

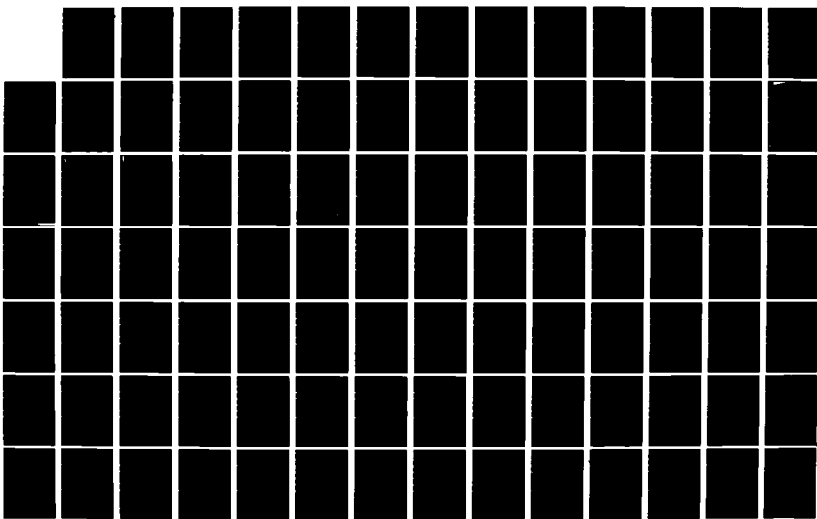
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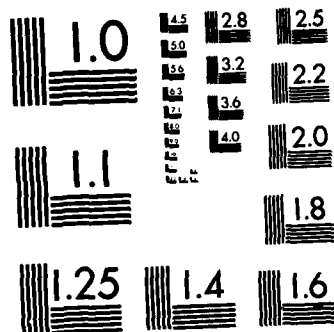
DEVELOPMENT AND TESTING OF A SUSTAINED RELEASE SYSTEM
FOR THE PREVENTION OF MALARIA(U) DYNATECH R/D CO
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DEVELOPMENT AND TESTING OF A SUSTAINED RELEASE SYSTEM FOR THE PREVENTION
OF MALARIA

Annual and Final Report

J. D. Gressar, Ph.D.
D. L. Wise, Ph.D.

September 1979

(Annual for the period March 1978-May 1979) (Final for June 1974-May 1979)

US Army Medical Research and Development Command
Fort Detrick, Frederick, MD 21701

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Dynatech R/D Company
a Division of Dynatech Corporation
Cambridge, MA 02139

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The matrices have been used as components of two dual drug systems. System I includes WR-7557 and WR-158122 in a 10/1 wt. ratio. System II includes DADDS and WR-158122 in a 10/1 wt. ratio.

Three baboons received System I with a one additional baboon serving as a control to receive a 10/1 mixture of the pure drugs. Two baboons received System II with two additional baboons serving as controls. All baboons received a total drug dose of 50 mg/kg.

Excretion data for System I tests are complete to day 168, WR-7557 recovery was almost complete (99% for the control, 90% for the three baboons receiving the matrix). Over 93% of the recovered material appeared in the urine. Excretion by the animals receiving the matrix was fairly constant to day 40 and virtually complete by day 80.

WR-158122 (System I) excretion continued to day 168 by animals receiving the matrix but ceased by day 98 from the control.

Excretion of WR-4593 (System II matrix) was an almost linear function of time for the 182 days of data. Excretion by the controls was similar except for an early burst of approximately 52 mg in about 3 days. Of the 216 mg recovered from the experimental animals, 199 mg were excreted in urine.

The pattern of excretion of WR-158122 derived from the System II matrix was similar to that observed for System I except that the rate for the former was about twice as rapid.

Analysis of tissues excised from System I baboons indicated only slight uptake of carbon-14 and tritium in the three animals receiving the matrix and none by the control. Tissues consistently showing tritium include bile, thymus, thyroid, liver and kidney. Tissues with consistent evidence of carbon-14 include blood, bile, thyroid, heart, gall bladder, liver and ileum.

Necropsies of System II baboons have been performed and tissues have been analyzed. As with the System I baboon, very little carbon-14 uptake was observed. However, virtually all tissues contained significant tritium derived from WR-4593. This result may be derived from method of labeling of this compound which involved exchange with tritiated water.

Unclassified

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FOREWORD

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



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TABLE OF CONTENTS

<u>Section</u>		<u>Page</u>
	LIST OF FIGURES	iv
	LIST OF TABLES	v
1	SUMMARY	1
	1.1 Review of First Year of Contract DAMD-17-74-C-4120	1
	1.2 Review of Second Year of Contract DAMD-17-74-C-4120	1
	1.3 Review of Third Year of Contract DAMD-17-74-C-4120	2
	1.4 Review of Fourth Year of Contract DAMD-17-74-C-4120	2
	1.5 Summary of Fifth Year of Contract DAMD-17-74-C-4120	3
2	WR-7557/WR-158122 DUAL DRUG SUSTAINED RELEASE SYSTEM: FABRICATION AND EVALUATION OF SYSTEM I	8
	2.1 Description of System I	8
	2.2 Excretion of Tritium Labeled Materials Derived from WR-158122	11
	2.3 Excretion of Carbon-14 Labeled Materials Derived from WR-158122	12
	2.4 Analysis of Drug Residues Remaining in Tissues After Sacrifice of Baboons	12
3	WR-4593/WR-158122 DUAL DRUG SUSTAINED RELEASE SYSTEM: FABRICATION AND EVALUATION OF SYSTEM II	22
	3.1 Description of System II	22
	3.2 Excretion of Tritium Labeled Materials Derived from WR-4593	24

TABLE OF CONTENTS
(Continued)

<u>Section</u>		<u>Page</u>
3.3	Excretion of Carbon-14 Labeled Materials Derived from WR-158122	27
3.4	Analysis of Drug Residues Remaining in Tissues After Sacrifice of Baboons	30
 <u>Appendices</u>		
A	System I: Excretion of Tritium Labeled Materials Derived from WR-7557	55
B	System I: Excretion of Carbon-14 Labeled Materials Derived from WR-158122	69
C	System II: Excretion of Tritium Labeled Materials Derived from WR-4593	82
D	System II: Excretion of Carbon-14 Labeled Materials Derived from WR-158122	96
E	Letter from Amershan Corporation Describing Preparation of Ring Labeled Acedapsone	110
F	Distribution List	112
G	Chronological Listing of Publications of Work Supported by Contract DAMD-17-74-64120	114

LIST OF FIGURES

<u>Figure</u>		<u>Page</u>
2.1	System I: Cumulative Excretion of Tritium Labeled Materials Expressed as Milligrams of WR-7557	20
2.2	System I: Cumulative Excretion of Carbon-14 Labeled Materials Expressed as Milligrams of WR-158122	21
3.1	System II Cumulative Excretion of Tritium Labeled Materials Expressed as Milligrams of WR-4593	25
3.2	System II: Cumulative Excretion of Carbon-14 Labeled Materials Expressed as Milligrams of WR-158122	29

LIST OF TABLES

<u>Table</u>		<u>Page</u>
1.1	Summary Description of Dual Drug Systems	6
1.2	Summary Description of Baboon Test Program	6
1.3	Excretions of Labeled Materials Derived from Sustained Release Matrices	7
2.1	Efficiency of Injection: Residues Remaining After Delivery of System I	10
2.2 a,b	Distribution of WR-7557 or Metabolites in Tissues of Four Baboons (System I)	15
2.3 a,b	Distribution of WR-158122 or Metabolites in Tissues of Four Baboons(System I)	17
2.4	Analysis of Residual Drug Remaining at Implantation and Injection Sites	19
3.1	Efficiency of Injection: Residues Remaining After Delivery of System II	23
3.2	Cumulative Excretion of WR-158122	28
3.3	Tissue Content of WR-158122: System II	31
3.4	Tissues Showing WR-4593 Derived Materials Present in Quantities Greater Than One Standard Deviation Above Mean Values	34
3.5 a,b	Distribution of WR-4593 or Metabolites in Tissues of Four Baboons (System II)	35
3.6 a,b	Distribution of WR-158122 or Metabolites in Tissues of Four Baboons (System II)	43
3.7	Analysis of Residual Drug Remaining at Injection Site (System II)	51

LIST OF TABLES

<u>Table</u>		<u>Page</u>
3.8	System II Material Balance	52
A.1	Measured Excretion of Tritium Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-7557 (System I)	56
A.2	Measured Excretion of Tritium Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-7557 (System I)	58
A.3	Measured Excretion of Tritium Labeled Materials in Urine Plus Feces of Four Baboons Expressed as Milligrams of WR-7557 (System I)	60
A.4	Cumulative Excretion of Tritium Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-7557 (System I)	62
A.5	Cumulative Excretion of Tritium Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-7557 (System I)	64
A.6	Cumulative Excretion of Tritium Labeled Materials in Urine Plus Feces of Four Baboons Expressed as Milligrams of WR-7557 (System I)	66
B.1	Measured Excretion of Carbon-14 Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-158122 (System I)	70
B.2	Measured Excretion of Carbon-14 Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-158122 (System I)	72
B.3	Measured Excretion of Carbon-14 Labeled Materials in Urine Plus Feces of Four Baboons Expressed as Milligrams of WR-158122 (System I)	74
B.4	Cumulative Excretion of Carbon-14 Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-158122 (System I)	76

LIST OF TABLES

<u>Table</u>		<u>Page</u>
B.5	Cumulative Excretion of Carbon-14 Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-158122 (System I)	78
B.6	Cumulative Excretion of Carbon-14 Labeled Materials in Urine Plus Feces of Four Baboons Expressed as Milligrams of WR-158122 (System I)	80
C.1	Measured Excretion of Tritium Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-4593 (System II)	84
C.2	Measured Excretion of Tritium Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-4593 (System II)	86
C.3	Measured Excretion of Tritium Labeled Materials in Urine Plus Feces of Four Baboons Expressed as Milligrams of WR-4593 (System II)	88
C.4	Cumulative Excretion of Tritium Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-4593 (System II)	90
C.5	Cumulative Excretion of Tritium Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-4593 (System II)	92
C.6	Cumulative Excretion of Tritium Labeled Materials in Urine Plus Feces of Four Baboons Expressed as Milligrams of WR-4593 (System II)	94
D.1	Measured Excretion of Carbon-14 Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-158122 (System II)	98
D.2	Measured Excretion of Carbon-14 Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-158122 (System II)	100

LIST OF TABLES

<u>Table</u>		<u>Page</u>
D.3	Measured Excretion of Carbon-14 Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-158122 (System II)	100
D.4	Cumulative Excretion of Carbon-14 Labeled Materials in Urine of Four Baboons Expressed as Milligrams of WR-158122 (System II)	104
D.5	Cumulative Excretion of Carbon-14 Labeled Materials in Feces of Four Baboons Expressed as Milligrams of WR-158122 (System II)	106
D.6	Cumulative Excretion of Carbon-14 Labeled Materials in Urine Plus Feces of Four Baboons Expressed as Milligrams of WR-158122 (System II)	108

Section 1

SUMMARY

1.1 Review of First Year of Contract DAMD-17-74-C-4120

The Dynatech R/D contract with WRAIR for development of sustained release delivery systems for antimalarial drugs was initiated June 24, 1974 under Contract DAMD-17-741C-4120.

During the first year of work the effects of polymer type, molecular weight, drug content and implant shape on the rate of WR-7557 in vitro release were evaluated. Two potential systems were identified: 1/16" diameter beads of a 50% L(+)-lactic/50% dl-lactic acid copolymer containing 33% WR-7557 and a 144 μ -177 μ powder of 100% poly-L(+)-lactic acid containing 20% WR-7557. In vivo evaluation in mice of 1/16" diameter beads of a 90% L(+)-lactic/10% glycolic acid copolymer containing 10% WR-7557 demonstrated that drug release was too slow for a three-month system.

Steady release of WR-158122 from a less than 44 μ spray dried powder of a 90% L(+)-lactic/10% glycolic acid copolymer containing 60% WR-158122 was also achieved in vitro, but at a rate much too slow for a three-month system. In vitro experiments with glycolic, lactic, and citric acid salts of WR-158122 showed increases in the release rate of this drug.

1.2 Review of Second Year of Contract DAMD-12-74-C-4120

The release of ³⁵S-labelled WR-7557 from three candidate polymeric matrices was measured in vitro and in vivo in mice. They were 1/16" diameter beads and 1/32" diameter rods of a 50% dl-lactic/50% L(+)-lactic acid copolymer containing 33.3% WR-7557 and a 90 to 180 μ cryogenically ground powder of a 100% poly L(+)-lactic acid containing 20% WR-7557. The three materials released the drug very slowly, both in vitro and in vivo. a 90 to 180 μ powder was ground from the 1/32" diameter rods to increase

the surface area and in vitro and in vivo evaluation initiated.

The release of WR-158122 was measured from finely divided particles. In vitro experiments showed the solubility of WR-158122 to be 0.02 µg/ml in pH 7 buffer. Steady release of WR-158122 in vivo from a less than 44µ spray dried powder of a 90% L(+)-lactic/10% glycolic acid copolymer containing 60% WR-158122 was demonstrated with an extrapolated duration of release of over 500 days. The glycolate salt increased the solubility of WR-158122 significantly, such that powdered matrices containing WR-158122 glycolate showed sustained WR-158122 in vivo release for an extrapolated duration of 230 days.

1.3 Review of Third Year of Contract DAMD-17-74-C-4120

During this year preparation and testing of systems for simultaneous delivery of two drugs was initiated. Matrices each containing 50w/w% of ³H-WR-7557 or ¹⁴C-WR-158122 in a 90L(+)/10G copolymer of 46,000 molecular weight- were blended to contain a 10/1 weight ratio of WR-7557 to WR-158122. Release of the drugs in Rhesus Monkeys and mice was measured. Both released virtually all tritiated materials within three weeks of injection. Carbon-14 release by monkeys proceeded at ~ 2.6 µg/day between weeks 3 and 13 from the matrix as compared with ~ 50 µg/day from a control of pure mixed drug (no polymer).

1.4 Review of Fourth Year of Contract DAMD-17-74-C-4120

During this year matrices containing 50 w/w% of ³H-WR-7557 or ¹⁴C-WR-158122 in 90 L+/10G copolymers of 220,000 and 49,000 respectively were prepared. The former was molded into 1.5 mm diameter beads, the latter cryogenically ground and sieved to 45-180µ particle size. A third matrix was prepared containing 50 w/w% acedapsone in the 49,000 molecular weight copolymer used for ¹⁴C-WR-158122.

The matrices were used as components of two dual drug systems. System I included WR-7557 and WR-158122 in a 10/1 weight ration. System II

included WR-4593 and WR-159122 in a 10/1 wt. ratio. Three baboons received System I with a one additional baboon serving as a control received a 10/1 mixture of the pure drugs. Two baboons received System II with two additional serving as controls. All baboons received a total drug dose of 50 mg/kg.

Preparation and evaluation of these systems form the subject of Section 2 and 3 of this report.

1.5 Summary of Fifth Year of Contract DAMD-17-74-C-4120

The purpose of this phase of Dynatech's program with Walter Reed Army Institute of Research is to develop and test two dual drug systems for malaria prophylaxis. Both systems have been tested in baboons at the University of Alabama Medical School under the direction of Dr. Lee R. Beck, Department of Obstetrics and Gynecology.

System I contains both sulfadiazine (WR-7557) and 2, 4-diamino-6-(2-naphthylsulfonyl) quinazoline (WR-158122). The former, tritium labeled, is incorporated at 50 wt. % loading into a 90L+/10G copolymer of 220,000 molecular weight. The latter, carbon-14 labeled, is also incorporated at 50 wt. % loading into a 90L+/10G copolymer of 49,000 molecular weight. The ratio by weight of the two matrices is ten parts WR-7557 to one part WR-158122. The WR-7557 matrix has been molded into 1.55 diameter beads for subcutaneous implant; the WR-158122 matrix has been cryogenically ground and sieved to retain the 45-180 μ particles for injection.

System II consists of the WR-158122 matrix described above as well as the matrix containing tritium labeled acedapsone (WR-4593) contained in the 90L+/10G copolymer (49,000 mol. wt.) used for WR-158122. The two drugs are present in the weight ratio ten parts WR-4593 to one part WR-158122. Both matrices were cryogenically ground and sieved to retain the 45-180 μ particles for injection.

A summary description of the two systems is presented in Table 1.1.

On May 24, 1978, three baboons recieved the System I matrices and a fourth was injected with equivalent doses of the pure drugs to serve as a control. System II was injected into two baboons on July 12, 1978. Two controls were also injected with equivalent doses of pure drugs. Table 1.2 summarizes the baboon test program.

Excretion data for System I tests were taken to day 168. WR-7557 recovery was almost complete (99% for the control, 90% for the three baboons receiving the matrix). Over 93% of the recovered material appeared in the urine. Excretion by the animals receiving the matrix was fairly content to day 40 and virtually complete by day 80.

WR-158122 (System I) excretion continued to day 168 by animals receiving the matrix but ceased by day 98 from the control.

Excretion of WR-4593 (System II matrix) was an almost linear function of time for the 203 days of data. Excretion by the controls was similar except for an early burst of approximately 52 mg in about 3 days. Of the 216 mg recovered from the experimental animals, 199 mg were excreted in urine.

The pattern of excretion of WR-158122 derived from the System II matrix was similar to that observed for System I except that the rate for the former was about twice as rapid.

Analysis of tissues excised from System I baboons indicated only slight uptake of carbon-14 and tritium in the three animals receiving the matrix and none by the control. Tissues consistently showing tritium include bile, thymus, thyroid, liver and kidney. Tissues with consistent evidence of carbon-14 include blood, bile, thyroid, heart, gall bladder, liver and ileum.

Necropsies of System II have been performed and tissues have been analyzed. As with System I baboons, very little carbon-14 uptake was observed. However, virtually all tissues contained significant tritium

derived from WR-4593. This result may derive from the method of labeling this compound which involved exchange with tritiated water.

Table 1.1

SUMMARY DESCRIPTION OF DUAL DRUG SYSTEMS

SYSTEM	SYSTEM I		SYSTEM II	
Drugs	WR-158122	WR-7557	WR-158122	WR-4593
Drug Label	C-14	H-3	C-14	H-3
Polymer Composition	90L+/10G	90L+/10G	90L+/10G	90L+/10G
Polymer Mol. Wt. ($\bar{M}_w$)	49,000	220,000	49,000	49,000
Wt. % of Drug in Matrix	50.0	50.0	50.0	50.0
Wt. Ratio of Matrix in System	1	10	1	10
Dosage Form	45-180 μ injectable powder	1.58 mm dia. implantable beads	45-180 μ injectable powder	45-180 μ injectable powder
Matrix Specific Activities	246.6 μ Ci/g	621.0 μ Ci/g	246.6 μ Ci/g	369.4 μ Ci/g
Pure Drug (Control) Activities	21.6 μ Ci/g	95.5 μ Ci/g	21.6 μ Ci/g	833.6 μ Ci/g

Table 1.2

SUMMARY DESCRIPTION OF BABOON TEST PROGRAM

SYSTEM	I	II
Date Initiated	5/24/78	7/12/78
Total Number of Baboons	4	4
Identification of Baboons Receiving Mixed Matrices	Nos. 28, 33, 46	Nos. 3, 11
Receiving Pure Mixed Drugs	No. 8	Nos. 27, 29
Wt. WR-7557 Matrix Implanted, g	1.3688	--
Wt. WR-158122 Matrix Injected, g	0.1400	0.1400
Wt. WR-4593 Matrix Injected, g	--	1.4005
Wt. WR-7557 Pure Drug Injected, g	0.7001	--
Wt. WR-158122 Pure Drug Injected, g	0.0699	0.0699
Wt. WR-4593 Pure Drug Injected, g	--	0.7004
Date Sacrificed	No. 8 11/14/78 No. 23 11/30/78 No. 33 11/14/78 No. 46 11/21/78	No. 3 2/1/79 No. 11 2/27/79 No. 27 3/6/79 No. 29 1/30/79

Table 1.3
EXCRETION OF LABELED MATERIALS DERIVED
FROM SUSTAINED RELEASE MATRICES

System/Drug (Baboon No.)	Mean Total (Urine + Feces) Excretion Rate Expressed as Mg Drug/Day in Indicated Time Interval						Total Mean % Recovery by Indicated Day
System I WR-7557 WR-158122 (Nos. 28, 33, 46)	Day 0-42	Day 42-64	Day 64-84	Day 84-98	Day 98-168	To Day 168	
	12.6	3.30	1.28	0.26	0.04	90.3	
	0.069	0.019	0.018	0.024	0.054	11.7	
System II WR-4593 WR-158122 (Nos. 27, 29)	Day 0-10	Day 10-63	Day 63-84	Day 84-126	Day 126-203	To Day 203	
	2.1	0.92	0.91	0.98	1.60	37.5	
	0.063	0.063	0.079	0.105	0.143	30.1	

Section 2

WR-7557/WR-158122 DUAL DRUG SUSTAINED RELEASE SYSTEM: FABRICATION AND EVALUATION OF SYSTEM I

2.1 Description of System I

System I consists of tritium labeled WR-7557 and carbon-14 labeled WR-158122, each separately incorporated into a polymeric excipient at 50.0 wt. % loading. The WR-7557 matrix was molded into 1/16 inch diameter (1.59 mm) beads for subcutaneous implant and the WR-158122 matrix was cryogenically ground and sieved to retain particles in the 45-180 μ range.

The polymeric excipient for WR-7557 is a copolymer synthesized from a mixture of 90 wt. % L(+)-lactic acid and 10 wt. % glycolic acid (indicated as 90L+/10G). The weight average molecular weight ($\bar{M}_w$) of this polymer is 220,000.

The excipient for WR-158122 is also a 90L+/10G copolymer with a weight average molecular weight of 49,000. The matrix was extruded as 1/16" diameter rods prior to cryogenic grinding.

Data for both matrices were presented in Dynatech Report No. 1791 (Progress Report No. 16), as well as was the protocol for delivery of each system and the schedule for urinary and fecal collection.

System I was delivered to baboons on May 24, 1978. The WR-7557 beads for each of the three experimental baboons were supplied in four vials, 94 beads in each. The entire contents of each vial were introduced in each of four incisions which were made parallel to the median line of the baboon's back, two on each side, approximately 5 cm. apart in each direction. Prior to suturing, the beads were distributed throughout the subcutaneous area. Each animal received ~136.8 mg of matrix (68.4 mg of WR-7557). Based on

the average baboon weight, this corresponds to a dose of ~ 47.2 mg/kg.

The WR-158122 matrix was injected into the hind quadrante as a suspension in 0.1% methocel. Approximately 140 mg was injected, giving an average dose of 4.8 mg/kg.

A fourth baboon served as a control. This animal received one intramuscular injection containing 700 mg of pure WR-7557 and 70 mg of WR-158122, neither drug being contained in polymer. Thus the control and experimental baboons received equivalent doses.

The quantity of drug or matrix actually delivered is presented as the percentage of material supplied in Table 2.1. All residues remaining after injection contained in the sample vials, syringes, needles, and pledgets used to exert pressure on the injection site were dissolved in 100 ml of p-dioxane for each baboon. Aliquots of this were counted to determine quantities not injected. Except in one case, results indicate successful injections: 96.2% of the WR-7557 control was delivered and between 91.1 and 84.1% of the WR-158122 control was delivered but this is questionable as significantly more than this was recovered.

No measure of WR-7557 matrix residue was determined as this material was subcutaneously implanted in bead form. Since all beads were delivered into the incisions, loss of material is negligible.

Table 2.1

EFFICIENCY OF INJECTION: RESIDUES REMAINING
AFTER DELIVERY OF SYSTEM I

<u>WR-7557</u>	<u>#8 (Control)</u>	<u>#28 (Exp.)⁽¹⁾</u>	<u>#33 (Exp.)</u>	<u>#46 (Exp.)</u>
³ H-activity	95.5	621.1	621.0	621.0
³ H Ci in residue ⁽²⁾	2.53 μ Ci/g	-	-	-
mg of residue	26.49	-	-	-
mg supplied	700.1	-	-	-
% injected	96.2	-	-	-
<u>WR-158122</u>				
¹⁴ C-activity	21.6	246.6	246.6	246.6
¹⁴ C- μ Ci in residue	1.36	6.53	5.65	5.48
mg of residue	63.0	26.48	22.91	22.22
mg supplied	69.9	140.0	140.0	140.0
% injected	9.87	81.1	83.6	84.13

(1) As WR-7557 was supplied in bead form, no loss was calculated as all beads were delivered.

(2) All weight units are for pure drug in reference to controls and matrix in reference to experimentals.

2.2 Excretion of Tritium Labeled Materials Derived from WR-7557

The description of System I and its delivery to baboons was given in Dynatech Report No. 1817 covering the period 24 June 1978 to 23 September 1978. Data for fecal and urinary excretion of labeled metabolites are complete to day 168. All animals have been sacrificed for determination of C-14 and H-3 labeled materials in tissues. Results of this study are given in section 2.3 of this report.

Excretion of tritiated materials derived from System I WR-7557 by the control (Baboon No. 8) was virtually complete by day 42 accounting for about 97% of the supplied dose. Excretion was erratic, especially between day 35 and 42 when the equivalent of approximately 280 mg of WR-7557 appeared in urine and feces. As expected, most appeared in the urine; about 5.3% (36.9 mg) appeared in feces. Between days 43 and 49 the equivalent of another 5.4 mg was excreted, but following day 49 to termination on day 168, no further tritiated materials appeared. Recovery of tritiated materials in urine plus feces accounted for 99% of the implanted dose with only 5.3% appearing in feces.

Average excretion of WR-7557 or its metabolites by the three experimental baboons (Numbers 28, 33, 46) was more uniform. Total excretion was fairly uniform to about day 42 at an average daily rate of 12.62 mg/day calculated as mg of WR-7557. Between days 42 and 60, the excretion rate was ~3.3 mg/day and between days 60 and 80, about 1.75 mg/day. By day 105 approximately 90% of the total dose had been recovered in urine plus feces with about 8.5% appearing in feces. Only minimal amounts of WR-7557 were excreted after day 105; by day 168 only 2.0 mg more appeared.

