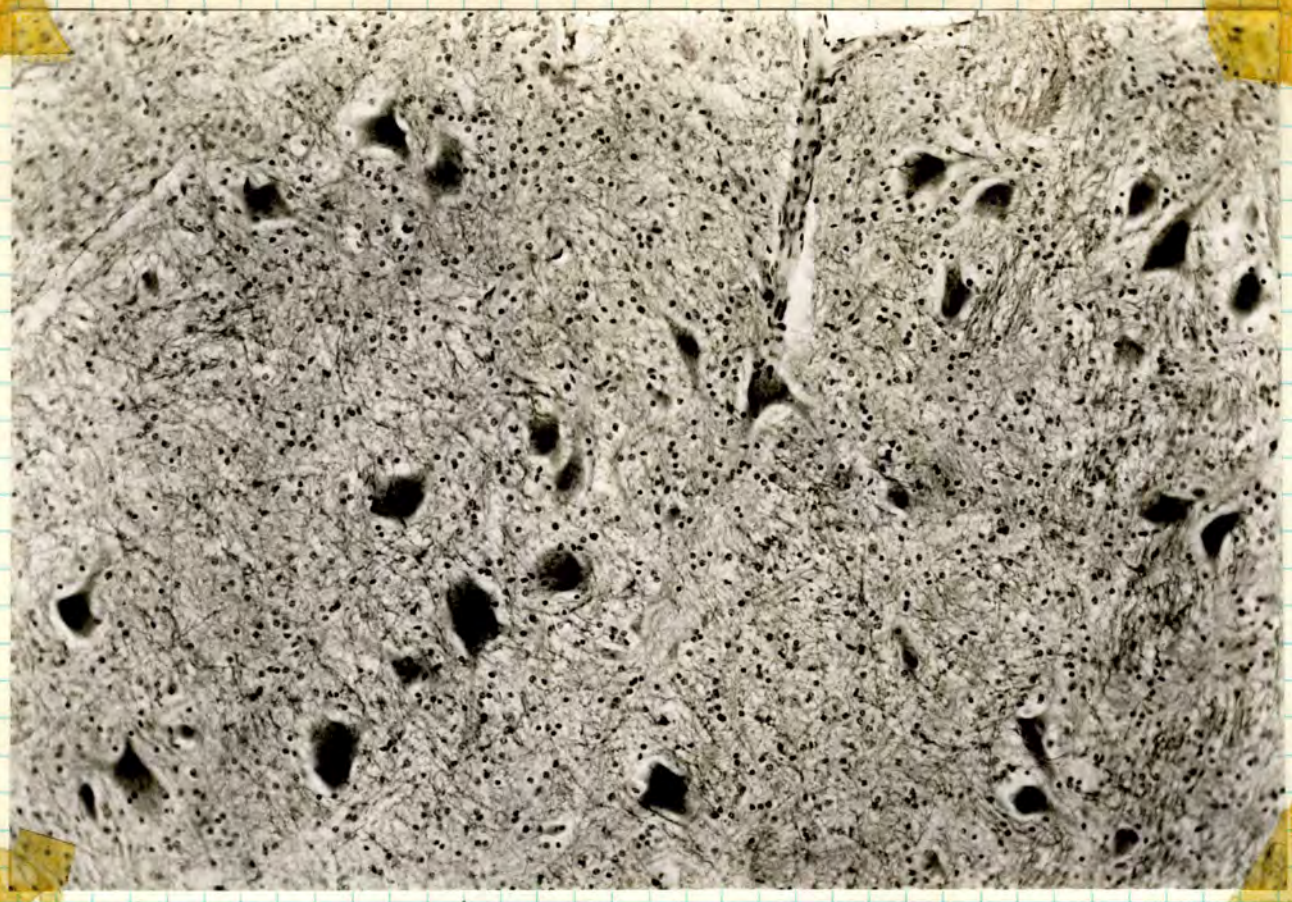
DATA

Schmidts' Photographs

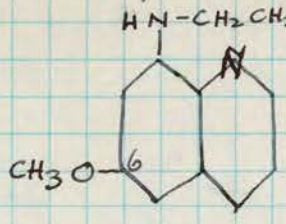


CONTROL M 1136 – Lateral Vestibular Nucleus

PLASMOCID – 1mg base/kilo per dose – t.i.d. – 11 doses
Killed 82 hrs. after beginning treatment.
M339 – Lateral Vestibular Nucleus – Iron Hematoxylin + Eosin KS 00

PLASMOCID — SN 3115 - Prepared by Dr. R. Elderfield
Obtained from Dr. L.H. Schmidt

8-(3-diethylaminopropyl-amino) 6-methoxyquinoline



The dihydroiodide (used at first) is 52.8% base
" dihydrochloride is 80% base.

