

THE ACTION OF THE LETHAL DOSE OF STROPHANTHIN IN NORMAL ANIMALS AND IN ANIMALS INFECTED WITH PNEUMONIA.

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The following experiments were undertaken for the purpose of ascertaining whether the action of a digitalis body when administered to animals suffering from pneumonia differed from its action when no infection or fever was present. That there is a difference of opinion regarding the action of the drug when given in acute infections is shown in the practice of clinicians.

For example, Mackenzie (1) doubts its value and says that digitalis "is often used when patients are dying of some grave affection, as pneumonia, as a last resort, probably more for the purpose of doing something than with expectation of great benefit. I have never seen much good follow the administration of digitalis in acute febrile states." Gibson (2) in his article on acute pneumonia also says, regarding the use of digitalis, that in the worst cases of pneumococcal poisoning the heart absolutely refuses to respond. On the other hand, in Krehl's clinic (3) digitalis is used in all cases of pneumonia with the belief that it has a beneficial effect.

On account of this difference of opinion, Gunn (4) recently performed experiments with the view of determining what influence the height of the temperature has on the action of digitalis. In his experiments he perfused excised rabbits' hearts with solutions of strophanthin at different temperatures. The perfusion was carried to the point of arrest of the heart's action. By this procedure Gunn demonstrated that with variations in temperature ranging from 28° to 41° C. strophanthin acts more quickly on the isolated heart as the temperature is raised. The conditions in Gunn's experiments are not analogous to those in pneumonia, since in the presence of this infection toxemia accompanies the increased temperature.

In the experiments now reported the attempt was made to duplicate the usual human conditions as nearly as possible. A digitalis

body was administered to animals suffering from an acute pneumonic infection and the effect compared with that obtained when the drug was given to healthy animals of the same species. A comparison of the results in the two groups we believe should yield information regarding the influence of infection on the action of the drug.

#### *Methods.*

The animals employed were cats and dogs. In each species one group was infected and another group was used as a control. The animals were infected by the method of intrabronchial insufflation described by Lamar and Meltzer (5). The organism used was an eighteen to twenty-four hour old broth culture of virulent pneumococci<sup>1</sup> belonging either to Type I or II (6), and was obtained from the laboratory of the Hospital. Of these cultures the cats received from 10 to 20 cc., and the dogs from 20 to 30 cc. The temperature of the animals was taken daily for several days before infection and also during the course of the disease.

The digitalis body employed was Thoms crystalline g-strophanthin (Merck). An alcoholic stock solution of the drug was made and from this an aqueous solution was prepared for immediate use. In the experiments on cats the aqueous solution was of such a strength that 10 cc. of solution contained 0.1 mg. of strophanthin. For the dogs a solution double this strength was employed. In all experiments the strophanthin was given intravenously. The animal was lightly anesthetized with ether, the femoral vein exposed, and a small glass cannula was inserted. This was connected with a burette containing the solution. The anesthetic was not continued beyond the time necessary for the insertion of the cannula. In injecting the strophanthin, an endeavor was made to maintain a uniform rate of flow. A lethal dose was given to each animal in approximately one hour, unless the animal died before the time required for administering the lethal dose had elapsed. The amount of strophanthin injected differed slightly in cats and dogs. In a large series of experiments on cats, Hatcher and Brody (7) and, later, Eggleston (8) found the lethal dose of strophanthin to be 0.1 mg. per kilo of

<sup>1</sup> The virulence was such that 0.000001 cc. was fatal in white mice.

body weight. In the present experiments on cats this amount was injected in both the control and the infected animals. In the dogs it was necessary first to estimate the minimal lethal dose (m.l.d.) in normal animals; it was found to be 0.12 mg. per kilo of body weight. Autopsies were performed on all the infected cats and on all cats in the control group which succumbed to the lethal dose of strophanthin. All the dogs, whether normal or infected, were autopsied. In a number of cats and dogs electrocardiograms were taken before infection and also just before injecting strophanthin. A series was also made during the period of injection.

