

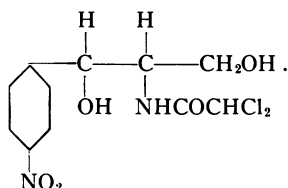
# CHLORAMPHENICOL (CHLOROMYCETIN), AN ANTIBIOTIC. PHARMACOLOGICAL AND PATHOLOGICAL STUDIES IN ANIMALS<sup>1, 2, 3</sup>

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Chloramphenicol is an antibiotic which initially was isolated from culture filtrates of the fungus *Streptomyces venezuelae* (1-3) by Bartz (4) and subsequently was synthesized chemically (5-7).

Chloramphenicol (Chloromycetin) is a pure chemical substance, *D*(-)*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol, and has the following chemical structure



It is a neutral white crystalline substance with a bitter taste and is stable in neutral and acid solutions. The drug is moderately soluble in water (0.25 per cent at room temperature, 0.65 per cent at 70° C and up to 15 per cent in propylene glycol, 5 per cent in 50 per cent acetamide), and is insoluble in vegetable oils. Solubility in urine or serum is about the same as in water. Solutions are stable on heating.

Material for this study consisted of crystalline chloramphenicol obtained from culture filtrates, and the synthetic product.

Chloramphenicol was administered intravenously in aqueous propylene glycol or acetamide solutions to small animals at a rate of 0.1 cc. per ten seconds; dogs received 1.0 to 3.0 cc./min. Acute toxicity results are based on a seven- to 14-day observation period and chronic tolerance studies were carried out for two to four weeks in small animals and for periods of three and five weeks and over four months in dogs. The Dragstedt *et al.* (8) method served to interpolate results.

<sup>1</sup> Presented at the Second National Symposium on Recent Advances in Antibiotics Research held in Washington, D. C., April 11-12, 1949, under the auspices of the Antibiotics Study Section, National Institutes of Health, Public Health Service, Federal Security Agency.

<sup>2</sup> Chloramphenicol is a generic name coined from the chemical structure of the compound.

<sup>3</sup> *Chloromycetin* is a designated trade mark under which it was originally studied in the laboratory.

## Acute Toxicity

Intravenous administration of a 0.5 per cent aqueous solution of chloramphenicol to 20-gram white mice caused slight transient ataxia with 125 to 150 mg./kg. doses. At lethal or near-lethal doses of 175 to 300 mg./kg., the mice became incoordinated, some were flaccidly prostrate and dyspneic, and death occurred within a few minutes from respiratory failure. The surviving animals appeared normal within a few minutes to one-half hour. Intraperitoneal and oral administration of toxic doses produced similar reactions. Perorally in single doses mice showed a slight dyspnea with 1.5 grams/kg. and dogs were free of reactions at 150 to 200 mg./kg. once or twice daily. Administration of a two-fold increase in the above amounts to dogs produced sporadic vomiting, acute diarrhea, irritability, occasional spasticity and clonic convulsive seizures. The comparative toxicities of the fermentation and synthetic products were nearly identical (Table I).

Intravenous administration of chloramphenicol to adult dogs in 60 to 87 per cent propylene glycol solution at a rate of 3 cc./min. caused transient rise of body temperature of 0.6 to 1.7° F. corresponding to temperature changes from equivalent amounts of propylene glycol alone. The pulse rate had a tendency to become slightly depressed, while the respiration rate increased. A transient hematuria appeared with 150 mg./kg. doses without progressive histopathologic changes in the kidneys. The hemogram was not altered in a seven-day observation period.

When chloramphenicol as a 10 per cent solution in propylene glycol was administered repeatedly at 30-minute intervals, 1 cc./min., intravenously to dogs under pentobarbital anesthesia and the carotid blood pressure and respiratory excursions were recorded by conventional methods,<sup>4</sup> no alteration in blood pressure or amplitude of excursions and respiratory rate occurred at 12.5 to 25 mg./kg.

<sup>4</sup> By Graham Chen.

TABLE I  
*Acute parenteral and oral toxicity of chloramphenicol prepared synthetically or by fermentation*

