.2	28.4	32.9	4.1L	30	59	5	273	0	5	Retic 1.2	25 MG
	0	47.3	15.4	5.5	86.0	28.0	32.6	4.8	26	63	5	311	0	5	Retic 0.9	
	2	47.8	15.8	5.5	86.9	28.7	33.1	5.3	31	58	4	315	0	6	Retic 0.6	
	3	47.9	16.1	5.5	87.1	29.3	33.6	5.2	30	58	5	311	0	6	Retic 1.2	
	7	46.4	15.5	5.4	85.9	28.7	33.4	4.6	27	61	3	295	0	6	Retic 1.2	
	14	48.4	16.4	5.6	86.4	29.3	33.9	4.6	28	59	6	283	0	6	Retic 1.4	
600																
	- 6	44.5	15.1	5.0	89.0	30.2	33.9	3.6L	40	47	5	176	0	6	Retic 1.3	25 MG
	0	48.0	16.2	5.4	88.9	30.0	33.8	8.2	22	70	5	204	0	2	Retic 1.3	
	2	47.5	16.0	5.2	91.3	30.8	33.7	6.6	45	44	5	204	0	5	Retic 1.6	
	3	44.4	15.4	4.9	90.6	31.4	34.7	5.4	40	50	5	201	0	4	Retic 1.0	
	9	47.1	15.2	5.2	90.6	29.2	32.3L	4.2	34	57	4	230	0	4	Retic 1.3	
	14	46.0	15.5	5.1	90.2	30.4	33.7	3.7L	43	47	5	223	0	4	Retic 1.6	
601																
	- 20	46.5	15.3	5.4	86.1	28.3	32.9	9.0	17L	70	10	252	0	2	Retic 1.2	P
	0	43.8	14.5	5.0	87.6	29.0	33.1	6.4	37	51	8	224	0	3	Retic 1.7	
	2	45.5	15.1	5.2	87.5	29.0	33.2	7.0	43	43	8	281	0	5	Retic 1.3	
	3	43.8	14.7	5.0	87.6	29.4	33.6	7.5	40	47	9	243	0	4	Retic 1.5	
	7	44.1	14.5	4.9	90.0	29.6	32.9	6.7	40	47	8	250	0	4	Retic 1.9	
	14	46.9	16.1	5.4	86.9	29.8	34.3	5.7	42	47	6	248	0	4	Retic 1.5	
602																
	- 6	44.7	14.8	5.2	86.0	28.5	33.1	5.6	33	55	8	273	0	3	Retic 0.8	P
	0	46.0	15.0	5.3	86.8	28.3	32.6	8.4	20	69	8	281	0	2	Retic 0.7	

H - HIGH
L - LOW

SUBJ CODE NO	STUDY DAY	HCT	HGB	RBC	MCV	MCH	MCHC	WBC	LYMPHS	SEGS	MONOS	PLTS	ATL	EOSIN	COMMENTS	DRUG DOSE OR PLACEBO (P)
	2	46.9	15.3	5.4	86.9	28.3	32.6	7.8	23	60	12	245	0	4	Retic 0.9	
	3	45.9	15.4	5.3	86.6	29.1	33.6	6.1	30	52	13H	226	0	4	Retic 0.7	
	7	43.6	14.5	5.1	85.5	28.4	33.3	8.9	15L	71	10	254	0	3	Retic 0.6	
	14	44.7	15.3	5.2	86.0	29.4	34.2	5.3	32	54	10	263	0	3	Retic 1.0	
603																
	- 6	45.8	16.0	5.2	88.1	30.8	34.9	4.5	35	50	8	254	0	5	Retic 1.1	30 MG
	0	48.4	16.2	5.3	91.3	30.6	33.5	6.1	40	45	9	276	0	5	Retic 0.8	
	2	46.7	15.4	5.1	91.6	30.2	33.0	5.1	34	49	9	245	0	7	Retic 0.7	
	3	47.8	15.3	5.3	90.2	28.9	32.0L	5.6	29	57	7	244	0	6	Retic 0.9	
	7	46.2	15.8	5.0	92.4	31.6	34.2	4.3	39	48	6	269	0	5	Retic 0.7	
	14	46.2	15.2	5.0	92.4	30.4	32.9	5.3	41	47	6	298	0	5	Retic 0.9	
604																
	- 6	45.6	16.1	5.2	87.7	31.0	35.3	5.5	23	64	9	247	0	2	Retic 0.9	P
	0	44.8	15.1	4.9	91.4	30.8	33.7	5.3	27	63	6	227	0	3	Retic 0.8	
	2	46.0	15.1	5.1	90.2	29.6	32.8	5.2	32	58	7	245	0	3	Retic 1.2	
	3	47.1	15.5	5.2	90.6	29.8	32.9	5.5	32	58	6	258	0	3	Retic 1.3	
	7	46.7	15.7	5.1	91.6	30.8	33.6	4.4	34	56	7	241	0	3	Retic 0.7	
	14	50.1	16.5	5.5	91.1	30.0	32.9	4.7	32	59	6	274	0	2	Retic 1.3	
605																
	- 27	44.9	15.0	5.0	89.8	30.0	33.4	5.4	22	65	8	220	0	3	Retic 1.2	30 MG
	0	41.8	14.4	4.7	88.9	30.6	34.4	5.7	28	56	9	224	0	5	Retic 1.4	
	2	46.0	15.3	5.3	86.8	28.9	33.3	7.3	27	59	10	285	0	4	Retic 1.9	
	3	46.2	15.4	5.2	88.8	29.6	33.3	7.0	29	58	8	250	0	3	Retic 2.1H	
	7	43.5	14.6	4.8	90.6	30.4	33.6	6.7	24	64	6	260	0	5	Retic 1.8	
	14	43.9	14.3	4.8	91.5	29.8	32.6	5.9	33	55	6	248	0	4	Retic 1.7	
606																
	- 62	49.0	16.0	5.6	87.5	28.6	32.7	6.2	36	51	9	230	0	3	Retic 0.3	P
	0	43.2	14.2	5.0	86.4	28.4	32.9	5.8	35	54	4	216	0	6	Retic 0.5	
	2	47.9	15.2	5.5	87.1	27.6	31.7L	6.7	42	47	5	228	0	5	Retic 0.8	
	3	46.9	15.0	5.5	85.3	27.3	32.0L	7.2	41	37L	10	218	0	9H	Retic 0.7	
	7	43.5	15.0	5.2	83.7	28.8	34.5	5.8	47H	39	7	252	0	6	Retic 0.3	
	14	43.1	14.1	5.1	84.5	27.6	32.7	5.9	40	47	6	249	0	6	Retic 0.7	
607																
	- 6	46.8	15.6	5.4	86.7	28.9	33.3	4.5	45	46	7	214	0	2	Retic 1.6	35 MG
	0	47.8	15.4	5.3	90.2	29.1	32.2L	4.2	54H	35L	9	219	0	2	Retic 1.1	
	2	47.0	15.0	5.3	88.7	28.3	31.9L	4.4	58H	32L	8	192	0	1	Retic 1.2	
	3	45.1	15.1	5.2	86.7	29.0	33.5	4.4	61H	28L	7	204	0	3	Retic 1.3	
	7	43.9	14.1	4.9	89.6	28.8	32.1L	4.5	42	49	6	192	0	2	Retic 1.1	
	14	46.3	14.7	5.2	89.0	28.3	31.7L	4.5	42	49	6	204	0	2	Retic 1.8	
608																
	- 48	46.5	15.3	5.4	86.1	28.3	32.9	9.0	17L	70	10	252	0	2	Retic 1.2	35 MG
	0	45.1	14.6	5.0	90.2	29.2	32.4L	6.3	32	58	7	250	0	3	Retic 1.3	
	2	41.6	13.7	4.7	88.5	29.1	32.9	6.9	34	55	8	232	0	3	Retic 1.1	
	3	44.5	14.7	5.1	87.3	28.8	33.0	7.5	38	51	6	255	0	4	Retic 1.7	
	7	44.6	14.2	5.1	87.5	27.8	31.8L	5.7	29	60	6	269	0	4	Retic 1.0	
	15	46.9	15.6	5.4	86.9	28.9	33.3	7.6	32	59	5	291	0	3	Retic 1.8	
609																
	- 86	44.1	14.2	4.7	93.8	30.2	32.2L	6.0	41	47	5	242	0	6	Retic 1.0	P
	0	45.6	14.9	4.9	93.1	30.4	32.7	4.7	44	45	7	306	0	3	Retic 0.9	
	2	46.5	15.4	5.1	91.2	30.2	33.1	6.0	47H	41	8	268	0	3	Retic 1.0	
	3	47.2	16.0	5.3	89.1	30.2	33.9	6.1	46	42	7	311	0	4	Retic 0.8	
	7	41.8	13.5	4.6	90.9	29.3	32.3L	6.8	37	51	7	248	0	4	Retic 0.7	
	14	44.3	14.4	4.8	92.3	30.0	32.5L	5.5	42	47	7	252	0	4	Retic 1.0	
610																
	- 83	49.0	16.0	5.6	87.5	28.6	32.7	6.2	36	51	9	230	0	3	Retic 0.3	P
	0	48.5	15.6	5.6	86.6	27.9	32.2L	6.2	40	49	7	252	0	3	Retic 0.7	
	2	44.6	15.1	5.4	82.6	28.0	33.9	6.2	51H	37L	8	212	0	3	Retic 1.2	
	3	44.9	15.5	5.5	81.6	28.2	34.5	7.4	47H	43	5	229	0	4	Retic 0.9	
	7	45.0	14.4	5.3	84.9	27.2	32.0L	6.1	37	53	5	228	0	4	Retic 0.4	
	14	42.5	13.9	4.9	86.7	28.4	32.7	6.7	47H	42	6	203	0	3	Retic 1.2	
611																
	- 6	47.5	15.4	5.5	86.4	28.0	32.4L	4.7	41	52	5	229	0	2	Retic 1.0	40 MG
	0	47.8	15.7	5.7	83.9	27.5	32.8	6.8	20	73	5	279	0	1	Retic 0.5	
	2	48.4	15.9	5.6	86.4	28.4	32.9	6.1	42	51	4	260	0	2	Retic 0.9	
	3	48.9	16.1	5.7	85.8	28.2	32.9	5.6	42	50	5	259	0	2	Retic 0.7	
	7	44.1	14.0	5.0	88.2	28.0	31.7L	4.8	40	51	6	241	0	2	Retic 1.0	
	14	44.9	14.6	5.2	86.3	28.1	32.5L	4.7	36	55	7	239	0	2	Retic 0.9	

