Effect of Vincristine Sulfate on *Pseudomonas* Infections in Monkeys

SAMUEL SASLAW, HAROLD N. CARLISLE, AND MOHAMMAD MOHEIMANI

Division of Infectious Diseases, Department of Medicine, The Ohio State University College of Medicine, Columbus, Ohio 43210

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In rhesus monkeys, intravenous challenge with 0.6×10^{10} to 2.2×10^{10} *Pseudomonas aeruginosa* organisms caused acute illness of 4 to 5 days' duration with spontaneous recovery in 13 of 15 monkeys; blood cultures became negative 3 to 17 days after challenge. Leukocytosis was observed in all monkeys. Intravenous or intratracheal inoculation of 2.0 to 2.5 mg of vincristine sulfate was followed by leukopenia in 4 to 5 days. Intravenous inoculation of 4.2×10^{10} to 7.8×10^{10} pyocin type 6 *Pseudomonas* organisms in monkeys given vincristine sulfate 4 days previously resulted in fatal infection in 11 of 14 monkeys, whereas none of four receiving *Pseudomonas* alone died. These studies suggest that an antimetabolite-induced leukopenia predisposes to severe *Pseudomonas* sepsis and that such monkeys may serve as a biological model for study of comparative efficacy of antimicrobial agents.

Pseudomonas infections have become an increasing problem in hospitalized patients in recent years (1, 5, 8). Sepsis due to *Pseudomonas* organisms has been a particular problem and is a frequent cause of death in granulocytopenic patients with cancer and leukemia (2, 4, 9, 28). As recently emphasized, there is need for controlled trials in man and animals to evaluate comparative efficacy of major drugs now employed for treatment of *Pseudomonas* sepsis (6).

Previous studies in this laboratory demonstrated varying degrees of toxicity and agranulocytosis in monkeys receiving different antineoplastic agents intratracheally or by aerosol (18). These routes of administration were selected as a possible approach towards treatment or palliation of primary or malignant disease of the lungs with possibly less hemotoxic side effects. On the basis of these observations, vincristine sulfate was selected in the present study as an agent which could be employed to induce granulocytopenia with lesser risk of drug toxicity in monkeys subsequently challenged with *Pseudomonas* organisms. It is the purpose of this report to describe the results obtained with monkeys as a biologic model for severe *Pseudomonas* sepsis which could perhaps be subsequently employed in studies of comparative efficacy of antibiotics.

MATERIALS AND METHODS

Monkeys. Forty-six fully conditioned, young adult monkeys (*Macaca mulatta*) weighing 3.4 to 4.7

kg were employed. Physical examinations, hematological and bacteriological studies, and tests for C-reactive protein (CRP) were conducted over a period of at least 2 weeks to establish normalcy of the monkeys before use in experiments.

Vincristine. Vincristine sulfate (Lilly), hereinafter to be referred to as VCR, was used in these studies (10). Each ampoule contained 5.0 mg of VCR and 50 mg of lactose; the accompanying diluent was 0.9% sodium chloride containing 0.9% benzyl alcohol. Concentrations of 1.5, 2.0, or 2.5 mg of VCR in 1.0 ml were prepared immediately before inoculation of monkeys.

***Pseudomonas* inoculum.** A pyocin type 6 strain of *Pseudomonas aeruginosa* (Bricker) isolated from the urine of a patient with chronic infection was used. Six-hour Trypticase soy broth (TSB; Baltimore Biological Laboratories) cultures, incubated over magnetic stirrers in a 37 C water bath, were centrifuged to a soft pellet in an International PR-2 refrigerated centrifuge. The cells were dispersed in 0.9% sodium chloride with the aid of glass beads and gentle mixing with a glass rod. The resulting smooth suspension was adjusted nephelometrically to the desired concentration by using a predetermined curve relating viable count to percent of light transmission at 550 nm in a Leitz Rouy Photometer. Surface plate counts were carried out by diluting the suspension in TSB and spreading 0.01-ml samples of the appropriate dilution over the surface of blood plates using a calibrated platinum loop. Plates were prepared from blood agar base (Difco) containing 5% bovine blood, and were dried overnight at room temperature to prevent excessive spreading of individual *Pseudomonas* colonies.

Inoculations. Monkeys inoculated intratracheally with VCR were anesthetized with sodium pentobarbital. Intravenous inoculations of VCR or *Pseudomonas* suspension were made into the saphenous vein of unanesthetized monkeys.