Animal	Route	Material and diluent	Number animals	M.T.D.* LD <sub>0</sub>	LD <sub>50</sub>
				mg./kg.	mg./kg.
Albino Mice	I.V.	Fermentation, 25–28% propylene glycol	455	50	109.5
	I.V.	Fermentation, water	964	125	195.4
	I.V.	Synthetic, water	375	125	202.6
	I.P.	Fermentation, acacia-water suspension	280	750	1320.0
	I.P.	Fermentation, water	170	625	1320.0
	Oral	Fermentation, acacia-water suspension	270	1500	2640.0
Albino Rats	I.V.	Fermentation, 60% propylene glycol	438	100	175.5
	I.V.	Synthetic, 60% propylene glycol	239	100	170.5
	I.V.	Fermentation, 50% acetamide	518	200	279.4
	I.V.	Synthetic, 50% acetamide	140	225	278.0
Dogs	I.V.	Fermentation, 75–85% propylene glycol	7	150**	—
	I.M.	Fermentation, peanut oil suspension	3	>101	—
	I.M.	Fermentation, 62% propylene glycol	8	>46.5	—
	Oral	By capsule, powder	7	>300	—
Rabbits	I.V.	Fermentation, 100% propylene glycol	25	75	117.0

\* Maximal tolerated dose (M.T.D.)—Survival of 100 per cent of animals.

\*\* Renal hemorrhage was frequent.

doses of chloramphenicol. An 11 and 71 per cent decrease in blood pressure occurred with 50 and 100 mg./kg. doses respectively and this was accompanied by slight increase in respiration rate and decrease in amplitude. Single doses to individual animals caused no blood pressure changes with 12.5 and 25 mg./kg., a fall of about 7 to 10 per cent was produced with 50 and 100 mg./kg. Increasing the injection rate had a tendency to cause a "speed-shock" and a 150 mg./kg. dose at 4 cc./min. produced a 97 per cent fall in blood pressure and death from respiratory failure. Analogous volumes of propylene glycol alone caused 5 to 10 per cent fall in blood pressure on repeated injections in the same animal and none when given in single doses to different animals (Figures 1 and 2).

### Chronic Toxicity

In chronic tolerance studies different dose levels of chloramphenicol were administered to different groups of mice, guinea pigs, rats, rabbits, and dogs. All animals were observed daily for food consumption, reactions and weekly body weight changes. Blood counts were made on guinea pigs, rats and dogs. The blood non-protein nitrogen, bromsulfalein liver and phenolsulfonphthalein kidney functions, urine analysis for albumin and sugar, and methemoglobin values were determined in dogs. The blood and urinary concentration of chloramphenicol was determined on mice, guinea pigs and dogs.

Urine volume excretion was determined in mice and dogs. The maximal tolerated doses (M.T.D.) which caused no reactions and produced only slight or no depression of normal body weight gain in animals and the 50 per cent lethal doses (LD<sub>50</sub>) are shown in Table II.

Subcutaneous injections of 50 to 100 mg./kg. twice daily in 10–20 per cent propylene glycol solution to 20-gram mice for 14 days showed a slight to 10 per cent weight gain depression. With 200 and 400 mg./kg. doses, the mice refused food and lost weight, and death of 20 and 100 per cent of animals occurred on respective doses. The sites of repeated injections became indurated and ulcerated. Death was due to anorexia and cachexia, complicated by ulcerations penetrating the abdominal wall.

When chloramphenicol was given to 20-gram mice in the diet, normal growth of animals was maintained on 0.125 and 0.25 per cent concentrations (203 and 385 mg./kg. per day) but with 0.5, 1.0 and 2.0 per cent concentrations (respectively 679, 1290 and 2060 mg./kg. daily) for a two-week period, mice lost from 0.85 to 4.0 grams in weight from anorexia without showing other reactions.

Oral administration to mice by cannula in acacia-water suspension of about 215 mg./kg. twice daily for four weeks caused no anorexia and allowed normal growth rate. A 311 mg./kg. dosage