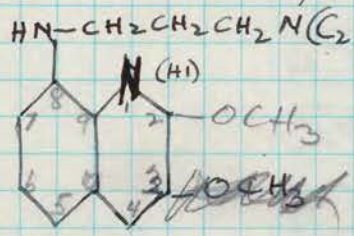
Dry drug kept in dessicator out of light.

Solution made up to contain 2 mg. base/ml. — kept in refrigerator for not longer than 1 week.

1 mg. base/kilo/bid. given to monkeys - each dose in 20cc H_2O

ISOPLASMOCID — SN 13058-17 - Prepared by Dr. J. B. Koepfli and K. Mislow
California Inst. of Technology
Pasadena, Calif.
Obtained from Dr. L.H. Schmidt

8-(3-diethylaminopropyl-amino) 2-methoxyquinoline



The dihydroiodide is 53% base.

Solution made up to contain 10 mg base/ml.

12 mg base/kilo/bid given to monkeys - each dose in 20cc/kg H_2O

According to Schmidt — 25, 50, 100 and 200 mg. base/kilo given as single dose orally - did not kill mice

40 mg. base/kilo per day ingested in diet caused weight loss in rat

Toxicity of Isoplasmocid for Mice by Intraperitoneal Route

Amt per 10 Gm.	Dose (1 dose)		No. of mice	Result	Mort
5 mg	500 mg base/kilo	—	10 mice	all dead within 2 min.	10/10
2 "	200 mg " / "	—	10 "	" " " 7 min.	10/10
1 mg	100 mg " / "	—	6 "	all prostrate but only 1 died	1/6
0.5 mg.	50 mg " / "	—	5 "	no prostration but some showed signs	0/5

NOTE — 100 mg base/kilo given twice a day i.p. killed 3 additional mice (out of 5 remaining) during next 2 days.

50 mg. base/kilo bid. produced convulsions, opisthotonos + other signs in most mice but all survived.

50 mg base/kilo bid. or (100 mg base/kilo/day) selected as test dose in conjunction with Lansing virus -

Toxicity of Plasmocid for Mice by Intraperitoneal Route

100 mg base/kilo single dose — 10 mice — convulsions in 2-3 min.
9 dead in 5 min.
1 " in 2 hrs. — 10/10

50 mg. base/kilo " — 10 mice — 1 dead with convuls. in few min.
— Others developed signs + died at intervals. — 10/10
— 5 dead within 6 hrs.
— 4 " next day
— 1 severe CNS — Killed 3rd day.

25 mg. base/kilo " — 10 mice — 3/10 dead in 6 hrs.
5/10 " in 24 hrs.
6/10 " " 48 " + 1 killed
8/10 " " 72 "

12.5 mg. base/kilo " — 10 mice — all alive* 7 hrs. and only 1 c̄ signs.
2nd dose given then.
next day — 2 dead 2 signs
3/10 at 48 hrs.

12.5 mg base/kilo/day 1 dose/day 10 mice — all OK at 24 hrs. 1st day 1 dead. 7 signs
3 died — (1 killed)
6 survived + recovered after cess. of drug

This dose selected for virus study { 12.5 mg base/kilo/day — in two doses of 6.25 mg base/kilo — 10 mice — OK.

Schmidt's remarks on what is known regarding chemical structure and CNS effects of 8-amino-quinolines.

All compounds in which the two side chain nitrogens ~~are~~ are separated by 2 or 3 Carbon atoms, thus:

$HN-(CH_2)_n NR_2$

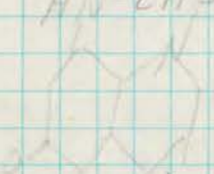
where $n = 2$ or $3 \rightarrow$ CNS effects

" $n = 4$ to $11 \rightarrow$ no CNS effects

One exception is where CH_3 group is substituted at position 4 on nucleus.