TABLE I.  
*Normal Cats Injected with Strophanthin.*

Date (1914).	Cat.	Sex.	Weight at time of injection.	Strophanthin injected.	Amount of m. l. d. + or -.	Result.	Duration of experiment.
Nov. 3	A	F.	<i>kilos</i> 2,200	<i>mg.</i> 0.22	<i>mg.</i> L*	D†	<i>min.</i> 52
" 3	B	M.	2,400	0.24	L	D	60
" 3	C	F.	2,100	0.21	L	D	110
" 7	E	M.	3,150	0.315	L	S	—
" 7	F	M.	3,000	0.3	L	D	50
" 7	G	F.	2,500	0.25	L	D	59
" 7	H	F.	2,850	0.285	L	D	70
" 10	I	F.	2,000	0.2	L	S	—
" 10	J	M.	3,650	0.365	L	D	65
" 10	K	F.	2,300	0.23	L	S	—
" 14	L	F.	2,925	0.253	L-0.0395	D	48
" 14	M	F.	4,050	0.405	L	D	63
" 14	N	M.	1,700	0.17	L	S	—
" 20	P	M.	3,300	0.33	L	D	60
" 20	Q	F.	1,975	0.187	L-0.01	D	27
" 20	R	F.	1,700	0.17	L	S	—
" 20	S	M.	1,800	0.18	L	S	—
" 25	T	F.	3,050	0.305	L	D	78
" 25	U	M.	2,800	0.28	L	S	—
" 25	V	M.	2,425	0.2425	L	S	—
" 25	W	M.	2,250	0.225	L	S	—

Total = 21.  
Died = 12 = 57.1 per cent.  
Survived = 9 = 42.9 per cent.

\* In the tables L represents the estimated lethal dose. L+ or - indicates the amounts more or less than the estimated lethal dose.

† D = died; S = survived.

In the experiments on cats, three groups were studied: a control group and two groups of infected animals. The control group con-

sisted of normal, uninfected animals, each of which received 0.1 mg. of strophanthin per kilo of body weight. This is the amount reported by Hatcher and Brody as the minimal lethal dose. The second group consisted of infected animals. They were otherwise untreated, and served the purpose of observing the course of the disease. The animals in the third group were also infected. Each of these received an amount of strophanthin equal to that given to the first group.

Group I (Table I) formed the control series of experiments. This group consisted of twenty-one cats, all of which were apparently normal and healthy. All received the estimated lethal dose of strophanthin (0.1 mg. per kilo of body weight) in the manner described. Of the twenty-one cats, twelve, or 57.1 per cent, died, while nine, or 42.9 per cent, survived. In the cats that died, the time that elapsed from the commencement of the injection until death occurred ranged from 27 to 110 minutes, the average time being 62 minutes. All the cats received the estimated lethal dose with the exception of animals L and Q. These two died when slightly less than the estimated amount had been injected. The low mortality in this group is a subject which will be discussed later.

TABLE II.  
*Cats Infected with Pneumococci, but Receiving No Strophanthin.*

Date of infection (1914).	No. of cat.	Sex.	Type of organism.	Highest temperature before and after infection.	Result.
				° C.	
Nov. 23	34	F.	II	38.5-38.8	D Nov. 26.
" 23	35	M.	II	38.4-39.6	S
" 23	36	M.	II	37.7-39.6	D " 27.
" 23	37	M.	II	38.2-38.6	S
" 24	38*	F.	I	38.2-38.8	D Dec. 14.
" 24	39	F.	I	38.6-39.3	S
" 24	40	M.	I	39.0-39.0	S
" 24	41	F.	I	38.4-39.2	S
" 27	42	M.	II	38.2-39.4	S
" 27	43	M.	II	39.0-39.6	S
" 27	44	M.	II	39.0-39.4	S
" 27	45*	F.	II	37.8-39.0	D " 14.

Died = 16.6 per cent.

\* The two cats, Nos. 38 and 45, which died three weeks after infection, evidently not from pneumonia, but from some intercurrent infection, are not considered in estimating the mortality for the series.

Group II (Table II) comprised twelve cats, each of which was infected by an intrabronchial insufflation of pneumococcus culture. Six of the animals developed very severe symptoms. The other six were only moderately ill. Of the former, one died on the third and one on the fourth day. The symptoms of the disease appeared eight to twelve hours after infection. The animals became listless and prostrated. Almost all showed a rise in temperature ranging from a fraction of a degree to  $3.6^{\circ}$  C. The symptoms of the disease apparently reached their height on about the second or third day after infection. At this point convalescence set in. Practically all the animals lost weight.