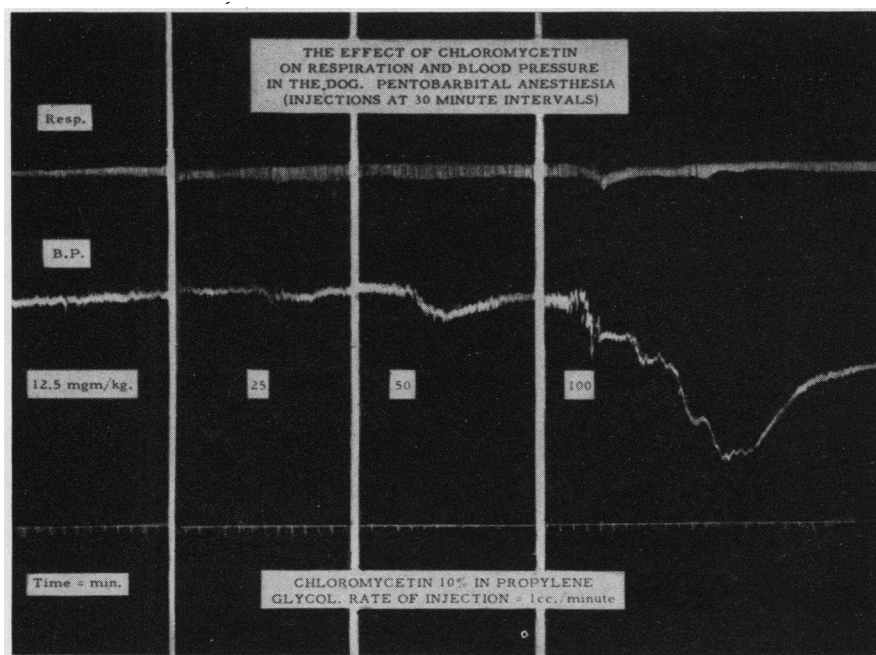


FIG. 1. INTRAVENOUS INJECTIONS OF CHLORAMPHENICOL IN ANESTHETIZED DOGS

Repeated injections caused no blood pressure changes with 12.5 and 25 mg./kg. A slight depression occurred with 50 mg./kg. and a rapid fall with 100 mg./kg. accompanied by decrease in amplitude and increase of respiratory rate. Increasing speed of injection to 4 cc./min. a 150 mg./kg. dose produced 97 per cent fall in blood pressure and death from respiratory failure.

twice daily produced death of 30 per cent of the animals. It was evident that daily oral intakes in mice of 385 to about 425 mg./kg. in divided doses constituted about the maximal tolerated amounts of chloramphenicol, whether administered in the food or by cannula.

Guinea pigs had considerable aversion to the diet (rabbit chow pellets) (9) containing chlo-

ramphenicol. This was overcome in part by starting animals first on 0.125 per cent (90<sup>5</sup> mg./kg. daily) and increasing the concentration for the second week to 0.25 per cent (153<sup>5</sup> mg./kg.) and to 0.5 per cent (256<sup>5</sup> mg./kg.) in the third week. On this schedule, guinea pigs maintained or increased their weight. When placed initially on a

<sup>5</sup> Actual amount ingested per day.

TABLE II  
*Chronic toxicity of chloramphenicol*

Animal	Mode and duration of administration	M.T.D.	LD <sub>50</sub>
		mg./kg./day	mg./kg.
Albino Mice	In diet ration, daily ingestion for 2 weeks	385	> 2060
	By cannula, in two divided doses daily for 4 weeks	425	> 622
	Subcutaneously in propylene glycol daily for 2 weeks	100	275
	Intraperitoneally in water once daily for 2 weeks	250	> 600
Guinea Pigs	In diet ration, daily ingestion for 2 to 4 weeks	250 (0.5%)	538 (1.0%)
Dogs	Orally by capsule for 3 and 5 weeks and over 4 months in two divided doses daily	> 200	—
	I.M. in propylene glycol for 24 days in two divided doses daily	> 74-93	—
	Orally by capsule for 7 days in single daily doses	> 300	—
Rabbits	I.M. in propylene glycol for 8 days in two divided doses daily	> 100	—

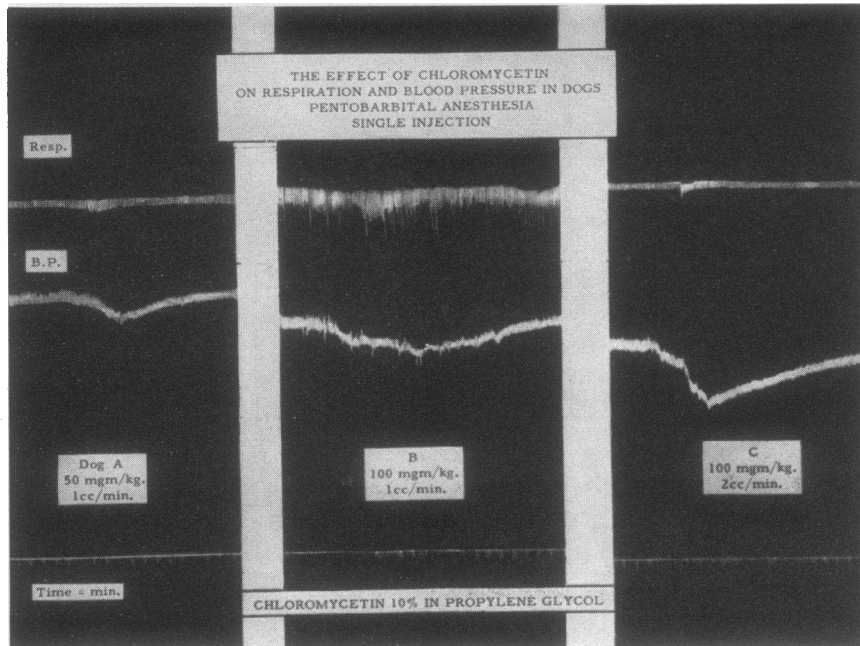


FIG. 2. INTRAVENOUS INJECTION OF CHLORAMPHENICOL IN ANESTHETIZED DOG(S)

Single injections of 50 and 100 mg./kg. at a rate of 1 cc./min. caused a slight blood pressure fall (7 to 10 per cent); doubling the injection rate caused the blood pressure to fall about 31 per cent.