Observations. Monkeys were examined at least twice daily for 3 weeks after inoculation, and daily thereafter for at least 3 months. Days of "acute illness" included the period during which the monkeys were very ill and exhibited fever, marked weakness, lethargy, and anorexia. At this time, they usually would sit in a corner of the cage with head hanging and arms clasped about the body; there would be little or no resistance to handling. Days of "total illness" included the first period plus the recovery phase in which there would still be some evidence of weakness, anorexia, and decreased activity, as compared to the alert, agile, and combative state associated with healthy monkeys. Laboratory studies included complete blood counts, blood cultures, and CRP tests. Blood culture bottles consisted of 20 ml of TSB in 60-ml rubber-capped wide-mouth vaccine vials; 2.0 ml (± 0.1 ml) of blood obtained by femoral venipuncture was added.

RESULTS

Response to *Pseudomonas* challenge in normal monkeys. Preliminary studies with 10 *Pseudomonas* strains inoculated intravenously at doses varying from 0.6 to 2.2×10^{10} organisms resulted in fatal infections in only 2 of 15 monkeys. As shown in Table 1, 9 of 13 survivors were acutely ill for 4 to 10 days and not fully recovered for 10 to 21 days; the other four monkeys showed less

severe but obvious illness for 8 to 12 days. Blood cultures were positive for periods varying from 3 to 17 days, and leukocytosis was observed for 7 to 24 days after challenge.

Other preliminary studies resulted in the employment of the Bricker strain of *P. aeruginosa* (pyocin type 6) in subsequent studies. This strain was the specific etiologic agent in a patient with a urinary tract infection, and caused acute, but nonfatal, infections in normal monkeys receiving 4.0 to 7.0×10^{10} organisms intravenously. Its sensitivity to anti-*Pseudomonas* antibiotics, such as gentamicin, colistin, carbenicillin, and tobramycin, was such that it could be considered as a representative strain suitable for use in anticipated studies of the comparative efficacy of these antibiotics in *Pseudomonas* sepsis in monkeys.

Response to vincristine. A total of 13 monkeys were given VCR only. Seven monkeys received intravenous inoculations, and six monkeys were inoculated intratracheally (Table 2). Three, two, and two monkeys were inoculated intravenously with 2.5, 2.0, and 1.5 mg, respectively, of VCR. Two (no. 264, 273) of the three monkeys given 2.5 mg showed no signs of illness after inoculation except for mild anorexia during the first 5 to 7 days. All CRP tests were negative in both monkeys. The third monkey (no. 138, Table 2) became less active on day 4 and then appeared weak, lethargic, and anorectic on days 5 to 7 associated with severe *Proteus mirabilis* diarrhea. It began to

TABLE 1. Response of rhesus monkeys to intravenous *Pseudomonas* challenge

Expt no.	Monkey no.	<i>Pseudomonas</i>		Duration (days) of:					
		Strain	Dose ($\times 10^{10}$)	Acute illness	Total illness	Fever	Positive blood culture	Positive C-reactive protein	Leukocytosis
1 ^a	1	HG	1.0	4	10	1	7	14	14
	2	4108	1.0	4	12	1	3	14	14
	3	3852	1.0	0	8	2	3	7	7
	4	3118	1.0	Died-day 2					
	5	3097	1.0	8	12	3	7	14	14
	6	3020	1.0	5	13	10	3	14	7
2 ^b	7	3020	2.2	8	21	10	17	17	24
	8	3020	2.2	5	17	14	14	17	24
	9	3020	0.6	0	12	10	17	17	24
	10	3020	0.6	0	9	6	3	17	17
3 ^c	11	3118	1.0	9	12	4			
	12	3661	1.0	0	10	2			
	13	4182	1.0	8	11	6			
	14	937	1.0	10	14	11			
	15	13	1.0	Died-day 2					

^a Inoculum estimated nephelometrically. Blood specimens obtained on days 3, 7, and 14.

^b Inoculum concentration determined by plate count. Blood specimens obtained on days 3, 5, 7, 10, 14, 17, 24, and 28.

^c Inoculum estimated nephelometrically. Blood specimens not obtained.