Group III (Table III) consisted of forty-three cats, all of which were infected. In seven, the culture used was obtained at autopsy from the heart's blood of infected cats; the rest were infected with organisms obtained in the manner already described. The symptoms of disease corresponded to those described under Group II. Ten cats failed to show a rise in temperature, but the temperature was not taken sooner than twenty-four hours after infection, and it is possible that, had readings been made at an earlier period, a rise might have been observed. A few animals which showed only a very slight reaction to the infecting organisms after the first insufflation, were reinfected. Strophanthin was given as nearly as possible at the height of infection; that is to say, on the second or third day, according to the observations made in Group II. Following the injection, twenty-three cats, or 53.5 per cent, died, and twenty, or 46.5 per cent, survived. The cats that died during or following the injection did so in from 25 to 108 minutes, the average time being 62 minutes. Nine cats succumbed before the injection was completed. They received slightly less than the estimated lethal dose. Three cats, Nos. 17, 48, and 53, through an error in calculation, received slightly more than the estimated lethal dose, but as these cats all survived the error does not affect the results.

A comparison of Groups I and III, the animals in both of which received strophanthin, shows that the mortality in each series, following the injection of the adopted lethal dose of the drug, was practically the same; *viz.*, 57.1 and 53.5 per cent. The course of the disease in the infected animals, however, was short; in many in-

TABLE III.

*Cats Infected with Pneumococci, and Later Injected with Strophanthin.*

Date (1914).	No. of cat.	Sex	Type of organism.	Weight on day of injection.	Strophanthin injected.	Amount of m. l. d. + or -.	Result.	Duration of experiment.	Highest temperature before and after infection.
				gm.	mg.	mg.		min.	° C.
Oct. 26	1	F.	I	2,250	0.203	L-0.022	D	47	37.8-39.2
" 26	2	F.	I	2,000	0.20	L	S	—	36.2-39.8
" 28	3	M.	II	1,750	0.175	L	D	57	—
" 28	4	F.	II	2,550	0.245	L-0.01	D	62	—
" 29	6	F.	I	2,000	0.15	L-0.051	D	45	36.7-39.0
" 29	7	F.	I	1,300	0.13	L	S	—	36.0-38.0
" 30	9	—	II	2,700	0.27	L	S	—	37.0-38.1
" 30	10	F.	I	2,250	0.225	L	S	—	37.2-37.8
Nov. 2	11	F.	II C*	1,500	0.15	L	D	57	37.8-37.8
" 11	12	M.	II C I	3,100	0.31	L	D	66	38.1-38.6
" 11	13	F.	II C I	1,875	0.1875	L	S	—	38.6-40.0
" 11	14	M.	I	2,575	0.2575	L	D	76	38.8-39.0
" 12	16	F.	II C	3,000	0.30	L	S	—	39.0-39.4
" 12	17	M.	II C	2,200	0.225	L+0.005	S	—	38.8-38.8
" 12	18	M.	II C	2,250	0.225	L	D	88	39.2-40.0
" 13	19	M.	II	3,600	0.3595	L-	S	—	39.0-39.2
" 13	22	M.	II	3,325	0.254	L-0.0785	D	42	39.2-39.0
" 18	23	F.	I	2,425	0.2425	L	D	80	39.1-38.6
" 18	24	M.	I	3,500	0.319	L-0.031	D	62	39.0-38.2
" 18	26	M.	I	2,475	0.2475	L	D	60	38.4-39.4
" 19	15	F.	II C Nov. 10 I " 17	2,900	0.183	L-0.107	D	25	38.6-39.6
" 19	27	M.	I	1,700	0.17	L	D	92	39.0-39.8
" 19	28	F.	I	2,225	0.2225	L	D	73	38.4-37.8
" 19	29	F.	I	2,350	0.235	L	D	108	38.2-39.0
" 23	30	F.	II	3,050	0.275	L-0.03	D	48	38.1-38.2
" 23	31	M.	II	3,750	0.375	L	S	—	38.0-40.6
" 23	32	F.	II	2,500	0.25	L	S	—	38.2-39.0
" 23	33	F.	II	2,575	0.2575	L	S	—	38.8-39.6
" 30	48	F.	II	2,700	0.271	L+0.001	S	—	38.8-40.6
Dec. 2	50	F.	II	3,000	0.30	L	D	60	38.5-39.0
" 2	51	F.	II	2,500	0.25	L	S	—	39.0-39.8
" 2	52	F.	II	2,900	0.29	L	D	60	37.5-38.3
" 2	53	M.	II	3,325	0.354	L+0.0215	S	—	38.2-39.3
" 3	55	M.	II	3,850	0.385	L	S	—	39.2-39.0
" 3	56	M.	II	2,950	0.295	L	S	—	38.2-41.2
" 4	57	F.	II	3,100	0.31	L	D	65	38.2-38.8
" 7	62	F.	II	3,000	0.3	L	S	—	38.2-39.4
" 8	63	M.	II	3,400	0.34	L	S	—	38.0-40.0
" 9	64	M.	I	2,500	0.25	L	S	—	37.6-39.2
" 10	65	F.	I	1,550	0.155	L	S	—	38.2-36.6
" 11	66	F.	I	3,050	0.265	L-0.04	D	63	38.0-38.0
" 15	60	F.	II	2,000	0.13	L-0.07	D	37	38.6-38.4
" 18	59	F.	II	1,600	0.16	L	D	46	38.4-39.4

