the course of treatment in Fig. 1. The peak values for both blood and urine were recorded for the first specimen collected after the initial dose, *i.e.*, at 2 hours. Subsequently, the blood levels steadily fell in both subjects and detectable amounts of drug were not demonstrable at 8 hours or thereafter. The urine levels of drug were approximately 200 γ/cc at 2 hours; they fell to approximately 50 γ/cc at 8 hours and remained at about that level for the next 10 days of treatment. During and immediately following the test no significant changes occurred in the blood of either subject as revealed by determination of hemoglobin, erythrocytes and leukocytes and by examination of blood smears. Urinalysis on the third day of therapy showed no abnormalities.

Data on the volunteers who received an initial dose of 2.0 g of Chloromycetin plus 0.5 g 8 hours later are given in Fig. 2. Relatively high levels of drug were found in the blood of both volunteers only 30 minutes after the antibiotic was first given by mouth; furthermore, at this time drug was already present in the urine in appreciable amounts. The blood levels were still well above 10 γ/cc at 2 hours and were above 5 γ/cc at the end of 8 hours. Urine levels were at their maxima at 2 hours reaching values of 670 and 380 γ/cc, respectively, in the subjects. The amounts diminished rapidly in successive samples and dropped to about 10 γ/cc at 8 hours.

Approximately 10% of the total amount of Chloromycetin given daily was recovered in an active form in the urine of both groups of volunteers.

No symptoms or signs of toxic effects attributable to the drug were observed by the 3 volunteer physicians either during the treatment or subsequently.

Conclusion. These limited trials indicate that Chloromycetin can be given orally to normal adult males in single doses of 2.0 g, or in daily doses of 1.0 g for 10 days without untoward reactions. The presence of appreciable amounts of drug in the blood and urine of volunteers 30 minutes after oral administration of Chloromycetin indicates that the antibiotic is absorbed rapidly from the gastrointestinal tract of man. Excretion or inactivation of the drug occurs rather rapidly, hence, in order to maintain appreciable levels of the antibiotic in the blood, frequent administration of the drug is indicated.

16378

Chloromycetin in the Treatment of Patients with Typhus Fever.

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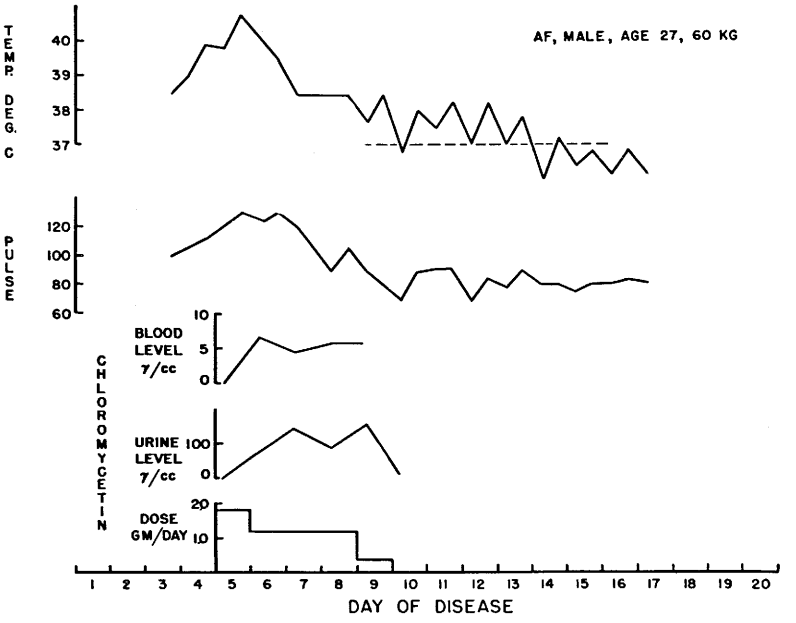
Recent reports indicate that Chloromycetin is effective in the treatment of experimental infections caused by *R. prowazeki*[1,2] and *R. mooseri* as well as other rickettsial and viral agents.[2] Data reported elsewhere[3] show that Chloromycetin can be given to normal men without untoward effects and that the levels of drug in the blood and urine of treated persons can be followed. This paper summarizes the information gained from the study of a small group of patients with typhus fever who were treated with Chloromycetin.