TABLE 2. Total leukocyte counts in monkeys given vincristine intravenously or intratracheally

Expt no.	Monkey no.	Vincristine ^a		BL ^b	Days after inoculation of vincristine									
		Dose	Route		4	5	7	10	12	14	18	21	25	28
1	138	2.5	IV	11.2 ^c	2.6	2.3	7.8	22.5	21.6	20.1	18.1	20.4	14.5	16.4
1	264	2.5	IV	9.7	3.1	5.1	5.9	8.0	9.1	12.4	8.4	9.8	11.9	12.2
1	273	2.5	IV	21.7	4.9	5.8	6.5	8.2	11.8	13.9	22.7	19.4	22.5	19.2
1	12	2.0	IV	10.2	4.4	3.2	7.8	5.3	6.4	7.7	9.1	8.2	6.7	12.1
1	283	2.0	IV	5.7	2.4	2.6	3.7	3.5	3.4	4.4	5.1	11.3	5.5	8.2
1	31	1.5	IV	14.9	11.5	7.0	8.8	12.5	9.4	9.8	18.8	21.2	18.5	21.1
1	268	1.5	IV	7.8	3.4	3.7	6.4	5.5	23.3	17.1	11.8	9.3	12.2	13.8
1	195	2.5	IT	12.4	13.6	8.9	18.5	12.4	9.5	11.1	11.7	10.8	11.8	12.5
1	271	2.5	IT	18.1	4.5	5.5	11.9	14.7	11.7	12.5	12.6	19.4	21.1	18.0
2	105	2.0	IT	12.6	4.6	3.7	4.5	8.4	12.1	16.4	10.2	11.4	12.8	8.2
2	106	2.0	IT	14.0	8.3	6.4	11.1	10.1	12.5	10.8	14.1	16.2	24.3	23.4
2	107	2.0	IT	15.9	3.4	2.9	2.4	11.0	17.8	26.5	19.6	Died-day 20		
2	109	2.0	IT	14.1	21.4	16.0	34.0	38.2	36.6	39.9	32.3	28.6	26.5	20.1

^a Mg in 1.0 ml of 0.9% sodium chloride. IV, Intravenously; IT, intratracheally

^b Mean of at least two baseline counts.

^c Total leukocyte counts expressed as thousands per cubic millimeter.

improve on day 8 and appeared normal with no diarrhea on day 11 and thereafter. CRP tests were positive on days 4 to 7. The monkey was leukopenic on days 4 and 5, but leukocytosis was observed on days 10 to 21 (Table 2). The other two monkeys given 2.5 mg of VCR exhibited significant leukopenia on days 4 to 7 as compared to baseline values.

Neither of the two monkeys (no. 12, 283) given 2.0 mg of VCR intravenously showed any evidence of illness, except for anorexia, and all CRP tests were negative. Both monkeys were leukopenic by days 4 to 5. No symptoms were observed in the two monkeys given 1.5 mg of VCR, and CRP tests remained negative. Decrease in total leukocytes was modest in one (no. 31, Table 2) of the two monkeys; the other monkey (no. 268) exhibited leukopenia on days 4 and 5, but counts were increased on days 12 and 14.

Two monkeys (no. 195, 271) given 2.5 mg of VCR intratracheally remained active and alert after inoculation, but both were mildly anorectic during the first week. All CRP tests were negative. One monkey (no. 271) showed a significant decrease in total leukocytes, whereas the other did not (Table 2).

One (no. 107) of four monkeys given 2.0 mg of VCR intratracheally exhibited mild lethargy and anorexia from day 3 through day 14. It was normal in appearance and activity on days 15 and 16 but became acutely ill suddenly during day 17. It became progressively worse on days 18 and 19 and died on day 20. Severe diarrhea was noted from day 17 up to death. Gross pathology was not remarkable except for evidence of severe

enteritis, which was shown to be due to *P. mirabilis*. CRP tests were positive from day 10 up to death. This monkey showed obvious leukopenia on days 4 to 7 and leukocytosis on days 14 and 18 (Table 2). A second monkey (no. 109) given 2.0 mg of VCR intratracheally was mildly lethargic on days 3 to 15 and had mild diarrhea on days 4 to 12. CRP tests were positive continuously from day 4 through day 21. This monkey did not show leukopenia; leukocyte counts on days 4 and 5 were higher than those prior to VCR. Leukocytosis (26,500 to 39,900 per mm³) beginning on day 7 persisted through day 25. Another monkey (no. 105) given 2.0 mg exhibited mild lethargy on days 3 to 5 only, and a single positive CRP test was obtained on day 4; it was relatively leukopenic on days 4, 5, and 7. The fourth monkey (no. 106) remained well after inoculation, and all CRP tests were negative; modest leukopenia was observed on days 4 and 5.