Total = 43.

Died = 23 = 53.5 per cent.

Survived = 20 = 46.5 per cent.

\* C indicates that the culture used was obtained from the heart's blood of a cat previously infected.

stances the animals were not seriously ill, and a number failed to show any increase in temperature, or showed an increase which was comparatively slight. It was considered inadvisable, therefore, to draw conclusions from these experiments. The attempt was accordingly made to enlarge our experience by performing experiments in dogs.

*The Action of Strophanthin in Normal and Infected Dogs.*

The experiments on dogs were undertaken with the expectation that they would show a greater degree of reaction to infection than cats. No standardization of strophanthin in dogs has been made (in so far as could be ascertained), so that it was necessary first to determine the lethal dose of the drug. Experiments were, therefore, carried out on ten dogs (Table IV) to determine the minimum lethal

TABLE IV.

*Dogs Injected with Strophanthin, To Estimate the Lethal Dose.*

Date (1915).	Dog.	Sex.	Weight at time of injection.	Total strophanthin injected.	Strophanthin injected per kilo of body weight.	Duration of experiment.	Deviation from average lethal dose.
			<i>gm.</i>	<i>mg.</i>	<i>mg.</i>	<i>min.</i>	<i>per cent</i>
Jan. 20	A	F.	8,000	0.98	0.122	47	2
" 21	B	F.	5,100	0.57	0.111	42	10
" 22	C	M.	7,350	1.07	0.145	110	16
" 25	D	F.	9,000	0.9	0.1	65	17
" 28	E	M.	5,700	0.704	0.123	53	1
Feb. 10	F	F.	5,750	0.75	0.130	95	5
" 10	G	M.	5,000	0.59	0.118	57	5
" 15	H	F.	5,300	0.606	0.114	68	8
" 15	I	F.	4,150	0.55	0.132	90	6
" 16	J	F.	4,750	0.71	0.149	93	20

Average dose per kilo = 0.124 mg.

dose. Before injection the animals were observed for a time under uniform conditions and all were apparently normal and healthy. The injections were made during the months of January and February. The females used were neither pregnant nor lactating. The animals were not fed for a period of eighteen hours preceding the experiment. This short fast was enforced so that the presence of food in the stomach should not influence the weight of the animal, and so that vomiting during the preliminary anesthesia might be prevented.

A fresh alcoholic solution of strophanthin was prepared and the aqueous solution made from this was of a strength such that 5 cc. represented 0.1 mg. of strophanthin. The solution was tested on three cats and was found to have the same effect as had the first stock solution. The lethal dose for these three animals was 0.108, 0.127, and 0.107 mg. per kilo of body weight, respectively.

The injection of strophanthin in dogs was made in a manner identical with that described for cats. The lethal dose for the ten dogs used was found to average 0.124 mg. per kilo of body weight. Death occurred in approximately 60 minutes. The dose ranged from 0.1 to 0.149 mg. per kilo of body weight. Of the ten dogs, seven showed a deviation of 10 per cent or less from the average m. l. d. The remaining three dogs, C, D, and J, gave respectively a deviation of 16 per cent above, 17 per cent below, and 20 per cent above the average. If the three dogs showing the greatest variation be deducted from the series, the result is not materially altered and the m. l. d. still remains 0.12 mg.

TABLE V.