0.5 per cent diet concentration, the animals consumed about one-third of the normal food intake for the first week and about three-quarters of normal subsequently. On a 1.0 per cent concentration in the diet, they consumed about one-fourth of normal food intake, lost on an average of 117 grams in weight in two weeks and six out of eight died from cachexia. The two surviving guinea pigs were cachectic, showed a slight hemoglobin concentration (120 per cent versus controls of 104 per cent), with rise of neutrophils to 77 per cent (controls 44 per cent), and the total white cell count remained about unchanged.

#### *Intramuscular Tolerance in Dogs*

A group of three young, recently acquired, street dogs weighing 11 to 14 kg. each and showing initial clinical symptoms of "distemper" (a slight body temperature rise, conjunctivitis and serous rhinitis) were each injected intramuscularly twice daily with 0.5 gram of the fermentation process chloramphenicol partly dissolved in 2 cc. of 62 per cent propylene glycol for 38 doses in 24 days. In the first seven to ten days of treatment the temperature of the dogs rose to 103.2 to 106° F. and

receded to normal at ten, 19, and 21 days respectively under treatment. During the fever period the dogs developed anorexia and considerable anemia with 2.5, 3.4 and 4.2 million erythrocytes per cu. mm. respectively. The red cell counts rose to 4.0, 3.4 and 5.5 million as the fever declined and the appetite of the dogs improved. Injections were followed by considerable to severe local tissue induration, extensive edema, hemorrhage and necrosis. Tentatively it was assumed that the anemia was associated with "distemper" and probably the severe local tissue changes were a contributory factor. Autopsy and microscopic tissue examination showed no significant pathologic changes in the liver, spleen, kidneys and other visceral organs, while the lungs showed residual inflammatory foci.

#### *Oral Tolerance in Dogs*

Initially 800 mg. or 86 mg./kg. of the fermentation process crystalline chloramphenicol was given to a dog, a single dose orally in a gelatin capsule. The animal remained free of systemic or gastrointestinal reactions. Two dogs were given 300 mg./kg. daily as a single dose for four days. Ani-

mals showed anorexia, lost weight and vomited occasionally. Rise of body temperature of 0.8 to 1.4° F. occurred on the first day; the temperature was normal subsequently. Two other dogs received 200 mg./kg. twice daily for 32 doses in 21 days. These animals developed severe anorexia, adipsia and lost 2.5 to 4.5 kg. in body weight. At the end of the third week the urine showed casts and a large amount of albumin. The body temperature remained normal. Another dog, fed 0.5 gram (73 mg./kg.) twice daily for 38 doses in 24 days, remained asymptomatic. This animal was studied for hematologic, bromsulfalein liver function, blood sugar and total non-protein nitrogen changes. The various test results showed normal values, and the urine remained free of albumin and sugar. Three additional dogs were given 75 mg./kg. twice daily of the fermentation product for 66 doses in 39 days and seven dogs were given synthetic chloramphenicol, 50, 75 and 100 mg./kg. twice daily respectively for 194 doses in 133 days. The dogs of the former group were fed chloramphenicol six days, and the latter five days each week. The daily dosage for each dog was adjusted at weekly intervals to the gain or loss in body weight. The animals of both groups remained in good physical condition; the first group gained 0.55 to 0.85 kg., the second group, 0.45 to 2.75 kg., while two animals remained about stationary (−0.25 to +0.3 kg.). Gastro-intestinal

reactions occurred rarely; one dog vomited once after the 30th dose (50 mg./kg.), the second animal vomited once after each of the 153rd and 166th doses, and a third animal after the 173rd dose (100 mg./kg.). No diarrhea was encountered. The animals showed no disturbances of vision, hearing or somatic reflexes. The urine remained free of sugar and albumin, but occasionally following catheterization injury, blood appeared in urine. The body temperature remained normal except in one animal following catheterization injury and ensuing cystitis. Blood pressures were determined three times on each dog of the second group by an indirect tail plethysmograph method and the readings fluctuated in a normal range of 135 to 165 mm. of mercury, while six untreated dogs showed blood pressure range of 135 to 172 mm. Examination of tissues at autopsy revealed no gross pathologic changes, except focal inflammatory hemorrhagic areas of the urinary bladder of an animal with chronic ulcerative cystitis. Volume of daily urine excretion was in the range of normal dogs.