Numerical data for day 0 until sacrifice are presented in Tables A.1 through A.6 of Appendix A. Cumulative excretion calculated as milligrams of WR-7557 is presented graphically as Figure 2.1 to day 168.

2.3 Excretion of Carbon-14 Labeled Materials Derived from System I WR-158122

Interpretation of data for excretion by the single control of carbon-14 labeled materials derived from WR-158122 is difficult in view of two factors. First, the quantity injected is in doubt as mentioned in Report No. 1817. Based on analysis of residual material remaining after injection, only 9.9 mg of drug was injected. However, fecal and urinary analysis indicates a recovery of 20.6 mg by day 168. This quantity had been excreted by baboon No. 8 by day 98 and no further carbon-14 activity was observed for the remainder of the experiment.

Total carbon-14 radioactivity excreted by the three experimental animals (Nos. 28, 33, 46) to day 168 was equivalent to 8.2 mg of WR-158122 with 5.4 mg appearing in urine.

The average rate of excretion in urine was fairly constant at ~ 31.9 $\mu\text{g/day}$. The average rate of total excretion (urine + feces) was more variable: to day 42, the rate was 69.8 $\mu\text{g/day}$. From day 42 to 105 the rate was lower, ~ 23.8 $\mu\text{g/day}$. Thereafter excretion was again more rapid: ~ 61.3 $\mu\text{g/day}$ between days 105 and 168.

2.4 Analysis of Drug Residues Remaining in Tissues After Sacrifice of Baboons

The four baboons used to test System I were sacrificed at intervals between November 14 and November 30, 1978 (i.e., between days 174 and 181 of the test). Each baboon was subject to a necropsy for determination of the tritium and carbon-14 content of the tissues indicated in Tables 2.2 and 2.3.

Isotopic content of tissue samples was determined by combustion to $^{14}\text{CO}_2$ and $^3\text{H}_2\text{O}$ followed by absorption into appropriate fluors for liquid scintillation counting. Methods of tissue preparation are indicated in the

second columns of each table. Samples were either combusted in toto, indicated as "whole"; taken as aliquots, indicated as such, or solubilized and taken as aliquots. Solubilization was necessary only for the tissues containing the drug or matrix residues.

Data and results for each baboon are presented for tritium and carbon-14 in Tables 2.2 and 2.3 respectively. Note that the first column for each baboon includes the total weight of the excised organ or volume of fluid (blood or bile). Where weights are not given, either this was not determined (as in the case of skin, fat, bone, etc.) or various parts of the organ were not determined separately (e.g. duodenum, ileum, jejunum). The second column for each baboon gives the measured DPM/g or DPM/ml and this is converted to micrograms in cases where total tissues weight or volume is known. Otherwise, it is given as microgram of drug per mg or ml of tissue.

Consistent with the excretion data for baboon number 8, neither tritium nor carbon-14 was observed in any organ. Although no organ accumulated large amounts of tritium, the sites of greatest concentration were bile, thyroid, thymus, liver and kidney with lesser amounts appearing in other tissues.

Carbon-14 accumulation in the experimental animals was also slight. Tissues showing consistent accumulation included blood, bile, thyroid, heart, gall bladder, liver and ileum. Although other tissue samples gave evidence of carbon-14, only these showed carbon-14 in all three experimental animals.

Analysis of the injection/implantation sites is presented in Table 2.4 complete. Sites were excised at the time of sacrifice and shipped to Dynatech with other tissues. Tissues incorporating residual drugs were dissolved in tissue solubilizer. Aliquot samples were combusted and analyzed as were excreta at SISA Inc. No sites were examined for the control, No. 8. Baboons Nos. 28, 33, and 46 each had 4 implantation sites and one injection

site. Data for Baboon No. 46 is incomplete in that implant sites to the left of the median line and the injection site were not delivered to Dynatech.

Baboon No. 28 had a total of 2.2 mg of WR-7557 remaining at the 4 implant sites. After 168 days 580.8 mg had been recovered in excreta. Thus of 700 mg delivered 83.3% was accounted for.

Recovery of WR-158122 from the injection site of this baboon amounted to 0.9 mg. In addition, 9.0 mg was detected in excreta. Analysis of the residual remaining of the injection accounted for 13.2 mg. Thus a material balance accounts for 33.0% of the drug.

Recovery of WR-158122 from the injection site of No. 33 amounted to 2.1 mg. An additional 8.6 mg was detected in excreta. Another 11.5 mg remained undelivered at the injection. Thus a material balance accounts for 31.7% of the intended dose of 70 mg.

Table 2.2A

DISTRIBUTION OF WR-7557 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM I)

TISSUE	PREP	BABOON					
		No. 8			No. 2E		
		Wt.,g, or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-158122	Wt.,g.,or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-7557
		10.5 32			17.6 35		
Baboon Wt., kg	--						
Hematocrit, PVC %	--						
Blood	Aliquot	~600ml	0	0	738ml	0	0
Marrow	"	--	0	0	--	0	0
Plasma	"	--	0	0	--	0	0
Hair	"	48	0	0	46	0	0
Bile	"	4.95ml	0	0	6.5ml	626.5	1.48
Nipple	"	--	0	0	--	0	0
Thyroid	Whole	1.0	0	0	3.0	66.0	0.072
Thymus	"	0.6	0	0	2.31	91.8	0.077
Brain		149.0			148.7		
Cerebrum	Homog.	128.5	0	0	--	0	0
Cerebellum	"	13.0	0	0	--	0	0
Medulla	"	7.5	0	0	--	0	0
Left Eye		7.5			10.5		
Tissue	Aliquot	--	0	0	--	0	0
Aq. Humor	"	--	0	0	--	0	0
Right Eye		8.5			11.6		
Tissue	"	--	0	0	--	0	0
Aq. Humor	"	--	0	0	--	0	0
Submaxillary Gland	Whole	1.4	0	0	9.0	0	0
Non-Pigmented Skin	Aliquot	--	0	0	--	0	0
Pigmented Skin	"	--	0	0	--	0	0
Ear	"	--	0	0	--	0	0
Skeletal Muscle	"	--	0	0	--	0	0
Endothermal Fat	Whole	--	0	0	--	0	0
Mesenteric Fat	Aliquot	--	0	0	--	0	0
Bone	"	--	0	0	--	0	0
Urinary Bladder	"	10.8	0	0	17.3	0	0
Gall Bladder	"	2.47	0	0	5.0	0	0
Pancreas	Homog.	12.0	0	0	33.1	0	0
Spleen	Aliquot	16.7	0	0	26.5	0	0
Periaortic Lymph	Whole	0.28	0	0	0.58	0	0
Adrenals	Aliquot	2.2	0	0	5.2	0	0
Kidney							
Left, Right	Homog.	28.5, 29.0	0	0	35.7, 36.5	857.1	22.44
Heart (Total)		48.0			61.0		
Left Ventricle	Aliquot	6.8	0	0	--	0	0
Right Auricle	"	1.22	0	0	--	0	0
Lung (Total)		81.1			130.0		
Left	Homog.	--	0	0	--	0	0
Right	"	--	0	0	--	0	0
Liver (Total)		246.4			365.8		
Left Lobe	"	--	0	0	--	136.3	0.05*
Right Lobe	"	--	0	0	--	0	0
Stomach		77.1			111.0		
Pyloric	Aliquot	--	0	0	--	0	0
Cardiac	"	--	0	0	--	0	0
Fundic	"	--	0	0	--	0	0
Small Intestine		77.9			351.1		
Duodenum	"	--	0	0	--	0	0
Ileum	"	--	0	0	--	0	0
Jejunum	"	--	0	0	--	0	0
Large Intestine		183.7			409.3		
Colon	"	--	0	0	--	0	0
Rectum	"	--	0	0	--	0	0
Ovary							
Left	Whole	0.57	0	0	1.0	0	0
Right	"	0.77	0	0	0.98	0	0
Uterus	Aliquot	1.76	0	0	13.12	0	0
Cervix	"	1.63	0	0	3.37	0	0

Table 2.2B

DISTRIBUTION OF WR-7557 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM I)

TISSUE	PREP	BABOON					
		No. 33			No. 46		
		Wt., g, or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-158122	Wt., g, or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-7557
Baboon Wt., kg		14.5			15.5		
Hematocrit, PVC %		42			38		
Blood	Aliquot	~590ml	0	0	520ml	0	0
Marrow	"	--	73.6	0.27*	--	0	0
Plasma	"	--	0	0	--	0	0
Hair	"	161	0	0	--	0	0
Bile	"	7ml	124.6	0.32	~3.0ml	445.9	0.485
Nipple	"	--	0	0	--	98.4	0.036*
Thyroid	Whole	1.12	108.8	0.044	2.0	243.7	0.177
Thymus	"	0.92	119.3	0.040	0.34	169.5	0.02
Brain		143.62			148.2		
Cerebrum	Homog.	1.21	0	0	--	25.9	0.009*
Cerebellum	"	14.17	0	0	--	0	0
Medulla	"	8.17	0	0	--	34.0	0.012*
Left Eye		7.7			7.47		
Tissue	Aliquot	--	0	0	--	0	0
Aq. Humor	"	--	0	0	--	0	0
Right Eye		2.9			11.33		
Tissue	"	--	0	0	--	0	0
Aq. Humor	"	--	0	0	--	0	0
Submaxillary Gland	Whole	2.85	91.6	0.095	2.76	20.9	0.021
Non-Pigmented Skin	Aliquot	--	213.8	0.08*	--	0	0
Pigmented Skin	"	--	0	0	--	13.5	0.005*
Ear	"	--	0	0	--	50.0	0.02*
Skeletal Muscle	"	--	86.9	0.03*	--	0	0
Endothermal Fat	Whole	--	0	0	--	0	0
Mesenteric Fat	Aliquot	--	0	0	--	0	0
Bone	"	--	0	0	--	0	0
Urinary Bladder	"	14.4	1.4	0.007	--	94.0	0.034*
Gall Bladder	"	2.4	17.4	0.015	2.97	143.8	0.155
Pancreas	Homog.	17.3	97.4	0.61	25.0	162.5	1.47
Spleen	Aliquot	16.2	0	0	19.5	0	0
Periaortic Lymph	Whole	0.11	0	0	0.56	167.1	0.034
Adrenals	Aliquot	2.15	58.6	0.046	3.14	64.2	0.073
Kidney							
Left, Right	Homog.	65.7	1271.8	30.30	24.0, 24.5	1439.1	25.31
Heart (Total)		67.8			62.7		
Left Ventricle	Aliquot	--	0	0	--	0	0
Right Auricle	"	--	267.1	0.10*	--	21.3	0.008*
Lung (Total)		105.8			125.8		
Left	Homog.	--	8.0	0.003*	--	56.9	0.021*
Right	"	--	0	0	--	84.2	0.03*
Liver (Total)		351.4			239.3		
Left Lobe	"	--	267.0	0.10*	--	409.3	0.15*
Right Lobe	"	--	110.7	0.04*	--	500.0	0.18*
Stomach		141.5			97.5		
Pyloric	Aliquot	--	0	0	--	0	0
Cardiac	"	--	89.8	0.033*	--	80.0	0.029*
Fundic	"	--	0	0	--	54.0	0.02*
Small Intestine		330.8			316.3		
Duodenum	"	--	0	0	--	0	0
Ileum	"	--	0	0	--	0	0
Jejunum	"	--	0	0	--	0	0
Large Intestine		292.0			279.4		
Colon	"	--	0	0	--	0	0
Rectum	"	--	0	0	--	0	0
Ovary							
Left	Whole	0.66	11.7	0.003	1.03	0	0
Right	"	1.00	0	0	1.00	40.7	0.015
Uterus	Aliquot	2.48	81.5	0.073	16.0	40.5	0.24
Cervix	"	1.62	69.9	0.041	6.0	63.9	0.14

WR-7557 reported as $\mu\text{g}/\text{g}$ tissue

Table 2.3A

DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM I)

TISSUE	PREP	BABOON					
		No.			No.		
		Wt.,g, or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-158122	Wt.,g.,or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-158122*
Baboon Wt., kg	---	10.5			17.6		
Hematocrit, PVC %	---	32			35		
Blood	Aliquot	~600ml	0	0	783ml	10.0	7.15
Marrow	"	---	0	0	---	0	0
Plasma	"	---	0	0	---	0	0
Hair	"	48	0	0	46	0	0
Bile	"	4.95ml	0	0	6.5ml	229.1	1.36
Nipple	"	---	0	0	---	0	0
Thyroid	Whole	1.0	0	0	3.0	49.5	0.14
Thymus	"	0.6	0	0	2.3	0	0
Brain		149.0			148.7		
Cerebrum	Homog.	128.5	0	0	---	0	0
Cerebellum	"	13.0	0	0	---	0	0
Medulla	"	7.5	0	0	---	0	0
Left Eye		7.5			10.5		
Tissue	Aliquot	---	0	0	---	0	0
Aq. Humor	"	---	0	0	---	0	0
Right Eye		8.5			11.6		
Tissue	"	---	0	0	---	0	0
Aq. Humor	"	---	0	0	---	0	0
Submaxillary Gland	Whole	1.4	0	0	9.0	0	0
Non-Pigmented Skin	Aliquot	---	0	0	---	0	0
Pigmented Skin	"	---	0	0	---	0	0
Ear	"	---	0	0	---	0	0
Skeletal Muscle	"	---	0	0	---	0	0
Endothermal Fat	"	---	0	0	---	0	0
Mesenteric Fat	"	---	0	0	---	26.7	0.02*
Bone	"	---	0	0	---	0	0
Urinary Bladder	"	10.08	0	0	17.3	0	0
Gall Bladder	"	2.47	0	0	5.0	295.2	1.35
Pancreas	Homog.	12.0	0	0	33.1	0	0
Spleen	Aliquot	16.7	0	0	26.5	0	0
Periaortic Lymph	Whole	0.28	0	0	0.58	0	0
Adrenals	Aliquot	2.2	0	0	5.2	0	0
Kidney							
Left, Right	Homog.	28.5, 29.0	0	0	35.7, 36.5	0	0
Heart (Total)		48.0			61.0		
Left Ventricle	Aliquot	6.8	0	0	---	0	0
Right Auricle	"	1.2	0	0	---	23.3	0.02*
Lung (Total)		81.1			130.0		
Left	Homog.	---	0	0	---	1147.6	1.05*
Right	"	---	0	0	---	0	0
Liver (Total)		264.4			365.8		
Left Lobe	"	---	0	0	---	203.9	0.19*
Right Lobe	"	---	0	0	---	102.0	0.09*
Stomach		77.1			111.0		
Pyloric	Aliquot	---	0	0	---	0	0
Cardiac	"	---	0	0	---	169.1	0.15*
Fundic	"	---	0	0	---	0	0
Small Intestine		77.9			351.1		
Duodenum	"	---	0	0	---	22.8	0.02*
Ileum	"	---	0	0	---	156.4	0.14*
Jejunum	"	---	0	0	---	56.2	0.05*
Large Intestine		183.7			409.3		
Colon	"	---	0	0	---	315.9	0.29*
Rectum	"	---	0	0	---	83.8	0.08*
Ovary							
Left	Whole	0.57	0	0	1.00	0	0
Right	"	0.77	0	0	0.98	0	0
Uterus	Aliquot	1.76	0	0	13.12	0	0
Cervix	"	1.63	0	0	3.37	0	0

Table 2.3B

DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM I)

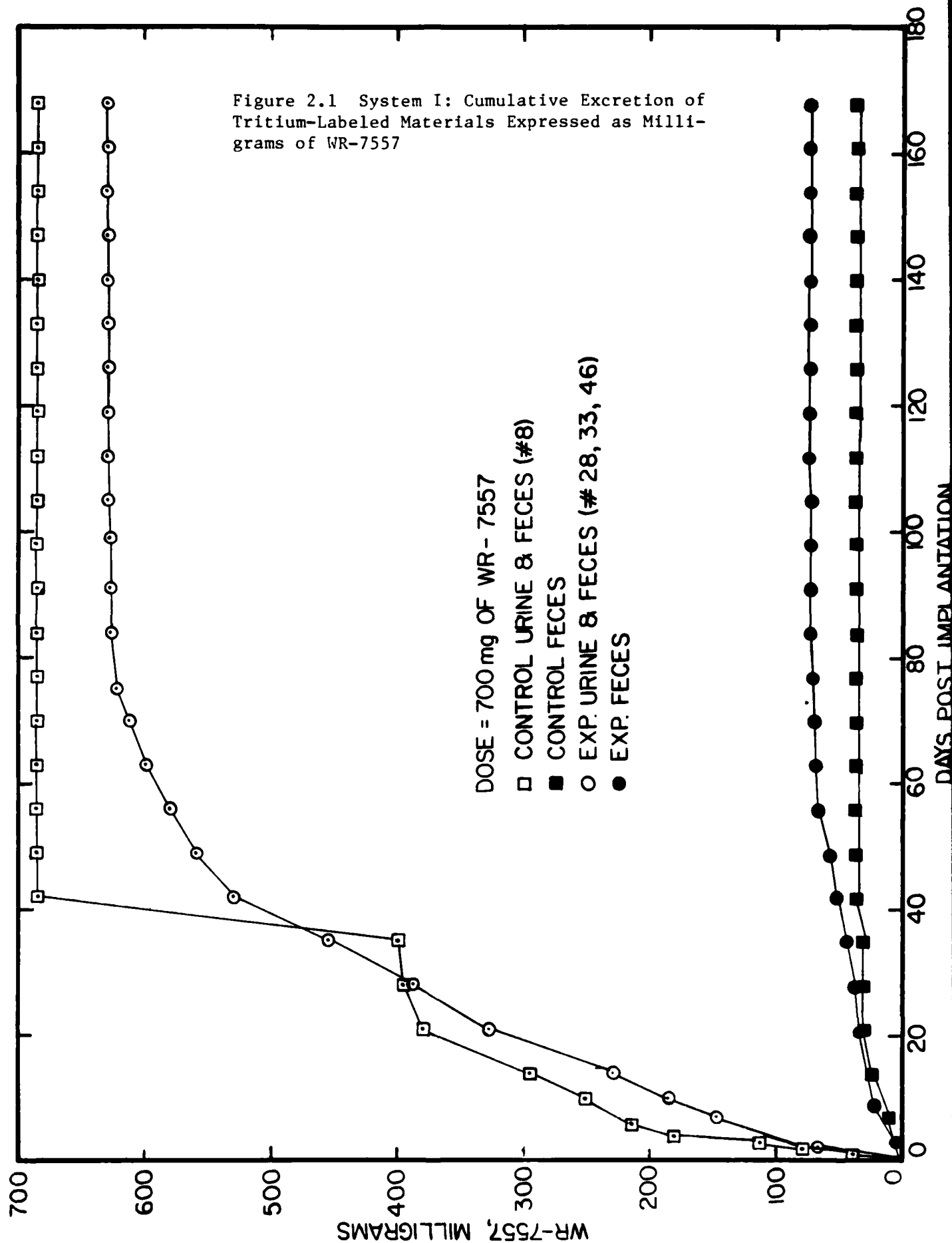
TISSUE	PREP	BABOON					
		No. 8			No. 28		
		Wt., g, or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-158122	Wt., g., or Vol., ml.	DPM/g or DPM/ml	Micrograms WR-158122*
Baboon Wt., kg	--	14.5			15.5		
Hematocrit, PVC %	--	42			38		
Blood	Aliquot	~590ml	68.7	37.0	520ml	0	0
Marrow	"	--	0	0	--	0	0
Plasma	"	--	0	0	--	0	0
Hair	"	161	0	0	--	0	0
Bile	"	7ml	256.0	1.64	2.0ml	337.9	0.93
Nipple	"	--	0	0	--	0	0
Thyroid	Whole	1.12	3.1	0.003	2.0	9.71	0.02
Thymus	"	0.92	0	0	0.34	0	0
Brain		143.6			148.2		
Cerebrum	Homog.	1.21	36.4	0.04	--	0	0
Cerebellum	"	14.17	12.6	0.16	--	0	0
Medulla	"	8.17	22.5	0.17	--	0	0
Left Eye		7.7			7.97		
Tissue	Aliquot	--	0	0	--	0	0
Aq. Humor	"	--	0	0	--	0	0
Right Eye		2.9			11.33		
Tissue	"	--	0	0	--	0	0
Aq. Humor	"	--	0	0	--	0	0
Submaxillary Gland	Whole	2.85	9.5	0.02	2.26	0	0
Non-Pigmented Skin	Aliquot	--	15.3	0.01*	--	0	0
Pigmented Skin	"	--	20.6	0.02*	--	0	0
Ear	"	--	53.7	0.05*	--	0	0
Skeletal Muscle	"	--	10.8	0.01*	--	0	0
Endothermal Fat	"	--	0	0	--	0	0
Mesenteric Fat	"	--	134.8	0.12*	--	0	0
Bone	"	--	0	0	--	0	0
Urinary Bladder	"	14.4	14.8	0.14	17.8	5.5	0.09
Gall Bladder	"	2.4	23.1	0.05	2.97	248.3	0.67
Pancreas	Homog.	17.3	0	0	25.0	0	0
Spleen	Aliquot	16.2	0	0	19.5	0	0
Periaortic Lymph	Whole	0.11	2.94	0.003	0.56	109.5	0.06
Adrenals	Aliquot	2.15	0	0	3.14	51.2	0.15
Kidney							
Left, Right	Homog.	65.7	45.91	2.75	24.0, 24.5	65.8	2.91
Heart (Total)		67.8			62.7		
Left Ventricle	Aliquot	--	46.9	0.04*	--	8.86	0.01*
Right Auricle	"	--	10.5	0.01*	--	47.8	0.04*
Lung (Total)		105.8			125.8		
Left	Homog.	--	0	0	--	11.1	0.01*
Right	"	--	0	0	--	11.5	0.01*
Liver (Total)		351.4			239.3		
Left Lobe	"	--	26.5	0.02*	--	9.0	0.01*
Right Lobe	"	--	5.78	0.01*	--	12.5	0.01*
Stomach		141.5			97.5		
Pyloric	Aliquot	--	0	0	--	0	0
Cardiac	"	--	0	0	--	0	0
Fundic	"	--	26.9	0.02*	--	0	0
Small Intestine		330.8			316.3		
Duodenum	"	--	20.1	0.02*	--	0	0
Ileum	"	--	9.7	0.01*	--	15.1	0.01*
Jejunum	"	--	0	0	--	0	0
Large Intestine		292.0			279.4		
Colon	"	--	9.4	0.01*	--	0	0
Rectum	"	--	24.9	0.02*	--	0	0
Ovary							
Left	Whole	0.66	0	0	1.03	0	0
Right	"	1.00	0	0	1.00	0	0
Uterus	Aliquot	2.48	0	0	16.0	84.4	1.23
Cervix	"	1.62	17.8	0.03	6.0	10.5	0.06

*WR-158122 reported as μ gram/ μ tissue

Table 2.4

SYSTEM I: ANALYSIS OF RESIDUAL DRUG REMAINING
AT IMPLANTATION AND INJECTION SITES

Baboon Number	Implant Sites (4/Baboon)			Injection Site	
	Implant Site (WR-7557 Beads)	³ H-DPM	WR-7557 Mg	¹⁴ C-DPM	WR-158122 Mg
#8 (Control)	No Site Sent		-	No Site Sent	-
#28	Lower Left	965,274.0	0.350	1,027,118.4	0.938
	Upper Left	1,217,986.5	0.042		
	Lower Right	2,212,294.7	0.802		
	Upper Right	1,652,790.1	<u>0.599</u>		
	TOTAL		2.193		
#33	Lower Left	2,100,343.3	0.762	2,290,194.4	2.092
	Upper Left	2,775,563.8	1.007		
	Lower Right	2,032,897.4	0.737		
	Upper Right	1,792,217.4	<u>0.650</u>		
	TOTAL		3.156		
#46	Lower Left	Not Sent	-	Not Sent	—
	Upper Left	372,617.2	0.135		
	Lower Right	Not Sent	-		
	Upper Right	1,866,844.6	<u>0.677</u>		
	TOTAL		0.812		



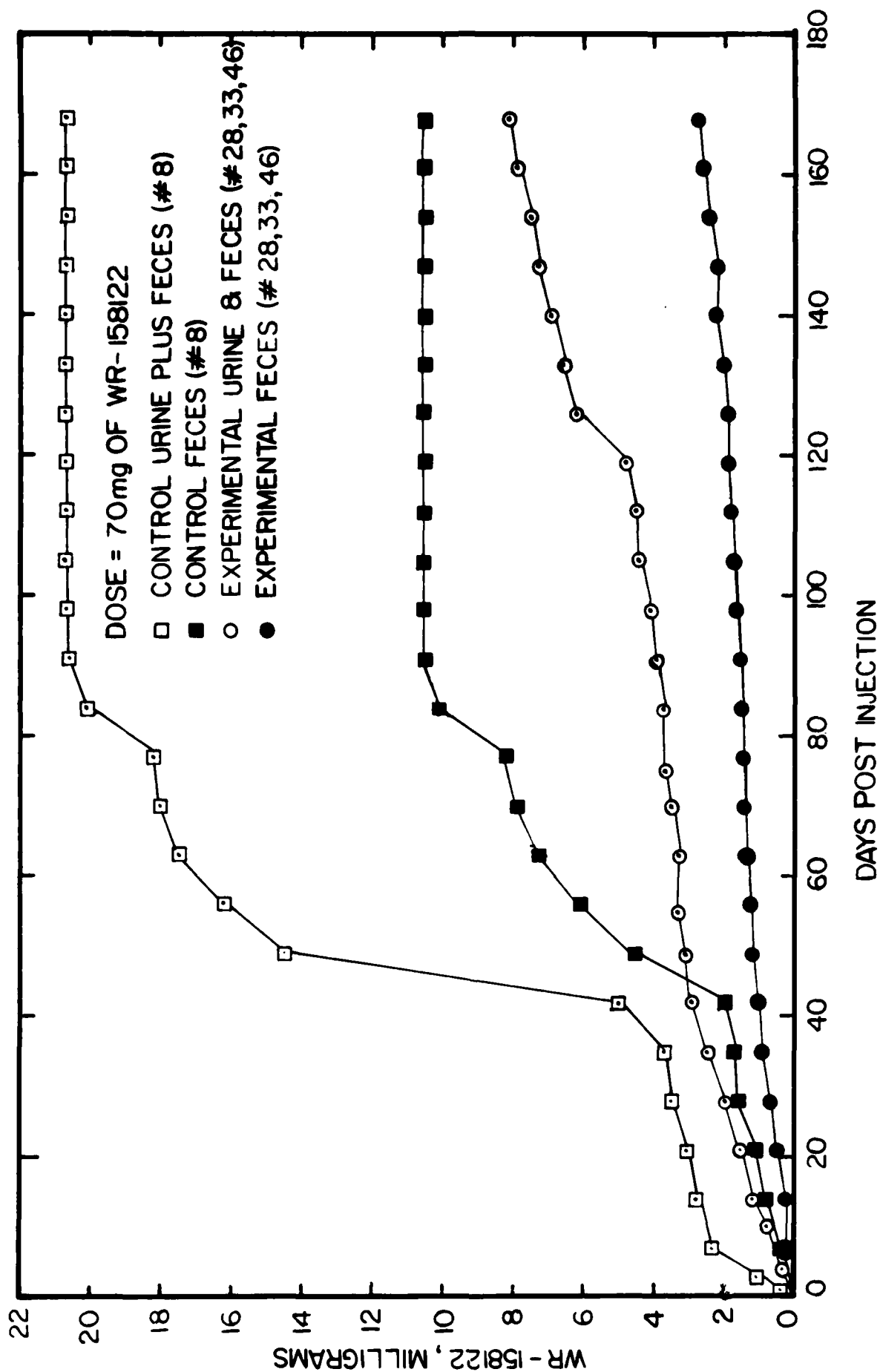


Figure 2.2 System I: Cumulative Excretion of Carbon-14-Labeled Materials Expressed as Milligrams of WR-158122

Section 3

WR-4593/WR-158122 DUAL DRUG SUSTAINED RELEASE SYSTEM: FABRICATION AND EVALUATION OF SYSTEM II

3.1 Description of System II

System II consists of tritium labeled WR-4593 and carbon-14 labeled WR-158122 each separately incorporated into a polymeric excipient at 50.0 wt. % loading. The same polymer was used as for WR-7557; i.e., the 90L+/10G copolymer of 49,000 weight average molecular weight. Each matrix was cryogenically ground and sieved to retain the 45-180 μ particle sizes. The WR-158122/polymer composite used for System II was of the same batch as used for System I. System II controls consisted of pure drug, administered to deliver the same dose as supplied by the composites.