Materials and Methods. The patients studied in the current investigation were hos-

1 Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., and Burkholder, P. R., *Science*, 1947, **106**, 417.

2 Smadel, J. E., and Jackson, E. B., *Science*, 1947, **106**, 418.

3 Ley, H. L., Jr., Smadel, J. E., and Crocker, T. T., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 9.



RASH		00	++	++	+	+	0	0	0	
WBC (X1000)			5.7	3.5	3.6	2.9	6.9			
HBG (GM)			12.2		9.8	9.5	9.5			
WEIL	OX 19	80		2560		5120				5120
FELIX	OX 2	0		0		40				320
RICK.	EPIDEMIC	0		160		1280				10240
AGGLN.	MURINE	0		40		320				2560
RICK.	EPIDEMIC	0		0		10				1280
C.F.	MURINE	0		0		0				0

FIG. 1.

pitalized in Mexico, D.F.* Crystalline Chloromycetin prepared in 0.1 g tablets for oral administration was supplied by the Research Laboratories of Parke, Davis and Company. Chloromycetin levels in the blood and urine of patients were determined by a modification of the method of Joslyn and Galbraith.[4] Specific rickettsial complement-fixation and agglutination tests were performed according to the standard procedure of the Army Medical Department Research and Graduate School.[5] The results of the Weil-Felix tests recorded on the graphs were done by the technique employed at the School;[5] comparative studies in which sera were tested with proteus antigens prepared at the School and at the Institute by the techniques employed in both laboratories gave comparable results. León's technique,[6] for the demonstration of specific typhus antigen in the urine of early typhus patients, was employed in two of the treated patients and

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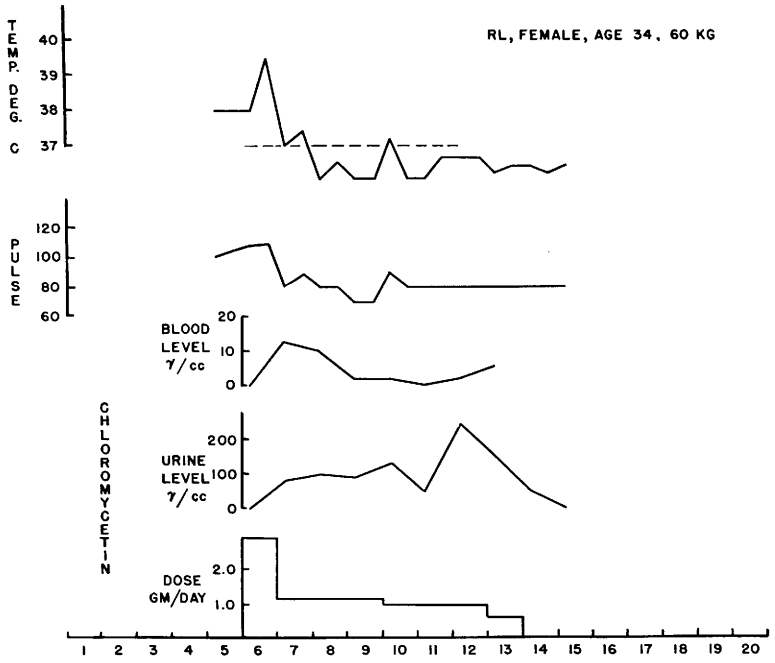
4 Joslyn, D. A., and Galbraith, M., personal communication, 24 October, 1947.

5 Plotz, H., "The Rickettsiae," chapter 32 in *Laboratory Methods of the United States Army*, edited by Simmons, J. S., and Gentzkow, C. J., Lea and Febiger, Philadelphia, 1944, pp. 559-578.