The hematology in these dogs remained relatively unchanged, although roughly about 300–350 cc. of blood were withdrawn from each dog for chloramphenicol determinations, N.P.N. and blood count studies (Figure 3). In one of these dogs the red cell counts decreased to 4.9 million per cu. mm. and hemoglobin values to 85 per cent. Autopsy revealed ulcerative cystitis and atrophic

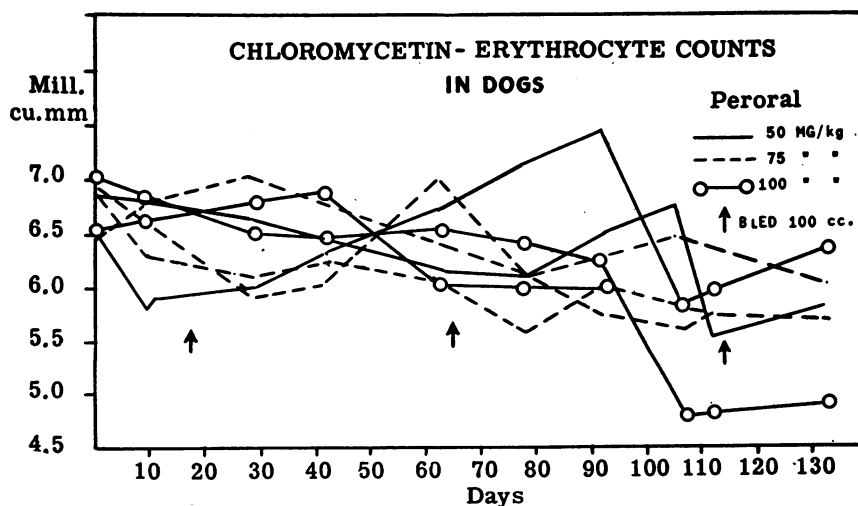


FIG. 3. RED CELL COUNTS IN DOGS WHICH RECEIVED CHLORAMPHENICOL FOR 194 DOSES IN 134 DAYS AND SUBJECTED TO FREQUENT HEMATOLOGIC AND BIOCHEMICAL STUDIES REMAINED ESSENTIALLY AT NORMAL LEVELS.

stomach mucosa. The leucocyte counts of treated animals remained in normal range and varied slightly from the pre-treatment values of 7,400 to 15,900, average of 12,400, to the last counts of 10,200 to 14,100 per cu. mm., average of 12,900. The animal with chronic cystitis and atrophic gastritis had an initial count of 18,200 leucocytes per cu. mm. and it remained at this level until the last three weeks when the leucocytes rose to 33,000 and the temperature to 103.3° F. The total blood non-protein nitrogen in the latter animal remained in a normal range (32–46 mg. per cent). The differential counts in the above dogs ranged from 71 to 90 per cent neutrophils prior to chloramphenicol administration and during the treatment period 80 to 90 per cent neutrophils, 10 to 17 per cent lymphocytes and scattered eosinophils and mononuclear cells. No tendency to agranulocytosis or abnormal cell morphology was observed.

The total blood non-protein nitrogen was determined in the morning before dosing, five to nine times on each dog. In this group of dogs the normal values ranged between 19 and 50 mg. per cent. Under chloramphenicol treatment non-protein nitrogen values showed sporadic fluctuation (Table III) which was not parallel to size of dosage or duration of treatment. Moreover, the fluctuation in values was not regularly sustained or cumulative, but paralleled the amount of meat

in the diet ration ingested previous to sampling.

Bromsulfalein liver function tests indicated dye retentions of less than 5 per cent in 30 minutes. Phenolsulfonphthalein excretion amounted to about 58 per cent at one hour as compared with 52 per cent in the pre-treatment period. Daily water intake was reduced by about 50 per cent of normal animals and the urine volume in treated dogs fluctuated from 21 to 32 cc./kg. in 24 hours as compared with 20 to 60 cc./kg. in the normal control period. Anuria was not in evidence, and the renal clearance of creatinine remained normal.