H -HIGH
L -LOW

APPENDIX C

HEMATOLOGY

SUBJ CODE NO	STUDY DAY	HCT	HGB	RBC	MCV	MCH	MCHC	MBC	LYMPHS	SEGS	MONOS	PLTS	ATL	EOSIN	COMMENTS	DRUG DOSE OR PLACEBO (P)
612																
	- 6	49.1	16.4	5.4	90.9	30.4	33.4	5.4	37	49	10	268	0	3	Retic 1.0	P
	0	48.0	16.0	5.5	87.3	29.1	33.3	7.9	31	60	6	262	0	2	Retic 0.6	
	2	48.0	15.9	5.4	88.9	29.4	33.1	6.5	42	46	7	268	0	3	Retic 1.2	
	3	50.6	16.6	5.7	88.8	29.1	32.8	7.4	42	49	5	270	0	3	Retic 0.3	
	7	49.4	15.7	5.4	91.5	29.1	31.8L	5.9	38	51	7	255	0	3	Retic 1.5	
	14	48.8	15.8	5.4	90.4	29.3	32.4L	6.7	32	58	8	277	0	2	Retic 0.8	
613																
	- 6	48.4	16.0	4.9	98.8	32.7	33.1	5.5	30	63	5	323	0	2	Retic 1.2	P
	0	44.1	14.3	4.5	98.0	31.8	32.4L	6.0	28	61	6	297	0	4	Retic 0.4	
	2	47.0	15.7	4.8	97.9	32.7	33.4	5.3	39	50	5	295	0	6	Retic 1.2	
	3	47.8	15.7	4.9	97.6	32.0	32.8	5.6	41	51	4	268	0	3	Retic 0.8	
	7	45.4	14.7	4.5	100.8H	32.7	32.4L	5.1	33	57	5	256	0	4	Retic 1.2	
	14	48.0	15.9	4.9	98.0	32.4	33.1	6.5	29	62	4	289	0	4	Retic 0.8	
614																
	- 6	47.7	15.4	5.3	90.0	29.1	32.3L	6.2	41	51	3	240	0	4	Retic 1.3	40 MG
	0	44.9	14.9	5.2	86.3	28.7	33.2	4.5	37	50	4	207	0	7	Retic 1.2	
	2	49.9	16.2	5.6	89.1	28.9	32.5L	4.7	38	48	4	227	0	9H	Retic 1.3	
	3	49.2	16.1	5.5	89.5	29.3	32.7	5.0	38	49	4	227	0	8H	Retic 0.6	
	7	46.3	14.5	5.1	90.8	28.4	31.3L	4.8	45	42	5	222	0	7	Retic 1.6	
	14	46.9	15.0	5.3	88.5	28.3	32.0L	4.9	37	46	10	247	0	6	Retic 1.3	
615																
	- 60	44.1	14.2	4.7	93.8	30.2	32.2L	6.0	41	47	5	242	0	6	Retic 1.0	45 MG
	0	43.8	15.1	4.9	89.4	30.8	34.5	4.7	45	45	4	307	0	3	Retic 1.9	
	2	46.7	15.6	5.2	89.8	30.0	33.4	5.4	47H	41	5	290	0	7	Retic 1.1	
	3	46.8	16.2	5.3	88.3	30.6	34.6	6.2	00L	00L	0L	293	0	0L	Retic 1.2	
	7	36.0L	12.5L	4.1L	87.8	30.5	34.7	5.7	42	48	7	268	0	3	Retic 1.4	
	14	45.0	14.7	4.9	91.8	30.0	32.7	5.2	41	50	6	306	0	3	Retic 1.7	
616																
	- 30	45.8	15.4	5.1	89.8	30.2	33.6	4.6	23	73	3	278	0	1	Retic 0.5	45 MG
	0	43.2	13.9	4.7	91.9	29.6	32.2L	2.5L	40	52	3	280	0	2	Retic 1.0	
	2	47.6	15.8	5.2	91.5	30.4	33.2	3.6L	40	52	4	266	0	4	Retic 1.1	
	3	47.1	16.1	5.3	88.9	30.4	34.2	4.4	43	51	4	263	0	1	Retic 1.2	
	7	37.7L	13.3L	4.3L	87.7	30.9	35.3	3.8L	30	63	5	237	0	1	Retic 0.8	
	14	46.1	15.1	5.0	92.2	30.2	32.8	4.4	29	65	4	301	0	1	Retic 1.1	
617																
	- 6	42.1	14.3	4.7	89.6	30.4	34.0	3.1L	52H	42	4	316	0	1	Retic 0.7	P
	0	37.6L	12.0L	4.2L	89.5	28.6	31.9L	3.3L	54H	40	2	277	0	1	Retic 1.3	
	2	37.1L	12.5L	4.1L	90.5	30.5	33.7	4.0L	49H	44	4	298	0	3	Retic 1.2	
	3	37.6L	12.9L	4.3L	87.4	30.0	34.3	5.1	39	54	5	304	0	1	Retic 1.5	
	7	34.6L	12.0L	4.0L	86.5	30.0	34.7	4.3	33	61	5	328	0	1	Retic 1.6	
	14	40.6	13.1L	4.4	92.3	29.8	32.3L	3.5L	46	47	6	404H	0	1	Retic 1.7	
618																
	- 6	47.7	16.2	5.5	86.7	29.5	34.0	6.4	35	59	4	241	0	1	Retic 0.9	P
	0	42.4	14.6	4.9	86.5	29.8	34.4	6.5	46	48	1L	278	0	2	Retic 1.1	
	2	43.8	14.6	5.0	87.6	29.2	33.3	7.2	53H	39	4	215	0	4	Retic 1.5	
	3	44.5	15.1	5.2	85.6	29.0	33.9	6.7	52H	43	2	201	0	2	Retic 1.3	
	7	39.0L	13.4	4.6	84.8	29.1	34.4	8.9	35	57	7	225	0	0L	Retic 1.1	
	14	40.9	13.6	4.6	88.9	29.6	33.3	11.5H	20	74H	5	276	0	1	Retic 2.0H	
619																
	- 6	46.2	15.6	5.0	92.4	31.2	33.8	3.4L	41	41	10	242	0	7	Retic 1.2	P
	0	50.1	16.1	5.2	96.3	31.0	32.1L	3.4L	37	48	9	248	0	6	Retic 1.5	
	2	48.5	16.2	5.2	93.3	31.2	33.4	3.8L	48H	40	7	215	0	5	Retic 0.7	
	3	48.8	16.1	5.0	97.6	32.2	33.0	4.6	45	38L	9	224	0	8H	Retic 1.1	
	7	48.0	15.4	5.1	94.1	30.2	32.1L	4.0L	36	43	11	262	0	9H	Retic 0.8	
	14	47.2	15.7	5.0	94.4	31.4	33.3	4.5	38	44	10	243	0	7	Retic 0.8	
620																
	- 90	44.7	14.8	5.2	86.0	28.5	33.1	5.6	33	55	8	273	0	3	Retic 0.8	50 MG
	0	48.3	15.6	5.4	89.4	28.9	32.3L	5.9	33	54	8	330	0	5	Retic 1.2	
	2	46.4	15.3	5.4	85.9	28.3	33.0	4.8	34	55	6	280	0	4	Retic 1.7	
	3	46.7	15.7	5.3	88.1	29.6	33.6	5.9	32	49	12	299	0	6	Retic 1.3	
	7	46.6	15.0	5.3	87.9	28.3	32.2L	6.0	29	56	9	346	0	5	Retic 0.5	
	14	44.3	14.7	5.2	85.2	28.3	33.2	5.5	32	50	11	278	0	6	Retic 0.4	
621																
	- 6	45.2	15.1	5.3	85.3	28.5	33.4	5.4	34	57	7	300	0	2	Retic 1.4	P
	0	53.4H	16.8	5.9H	90.5	28.5	31.5L	8.8	36	56	6	309	0	1	Retic 1.6	
	2	49.5	16.1	5.5	90.0	29.3	32.5L	6.3	37	54	6	271	0	2	Retic 1.2	
	3	47.9	15.4	5.2	92.1	29.6	32.2L	7.5	40	48	10	276	0	2	Retic 1.7	

H - HIGH
L - LOW

SUBJ CODE NO	STUDY DAY	HCT	HGB	RBC	MCV	MCH	MCHC	WBC	LYMPHS	SEGS	MONOS	PLTS	ATL	EOSIN	COMMENTS	DRUG DOSE OR PLACEBO (P)
	7	44.0	15.1	5.3	83.0	28.5	34.3	6.9	41	51	6	317	0	2	Retic 0.7	
	14	46.2	15.2	5.3	87.2	28.7	32.9	8.0	34	59	5	349H	0	1	Retic 1.2	
622																
	- 6	47.9	16.1	5.7	84.0	28.2	33.6	3.8L	52H	39	5	269	0	4	Retic 0.5	50 MG
	0	48.1	15.6	5.4	89.1	28.9	32.4L	3.8L	55H	38L	3	280	0	4	Retic 1.2	
	2	52.5H	17.0	6.1H	86.1	27.9	32.4L	3.8L	52H	42	3	248	0	2	Retic 0.7	
	3	53.5H	17.6H	6.3H	84.9	27.9	32.9	5.4	50H	40	6	264	0	4	Retic 1.0	
	7	45.6	14.6	5.3	86.0	27.5	32.0L	3.9L	52H	39	6	260	0	3	Retic 0.6	
	14	48.0	16.2	5.6	85.7	28.9	33.8	4.1L	50H	40	5	317	0	4	Retic 0.7	
623																
	- 13	42.5	14.3	5.2	81.7	27.5	33.6	5.3	33	58	5	211	0	3	Retic 0.7	60 MG
	0	46.7	14.9	5.4	86.5	27.6	31.9L	5.5	38	53	5	217	0	3	Retic 0.8	
	2	44.5	14.4	5.2	85.6	27.7	32.4L	5.1	50H	37L	8	194	0	5	Retic 2.0H	
	3	42.5	13.9	4.8	88.5	29.0	32.7	3.7L	58H	26L	8	183	0	8H	Retic 1.6	
	7	40.2	13.5	4.8	83.8	28.1	33.6	5.4	30	59	6	183	0	4	Retic 1.3	
	15	45.3	14.8	5.2	87.1	28.5	32.7	4.5	37	54	5	220	0	3	Retic 1.0	
624																
	- 6	48.0	15.8	4.8	100.H	32.9	32.9	4.7	35	54	7	237	0	3	Retic 1.4	60 MG
	0	47.7	15.3	4.8	99.4H	31.9	32.1L	5.3	22	59	11	268	0	7	Retic 0.7	
	2	49.4	16.0	4.9	100.H	32.7	32.4L	6.5	32	56	8	251	0	4	Retic 1.9	
	3	48.0	15.8	4.6	104.H	34.3H	32.9	5.9	39	51	7	246	0	3	Retic 1.2	
	7	45.1	14.8	4.6	98.0	32.2	32.8	5.1	35	52	9	248	0	3	Retic 0.8	
	14	52.4H	16.9	5.1	102.H	33.1	32.3L	8.1	24	67	6	237	0	2	Retic 1.3	
625																
	- 6	51.7H	16.9	6.0H	86.2	28.2	32.7	4.1L	30	57	6	265	0	5	Retic 2.0H	P
	0	49.5	16.8	6.2H	79.8L	27.1	33.9	4.9	33	54	6	338	0	6	Retic 1.1	
	2	53.6H	17.1	6.1H	87.9	28.0	31.9L	5.5	30	53	8	299	0	8H	Retic 1.7	
	3	50.7H	16.9	6.2H	81.8	27.3	33.3	4.9	32	53	8	344	0	7	Retic 1.9	
	7	51.8H	17.0	6.2H	83.5	27.4	32.8	4.8	25	58	7	314	0	8H	Retic 0.6	
	15	49.4	16.6	6.1H	81.0	27.2	33.6	5.0	28	57	6	308	0	7	Retic 1.0	
626																
	- 6	47.2	15.7	5.1	92.5	30.8	33.3	6.9	27	64	6	326	0	2	Retic 2.0H	P
	0	45.4	14.5	5.0	90.8	29.0	31.9L	7.1	29	60	8	314	0	3	Retic 0.5	
	2	49.9	16.2	5.3	94.2	30.6	32.5L	10.0H	43	45	8	342	0	3	Retic 1.1	
	3	51.3H	16.6	5.3	96.8	31.3	32.4L	9.3	39	47	10	350H	0	4	Retic 1.0	
	7	41.8	13.9	4.6	90.9	30.2	33.3	7.6	36	55	5	295	0	3	Retic 1.0	
	15	42.6	13.9	4.7	90.6	29.6	32.6	7.4	30	60	6	281	0	4	Retic 1.4	