6 León, A. P., *Rev. Inst. Salub. y Enf. Trop.*, 1942, **3**, 201.

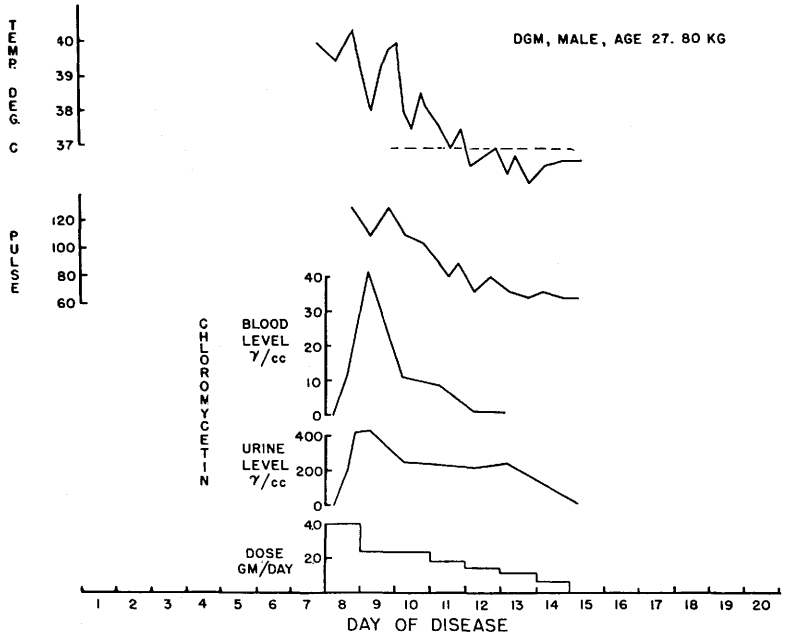


RASH			++	++	++	+	+	0	0	0				
LEONS TEST			Pos (1/8)											
WBC (X 1000)			12.4	10.4	7.6			7.3			10.7			
HBG (GM)			12.1	11.1	11.5			12.3				13.2		
WEIL	OX 19	40				80	80	160	160	160		160		
FELIX	OX 2	0				0	0	0	0	0		0		
RICK. AGGLN.	EPIDEMIC	80				640	1280		1280			1280		
	MURINE	40				80	160		320			160		
RICK. C.F.	EPIDEMIC	80				640	1280		1280	1280+		640		
	MURINE	5				80	160		320	160		160		

FIG. 2.

found to be positive in each instance.

Results. Five patients with typhus fever were treated with Chloromycetin. More complete and definitive information was obtained on the 3 adults than on the 2 children; therefore, each of the former will be discussed in some detail while the latter will be presented briefly. Data on the first patient A.F., are given in Fig. 1. This man received an initial dose of 1.0 g of drug by mouth on the morning of the fifth day of illness and subsequently was given 0.2 g every 4 hours throughout the next 3 days and part of the fourth day. The levels of Chloromycetin in the blood and urine of this patient ranged around values of 5 and 100 γ per ml, respectively. During the course of therapy the white blood cells diminished progressively from 5,700 on the fifth day of disease to 2,900 on the eighth day. At this point ideas were entertained about the possible relationship between the drug and the leukopenia. These were dismissed on the ninth day when the patient's white cell count rose to 6,900 while he was still on therapy. There was a reduction in the hemoglobin content of the blood between the fifth and seventh days, however, it was assumed that the patient actually had a moderate anemia at the onset of his illness and that the initial value of 12.2 g was dependent upon hemoconcentration during the period of high fever. The serological data presented in Fig. 1 indicate that this patient had epidemic typhus. It is difficult to say how much patient A.F. was