### Pathology

Pathologic tissue changes in non-toxic dose range of chloramphenicol were essentially absent. In the toxic range the pathology was related to a "shock-like" effect of chloramphenicol, resulting in prostration, severe respiratory depression or failure, fall of blood pressure, thready pulse, and anoxia. The visceral organs were congested with scattered petechial hemorrhages; the kidneys were moderately swollen and renal hemorrhage occurred on intravenous administration, probably due to propylene glycol (10). The animals either died from respiratory failure within a few minutes after intravenous administration or within two hours on oral administration. The tissues of surviving animals, at the end of the seven-day observation period, on microscopic examination, were essentially free of acute degenerative changes. Tissues of dogs on daily oral intake of 100 to 200 mg./kg. for over four months were free of acute or cumulative chronic degenerative changes except some hydropic changes in capillaries of the glomerulae. Since renal hemorrhage occurred on intravenous administration of maximal tolerated doses of propylene glycol solutions of chloramphenicol, the differential histopathologic changes are under further investigation and will be reported on at a later date.

### Blood Serum and Urinary Concentration and Excretion

A four-hour turbidimetric method (11), employing *Shigella sonnei* as a test organism, was used to determine chloramphenicol concentration in blood serum, urine, bile and spinal fluid. One µg./cc. is the threshold of the test sensitivity. In-

TABLE III

Total blood non-protein nitrogen in chloramphenicol-fed dogs

Dogs. ....	1	2	3	4	5	6	7	8	9	10	11
Blood sampled at days	Chloramphenicol in milligrams per kilogram twice daily										
	73	75	75	75	50	50	75	75	75	100	100
	Total blood non-protein nitrogen, milligrams per cent										
0	28	34	19	30	31	34	42	29	50	24	21
3	36	42		44	35						
10	51	27	26	21		39	58	35	60	27	40
17	54			32							
32		23	36	47	43	45	39	31	48	44	43
38		53	43	46					53		43
63					38	36	35	45		49	41
78					50	43	30	59	34	44	39
92					44	49	31	40	34	40	44
106					36	—	30	45	28	50	—
112					41	46	48	—	26	46	42
133					39	35	48	47	53	42	32
Average	48	36	35	36	41	42	40	43	42	42	40

travenous administration produced initial blood serum concentration of 17 to 45  $\mu\text{g./cc.}$  at 15 minutes, roughly proportional to 19 and 50 mg./kg. dosage. The serum levels rapidly decreased to below 1.0  $\mu\text{g./cc.}$  at four and six hours respectively (Figure 4). Intramuscular administration in peanut oil suspension of 90 to 101 mg./kg. produced serum levels of 1.5 to 7.5  $\mu\text{g./cc.}$  for a seven-hour period and less than 1  $\mu\text{g./cc.}$  at the 16th hour. When chloramphenicol in propylene glycol was given twice daily intramuscularly in doses of 37 to 46.5 mg./kg., the serum levels varied from 0 to 4  $\mu\text{g./cc.}$  at two hours after the first dose, 3 to 6  $\mu\text{g./cc.}$  at two hours after the second daily dose, and 0.0 to 1.0  $\mu\text{g./cc.}$  on the following morning. Oral administration in dogs of single doses of 86 and 150 mg./kg. provided serum levels from 8 to 39  $\mu\text{g./cc.}$  at two hours, 10.6 to 20  $\mu\text{g./cc.}$  at eight hours and less than 1  $\mu\text{g./cc.}$  at 12 hours. Dogs treated perorally twice daily for over four months were sampled four times at different 24-hour intervals and the average serum levels for an eight-hour period ranged from 6.2 to 9.8  $\mu\text{g./cc.}$  for the 50 mg./kg. dose, 19.1 to 25.8  $\mu\text{g./cc.}$  for the 75 mg./kg. dose and 26.6 to 36.4  $\mu\text{g./cc.}$  for the 100 mg./kg. dosage. The blood

serum contained no chloramphenicol 18 hours after the second daily oral dose. Bile contained 10 to 30  $\mu\text{g./cc.}$  at two hours after dosing and cerebrospinal fluid 0 to 2.5  $\mu\text{g./cc.}$  after the first and 3 to 4  $\mu\text{g./cc.}$  after the second 75 mg./kg. daily dosing. A dosage of 200 mg./kg. twice daily showed serum levels of 80, 120, 20 and 0 at six, eight, 12 and 24 hours respectively.

In mice following subcutaneous administration of 100 mg./kg. twice daily, the blood serum contained 11  $\mu\text{g./cc.}$  and urine 60  $\mu\text{g./cc.}$  Guinea pigs receiving perorally by cannula 750 mg./kg. showed 2.3  $\mu\text{g./cc.}$  of serum at two hours and none at four hours, and when given the same amounts subcutaneously in propylene glycol, the serum contained 7.8  $\mu\text{g./cc.}$  at 30 minutes, 10.1, 3.9, 2.3, and 2.2  $\mu\text{g./cc.}$  at two, eight, 16 and 24 hours respectively, indicating that chloramphenicol orally in guinea pigs is either poorly absorbed or rapidly degraded in the body.