H - HIGH
L - LOW

APPENDIX D

HAPTOGLOBIN VALUES

SUBJECT	Drug Dose or Placebo(P)	Study Day Scr	0	2	3	7	14
583	P	106	108	110	112	135	114
584	P	106	70	61	58	56	52
585	1mg	86	81	82	76	90	82
586	1mg	162H	149	155H	149	150	147
587	P	85	110	100	100	120	96
588	P	97	102	250H	170H	94	163H$
589	5mg	67	76	94	76	57	121
590	5mg	36	34	58	54	37	33
591	P	98	53	62	64	--	--
592	15mg	64	70	126	64	95	78
593	P	60	56	61	64	86	56
594	15mg	150	130	56	150	86	111
595	P	84	129	115	104	105	56
596	P	110	94	110	109	125	89
597	20mg	86	91	112	117	105	112
598	20mg	110	113	104	91	155H	99
599	25mg	72	59	68	67	72	72
600	25mg	86	95	112	100	84	77
601	P	155H	54	70	65	74	69
602	P	61	48	95	107	74	72
603	30mg	65	90	98	103	77	85
604	P	60	56	69	67	64	58
605	30mg	260H	149	147	150	130	129
606	P	85	91	101	100	103	92
607	35mg	102	106	112	71	91	108
608	35mg	155H	69	70	103	58	71
609	P	97	101	107	103	81	86
610	P	85	97	86	102	122	93
611	40mg	93	90	120	110	80	118
612	P	80	62	87	87	76	78
613	P	57	17L	24	26	20	8L*
614	40mg	78	74	89	83	80	63
615	45mg	97	91	87	100	88	92
616	45mg	80	61	72	77	56	70
617	P	91	68	81	91	91	102
618	P	125	100	79	96	80	108
619	P	73	80	93	89	83	95
620	50mg	61	83	85	79	83	78
621	P	99	102	103	95	89	66
622	50mg	73	75	89	95	70	77
623	60mg	87	76	80	77	90	116
624	60mg	53	40	54	57	58	89
625	P	79	88	84	86	109	93
626	P	155H	151H	165H	149	114	162H

$ H- High
* L- Low

Normal range: 18.7-150.8 mg/dl

APPENDIX E

INDIVIDUAL CLINICAL SUMMARIES

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#583 EXPERIMENT#21 GROUP# 1 DRUG(NO mg) PLACEBO

SYMPTOMS: 1s: 1830-cramps in biceps
2330-nausea for about 5 minutes.
2s: 0730-stomach "cramps and spasms"

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	Peroneal pattern of atrophy of rt. leg (2ndary to infantile poliomyelitis).	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	MCHC	32.1	Low *
0s-3s:	Lymphs	49-51	High (3x) *
2s:	Segs	38	Low
7s:	MCHC	32.4	Low
	Monos	13	High

CHEMISTRIES:

Scr:	SGOT	38	High
	T Prot.	8.2	High
0s:	SGOT	41	High
2s:	Phos.	5.4	High
3s:	Phos.	5.4	High
7s:	Data discarded +		

URINALYSIS: ----

CONCLUSIONS: Subject received placebo. Had no new physical findings but had a number of subjective medical complaints. SGOT,SGPT, LDH elevations on 7s after 4 days out of facility and hard physical workout. Enzymes returned to normal in 7 days.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.
+ Outlying data (high SGOT,SGPT) led to discarding all chemistry data from this day.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#584 EXPERIMENT#21 GROUP# I DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	
HEMATOLOGY:		
Scr: Retic.	0.2	Low
CHEMISTRIES:		
3s: SGPT	52	High *
URINALYSIS:	----	

CONCLUSIONS: Subject received placebo, had no symptoms and no physical abnormalities. He had a few inconsistent and minor laboratory deviations from normal.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#585 EXPERIMENT#21 GROUP# I DRUG(1 mg) PLACEBO

SYMPTOMS:
1s: 1230"Gassiness, Queasiness"
2s: 0730-recurrence of above,headache
3s: Muscle pain of anterior chest, headache.
7s: Recurrences of above while out of facility.

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	The complaints voiced by this subject were not accompanied by physical abnormality.
VITAL SIGNS:	----	
HEMATOLOGY:	----	

CHEMISTRIES:

0s:	LDH	112	Low
14s:	CO_2	33	High

URINALYSIS: ----

CONCLUSIONS: Subject had many complaints which could be related to his receiving 1 mg of the drug. The fact that the symptoms persisted to the 7th day suggest that it was not a dose/response phenomenom. Laboratory values were not significantly affected.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#586 EXPERIMENT#21 GROUP#I DRUG(1 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT	
PHYSICAL EXAM:	----			
VITAL SIGNS:	----			
HEMATOLOGY:	----			
Scr:	Hapt.	162	High	+
:	Eosins	0	Low	
0s:	Eosins	0	Low	
2s:	Hapt.	155	High	
CHEMISTRIES:				
2s:	T Prot.	6.0	Low	
7s:	Na	144	High	
14s:	T Prot.	6.0	Low	
URINALYSIS:	----			

CONCLUSIONS: Subject received 1 mg of drug. No associated symptoms or physical findings. No evidence of methemogobinemia or hemolysis.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities noted.
+ Inclusion of subject in study due to laboratory error in reporting high abnormal values.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#587 EXPERIMENT#21 GROUP# 2 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:	----		
2s:	MCHC	31.7	Low *
CHEMISTRIES:			
0s:	Cl	97	Low
2s:	Phos.	5.1	High
	LDH	107	Low
3s:	Phos.	5.7	High
14s:	Trigly.	29	Low
	LDH	101	Low
URINALYSIS:	----		

CONCLUSIONS: Subject receiving placebo had no symptoms and no abnormal physical findings. Minor variations in laboratory values not consequential to this study.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#588 EXPERIMENT#21 GROUP# 2 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	MCHC	32.2	Low *
0s:	MCHC	32.5	Low
2s:	Lymphs	56	High
	Segs	30	Low
	Hapt.	250	High *
3s:	Hapt.	170	High *
7s:	Eosins	8	High
14s:	Eosins	9	High
	Hapt.	163	High *

CHEMISTRIES

Scr:	Cl	108	High
7s:	Ca	8.8	Low
14s:	Ca	8.8	Low

URINALYSIS: ----

CONCLUSIONS: Subject received placebo, had no symptoms nor abnormalities on physical exam. Laboratory studies showed minor deviations not related to study participation.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#589 EXPERIMENT#21 GROUP# 2 DRUG(5 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

0s:	RBC	5.8	High
3s:	RBC	5.8	High
14s:	RBC	5.8	High
	Retic.	2.3	High

CHEMISTRIES:

Scr-3s:	Phos	5.4-6.2	High (4x)
Scr:	K+	3.5	Low
	CO_2	33	High
2s:	K+	3.6	Low
3s:	Na	144	High
7s:	Na	145	High
	Uric H+	8.1	High

URINALYSIS: ----

CONCLUSIONS: Subject received drug. Had no symptoms nor physical findings attributable to drug effect. RBC was consistently slightly over the upper limits of normal. Retic count slightly elevated in screening, 2s,7s,14s. Haptoglobin fell within the treatment period, although stayed within the normal range. These finding are consistent with but not diagnostic of slight aggravation of a pre-existing mild hemolytic condition.

*NCSICS-Not clincally significant in context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#590 EXPERIMENT#21 GROUP#2 DRUG(5 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
Scr:	Hct.	51.1	High
0s:	WBC	4.0	Low
14s:	WBC	4.0	Low
CHEMISTRIES:			
Scr-2s:	Chol.	230-234	High (3x; highest at Scr.)
0s:	Uric H+	8.1	High
	SGOT	11	Low
7s:	K+	3.6	Low
		235	High
14s:	Glucose	112	High
	Ca	8.7	Low
URINALYSIS:	----		

CONCLUSIONS: Subject received drug, had no symptoms nor physical findings attributable to drug effect. CBC and chemistry abnormalities inconsequential. No evidence of hemolysis and no methemoglobinemia.

*NCSICS-Not clinically significant in the context of this study.
-----Done as scheduled,no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#591 EXPERIMENT#21 GROUP# 2 DRUG(NO mg) PLACEBO

SYMPTOMS: 1s: 1500, 2130-had very runny bowel movements. No associated symptoms(had several diet sodas)

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	
HEMATOLOGY:	----	
Scr: Hct.	51.1	High *
CHEMISTRIES:		
0s: Uric H+	10.5	High
URINALYSIS:	----	

CONCLUSIONS: This subject received placebo, and had two "runny bowel movements" on the day of dosing. His laboratory findings showed no consistent abnormalities. He failed to return for the 7s and 14s evaluations, and was lost to follow-up.

----Done as scheduled, no abnormalities.
*NCSICS-Not clinically significant in the context of this study.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#592 EXPERIMENT#21 GROUP# 2 DRUG(15 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	RBC	4.2	Low
	MCV	104	High
	MCH	34.8	High
	Plts.	350	High *
0s:	Plts.	355	High
2s:	MCH	26.8	Low
	MCHC	32.2	High
7s:	Plts.	356	High
14s:	Plts.	376	High

CHEMISTRIES:

Scr:	SGOT	11	Low
0s:	Cl	96	Low
2s:	Na	135	Low
	K+	3.5	Low
	Glob.	3.5	High

URINALYSIS: ----

CONCLUSIONS: Subject who received drug had no symptoms and no physical abnormalities. There were minor, insignificant changes in the blood chemistries. No methemoglobinemia and no evidence of hemolysis.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#593 EXPERIMENT#21 GROUP# 3 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	
HEMATOLOGY:	----	

CHEMISTRIES

3s:	Chol.	232	High

URINALYSIS: ----

CONCLUSIONS: Subject received placebo; he had no symptoms, no positive physical findings and no significant laboratory abnormalities.

*NCSICS- Not clinically significant in the context of this study.
-----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#594 EXPERIMENT#21 GROUP# 3 DRUG(15 mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
Scr:	MCHC	31.3	Low
	Lymphs	49	High
0s:	MCHC	31.7	Low
7s:	Lymphs	50	High
14s:	Lymphs	54	High
	Segs	38	Low
CHEMISTRIES			
Scr:	Glob.	3.5	High
0s:	Glob.	3.4	High
3s:	T Prot.	8.2	High
	Glob.	3.6	High
7s:	LDH	116	Low
14s:	K+	3.6	Low
URINALYSIS:	----		

CONCLUSIONS: Subject received 15mg of drug. No consistent or significant changes in blood chemistries or hematology values. No evidence of hemolysis and no methemoglobinemia.

---- Done as scheduled, no abnormalities.
* NCSCIS, Not clinically significant in the context of this study.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#595 EXPERIMENT# 21 GROUP#4 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	Plts.	126	Low
0s:	WBC	4.0	Low
2s:	MCHC	32.1	Low

CHEMISTRIES:

Scr:	T Bili.	1.3	High
0s:	Na	144	High
	Uric H+	3.7	Low
2s:	K+	3.6	Low
7s:	Ca	8.9	Low
14s:	Creat.	0.8	Low
	SGPT	48	High

URINALYSIS:

Subject had WBC's of 35/HPF on 0s. Repeat on 1s showed 2-6 WBC/HPF. 9-7 WBC/HPF noted thereafter. NCSICS*

CONCLUSIONS: Subject received placebo. No symptoms nor positive physical findings noted. No significant abnormalities of laboratory results except for a few WBC noted in urinalysis.

----Done as scheduled, no abnormalities.

*NCSICS-Not clinically significant in the context of this study.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#596 EXPERIMENT#21 GROUP#4 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	
HEMATOLOGY:	----	

CHEMISTRIES:

0s:	Glucose	111	High
2s:	Na	144	High
	Phos.	5.3	High
14s:	Creat.	0.8	Low

URINALYSIS: ----

CONCLUSIONS: Subject received placebo had no symptoms, no positive physical findings and no significant abnormalities of laboratory examinations.

* NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#597 EXPERIMENT#21 GROUP#4 DRUG(20 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr-14s:	Lymphs	48-52	High (6x)
Scr:	MCV	78.7	Low *
	WBC	3.7	Low *
0s-14s:	MCH	26.0-26.6	Low *(5x)
2s-14s:	MCV	78.1-80.4	Low (4x)
3s:	Segs	38	Low
14s:	WBC	4.0	Low

CHEMISTRIES

2s:	Phos.	5.1	High
3s:	Phos.	5.2	High
7s:	SGOT	47	High

URINALYSIS: ----

CONCLUSIONS: Subject received 20 mg of drug and had no symptoms nor abnormal physical findings. No significant deviations from normal were noted in his laboratory examinations. There was no evidence of methemoglobinemia nor of hemolysis.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#598 EXPERIMENT#21 GROUP#4 DRUG(20 mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
2s:	MCHC	32.5	Low *
	Hct.	52.3	High *
	MCV	100	High *
7s:	Hapt.	155	High *
14s:	Retic.	2.0	High *
CHEMISTRIES:			
Scr:	Trigly.	331	High
2s:	Phos.	5.0	High
	Trigly.	387	High
3s:	Trigly.	272	High
7s:	Uric H+	7.9	High
14s:	Creat.	0.8	Low
	Trigly.	302	High
URINALYSIS:	----		

CONCLUSIONS: Subject received 20 mg of drug. No symptoms and no physical examination abnormalities noted. Triglyceride elevation after drug administration more likely constitutional than drug effect because of presence at screening and at 14s after returning to normal on 7s. Haptoglobin fell from 155(7s) to 99 (14s); **Retic. count rose from 1.0% to 2.0%, the Hct fell from 45.4 to 43.2, the Hgb fell from 15.5 to 15.2 in the same interval. Those findings are consistent with but not diagnostic of hemolysis. Methemoglobin was not detected.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled,no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#599 EXPERIMENT#21 GROUP#5 DRUG(25 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	
HEMATOLOGY:		
Scr: WBC	4.1	Low
CHEMISTRIES:		
Scr-14s: Glob.	3.5-3.8	High (6x)
7s: Glucose	60	Low
URINALYSIS:	----	

CONCLUSIONS: Subject received 25 mg of drug and had no symptoms; nor did he develop any abnormal physical findings. Laboratory deviatons were minimal. No evidence of hemolysis, no methemoglobin.

*NCSICS:Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#600 EXPERIMENT#21 GROUP#5 DRUG(25 mg)
PLACEBO

SYMPTOMS: 1s:"not hungry"; refused lunch. Evening meal eaten.

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	WBC	3.6	Low
9s:	MCHC	32.3	Low *
14s:	WBC	3.7	Low

CHEMISTRIES:

2s:	Na	148	High
	Cl	108	High
14s:	Uric H+	3.7	Low

URINALYSIS: ----

CONCLUSIONS: Subject received 25 mg of drug. He remained asymptomatic and developed no physical abnormalities. His laboratory studies were unremarkable. No hemolysis was seen; no methemoblobin detected.

*NCSICS:Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#601 EXPERIMENT#21 GROUP# 5 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	Lymphs	17	Low *
	Hapt.	155	High *

CHEMISTRIES:

2s:	Phos.	5.6	High
3s:	Phos.	5.2	High
7s:	T Bili.	1.5	High

URINALYSIS: ----

CONCLUSIONS: Subject received placebo. Had no symptoms and had no positive physical findings. Transient, unexplained elevation of bilirubin, NCSICS*.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#602 EXPERIMENT#21 GROUP#5 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	
HEMATOLOGY:		
3s: Monos	13	High *
7s: Lymphs	15	Low *
CHEMISTRIES:		
7s: K+	3.6	Low
URINALYSIS:	----	

CONCLUSIONS: Subject received placebo. Had no symptoms, abnormal physical findings nor abnormal laboratory findings as a result of his participation.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#603 EXPERIMENT#21 GROUP# 6 DRUG(30 mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

3s:	MCHC	32.0	Low *

CHEMISTRIES:

Scr:	Glob.	1.8	Low
2s:	BUN	21	High *
	Creat.	1.6	High
3s:	BUN	21	High
	Cl	95	Low
	CO_2	33	High
	T Prot.	6.0	Low
	Glob.	1.8	Low
7s:	BUN	21	High

URINALYSIS: ----

CONCLUSIONS: Subject received placebo. No symptoms nor positive physical findings noted. Laboratory values were not exceptional or noteworthy.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#604 EXPERIMENT# 21 GROUP#6 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	
HEMATOLOGY:		

CHEMISTRIES:

0s:	K^+	3.5	Low
2s:	Ca	8.8	Low
3s:	Cl	95	Low
	CO_2	33	High
7s:	K^+	3.5	Low

URINALYSIS: ----

CONCLUSIONS: Subject received placebo. No symptoms nor abnormal physical findings were observed. A number of laboratory abnormalities of the serum electrolytes were observed which were not significant in the context of this study.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#605 EXPERIMENT#21 GROUP#6 DRUG(30 mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
Scr:	Hapt.	260	High
3s:	Retic.	2.1	High
CHEMISTRIES:			
Scr:	Na	145	High
	CO_2	33	High
	Chol.	229	High
	SGPT	53	High
0s:	CO_2	36	High
3s:	Cl^2	95	Low
	CO_2	34	High
	SGPT	60	High
7s:	SGPT	46	High
14s:	SGOT	11	Low
URINALYSIS:	----		

CONCLUSIONS: Subject received 30 mg of drug; had no symptoms or abnormal physical findings. Retic count increased during study period, peaking on 7s. SGPT was high at screening but normal on 0s. Subsequent SGPT elevations probably not study related. No methmoglobinemia.

*NCSICS-Not clinically significant in the context of this study.
-----Done as scheduled,no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#606 EXPERIMENT#21 GROUP#6 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
2s:	MCHC	31.7	Low
3s:	MCHC	32.0	Low
	Segs	37	Low *
	Eosins	9	High *
7s:	Lymphs	47	High *
CHEMISTRIES:			
Scr:	Chol.	120	Low
	LDH	112	Low
2s:	Chol	121	Low
	LDH	90	Low
3s:	Cl	94	Low
	SGOT	11	Low
7s:	K+	3.6	Low
	Chol.	120	Low
	Trigly.	25	Low
14s:	Trigly.	19	Low
URINALYSIS:	----		

CONCLUSIONS: Subject received placebo. No clinical evidence of adverse effect from participation.

*NCSICS-Not clinically significant in the context of this study.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#607 EXPERIMENT#21 GROUP# 7 DRUG(35 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

0s-3s:	Lymphs	54-61	High (3x) *
:	Segs	28-35	High (3x) *
0s:	MCHC	32.2	Low *
2s:	MCHC	31.9	Low
7s:	MCHC	32.1	Low
14s:	MCHC	31.7	Low

CHEMISTRIES:

Scr:	Chol.	229	High
	Glob.	3.4	High
0s:	Glucose	72	Low
2s:	Na	135	Low
	K+	3.6	Low
	Ca	8.8	Low
3s:	LDH	109	Low
7s:	Creat.	0.8	Low
14s:	Chol.	241	High

URINALYSIS: ----

CONCLUSIONS: Subject received 35 mg of drug. He had no symptoms and no noteworthy physical abnormalities. Laboratory deviations from normal were minimal and suggested no drug effect. No evidence of hemolysis was noted, no methemoglobinemia was detected.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#608 EXPERIMENT#21 GROUP#7 DRUG(35 mg)
PLACEBO

SYMPTOMS: 2s noted fatigue, possibly due to lack of sleep.

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	Hapt.	155	High *
	Lymphs	17	Low *
0s:	MCHC	32.4	Low
7s:	MCHC	31.8	Low

CHEMISTRIES:

2s:	Na	135	Low
	Ca	8.6	Low
14s:	LDH	108	Low

URINALYSIS: ----

CONCLUSIONS: Subject received 35 mg of drug; he developed no symptoms and had no physical abnormalities. There were minor variations in the laboratory findings of no evident clinical significance. There was no evidence of hemolysis and methemoglobin was not detected.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT# 609 EXPERIMENT#21 GROUP#7 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:	----		
Scr:	MCHC	32.2	Low *
2s:	Lymphs	47	High *
7s:	MCHC	32.3	Low
14s:	MCHC	32.5	Low
CHEMISTRIES:			
Scr:	Cl	108	High
0s:	Glucose	65	Low
2s:	Na	135	Low
	Ca	8.9	Low
3s:	LDH	114	Low
14s:	K+	3.6	Low
URINALYSIS:	----		

CONCLUSIONS: Subject received placebo, and had no adverse effect as measured by symptoms, physical examinations or laboratory findings.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#610 EXPERIMENT# 21 GROUP#7 DRUG(NO mg) PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
0s:	MCHC	32.2	Low
2s:	Lymphs	51	High *
	Segs	37	Low *
3s:	Lymphs	47	High
7s:	MCHC	32.0	Low
14s:	Lymphs	47	High
CHEMISTRIES:			
0s:	SGOT	8	Low
2s-14s:	LDH	71-112	Low (4x)
2s:	Na	133	Low
	Cl	96	Low
	Ca	8.4	Low
	SGOT	10	Low
	SGPT	4	Low
3s:	CO_2	33	High
7s:	BUN	21	High
URINALYSIS:			
3s:	WBC 35-36/HPF, next specimen clear of WBC.		

CONCLUSIONS: Subject received placebo and showed no evidence of adverese reaction to participation by any of the observations outlined in the protocol.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#611 EXPERIMENT#21 GROUP#8 DRUG(40 mg) PLACEBO

SYMPTOMS: None

		ABNORMALITIES	COMMENT
PHYSICAL EXAM:		----	
VITAL SIGNS:		----	
HEMATOLOGY:			
Scr:	MCHC	32.4	Low
7s:	MCHC	31.7	Low
14s:	MCHC	32.5	Low
CHEMISTRIES:			
Scr:	T Prot.	5.6	Low *
	Glob.	1.6	Low
0s:	Creat.	0.8	Low
2s-14s:	T Prot.	5.7-5.8	Low (4x)
	Glob.	1.7-1.8	Low (4x)
2s:	CO_2	33	High
3s:	CO_2	33	High
	Na^2	145	High
	K+	5.6	High
	Uric H+	3.4	Low
14s:	CO_2	33	High
URINALYSIS:		----	

CONCLUSIONS: Subject received 40 mg of drug. There were no abnormal physical findings and no symptoms were noted. Low borderline serum proteins noted on screening perisisted throughout study. His CO2 was also marginally elevated on screening. It is unlikely that the above changes were caused or aggravated by the drug. No evidence of hemolysis was noted, no methemoglobin was detected.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#612 EXPERIMENT#21 GROUP#8 DRUG(NO mg) PLACEBO

SYMPTOMS: Subject reported slight sore throat on 3s in the a.m. No complaints thereafter.