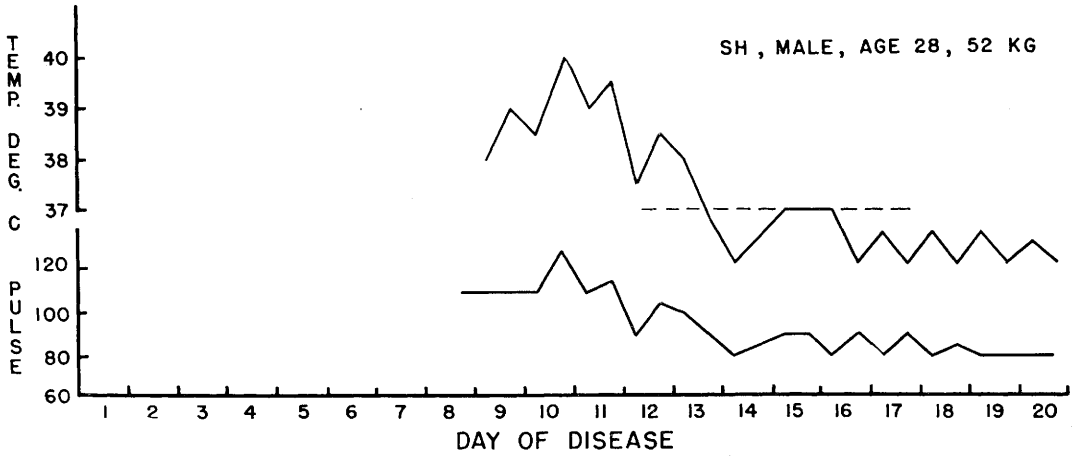


DELIRIUM						++	++	++	++	0	0	0							
RASH						+++	+++	+++	+++	+++	++	+	0	0	0				
WEIL	OX 19	640				5120			5120						5120				
FELIX	OX 2	0				80			80						80				
RICK. AGGLN.	EPIDEMIC	40						5120							10240				
	MURINE	0						640							1280				
RICK. CF.	EPIDEMIC	0						0							80				
	MURINE	0						0							0				

FIG. 3.

benefited by treatment with Chloromycetin. In retrospect, it was the impression of the group that patient A.F. had been treated with doses of drug which were too small and that the antibiotic had been given for too short a period of time.

Patient R.L., whose record is summarized in Fig. 2, lived with patient A.F. Her disease, characterized initially by feverishness and headache, began on the day that patient A.F. was hospitalized. She had a cutaneous rash when admitted on the fifth day of her illness. León's test performed with a sample of her urine taken on the morning of the sixth day gave a positive reaction; a Weil-Felix test on serum obtained at this time was positive at a dilution of 1/40. The patient was given 2.0 g of Chloromycetin at noon on the sixth day. At 1:00 p. m. she vomited and was promptly given 0.5 g of Chloromycetin. This was followed by administration of 0.2 g every 4 hours until the morning of the 13th day of her illness. The blood level of Chloromycetin reached 11.5 γ per ml on the morning of the second day of treatment and remained in this range the next day, but subsequently dropped to a value of about one γ per ml, see Fig. 2. The urine level ranged around 100 γ per ml for several days but reached 220 γ per ml on the seventh day of treatment. The abrupt return of the patient's temperature and pulse to the normal range following administration of Chloromycetin at first led to the suspicion that she did not have typhus, but the serological data subsequently indicated that this woman was infected with *R. prowazeki*. Other clinical abnormalities abated more slowly than the fever; thus, on the morning of the seventh day when the temperature was 37°C, the rash remained unchanged, the patient

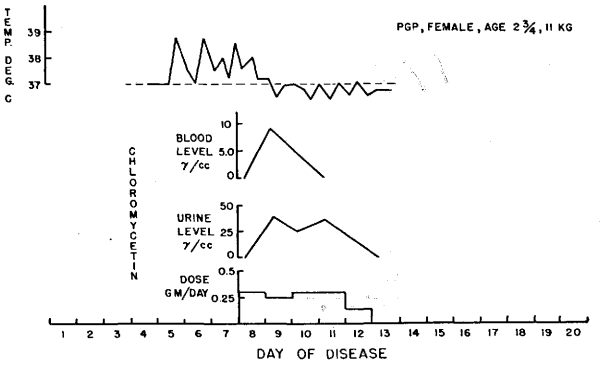


RASH		++ ++ ++ + 0 0 0		
WEIL FELIX	OX 19	160	160	320
	OX 2	0	40	40
RICK. AGGLN.	EPIDEMIC	2560	5120	10240+
	MURINE	320	1280	2560
RICK. C.F.	EPIDEMIC	160	160	320
	MURINE	0	0	0