Activities reported in Table 1.1 are as follows. For the pure drug used as controls, C-14 activity was 21.6 μ Ci/g and H-3 activity was 833.6 μ Ci/g. Activities of the drug/polymer composite were 246.6 μ Ci/g for C-14 and 369.4 μ Ci/g for H-3.

System II was injected into baboons on July 12, 1978. Two animals, used as controls, were injected in the hind quadrants with a mixture of pure drugs containing 700 mg of WR-4593 and 70 mg of WR-158122. The two experimental animals were also injected in the hind quadrants with a mixture of 1400 mg of the WR-4593 matrix and 140 mg of the WR-158122 matrix.

The efficiencies of injections were determined as for System I. As reported in Dynatech Report No. 1817 to WRAIR, the percentage of the materials supplied which were actually injected, ranges from 95.6 to 99.5% for the WR-158122 controls and composite and from 98.8 to 99.4% for the WR-4593 controls and composite. These data are presented in Table 3.1.

Table 3.1
EFFICIENCY OF INJECTION: RESIDUES REMAINING
AFTER DELIVERY OF SYSTEM II

<u>WR-4593</u>	<u>#3 (Control)</u>	<u>#11 (Control)</u>	<u>#27 (Exp.)</u>	<u>#29 (Exp.)</u>
³ H-DPM	12409566.8	15483734.3	14039857.7	6570611.7
³ H-activity ⁽¹⁾	833.6 μ Ci/g	833.6 μ Ci/g	369.4 μ Ci/g	369.4 μ Ci/g
mg of residue ⁽¹⁾	6.71	8.37	17.12	8.01
mg supplied	700.4	700.4	1400.5	1400.5
% injected	99.0	98.8	98.8	99.4
 <u>WR-158122</u>				
¹⁴ C-DPM	81619.2	147785.0	1641427.7	355982.8
¹⁴ C-activity	21.6 μ Ci/g	21.6 μ Ci/g	246.6 μ Ci/g	246.6 μ Ci/g
mg of residue	1.70	3.08	3.00	0.65
mg supplied	69.9	69.9	140.0	140.0
% injected	97.6	95.6	97.9	99.5

(1) Note: All weight units are for pure drug in reference to controls and for matrix in reference to experimentals.

Results of tissue analysis for tritium (Section 3.4) derived from WR-4593 were unexpected in that all tissues inspected showed a reasonably uniform distribution of the isotope. Therefore, the preparation of this compound was checked with Amersham Corp. the supplier. Their response, enclosed as Appendix E of this report, indicates that the ring-³H acedap-sone ordered by Dynatech was prepared by an exchange procedure with Dimethylformamide containing 10% tritiated water. This method is stated to label preferentially aromatic hydrogens over any available aliphatic hydrogens.

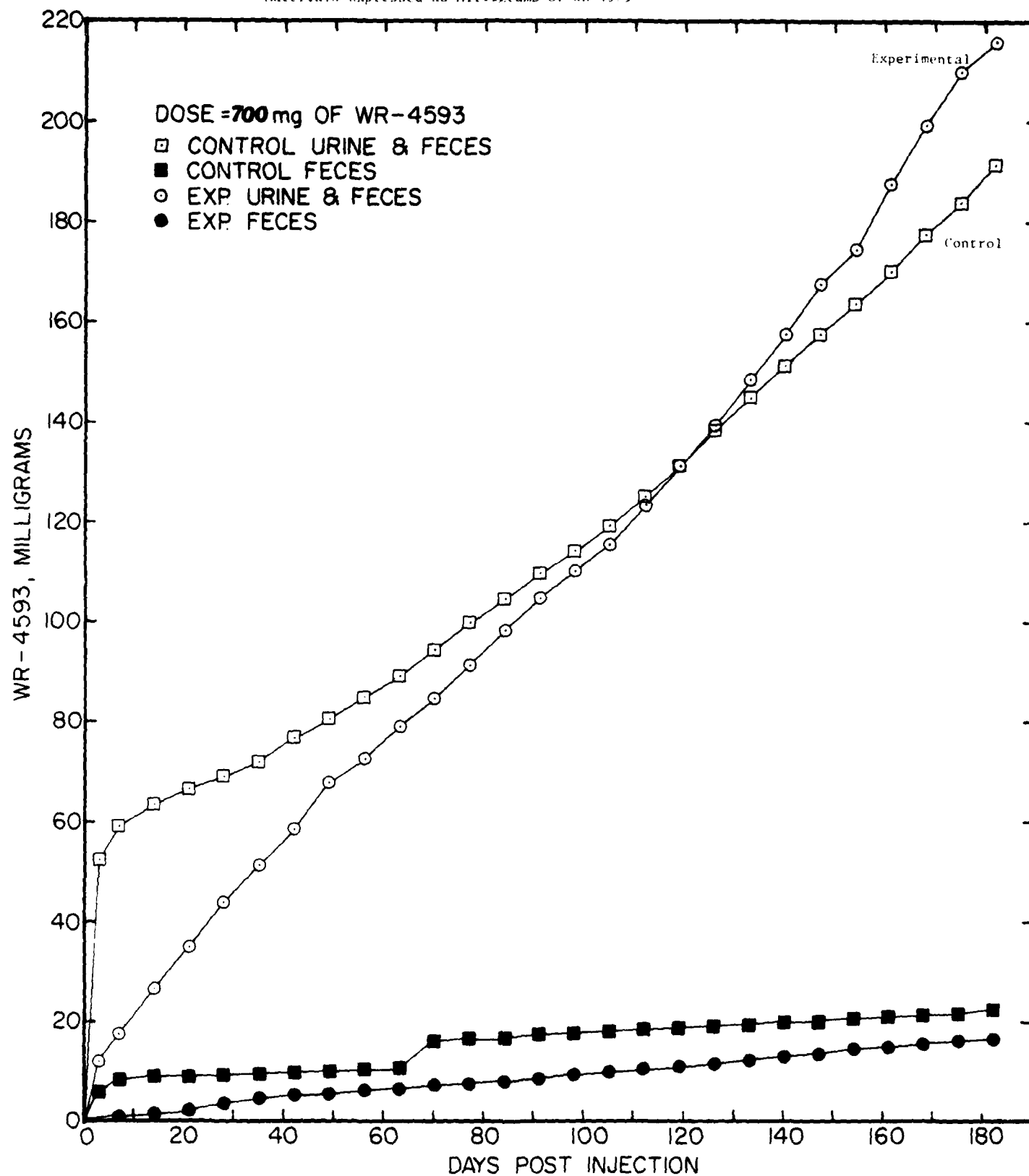
3.2 Excretion of Tritium Labeled Materials Derived from WR-4593

Interpretation of data for excretion of tritium labeled materials derived from WR-4593 is ambiguous due to the likelihood of general labeling. Excretion results may therefore reflect tritium exchange with tissue fluid, and/or amide hydrolysis allowing migration of tritiated acetyl groups.

Although excreta were collected to the day of sacrifice for each animal, and complete excretion data is reported in Appendix C for WR-4593, graphical presentation (Fig. 3.1) is only up to day 203 as it is only up to this point that mean values could be calculated for controls or experimental animals. Thus to day 203 recovery for the controls accounted for 275 mg (39.3% of the initial dose of 700 mg) of which 255 mg (36.4%) appeared in urine. Data for the two animals receiving the drug/polymer composites are similar: a mean total of 263 mg (37.6%) was recovered of which 241 mg (34.4%) was isolated in urine.

As indicated in Figure 3.1, total (i.e., urine plus feces), excretion by the experimentals proceeded at a near linear rate for the duration of the observations with a slight acceleration following day 105. This group also showed a small early burst of ~12.1 mg in the first three days.

Figure 3.1 System II: Cumulative Excretion of Tritium-Labeled Materials Expressed as Milligrams of WR-4593



In comparison, the control baboons excreted an average of 52.3 mg in the first three days. The early burst leveled off to a fairly constant rate of excretion following day 6. However, this rate did tend to accelerate slightly: between days 10 and 105 the rate was ~1.0 mg/day and between days 105 to 203, 1.5 mg/day.

The observed duration of WR-4593 excretion lasted until animal sacrifice in both controls and experimentals. If cumulative total excretion remained a linear function of time to 100% excretion the extrapolated duration of the control group would be 517 days (203 days/0.393). As used in leprosy treatment a typical dose (350mg) shows reasonably constant plasma sulfone levels for about 80 days (C.R. Boughton et. al, Med. J. Australia, 1258 (1971)). Assuming for discussion that duration is approximately proportional to dose then the human dose if scaled up to 700 mg should last only 118 days, i.e. $\frac{517}{350} \times 80$.

Although species difference may account in part for the shorter calculated duration in humans, an additional factor may contribute. The Dynatech preparations, both control and ground composites, were suspended in a 1% aqueous Methocel solution for intramuscular injection. For use in leprosy treatment, the suspending vehicle is 40% benzyl benzoate, 60% castor oil. Solubility of WR-4593 in water is given as 3.0 µg/ml while in the benzyle benzoate/castor oil it is 26 µg/ml, 8.7x greater. (Merck Index, 9th ed., 1976). A comparison may be made by considering a mass of crystals suspended in a droplet of oil which also maintains a drug concentration of 26 µg/ml. The driving force of release of the drug into the surrounding aqueous environment is governed by the concentration difference between the oil and water phases. Alternatively, a suspension of the drug in an aqueous medium results in "droplets" containing crystals and saturated with drug at 3µg/ml. The driving force for release to the unsaturated aqueous environment is therefore less.

3.3 Excretion of Carbon-14 Labeled Materials Derived from WR-158122

Excretion of carbon-14 labeled materials by the two control baboons was erratic. Large increments ~20 mg in urine appeared between days 29 and 35 and again for days 169-175. Excretions of about 10-12 mg were observed between days 176-182 and again between days 190-196. Similarly, large quantities appeared in the feces at these times. Total measured excretion considerably exceeds the delivered dose: a mean of ~132 mg was recovered by day 203 as compared to 70 mg delivered. Individually, the two controls had excreted 104 and 161 mg each.

By the time of sacrifice, excretion by both controls appeared to be almost complete: between day 197 and 203 No. 3 excreted only 0.14 mg in urine and feces. Sacrifice of No. 11 occurred in day 230; for three weeks prior to that no carbon-14 had been observed in excreta.

In comparison, excretion of carbon-14 labeled materials by the animals receiving the matrix was much more uniform (See Figure 3.2). By day 203 an average of 21 (30% of the initial dose) mg had been recovered of which 7.4 (10.6%) mg appeared in feces.

Both total and fecal excretion of WR-158122 by the experimental animals (Nos. 27, 29) were fairly linear functions of time. Mean fecal excretion occurred at 36.4 µg/day; total excretion rate was 103.6 µg/day.

A comparison with excretion of WR-158122 by baboons receiving System I and System II composites shows variation by a factor of two. The following table summarizes the total excretion of WR-158122 by the two sets of baboons at day 168.

Table 3.2

CUMULATIVE EXCRETION OF WR-158122

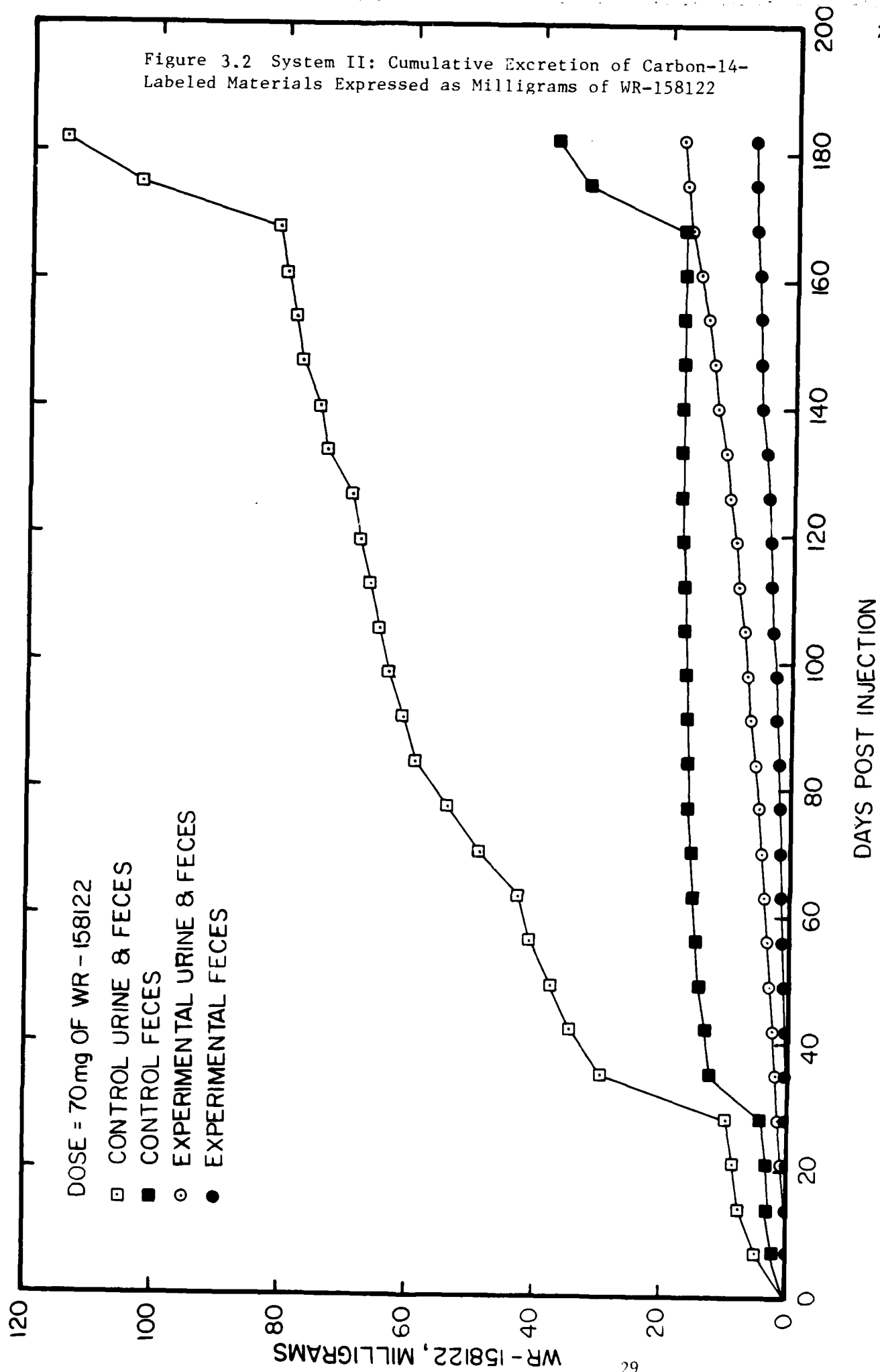
	<u>System I</u>	<u>System II</u>
Total	8.2 ± 0.6	16.4 ± 6.0
<u>Feces Only</u>	<u>2.8 ± 0.3</u>	<u>6.3 ± 1.9</u>

Although the two sets differ by a factor of two, it should be noted that populations include only three and two animals.

Excretion data are given in Appendix D and are displayed in Figure 3.2.

By day 203, a mean of 132 mg had been excreted by the two controls, a quantity greater by 88.6% than the initial dose. No satisfactory explanation exists although the following may have contributed. The tritium activity of the WR-4593 is ~40X greater than the C-14 activity of the WR-158122. In addition, 10X more of the former was injected than of the latter. Products of combustion of excretion are separated by first freezing out the water in a dry ice/alcohol bath. The remaining CO₂ is then absorbed into Riafluor for 1sc. Carbon dioxide is counted with a wide channel since ostensibly it is uncontaminated. Due to the high H-3 activity, very slight contamination of the CO₂ by H₂O may be counted as C-14. This explanation is not complete because during days 211-231 no C-14 was observed although tritium was observed. This problem was not encountered with baboons nos. 27 and 29.

Figure 3.2 System II: Cumulative Excretion of Carbon-14-Labeled Materials Expressed as Milligrams of WR-158122



3.4 Analysis of Drug Residues Remaining in Tissues After Sacrifice of Baboons

As were the animals used in evaluation of System I, the four baboons used in this study were also sacrificed according to the following schedule:

<u>Baboon No.</u>	<u>Date of Sacrifice</u>	<u>Days in Study</u>
3 (control)	2/1/79	204
11 (control)	2/27/79	230
27 (Experimental)	3/6/79	237
29 (Experimental)	1/30/79	202

Tissue analysis was performed as for the previous baboons, and the complete data presentation in Tables 3.5 and 3.6 uses the format of Tables 2.2 and 2.3.

Very little WR-158122 was sequestered in any tissues of either controls or experimentals. The only reservoirs of drug, summarized in Tables 3.6 a and b, are indicated in Table 3.3 as micrograms of WR-158122/gm (or ml) of tissue or fluid (blood, plasma, or bile).

Tritium uptake by tissues was ubiquitous and reasonable uniform. Such wide distribution led to the suspicion that the WR-4593, the tritium source, was not solely ring labeled. An inquiry to Amersham Corporation concerning the method of preparation indicated that some tritium label could be on the acetyl groups (See Section 3.1 and Appendix E); thus hydrolysis of the amide linkages would lead to uptake of these groups by many organs.

A second possibility is that proton exchange occurred with tissue fluid. To check this excess WR-4593 was stirred at room temperature in distilled water. After two days the suspension was filtered and the supernatant counted for tritium. An average of duplicate samples indicated

Table 3.3				
TISSUE CONTENT OF WR-158122: SYSTEM II				
Tissue	3(Control)	11(Control)	27(Exp.)	29(Exp.)
Blood	8.84	0	0.021	0.080
Plasma	4.62	2.90	0.060	0.11
Bile	1.56	1.10	1.51	0.38
Nipple	3.07	2.31	0.098	0
Non-Pigmented Skin	3.54	7.23	0.19	0
Ear	5.13	5.29	0.082	0
Periaortic Lymph	0.55	5.75	0.15	0.080
Inguinal Lode	1.10	6.02	-	0.075
Ileum	0.97	0	0	0

a concentration of 0.211 $\mu\text{Ci/ml}$ which when calculated as acedapsone is 0.25 mg/ml. As the reported solubility of acedapsone is only 0.003 mg/ml (Merck Index, 9th ed., 1978) it is likely that exchange does occur. Under the conditions of labeling described in Appendix E, it is quite likely that the nitrogens of the amide groups were tritiated. Rapid exchange would occur from these positions.

A summary of Table 3.5 a and b is presented in Table 3.4. Entries include tissues showing the highest levels of tritium activity. Levels are reported as $\mu\text{g drug/gr}$ of tissue. The number in parentheses to the right of each entry indicates the number of standard deviation units that this entry is above the mean. Only activities greater than one standard deviation above the overall mean of controls or experimentals are given.

Drug remaining at injection sites is presented in Table 3.7. Based in total initial doses, the quantities of WR-158122 recovered from each control is 3.1 and 1.7%. From the experimentals 0.03 and 0.91% was recovered.

Somehwat more WR-4593 was recovered: From controls 8.37 and 12.70% were recovered; from experimentals 2.36 and 5.71%.

A material balance for System II is given in Table 3.8. WR-4593 recovery in both control and experimental animals is approximately 47%. The quantity remaining in tissues was calculated as the mean tissue content per unit weight for each animal multiplied by the weight of the animal. The remainder of the tritium may have been expired as tritiated water, or possibly excision of the injection site was incomplete.

Mean recovery of WR-158122 is 34.2% for the experimental animals, Nos. 27 and 29. Here again, a possible explanation is incomplete recovery from the injection site.

Mean recovery of WR-158122 from Nos. 3 and 11, the controls, is almost 300%. An explanation of this was offered in Section 3.3.