Thus, six of seven monkeys inoculated intravenously with 1.5 to 2.5 mg of VCR showed significant leukopenia by day 4. After intratracheal inoculation of 2.0 to 2.5 mg of VCR, four of six showed leukopenia by days 4 to 5. As in previous studies (18), the leukopenia induced by VCR was predominantly in the granulocyte series.

Effect of VCR on *Pseudomonas* infections. In the first of four experiments (Table 3), two monkeys each were inoculated intratracheally with 2.5 mg of VCR in 1.0 ml of diluent, and two additional monkeys each were given 1.0 ml of diluent by the same route. All four monkeys were challenged intravenously 4 days later with 4.2×10^{10} *Pseudomonas* organisms. None of the four mon-

TABLE 3. Effect of vincristine on response of monkeys to intravenous *Pseudomonas* challenge

Expt no.	Monkey no.	Vincristine ^a (route)	<i>Pseudo- monas</i> dose ($\times 10^{10}$)	Mortality ^b	Total mortality	Day of death	Duration (days) in survivors of:			
							Acute illness	Total illness	Positive blood culture	Positive C-reactive protein
1	112	IT	4.2				8	12	17	28
1	113	IT	4.2	1/2		2				
2	114	IT	6.8			3				
2	126	IT	6.8			2				
2	166	IT	6.8				8	15	14	28
2	173	IT	6.8	3/4		2				
3	252	IT	7.8			2				
3	255	IT	7.8			1				
3	256	IT	7.8	3/3		2				
4	190	IT	6.4	1/1	8/10	3				
3	205	IV	7.8				7	12	8	17
3	206	IV	7.8			2				
3	257	IV	7.8	2/3		1				
4	265	IV	6.4	1/1	3/4	2				
1	135	None-IT	4.2				0	8	3	14
1	138	None-IT	4.2	0/2			7	9	3	10
2	121	None-IT	6.8				7	12	6	21
2	123	None-IT	6.8	0/2	0/4		9	13	6	17

^a At 2.5 mg per 1.0 ml of 0.9% sodium chloride. IT, Intratracheally; IV, intravenously; None, 1.0 ml of 0.9% sodium chloride. Vincristine given 4 days prior to *Pseudomonas* challenge.

^b Number that died over total number.

keys showed any evidence of illness on the day of challenge, with the exception that both monkeys given VCR were anorectic. CRP tests were negative in all four monkeys. On the morning of the day after challenge, all four monkeys were weak, lethargic, and anorectic, but not acutely ill. One (no. 113, Table 3) of the two monkeys given VCR became worse during the day and died on day 2. At autopsy, the lungs showed scattered areas of hemorrhage and congestion, the liver was pale, mottled, and slightly enlarged, and the spleen was dark in color and about twice normal size. *Pseudomonas* was isolated from all major organs and heart blood. The other monkey (no. 112) given VCR became progressively worse during days 1 and 2 and was acutely ill on days 3 to 8. Subsequent recovery was complete by day 13. One (no. 135) of two monkeys not given VCR did not become acutely ill; mild symptoms were noted for only 8 days. The other monkey (no. 138) was acutely ill for 7 days, but then recovered very rapidly and appeared normal after day 9.

The surviving monkey (no. 112) pretreated with VCR exhibited positive blood cultures (Table 3) for 17 days, whereas cultures were negative after day 3 in the two control monkeys not given VCR. Similarly, CRP tests (Table 3) were positive continuously for 28 days in the surviving monkey given VCR, and for 10 and 14 days in the two controls. As shown in Table 4, both monkeys (no.

112, 113) pretreated with VCR were relatively leukopenic on the day of *Pseudomonas* challenge; total leukocyte counts were 4,200 and 5,100 per mm³ as compared to 10,700 and 16,000 per mm³, respectively, before administration of VCR. Counts were depressed still further to only 400 and 500 per mm³, respectively, on the day after challenge; corresponding total neutrophil counts were only 200 and 100 per mm³, respectively. The VCR-treated monkey (no. 112) that survived showed a marked increase in leukocytes from 1,000 per mm³ on day 3 to 19,500 per mm³ on day 6, and leukocytosis was observed through day 21. Leukocytosis was also observed in both monkeys (no. 135, 138) receiving *Pseudomonas* only (Table 4).