#### Urinary Excretion

Urine was collected from dogs by catheterization, and from small animals in a metabolism cage. Chloramphenicol concentration in urine attained maximum levels at two to eight hours, depending

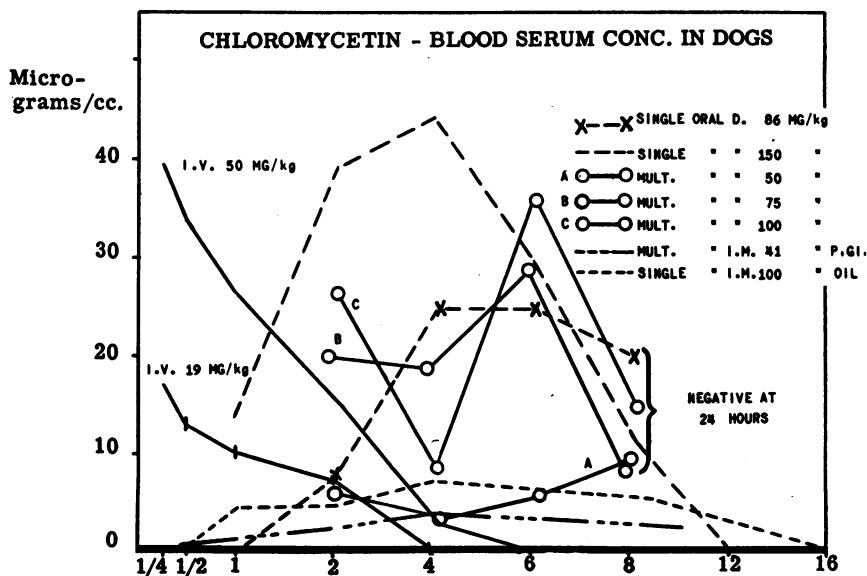


FIG. 4

Maximum serum levels occurred between two and six hours following oral administration and serum was negative in 12 to 24 hours. Chloramphenicol disappeared rapidly from serum on intravenous administration with negative findings at four to six hours.

upon mode of administration (Figure 5). Intravenous administration of single doses of 19 and 50 mg./kg. produced over 600  $\mu\text{g./cc.}$  of urine at two hours followed by gradual fall to 3 to 4  $\mu\text{g.}$  at 24 hours. Following oral single dose administration of 86 to 150 mg./kg. the urinary concentration reached a maximum of 1360 to 2500  $\mu\text{g./cc.}$  in four to six hours and 23 to 121  $\mu\text{g./cc.}$  at 24 hours. When given in oil suspension, a maximum concentration of 480  $\mu\text{g./cc.}$  was reached at eight hours and 7.5  $\mu\text{g./cc.}$  at 48 hours. Oral administration of two doses per day of 50 to 100 mg./kg. produced the first peak of 228 to 591 at two hours and the second peak at eight hours with 270

to 1300  $\mu\text{g./cc.}$ , with 25 to 76  $\mu\text{g./cc.}$  at 24 hours. When given in propylene glycol, 41 mg./kg. twice daily intramuscularly, the two-hour averages for urinary concentration were 148  $\mu\text{g./cc.}$  and the 24-hour levels were 63 to 164  $\mu\text{g./cc.}$  (Table IV). The urinary excretion of chloramphenicol for a 24-hour period in dogs accounted for only 3.5 to 8.7 per cent of the total administered. Blood serum studies indicated absence of chloramphenicol in serum in four to six hours following intravenous and in 12 to 16 or 24 hours following oral or intramuscular administration, while urine contained considerable amounts at 24 hours, indicating absorption of Chloromycetin by tissues from