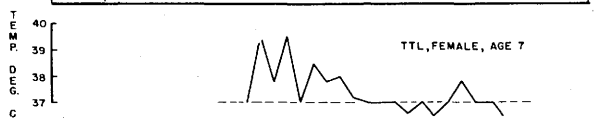
FIG. 4.

complained of headache and insomnia, and she still had flushed facies and conjunctival injection, as well as slight tremor of the tongue. The following day the patient was much improved and on the ninth day after onset she had no complaints, the rash was fading, and the conjunctival injection as well as the tremor and dryness of the tongue were gone. On the 12th day the patient was cheerful and sat up in bed. She was discharged from the hospital on the 15th day after onset.

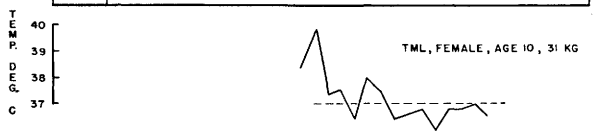
Patient D.G.M. was admitted to the hospital on the seventh day of an illness which appeared typical of typhus fever. He was extremely ill with a fever of 40°C and had an extensive, discrete macular rash which was not yet hemorrhagic. The Weil-Felix test at this time was positive at a dilution of 1/640. At 1:00 p. m. on the eighth day of illness the patient was given 1.5 g of Chloromycetin by mouth, this was repeated at 2:00 p. m. Subsequently he received 0.2 g every 2 hours day and night until the morning of the 11th day at which time the dosage was reduced to 0.2 g every 3 hours. The following day the drug was further reduced to 0.2 g every 4 hours and the drug was discontinued on the morning of the 14th day. The blood level of Chloromycetin rose rapidly and reached a value of 40.5 γ per ml at 8:00 a. m. on the morning of the second day of therapy; similarly the urine level had risen progressively and reached a value of 400 γ per ml at this time, (See Fig. 3.) During the next few days the blood level of drug ranged between 10 and 5 γ per ml and the urine around a value of 100 γ per ml. Although the temperature dropped to 38°C on the morning after therapy was begun, the patient showed no other obvious evidence of improvement; the semidelirium continued, the rash had become petechial in some areas, the conjunctivae were still markedly injected, and fine tremors of the tongue and extended fingers continued unabated, furthermore, that afternoon the temperature returned to 40°C. On the morning of the tenth day the temperature was 37.5°C, the cutaneous lesions were unchanged and delirium still persisted. Despite the pos-



WBC (X 1000)		9.2			
HBG (GM)		8.5			
WEIL	OX 19	5120+	5120+	5120+	5120+
FELIX	OX 2	0	80	80	80
RICK.	EPIDEMIC	160	320	320	160
AGGLN.	MURINE	1280	2560	2560	5120
RICK.	EPIDEMIC	0	0	0	0
C.F.	MURINE	0	0	0	80



RASH		+	+	+	0	0	0
WEIL	OX 19			1280		2560	
RICK.	OX 2			320		320	
RICK.	EPIDEMIC			80		640	
AGGLN.	MURINE			1280		2560	
RICK.	EPIDEMIC			0		640	
C.F.	MURINE			0		80	