Similar results were obtained in three additional experiments in which monkeys were inoculated intratracheally or intravenously with 2.5 mg of VCR and challenged 4 days later with the *Pseudomonas* (Table 3). In experiments 1 to 4 combined, all 18 monkeys appeared normal on the day of *Pseudomonas* challenge, with the exception that the 14 monkeys pretreated with VCR exhibited varying degrees of anorexia. CRP tests were negative in all 18 monkeys. Eight of ten, and three of four monkeys given VCR intratracheally and intravenously, respectively, died 1 to 3 days after challenge with 4.2 to 7.8×10^{10} *Pseudomonas* organisms, whereas no deaths were ob-

TABLE 4. Total leukocyte counts in monkeys given vincristine intratracheally or intravenously four days prior to *Pseudomonas* challenge

Expt no.	Mon-key no.	Vincristine ^a (route)	<i>Pseudomonas</i> dose ^b	Day after <i>Pseudomonas</i> challenge										
				BL ^c	0 ^d	1	3	6	8	10	14	17	21	28
1	112	IT	4.2	16.0 ^e	5.1	0.5	1.0	19.5	22.4	19.2	20.1	32.1	23.6	12.7
1	113	IT	4.2	10.7	4.2	0.4	D2 ^f							
2	114	IT	6.8	9.9	8.0	2.5	D3							
2	126	IT	6.8	10.0	3.3	0.3	D2							
2	166	IT	6.8	14.5	6.2	3.0	7.3	66.3	44.8	34.1	50.3	23.9	30.9	10.2
2	173	IT	6.8	12.6	4.1	0.3	D2							
3	252	IT	7.8	9.7	9.4	0.4	D2							
3	255	IT	7.8	11.2	1.7	D1								
3	256	IT	7.8	11.3	4.9	1.4	D2							
4	190	IT	6.4	14.6	9.7	1.8	0.7	D3						
3	205	IV	7.8	10.9	5.6	2.5	2.1	25.6	34.3	50.7	42.9	22.5	29.4	13.2
3	206	IV	7.8	7.7	2.6	1.1	D2							
3	257	IV	7.8	13.3	2.7	D1								
4	265	IV	6.4	8.4	0.6	0.2	D2							
1	135	None-IT	4.2	14.4	17.2	15.1	18.6	29.9	26.1	29.6	28.9	21.9	17.6	8.1
1	138	None-IT	4.2	14.6	10.4	15.2	15.9	21.0	19.0	19.6	18.6	18.3	13.0	10.1
2	121	None-IT	6.8	12.9	12.0	15.6	15.9	41.4	32.2	35.0	23.0	23.6	21.7	16.5
2	123	None-IT	6.8	12.7	14.9	16.4	13.4	57.9	63.5	31.3	19.6	20.1	18.2	13.8

^a At 2.5 mg per 1.0 ml of 0.9% sodium chloride. IT, Intratracheally; IV, intravenously; None, 1.0 ml of 0.9% sodium chloride.

^b Figures shown to be multiplied by 10¹⁰.

^c Mean of at least two baseline counts.

^d Day 0 = day of *Pseudomonas* challenge.

^e Total leukocyte counts expressed as thousands per cubic millimeter.

^f D2, Died on day 2.

served in four control monkeys challenged with the *Pseudomonas* but not given VCR. The 10 monkeys that died in experiments 2 to 4 exhibited gross pathology similar to that seen in the monkey that died in experiment 1, and *Pseudomonas* was isolated from all major organs and heart blood of all monkeys.

Duration of illness in the three surviving VCR-treated monkeys in experiments 1 to 4 was not markedly different from that in four control monkeys. The three survivors (no. 112, 205, 166) given VCR were apparently fully recovered after days 12, 12, and 15, respectively, and the control monkeys (no. 135, 138, 121, 123) appeared normal after days 8, 9, 12, and 13, respectively. However, blood cultures were positive for 8, 14, and 17 days in the three given VCR and for only 3, 3, 6, and 6 days in the four controls. CRP tests were positive for 17, 28, and 28 days in the three survivors pretreated with VCR and for 10, 14, 17, and 21 days in the controls.