CH_3

$HN-CH\,CH_2\,CH_2\,CH_2\,NH\,CH(CH_3)_2$



isopentaquine

Pamaquine (30 mg daily)

isopentaquine (240 mg)

25 - 28 Gm

256

50 mg

5 mice - 100 mg/kilo

5 mice - 50 mg/kilo

5 mice - 25 mg/kilo

5 mice - 12.5 mg/K

0.5 cc i.p

0.4 c

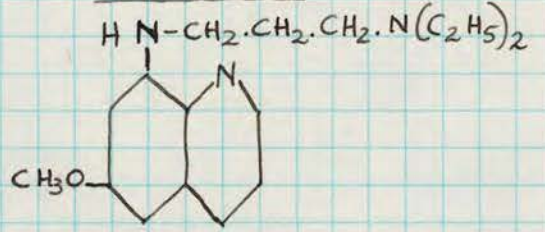
20

30

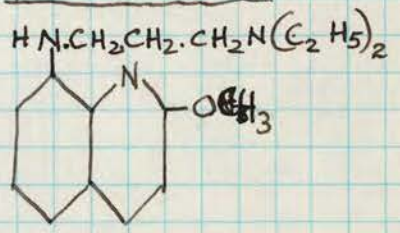
Preliminary Observations on the Effect of Certain 8-Amino-quinoline Compounds on the Neurones and Experimental Poliomyelitis in Rhesus Monkeys

Compounds studied:

Plasmocid



Isoplasmocid



Effect on Neurones:

Plasmocid: Acute necrosis especially of oculomotor, trochlear, abducens, vestibular, cuneate, lateral reticular and certain other nuclei, followed by focal inflammatory reaction. Varying proportion of anterior horn cells of spinal cord show chromatolysis. Clinically – marked neurological signs

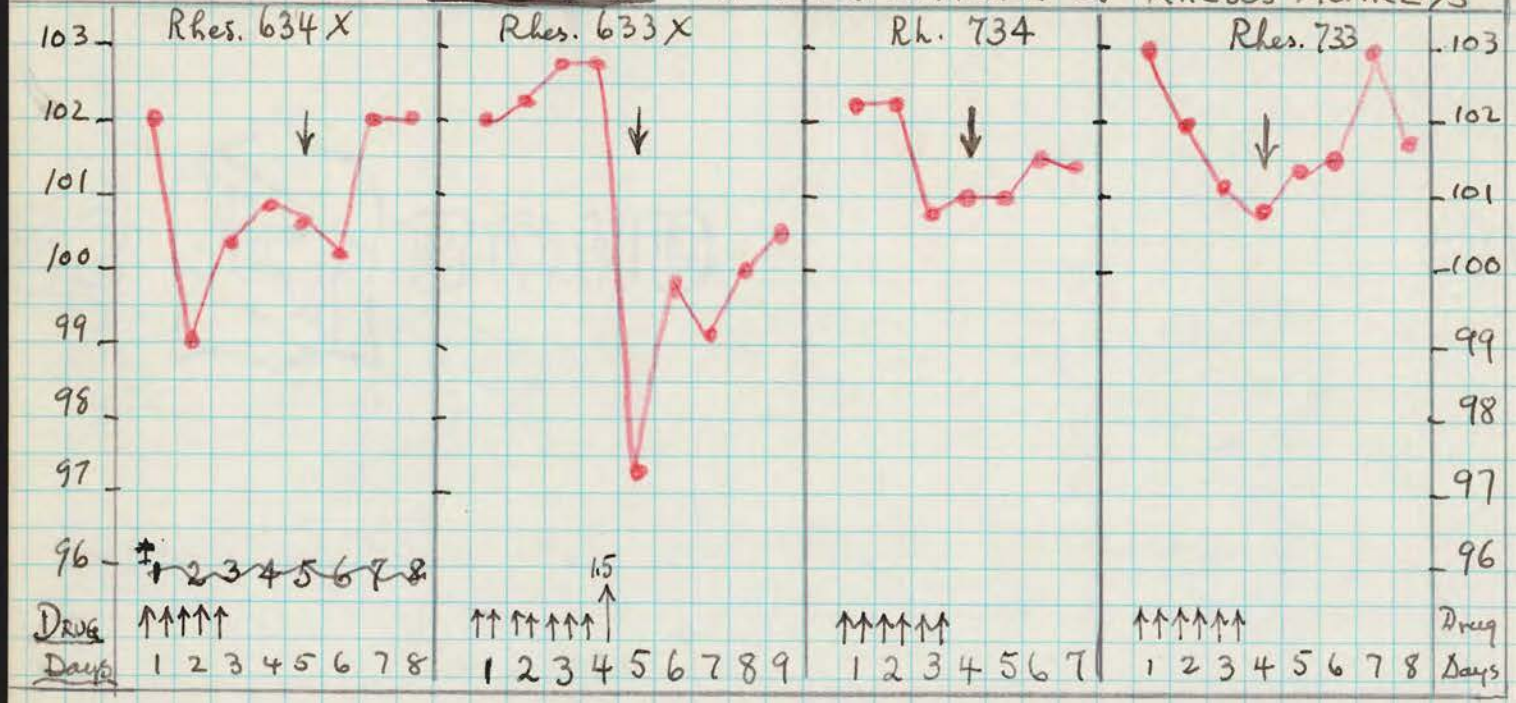
Isoplasmocid: Chromatolytic changes without necrosis or inflammatory reaction. Clinically – no neurological signs.