Table 3.4

TISSUES SHOWING WR-4593 DERIVED MATERIALS PRESENT IN QUANTITIES GREATER THAN ONE STANDARD DEVIATION ABOVE MEAN VALUE

MEAN VALUES	3(Control)	11(Control)	27(Exp.)	29(Exp.)
Mean, µg/g	1.65	2.15	1.98	2.01
Standard Deviation	0.98	2.01	1.23	1.58
Variance	0.93	3.95	1.49	2.46
Overall Mean	1.91		2.00	
Overall Std Deviation	1.60		1.41	
Overall Variance	2.55		1.98	
TISSUES				
Marrow		5.14(2.02) ⁽¹⁾		
Bile			6.13(2.93)	4.06(1.46)
Endothermal Fat				3.71(1.21)
Mesenteric Fat	3.68(1.11)		3.63(1.16)	4.31(1.64)
Pancreas	3.51(1.00)	7.89(3.74)	5.44(2.44)	6.28(3.04)
Spleen		3.71(1.13)		
Adrenals	6.38(2.79)	12.65(6.71)		10.26(5.86)
Kidney				
Left		5.16(2.03)	5.05(2.16)	3.90(1.35)
Right		5.16(2.03)	4.94(2.09)	4.27(1.61)
Stomach			4.58(1.83)	
Cardiac				

(1) Number of standard deviates above mean

Table 3.5A
DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 3 (Control)			BABOON NO. 11 (Control)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593
	Baboon Wt. kg. Hematocrit, PVCZ		15.9 40			12.3 36	
Aliquot	Blood	390	1404.9	0.76	425	1297.4	0.70
Aliquot	Marrow		4470.5	2.42		9508.2	5.14
Aliquot	Plasma		1356.0	0.73		2853.4	1.54
Aliquot	Hair	140	966.7	0.52	140	2343.0	1.27
Aliquot	Bile	5.0	3546.5	1.92	8.5	5606.9	3.03
Aliquot	Nipple		1944.3	1.05		1479.2	0.80
Whole	Thyroid	4.0	4161.6	2.25	1.5	5074.0	2.74
Whole	Thymus	0.50	1086.9	0.59	0.25	3729.0	2.02
	<u>Brain</u>						
Homog.	Cerebrum		2086.4	1.13		1533.0	0.83
Homog.	Cerebellum		2593.5	1.40		1670.3	0.90
Homog.	Medulla		2253.5	1.22		1516.9	0.82
	<u>Left Eye</u>	6.0			7.0		
Aliquot	Tissue					3052.7	1.65
Aliquot	Aq. Humor					2617.4	1.41
	<u>Right Eye</u>	6.0			7.0		
Aliquot	Tissue		2261.3	1.22		3322.8	1.80
Aliquot	Aq. Humor		3024.4	1.63		3117.7	1.68
Whole	Submaxillary Gland	4.0	3572.1	1.93	3.0	4906.2	2.65

Table 3.5A
DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 3 (Control)			BABOON NO. 11 (Control)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593
	Baboon Wt. kg. Hematocrit, PVCZ		15.9 40			12.3 36	
Aliquot	Non-Pigmented Skin		1840.2	0.99		1652.1	0.89
Aliquot	Pigmented Skin		2084.7	1.13		1566.1	0.85
Aliquot	Ear		2133.4	1.15		1598.3	0.86
Aliquot	Skeletal Muscle		2079.6	1.12		1197.5	0.65
Aliquot	Endothermal Fat		4121.5	2.23		6216.3	3.36
Aliquot	Mesenteric Fat		6813.9	3.68		5155.9	2.79
Aliquot	Bone		807.9	0.44		1122.7	0.61
Aliquot	Urinary Bladder	24	3127.3	1.69	18	1832.9	0.99
Aliquot	Gall Bladder	5.0	2552.1	1.38	5.0	4240.9	2.29
Homog.	Pancreas	15	6489.7	3.51	18	14589.5	7.89
Aliquot	Spleen	30	3192.5	1.73		6857.0	3.71
Whole	Periaortic Lymph		1950.2	1.05		3326.8	1.80
Whole	Inguinal Node	3.0	2807.5	1.52	4.2	2114.9	1.14
Aliquot	Adrenals	3.0	11815.4	6.38	2.0	23408.1	12.65
	<u>Kidney</u>						
Homog.	Left	28	5710.2	3.09	20	9556.4	5.16
Homog.	Right	28	6090.8	3.29	20	9549.1	5.16
	<u>Heart (Total)</u>	55			55		
Aliquot	Right Ventricle		2961.3	1.60		3905.5	2.11
Aliquot	Left Auricle		2816.0	1.52		3847.2	2.08

Table 3.5A

**DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)**

		BABOON NO. 3 (Control)			BABOON NO. 11 (Control)		
PREP	TISSUE	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593
	Baboon Wt. kg. Hematocrit, PVC%		15.9 40			12.3 36	
Homog.	<u>Lung (Total)</u>	110			92		
	Left		3717.7	2.01		4045.6	2.19
Homog.	Right		3351.8	1.81		4127.9	2.23
	<u>Liver (Total)</u>	220			185		
Homog.	Left Lobe		2415.8	1.31		2122.4	1.15
Homog.	Right Lobe		2418.5	1.31		2779.7	1.50
Homog.	Cardiac Lobe		2405.8	1.30		3365.7	1.82
Homog.	Spigellian Lobe		2072.7	1.12		2880.9	1.56
	<u>Stomach</u>	103			98		
Aliquot	Pyloric		2812.5	1.52		3250.9	1.76
Aliquot	Cardiac		2240.3	1.21		2786.3	1.51
Aliquot	Fundic		3019.7	1.63		3128.0	1.69
	<u>Small Intestine</u>	206			210		
Aliquot	Duodenum		2791.4	1.51		3514.0	1.90
Aliquot	Ileum		2431.4	1.31		1974.4	1.07
Aliquot	Jejunum		3264.0	1.76		2461.5	1.33
	<u>Large Intestine</u>	175			168		
Aliquot	Ascending Colon		1706.8	0.92		2785.7	1.51
Aliquot	Transverse Colon		2049.7	1.11		3190.1	1.72
Aliquot	Rectum		2614.0	1.41		5002.8	2.70

Table 3.5A

DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 3 (Control)			BABOON NO. 11 (Control)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593
	Baboon Wt. kg. Hematocrit, PVCZ		15.9 40			12.3 36	
Whole	Ovary						
Whole	Left	1.2			3.0	1754.3	0.95
Aliquot	Right	1.5	2621.5	1.42	2.8	2038.7	1.10
Aliquot	Uterus	10	3624.9	1.96	11	2567.1	1.39
Aliquot	Cervix	4.0	2817.1	1.52	6.0	1765.7	0.95
			Mean	1.65		Mean	2.15
			Standard Deviation	0.98		Deviation	2.01
			Variance	0.93		Variance	3.95
			(1) All values expressed as $\mu\text{g}/\text{gram}$ of tissue or as $\mu\text{g}/\text{ml}$ of fluid				

Table 3.5B
DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms ⁽¹⁾ WR-4593	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms ⁽¹⁾ WR-4593
	Baboon Wt. kg. Hematocrit, PVCZ		14.5 31			16.4 32	
Aliquot	Blood		2545.0	1.55	400	1387.0	0.85
Aliquot	Marrow		2692.0	1.64		5129.7	3.13
Aliquot	Plasma		3167.2	1.93		2159.7	1.32
Aliquot	Hair	160	0	0	120	2111.1	1.29
Aliquot	Bile	7.5	10059.6	6.13	7.0	6663.6	4.06
Aliquot	Nipple		3112.1	1.90		1588.4	0.97
Whole	Thyroid	3.0	2694.8	1.64	4.0	3722.3	2.27
Whole	Thymus		2977.3	1.82	0.7	2814.7	1.72
	<u>Brain</u>						
Homog.	Cerebrum		2704.1	1.67		2315.9	1.41
Homog.	Cerebellum		2931.9	1.79		2337.9	1.43
Homog.	Medulla		1710.6	1.04		1921.7	1.17
	<u>Left Eye</u>						
Aliquot	Tissue		2997.1	1.83		2337.1	1.42
Aliquot	Aq. Humor		3025.7	1.84		3077.3	1.88
	<u>Right Eye</u>						
Aliquot	Tissue		2174.9	1.33		2582.1	1.57
Aliquot	Aq. Humor		3025.9	1.84		2631.3	1.60
Whole	Submaxillary Gland	8.0	3183.1	1.94	6.0	3641.3	2.22

Table 3.5B
DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-4593 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-4593 (1)
	Baboon Wt. kg. Hematocrit, PVCZ		14.5 31			16.4 32	
Aliquot	Non-Pigmented Skin		2748.2	1.68		1688.3	1.03
Aliquot	Pigmented Skin		2914.9	1.78		3001.1	1.22
Aliquot	Ear		3182.7	1.94		2069.1	1.26
Aliquot	Skeletal Muscle		2441.1	1.49		1973.6	1.20
Whole	Endothermal Fat		5271.3	3.21		6078.8	3.71
Aliquot	Mesenteric Fat		5952.8	3.63		7072.1	4.31
Aliquot	Bone		1648.2	1.00		913.7	0.56
Aliquot	Urinary Bladder	15	2794.2	1.70	26	2115.5	1.29
Aliquot	Gall Bladder	6.0	3684.2	2.25	7.0	3005.9	1.83
Homog.	Pancreas	16	8924.4	5.44	20	10292.9	6.28
Aliquot	Spleen	22	2369.9	1.44	28	2864.3	1.75
Whole	Periaortic Lymph	0.4	2078.7	1.27		2132.1	1.30
Whole	Inguinal Node				4.0	2077.3	1.27
Aliquot	Adrenals	3.0	4581.9	2.79	8.0	16824.7	10.26
	Kidney						
Homog.	Left	28	8277.3	5.05	34	6394.2	3.90
Homog.	Right	26	8103.9	4.94	34	7007.7	4.27
	Heart (Total)						
Aliquot	Right Ventricle		3206.2	1.95		3087.4	1.88
Aliquot	Left Auricle		1045.8	0.64		2199.9	1.34

Table 3.5B
DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593
	Baboon Wt. kg. Hematocrit, PVCZ		14.5 31			16.4 32	
	<u>Lung (Total)</u>	75			132		
Homog.	Left		3928.6	2.40		4007.6	2.44
Homog.	Right		3198.8	1.95		3822.4	2.33
	<u>Liver (Total)</u>						
Homog.	Left Lobe		2397.2	1.45		2592.1	1.58
Homog.	Right Lobe		2684.5	1.64		2449.7	1.49
Homog.	Cardiac Lobe		2899.9	1.77		2766.3	1.69
Homog.	Spigellian Lobe		2111.1	1.29		2683.5	1.64
	<u>Stomach</u>						
Aliquot	Pyloric		2053.8	1.25		2199.7	1.34
Aliquot	Cardiac		7515.3	4.58		2371.3	1.45
Aliquot	Fundic		1871.8	1.14		2844.4	1.73
	<u>Small Intestine</u>						
Aliquot	Duodenum		2174.5	1.33		2653.7	1.62
Aliquot	Ileum		1882.7	1.15		2172.2	1.32
	<u>Large Intestine</u>						
Aliquot	Ascending Colon		2124.3	1.30		1884.3	1.15
Aliquot	Transverse Colon		2632.9	1.61		2772.8	1.69
Aliquot	Rectum		1748.2	1.07		2043.5	1.25

Table 3.5B

**DISTRIBUTION OF WR-4593 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)**

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms (1) WR-4593
	Baboon Wt. kg. Hematocrit, PVC%		14.5 31			16.4 32	
Whole	Ovary						
Whole	Left	0.8	1922.6	1.17	2.0	1465.5	0.89
Aliquot	Right	0.9	1725.0	1.05	3.0	1932.0	1.18
Aliquot	Uterus	32	2472.1	1.51	22	2772.1	1.69
Aliquot	Cervix	32	2342.9	1.43	22	1976.3	1.20
			Mean	1.98		Mean	2.01
			Standard Deviation	1.23		Standard Deviation	1.58
			Variance	1.49		Variance	2.46
			(1) All values expressed as $\mu\text{g}/\text{gram}$ of tissue or as $\mu\text{g}/\text{ml}$ of fluid				

Table 3.6A
DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 3 (Control)				BABOON NO. 11 (Control)			
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		15.9 40			12.3 36			
Aliquot	Blood	390	424.0	8.84	425	0	0	425	0
Aliquot	Marrow		0	0		0	0		0
Aliquot	Plasma		221.5	4.62		139.0	2.90		
Aliquot	Hair	140	0	0	140	0	0		0
Aliquot	Bile	5.0	74.9	1.56	8.5	52.8	1.10		
Aliquot	Nipple		147.2	3.07		111.0	2.31		
Whole	Thyroid	4.0	0	0	1.5	0	0		0
Whole	Thymus	0.50	0	0	0.25	0	0		0
Homog	Brain (Total)	141			145				
Homog	Cerebrum		0	0		0	0		0
	Cerebellum		0	0		0	0		0
	Medulla								
	Left Eye	6.0			7.0				
Aliquot	Tissue		0	0		0	0		0
Aliquot	Aq. Humor		0	0		0	0		0
	Right Eye	6.0			7.0				
Aliquot	Tissue		0	0		0	0		0
Aliquot	Aq. Humor		0	0		0	0		0
Whole	Submaxillary Gland	4.0	0	0	3.0	0	0		0

Table 3.6A (Continued)

DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 3 (Control)			BABOON NO. 11 (Control)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		15.9 40			12.3 36	
Aliquot	Non-Pigmented Skin		169.7	3.54		346.7	7.23
Aliquot	Pigmented Skin		0	0		0	0
Aliquot	Ear		245.8	5.13		253.7	5.29
Aliquot	Skeletal Muscle		0	0		0	0
Whole	Endothermal Fat		0	0		0	0
Aliquot	Mesenteric Fat		0	0		0	0
Aliquot	Bone		0	0		0	0
Aliquot	Urinary Bladder	24	0	0		0	0
Homog.	Gall Bladder	5.0	0	0	18	0	0
Homog.	Pancreas	15	0	0	5.0	0	0
Aliquot	Spleen	30	0	0	18	0	0
Whole	Periaortic Lymph		26.2	0.55	22.5	0	0
Whole	Inguinal Node	3.0	52.6	1.10		275.9	5.75
Aliquot	Adrenals	3.0	0	0	4.2	288.7	6.02
Homog	Kidney		0	0	2.0	0	0
	Left	28	0	0		0	0
	Right	28	0	0	20	0	0
Aliquot	Heart (Total)		0	0			
	Right Ventricle		0	0		0	0

Table 3.6A (Continued)
DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 3 (Control)			BABOON NO. 11 (Control)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/-1	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		15.9 40			12.3 36	
Aliquot	Left Auricle		0	0		0	0
	Lung (Total)	110			92	0	0
Homog.	Left		0	0		0	0
Homog.	Right		0	0		0	0
	Liver (Total)	220			185	0	0
Homog.	Left Lobe		0	0		0	0
Homog.	Right Lobe		0	0		0	0
Homog.	Cardiac Lobe		0	0		0	0
Homog.	Spigellian Lobe		0	0		0	0
	Stomach						
Aliquot	Pyloric		0	0		0	0
Aliquot	Cardiac		0	0		0	0
Aliquot	Fundic		0	0		0	0
	Small Intestine	206			210		
Aliquot	Duodenum		0	0		0	0
Aliquot	Ileum		46.5	0.97		0	0
Aliquot	Jejunum		0	0		0	0
	Large Intestine	175			168		
Aliquot	Ascending Colon		0	0		0	0

Table 3.6A (Continued)
DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 3 (Control)			BABOON NO. 11 (Control)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		15.9 40			12.3 36	
Aliquot	Transverse Colon						
Aliquot	Rectum		0	0		0	0
	Ovary		0	0		0	0
Whole	Left	1.2	0	0	3.0	0	0
Whole	Right	1.5	0	0	2.8	0	0
Aliquot	Uterus	10	0	0	11	0	0
Aliquot	Cervix	4.0	0	0	6.0	0	0
(1) All values express as µg/gram of tissue or as µg/ml of fluid							

Table 3.6B

DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		14.5 31			16.4 32	
Aliquot	Blood		23.0	0.021	400	87.9	0.080
Aliquot	Marrow		0	0		0	0
Aliquot	Plasma		66.2	0.060		122.7	0.11
Aliquot	Hair	160	0	0	120	0	0
Aliquot	Bile	7.5	1656.2	1.51	7.0	421.3	0
Aliquot	Nipple		107.3	0.098		0	0
Whole	Thyroid	3.0	0	0	4.0	0	0
	<u>Brain</u>						
Homog.	Cerebrum		0	0		0	0
Homog.	Cerebellum		0	0		0	0
Homog.	Medulla		0	0		0	0
	<u>Left Eye</u>						
Aliquot	Tissue		0	0		0	0
Aliquot	Aq. Humor		0	0		0	0
	<u>Right Eye</u>						
Aliquot	Tissue		0	0		0	0
Aliquot	Aq. Humor		0	0		0	0
Whole	Submaxillary Gland	8.0	0	0		0	0

Table 3.6B (Continued)

DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		14.5 31			16.4 32	
Aliquot	Non-Pigmented Skin		209.9	0.19		0	0
Aliquot	Pigmented Skin		0	0		0	0
Aliquot	Ear		89.4	0.082		0	0
Aliquot	Skeletal Muscle		0	0		0	0
Whole	Endothermal Fat		0	0		0	0
Aliquot	Mesenteric Fat		0	0		0	0
Aliquot	Bone		0	0		0	0
Aliquot	Urinary Bladder	15	0	0	26	0	0
Aliquot	Gall Bladder	6.0	0	0	7.0	0	0
Homog.	Pancreas	16	0	0	20	0	0
Aliquot	Spleen	22	0	0	28	0	0
Whole	Periaortic Lymph	0.4	164.2	0.15		87.1	0.080
Whole	Inguinal Node	-			4.0	82.4	0.075
Aliquot	Adrenals	3.0	0	0	8.0	0	0
	<u>Kidney</u>						
Homog.	Left	28	0	0	34	0	0
Homog.	Right	26	0	0	34	0	0

Table 3.6B (Continued)

DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYSTEM II)

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		14.5 31			16.4 32	
	<u>Heart (Total)</u>	53			65		
Aliquot	Right Ventricle		0	0		0	0
Aliquot	Left Auricle		0	0		0	0
	<u>Lung (Total)</u>						
Homog.	Left		0	0		0	0
Homog.	Right		0	0		0	0
	<u>Liver (Total)</u>	210			358		
Homog.	Left Lobe		0	0		0	0
Homog.	Right Lobe		0	0		0	0
Homog.	Cardiac Lobe		0	0		0	0
Homog.	Spigelian Lobe		0	0		0	0
	<u>Stomach</u>	138			123		
Aliquot	Pyloric		0	0		0	0
Aliquot	Cardiac		0	0		0	0
Aliquot	Fundic		0	0		0	0
	<u>Small Intestine</u>	208					
Aliquot	Duodenum		0	0		0	0
Aliquot	Ileum		0	0		0	0
Aliquot	Jejunum		0	0		0	0

Table 3.6B (Continued)

DISTRIBUTION OF WR-158122 OR METABOLITES IN TISSUES
OF FOUR BABOONS (SYST^m II)

PREP	TISSUE	BABOON NO. 27 (Experimental)			BABOON NO. 29 (Experimental)		
		Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)	Wt., g. or Vol., ml	DPM/g or DPM/ml	Micrograms WR-158122 (1)
	Baboon Wt. kg. Hematocrit, PVC%		14.5 31			16.4 32	
	Large Intestine	238			398		
Aliquot	Ascending Colon		0	0		0	0
Aliquot	Transverse Colon		0	0		0	0
Aliquot	Rectum		0	0		0	0
	Ovary						
Whole	Left	0.08	0	0	2.0	0	0
Whole	Right	0.09	0	0	3.0	0	0
Aliquot	Uterus	32	0	0	22	0	0
Aliquot	Cervix	32	0	0	22	0	0
	(1) All values expressed as $\mu\text{g}/\text{gram}$ of tissue or as $\mu\text{g}/\text{ml}$ of fluid						

Table 3.7

ANALYSIS OF RESIDUAL DRUG REMAINING
AT INJECTION SITE (SYSTEM II)

Baboon Number	Total Recovery at Injection Site					
	C-14 DPM	mg WR-158122	%Initial Dose	H-3 DPM	mg WR-4593	%Initial Dose
3	104,106.7	2.17	3.1	108,509,760.0	58.6	8.37
11	56,254.1	1.17	1.7	164,578,336.4	88.9	12.70
27	21,562.2	0.02	0.03	27,070,648.9	16.5	2.36
29	693,101.3	0.63	0.91	58,223,095.4	40.0	5.71

Activity: No. 3,11:

C-14 = 21.6 μ Ci/g; H-3 = 833.6 μ Ci/g(per gram of drug)

No. 27,29:

C-14 = 246.6 μ Ci/g; H-3 = 369.4 μ Ci/g (per gram of matrix)

Dose:

WR-158122: 70 mg

WR-4593: 700 mg

Table 3.8

SYSTEM II MATERIAL BALANCE

Baboon Identity	Origin	WR-4593		WR-158122	
		mg Recovered	% Recovered (1)	mg Recovered	% Recovered (2)
No. 3 (Control)	Urine	328.0		107.4	
	Feces	14.4		54.1	
	Tissue	26.2		0	
	Injection Site	<u>8.4</u>		<u>2.2</u>	
	Total	377.0	53.9	163.7	233.7
No. 11 (Control)	Urine	209.6		82.1	
	Feces	38.2		23.0	
	Tissue	26.5		0	
	Injection Site	<u>12.7</u>		<u>1.2</u>	
	Total	287.0	41.0	106.3	151.8
Control Mean, Total		332.0 $\pm$ 45.0	47.5 $\pm$ 6.5	135.0 $\pm$ 28.7	192.8 $\pm$ 41.0

Continued . . .

Table 3.8 (Continued)

SYSTEM II MATERIAL BALANCE

Baboon Identity	Origin	WR-4593		WR-158122	
		mg Recovered	% Recovered (1)	mg Recovered	% Recovered (2)
No. 27 (Exp.)	Urine	326.7		21.0	
	Feces	30.7		10.5	
	Tissue	28.7		0	
	Injection Site	<u>2.4</u>		<u>0</u>	
	Total	388.5	55.5	31.5	44.9
No. 29 (Exp.)	Urine	205.7		10.4	
	Feces	13.9		5.3	
	Tissue	33.0		0	
	Injection Site	<u>5.7</u>		<u>0.6</u>	
	Total	258.3	36.9	16.3	23.4
Experimental Mean, Total		323.4 ± 65.1	46.2 ± 9.3	23.9 ± 7.6	34.2 ± 10.8

(1) Initial Dose = 700 mg (2) Initial Dose = 70 mg

Appendix A

SYSTEM I

^3H - WR-7557: Dose = 700 mg
 ^{14}C - WR-158122: Dose = 70 mg

EXCRETION OF TRITIUM LABELED MATERIALS
DERIVED FROM SYSTEM I WR-7557 BY BABOONS

Appendix A

SYSTEM I

3 H - WR-7557: Dose = 700 mg.
14C - WR-158122: Dose = 70 mg.

EXCRETION OF TRITIUM LABELED MATERIALS
DERIVED FROM SYSTEM I WR-7557 BY BALBOONS

Table A.1

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS
IN URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	40.1	47.5	46.5	34.2	42.7 $\pm$ 3.5
2	41.0	21.5	36.4	11.9	23.3 $\pm$ 5.8
3	32.2	9.9	36.9	16.7	21.2 $\pm$ 6.6
4	69.2	33.3	7.8	14.9	18.7 $\pm$ 6.2
5	20.2	8.2	7.9	22.4	14.4 $\pm$ 6.3
6	6.6	14.1	14.8	7.7	12.2 $\pm$ 1.8
7	5.8	8.0	2.8	7.7	6.2 $\pm$ 1.4
8	7.7	14.3	11.8	5.1	10.4 $\pm$ 2.2
9	6.1	11.1	4.9	10.0	8.7 $\pm$ 1.6
10	6.7	23.1	4.3	11.2	12.9 $\pm$ 4.5
11	8.9	12.4	11.5	15.1	13.0 $\pm$ 0.9
12	6.2	6.0	20.7	7.1	11.3 $\pm$ 3.9
13	6.5	5.7	4.3	5.7	5.2 $\pm$ 0.4
14	14.1	5.3	6.0	6.1	5.8 $\pm$ 0.2
15-21	78.5	93.4	99.8	79.0	90.7 $\pm$ 5.0
22-28	15.8	46.9	73.7	45.4	55.3 $\pm$ 7.5
29-35	1.7	46.7	70.7	58.9	58.8 $\pm$ 5.7
36-42	154.0	41.7	103.3	63.7	69.6 $\pm$ 14.7
43-49	1.6	24.1	48.2	5.0	25.7 $\pm$ 10.2
50-56	0	20.4	27.7	15.1	21.0 $\pm$ 3.0
57-63	0	16.0	16.2	16.3	16.1 $\pm$ 0.1
64-70	0	12.2	10.6	17.1	13.0 $\pm$ 1.6
71-77	0	6.0	6.7	10.7	7.3 $\pm$ 1.0
78-84	0	2.7	2.1	7.3	4.0 $\pm$ 1.3
85-91	0	1.4	1.1	3.6	2.0 $\pm$ 0.6
92-98	0	1.1	0.6	1.4	1.0 $\pm$ 0.2
99-105	0	0.3	0.5	0.9	0.6 $\pm$ 0.1

Table A.1

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS IN
URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	0	0	0.09	0.57	0.22 $\pm$ 0.18
113-119	0	0	0.06	0.11	0.06 $\pm$ 0.03
120-126	0	0	0.09	0.01	0.03 $\pm$ 0.03
127-133	0	0	0.04	0	0.01 $\pm$ 0.01
134-140	0	0	0.22	0.44	0.22 $\pm$ 0.13
141-147	0	0	0.07	0.25	0.11 $\pm$ 0.07
148-154	0	0	0.07	0.19	0.09 $\pm$ 0.06
155-161	0	0	0.16	0.61	0.26 $\pm$ 0.18
162-168	0	0	0.15	0.44	0.20 $\pm$ 0.13

Table A.2

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS
IN FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	0.2	0.1	0.	2.2	0.8 $\pm$ 0.6
2	0.	0.4	0.4	3.3	1.4 $\pm$ 0.8
3	0.	0.4	0.1	4.2	0.6 $\pm$ 1.1
4	0.	1.7	2.0	3.0	2.2 $\pm$ 0.3
5	2.5	1.4	3.3	1.6	2.1 $\pm$ 0.5
6	3.7	2.1	1.4	2.0	1.8 $\pm$ 0.2
7	3.2	1.5	1.6	1.4	1.5 $\pm$ 0.1
8	3.8	2.9	1.5	4.0	2.8 $\pm$ 0.6
9	1.4	1.4	1.0	4.0	2.1 $\pm$ 0.8
10	1.6	1.8	1.2	1.6	1.5 $\pm$ 0.1
11	1.6	1.0	1.2	1.1	1.1 $\pm$ 0.1
12	1.6	1.0	1.4	1.5	1.3 $\pm$ 0.1
13	1.5	1.2	1.4	4.3	2.3 $\pm$ 0.8
14	2.9	2.1	1.1	1.5	1.5 $\pm$ 0.2
15-21	6.1	8.5	7.5	7.7	7.9 $\pm$ 0.2
22-28	1.1	3.3	7.4	3.3	4.7 $\pm$ 1.1
29-35	0.	4.0	3.7	21.3	9.7 $\pm$ 4.7
36-42	4.8	5.1	6.4	3.4	5.0 $\pm$ 0.7
43-49	0	2.0	2.9	2.8	2.6 $\pm$ 0.2
50-56	0	1.9	1.1	5.3	2.8 $\pm$ 1.2
57-63	0	0.8	0.8	1.8	1.1 $\pm$ 0.3
64-70	0	0.5	0.4	1.0	2.1 $\pm$ 0.4
71-77	0	0	0.2	1.1	0.6 $\pm$ 0.3
78-84	0	0.3	0.2	0.7	0.4 $\pm$ 0.1
85-91	0	0.2	0.2	0.4	0.2 $\pm$ 0.1
92-98	0	0.2	0.2	0.3	0.1 $\pm$ 0.03
99-105	0	0.2	0.2	0.2	0.1 $\pm$ 0.01

Table A.2

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS IN
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	0	0.14	0.10	0.19	0.14 $\pm$ 0.03
113-119	0	0.10	0.07	0.21	0.13 $\pm$ 0.04
120-126	0	0.19	0.11	0.08	0.13 $\pm$ 0.03
127-133	0	0.09	0.05	0.17	0.10 $\pm$ 0.04
134-140	0	0.02	0	0.28	0.10 $\pm$ 0.09
141-147	0	0	0.08	0.09	0.06 $\pm$ 0.03
148-154	0	0	0	0.02	0.01 $\pm$ 0.01
155-161	0	0.05	0	0.02	0.02 $\pm$ 0.01
162-168	0	0.09	0	0.11	0.07 $\pm$ 0.04