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

7s:	MCHC	31.8	Low
14s:	MCHC	32.4	Low

CHEMISTRIES:

Scr-7s:	CO_2	33	High (5x)
Scr-2s:	Creat.	0.8	Low (3x)
2s:	Phos.	5.3	High
3s:	Phos.	5.0	High
	Uric H+	3.3	Low
	Na	147	High
7s:	Creat.	0.8	Low
14s:	Creat.	0.8	Low

URINALYSIS: ----

CONCLUSIONS: Subject received placebo and had no symptoms, abnormal physical findings, nor laboratory findings that could be attributed to adverse effect from study participation.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#613 EXPERIMENT# 21 GROUP#8 DRUG(NO mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	---		
VITAL SIGNS:	----		
HEMATOLOGY:			
0s:	Hapt.	17	Low
:	MCHC	32.4	Low *
7s:	MCHC	32.4	Low
	MCV	100	High *
14s:	Hapt.	8	Low
CHEMISTRIES:			
2s:	CO_2	33	High
	Ca	8.9	Low
3s:	Uric H+	3.6	Low
URINALYSIS:	----		

CONCLUSIONS: Subject received placebo and participated throughout the study period withou ill effect. Laboratory deviations were not unusual except for an unexplained low haptoglobin throughout study, exclusive of screening.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#614 EXPERIMENT#21 GROUP#8 DRUG(40 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	MCHC	32.3	Low *
2s:	MCHC	32.5	Low
	Eosin	9	High *
3s:	Eosin	8	High
7s:	MCHC	31.3	Low
14s:	MCHC	32.0	Low

CHEMISTRIES:

Scr-3s:	Uric H+	2.8-3.8	Low (4x)
0s:	Glob.	3.6	High
2s:	Creat.	0.8	Low
	CO_2	33	High
14s:	Glob.	3.4	High

URINALYSIS:

3s: 10-12 WBC/HPF with clumping. Repeat was clear.

CONCLUSIONS: Subject received 40 mg of drug. There were no subsequent symptoms nor physical abnormalities. No laboratory changes were identified consistent with adverse drug effect. There was no evidence of hemolysis and no methemoglobin.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#615 EXPERIMENT# 21 GROUP#9 DRUG(45 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr:	MCHC	32.2	Low *
2s:	Lymphs	47	High *
3s:	Lymphs	0§	
	Segs	0§	§Disintegrated cells,
	Monos	0§	tests not performed.
	Eosins	0§	
7s:	Hct.	36.0	Low+
	Hgb.	12.5	Low+
	RBC	4.1	Low+

+Isolated findings of doubtful validity

CHEMISTRIES:

Scr:	Cl	108	High
0s:	LDH	113	Low
3s:	Glob.	3.6	High
7s:	K+	3.4	Low
	Ca	8.8	Low
	Phos.	2.4	Low
14s:	SGOT	39	High

URINALYSIS: ----

CONCLUSIONS: Subject received 45 mg of drug and had no subsequent symptoms or positive physical findings. He had a variety of laboratory abnormalities, none fitting any particular pathophysiological pattern. He had no clear evidence of hemolysis, methemoglobin was not detected.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT# 616 EXPERIMENT#21 GROUP#9 DRUG(45 mg)
PLACEBO

SYMPTOMS: 2s: "stomach felt funny" in the a.m. No complaints after lunch.

		ABNORMALITIES	COMMENT	
PHYSICAL EXAM:		----		
VITAL SIGNS:		----		
HEMATOLOGY:				
0s:	MCHC	32.2	Low *	
	WBC	2.5	Low *	
2s:	WBC	3.6	Low	
7s:	WBC	3.8	Low	
	Hct.	37.7	Low +	+Isolated findings
	Hgb.	13.3	Low +	of doubtful validity
CHEMISTRIES:				
Scr:	CO_2	34	High	
0s:	Ca	8.9	Low	
2s-14s:	CO_2	34	High (4x)	
3s:	Urfc H+	3.5	Low	
7s:	K+	3.5	Low	
	Ca	8.9	Low	
	T Prot.	6.0	Low	
URINALYSIS:		----		

CONCLUSIONS: Subject received drug. On the morning of dosing he reported "feeling funny in the stomach". Otherwise asymptomatic. No positive physical findings. Laboratory deviations were minor variations of values noted at screening. There was no hemolysis detected and no methemoglobin noted.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#617 EXPERIMENT#21 GROUP#9 DRUG(NO mg) PLACEBO

SYMPTOMS: 2s: had 4 semi-formed stools between 10 am and 8 pm.

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
Scr-2s:	WBC	3.1-4.0	Low (3x)
	Lymphs	49-54	High (3x)
0s:	MCHC	31.9	Low
0s-7s:	Hct.	34.6-37.6	Low (4x)
	RBC	4.0-4.2	Low (4x)
0s-14s:	Hgb.	12.0-13.1	Low (5x)
14s:	MCHC	32.3	Low
	WBC	3.5	Low
	Plts.	404	High
	Retic.	1.7	High
CHEMISTRIES:			
Scr-3s:	Uric H+	2.7-3.8	Low (4x)
Scr:	Cl	96	Low
0s:	BUN	6	Low
	Trigly.	31	Low
	T Prot.	6.0	Low
2s:	CO_2	33	High
7s:	Data discarded +		
14S:	Trigly.	26	Low
URINALYSIS:	-----		

CONCLUSIONS: Subject received placebo. He had for soft stools on 2s but no abnormal physical findings. He had a variety of laboratory abnormalities, some unexpected and inexplicable. In retrospect, he was not an ideal subject, but he makes an interesting "control". Had he received the drug, his course would have been problematic.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.
+ Outlying values caused all chemistry data from day 7s to be discarded.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#618 EXPERIMENT# 21 GROUP#9 DRUG(NO mg) PLACEBO

SYMPTOMS: 2s: "appetite not up to par"

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
0s:	Monos	1	Low
2s:	Lymphs	53	High *
3s:	Lymphs	52	High
7s:	Hct.	39.0	Low *
	Eosins	0	Low
14s:	WBC	11.5	High
	Segs	74	High
	Retic	2.0	High *
CHEMISTRIES:			
Scr:	CO_2	33	High
0s-3s:	Uric H+	2.8-3.8	Low (3x)
0s:	K+	3.5	Low
7s:	Glucose	58	Low
	Cl	108	High
URINALYSIS:	----		

CONCLUSIONS: Subject received placebo. He had no noteworthy physical findings and no symptoms of drug intolerance. His laboratory values showed a few unexplained departures from normal.

NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#619 EXPERIMENT#21 GROUP#10 DRUG(NO mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	-----		
VITAL SIGNS:	----		
HEMATOLOGY:			
Scr-2s:	WBC	3.4-3.8	Low (3x) *
0s:	MCHC	32.1	Low *
2s:	Lymphs	48	High
3s:	Segs	38	Low
	Eosins	8	High
7s:	MCHC	32.1	Low
	WBC	4.0	Low
	Eosins	9	High
CHEMISTRIES:			
0s:	Trigly.	29	Low
2s:	CO_2	33	High
3s:	CO_2	33	High
3s-14s:	Creat.	0.8	Low
URINALYSIS:	----		

CONCLUSIONS: Subject received placebo. Had no symptoms and no abnormal physical findings. Laboratory values had no more than the expected variations from normal.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#620 EXPERIMENT# 21 GROUP#10 DRUG(50 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
	0s: MCHC	32.3	Low *
	7s: MCHC	32.2	Low
CHEMISTRIES:			
	2s: Uric H+	3.7	Low
URINALYSIS:	-----		

CONCLUSIONS: Subject received 50 mg of drug without symptoms or abnormal physical findings. There is no apparent relationship between the laboratory abnormalities and the administration of the drug. No hemolysis was noted; no methemoglobinemia was seen.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT# 621 EXPERIMENT# 21 GROUP#10 DRUG(NO mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
0s-3s:	MCHC	31.5-32.5	Low (3x) *
0s:	Hct.	53.4	High
	RBC	5.9	High
14s:	Plts.	349	High
CHEMISTRIES:			
Scr-2s:	CO_2	33	High (3x)
0s-14s:	Chol.	231-265	High (5x)
0s:	Cl	97	Low
3s:	Trigly.	276	High
URINALYSIS:	----		

CONCLUSIONS: Subject received placebo and had no symptoms or physical findings suggestive of drug intolerance. His laboratory deviations from normal were unremarkable.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#622 EXPERIMENT#21 GROUP#10 DRUG(50 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
Scr-14s:	Lymphs	50-55	High (6x) *
Scr-2s:	WBC	3.8	Low (3x) *
0s:	MCHC	32.4	Low *
:	Segs	38	Low
2s:	Hct.	52.5	High
	RBC	6.1	High
	MCHC	32.4	Low
3s:	Hct.	53.5	High
	Hgb.	17.6	High
	RBC	6.3	High
7s:	MCHC	32.0	Low
	WBC	3.9	Low
14s:	WBC	4.1	Low
CHEMISTRIES:			
2s:	CO_2	33	High
3s:	CO_2	33	High
	Creat.	0.8	Low
7s:	SGOT	42	High
	SGPT	46	High
URINALYSIS:			
14s:	Protein 1+		NCSICS*

CONCLUSIONS: Subject received 50 mg of drug; he had no symptoms and no positive physical findings. His laboratory findings showed a few marginal deviations from normal, none of them forming a pathophysiological pattern. Neither hemolysis nor methemoglobinemia was detected.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#623 EXPERIMENT#21 GROUP#11 DRUG(60 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
	0s: MCHC	31.9	Low *
	2s: MCHC	32.4	Low
	Lymphs	50	High *
	Segs	37	Low *
	Retic.	2.0	High
	3s: WBC	3.7	Low
	Lymphs	58	High
	Segs	26	Low
	Eosins	8	High
CHEMISTRIES:			
	0s: SGOT	2	Low
	3s: Glucose	110	High
	7s: Glucose	115	High
URINALYSIS:	----		

CONCLUSIONS: Subject received 60 mg of drug and tolerated it well, having no symptoms and no positive physical findings. His laboratory findings suggest no pathophysiological processes. No hemolysis was noted and there was no methemoglobinemia.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#624 EXPERIMENT# 21 GROUP#11 DRUG(60 mg)
PLACEBO

SYMPTOMS: None

	ABNORMALITIES		COMMENT
PHYSICAL EXAM:	----		
VITAL SIGNS:	----		
HEMATOLOGY:			
Scr-3s:	MCV	99.4-100.4	High (4x)
0s:	MCHC	32.1	Low *
2s:	MCHC	32.4	Low
3s:	MCH	34.3	High
14s:	Hct.	52.4	High
	MCV	102	High
	MCHC	32.3	Low
CHEMISTRIES:			
0s:	Creat.	0.8	Low
	Ca	8.9	Low
	SGOT	42	High
2s:	Na	139	Low
	CO_2	34	High
	Uric H+	3.8	Low
3s:	Uric H+	3.8	Low
7s:	BUN	24	High
	Uric H+	3.6	Low
15s:	Chol.	122	Low
	Glob.	3.5	High
URINALYSIS:			

CONCLUSIONS: Subject received 60 mg of drug. He had no symptoms and no positive physical findings. His laboratory abnormalities fit no identifiable pathophysiological pattern. There was no evidence of hemolysis or methemoglobinemia.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#625 EXPERIMENT#21 GROUP#11 DRUG(No mg) PLACEBO

SYMPTOMS: None.

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr-14s:	RBC	6.0-6.2	High (6x)
Scr:	Hct.	51.7	High
	WBC	4.1	Low
	Retic.	2.0	High *
2s:	MCHC	31.9	Low
:	Eosins	8	High
2s-7s:	Hct.	50.7-53.6	High (3x)
7s:	Eosin	8	High

CHEMISTRIES:

Scr:	Cl	109	High
	SGOT	11	Low
0s:	Creat.	0.8	Low
2s:	Glucose	113	High.
3s:	Glucose	110	High
	Trigly.	343	High
	SGPT	61	High
7s:	SGPT	71	High
15s:	Glucose	113	High

URINALYSIS: ----

CONCLUSIONS: Subject received placebo. He had no symptoms and no abnormal physical findings during the scheduled period of observation. He had triglyceride and SGPT elevations on the third day of the study, possibly related to unscheduled dietary intake. SGPT and triglycerides returned to normal by the end of the observation period. No adverse effect from study participation.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

INDIVIDUAL CLINICAL SUMMARY

SUBJECT#626 EXPERIMENT# 21 GROUP#11 DRUG(NO mg) PLACEBO

SYMPTOMS: Subject vomited about 1 pint of yellowish liquid about 10 minutes after ingesting capsules. for the rest of that morning, he felt lethargic. No remarkable symptoms thereafter.