Marked leukopenia followed by leukocytosis in survivors was the principal hematologic finding in monkeys given VCR before *Pseudomonas* challenge, whereas only leukocytosis was observed in the control monkeys receiving only the *Pseudo-*

monas. As shown in Table 4, 11 of 14 monkeys pretreated with VCR in experiments 1 to 4 exhibited relative leukopenia on the day of *Pseudomonas* challenge (day 0) as compared to baseline counts. On the day after challenge (day 1), counts in all 12 monkeys that were still alive were lower than on day 0 and ranged from 200 to 3,000 per mm³ (mean, 1,200), as compared to 600 to 9,700 (mean, 5,300) on day 0 and 7,700 to 16,000 (mean, 11,400) before inoculation of VCR. Of particular interest, six monkeys exhibited total leukocyte counts of only 200 to 500 per mm³. Only four of the VCR-treated monkeys were still alive on the morning of day 3. One (no. 190, Table 4) was moribund at the time and had a leukocyte count of only 700 per mm³; it died later the same day. The other three monkeys had counts of 1,000, 2,100, and 7,300 per mm³ on day 3 and survived. Counts increased markedly to 19,500, 25,600, and 66,300 per mm³ on day 6 in these three monkeys, respectively, and leukocytosis persisted through day 21. Leukocyte counts in the four control monkeys not given VCR did not change significantly on days 1 and 3. All four monkeys exhibited leukocytosis on day 6 and subsequently for varying periods, as shown in Table 4.

DISCUSSION

Intravenous challenge of normal rhesus monkeys with *Pseudomonas* organisms caused acute illness of 4 to 8 days' duration with spontaneous recovery in 13 of 15 monkeys; blood cultures became negative 3 to 17 days after inoculation, and leukocytosis was observed in all monkeys. As in previous studies (19), the incidence of positive CRP test results usually paralleled the presence of positive blood cultures and active disease or complications thereof. Intravenous or intratracheal inoculation of vincristine sulfate usually resulted in leukopenia by days 4 to 5. Intravenous challenge of *Pseudomonas* organisms during this leukopenic phase was followed by a mortality of 11 of 14 monkeys, 36 to 72 hr later, whereas none of four monkeys receiving *Pseudomonas* alone died. Leukocytosis was observed in all of the latter four. In the three survivors pretreated with VCR, marked leukocytosis was noted on day 6 after challenge. These observations are in accord with clinical studies wherein leukopenia predisposes to *Pseudomonas* sepsis (2, 9, 28). Inability to respond with significant leukocytosis is an unfavorable prognostic sign in humans (3), and antimetabolites employed in therapy may contribute to this chain of circumstances. Thus, it is not unreasonable to use an antimetabolite in establishing a biological model for lethal *Pseudomonas* infections rather than attempting to evaluate comparative efficacy of antibiotics in the usually nonfatal infection in normal monkeys. In using such a model with lethality as a definitive end point, efficacy of antibiotics can really be put to a more stringent test as has been demonstrated in previous studies (19) from this laboratory with streptococcal (11, 16, 20-22), staphylococcal (11, 14, 15, 17, 23-25), tularemic (7), and rickettsial infections (13, 26). As in the evaluation of a patient's disease, one must attempt to relate the role of drug toxicity in the overall picture of the underlying disease in general and superimposed infection in particular. In the present study, 1 of 13 monkeys died from effects related to vincristine alone with a *Proteus mirabilis* enteritis. Severe enteritis is not an uncommon complication in monkeys made cytopenic, as demonstrated in earlier studies from this laboratory with nutritional cytopenia (27, 29), or after total body irradiation (12). It is not the purpose of this paper to discuss the toxicology and pharmacology of VCR which has been described in detail previously (10). In this latter study, leukopenia was generally observed in a variety of animals including monkeys, and no characteristic laboratory or gross findings at autopsy in animals receiving toxic doses. In the subsequent use of this

model in evaluating comparative efficacy of antibiotics, certain animals had to be excluded from such studies due to significantly great toxicity effects and will be discussed in detail in a separate report. In essence, of 159 monkeys given VCR, 134 or 84.3% were suitable for use in *Pseudomonas* challenge based on their general appearance four days after administration of VCR, and were employed in studies of comparative efficacy of antibiotics.

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