Table A.3

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS
IN URINE PLUS FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	40.3	47.6	46.5	36.4	43.5 $\pm$ 2.9
2	41.0	21.9	36.8	15.2	24.6 $\pm$ 5.2
3	32.2	10.3	37.0	20.9	22.7 $\pm$ 6.3
4	69.2	35.0	9.8	17.9	20.9 $\pm$ 6.1
5	22.7	9.6	11.2	24.0	14.9 $\pm$ 3.7
6	10.3	16.2	16.2	9.7	14.0 $\pm$ 1.8
7	9.0	9.5	4.4	9.1	7.7 $\pm$ 1.3
8	11.5	17.2	13.3	9.1	13.2 $\pm$ 1.9
9	7.5	12.5	5.9	14.0	10.8 $\pm$ 2.0
10	8.3	24.9	5.5	12.8	14.4 $\pm$ 4.4
11	10.5	13.4	12.7	16.2	14.1 $\pm$ 0.9
12	7.8	7.0	22.1	8.6	12.6 $\pm$ 3.9
13	8.0	6.9	5.7	10.0	7.5 $\pm$ 1.0
14	17.0	7.4	7.1	7.6	7.4 $\pm$ 0.1
15-21	84.6	101.9	107.3	86.7	98.6 $\pm$ 5.0
22-28	16.9	50.2	81.1	48.7	60.0 $\pm$ 8.6
29-35	1.7	50.7	74.4	80.2	69.4 $\pm$ 7.4
36-42	288.8	46.8	109.7	68.1	74.9 $\pm$ 15.1
43-49	4.6	26.1	51.1	7.8	28.3 $\pm$ 10.2
50-56	0	22.4	28.8	20.4	23.8 $\pm$ 2.1
57-63	0	16.8	16.9	18.1	17.6 $\pm$ 0.3
64-70	0	12.7	11.0	18.1	13.9 $\pm$ 1.7
71-77	0	6.9	6.9	13.6	8.5 $\pm$ 1.3
78-84	0	3.0	2.3	7.9	4.4 $\pm$ 1.4
85-91	0	1.5	1.3	4.0	1.9 $\pm$ 0.7
92-98	0	1.2	0.7	1.7	1.2 $\pm$ 0.2
99-105		0.5	0.6	1.7	0.7 $\pm$ 0.1

Table A.3

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS IN URINE PLUS
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	0	0.14	0.19	0.76	0.36 $\pm$ 0.20
113-119	0	0.10	0.13	0.32	0.18 $\pm$ 0.07
120-126	0	0.19	0.20	0.09	0.16 $\pm$ 0.04
127-133	0	0.09	0.09	0.17	0.12 $\pm$ 0.03
134-140	0	0.02	0.22	0.72	0.32 $\pm$ 0.21
141-147	0	0	0.15	0.34	0.16 $\pm$ 0.10
148-154	0	0	0.07	0.21	0.27 $\pm$ 0.15
155-161	0	0.05	0.16	0.63	0.28 $\pm$ 0.18
162-168	0	0.09	0.15	0.56	0.27 $\pm$ 0.15

Table A.4

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS
IN URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	40.1	47.5	46.5	34.2	42.7 $\pm$ 3.5
2	81.1	69.0	82.9	46.1	66.0 $\pm$ 8.8
3	113.3	78.9	119.8	62.8	87.2 $\pm$ 13.9
4	182.5	112.2	127.6	77.7	105.8 $\pm$ 12.0
5	202.7	120.4	135.5	100.1	118.7 $\pm$ 8.4
6	209.3	134.5	150.3	107.8	130.9 $\pm$ 17.5
7	215.1	142.5	153.1	115.5	137.0 $\pm$ 9.1
8	222.8	156.8	164.9	120.6	147.4 $\pm$ 11.1
9	228.9	167.9	169.8	130.6	156.1 $\pm$ 10.4
10	235.6	191.0	174.1	141.8	169.0 $\pm$ 11.8
11	244.5	203.4	185.6	156.9	182.0 $\pm$ 11.1
12	250.7	209.4	206.3	164.0	193.2 $\pm$ 12.0
13	257.2	215.1	210.6	169.7	198.5 $\pm$ 11.8
14	271.3	220.4	216.6	175.8	204.3 $\pm$ 11.7
15-21	349.8	313.8	316.4	254.8	295.0 $\pm$ 16.4
22-28	365.6	360.7	390.1	300.2	350.5 $\pm$ 21.6
29-35	367.3	407.4	460.8	359.1	409.3 $\pm$ 24.0
36-42	651.3	449.1	564.1	422.8	478.7 $\pm$ 35.5
43-49	655.9	473.2	612.3	427.7	504.4 $\pm$ 45.3
50-56	655.9	493.6	640.0	442.3	525.5 $\pm$ 48.3
57-63	655.9	509.6	650.1	459.0	531.5 $\pm$ 48.2
64-70	655.9	521.8	666.7	470.1	531.5 $\pm$ 46.9
71-77	655.9	528.7	673.4	486.6	562.5 $\pm$ 46.2
78-84	655.9	531.4	675.5	492.8	566.9 $\pm$ 45.2
85-91	655.9	532.8	676.6	497.4	568.9 $\pm$ 44.7
92-98	655.9	533.9	677.2	498.0	569.2 $\pm$ 44.6
99-105	655.9	534.1	677.6	497.7	570.5 $\pm$ 44.5

Table A.4

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS IN
URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	655.9	534.1	677.7	500.3	570.7 $\pm$ 54.4
113-119	"	"	677.8	500.4	570.8 $\pm$ 54.4
120-126	"	"	677.8	500.4	570.8 $\pm$ 54.4
127-133	"	"	677.9	500.4	570.8 $\pm$ 54.4
134-140	"	"	678.1	500.8	571.0 $\pm$ 54.4
141-147	"	"	678.2	501.1	571.1 $\pm$ 94.2
148-154	"	"	678.2	501.3	571.2 $\pm$ 54.3
155-161	"	"	678.4	501.9	571.5 $\pm$ 54.3
162-168	"	"	678.6	502.3	571.7 $\pm$ 54.3

Table A.5

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS
IN FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-754
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error	
	8 (Control.)	28 (Exp.)	33 (Exp.)	46 (Exp.)		
1	0.2	0.1	0.0	2.2	0.8 $\pm$	0.6
2	0.2	0.5	0.4	5.5	2.1 $\pm$	1.4
3	0.2	0.9	0.5	9.7	3.7 $\pm$	2.5
4	0.2	2.6	2.5	12.7	5.9 $\pm$	2.8
5	2.7	4.0	5.8	14.3	8.0 $\pm$	2.6
6	5.2	6.1	7.2	16.3	9.9 $\pm$	2.6
7	8.9	7.6	8.8	17.7	11.4 $\pm$	2.6
8	12.1	10.5	10.3	21.7	14.2 $\pm$	3.1
9	15.9	11.9	11.3	25.7	16.3 $\pm$	3.8
10	17.3	13.7	12.5	27.3	17.8 $\pm$	3.9
11	18.9	14.7	13.7	28.4	18.9 $\pm$	3.9
12	20.5	15.7	15.1	29.9	20.2 $\pm$	4.0
13	22.0	16.9	16.5	34.2	22.5 $\pm$	4.8
14	24.9	19.0	17.6	35.7	24.1 $\pm$	4.8
15-21	31.0	27.5	25.1	43.4	32.0 $\pm$	4.7
22-28	32.1	30.8	32.5	46.7	36.7 $\pm$	4.1
29-35	32.1	34.8	36.2	68.0	46.3 $\pm$	8.9
36-42	36.9	39.9	42.6	71.4	51.3 $\pm$	8.2
43-49	36.9	41.9	45.5	74.2	53.5 $\pm$	8.3
50-56	36.9	43.8	46.6	79.5	56.6 $\pm$	9.3
57-63	36.9	44.7	47.3	81.4	57.8 $\pm$	9.6
64-70	36.9	45.2	47.7	82.4	58.4 $\pm$	9.8
71-77	36.9	45.2	48.0	83.4	58.9 $\pm$	10.0
78-84	36.9	45.5	48.2	84.1	59.3 $\pm$	10.1
85-91	36.9	45.7	48.3	84.6	59.5 $\pm$	10.2
92-98	36.9	45.8	48.5	84.8	59.7 $\pm$	10.3
99-105	36.9	46.0	48.6	85.3	59.9 $\pm$	10.3

Table A.5

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS IN
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	36.9	46.1	48.7	85.2	60.0 $\pm$ 12.6
113-119	"	46.2	48.8	85.4	60.1 $\pm$ 12.7
120-126	"	46.4	48.9	85.5	60.3 $\pm$ 12.6
127-133	"	46.5	48.9	85.7	60.4 $\pm$ 12.7
134-140	"	46.5	48.9	85.9	60.4 $\pm$ 12.8
141-147	"	46.5	49.0	86.0	60.5 $\pm$ 14.6
148-154	"	46.5	49.0	86.0	60.5 $\pm$ 12.8
155-161	"	46.6	49.0	86.1	60.6 $\pm$ 12.8
162-168	"	46.7	49.0	86.2	60.6 $\pm$ 12.8

Table A.6

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS
IN URINE PLUS FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557
(SYSTEM 1)

Day	Baboon Number				Mean $\pm$ Std. Error
	3 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	40.3	47.6	46.5	36.4	43.5 $\pm$ 2.9
2	81.3	69.5	83.3	51.6	68.1 $\pm$ 7.5
3	113.5	79.8	120.3	72.5	90.0 $\pm$ 12.1
4	182.7	114.8	130.1	90.4	111.8 $\pm$ 9.4
5	265.4	124.4	141.3	114.4	126.7 $\pm$ 6.4
6	215.7	140.6	157.3	124.1	140.7 $\pm$ 7.9
7	224.7	150.1	161.9	133.3	148.4 $\pm$ 6.8
8	256.2	167.3	175.2	142.3	161.6 $\pm$ 8.1
9	243.7	179.8	181.1	156.3	172.4 $\pm$ 6.6
10	252.0	204.7	186.6	169.1	186.8 $\pm$ 8.4
11	262.5	218.1	199.3	185.3	200.9 $\pm$ 7.7
12	270.4	225.1	221.4	193.9	213.5 $\pm$ 8.0
13	278.4	232.0	227.1	203.9	221.0 $\pm$ 7.1
14	285.4	239.4	234.2	211.5	228.4 $\pm$ 7.0
15-21	300.0	341.3	341.5	298.2	327.0 $\pm$ 11.8
22-28	396.9	391.5	422.6	346.9	387.0 $\pm$ 18.0
29-35	398.5	442.2	497.0	427.1	455.5 $\pm$ 17.3
36-42	607.4	489.0	606.7	495.2	530.3 $\pm$ 31.2
43-49	622.3	515.1	657.8	503.0	558.6 $\pm$ 40.6
50-56	622.3	537.5	686.6	523.3	582.5 $\pm$ 42.6
57-63	622.3	554.3	703.5	541.4	599.7 $\pm$ 42.5
64-70	622.3	567.0	714.4	552.5	613.6 $\pm$ 41.2
71-77	622.3	573.9	721.3	571.1	622.1 $\pm$ 40.5
78-84	622.3	576.9	723.7	578.9	623.5 $\pm$ 39.7
85-91	622.3	576.4	725.0	582.9	623.8 $\pm$ 39.3
92-98	622.3	579.7	725.7	584.6	623.8 $\pm$ 39.1
99-100	622.3	580.1	726.3	585.7	623.8 $\pm$ 39.0

Table A.6

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS IN URINE PLUS
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-7557 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	692.8	580.2	726.5	586.5	631.2 $\pm$ 47.7
113-119	"	580.3	726.6	586.8	631.2 $\pm$ 47.7
120-126	"	580.5	726.8	586.9	631.4 $\pm$ 47.7
127-133	"	580.6	726.9	587.0	631.5 $\pm$ 47.7
134-140	"	580.6	727.1	587.8	631.8 $\pm$ 47.7
141-147	"	580.6	727.3	588.1	632.1 $\pm$ 47.7
148-154	"	580.6	727.4	588.3	632.2 $\pm$ 47.6
155-161	"	580.7	727.5	588.9	632.4 $\pm$ 47.6
162-168	"	580.8	727.7	589.5	632.7 $\pm$ 47.6

Appendix B

SYSTEM I

^3H - WR-7557: Dose = 700 mg

^{14}C - WR-158155: Dose = 70 mg

EXCRETION OF CARBON-14 LABELED MATERIALS
DERIVED FROM SYSTEM I WR-158122 BY BABOONS

Appendix B

SYSTEM I

^3H - WR-7557: Dose = 700 mg.

^{14}C - WR-158122: Dose = 70 mg.

EXCRETION OF CARBON-14 LABELED MATERIALS
DERIVED FROM SYSTEM I WR-158122 BY BLOODS

Table B.1

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS
IN URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	0.41	0.12	0.09	0	0.07 $\pm$ 0.03
2	0.23	0.05	0	0.03	0.03 $\pm$ 0.01
3	0.45	0.11	0.20	0.06	0.12 $\pm$ 0.06
4	0.43	0.09	0.07	0.07	0.07 $\pm$ 0.06
5	0.02	0.02	0.13	0.07	0.07 $\pm$ 0.03
6	0.47	0.11	0.05	0.03	0.06 $\pm$ 0.02
7	0	0.03	0.02	0.06	0.04 $\pm$ 0.01
8	0	0.03	0.06	0.02	0.04 $\pm$ 0.01
9	0	0.05	0	0.07	0.04 $\pm$ 0.02
10	0	0.06	0.03	0.02	0.04 $\pm$ 0.01
11	0	0.03	0.03	0.05	0.04 $\pm$ 0.01
12	0	0.05	0	0.03	0.03 $\pm$ 0.01
13	0	0.05	0.02	0.04	0.04 $\pm$ 0.01
14	0	0.02	0.04	0.02	0.20 $\pm$ 0.01
15-21	0	0.27	0.52	0.18	0.32 $\pm$ 0.03
22-28	0	0.23	0.27	0	0.17 $\pm$ 0.07
29-35	0	0.30	0.39	0.24	0.31 $\pm$ 0.03
36-42	1.01	0.21	0.63	0	0.28 $\pm$ 0.15
43-49	7.08	0.18	0.05	0.19	0.14 $\pm$ 0.04
50-56	0	0	0.04	0	0.01 $\pm$ 0.01
57-63	0	0	0	0.01	0
64-70	0	0	0.13	0.11	0.12 $\pm$ 0.05
71-77	0	0	0.21	0.15	0.18 $\pm$ 0.05
78-84	0	0	0.05	0.12	0.08 $\pm$ 0.03
85-91	0	0	0.19	0.17	0.08 $\pm$ 0.05
92-98	0	0.20	0.11	0.12	0.12 $\pm$ 0.04
99-105	0	0.57	0.13	0	0.23 $\pm$ 0.14

Table B.1

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS IN URINE OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	0	1.24	0.41	0.34	0.66 $\pm$ 0.29
113-119	0	1.22	0.35	0.22	0.60 $\pm$ 0.31
120-126	0	0.21	0.48	0.18	0.29 $\pm$ 0.10
127-133	0	0.28	0.35	0.17	0.27 $\pm$ 0.05
134-140	0	0.15	0.10	0.25	0.17 $\pm$ 0.04
141-147	0	0.20	0.13	0.09	0.14 $\pm$ 0.03
148-154	0	0.19	0.15	0.11	0.15 $\pm$ 0.02
155-161	0	0.04	0.26	0.51	0.27 $\pm$ 0.14
162-168	0	0.22	0.20	0	0.14 $\pm$ 0.07

Table B.2

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS
IN FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	0	0	0	0.01	0
2	0	0.01	0	0.02	0.01 $\pm$ 0.01
3	0	0	0	0.06	0.02 $\pm$ 0.02
4	0	0.01	0.02	0.03	0.02 $\pm$ 0.01
5	0.04	0.01	0.03	0.06	0.03 $\pm$ 0.01
6	0.17	0.02	0.03	0.01	0.02 $\pm$ 0.01
7	0.17	0.03	0.03	0.02	0.02 $\pm$ 0.01
8	0.17	0.03	0.04	0.07	0.05 $\pm$ 0.01
9	0.06	0.02	0.02	0.04	0.03 $\pm$ 0.01
10	0.04	0.02	0.02	0.02	0.02 $\pm$ 0.01
11	0.03	0.02	0.01	0.02	0.02 $\pm$ 0.01
12	0.03	0.02	0.02	0.03	0.02 $\pm$ 0.01
13	0.03	0.02	0.02	0.04	0.03 $\pm$ 0.01
14	0.07	0.02	0.03	0.02	0.02 $\pm$ 0.01
15-21	0.31	0.19	0.19	0.26	0.21 $\pm$ 0.01
22-28	0.44	0.17	0.18	0.12	0.16 $\pm$ 0.02
29-35	0.19	0.12	0.12	0.64	0.29 $\pm$ 0.14
36-42	0.27	0.17	0.18	0.09	0.15 $\pm$ 0.02
43-49	2.46	0.12	0.10	0.10	0.11 $\pm$ 0.01
50-56	1.67	0.06	0.03	0.19	0.13 $\pm$ 0.03
57-63	1.31	0.05	0.05	0.08	0.13 $\pm$ 0.01
64-70	0.44	0.03	0.04	0.04	0.07 $\pm$ 0.01
71-77	0.27	0	0.04	0.07	0.06 $\pm$ 0.02
78-84	1.97	0.03	0.06	0.05	0.15 $\pm$ 0.01
85-91	3.11	0.03	0.06	0.12	0.15 $\pm$ 0.02
92-98	0.11	0.05	0.07	0.12	0.10 $\pm$ 0.01
99-105	0	0.06	0.10	0.07	0.07 $\pm$ 0.01

Table B.2

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS IN FECES OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	0	0.08	0.09	0.11	0.09 $\pm$ 0.01
113-119	0	0.06	0.08	0.02	0.05 $\pm$ 0.02
120-126	0	0.10	0.13	0.10	0.11 $\pm$ 0.01
127-133	0	0.09	0.08	0.14	0.10 $\pm$ 0.02
134-140	0	0.14	0.11	0.24	0.16 $\pm$ 0.04
141-147	0	0.10	0.12	0.05	0.09 $\pm$ 0.02
148-154	0	0.46	0.11	0.08	0.22 $\pm$ 0.12
155-161	0	0.03	0.16	0.10	0.10 $\pm$ 0.04
162-168	0	0.13	0.10	0.25	0.16 $\pm$ 0.05

Table B.3

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS IN
URINE PLUS FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	0.41	0.12	0.09	0.01	0.07 $\pm$ 0.03
2	0.23	0.06	0	0.05	0.04 $\pm$ 0.02
3	0.45	0.11	0.20	0.12	0.14 $\pm$ 0.02
4	0.42	0.10	0.09	1.10	0.10 $\pm$ 0.01
5	0.66	0.03	0.16	0.13	0.11 $\pm$ 0.03
6	0.64	0.13	0.08	0.04	0.08 $\pm$ 0.02
7	0.17	0.06	0.05	0.02	0.06 $\pm$ 0.01
8	0.17	0.06	0.10	0.09	0.08 $\pm$ 0.01
9	0.06	0.07	0.02	0.11	0.07 $\pm$ 0.02
10	0.04	0.08	0.05	0.04	0.06 $\pm$ 0.01
11	0.63	0.05	0.04	0.07	0.05 $\pm$ 0.01
12	0.63	0.07	0.02	0.06	0.05 $\pm$ 0.01
13	0.04	0.07	0.04	0.03	0.06 $\pm$ 0.01
14	0.05	0.04	0.07	0.04	0.05 $\pm$ 0.01
15-21	0.31	0.46	0.71	0.44	0.54 $\pm$ 0.07
22-28	0.41	0.40	0.45	0.12	0.32 $\pm$ 0.09
29-35	0.12	0.42	0.51	0.33	0.60 $\pm$ 0.11
36-42	1.25	0.33	0.81	0.09	0.43 $\pm$ 0.17
43-49	9.53	0.30	0.15	0.29	0.25 $\pm$ 0.04
50-56	1.69	0.06	0.07	0.12	0.11 $\pm$ 0.04
57-63	1.31	0.65	0.05	0.02	0.05 $\pm$ 0.03
64-70	0.15	0.03	0.22	0.12	0.15 $\pm$ 0.05
71-77	0.27	0	0.25	0.13	0.13 $\pm$ 0.06
78-84	1.97	0.03	0.11	0.13	0.11 $\pm$ 0.04
85-91	0.14	0.04	0.25	0.15	0.14 $\pm$ 0.06
92-98	0.04	0.25	0.13	0.12	0.13 $\pm$ 0.03
99-105	0	0.63	0.41	0.02	0.12 $\pm$ 0.14

Table B.3

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS IN URINE PLUS
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	0	1.32	0.50	0.45	0.76 $\pm$ 0.28
113-119	0	1.28	0.43	0.24	0.65 $\pm$ 0.32
120-126	0	0.31	0.61	0.28	0.40 $\pm$ 0.11
127-133	0	0.37	0.43	0.31	0.37 $\pm$ 0.04
134-140	0	0.29	0.21	0.49	0.33 $\pm$ 0.08
141-147	0	0.30	0.25	0.14	0.23 $\pm$ 0.05
148-154	0	0.65	0.26	0.19	0.37 $\pm$ 0.14
155-161	0	0.07	0.42	0.61	0.37 $\pm$ 0.16
162-168	0	0.35	0.30	0.25	0.30 $\pm$ 0.03

Table B.4

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS
IN URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8(Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	0.41	0.12	0.09	0	0.07 $\pm$ 0.03
2	0.64	0.17	0.09	0.03	0.10 $\pm$ 0.03
3	1.09	0.28	0.30	0.09	0.22 $\pm$ 0.06
4	1.52	0.37	0.37	0.16	0.30 $\pm$ 0.06
5	1.54	0.39	0.50	0.23	0.37 $\pm$ 0.06
6	1.99	0.50	0.55	0.26	0.43 $\pm$ 0.07
7	1.99	0.53	0.57	0.31	0.47 $\pm$ 0.07
8	1.99	0.56	0.63	0.33	0.51 $\pm$ 0.07
9	1.99	0.61	0.63	0.40	0.55 $\pm$ 0.01
10	1.99	0.68	0.66	0.42	0.59 $\pm$ 0.07
11	1.99	0.71	0.69	0.46	0.62 $\pm$ 0.06
12	1.99	0.76	0.69	0.49	0.65 $\pm$ 0.07
13	1.99	0.81	0.72	0.53	0.68 $\pm$ 0.07
14	1.99	0.83	0.76	0.55	0.71 $\pm$ 0.07
15-21	1.99	1.09	1.28	0.73	1.03 $\pm$ 0.13
22-28	1.99	1.32	1.54	0.73	1.20 $\pm$ 0.20
29-35	1.99	1.62	1.93	0.97	1.51 $\pm$ 0.23
36-42	2.99	1.83	2.56	0.97	1.79 $\pm$ 0.38
43-49	10.07	2.01	2.61	1.16	1.93 $\pm$ 0.42
50-56	10.07	2.01	2.65	1.16	1.94 $\pm$ 0.43
57-63	10.07	2.01	2.65	1.17	1.94 $\pm$ 0.43
64-70	10.07	2.01	2.83	1.26	2.07 $\pm$ 0.45
71-77	10.07	2.01	3.04	1.33	2.11 $\pm$ 0.50
78-84	10.07	2.01	3.09	1.45	2.18 $\pm$ 0.48
85-91	10.07	2.01	3.28	1.50	2.26 $\pm$ 0.53
92-98	10.07	2.21	3.39	1.55	2.38 $\pm$ 0.54
99-105	10.07	2.78	3.70	1.55	2.48 $\pm$ 0.62

Table B.4

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS IN URINE OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	10.07	4.02	4.11	1.89	3.34 $\pm$ 0.73
113-119	"	5.24	4.46	2.11	3.94 $\pm$ 0.94
120-126	"	5.45	4.94	2.29	4.23 $\pm$ 0.98
127-133	"	5.73	5.29	2.46	4.49 $\pm$ 1.02
134-140	"	5.88	5.39	2.71	4.66 $\pm$ 0.99
141-147	"	6.08	5.52	2.80	4.80 $\pm$ 1.01
148-154	"	6.27	5.67	2.91	4.95 $\pm$ 1.03
155-161	"	6.31	5.93	3.42	5.22 $\pm$ 0.91
162-168	"	6.53	6.13	3.42	5.36 $\pm$ 0.98

Table B.5

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS
IN FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM I)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	26 (Exp.)	33 (Exp.)	46 (Exp.)	
1	0	0	0	0	0
2	0	0	0	0.03	0.01 $\pm$ 0.01
3	0	0	0	0.09	0.03 $\pm$ 0.03
4	0	0.02	0.02	0.12	0.05 $\pm$ 0.03
5	0.04	0.03	0.05	0.18	0.09 $\pm$ 0.04
6	0.21	0.05	0.60	0.19	0.11 $\pm$ 0.04
7	0.38	0.07	0.11	0.21	0.13 $\pm$ 0.03
8	0.55	0.11	0.11	0.28	0.18 $\pm$ 0.04
9	0.61	0.13	0.16	0.32	0.20 $\pm$ 0.05
10	0.64	0.15	0.18	0.34	0.22 $\pm$ 0.05
11	0.67	0.16	0.19	0.36	0.24 $\pm$ 0.05
12	0.70	0.18	0.22	0.39	0.26 $\pm$ 0.05
13	0.73	0.21	0.24	0.43	0.29 $\pm$ 0.06
14	0.81	0.22	0.27	0.46	0.32 $\pm$ 0.06
15-21	1.12	0.41	0.45	0.72	0.53 $\pm$ 0.08
22-28	1.52	0.58	0.64	0.84	0.69 $\pm$ 0.06
29-35	1.72	0.70	0.76	1.43	0.98 $\pm$ 0.20
36-42	1.99	0.88	0.94	1.57	1.13 $\pm$ 0.18
43-49	4.45	1.00	1.04	1.67	1.24 $\pm$ 0.22
50-56	6.14	1.06	1.07	1.86	1.33 $\pm$ 0.27
57-63	7.45	1.11	1.12	1.94	1.39 $\pm$ 0.28
64-70	7.75	1.14	1.16	2.02	1.44 $\pm$ 0.29
71-77	8.12	1.14	1.26	2.10	1.48 $\pm$ 0.31
78-84	10.37	1.17	1.26	2.16	1.53 $\pm$ 0.32
85-91	10.52	1.26	1.32	2.25	1.59 $\pm$ 0.33
92-98	10.15	1.25	1.39	2.32	1.65 $\pm$ 0.34
99-107	10.55	1.31	1.43	2.41	1.74 $\pm$ 0.34