	ABNORMALITIES	COMMENT
PHYSICAL EXAM:	----	
VITAL SIGNS:	----	

HEMATOLOGY:

Scr-2s:	Hapt.	151-165	High (3x)
Scr:	Retic.	2.0	High *
0s-2s:	MCHC	31.9-32.5	Low (3x) *
2s:	WBC	10.0	High
3s:	Hct.	51.3	High
	Plts.	350	High
15s:	Hapt.	162	High

CHEMISTRIES:

0s:	Glucose	70	Low
3s:	Glucose	113	High
	Na	135	Low
7s:	K+	3.5	Low

URINALYSIS: ----

CONCLUSIONS: Subject received placebo. Subject had vomiting on one occasion, cause unknown. Physical examination was negative throughout the study, laboratory studies unremarkable. No adverse effects from study participation.

*NCSICS-Not clinically significant in the context of this study.
----Done as scheduled, no abnormalities.

B

BIO - MED, Inc.

4401 HARTWICK ROAD · COLLEGE PARK, MARYLAND 20740 · TELEPHONE (202) 882-0977

TITLE: PHASE I SAFETY AND TOLERANCE TESTING FOR THE PEDICULICIDE, ABATE®: CUTANEOUS TOXICITY AND SENSITIVITY

PRINCIPAL INVESTIGATOR: RICHARD C. REBA, M.D.

CLINICAL DIRECTOR: KEVIN G. BARRY, M.D.

ASSOCIATE DIRECTOR: LESLIE B. ALTSTATT, M.D.

INSTITUTIONAL REVIEW BOARD MEMBERS:

GEORGE BANNING, JR., M.D., CHAIRMAN
JAMES A. DUKE, PhD.
DONALD M. HEIN
JUDY HANNAH
ANGELO J. TROISI

Phase I Safety and Tolerance Testing for the Pediculicide ABATE®* : Cutaneous Toxicity and Sensitivity.

INTRODUCTION

ABATE®(0,0,0',0'-tetramethyl 0,0'-thiodi-p-phenylene phosphorothioate) is a potent pediculicide shown to be effective against strains of lice resistant to standard treatment. When prepared in a concentration of 2%, the drug has great potential to meet the military requirement for a raw dust-type pediculicide for the control of lice and lice-borne diseases.

The need for a new pediculicide is based on 1) the development of lice resistance to lindane and malathion, the currently registered pediculicides; 2)the short shelf life of malathion dust and; 3) the possible cancellation of lindane as an acceptable product.

PREVIOUS STUDIES OF ABATE:

Extensive animal toxicology studies have been done. These are presented in tabular form in the appendix. The relevant findings are as follows:

1. An oral LD_{50} in rats of 2.03-2.33 g/kg for technical ABATE (90% pure).[1]

2. A dermal LD_{50} in rabbits of .97-1.93 g/kg for technical ABATE.[1]

3. Reduction or inhibition of cholinesterase in animals during feeding studies.[1,2]

4. No evidence of skin irritation or teratogenicity in rabbits.[2,3]

5. ABATE, applied in low doses, does not appear to be absorbed through the intact or abraded skin of rabbits.[4]

6. Mutagenic (Ames Salmonella/microsome test) studies negative.[5]

Testing of the substance in humans has also been reported:

1. No clinical symptoms attributable to ABATE were noted in 2000 villagers who drank water treated with ABATE (1ppm) during a continuous 19 month period. There was no significant change in red blood cell or plasma cholinesterase levels in those individuals monitored.

*Registered trademark of American Cyanamid Company

Furthermore, there was "... no change in the birth or death rate, number of spontaneous abortions, or number of stillbirths. No congenital abnormalities occurred during the study, nor were there any unusual illnesses or deaths among the residents..."[6]

2. 19 male volunteers were administered technical ABATE (90% pure) in oral doses of either 1) 64 mg/man/day for 4 weeks or 2) increasing doses over 4 weeks beginning at 2 mg/man/ day rising to a dose level of 256 mg/man/day for five days. No clinical symptoms or adverse reactions resulting from the administration of the compound were observed, nor was there a significant difference in red blood cell or plasma cholinesterase levels between subjects and controls.[7]

3. A formulation of 2% ABATE in pyrax powder was "sleeve tested" on US Marines who were exposed to 3-6 grams for 12 hours/day, 4 days/week, for six weeks. " The treated sleeves did not cause any ill effects in the research subjects, and the results of all laboratory medical tests remained within normal ranges."[8]

4. 2% ABATE in pyrax powder was applied for 48 hours to a small area of intact skin of 31 volunteers. Two weeks later, a challenge dose was applied to the same area. No evidence of irritation or sensitization was found.[4]

5. 96 volunteers were treated with a single dermal application of 2 ounces of 2% ABATE in pyrax powder for 25 days. Findings were summarized as follows:

> During the test the attending physician found no test subjects who manifested symptoms which could be attributed to the treatments. There were no reports of skin irritation from the test subjects. The screening evaluation of whole blood ChE (cholinesterase) indicated no pre- or post treatment depression of ChE activity. Evaluation of LDH, SGOT, and SGPT results indicated that no changes in liver function occurred in the test groups. The SGOT results provide evidence that no damage to skeletal muscle or myocardium occurred. BUN results provide evidence that no changes in kidney function were experienced during the test.
> ...ABATE does not appear to be absorbed through the intact skin of man when applied in a pyrax formulation to the skin of man for 24 days and serum ChE activity is used as an indicator of absorption.[9]

The above studies suggest that the application of small quantities of the 2% preparation of ABATE in pyrax powder to the skin of healthy subjects would be associated with very

little risk. However, no studies have been done which provide an estimate of the prevalence of cutaneous toxicity and hypersensitivity from the application of ABATE.

We propose to study the 2% dust preparation of ABATE using healthy "free-standing"[10] volunteers and standard skin-exposure techniques to demonstrate cutaneous toxicity and hypersensitivity. With these exposure methods, acute, direct skin toxicity and hypsersensitivity due to circulating antibody would be manifested in 2-4 hours. Closed patch testing would detect cell mediated hypersensitivity 24-48 hours after application.

MATERIALS AND METHODS:

Healthy male subjects between the ages of 18 and 35 years will be recruited from the Washington, D.C. metropolitan area. Subjects will be screened by personal interview, and a physical evaluation consisting of a physical examination, blood chemistries, a CBC, whole blood cholinesterase levels and a urinalysis. The following criteria must be met:

1. No current or recent episode (last 5 years) of atopic dermatitis.
2. No current or recent episode (last 5 years) of moderate or severe allergic problems such as asthma, hay fever, drug or food allergy.
3. No current contact dermatitis of any kind.
4. No current use of antihistamines or immunosuppresants.
5. No moderate to severe dermatophytosis.
6. By his own declaration, the subject must be in good health.
7. A physical evaluation showing good general health and the absence of any medical conditions which would increase the risk of participation for that subject or compromise the design of the study.

A sufficient number of subjects will be recruited until either 200 have been tested or until 10 instances of direct irritation or sensitivity have been identified (see "statistical considerations"). Subjects who are tested by direct exposure for toxicity and antibody-mediated hypersensistivity and found to be positive may not participate further as subjects for closed-patch testing.

Potential study subjects will be presented with a written explanation of the study (see appendix) and will have an explicit opportunity to ask questions about the study and their role in it. All subjects must sign the informed consent document (see appendix) before they will be allowed to participate.

Two types of skin testing will be sequentially performed: 1. Immediate reactions studies: Direct application studies for immediate toxicity and antibody mediated hypersensitivity and 2. Delayed reaction studies: Closed patch testing group for cell mediated hypersensitivity.

PROCEDURES

This will be a single blind design, with a control substance (vehicle without active pediculicide) and 2% ABATE applied to orthogonal areas of the ventral surface of the forearm. Qualifying subjects will report to the clinical facility on day 1 for their assigned starting date(see schematic). Each subject will have a 3X3 cm area of the ventral surface of each forearm marked in a water-resistant ink with a felt-tip pen.The test substances will be delivered by metal scoops pre-set to measure out 1 gram of each test substance. The substance will be spread over the test area, then removed by dry brushing 5 minutes after application (brushing will be done in plastic bags to minimize air contamination). The test substances will be reapplied in a like manner on study day 3 as on day 1, and the sites will be examined 5 minutes and at two hours after application, before each reapplication and 7 days after the initial application (see study schematic).

Any subject showing a positive reaction (see appendix) will be referred to the consulting dermatologist for evaluation and any required treatment. Such reactions will be carefully described and photographed.

Subjects not showing a positive reaction after 2 hours will be entered into the Delayed sensitivity phase of the study which is described below.

Subjects from the direct application study will be participants in the closed patch testing except for individuals who react positively in the Immediate Reaction phase of the study who will be excluded.

A placebo and an active substance will be applied simultaneously, without disclosing their identity to the subject.

This group of subjects will have the test substances applied in pairs to the lumbar area of the skin of the back (one each to either side of the spine) in standard aluminum testing discs containing 1 gm of the test substance (placebo in one, control in the other).

These discs will remain in place for 48 hours, held by "scanpor" tape. Subjects will be examined at the removal of the discs and again at 24 hours and 5 days after removal.

Subjects without positive reactions will have the procedure repeated in 30 days.*

Study Schematic: Skin testing is outlined in the schematic below:

STUDY DAYS	SD1	SD3	SD4	SD8	SD30	SD32	SD33	SD37
DIRECT APPLIC.	X	X			X	X		
DISC APPLIC.	X				X			
DISC REMOVAL		X				X		
SITE EXAM	X	X	X	X	X	X	X	X
LABORATORY §		X+		X		X+		X

§ Blood examinations include a) a CBC with differential count, platelet count, RBC indices and reticulocyte count b) blood chemistries glucose, BUN, creatinine, sodium, potassium, chloride, carbon dioxide, uric acid, total protein, albumin, globulin, calcium, phosphorous , cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, and total bilirubin c) whole blood cholinesterase levels will be performed in screening and on days shown above(X+). Also, a complete urinalysis will be done at the time of each clinical blood test.

Applications of the test substances will be made in a manner that will minimize air contamination. Particular care will be taken to insure that personnel administering the test substances are not placed at risk. Cholinesterase levels of blood and serum will be measured weekly on techinical personnel.

Forms for the orderly collection of data have been designed. Samples are included in the appendix. Registered nurses will apply the test substances, with a physician in attendance at all times. All evaluations of dermal reactions will be performed by a physician.

Subjects will be advised of the possibility of delayed local or systemic reactions, and will be advised to seek medical assistance promptly (at Bio-Med, Inc. or elsewhere, depending upon the circumstances) should such reactions occur.

*Direct application and closed patch testing will be repeated at 30 days to detect induced hypersensitivity to ABATE.

The written instructions that will be given to each subject describing the care of the exposure site and management of skin reactions are included in the appendix.

At the conclusion of each subject's participation in the study, the physical evaluation will be repeated (P.E.,Blood chemistries, CBC, UA). Any significant abnormalities will be cause for follow-up until normalcy occurs or proper medical disposition has been made.

ANALYSIS AND INTERPRETATION OF DATA

All reactions will be noted as positive or negative. The severity of positive reactions will be graded from "?" to "+++"(see appendix). These reactions will be tabulated for each subject and analyzed as described below.