Effect on Experimental Poliomyelitis Following Intracerebral Inoculation of 50 PD_{50} of Virus

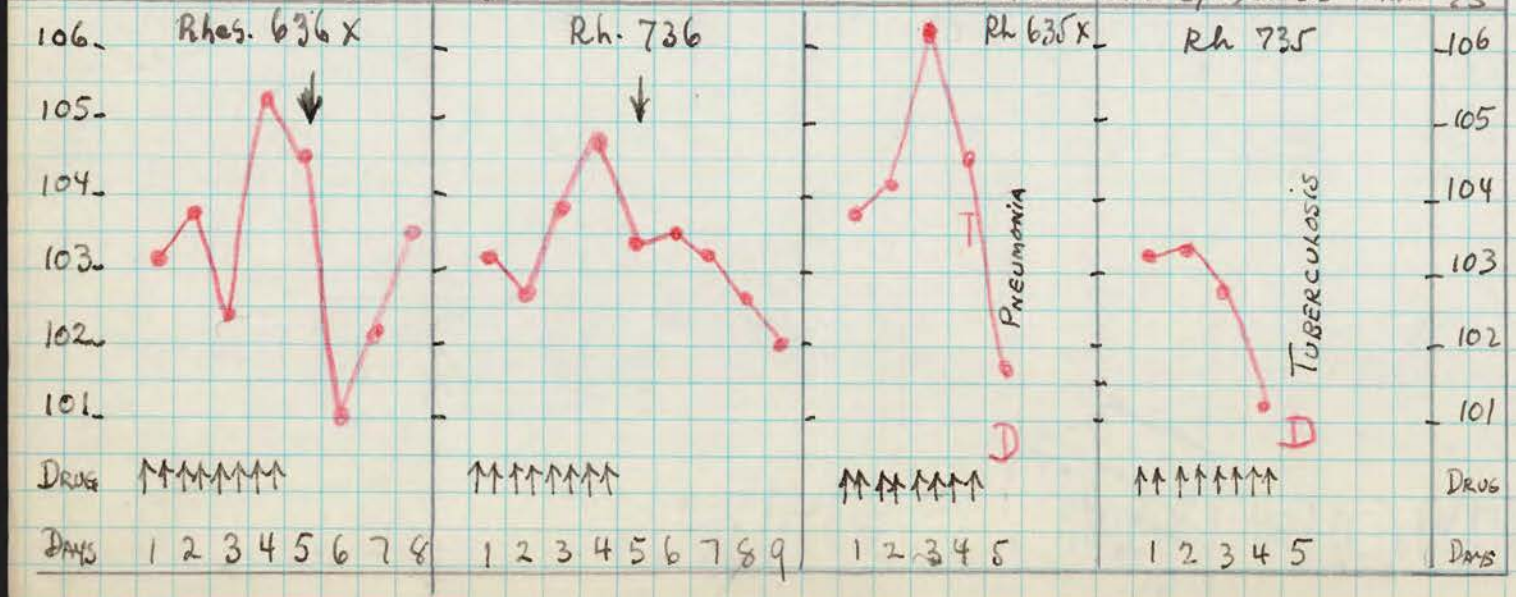
Group	Day of Paralysis	Day of Death	Histological Examination	Effect suggested by data
Controls – Virus Only	6, 6, 7, 7, 8, 9, 10, 11	10, 15, 17, 18, 18, 24, S, S		
Plasmocid 1 mg. base/kilo/b.i.d. 5–8 doses only before virus	0, 0, 0, 6	6, 6, 7, 8	Extensive necrosis and neuronophagia of almost all anterior horn cells in spinal cord	"Polio Synergist"
Isoplasmocid 12 mg. base/kilo/b.i.d.				
Test 1 – 4 days before virus	9, 18	30, S		
Test 2 – 4 days before virus + 4 days after virus	0, 0, 0, 0	2, 7, 9, S(K36)	No Polio	"Polio Antagonist"