*Dogs Infected with Pneumococci and Later Injected with Strophanthin.*

Date (1915).	No. of dog	Sex.	Type of organism.	Weight before infection.	Weight at time of injection.	Total strophanthin injected.	Strophanthin injected per kilo of body weight.	Duration of experiment.	Deviation from average lethal dose.	Highest temperature before and after infection.
				<i>gm.</i>	<i>gm.</i>	<i>mg.</i>	<i>mg.</i>	<i>min.</i>	<i>per cent</i>	<i>°C.</i>
Jan. 15	1	F.	II	9,000	7,900	1.237	0.137	108	10	38.8-39.2
" 18	3	F.	II	8,150	7,300	1.105	0.151	85	20	39.0-40.9
" 26	4	M.	II	9,400	8,800	1.146	0.130	78	4	39.8-39.5
Feb. 1	5	M.	II	8,500	7,800	0.82	0.105	55	16	39.8-39.5
" 3	6	M.	II	9,000	7,900	0.88	0.111	73	11	39.6-39.2
" 4	8	F.	II	8,300	8,050	1.01	0.125	95	0	39.8-39.6
" 17	10	F.	II	5,800	5,750	0.68	0.118	73	6	38.2-40.4
" 19	11	M.	II	6,350	6,150	0.614	0.0998	55	20	38.8-39.8
" 24	12	M.	I	8,600	7,500	1.08	0.144	115	15	39.0-39.8
" 26	14	M.	I	8,500	8,250	1.1	0.133	90	6	38.5-41.5

Average lethal dose per kilo = 0.125 mg.

A series of ten experiments was next carried out to ascertain the lethal dose in pneumonic dogs (Table V). These animals were infected by the method described. In the reaction to the infection, the dogs displayed symptoms similar to those described for the cats. They became listless and usually refused to eat. The respirations



appeared to be somewhat labored and were increased in rate. In all the dogs there was a loss in weight, amounting in two to more than 1,000 grams. The temperature following infection usually rose. In seven dogs the increase ranged from a fraction of a degree to 3° C. Three dogs, however, failed to show an increase, but in these the temperature was not taken until twenty-four hours after infection with pneumococci. The injection of strophanthin was made during the second twenty-four hours following infection because this was the time when the animals were most severely ill. Lamar and Meltzer (5) and, later, Wollstein and Meltzer (9) also give this time as the period of the maximum reaction. The average amount of strophanthin per kilo of body weight injected was 0.125 mg., which was practically the same as the lethal dose required in the normal dogs. The range of the dosage for the infected dogs varied from 0.099 to 0.151 mg. per kilo of body weight. In six of these dogs the amount of strophanthin injected fell within 11 per cent of the average. The remaining four dogs, Nos. 3, 5, 11, and 12, showed respectively a variation of 20 per cent above, 16 per cent below, 20 per cent below, and 15 per cent above. If the four animals showing the greatest variation are omitted from the series it is found that the average m. l. d. of the remaining six dogs is still 0.12 mg. The time which elapsed between the commencement of the injection and the death of the animal varied from 55 to 115 minutes, the average time being 82 minutes. A comparison, then, of the normal and infected dogs shows the lethal dose of strophanthin in each to be the same.

*Autopsy Findings.*—Autopsies were performed on all the cats and dogs in both the normal and infected series, except on the cats in Group I that survived the injection of strophanthin and on the cats in Group II that survived the infection. Autopsies performed on cats of the control series (Group I) killed by strophanthin showed the lungs to be normal. Two cats of Group II, Nos. 34 and 36, died during the height of the infection. No. 34 showed a massive consolidation of the entire left lung, and also of the middle and posterior lobes of the right. No. 36 showed scattered areas of consolidation throughout all the lobes of both lungs, the left lung being almost entirely consolidated. A well marked fibrinous exudate covered the

pleura and a moderate amount of fluid was found in both pleural cavities. Two other cats belonging to this group died at a period three weeks after infection, but their death was evidently due to an intercurrent disease. Autopsies on these animals showed small, scattered, abnormal areas in both lungs suggestive of an old pneumonic process.

Autopsies were performed on all the animals of Group III. The lungs in each instance showed definite signs of consolidation. The involvement varied in extent from a portion of one lobe to an entire lung. The gross examination showed the area involved to be deeply congested and the overlying pleura to be somewhat dull and lacking in luster. In a number of the animals the pleura showed the presence of a small amount of serofibrinous exudate. Two animals, Nos. 33 and 55, developed a fibrinopurulent pleurisy, and one, No. 33, also showed a well marked pericarditis. The portion of the lung involved was usually firm, inelastic, and friable. On section the lungs were firm; the cut surface was uniformly dark red with a tendency to be dry. On compression, a small quantity of bloody fluid exuded from the surface. Small portions of tissue cut from the consolidated areas sank in water. The gross appearance of the lungs in dogs was similar to that in the cats. Blood cultures were made at the time of autopsy from the heart's blood in fourteen cats; of these, twelve contained pneumococci.