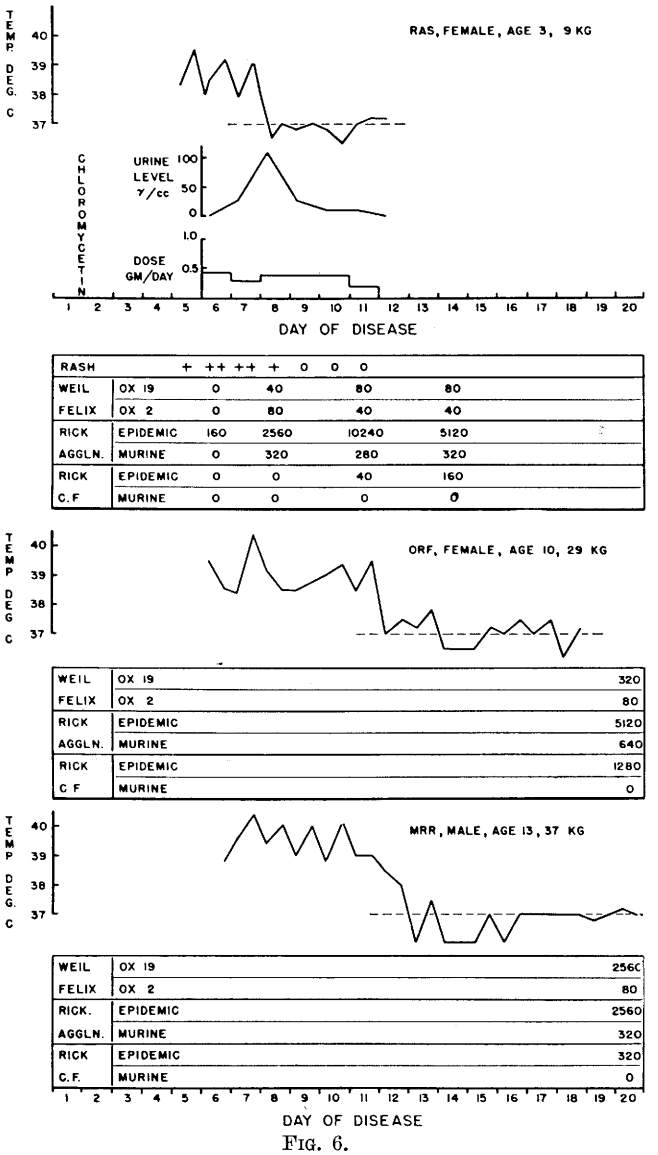
WEIL	OX 19	2560	5120
FELIX	OX 2	160	640
RICK.	EPIDEMIC	40	320
AGGLN.	MURINE	320	5120
RICK.	EPIDEMIC	0	0
C.F.	MURINE	0	0

WEIL	OX 19	320	160
FELIX	OX 2	40	0
RICK.	EPIDEMIC	320	320
AGGLN.	MURINE	5120	2560
RICK.	EPIDEMIC	0	0
C.F.	MURINE	0	80

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
DAY OF DISEASE

FIG. 5.

sibility that the drug therapy might be contributing to the delirium, Chloromycetin was continued. The next day the patient's temperature was normal and he was lucid; therefore, it is assumed that the drug had not played any role in producing the patient's confused mental state. The improvement from the 11th day was obvious. It was the impression of the group that this patient represented an extremely severe case of epidemic typhus, in



RASH		+	++	++	+	0	0	0
WEIL	OX 19	0		40		80		80
FELIX	OX 2	0		80		40		40
RICK	EPIDEMIC	160		2560		10240		5120
AGGLN.	MURINE	0		320		280		320
RICK	EPIDEMIC	0		0		40		160
C.F	MURINE	0		0		0		0

WEIL	OX 19	320
FELIX	OX 2	80
RICK	EPIDEMIC	5120
AGGLN.	MURINE	640
RICK	EPIDEMIC	1280
C F	MURINE	0

WEIL	OX 19	2560
FELIX	OX 2	80
RICK.	EPIDEMIC	2560
AGGLN.	MURINE	320
RICK	EPIDEMIC	320
C.F.	MURINE	0

FIG. 6.

whom the prognosis on the eighth day was ominous, who recovered more rapidly than one would have expected.