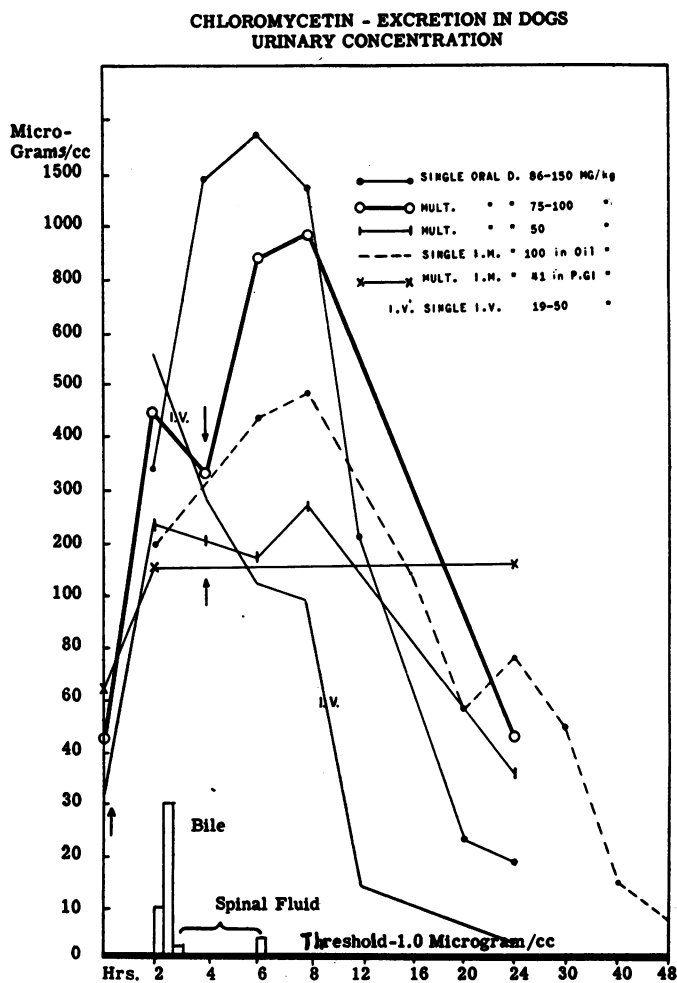


FIG. 5

High concentration of Chloromycetin occurred between two and 12 hours, peak at about eight hours, and the urinary excretion was prolonged over a 24-hour period.



TABLE IV  
*Urinary concentration of chloramphenicol in dogs*

Number tests	Route	mg./kg. $\times$ daily	Hour intervals of sampling urine											
			0	2	4	6	8	12	16	20	24	30	40	48
			<i>micrograms per cubic centimeter</i>											
4	I.V.	19-50 $\times$ 1	0	485	137	47	23	14	—	—	3.3			
1	Oral	86 $\times$ 1	0	283	1360	2540	2080	—	—	—	121			
4	Oral	150 $\times$ 1	0	383	1487	1040	694	206	341	23	19.2			
6	Oral	50 $\times$ 2*	31	228	190	171	269	—	—	—	36			
20	Oral	75 $\times$ 2*	47	304	336	891	620	—	—	—	65			
6	Oral	100 $\times$ 2*	43	591	337	864	1300	—	—	—	25			
6	I.M. Oil	90-101 $\times$ 1	0	177	307	429	480	—	132	58	76	48	15	7.5
6	I.M. Pr. Gl.	41 $\times$ 2*	63	148	—	—	—	—	—	—	164			

\* Second dose was administered at the end of the fourth hour.

which it is gradually liberated and excreted in the urine.

#### SUMMARY

1. Chloramphenicol (Chloromycetin) is moderately soluble (0.5 per cent) in water, urine and serum, propylene glycol (15 per cent), 50 per cent acetamide-water solution (5 per cent), and is insoluble in vegetable oils. Animal studies have indicated identical pharmacologic properties for material produced by fermentation and by chemical synthesis.

2. Chloramphenicol was readily absorbed following parenteral and oral administration and was found in blood serum, urine, bile and cerebrospinal fluid within two hours of administration.

3. It disappeared relatively rapidly from the blood stream, within four to six hours after intravenous and 12 to 16 hours after oral administration, with maximum blood serum concentration occurring between two and six hours and maximal urinary concentration between two and 12 hours. The urinary excretion persisted for over a 24-hour period with total recovery of 3.5 to 8.7 per cent.

4. Chloramphenicol was relatively non-toxic to animals and possessed no cumulative toxic effect on oral dosage of 100 to 200 mg./kg. per day to dogs for over a four-months period. The intravenous administration of 12.5, 25 and 50 mg./kg. was within the well-tolerated range. It caused no cumulative toxic effect on hemopoiesis, liver and kidney functions and visceral tissues. Blood pressure and respiration remained unaffected on

oral intake of 200 mg./kg. per day, and on intravenous administration to barbiturized dogs of 12.5 to 25 mg./kg. Gastro-intestinal reactions were uncommon, somatic reflexes, ocular and auditory functions remained undisturbed.

5. Lethal or near-lethal amounts of chloramphenicol orally and parenterally caused acute respiratory depression or failure, accompanied by fall of blood pressure and anoxia. Transient renal hematuria, probably of glomerular origin, and hydropic degeneration of glomerular capillaries occurred on administration of toxic amounts.

6. Intramuscular administration of oil suspensions or propylene glycol solution in doses of 0.5 to 1.0 gram caused considerable local tissue induration and necrosis, and a transient induration with 0.1 to 0.2 gram doses.

7. Oral administration of chloramphenicol to dogs provided measurable levels in the blood for about eight hours and in the urine for 24 hours.

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