Table B.5

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS IN FECES OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	10.56	1.39	1.58	2.52	1.83 $\pm$ 0.33
113-119	"	1.45	1.66	2.54	1.88 $\pm$ 0.33
120-126	"	1.55	1.79	2.64	1.99 $\pm$ 0.33
127-133	"	1.64	1.87	2.78	2.09 $\pm$ 0.34
134-140	"	1.78	1.98	3.02	2.26 $\pm$ 0.38
141-147	"	1.88	2.10	3.07	2.35 $\pm$ 0.37
148-154	"	2.34	2.21	3.15	2.57 $\pm$ 0.29
155-161	"	2.37	2.37	3.25	2.66 $\pm$ 0.29
162-168	"	2.50	2.47	3.50	2.82 $\pm$ 0.34

Table B.6

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS IN
URINE PLUS FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WK-158122
(SYSTEM 1)

Day	Baboon Number				Mean $\pm$ Std. Error
	8 (Control)	28 (Exp.)	33 (Exp.)	46 (Exp.)	
1	0.41	0.12	0.09	0.01	0.07 $\pm$ 0.13
2	0.64	0.17	0.09	0.64	0.11 $\pm$ 0.03
3	1.09	0.29	0.30	0.18	0.26 $\pm$ 0.03
4	1.52	0.39	0.39	0.25	0.35 $\pm$ 0.03
5	1.57	0.42	0.55	0.40	0.46 $\pm$ 0.04
6	2.21	0.55	0.63	0.44	0.54 $\pm$ 0.04
7	2.38	0.61	0.68	0.52	0.60 $\pm$ 0.04
8	2.55	0.67	0.77	0.61	0.68 $\pm$ 0.04
9	2.61	0.74	0.79	0.71	0.75 $\pm$ 0.02
10	2.64	0.83	0.84	0.75	0.81 $\pm$ 0.02
11	2.67	0.87	0.89	0.82	0.86 $\pm$ 0.02
12	2.70	0.95	0.91	0.88	0.91 $\pm$ 0.02
13	2.73	1.02	0.96	0.96	0.98 $\pm$ 0.02
14	2.81	1.05	1.02	1.01	1.02 $\pm$ 0.01
15-21	3.12	1.51	1.73	1.45	1.56 $\pm$ 0.07
22-28	3.53	1.91	2.18	1.57	1.89 $\pm$ 0.14
29-35	3.77	2.33	2.69	2.45	2.49 $\pm$ 0.09
36-42	5.31	2.71	3.50	2.54	2.93 $\pm$ 0.24
43-49	14.52	3.61	3.65	2.83	3.16 $\pm$ 0.25
50-56	16.11	3.07	3.72	3.62	3.27 $\pm$ 0.22
57-63	17.52	3.12	3.77	3.11	3.33 $\pm$ 0.22
64-70	17.92	3.15	3.95	3.36	3.48 $\pm$ 0.26
71-77	18.19	3.15	4.24	3.45	3.61 $\pm$ 0.31
78-84	20.15	3.18	4.55	3.61	3.71 $\pm$ 0.34
85-91	20.55	3.21	4.60	3.75	3.85 $\pm$ 0.40
92-98	20.63	3.65	4.73	3.87	4.04 $\pm$ 0.23
99-105	20.63	4.09	5.19	3.55	4.41 $\pm$ 0.39

Table B.6

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS IN URINE PLUS
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM I)

DAY	BABOON NUMBER				MEAN $\pm$ STD. ERROR
	8	28	33	46	
106-112	20.63	5.41	5.69	4.41	5.17 $\pm$ 0.39
113-119	"	6.69	6.12	4.65	5.82 $\pm$ 0.61
120-126	"	7.00	6.73	4.93	6.22 $\pm$ 0.65
127-133	"	7.37	7.16	5.24	6.59 $\pm$ 0.68
134-140	"	7.66	7.37	5.73	6.92 $\pm$ 0.60
141-147	"	7.96	7.62	5.87	7.15 $\pm$ 0.65
148-154	"	8.61	7.88	6.06	7.52 $\pm$ 0.76
155-161	"	8.68	8.30	6.67	7.88 $\pm$ 0.62
162-168	"	9.03	8.60	6.92	8.18 $\pm$ 0.64

Appendix C

SYSTEM II

^3H - WR-4593: Dose = 700 mg

^{14}C - WR-158122: Dose = 70 mg

EXCRETION OF TRITIUM LABELED MATERIALS
DERIVED FROM SYSTEM II WR-4593 BY BABOONS

Appendix C

SYSTEM II

^3H - WR-4593: Dose = 700 mg

^{14}C - WR-158122: Dose = 70 mg

EXCRETION OF TRITIUM LABELED MATERIALS
DERIVED FROM SYSTEM II WR-4593 BY BABOONS

Table C.1

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS

IN URINE OF FOUR BARBONS EXPRESSED AS MILLIGRAMS OF WR-4593

(SYSTEM II)

	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	73.97	42.07 $\pm$ 36.80	5.54	1.49	3.51 $\pm$ 2.02
2	3.77	2.72 $\pm$ 0.77	6.81	1.58	4.19 $\pm$ 2.61
3	3.07	1.64 $\pm$ 0.59	6.65	1.32	3.93 $\pm$ 2.66
4	1.14	1.37 $\pm$ 0.72	2.55	2.02	2.28 $\pm$ 0.26
5	0.43	0.83 $\pm$ 0.15	0.72	1.07	0.89 $\pm$ 0.17
6	3.17	1.11 $\pm$ 0.66	0.63	1.42	1.02 $\pm$ 0.39
7	4.77	1.22 $\pm$ 0.13	0.47	0.85	0.65 $\pm$ 0.12
8	0.43	0.33 $\pm$ 0.32	0.30	0.75	0.52 $\pm$ 0.22
9	0.13	0.37 $\pm$ 0.05	1.83	1.72	1.77 $\pm$ 0.05
10	0.37	0.21 $\pm$ 0.01	2.10	0.90	1.50 $\pm$ 0.60
11	0.37	0.13 $\pm$ 0.13	1.96	1.21	1.58 $\pm$ 0.37
12	1.14	0.97 $\pm$ 0.22	1.63	1.33	1.55 $\pm$ 0.12
13	0.11	0.75 $\pm$ 0.24	1.27	0.60	0.98 $\pm$ 0.39
14	0.24	0.32 $\pm$ 0.14	0.49	0.84	0.53 $\pm$ 0.19
15	2.41	2.04 $\pm$ 0.81	11.7	0.33	8.82 $\pm$ 2.88
16	3.13	2.22 $\pm$ 0.44	7.51	7.34	6.37 $\pm$ 1.13
17-18	2.60	2.79 $\pm$ 0.19	8.63	4.80	6.70 $\pm$ 1.90
19-20	4.72	4.65 $\pm$ 0.37	9.33	3.70	6.52 $\pm$ 2.82
21-22	5.45	3.56 $\pm$ 0.11	10.04	7.07	8.55 $\pm$ 1.48
23-24	3.45	4.02 $\pm$ 0.56	5.02	3.86	4.44 $\pm$ 0.58
25-26	3.92	3.89 $\pm$ 0.34	6.78	4.91	5.84 $\pm$ 0.93

Table C.1
MEASURED EXCRETION OF TRITIUM LABELED MATERIALS IN URINE OF FOUR BABOONS
EXPRESSED AS MILLIGRAMS OF WR-4593 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	5.30	4.54	4.92 $\pm$ 0.38	5.97	4.93	5.45 $\pm$ 0.52
71-77	5.35	4.63	4.99 $\pm$ 0.36	6.38	5.66	6.02 $\pm$ 0.36
78-84	5.52	3.34	4.43 $\pm$ 1.09	5.60	6.98	6.29 $\pm$ 0.69
85-91	6.27	3.45	4.86 $\pm$ 1.41	4.29	7.91	6.10 $\pm$ 1.81
92-98	3.09	4.66	3.88 $\pm$ 0.78	5.17	4.02	4.60 $\pm$ 0.57
99-105	7.04	2.35	4.70 $\pm$ 2.35	5.63	3.79	4.71 $\pm$ 0.92
106-112	6.75	4.13	5.44 $\pm$ 1.31	8.31	6.78	7.55 $\pm$ 0.76
113-119	6.19	5.26	5.73 $\pm$ 0.47	7.12	6.89	7.01 $\pm$ 0.11
120-126	6.41	7.11	6.76 $\pm$ 0.35	8.16	7.50	7.83 $\pm$ 0.33
127-133	6.54	5.73	6.14 $\pm$ 0.40	9.12	7.54	8.33 $\pm$ 0.79
134-140	7.45	4.93	6.19 $\pm$ 1.26	9.12	7.54	8.33 $\pm$ 0.79
141-147	6.42	5.16	5.79 $\pm$ 0.63	10.96	8.20	9.58 $\pm$ 1.38
148-154	6.73	4.46	5.60 $\pm$ 1.14	5.63	6.05	5.84 $\pm$ 0.21
155-161	7.46	5.10	6.28 $\pm$ 1.18	15.80	9.27	12.54 $\pm$ 3.27
162-168	7.57	6.13	6.85 $\pm$ 0.72	11.96	10.67	11.32 $\pm$ 0.64
169-175	6.80	5.28	6.04 $\pm$ 0.54	9.60	10.90	10.25 $\pm$ 0.46
176-182	7.65	6.83	7.24 $\pm$ 0.29	9.24	1.37	5.31 $\pm$ 2.79
183-189	35.60	30.59	33.10 $\pm$ 1.77	19.21	9.89	14.55 $\pm$ 3.30
190-196	56.96	18.81	37.89 $\pm$ 13.49	14.81	21.51	18.16 $\pm$ 2.37
197-203	12.53	6.11	9.32 $\pm$ 2.27	12.77	6.04	9.41 $\pm$ 2.38
204-210	Sac.	5.88	5.88	5.36	Sac.	5.36
211-217	--	11.56	11.56	12.24	--	12.24
218-224	--	6.08	6.08	9.98	--	9.97
225-231	--	4.71	4.75	10.71	--	10.71

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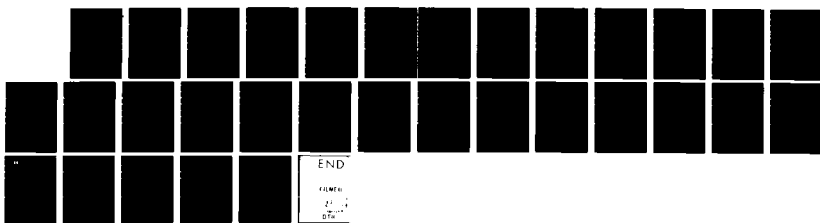
DEVELOPMENT AND TESTING OF A SUSTAINED RELEASE SYSTEM
FOR THE PREVENTION OF MALARIA(U) DYNATECH R/D CO
CAMBRIDGE MASS J D GRESSER ET AL. SEP 79 1947 (NRA-5)
DAND17-74-C-4128

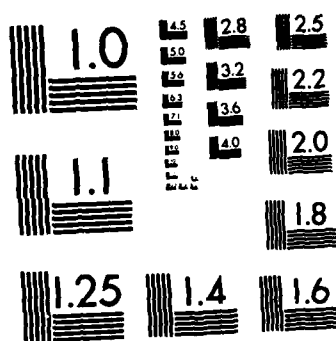
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Table C.2

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS
IN FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-4593
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0.05	0.37	0.21 $\pm$ 0.16	0.05	0.17	0.11 $\pm$ 0.06
2	0.26	6.05	3.50 $\pm$ 2.54	0.03	0.16	0.09 $\pm$ 0.06
3	4.00	3.15	2.11 $\pm$ 1.05	0.14	0.16	0.15 $\pm$ 0.01
4	0.37	2.35	1.36 $\pm$ 0.99	0.09	0.15	0.11 $\pm$ 0.04
5	0.17	0.89	0.53 $\pm$ 0.36	0.03	0.24	0.13 $\pm$ 0.10
6	0.14	0.50	0.32 $\pm$ 0.18	0.12	0.09	0.10 $\pm$ 0.02
7	0.26	0.35	0.20 $\pm$ 0.14	0.22	0.06	0.14 $\pm$ 0.03
8	0.05	0.26	0.15 $\pm$ 0.10	0.11	0.06	0.08 $\pm$ 0.02
9	0.05	0.07	0.06 $\pm$ 0.01	0.06	0.07	0.06 $\pm$ 0.01
10	0.05	0.11	0.08 $\pm$ 0.03	0.14	0.06	0.10 $\pm$ 0.04
11	0.05	0.08	0.06 $\pm$ 0.01	0.13	0.06	0.09 $\pm$ 0.03
12	0.03	0.07	0.05 $\pm$ 0.02	0.03	0.08	0.05 $\pm$ 0.02
13	0.05	0.07	0.06 $\pm$ 0.01	0.12	0.08	0.10 $\pm$ 0.02
14	0.02	0.06	0.04 $\pm$ 0.02	0.16	0.05	0.10 $\pm$ 0.05
15-21	0.23	0.34	0.28 $\pm$ 0.05	0.84	0.40	0.62 $\pm$ 0.22
22-28	0.19	0.39	0.29 $\pm$ 0.10	2.71	0.47	1.59 $\pm$ 1.12
29-35	0.15	0.26	0.21 $\pm$ 0.06	1.10	0.40	0.75 $\pm$ 0.35
36-42	0.13	0.17	0.17 $\pm$ 0.01	0.72	0.70	0.71 $\pm$ 0.01
43-49	0.17	0.33	0.25 $\pm$ 0.08	0.56	0.57	0.56 $\pm$ 0.01
50-56	0.25	0.40	0.33 $\pm$ 0.07	0.47	0.57	0.52 $\pm$ 0.05
57-63	0.34	0.36	0.35 $\pm$ 0.01	0.50	0.36	0.43 $\pm$ 0.07

Table C.2

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS IN FECES OF FOUR BABOONS:
EXPRESSED AS MILLIGRAMS OF WR-4593 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	0.34	0.36	0.35 $\pm$ 0.01	0.47	0.36	0.42 $\pm$ 0.06
71-77	0.34	0.28	0.31 $\pm$ 0.03	0.52	0.39	0.46 $\pm$ 0.06
78-84	0.37	0.34	0.36 $\pm$ 0.01	0.72	0.35	0.54 $\pm$ 0.18
85-91	0.47	0.45	0.46 $\pm$ 0.01	0.79	0.45	0.62 $\pm$ 0.17
92-98	0.43	0.25	0.34 $\pm$ 0.09	0.60	0.56	0.58 $\pm$ 0.02
99-105	0.41	0.36	0.39 $\pm$ 0.03	0.76	0.37	0.57 $\pm$ 0.20
106-112	0.52	0.33	0.43 $\pm$ 0.09	0.80	0.47	0.64 $\pm$ 0.16
113-119	0.45	0.31	0.38 $\pm$ 0.07	0.78	0.33	0.56 $\pm$ 0.23
120-126	0.40	0.22	0.31 $\pm$ 0.09	0.69	0.53	0.61 $\pm$ 0.08
127-133	0.33	0.29	0.31 $\pm$ 0.02	0.82	0.27	0.57 $\pm$ 0.30
134-140	0.30	0.32	0.31 $\pm$ 0.01	1.31	0.48	0.90 $\pm$ 0.42
141-147	0.46	0.40	0.43 $\pm$ 0.03	0.78	0.39	0.59 $\pm$ 0.20
148-154	0.37	0.45	0.41 $\pm$ 0.04	1.15	0.42	0.79 $\pm$ 0.37
155-161	0.39	0.40	0.40 $\pm$ 0.01	0.71	0.33	0.52 $\pm$ 0.19
162-168	0.41	0.32	0.37 $\pm$ 0.04	0.75	0.28	0.52 $\pm$ 0.23
169-175	0.61	0.35	0.48 $\pm$ 0.09	0.76	0.53	0.65 $\pm$ 0.08
176-182	0.29	0.33	0.31 $\pm$ 0.01	0.62	0.34	0.48 $\pm$ 0.01
183-189	0.91	0.04	1.48 $\pm$ 0.40	2.54	0.65	1.60 $\pm$ 0.67
190-196	1.61	1.50	1.56 $\pm$ 0.04	3.73	1.00	2.37 $\pm$ 0.97
197-203	0.36	0.32	0.34 $\pm$ 0.01	0.74	0.44	0.59 $\pm$ 0.11
204-210	Sac	0.31	0.31	0.70	Sac	0.70
211-217	--	0.15	0.15	0.49	--	0.49
218-224	--	0.16	0.16	0.41	--	0.41
225-231	--	0.12	0.12	0.32	--	0.32

Table C.3

MEASURED EXCRETION OF TRITIUM LABELED MATERIALS
IN URINE PLUS FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-4593
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	79.77	5.54	42.28 $\pm$ 36.74	5.59	1.66	3.62 $\pm$ 1.96
2	4.53	9.07	6.30 $\pm$ 1.77	6.84	1.74	4.29 $\pm$ 2.55
3	3.77	4.20	3.75 $\pm$ 0.44	6.79	1.48	4.13 $\pm$ 2.65
4	2.46	3.00	2.73 $\pm$ 0.27	2.63	2.17	2.40 $\pm$ 0.23
5	9.60	1.63	1.11 $\pm$ 0.51	0.75	1.31	1.03 $\pm$ 0.28
6	0.60	2.31	1.46 $\pm$ 0.84	0.75	1.51	1.13 $\pm$ 0.38
7	1.22	1.78	1.50 $\pm$ 0.20	0.69	0.91	0.80 $\pm$ 0.11
8	0.40	1.69	1.06 $\pm$ 0.63	0.41	0.91	0.61 $\pm$ 0.20
9	0.40	0.39	0.43 $\pm$ 0.04	1.89	1.79	1.84 $\pm$ 0.05
10	0.36	0.43	0.29 $\pm$ 0.03	2.24	0.96	1.60 $\pm$ 0.64
11	0.25	0.65	0.50 $\pm$ 0.15	2.09	1.27	1.68 $\pm$ 0.41
12	0.27	1.57	0.92 $\pm$ 0.64	1.71	1.51	1.61 $\pm$ 0.10
13	0.60	0.17	0.41 $\pm$ 0.24	1.49	0.63	1.08 $\pm$ 0.40
14	9.13	0.30	0.36 $\pm$ 0.06	0.89	0.39	0.64 $\pm$ 0.25
15-21	0.54	3.89	3.21 $\pm$ 0.67	12.60	6.40	9.50 $\pm$ 3.10
22-23	2.81	2.21	2.51 $\pm$ 0.39	10.22	5.71	7.96 $\pm$ 2.25
24-25	2.84	3.17	3.00 $\pm$ 0.16	9.70	5.20	7.45 $\pm$ 2.25
26-42	4.46	5.19	4.82 $\pm$ 0.36	10.07	4.40	7.23 $\pm$ 2.83
43-49	3.62	4.01	3.81 $\pm$ 0.19	10.60	7.64	9.12 $\pm$ 1.48
50-56	3.72	4.99	4.35 $\pm$ 0.63	5.49	4.43	4.96 $\pm$ 0.53
57-63	4.27	4.21	4.24 $\pm$ 0.93	7.20	5.27	6.27 $\pm$ 1.00

Table C.3
MEASURED EXCRETION OF TRITIUM LABELED MATERIALS IN URINE PLUS FECES OF FOUR BABOONS
EXPRESSED AS MILLIGRAMS OF WR-4593 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	5.64	4.90	5.27 $\pm$ 0.37	6.44	5.29	5.87 $\pm$ 0.57
71-77	5.69	4.91	5.30 $\pm$ 0.39	6.90	6.05	6.48 $\pm$ 0.42
78-84	5.89	3.68	4.79 $\pm$ 1.10	6.32	7.33	6.83 $\pm$ 0.50
85-91	6.74	3.90	5.32 $\pm$ 1.42	5.08	8.36	6.72 $\pm$ 1.64
92-98	3.52	4.91	4.22 $\pm$ 0.69	5.77	4.58	5.18 $\pm$ 0.59
99-105	7.45	2.71	5.08 $\pm$ 2.37	6.39	4.16	5.28 $\pm$ 1.12
106-112	7.27	4.46	5.87 $\pm$ 1.41	9.11	7.25	8.18 $\pm$ 0.93
113-119	6.64	5.87	6.26 $\pm$ 0.38	7.90	7.22	7.56 $\pm$ 0.34
120-126	6.81	7.33	7.07 $\pm$ 0.26	8.85	8.03	8.44 $\pm$ 0.41
127-133	6.87	6.02	6.45 $\pm$ 0.47	9.99	7.81	8.90 $\pm$ 1.09
134-140	7.75	5.25	6.50 $\pm$ 1.25	10.43	8.02	9.23 $\pm$ 1.20
141-147	6.88	5.56	6.22 $\pm$ 0.66	11.74	8.59	10.17 $\pm$ 1.58
148-154	7.10	4.91	6.01 $\pm$ 1.10	6.78	6.47	6.63 $\pm$ 0.16
155-161	7.85	5.50	6.68 $\pm$ 1.17	16.51	9.60	13.16 $\pm$ 3.35
162-168	7.98	6.45	7.22 $\pm$ 0.76	12.71	10.95	11.83 $\pm$ 0.88
169-175	7.41	5.63	6.52 $\pm$ 0.63	10.36	11.43	10.90 $\pm$ 0.38
176-182	7.94	7.16	7.55 $\pm$ 0.28	9.86	1.71	5.79 $\pm$ 2.89
183-189	36.51	32.63	34.57 $\pm$ 1.37	21.75	10.54	16.15 $\pm$ 3.96
190-196	58.57	20.31	39.44 $\pm$ 13.53	18.54	22.51	20.53 $\pm$ 1.40
197-203	12.89	6.43	9.66 $\pm$ 2.28	13.51	6.48	10.00 $\pm$ 2.49
204-210	Sac	6.19	6.19	6.06	Sac	6.06
211-217	--	11.71	11.71	12.73	--	12.73
218-224	--	6.24	6.24	10.38	--	10.38
225-231	--	4.83	4.83	11.03	--	11.03

Table C.3
MEASURED EXCRETION OF TRITIUM LABELED MATERIALS IN URINE PLUS FECES OF FOUR BABOONS
EXPRESSED AS MILLIGRAMS OF WR-4593 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	5.64	4.90	5.27 $\pm$ 0.37	6.44	5.29	5.87 $\pm$ 0.57
71-77	5.69	4.91	5.30 $\pm$ 0.39	6.90	6.05	6.48 $\pm$ 0.42
78-84	5.89	3.68	4.79 $\pm$ 1.10	6.32	7.33	6.83 $\pm$ 0.50
85-91	6.74	3.90	5.32 $\pm$ 1.42	5.08	8.36	6.72 $\pm$ 1.64
92-98	3.52	4.91	4.22 $\pm$ 0.69	5.77	4.58	5.18 $\pm$ 0.59
99-105	7.45	2.71	5.08 $\pm$ 2.37	6.39	4.16	5.28 $\pm$ 1.12
106-112	7.27	4.46	5.87 $\pm$ 1.41	9.11	7.25	8.18 $\pm$ 0.93
113-119	6.64	5.87	6.26 $\pm$ 0.38	7.90	7.22	7.56 $\pm$ 0.34
120-126	6.81	7.33	7.07 $\pm$ 0.26	8.85	8.03	8.44 $\pm$ 0.41
127-133	6.87	6.02	6.45 $\pm$ 0.47	9.99	7.81	8.90 $\pm$ 1.09
134-140	7.75	5.25	6.50 $\pm$ 1.25	10.43	8.02	9.23 $\pm$ 1.20
141-147	6.88	5.56	6.22 $\pm$ 0.66	11.74	8.59	10.17 $\pm$ 1.58
148-154	7.10	4.91	6.01 $\pm$ 1.10	6.78	6.47	6.63 $\pm$ 0.16
155-161	7.85	5.50	6.68 $\pm$ 1.17	16.51	9.60	13.16 $\pm$ 3.35
162-168	7.98	6.45	7.22 $\pm$ 0.76	12.71	10.95	11.83 $\pm$ 0.88
169-175	7.41	5.63	6.52 $\pm$ 0.63	10.36	11.43	10.90 $\pm$ 0.38
176-182	7.94	7.16	7.55 $\pm$ 0.28	9.86	1.71	5.79 $\pm$ 2.89
183-189	36.51	32.63	34.57 $\pm$ 1.37	21.75	10.54	16.15 $\pm$ 3.96
190-196	58.57	20.31	39.44 $\pm$ 13.53	18.54	22.51	20.53 $\pm$ 1.40
197-203	12.89	6.43	9.66 $\pm$ 2.28	13.51	6.48	10.00 $\pm$ 2.49
204-210	Sac	6.19	6.19	6.06	Sac	6.06
211-217	--	11.71	11.71	12.73	--	12.73
218-224	--	6.24	6.24	10.38	--	10.38
225-231	--	4.83	4.83	11.03	--	11.03

Table C.4

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS
IN URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF NR-4593
(SYSTEM II)