Exh. I. (August 3 - 1948)

EFFECT OF PLASMACID ON TEMPERATURE OF RHESUS MONKEYS



Effect of SN-13058 on Temperature of Rhesus Monkeys



Effect of Plasmocid and SN-13058 on Course of Poliomyelitis Infection in Rhesus Monkeys.

(Ex 8 I) August 3. 1948

Group	Monkey No.	Days after Inoculation of Virus 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 21 22 23 24	
Control	664x	- - - - - F F PP PP PP Pr. D	F_5 P_7 D_{10}
	663x	- - - - - F PF PP PP PP Pr. Pr. Pr. Pr. Pr Pr Pr. Pr Pr. D	F_5 P_6 D_{18}
1cc 1:500 Hoferkamp virus	665x	- - - - - F F F pFP PP PP s PP s s s s s s s s s s D	F_5 P_8 D_{24}
	666x	- - - - - - - - - F Tr F Tr PP PP PP PP PP PP PP PP PP PPPP PP PP PP	F_8 P_{11} S
Plasmocid	633x	- - - - - - D	D_6 - Polio
	733	- - - F F D	F_4 D_6 - Polio
	634x	- - - F F - D	F_4 D_7 - Polio
	734	- - - - - PP PP Pr. D	P_6 D_8
SN 13058 12 mg/kilo/bid. for 4 days before virus	736	- - - - - - - F F FP PP PP Pr Pr Pr Pr Pr Pr Pr Pr Pr.	F_7 P_9 D_{30}
	636x	- - - - - - - - - - - - - F F - F? F? P PP PP	F_{14} P_{18} S
Previous Controls Inoc. with Same Dose of this Virus	138	- - - - F PP (6)	
	139	- - - - - - F F F P (9) PP Pr. Pr. Pr Pr Pr Pr Pr Pr Pr Pr D 31 days	
	140	- - - - F WW WW Pr D (6)	
	421	W PP (6)	
	508	WW PP PP PP D (6)	
	509	PP PP PP PP PP (7) s s s s s s s s s s s s s Survived	

Isoplasmocid and Polio in Monkeys – Expt of Sept 3, 1948

Group	Monkey No.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	
Control Icc 1:500 Hofenkamp virus	610X	– – – – F P P_{pp}^{pp} P_r . . . . . D	$P_6 D_{15}$
	605X	– F – – F F P_p P_r . . . . . D	$P_7 D_{17}$
	606X	– – – – – F – – P_p P_r . . . . . D	$P_9 D_{18}$
	676X	F F F F P P_p P_{pp}^{pp}	P_{10} S
Sn 13058 12mg. base/kilo b.i.d. for 4 days before virus and then as indicated by arrows	612X	↑↑ ↑↑ ↑↑ ↑↑ –	OK; K36
	602X	↑↑ ↑↑ ↑↑ ↑↑ D	D_9 – no polio
	609X	↑↑ D	D_7 – no polio
	677X	↑↑ ↑ D	D_2 – no polio

	Day of Paralysis	Day of Death	Remarks
Controls	6, 6, 7, 7, 8, 9, 10, 11	10, 15, 17, 18, 18, 24, S, S	
Plasmocid – 1mg. base/kilo/bid Given only before virus	0, 0, 0, 6	6, 6, 7, 8	All extensive polio
Isoplasmocid – 12mg base/kilo bid			
24mg/day 4 days before virus only	9, 18	30, S	
24mg. { 4 days before virus and 4 days after virus	0, 0, 0, 0	2, 7, 9, S (K36)	No Polio

Isoplasmocid in Monkeys (Schmidt)

24 mg base/kilo/day — 8 mg t.i.d.