Fig. 4 summarizes the data on temperature, pulse and serological response of an untreated adult case of epidemic typhus observed in the Hospital General during the period of study.

During the investigation 7 cases of typhus fever were followed in the Hospital del Niño. On the basis of serological findings, 4 of these subsequently were proved to be murine typhus and 3 epidemic typhus. One child with each type of disease was treated with Chloromycetin; the detailed records on these 2 treated children are illustrated in Fig. 5 and 6, respectively. Fig. 5 also contains information on the 3 untreated children who had murine typhus, and Fig. 6 the data on the 2 untreated children with epidemic typhus. In general, the children received orally amounts of drug which were comparable to that given to adult patients on the basis of body weight. Thus, patient P.G.P. received about as much as A.F., the first patient treated,

and patient R.A.S. was given a dosage intermediate between that given to adults A.F. and R.L. Typhus fever in children is generally so mild that evaluation of any therapeutic agent is extremely difficult even when large numbers of cases are investigated. It was our impression that Chloromycetin therapy produced no untoward effects in these children and may have been of some benefit.

Conclusion. On the basis of these limited observations, it may be concluded that the administration of Chloromycetin to patients with typhus fever is a relatively safe procedure. Furthermore, the chemotherapeutic effect obtained in the few patients treated was sufficiently encouraging to warrant further tests with the drug. It is suggested that chloromycetin be employed in oral treatment of the next group of patients to be studied according to the following schedule; an initial dose of 40 mg per kilo body weight followed by a total daily dose of 35 mg per kilo body weight, given in divided amounts at 2-hour intervals, until obvious improvement in the patient's condition is noted; subsequently maintenance dose of 20 mg per kilo body weight per day given in divided amounts at 4-hour intervals, until the 13th or 14th day after onset.

16379

Active and Inactive Murine Poliomyelitis Virus as Interfering Agents Against Poliomyelitic Infection in Monkeys.*

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It has previously been shown that live mouse-adapted human poliomyelitis virus has the ability of interfering with the propagation of simian poliomyelitis virus in rhesus monkeys. Such interference is demonstrable (a) by the intracerebral injection of a mixture of murine (SK, MM) and simian (Aycock, RMV) virus, or (b) by the peripheral administration of large amounts of murine virus during the early incubation period of poliomyelitic infection.[1] The mechanism of this antagonism is not known even though several hypotheses have been advanced as possible explanations.[2,3]

In an attempt to throw more light on this problem it seemed of interest to investigate whether the interfering effect can be elicited with inactivated or attenuated murine virus as well as with active virus. The following report deals with an exploration of this question. The murine virus used was the MM strain, the simian virus was the Aycock strain. The methods chosen for inactivation were (a) desiccation, (b) exposure to radioactive sodium, (c) ultraviolet irradiation, and (d) chlorination.

Methods: Desiccation. Brains from infected mice were harvested at the height of paralysis, placed in an open Petri dish, and dried in a desiccator over sodium hydroxide at 37°C., 20-22°C or 4°C for various lengths of time. The procedure was carried out either *in vacuo* or in nitrogen atmosphere. It was found that the virus preserved its full virulence (10^{-9} to 10^{-10} i.c. or i.p.) for the longest period tested, *i.e.* 20 days, when dried in the icebox at 4°C. At room temperature (20-22°C.) the virus suffered a progressive loss of virulence

* Aided by grants from the Philip Hanson Hiss, Jr., Memorial Fund and from anonymous donors.

1 Jungeblut, C. W., and Sanders, M., *J. Exp. Med.*, 1940, **72**, 407; Sanders, M., and Jungeblut, C. W., *J. Exp. Med.*, 1942, **75**, 631; Jungeblut, C. W., and Sanders, M., *J. Exp. Med.*, 1942, **76**, 127.

2 Jungeblut, C. W., *J. Exp. Med.*, 1945, **81**, 275.

3 Gard, S., *Acta Med. Scand.*, 1944, **119**, 27.