<u>Day</u>	<u>3 (Control)</u>	<u>11 (Control)</u>	<u>Mean $\pm$ Std. Error</u>	<u>- 27 (Exp.)</u>	<u>29 (Exp.)</u>	<u>Mean $\pm$ Std. Error</u>
1	78.97	5.17	42.07 $\pm$ 36.90	5.54	1.49	3.52 $\pm$ 2.03
2	82.54	7.19	44.87 $\pm$ 37.68	12.35	3.07	7.71 $\pm$ 4.64
3	84.77	8.24	46.51 $\pm$ 38.27	19.00	4.39	11.70 $\pm$ 7.31
4	86.88	8.89	47.88 $\pm$ 38.99	21.55	6.41	13.98 $\pm$ 7.57
5	87.29	9.63	48.46 $\pm$ 38.83	22.27	7.48	14.88 $\pm$ 7.49
6	87.77	11.44	49.61 $\pm$ 38.17	22.90	8.90	15.90 $\pm$ 7.00
7	88.03	12.87	50.90 $\pm$ 38.03	23.37	9.75	16.56 $\pm$ 5.81
8	89.31	14.30	51.81 $\pm$ 37.51	23.67	10.50	17.09 $\pm$ 6.58
9	89.71	14.62	52.18 $\pm$ 37.56	25.50	12.22	18.86 $\pm$ 5.64
10	90.05	14.94	52.50 $\pm$ 37.56	27.60	13.12	20.36 $\pm$ 7.24
11	90.35	15.51	52.93 $\pm$ 37.42	29.56	14.33	21.95 $\pm$ 7.62
12	90.60	17.01	53.81 $\pm$ 36.80	31.24	15.76	23.50 $\pm$ 7.74
13	91.21	17.11	54.15 $\pm$ 37.05	32.61	16.36	24.49 $\pm$ 8.13
14	91.62	17.35	54.49 $\pm$ 37.14	33.34	16.70	25.06 $\pm$ 8.32
15-16	93.05	20.90	57.42 $\pm$ 36.52	45.10	22.70	33.90 $\pm$ 11.20
17-18	95.11	22.72	59.64 $\pm$ 35.92	52.61	27.94	40.28 $\pm$ 12.34
19-20	99.24	25.61	62.43 $\pm$ 36.82	61.21	32.74	46.98 $\pm$ 14.24
21-22	107.52	30.63	67.03 $\pm$ 36.45	70.56	36.44	53.50 $\pm$ 17.06
23-24	105.97	34.31	70.64 $\pm$ 36.33	80.60	43.51	62.06 $\pm$ 18.55
25-26	110.43	38.90	74.67 $\pm$ 35.77	85.62	47.37	66.50 $\pm$ 19.13
27-28	114.36	42.75	78.56 $\pm$ 35.81	92.40	52.28	72.34 $\pm$ 20.06

Table C.4

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS IN URINE OF FOUR BABOONS EXPRESSED
AS MILLIGRAMS OF WR-4593 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	119.66	47.29	83.48 $\pm$ 36.18	98.37	57.21	77.29 $\pm$ 20.58
71-77	125.01	51.92	83.47 $\pm$ 36.54	104.75	62.87	83.81 $\pm$ 20.94
78-84	130.53	55.26	92.90 $\pm$ 37.63	110.35	69.85	90.10 $\pm$ 20.25
85-91	136.80	58.71	97.76 $\pm$ 39.05	114.64	77.76	96.20 $\pm$ 18.44
92-98	139.89	63.37	101.63 $\pm$ 38.26	119.81	81.78	100.80 $\pm$ 19.01
99-105	146.93	65.72	106.33 $\pm$ 40.60	125.44	85.57	105.51 $\pm$ 19.93
106-112	153.68	69.85	111.77 $\pm$ 41.92	133.75	92.35	113.05 $\pm$ 20.70
113-119	159.87	75.11	117.49 $\pm$ 42.38	140.87	99.24	120.06 $\pm$ 20.82
120-126	166.28	82.22	124.25 $\pm$ 42.03	149.03	106.74	127.86 $\pm$ 21.14
127-133	177.82	87.95	130.39 $\pm$ 42.43	158.15	114.28	136.22 $\pm$ 21.93
134-140	180.27	92.88	136.58 $\pm$ 43.69	167.27	121.82	144.55 $\pm$ 22.73
141-147	186.69	98.04	142.37 $\pm$ 44.33	178.23	130.02	154.13 $\pm$ 24.11
148-154	193.42	102.50	147.96 $\pm$ 45.46	183.86	136.07	159.97 $\pm$ 23.89
155-161	200.88	107.60	154.24 $\pm$ 46.64	199.66	145.34	172.50 $\pm$ 27.16
162-168	208.45	113.73	101.09 $\pm$ 47.36	211.62	156.01	183.82 $\pm$ 20.73
169-175	215.25	119.01	167.13 $\pm$ 48.12	221.22	166.91	194.07 $\pm$ 27.16
176-182	222.90	125.84	174.37 $\pm$ 48.53	230.46	168.28	199.37 $\pm$ 31.09
183-189	258.50	156.43	207.47 $\pm$ 36.09	249.67	178.17	213.92 $\pm$ 25.28
190-196	315.46	175.24	245.35 $\pm$ 49.58	264.48	199.68	223.08 $\pm$ 16.55
197-203	327.99	181.35	254.67 $\pm$ 51.85	277.25	205.72	241.49 $\pm$ 25.29
204-210	Sac	187.23	187.23	282.61	Sac	282.61
211-217	--	198.79	198.79	294.85	--	294.85
218-224	--	204.87	204.87	304.82	--	304.82
225-231	--	209.58	209.58	315.53	--	315.53
232-238	--	Sac	--	--	--	--

Table C.5

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS
IN FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-4593
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0.05	0.37	0.21 $\pm$ 0.16	0.05	0.17	0.11 $\pm$ 0.06
2	1.01	6.42	3.72 $\pm$ 2.71	0.08	0.33	0.21 $\pm$ 0.13
3	2.09	9.57	5.83 $\pm$ 3.74	0.22	0.49	0.36 $\pm$ 0.14
4	2.45	11.92	7.19 $\pm$ 4.73	0.30	0.64	0.47 $\pm$ 0.17
5	3.53	12.81	7.72 $\pm$ 5.09	0.33	0.88	0.61 $\pm$ 0.28
6	2.77	13.31	8.04 $\pm$ 5.27	0.45	0.97	0.71 $\pm$ 0.26
7	2.83	13.66	8.25 $\pm$ 5.42	0.67	1.03	0.85 $\pm$ 0.18
8	2.10	13.92	8.40 $\pm$ 5.52	0.78	1.09	0.94 $\pm$ 0.16
9	3.93	13.99	8.46 $\pm$ 5.53	0.84	1.16	1.00 $\pm$ 0.16
10	2.93	14.10	8.54 $\pm$ 5.56	0.98	1.22	1.10 $\pm$ 0.12
11	3.09	14.18	8.61 $\pm$ 5.58	1.11	1.28	1.20 $\pm$ 0.09
12	3.06	14.25	8.66 $\pm$ 5.60	1.14	1.36	1.25 $\pm$ 0.11
13	3.11	14.32	8.72 $\pm$ 5.61	1.26	1.44	1.35 $\pm$ 0.09
14	3.13	14.36	8.76 $\pm$ 5.62	1.42	1.49	1.46 $\pm$ 0.04
15-21	3.36	14.72	9.04 $\pm$ 5.68	2.26	1.89	2.08 $\pm$ 0.19
22-28	3.55	15.11	9.33 $\pm$ 5.78	4.97	2.36	3.67 $\pm$ 1.31
29-35	3.70	15.39	9.55 $\pm$ 5.84	6.07	2.76	4.42 $\pm$ 1.66
36-42	3.88	15.56	9.72 $\pm$ 5.84	6.79	3.46	5.13 $\pm$ 1.67
43-49	4.05	15.89	9.97 $\pm$ 5.92	7.35	4.03	5.68 $\pm$ 1.66
50-56	4.31	16.29	10.30 $\pm$ 6.00	7.82	4.60	6.21 $\pm$ 1.61
57-63	4.65	16.65	10.65 $\pm$ 6.00	8.32	4.96	6.64 $\pm$ 1.68

Table C. 5

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS IN FECES OF FOUR BABOONS
EXPRESSED AS MILLIGRAMS OF WR-4593 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	4.99	27.24	16.12 $\pm$ 11.13	8.79	5.32	7.06 $\pm$ 1.74
71-77	5.33	27.52	16.43 $\pm$ 11.10	9.31	5.71	7.51 $\pm$ 1.80
78-84	5.70	27.86	16.78 $\pm$ 11.08	10.03	6.06	8.05 $\pm$ 1.99
85-91	6.17	28.31	17.24 $\pm$ 11.07	10.82	6.51	8.67 $\pm$ 2.16
92-98	6.60	28.56	17.58 $\pm$ 5.49	11.42	7.07	9.25 $\pm$ 2.18
99-105	7.01	28.92	17.97 $\pm$ 10.96	12.18	7.44	9.81 $\pm$ 2.37
106-112	7.53	29.25	18.39 $\pm$ 10.86	12.98	7.91	10.45 $\pm$ 2.54
113-119	7.98	29.56	18.77 $\pm$ 10.79	13.76	8.24	11.00 $\pm$ 2.76
120-126	8.38	29.78	19.08 $\pm$ 10.70	14.45	8.77	11.61 $\pm$ 2.84
127-133	8.71	30.07	19.39 $\pm$ 10.68	15.32	9.04	12.18 $\pm$ 3.14
134-140	9.01	30.39	19.70 $\pm$ 10.69	16.63	9.52	13.08 $\pm$ 3.56
141-147	9.47	30.79	20.13 $\pm$ 10.66	17.41	9.91	13.66 $\pm$ 3.75
148-154	9.84	31.24	20.54 $\pm$ 10.70	18.56	10.33	14.45 $\pm$ 4.12
155-161	10.23	31.64	20.94 $\pm$ 10.71	19.27	10.66	14.97 $\pm$ 4.31
162-168	10.64	31.96	21.31 $\pm$ 10.66	20.02	10.94	15.48 $\pm$ 4.54
169-175	11.25	32.21	21.78 $\pm$ 10.53	20.78	11.47	16.13 $\pm$ 4.66
176-182	11.54	33.64	22.59 $\pm$ 11.05	21.40	11.81	16.61 $\pm$ 4.80
183-189	12.45	35.08	23.77 $\pm$ 8.00	23.94	12.46	18.20 $\pm$ 4.06
190-196	14.06	37.18	25.62 $\pm$ 8.17	27.07	13.46	20.57 $\pm$ 5.02
197-203	14.42	37.50	25.96 $\pm$ 8.16	28.41	13.90	21.16 $\pm$ 5.13
204-210	Sac	37.81	37.81	29.11	Sac	29.11
211-217	--	37.96	37.96	29.60	--	29.60
218-224	--	38.12	38.12	30.01	--	30.01
225-231	--	38.24	38.24	30.33	--	30.33

Table C.6

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS
IN URINE PLUS FECES OF FOUR BADGERS EXPRESSED AS MILLIGRAMS OF WR-4593
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	79.02	5.54	42.28 $\pm$ 36.74	5.59	1.66	3.63 $\pm$ 1.97
2	83.55	13.61	43.53 $\pm$ 34.97	12.43	3.40	7.92 $\pm$ 4.52
3	86.05	17.61	52.34 $\pm$ 34.53	19.22	4.88	12.05 $\pm$ 7.17
4	89.32	20.81	55.07 $\pm$ 34.26	21.85	7.05	14.45 $\pm$ 7.40
5	89.92	22.44	55.18 $\pm$ 33.75	22.60	8.36	15.48 $\pm$ 7.12
6	90.54	24.75	57.65 $\pm$ 32.90	23.35	9.87	16.61 $\pm$ 6.74
7	91.73	26.53	59.15 $\pm$ 32.62	24.04	10.78	17.41 $\pm$ 6.63
8	92.19	26.22	60.21 $\pm$ 31.99	24.45	11.59	18.02 $\pm$ 6.43
9	92.67	28.61	60.64 $\pm$ 32.03	26.34	13.38	19.86 $\pm$ 6.48
10	93.03	29.04	61.04 $\pm$ 32.09	26.58	14.34	21.46 $\pm$ 7.12
11	93.39	29.63	61.54 $\pm$ 31.85	30.67	15.61	23.14 $\pm$ 7.53
12	93.66	31.26	62.45 $\pm$ 31.20	32.38	17.12	24.75 $\pm$ 7.63
13	94.32	31.43	62.88 $\pm$ 31.45	33.87	17.80	25.84 $\pm$ 8.04
14	94.75	31.73	63.24 $\pm$ 31.51	34.76	18.19	26.48 $\pm$ 8.29
15-21	97.29	35.62	66.45 $\pm$ 30.84	47.56	24.59	35.98 $\pm$ 11.39
22-23	100.10	37.83	68.97 $\pm$ 31.14	57.58	30.30	43.94 $\pm$ 13.64
24-25	102.94	41.00	71.97 $\pm$ 30.97	67.28	35.50	51.39 $\pm$ 15.89
26-27	107.40	46.19	76.89 $\pm$ 30.61	77.35	39.90	58.63 $\pm$ 18.73
28-29	111.02	50.20	80.61 $\pm$ 20.41	87.95	47.54	67.75 $\pm$ 20.21
30-36	114.74	55.19	84.97 $\pm$ 29.78	93.44	51.97	72.71 $\pm$ 20.74
37-53	119.01	59.40	89.21 $\pm$ 29.81	100.72	57.24	78.98 $\pm$ 21.74

Table C.6

CUMULATIVE EXCRETION OF TRITIUM LABELED MATERIALS IN URINE PLUS FECES OF FOUR
BABOONS EXPRESSED AS MILLIGRAMS OF WR-4593 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	124.65	64.30	94.48 $\pm$ 30.18	107.16	62.53	84.85 $\pm$ 22.32
71-77	130.34	69.21	99.78 $\pm$ 30.57	114.06	68.58	91.32 $\pm$ 22.74
78-84	136.23	72.89	104.56 $\pm$ 29.67	120.38	75.91	98.15 $\pm$ 22.24
85-91	142.97	76.79	109.88 $\pm$ 33.09	125.46	84.27	104.87 $\pm$ 20.60
92-98	146.49	81.70	114.10 $\pm$ 32.40	131.23	88.85	110.04 $\pm$ 21.19
99-105	153.94	84.41	119.18 $\pm$ 34.77	137.62	93.01	115.32 $\pm$ 22.31
106-112	161.21	88.87	125.04 $\pm$ 36.17	146.73	100.26	123.50 $\pm$ 23.24
113-119	167.85	94.74	131.30 $\pm$ 36.56	154.63	107.48	131.06 $\pm$ 23.58
120-126	174.66	102.07	138.37 $\pm$ 36.30	163.48	115.51	139.50 $\pm$ 23.99
127-133	181.53	108.09	144.81 $\pm$ 36.72	173.47	123.32	148.40 $\pm$ 25.08
134-140	189.28	113.34	151.31 $\pm$ 37.97	183.90	131.34	157.62 $\pm$ 26.28
141-147	196.16	118.90	157.53 $\pm$ 38.63	195.64	139.93	167.79 $\pm$ 27.86
148-154	203.26	123.81	163.54 $\pm$ 39.73	202.42	146.40	174.41 $\pm$ 28.01
155-161	211.11	129.31	170.21 $\pm$ 40.90	218.93	156.00	187.47 $\pm$ 31.47
162-168	219.09	135.76	177.43 $\pm$ 41.67	231.64	166.95	199.30 $\pm$ 32.35
169-175	226.50	141.39	183.95 $\pm$ 42.56	242.00		210.19 $\pm$ 31.81
176-182	234.44	148.55	191.50 $\pm$ 42.95	251.86	80.09	215.98 $\pm$ 35.89
183-189	270.95	181.18	226.07 $\pm$ 31.74	273.61	190.63	232.12 $\pm$ 29.34
190-196	329.52	201.49	265.51 $\pm$ 45.27	292.15	213.14	252.65 $\pm$ 27.93
197-203	342.31	207.92	275.17 $\pm$ 47.55	305.66	219.62	262.64 $\pm$ 30.42
204-210	Sac	214.11	214.11	311.72	Sac	311.72
211-217	--	225.82	225.82	324.45	--	324.45
218-224	--	232.06	232.06	334.83	--	334.83
225-231	--	236.89	236.89	345.86	--	345.86

Appendix D

SYSTEM II

^3H - WR-4593: Dose = 700 mg.

^{14}C - WR-158122: Dose = 70 mg.

EXCRETION OF CARBON-14-LABELED MATERIALS
DERIVED FROM SYSTEM II WR-158122 BY BABOONS

Appendix D

SYSTEM II

^3H - WR-4593: Dose = 700 mg.

^{14}C - WR-158122: Dose = 70 mg.

EXCRETION OF CARBON-14-LABELED MATERIALS
DERIVED FROM SYSTEM II WR-158122 BY BABOONS

Table D.1

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS
IN URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0.22	0.20	0.56 $\pm$ 0.36	0.03	0.04	0.03 $\pm$ 0.005
2	0.52	0.27	0.26 $\pm$.05	0.33	0.01	0.17 $\pm$ 0.16
3	1.44	0.22	0.81 $\pm$ 0.64	0.08	0.02	0.05 $\pm$ 0.13
4	0.41	0.05	0.23 $\pm$ 0.16	0.05	0	0.03 $\pm$ 0.03
5	3.29	0.09	0.29 $\pm$ 0.15	0.02	0.01	0.02 $\pm$ 0.01
6	0.12	0.56	0.34 $\pm$ 0.22	0.02	0.02	0.02 $\pm$ 0
7	0.13	0.48	0.30 $\pm$ 0.17	0.01	0	0.01 $\pm$ 0.01
8	1.03	0.59	0.33 $\pm$ 0.25	0.01	0.01	0.01 $\pm$ 0
9	0.07	0.44	0.25 $\pm$ 0.13	0.04	0.03	0.04 $\pm$ 0.01
10	0.02	0.53	0.27 $\pm$ 0.25	0.03	0.02	0.03 $\pm$ 0.01
11	3.03	0.63	0.33 $\pm$ 0.29	0.03	0.04	0.04 $\pm$ 0.01
12	0.07	0.56	0.26 $\pm$ 0.22	0.08	0.03	0.05 $\pm$ 0.02
13	0.07	0.03	0.11 $\pm$ 0.02	0.03	0.02	0.02 $\pm$ 0.01
14	0.07	0.16	0.12 $\pm$ 0.04	0.03	0.01	0.02 $\pm$ 0.01
15	1.07	0.65	0.89 $\pm$ 0.24	0.34	0.22	0.28 $\pm$ 0.06
16-18	0.03	0.34	0.35 $\pm$ 0.01	0.20	0.19	0.19 $\pm$ 0.01
19-20	14.03	6.86	11.53 $\pm$ 4.67	0.49	0.23	0.36 $\pm$ 0.13
21-22	6.07	2.54	4.30 $\pm$ 1.76	0.37	0.24	0.30 $\pm$ 0.06
23-24	3.80	1.61	2.70 $\pm$ 1.09	0.54	0.34	0.44 $\pm$ 0.10
25-26	1.75	3.21	2.49 $\pm$ 1.01	0.26	0.25	0.25 $\pm$ 0.01
27-28	1.79	0.64	1.21 $\pm$ 0.57	0.27	0.33	0.30 $\pm$ 0.03

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permit further distribution.

Table D.1
MEASURED EXCRETION OF CARBON-14-LABELED MATERIALS IN URINE OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	6.70	4.69	5.70 $\pm$ 1.00	0.40	0.44	0.42 $\pm$ 0.02
71-77	3.79	5.35	4.57 $\pm$ 0.78	0.36	0.27	0.32 $\pm$ 0.04
78-84	6.87	3.19	5.03 $\pm$ 1.84	0.22	0.52	0.37 $\pm$ 0.15
85-91	2.28	0.58	1.43 $\pm$ 0.85	0.21	0.47	0.34 $\pm$ 0.13
92-98	4.20	0.38	2.29 $\pm$ 1.91	0.39	0.20	0.30 $\pm$ 0.09
99-105	2.01	0.93	1.47 $\pm$ 0.54	0.28	0.21	0.25 $\pm$ 0.04
106-112	1.94	0.52	1.23 $\pm$ 0.71	0.68	0.38	0.53 $\pm$ 0.15
113-119	1.76	0.94	1.35 $\pm$ 0.41	0.45	0.37	0.41 $\pm$ 0.04
120-126	1.62	0.60	1.11 $\pm$ 0.51	0.57	0.48	0.53 $\pm$ 0.04
127-133	1.39	6.34	3.87 $\pm$ 2.47	0.53	0.30	0.42 $\pm$ 0.11
134-140	1.05	1.32	1.19 $\pm$ 0.13	0.75	0.42	0.59 $\pm$ 0.16
141-147	1.28	4.46	2.87 $\pm$ 1.59	0.83	0.19	0.51 $\pm$ 0.32
148-154	1.56	0.48	1.02 $\pm$ 0.54	0.83	0.40	0.62 $\pm$ 0.21
155-161	1.80	0.71	1.26 $\pm$ 0.54	1.57	0.64	1.11 $\pm$ 0.47
162-168	2.09	0.51	1.30 $\pm$ 0.75	1.19	0.63	0.91 $\pm$ 0.28
169-175	7.90	5.62	6.76 $\pm$ 1.14	0.98	0.51	0.75 $\pm$ 0.24
176-182	5.63	7.71	6.67 $\pm$ 1.04	0.64	0.27	0.46 $\pm$ 0.19
183-189	3.41	9.51	6.46 $\pm$ 2.16	0.98	0.71	0.85 $\pm$ 0.10
190-196	14.73	4.75	9.74 $\pm$ 3.53	0.40	0.59	0.50 $\pm$ 0.07
197-203	0.06	1.91	0.99 $\pm$ 0.65	1.31	0.58	0.95 $\pm$ 0.26
204-210	Sac	0.97	0.97	0.53	Sac	0.53
211-217	--	0	0	0.90	--	0.90
218-224	--	0	0	1.11	--	1.11
225-231	--	0	0	0.92	--	0.92

Table D.2

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS
IN FECES OF FOUR BALBOONS EXPOSED AS MILLIGRAMS OF WR-158122
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0	0.61	0.005 $\pm$ 0.005	< 0.001	0.02	0.01 $\pm$ 0.01
2	0.11	0.74	0.42 $\pm$ 0.31	< 0.001	0.03	0.015 $\pm$ 0.015
3	0.14	0.50	0.32 $\pm$ 0.18	< 0.001	0.01	0.005 $\pm$ 0.005
4	0.14	0.56	0.35 $\pm$ 0.21	0.01	0.01	0.01 $\pm$ 0.00
5	0.13	0.60	0.36 $\pm$ 0.23	< 0.001	0.01	0.005 $\pm$ 0.004
6	0.03	0.65	0.37 $\pm$ 0.29	< 0.001	0.01	0.005 $\pm$ 0.004
7	0.13	0.84	0.43 $\pm$ 0.49	< 0.001	0.01	0.005 $\pm$ 0.004
8	0.04	0.79	0.41 $\pm$ 0.37	< 0.001	0.01	0.005 $\pm$ 0.004
9	0.02	0.14	0.03 $\pm$ 0.06	0.01	0.01	0.01 $\pm$ 0.00
10	0.02	0.12	1.05 $\pm$ 0.94	0.01	0.01	0.01 $\pm$ 0.00
11	0.01	0.06	0.03 $\pm$ 0.02	0.02	0.02	0.02 $\pm$ 0.00
12	0.01	0.06	0.03 $\pm$ 0.02	0.0	0.02	0.01 $\pm$ 0.01
13	0.02	0.07	0.04 $\pm$ 0.02	0.02	0.02	0.02 $\pm$ 0.00
14	0	0.03	0.04 $\pm$ 0.04	0.02	0.01	0.015 $\pm$ 0.005
15-21	0.13	0.39	0.29 $\pm$ 0.19	0.20	0.03	0.14 $\pm$ 0.06
22-26	0.12	1.50	0.84 $\pm$ 0.65	0.24	0.15	0.19 $\pm$ 0.04
27-35	11.23	5.11	8.17 $\pm$ 3.06	0.42	0.12	0.27 $\pm$ 0.15
36-42	1.06	0.32	0.63 $\pm$ 0.37	0.14	0.05	0.09 $\pm$ 0.04
43-49	1.11	0.75	0.43 $\pm$ 0.32	0.14	0.17	0.15 $\pm$ 0.02
50-56	0.85	0.99	0.92 $\pm$ 0.06	0.16	0.22	0.19 $\pm$ 0.03
57-63	0.73	0.59	0.66 $\pm$ 0.07	0.21	0.15	0.18 $\pm$ 0.03
						+

Table D.2
MEASURED EXCRETION OF CARBON-14-LABELED MATERIALS IN FECES OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF NR-158122 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	0.41	0.38	0.40 $\pm$ 0.01	0.17	0.16	0.17 $\pm$ 0.01
71-77	0.86	0.23	0.55 $\pm$ 0.32	0.23	0.22	0.23 $\pm$ 0.01
78-84	0.14	0.19	0.17 $\pm$ 0.03	0.24	0.12	0.18 $\pm$ 0.06
85-91	0.01	0.46	0.24 $\pm$ 0.23	0.45	0.31	0.38 $\pm$ 0.07
92-98	0.18	0.11	0.15 $\pm$ 0.04	0.19	0.34	0.27 $\pm$ 0.08
99-105	0.30	0.32	0.31 $\pm$ 0.01	0.59	0.25	0.42 $\pm$ 0.17
106-112	0.48	0.08	0.28 $\pm$ 0.20	0.52	0.28	0.39 $\pm$ 0.13
113-119	0.07	0.15	0.11 $\pm$ 0.04	0.16	0.17	0.17 $\pm$ 0.01
120-126	0.28	0.07	0.18 $\pm$ 0.11	0.54	0.30	0.42 $\pm$ 0.12
127-133	0.37	0.22	0.30 $\pm$ 0.08	0.53	0.18	0.42 $\pm$ 0.11
134-140	0.10	0	0.05 $\pm$ 0.05	1.36	0.20	0.78 $\pm$ 0.58
141-147	0.01	0	0.01 $\pm$ 0.01	0.43	0.15	0.29 $\pm$ 0.14
148-154	0.09	0.03	0.06 $\pm$ 0.03	0.48	0.23	0.36 $\pm$ 0.13
155-161	0	0	0 $\pm$ 0	0.33	0.18	0.26 $\pm$ 0.08
162-168	0	0	0 $\pm$ 0	0.32	0.12	0.22 $\pm$ 0.10
169-175	25.89	3.82	14.86 $\pm$ 11.04	0.33	0.29	0.31 $\pm$ 0.02
176-182	7.22	2.82	5.02 $\pm$ 2.20	0.05	0.14	0.10 $\pm$ 0.05
183-189	0.72	0.06	0.39 $\pm$ 0.23	0.26	0.17	0.22 $\pm$ 0.03
190-196	0.73	0	0.37 $\pm$ 0.26	0.38	0.14	0.26 $\pm$ 0.08
197-203	0.08	0	0.04 $\pm$ 0.03	0.27	0.23	0.25 $\pm$ 0.01
204-210	Sac	0	0	0.31	Sac	0.31
211-217	--	0	0	0.24	--	0.24
218-224	--	0	0	0.19	--	0.19
225-231	--	0	0	0.07	--	0.07
232-238	--	Sac	--	0.21	--	0.21