1 monkey — died on 6th day

48 mg base/kilo/day — 16 mg t.i.d.

1 monkey — died on 6th day

96 mg base/kilo/day — died 3rd day —

24 mg /kilo/day — ~~2nd~~ Dead 5 days

12 mg /kilo/day — Dead 16th day

6 mg / " / " — Lived for 16 days — developed cellulitis WBC-down. — clinically not very ill.

12 mg /kilo/day — died 12th day

12 mg / " / " — Survived 14 days — no ill effects
12 mg / " / " — " " — " "
12 mg / " / " + folic acid — " " — " "
12 mg " " + " " — " " — " "
12 mg / " / " + " " — Died 11th day
12 mg / " / " + liver conc. — Survived 14 days — no ill effects
12 mg / " / " + " " — Died 13th day — cellulitis
12 mg / " / " + folic acid — Survived 14 days — OK.
12 mg " " + " " — Died 7 days.

	Dose mg base/kilo/day	No of Monkeys	No. died	Day of Death
(32 mg tid)	96	1	1	3
(16 mg tid)	48	1	1	6
(8 mg tid)	24	2	2	5, 6
(4 mg tid)	12	11	5	7, 11, 12, 13-c, 16, S, S, S, S

Drug for 14 days

Projected Expt III with Isoplasmocid and Polio

Group I – 8 mg. base/kilo/day – given in 3 doses as follows

9 A.M. – 2 mg

3 P.M. – 2 mg.

9 P.M. – 4 mg.

7 monkeys – 6 will get virus on 5th day
1 will get only drug

Group II – 4 mg. base/kilo/day – given in 3 doses

9 A.M. – 1 mg.

3 P.M. – 1 mg.

9 P.M – 2 mg.

7 monkeys – 6 will get virus on 5th day
1 will get only drug.

Group III – No drug – virus only

4 monkeys

8 mg base/kilo/day = @ 48 mg per monkey/day = 1440 mg for 30 days
× 7
10.080 Gm. for 7 monkeys for 30 days.

or 19.02 Gm. of Drug needed for Group I

and 9.51 " " " " " II

Total 28.53 Gm. of drug needed for 30 days

Plan – Give drug for 4 days before virus and for 21 days after virus

Allow animals to go for 35 days after virus
Then sacrifice all for histology and some for virus tests

ISOPLASMOCID + POLIO
EXP. III
November 3 '48

GROUP	Monkey No.	Day of Paralysis	Day of Death after virus	Histology	Remarks
CONTROL VIRUS ONLY	1030	5	20		
	1031	5	5		
	1032	6	13		
	1033	8	5		
8 mg. base/kilo/day 2 mg - 8 AM 2 mg - 2 PM 4 mg - 8 PM	1019	—	<1		Inoculation accident - bacteremia
	1020	6	9	Focal Polio	Prob. drug death
	1022	—	7	No Polio	Pulmonary edema & Lobular pneumonia
	1017	11	14	Polio	Resuscitated
	1018	— ?	11	Focal Polio	Pulmonary edema
	1021	—	14	No Polio	" " Pneum.
4 mg. base/kilo/day 1 mg - 8 AM 1 mg - 2 PM 2 mg - 8 PM.	1023	—	7	No Polio	Pulmon. edema Lob. pneumonia?
	1028	7	36	Polio	
	1026	8	42	Polio	
	1027	? 8	9	Focal Polio	Probably drug death
	1024	13	Killed 43 days	Polio	
	1025	0	Survived (K 32)	No Polio	
Drug Control 8 mg/kilo/day No virus	1016		5		
4 mg/kilo/day	1029		5		

8 mg base / kilo / day × 3 = 24 mg base / kilo / day / monkeys

× 25 days

120
48

600 mg base / monkey for 25 days

× 20 monkeys

12.000 GM. base for 20 monkeys

24 mg
20

480 mg / monkey / 20 days

× 10

4.800 GM for 10 monkeys

17 GM base

1700 | 53
159 32 GM.
110