Using the occurrence of toxicity and hypersensitivity in our subject population, we will make estimates of the frequency of those phenomena and we will wish to know the confidence limits (CL) of those estimates. We will especially be interested in calculating the confidence limits in series of moderate sizes (100-500) where the observed frequency was zero.

Under the conditions of an observed frequency of zero, the upper 95% CL may be calculated as:

$$=1-e^{\ln(1-CL)/N}$$

From that formulation,this Table may be derived:

EXAMPLES OF 95%CL IN SAMPLES WITH OBSERVED "ZERO"FREQUENCY

SAMPLE SIZE(N)	UPPER 95%CL DOES NOT EXCEED--
100	3.00%
200	1.50%
300	1.00%
400	0.75%

The price for increasing assurance about the prevalence of toxicity and hypersensitivity in the general population is apparent. It must be noted that these estimates are based upon assumptions of optimal conditions in the conduct of the experiment, and therefore significant time effects, for example, will substantially increase the required number of subjects.

Should it become necessary to do so, the Principal Investigator, acting witn the concurrence of the COTR, may enroll more than 200 subjects in each of the treatment groups.

References

1. American Cyanamid's Medical Department Toxicity Reports; American Cyanamid, Princeton, N.J.; in IND No.14,252

2. USAEHA-MT "Preliminary Assessment of Relative Toxicity of Candidate Louse Powder Containing ENT 27165" Project No. 33-1-67 April 1967; in IND No. 14,252

3. USAEHA "Toxicological Assessment of ABATE: Effect of ABATE Formulations on the Embryonic Development of Rabbits" Project No. 51-1302-78; in IND No. 14,252

4. USAEHA-MT "Assesment of Relative Toxicity of Candidate Louse Toxicant ENT 27165" Study No. 33-001-70 July-Nov 1969; in IND No. 14,252

5. Litton Bionetics, Inc. "Mutagenicity Evaluation of ABATE-Technical Grade" LBI Project No. 20838 Sept. 1977 Litton Bionetics, Kensington, Md.; in IND No. 14,252

6. Laws, Jr.,E.R. et al "Field Study of the Safety of ABATE for Treating Potable Water and Observations on the Effectiveness of a Control Programme involving both ABATE and Malathion"; Bull. WHO 38:439-445, 1968; in IND No. 14,252, Supplement No. 1

7. Laws, Jr.,E.R. et al "Toxicology of ABATE in Volunteers"; Arch. Env. Health 14:289-291, Feb. 1967; in IND No. 14,252, Supplement No. 1

8. Cole, M.M. et al "Sleeve Tests of Insecticidal Powders for Control of Body Lice"; J. Econ. Ento. 62(1):198-200 Feb. 1969; in IND No. 14,252, Supplement No. 1

9. USAEHA-M Toxicologic and Entomologic Special Study No. 99-006-70/71: Human Exposure to 2 Percent ENT 27165 in Pyrax Powder and 2 Percent ENT 27041" Jan-Mar 1970 in IND No. 14,252, Supplement No. 1

10. Marzuli, Francis N. and Maibach, Howard I., eds. Dermatotoxicology and Pharmacology; Hemisphere Publishing Corp.; 1977

TABULAR PRESENTATION OF ANIMAL EXPERIMENTATION OF ABATE

TEST	RESULTS	INTERPRETATION
TECHNICAL ABATE (90% pure)		
ORAL LD_{50} Rats	[1]* Male - 2.03(1.26-3.2)g/kg Female - 2.33(1.66-3.27)g/kg	[4](App.A) Moderately toxic substance
Mice	4.7(4.1-5.4)g/kg	[2] Consistent with other toxicity data
DERMAL LD_{50} Rabbits: 24 hour contact with shaved skin	[1] Male - 1.93(1.33-2.79)g/kg Female - .97(.57-1.65)g/kg	[4](App.A) Moderately toxic
PRIMARY IRRITATION Skin-Rabbits: 93.7% pure compound	No irritation of intact or abraded skin	[2] USAEHA PIEP Category I (unrestricted use for application to human skin)
Eye-(Rabbits?) .2 ml 93.7%	Slight irritating reaction at 24 hours; eyes normal at 48 hours	[2] USAEHA PIEP Category A (unrestricted use)
Eye-Rabbits: .1 ml 90% pure compound	[1] Not irritating	
SKIN SENSITIZATION Guinea pigs	[2] Challenge dose produces no response greater than "sensitizing" doses	
SUBACUTE ORAL TOXICITY: TECHNICAL ABATE Rats: 10 mg/kg/day for 44 days	31% inhibition or reduced cholinesterase (ChE) after 14 days; 47% ChE inhibition after 11 days; symptoms of organophosphate poisoning observed	[2] Compound may cause a decrease in cholinesterase activity

TABULAR PRESENTATION OF ANIMAL EXPERIMENTATION OF **ABATE**

TEST	RESULTS	INTERPRETATION
Rats: 100 mg/kg/day for 44 days	64% inhibition of red cell ChE after 3 days; 87% ChE inhibition after 11 days; symptoms of organophosphate poisoning observed [2]	Compound may cause symptoms of increased cholinergic activity. [2]
Rabbits: 10 mg/kg/day for 44 days	26% inhibition of red cell ChE after 7 days; 47% inhibition of ChE after 35 days; no symptoms of organophosphate poisoning observed [2]	Compound may cause decrease in ChE activity. [2]
Rabbits: 100 mg/kg/day for 5 days	38% of animals died; 50% of all rabbits showed necrosis of the liver [1]	Compound may cause diffuse or focal necrosis.
Rats: 2 ppm/day for 92 days	No treatment related effects [1]	
Rats: 6 ppm/day for 92 days	Males:Borderline inhibition of red blood cell (RBC) ChE [1]	
Rats: 18 ppm/day for 92 days	Inhibition of RBC ChE, borderline brain ChE inhibition; RBC ChE returned to normal within 2 weeks post treatment [1]	
Rats: 54 ppm/day for 92 days	Inhibition of RBC, plasma and brain ChE; 2 weeks post treatment RBC and plasma ChE in males still depressed [1]	
Rats: 350 ppm/day for 86 days	Slight decrease in total weight gain of females relative to controls; marked RBC, plasma and brain ChE inhibition; significant decrease in liver weight in males [1]	
Dogs: 2,6, or 18 ppm/day for 90 days	No treatment related effects	

TABULAR PRESENTATION OF ANIMAL EXPERIMENTATION OF ABATE

TEST	RESULTS	INTERPRETATION
Dogs: 700 ppm/day for 1 week, then 500 ppm/day for 11 weeks	[1] Initial "cholinergic signs", marked RBC, plasma and brain ChE inhibition; no gross or microscopic pathology	
DERMAL APPLICATION: TECHNICAL ABATE Rats: (intact/abraded skin) 12 mg/kg/day ABATE in aqueous emulsion 5 days/wk for 3 weeks	[1] No significant treatment related effects (ChE not monitored)	
Rats: (intact/abraded skin) 60 mg/kg/day as above	[1] Male - significantly lower mean weight gain relative to controls Female - increase in liver and kidney weight, no gross or histopathology (ChE not monitored)	
90 DAY WEAR TEST: RABBITS Continuous wear with reapplications 1/week		
TECHNICAL ABATE (86.2%) with .5 ml. acetone (85.7 mg/kg) intact skin	[4] Isolated changes in serum amylase, ChE and BUN significant at .01 level relative to cage controls	
2% ABATE/pyrax powder (4.3 g powder/kg) intact skin	[4] No significant skin irritation; no significant difference in hematology, blood chemistries, pathology, weight gain or organ/body weight ratios relative to cage controls	[4] ABATE, at the dosages applied, does not appear to be absorbed through the intact or abraded skin of rabbits when ChE is used as an index of absorption.
2% ABATE/pyrax powder with .1 ml "artificial sweat" (4.3 g powder/kg) intact skin	[4] No physiologically significant changes noted	

TABULAR PRESENTATION OF ANIMAL EXPERIMENTATION OF ABATE

TEST	RESULTS	INTERPRETATION
90 DAY WEAR TEST, Continued		
2% ABATE/pyrax powder(as above) abraded skin	[4] Isolated changes in BUN and serum amylase levels significant at .01 level relative to cage controls.	as above
EMBRYOTOXICITY/ TERATOGENICITY Pregnant rabbits dosed with formulations of ABATE days 6-18 of pregnancy		
TECHNICAL ABATE suspension in 10% gum Acacia		
Oral: 32 mg/kg/day	[3] Significant decrease in RBC ChE; slight decrease in gestation indices(litters born alive/pregnancies);33% doe mortality; no gross pathology	
Dermal: 164 mg/kg/day	Significant decrease in RBC, plasma ChE; slight decrease in gestation indices; decrease implantations; embryotoxic (decrease live fetuses, total fetuses, and fetal weight). 40% doe mortality; no gross pathology	[3] No teratological hazard in rabbits at compound levels which produce toxic effects.
10% ABATE/pyrax powder		
Dermal:163 mg ABATE/kg/day	Significant decrease RBC ChE; decrease in fertility indices no gross pathology	[3] No teratological hazard
2% ABATE/pyrax powder		
Dermal:16.3 mg ABATE/kg/day	[3] No treatment related effects	

TABULAR PRESENTATION OF ANIMAL EXPERIMENTATION OF ABATE

TEST	RESULTS	INTERPRETATION
SUCCESSIVE GENERATION FEEDING[1]		
Rats: 25 or 125 ppm ABATE/ day for 3 generations	No treatment related effects on lactation or reproduction	
SYNERGISM[2]		
Rats: oral 1/8 LD_{50}ABATE +1/8 LD_{50}malathion	All test animals died	Results indicate a four fold potentiation when malathion and ABATE are given together.

* References: same as those cited in text

PATCH TESTING READING AND INTERPRETATION *

Reading the Test Results: *At each test reading, it is traditional to note the result as negative or positive, and grade the positive results on a quantitive scale. The International Contact Dermatitis Research Group has recommended a 1+ representing erythema and edema, 2+ showing vesicles in addition, and 3+ being a very severe reaction. Weak and questionable reactions are recorded by a question mark.*

Interpretation Key: Cutaneous Reaction

?	*doubtful reaction; faint macular erythema only*
+	*weak (non-vesicular) positive reaction; erythema, infiltration, possibly papules*
++	*strong (vesicular) positive reaction; erythema, infiltration, papules, vesicles*
+++	*extreme positive reaction; bullous reaction*
-	*negative reaction*

At each examination patients will be asked if they have irritation of the skin, increased sensitivity, mild or severe itching or burning.

The skin will be stroked lightly to determine Hyperesthesia.

* Provided by Consulting Dermatologist

ABATE PROTOCOL
INDIVIDUAL DATA COLLECTION
WORK SHEET

Subject's Name: _____

Accession Number: _____

Portion of Study: OPEN PATCH CLOSED PATCH

Day of Study: _____

Reason for visit: _____

Procedures: _____

_____

_____

Examinations: _____

_____

_____

_____

Instruction and Disposition: _____

_____

_____

EXPLANATION FOR POTENTIAL SUBJECTS
EXPERIMENT NUMBER 23

ABATE®* : Cutaneous Toxicity and Sensitivity

Gentlemen:

The study now being considered is designed to measure human sensitivity to an insecticide called ABATE® when applied as a powder to the skin. ABATE is being considered by the U.S. Army as an agent to control the spread of lice, which can carry diseases such as trench fever, relapsing fever, and epidemic typhus. Historically, the possible spread of louse-borne diseases has threatened the health of many fighting forces, including those of the United States, as seen in World War II and in the Korean War.

ABATE is being considered as an agent to control lice for several reasons:

1) Lice are developing resistance to the agents in current use.
2) ABATE has demonstrated effectiveness in killing lice.
3) ABATE has a longer shelf-life than current agents;
4) ABATE is considered by the Environmental Protection Agency to be the least toxic of avail[illegible] organophosphates.