Table D.3

MEASURED EXCRETION OF CARBON-14 LABELED MATERIALS
IN URINE PLUS FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0.92	0.21	0.56 $\pm$ 0.25	0.02	0.06	0.04 $\pm$ 0.02
2	0.60	0.95	0.69 $\pm$ 0.18	0.33	0.04	0.18 $\pm$ 0.14
3	1.35	0.72	1.13 $\pm$ 0.22	0.08	0.03	0.05 $\pm$ 0.02
4	0.55	0.61	0.58 $\pm$ 0.02	0.07	0.01	0.04 $\pm$ 0.03
5	0.50	0.63	0.60 $\pm$ 0.06	0.02	0.02	0.02 $\pm$ 0.00
6	0.22	1.22	0.71 $\pm$ 0.36	0.92	0.03	0.025 $\pm$ 0.005
7	0.18	1.32	0.74 $\pm$ 0.41	0.91	0.01	0.01 $\pm$ 0.00
8	0.12	1.38	0.75 $\pm$ 0.44	0.01	0.01	0.01 $\pm$ 0.00
9	0.20	0.52	0.33 $\pm$ 0.17	0.35	0.04	0.045 $\pm$ 0.005
10	0.01	0.55	0.34 $\pm$ 0.21	0.04	0.03	0.035 $\pm$ 0.005
11	0.05	0.69	0.37 $\pm$ 0.23	0.05	0.06	0.055 $\pm$ 0.005
12	0.05	0.54	0.29 $\pm$ 0.17	0.08	0.05	0.065 $\pm$ 0.015
13	0.15	0.16	0.15 $\pm$ 0.3	0.05	0.04	0.045 $\pm$ 0.005
14	0.03	0.24	0.15 $\pm$ 0.06	0.05	0.01	0.03 $\pm$ 0.02
15-21	1.32	1.04	1.13 $\pm$ 0.19	0.54	0.30	0.42 $\pm$ 0.12
22-28	0.53	1.86	1.19 $\pm$ 0.47	0.44	0.34	0.39 $\pm$ 0.05
29-35	27.44	11.97	19.70 $\pm$ 5.47	0.91	0.25	0.58 $\pm$ 0.33
36-42	7.13	2.86	4.99 $\pm$ 1.51	0.51	0.29	0.40 $\pm$ 0.11
43-49	4.91	1.14	3.02 $\pm$ 1.33	0.68	0.51	0.59 $\pm$ 0.08
50-56	2.64	4.20	3.42 $\pm$ 0.55	0.42	0.47	0.44 $\pm$ 0.02
57-63	2.52	1.23	1.87 $\pm$ 0.46	0.48	0.48	0.48 $\pm$ 0.00

Table D.3

MEASURED EXCRETION OF CARBON-14-LABELED MATERIALS IN URINE PLUS
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	7.11	5.07	6.09 $\pm$ 1.02	0.57	0.60	0.59 $\pm$ 0.01
71-77	4.65	5.58	5.12 $\pm$ 0.47	0.58	0.49	0.54 $\pm$ 0.04
78-84	7.01	3.38	5.20 $\pm$ 1.82	0.46	0.64	0.55 $\pm$ 0.09
85-91	2.29	1.04	1.67 $\pm$ 0.62	0.66	0.78	0.72 $\pm$ 0.06
92-98	4.38	0.39	2.39 $\pm$ 1.99	0.58	0.54	0.56 $\pm$ 0.02
99-105	2.31	1.25	1.78 $\pm$ 0.53	0.87	0.46	0.67 $\pm$ 0.21
106-112	2.42	0.60	1.51 $\pm$ 0.91	1.20	0.66	0.75 $\pm$ 0.22
113-119	1.83	1.09	1.46 $\pm$ 0.37	0.61	0.54	0.58 $\pm$ 0.04
120-126	1.90	0.67	1.29 $\pm$ 0.62	1.11	0.78	0.95 $\pm$ 0.14
127-133	1.76	6.56	4.16 $\pm$ 2.40	1.06	0.48	0.77 $\pm$ 0.29
134-140	1.15	1.32	1.24 $\pm$ 0.08	2.11	0.62	1.37 $\pm$ 0.74
141-147	1.29	4.46	2.88 $\pm$ 1.58	1.26	0.34	0.80 $\pm$ 0.46
148-154	1.65	0.51	1.08 $\pm$ 0.57	1.31	0.63	0.97 $\pm$ 0.34
155-161	1.80	0.71	1.26 $\pm$ 0.54	1.90	0.82	1.36 $\pm$ 0.54
162-168	2.09	0.51	1.30 $\pm$ 0.79	1.51	0.75	1.13 $\pm$ 0.38
169-175	33.79	9.44	21.62 $\pm$ 12.18	1.31	0.80	1.06 $\pm$ 0.26
176-182	12.85	10.53	11.69 $\pm$ 1.16	0.69	0.41	0.55 $\pm$ 0.14
183-189	4.13	9.57	6.85 $\pm$ 1.92	1.24	0.88	1.06 $\pm$ 0.13
190-196	15.46	4.75	10.11 $\pm$ 3.79	0.78	0.73	0.76 $\pm$ 0.02
197-203	0.14	1.91	1.03 $\pm$ 0.63	1.58	0.81	1.20 $\pm$ 0.27
204-210	Sac	0.97	0.97	0.84	Sac	0.84
211-217	--	0	0	1.14	--	1.14
218-224	--	0	0	1.30	--	1.30
225-231	--	0	0	0.99	--	0.99
232-238	--	Sac	--	0.81	--	0.81

Table D.4

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS
IN URINE OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF UR-158122
(SHEET: II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0.02	0.20	0.56 $\pm$ 0.26	0.03	0.04	0.04 $\pm$ 0.01
2	1.27	0.41	0.63 $\pm$ 0.42	0.36	0.05	0.21 $\pm$ 0.15
3	2.55	0.63	1.64 $\pm$ 1.01	0.44	0.07	0.26 $\pm$ 0.19
4	2.04	0.68	1.67 $\pm$ 1.19	0.50	0.07	0.29 $\pm$ 0.21
5	2.75	0.76	2.11 $\pm$ 1.35	0.52	0.08	0.30 $\pm$ 0.22
6	1.37	1.02	2.45 $\pm$ 1.10	0.54	0.10	0.32 $\pm$ 0.22
7	2.70	1.80	2.75 $\pm$ 0.95	0.55	0.10	0.33 $\pm$ 0.22
8	2.73	2.29	3.09 $\pm$ 0.70	0.56	0.11	0.34 $\pm$ 0.23
9	1.31	2.03	3.24 $\pm$ 0.51	0.60	0.14	0.37 $\pm$ 0.23
10	2.87	3.26	3.62 $\pm$ 0.26	0.63	0.16	0.40 $\pm$ 0.23
11	2.01	3.99	3.95 $\pm$ 0.04	0.63	0.20	0.42 $\pm$ 0.22
12	2.05	4.47	4.21 $\pm$ 0.26	0.71	0.23	0.47 $\pm$ 0.24
13	3.10	4.56	4.33 $\pm$ 0.33	0.74	0.25	0.50 $\pm$ 0.25
14	4.17	4.72	4.45 $\pm$ 0.26	0.77	0.26	0.52 $\pm$ 0.26
15-21	5.31	5.37	5.34 $\pm$ 0.04	1.11	0.28	0.79 $\pm$ 0.51
22-28	5.65	5.73	5.69 $\pm$ 0.04	1.31	0.47	0.89 $\pm$ 0.42
29-36	21.03	12.59	17.25 $\pm$ 1.54	1.83	0.70	1.29 $\pm$ 0.59
37-42	27.26	15.13	21.53 $\pm$ 6.40	2.25	0.94	1.60 $\pm$ 0.66
43-49	31.73	16.74	24.24 $\pm$ 7.50	2.79	1.28	2.04 $\pm$ 0.76
50-55	33.51	19.95	26.73 $\pm$ 6.76	3.05	1.53	2.29 $\pm$ 0.76
57-63	35.00	20.59	27.93 $\pm$ 7.36	3.32	1.86	2.59 $\pm$ 0.73

Table D.4
CUMULATIVE EXCRETION OF CARBON-14-LABELED MATERIALS IN URINE OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	42.00	25.28	33.64 $\pm$ 8.36	3.72	2.30	3.01 $\pm$ 0.71
71-77	45.79	30.63	35.21 $\pm$ 7.58	4.08	2.57	3.33 $\pm$ 0.76
78-84	52.66	33.82	43.24 $\pm$ 9.42	4.30	3.09	3.70 $\pm$ 0.61
85-91	54.94	34.40	44.67 $\pm$ 10.27	4.51	3.56	4.04 $\pm$ 0.47
92-98	59.14	34.78	46.96 $\pm$ 12.18	4.90	3.76	4.33 $\pm$ 0.57
99-105	61.15	35.71	48.43 $\pm$ 12.72	5.18	3.97	4.58 $\pm$ 0.61
106-112	63.09	36.23	49.66 $\pm$ 13.43	5.86	4.35	5.11 $\pm$ 0.76
113-119	64.85	37.17	51.01 $\pm$ 13.84	6.31	4.72	5.52 $\pm$ 0.79
120-126	66.47	37.77	52.12 $\pm$ 14.34	6.88	5.20	6.04 $\pm$ 0.84
127-133	67.86	44.11	55.99 $\pm$ 11.87	7.41	5.50	6.46 $\pm$ 0.95
134-140	68.91	45.43	57.17 $\pm$ 11.73	8.16	5.92	7.04 $\pm$ 1.12
141-147	70.19	49.89	60.04 $\pm$ 10.15	8.99	6.11	7.55 $\pm$ 1.44
148-154	71.75	50.37	61.06 $\pm$ 10.69	9.82	6.51	8.17 $\pm$ 1.65
155-161	73.55	51.08	62.32 $\pm$ 11.23	11.39	7.15	9.27 $\pm$ 2.12
162-168	75.64	51.59	63.63 $\pm$ 12.03	12.58	7.78	10.18 $\pm$ 2.40
169-175	83.54	57.21	70.38 $\pm$ 13.17	13.56	8.29	10.93 $\pm$ 2.64
176-182	89.17	64.92	77.05 $\pm$ 12.13	14.20	8.56	11.38 $\pm$ 2.82
183-189	92.58	74.43	83.51 $\pm$ 6.42	15.18	9.27	12.23 $\pm$ 2.09
190-196	107.21	79.18	93.25 $\pm$ 9.95	15.58	9.86	12.72 $\pm$ 2.02
197-203	107.37	81.09	94.23 $\pm$ 9.29	16.89	10.44	13.67 $\pm$ 2.28
204-210	Sac	82.06	82.06	17.42	Sac	17.42
211-217	--	82.06	82.06	18.32	--	18.32
218-224	--	82.06	82.06	19.43	--	19.43
225-231	--	82.06	82.06	20.35	--	20.35
232-238	--	Sac	--	20.95	--	20.95

Table D.5

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS
IN FECES OF FOUR RABBITTS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM II)

Day	3 (Control)	14 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0	0.01	0.01 $\pm$ 0.01	0	0.02	0.01 $\pm$ 0.01
2	0.11	0.75	0.43 $\pm$ 0.32	0	0.05	0.03 $\pm$ 0.02
3	0.25	1.35	0.75 $\pm$ 0.50	0	0.06	0.03 $\pm$ 0.03
4	0.59	1.91	1.19 $\pm$ 0.71	0.01	0.07	0.04 $\pm$ 0.03
5	0.52	2.41	1.47 $\pm$ 0.95	0.01	0.08	0.05 $\pm$ 0.04
6	0.60	3.07	1.84 $\pm$ 1.24	0.01	0.09	0.05 $\pm$ 0.04
7	0.66	3.31	2.27 $\pm$ 1.64	0.01	0.10	0.06 $\pm$ 0.05
8	0.67	4.70	2.69 $\pm$ 2.02	0.01	0.11	0.06 $\pm$ 0.05
9	0.69	4.84	2.77 $\pm$ 2.03	0.02	0.12	0.07 $\pm$ 0.05
10	0.71	4.96	2.84 $\pm$ 2.13	0.03	0.13	0.08 $\pm$ 0.05
11	0.72	5.01	2.87 $\pm$ 2.15	0.03	0.15	0.10 $\pm$ 0.05
12	0.73	5.00	2.91 $\pm$ 2.13	0.03	0.17	0.11 $\pm$ 0.06
13	0.71	5.15	2.95 $\pm$ 2.20	0.07	0.19	0.13 $\pm$ 0.06
14	0.73	5.23	2.99 $\pm$ 2.24	0.09	0.20	0.15 $\pm$ 0.06
15-21	0.91	5.62	3.28 $\pm$ 2.34	0.29	0.28	0.29 $\pm$ 0.01
22-28	1.13	7.12	4.13 $\pm$ 3.00	0.53	0.43	0.48 $\pm$ 0.05
29-35	12.36	12.23	12.30 $\pm$ 0.87	0.95	0.55	0.75 $\pm$ 0.20
36-42	13.42	12.55	12.99 $\pm$ 0.44	1.09	0.60	0.85 $\pm$ 0.25
43-49	14.50	13.30	13.92 $\pm$ 0.62	1.23	0.77	1.00 $\pm$ 0.23
50-56	15.30	14.29	14.84 $\pm$ 0.55	1.39	0.99	1.19 $\pm$ 0.20
57-62	16.12	14.03	15.10 $\pm$ 1.02	1.60	1.14	1.37 $\pm$ 0.23

Table D.5

CUMULATIVE EXCRETION OF CARBON-14-LABELED MATERIALS IN FECES OF
FOUR BABOONS EXPRESSED AS MILLIGRAMS OF NR-158122 (SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	16.53	14.46	15.50 $\pm$ 2.64	1.77	1.30	1.54 $\pm$ 0.23
71-77	17.39	14.69	16.04 $\pm$ 1.35	2.00	1.52	1.76 $\pm$ 0.24
78-84	17.53	14.88	16.21 $\pm$ 1.32	2.24	1.64	1.94 $\pm$ 0.30
85-91	17.54	15.34	16.44 $\pm$ 1.10	2.69	1.95	2.32 $\pm$ 0.37
92-98	17.72	15.45	16.59 $\pm$ 1.09	2.88	2.29	2.59 $\pm$ 0.30
99-105	18.02	15.77	16.90 $\pm$ 1.12	3.47	2.54	3.01 $\pm$ 0.47
106-112	18.50	15.85	17.18 $\pm$ 1.32	3.99	2.82	3.41 $\pm$ 0.59
113-119	18.57	16.00	17.29 $\pm$ 1.29	4.15	2.99	3.57 $\pm$ 0.58
120-126	18.85	16.07	17.46 $\pm$ 1.39	4.69	3.29	3.99 $\pm$ 0.7
127-133	19.22	16.29	17.76 $\pm$ 1.46	5.22	3.47	4.35 $\pm$ 0.88
134-140	19.32	16.29	17.81 $\pm$ 1.51	6.58	3.67	5.13 $\pm$ 1.46
141-147	19.33	16.29	17.81 $\pm$ 1.52	7.01	3.82	5.42 $\pm$ 1.60
148-154	19.42	16.32	17.87 $\pm$ 1.55	7.49	4.05	5.77 $\pm$ 1.72
155-161	19.42	16.32	17.87 $\pm$ 1.55	7.82	4.23	6.03 $\pm$ 1.80
162-168	19.42	16.32	17.87 $\pm$ 1.55	8.14	4.35	6.25 $\pm$ 1.90
169-175	45.31	20.14	32.73 $\pm$ 12.59	8.47	4.64	6.56 $\pm$ 1.92
176-182	52.53	22.96	37.75 $\pm$ 14.79	8.52	4.78	6.65 $\pm$ 1.87
183-189	53.25	23.02	38.14 $\pm$ 10.69	8.78	4.95	6.87 $\pm$ 1.35
190-196	53.98	23.02	38.50 $\pm$ 10.95	9.16	5.09	7.13 $\pm$ 1.44
197-203	54.06	23.02	38.54 $\pm$ 10.97	9.43	5.32	7.38 $\pm$ 1.45
204-210	Sac	23.02	23.02	9.74	Sac	9.74
211-217	--	23.02	23.02	9.98	--	9.98
218-224	--	23.02	23.02	10.17	--	10.17
225-231	--	23.02	23.02	10.24	--	10.24

Table D.6

CUMULATIVE EXCRETION OF CARBON-14 LABELED MATERIALS
IN URINE AND FECES OF FOUR BABOONS EXPOSED AS MILLIGRAMS OF WR-158122
(SYSTEM II)

Day	3 (Control)	11 (Control)	Mean $\pm$ Std. Error	27 (Exp.)	29 (Exp.)	Mean $\pm$ Std. Error
1	0.27	0.21	0.56 $\pm$ 0.36	0.02	0.06	0.04 $\pm$ 0.02
2	1.35	1.16	1.25 $\pm$ 0.60	0.35	0.10	0.22 $\pm$ 0.12
3	3.90	1.90	2.30 $\pm$ 0.51		0.13	0.28 $\pm$ 0.15
4	4.15	2.40	2.27 $\pm$ 0.42	0.50	0.14	0.32 $\pm$ 0.18
5	3.97	3.17	3.57 $\pm$ 0.40	0.52	0.16	0.34 $\pm$ 0.18
6	1.77	4.29	4.20 $\pm$ 0.11	0.54	0.19	0.36 $\pm$ 0.17
7	1.33	5.71	5.02 $\pm$ 0.69	0.55	0.20	0.37 $\pm$ 0.17
8	0.65	7.09	5.77 $\pm$ 1.32	0.56	0.21	0.38 $\pm$ 0.17
9	1.13	7.67	6.10 $\pm$ 1.11	0.61	0.25	0.43 $\pm$ 0.18
10	1.50	8.32	6.45 $\pm$ 1.87	0.65	0.23	0.46 $\pm$ 0.18
11	1.50	9.01	6.62 $\pm$ 2.19	0.70	0.34	0.52 $\pm$ 0.18
12	4.39	9.55	7.11 $\pm$ 2.43	0.73	0.39	0.58 $\pm$ 0.19
13	1.81	9.71	7.27 $\pm$ 2.43	0.83	0.43	0.63 $\pm$ 0.20
14	1.31	9.95	7.43 $\pm$ 2.51	0.66	0.44	0.66 $\pm$ 0.22
15	3.21	10.90	8.61 $\pm$ 2.37	1.42	0.74	1.08 $\pm$ 0.34
16-18	6.77	12.85	9.81 $\pm$ 3.04	1.86	1.08	1.47 $\pm$ 0.39
19-21	34.21	24.82	29.51 $\pm$ 4.70	2.77	1.33	2.05 $\pm$ 0.72
22-24	41.31	27.63	34.51 $\pm$ 6.83	3.23	1.62	2.45 $\pm$ 0.83
25-29	46.25	28.32	37.53 $\pm$ 8.72	3.96	2.13	3.04 $\pm$ 0.91
30-35	40.89	33.02	40.95 $\pm$ 7.94	4.38	2.60	3.49 $\pm$ 0.89
36-40	51.41	34.25	42.83 $\pm$ 8.58	4.85	3.08	3.97 $\pm$ 0.89

Table D.6
CUMULATIVE EXCRETION OF CARBON-14-LABELED MATERIALS IN URINE PLUS
FECES OF FOUR BABOONS EXPRESSED AS MILLIGRAMS OF WR-158122
(SYSTEM II)

DAY	BABOON NO.					
	#3	#11	Mean $\pm$ Std. Error	#27	#29	Mean $\pm$ Std. Error
64-70	58.52	39.32	48.92 $\pm$ 9.60	5.43	3.68	4.56 $\pm$ 0.88
71-77	63.17	44.90	54.04 $\pm$ 9.14	6.01	4.17	5.09 $\pm$ 0.96
78-84	70.18	48.28	59.23 $\pm$ 10.95	6.47	4.81	5.64 $\pm$ 0.83
85-91	72.47	49.32	60.90 $\pm$ 11.58	7.13	5.59	6.36 $\pm$ 0.77
92-98	76.85	49.71	63.28 $\pm$ 13.57	7.71	6.13	6.92 $\pm$ 0.79
99-105	79.16	50.96	65.06 $\pm$ 14.09	8.58	6.59	7.59 $\pm$ 1.00
106-112	81.58	51.56	66.57 $\pm$ 15.01	9.78	7.25	8.52 $\pm$ 1.27
113-119	83.41	52.65	68.03 $\pm$ 15.38	10.39	7.79	9.09 $\pm$ 1.30
120-126	85.31	53.32	69.32 $\pm$ 12.71	11.50	8.57	10.04 $\pm$ 1.46
127-133	87.07	59.88	73.48 $\pm$ 13.60	12.56	9.05	10.81 $\pm$ 1.75
134-140	88.22	61.20	74.71 $\pm$ 13.51	14.67	9.67	12.17 $\pm$ 2.50
141-147	89.51	65.66	77.59 $\pm$ 11.92	15.93	10.01	12.97 $\pm$ 2.90
148-154	91.16	66.17	78.67 $\pm$ 12.49	17.24	10.64	13.94 $\pm$ 3.30
155-161	92.96	66.88	79.92 $\pm$ 13.04	19.14	11.46	15.30 $\pm$ 3.83
162-168	95.05	67.39	81.22 $\pm$ 13.83	20.65	12.21	16.43 $\pm$ 4.22
169-175	128.85	77.35	103.10 $\pm$ 25.75	22.03	12.93	17.48 $\pm$ 4.55
176-182	141.70	87.88	114.79 $\pm$ 26.91	22.72	13.34	18.03 $\pm$ 4.69
183-189	145.83	97.45	121.64 $\pm$ 24.19	23.96	14.22	19.09 $\pm$ 4.87
190-196	161.29	102.20	131.75 $\pm$ 29.55	24.74	14.95	19.85 $\pm$ 4.90
197-203	161.43	104.11	132.77 $\pm$ 28.66	26.32	15.76	21.04 $\pm$ 5.28
204-210	Sac	105.08	105.08	27.16	Sac	27.16
211-217	--	105.08	105.08	28.30	--	28.30
218-224	--	205.08	105.08	29.60	--	29.60
225-231	--	105.08	105.08	30.59	--	30.59

APPEDNIX E

LETTER FROM AMERSHAM CORPORATION DESCRIBING
PREPARATION OF RING LABELED ACEDAPSONE AS
ORDERED BY DYNATECH R/D CO ON PO 17258 (9/28/77)



Amersham

AMERSHAM CORPORATION
A SUBSIDIARY OF THE RADIOCHEMICAL CENTRE

2636 S. Clearbrook Dr., Arlington Heights, IL 60005 312/593-6300

May 15, 1979

Dr. Joseph Gresser
Dynatech R and D Corp.
99 Eirie St.
Cambridge, Mass. 02139

Dear Dr. Gresser:

Thank you for your recent inquiry concerning [*ring*-³H]acedapsone, TRQ.1207.

The compound was prepared by an exchange procedure with dimethylformamide containing 10 percent tritiated water. Approximately 100 milligrams of the compound was heated for 8 to 9 hours at near reflux temperatures in a sealed tube. The crude product was purified by column chromatography on silica gel eluting with chloroform/acetone.

This exchange procedure has been shown to preferentially label aromatic hydrogens over any available aliphatic hydrogens. The enclosed review includes a section on methods of preparing tritium labelled compounds, pages 12-15.

There are examples of this exchange procedure's preference for labelling aromatic hydrogens, i.e., vinblastine sulfate, acetanilide, polynuclear aromatic hydrocarbons and naphthalene sulfonic acid derivatives. However, exchange methods in general tend to be less specific than chemical methods, i.e., reduction of unsaturated compounds or replacement of halogens with tritium.

While our experience with labelling similar compounds to acedapsone indicates most of the tritium label should be in the ring, there could be a considerable percentage of total tritium label in the acetyl moiety. With the use of tritium nuclear magnetic resonance spectroscopy, the position of label can be assigned with absolute certainty. The analysis method is available on tritium labelled custom preparations by Amersham Corporation. Charges for analysis are in the range of \$400-\$700, depending on the actual compound.

I hope the above information is helpful in your investigation concerning the [*ring*-³H]acedapsone and should you have any additional questions, please do not hesitate to contact me.

Sincerely yours,

Kenneth C. Kolwyck

Kenneth C. Kolwyck
Assistant Technical Services Manager
Research Products

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KCK/...

APPENDIX F

DSITRIBUTION LIST

DISTRIBUTION LIST

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APPENDIX G

CHRONOLOGICAL LISTING OF PUBLICATIONS OF WORK
SUPPORTED BY CONTRACT DAMD-17-74-C4120

Publications List

1. Sustained Release of an Antimalarial Drug Using a Copolymer of Glycolic/Lactic Acid
D.L. Wise, G.J. McCormick, and G.P. Willet
Life Sciences, 19, 867 (1976)
2. Sustained Release of Sulfadiazine
D.L. Wise, G.J. McCormick, G.P. Willet, L.C. Anderson, and J.F. Howes
J. Pharm. Pharmacol., 30, 686 (1978)
3. Sustained Release of a Dual Antimalarial System
D.L. Wise, J.D. Gresser, G.J. McCormick
J. Pharm. Pharmacol., 31, 201 (1978)

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