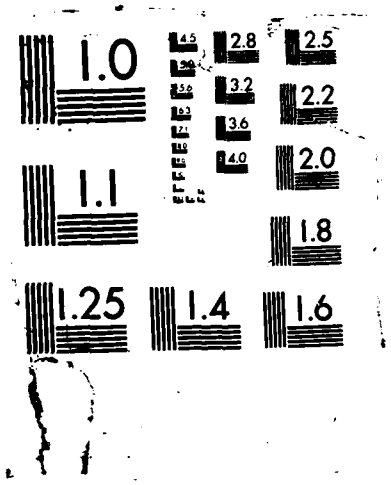
While ABATE is currently registered with the E.P.A. f[illegible] control of several species of insects, its use as [illegible] applied to humans to kill body lice is still under [illegible]gation. As a member of the family of organophos[illegible] kills lice by interfering with the normal [illegible] insect's nervous system. Normally, a [illegible] acetylcholine, which plays a role in the [illegible] impulse between nerve fibers, is ne[illegible] called cholinesterase. This neutrali[illegible] fiber to return to its non-transmit[illegible] to transmit the next impulse. AB[illegible] cholinesterase, preventing [illegible] acetylcholine, resulting in the [illegible] function properly.

As intended for use on [illegible] powder consisting of 2% [illegible] medium, which is compo[illegible]imately 80%) and [illegible] animal tests of [illegible] for periods up [illegible] ferences betwe[illegible]

*Regis[illegible]

AD-A107 423 ARMY DRUG DEVELOPMENT PROGRAM PHASE 1 CLINICAL TESTING 2/2
(U) BIO-MED INC COLLEGE PARK MD R C REBA APR 85
DAMD17-75-C-5036

UNCLASSIFIED F/G 6/15 NL


1.0
1.1
1.25
1.4
1.6
2.8
3.2
3.6
4.0
2.5
2.2
2.0
1.8

cholinesterase levels, blood cell counts, weight gain, skin irritation, and health of internal organs. Other studies in animals indicate that ABATE in the same formulation would not present a toxic hazard to man when applied once to the skin, and that absorption would be expected to be less than 3% of the applied dose. These studies indicate that the majority of the chemical would be excreted from the body within 24 hours through the urine, with elimination essentially complete after 3 days. The tests provided no evidence that the compound was retained in the animals generally or in specific areas.

ABATE in the 2% formulation has been tested in humans for possible ill effects. In a 19-month study in Puerto Rico, the people of a village of about 2,000 drank water treated with ABATE, consuming approximately 1 mg/man/day, with no clinical symptoms attributable to the insecticide observed. In another study, 28 male volunteers were given either a dose of 256 mg/man/day for 5 days, or a dose of 64 mg/man /day for 28 days without developing clinical symptoms or side effects attributable to ABATE. Levels of cholinesterase in red cells or plasma were not affected adversely.

ABATE has also been tested in the 2% formulation as a powder applied to the skin of human subjects. When applied to 1 square inch of the arm of 31 men for 48 hours, there was no evidence that the skin had developed sensitivity to ABATE. In a separate study, subjects wore clothing treated with 3 to 6 grams of ABATE for 12 hours/day, 4 days/week, for 6 weeks. There were no ill effects on the subjects, and the results of all laboratory medical tests remained within normal range.

These studies suggest that there would be very little risk in applying small quantities of ABATE 2% to the skin of healthy human subjects. The study currently being undertaken is designed to see if ABATE 2% causes irritation when applied directly to the skin, or if it causes the skin to become sensitized to future applications. There will be two separate test periods in this study: I) The Immediate Reaction Testing period and II) The Delayed Reaction or closed patch testing period.

I. The Immediate Reaction Testing period

Those of you who qualify will report to the clinical facility on Study Day 1, a Monday, for your assigned sub-group. Each of you will have an area approximately 1 inch square marked with water-resistant ink on the inside of both your left and right forearm. One gram of ABATE 2% will be applied to one arm, while 1 gram of pyrax powder with no ABATE will be applied to the other. To help ensure that you will treat the application sites without bias, you will not be told which site is receiving which treatment. After 5

minutes, the powders will be dusted off and the sites examined for any skin irritation, known as a positive reaction. Those participants who experience positive reactions will be referred to the consulting dermatologist and will not participate in any further testing.

Those who show no reaction to the application two hours after application of the substance will enter into the delayed reaction study period.

II. Delayed Sensitivity Period:

Those of you referred on for Delayed Sensitivity testing will have two perforated discs, one containing the drug ABATE and the other containing placebo, applied to each side of your lower back. You must keep those discs in place and dry for the next 48 hours. Two days after application (study day 3), you will return to the clinical facility where the discs will be removed and the underlying skin will be examined. On that same visit, the dry powder will once more be applied to the skin of your forearm for 5 minutes, and you will be observed for two hours for reactions. You will return the next day for site examination. You will return one week (7 full days) after the first application of the test substance for evaluation of the test sites on both your forearm and back. Laboratory tests (blood tests and urinalysis) will be done on this day as well. Thirty days after your initial test application, the entire testing procedure will be repeated. The test powder will be applied to your forearm and the application sites examined at five minutes and again at two hours after application. If there is no reaction, the perforated discs will be applied. You will return 48 hours later (study day 32) for disc removal, reapplication of the test powder to your forearm, and examination of the test sites as done before. You will return the next day for site examination. Your final visit will be on study day 37 when you will have a complete physical evaluation including laboratory tests and a physical examination. If your evaluation is normal you will be dismissed from the study. In the event of any abnormality, you will be carefully followed until normalcy is re-established or proper medical disposition has been made.

If there is a positive reaction at any time, you will be referred to a consulting dermatologist for evaluation and treatment if necessary, and you will not participate in any further testing. Photographs of the sites will be taken in these cases.

Instructions for the Care of the Sites and Possible Reaction

1) During the periods of testing (study Days 1 through 8 and 30 through 37), keep the areas of application dry. Do not wash them.
2) Do not apply ointments, lotions, powders or sprays to the areas during the test periods.
3) If you experience a reaction during the day, and you are not scheduled to come in to BIO-MED that day, call and arrange a visit. If you experience a reaction during the night or over the weekend which you feel requires medical attention, call Dr. Kevin G. Barry at 561-4992.
4) The possible skin reactions are similar to those of a localized sunburn. These may vary from redness at the site of application to blistering.

The study is outlined in the schematic below:

DAY OF STUDY	SD1	SD3	SD4	SD8	SD30	SD32	SD33	SD37
POWDER APPLIC	X	X			X	X		
DISC APPLIC.	X				X			
DISC REMOV		X				X		
SITE EXAM	X	X	X	X	X	X	X	X
LABORATORY§		X		X		X		X

§ Laboratory will include complete blood testing and urinalysis. Blood will be obtained by venipuncture.

You should know the policies and procedures followed at BIO-MED, Inc. to minimize the risk to your health and well-being. They are:

1. All procedures are conducted by a physician licensed in Maryland, or by a registered nurse or technician directly under the physician's supervision.

2. Each study to be conducted at BIO-MED, Inc. is reviewed by other agencies for compliance with Department of Health and Human Services Guidelines regarding subject participation in medical experiments. Those agencies are:

   a. The Food and Drug Administration.
   This arm of the Federal Government reviews study proposals for investigational new drugs.

   b. The Regulatory Agencies of the sponsoring bodies.
   In the case of studies sponsored by the U.S. Army, studies must be approved by the Human Use Committee of the Office of the Surgeon General of the U.S. Army.

c. <u>The Institutional Review Board of BIO-MED, Inc.</u> This board in made up of informed citizens from the local community. The board reviews each proposed study to see that the risks to the subjects are minimal, precautions are taken to avoid risk when possible, and that risks are fully disclosed to the subjects. The members of this board occasionally visit the clinical facility to inspect the conduct of the study.

3. To further insure your personal protection the following standard procedures are established:

   a. Should you require emergency medical treatment, you will be taken to nearby Doctor's Hospital of Prince George's County.

   b. As a temporary employee of BIO-MED, Inc. you are protected by Workmen's Compensation for disability resulting by reason of your employment.

   c. At the conclusion of your participation in the study, you will have a complete physical evaluation including a physical examination, blood tests and urinalysis. Any significant abnormalities will be followed up until normalcy is reestablished or proper medical disposition has been made.

After a member of the investigating team has explained the nature, design and risks of the study, and is satisfied that you understand both the study and the written informed consent form, you will be permitted to sign the form. No subject may participate without a signed consent. By signing the informed consent, you signify that the study has been explained to you with regard to its risks and requirements, and that you wish to participate.

It should be clear to you that your participation in this study is of no medical benefit to you personally. The benefit, rather, is to others who live in parts of the world where louse infestation is a serious problem, including Americans, both civilian and military, who may be exposed to it while traveling in these areas. Your participation must be entirely voluntary with full knowledge of the personal risks and general benefits involved. Furthermore, you retain the right to withdraw your consent at any time without fear of any consequences.

SUBJECT AGREEMENT
CONSENT TO PARTICIPATE AS A STUDY SUBJECT

I, _____ hereby give my informed consent to participate as a study subject in the study entitled "ABATE®: Cutaneous Toxicity and Sensitivity."

The implications of my voluntary participation; the nature, duration and purpose; and the methods by which it is to be conducted and the inconveniences and hazards which may reasonably be expected have been explained to me by Dr. _____, and are set forth in the document titled "Explanation for Potential Subjects, Experiment Number____ : ABATE®: Cutaneous Toxicity and Sensitivity.", which I have initialed.

I understand that unexpected reactions may occur with any drug. The known discomforts and potential risks of participation as a subject in this study have been explained to me and I freely and voluntarily accept them. I understand that I will receive no direct therapeutic benefit from participation in the study.

I understand that as a temporary employee of BIO-MED, Inc., Workmen's Compensation is provided for any disability resulting by reason of my position as employee.

All questions and inquiries I have made regarding the study have been answered to my satisfaction and I understand that I have the right to ask questions concerning the study at any time and have them answered to my satisfaction. Further, I understand I am free to withdraw, without prejudice, my consent and participation from the project at any time; however, I may be requested to undergo further examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being.

I consent to the taking and publication of any photographs in the course of the study for the purpose of advancing medical science, provided that my identity will remain confidential.

I certify that I have read and understand the above consent and that the explanations therein were made to me and that all inapplicable paragraphs, if any, were stricken before I signed.

_____ _____
Date Signature Investigator Certification

Address _____ _____
Witness

_____

REAFFIRMATION OF CONSENT:

_____ _____
Date Signature Witness

BIO - MED, Inc.

4401 Hartwick Road · College Park, Maryland 20740 · Telephone: (202) 882-0977

TO: Subjects in the "ABATE" study at BIO-MED, Inc.

INSTRUCTIONS FOR CARE OF APPLICATION SITES AND POSSIBLE REACTIONS

You have had a substance called "ABATE", a specialized insecticide, applied to your skin.

The areas of application must be kept clean and dry during the testing period (study days 1 through 8 and 30 through 37). Do NOT wash the application sites during this time.

Do NOT apply any ointments, lotions, powders or sprays to the areas during the testing period.

If a disc containing powder has been applied, you must keep that site clean and dry until the disc is removed.

If you have itching or discomfort at the site where ABATE has been applied, please call BIO-MED, Inc. for instructions or return directly to the clinic. If you experience a reaction during the night or over the weekend which you feel requires medical attention, call your family physician or Dr. Kevin G. Barry at 561-4992.

Possible skin reactions: these may vary from redness at the site of application to blistering. The possible changes are similar to those of a localized sunburn.

END

FEb.

1988

DTIC