Microscopic examination of the lung tissue showed the alveoli to be filled with an exudate consisting chiefly of leucocytes. A few large lymphocytes, red blood cells, and desquamated epithelial cells were also present. Only small quantities of fibrin were contained in the alveolar exudate. The amount of fibrin found in the pneumonias in cats was slightly more than that found in the dogs. The walls of the alveoli were only moderately congested. The bronchi contained small amounts of exudate, consisting chiefly of red and white blood cells with particles of desquamated epithelium and small amounts of fibrin.

*Electrocardiograms.*—Electrocardiograms were made of ten infected cats, of seven normal dogs, and of all the infected dogs. Non-polarizable electrodes were placed on the right fore and the left hind leg. Control curves were obtained before infection of the

animals, before injection of strophanthin, and also at ten minute intervals after the injection was begun. The principal changes found to follow the injection were increase in the conduction time, alterations in the size and form of the T wave, and the production of extrasystolic irregularities. Changes in the P-R time occurring during the course of the strophanthin injection were seen in four of the ten cats. In these there was an increase of 0.02 of a second or more. In the remaining six cats there was no alteration in the conduction time. Changes in the P-R time were also seen in five of the normal and in six of the infected dogs. In all of these there was an increase of 0.02 of a second or more (Figs. 1 B and 3 C). The remaining dogs of both groups showed no important change in the P-R time. Blocking of the auricular impulse occurred in two of the normal and in three of the infected dogs (Figs. 2 B and 3 B).

Alterations in the T wave have recently been shown to occur in man during the administration of digitalis (10). The curves of cats and dogs displayed similar changes (Figs. 4, 5, and 6). Of the ten cats, a negative T wave was present in the control curves of two, and became deeper after the injection (Fig. 5 B). In two others a diphasic T wave became negative, and in a fifth an upwardly directed T wave became markedly diminished in height (Fig. 6). In the remaining five cats, the strophanthin produced no demonstrable change in this wave. In two of the seven normal dogs, the T wave in the control electrocardiogram was positive. After injection it became diphasic in one, and negative (Fig. 1 B) in the other. The remaining five dogs all showed negative T waves in the control curve. On the form of these strophanthin appeared to have no influence. In the ten infected dogs changes occurred more often. In six animals the T wave was positive in the control curve and became negative under the influence of strophanthin (Figs. 3 B and 3 C). In the seventh a negative T wave became diphasic. In the remaining three dogs negative T waves in the control curve became deeper under the influence of the drug (Fig. 4 B). Changes in the T wave were observed, therefore, five times in ten cats, and in twelve of seventeen dogs.

Extrasystolic (11) irregularities occurred in all the animals following the injection (Figs. 3 D and 6 B). Several of the cats

which received the average lethal dose of strophanthin and survived showed an irregularity of this type to a marked degree. When electrocardiograms were made of these animals, twenty-four hours later, the heart rhythm was again normal (Fig. 6). In one cat that survived the injection of strophanthin, persistence of a change of shape in the T wave continued for a period of at least forty-eight hours (Fig. 5). In all the dogs and in the cats that died, extrasystoles multiplied in frequency. At the time of death fibrillation of the ventricles occurred.

#### SUMMARY AND DISCUSSION.

The results of these experiments permit a comparison of the action of strophanthin in the normal and the infected animals. In cats the percentage of deaths following the injection of 0.1 mg. of strophanthin per kilo of body weight was the same in normal and in pneumonic cats. The number of recoveries in this series was larger than was expected. This result was due to the fact that the dose injected was not the lethal dose, but the average lethal dose (0.1 mg.) determined by Hatcher and Brody (7) and by Eggleston (8). The doses which the latter actually injected ranged from 0.085 mg. to 0.16 mg.; from these the average minimal lethal dose was calculated. In adopting the average dose as the standard one to inject, those of our cats that required more than 0.1 mg. naturally survived. The death rate was therefore low. The plan employed in dogs differed from that used in cats. A lethal dose was injected in each dog. Death occurred when an average of 0.12 mg. of strophanthin per kilo of body weight was injected. The same dose was required in normal and pneumonic dogs. The effect of strophanthin in both groups of infected and non-infected cats and dogs is, therefore, identical.

Whether the uniformity of strophanthin action in the two experimental groups may serve as the basis for assuming a like uniformity of action in normal individuals and in pneumonia patients is a subject which requires further analysis. The difficulty in transferring the experimental results to patients lies in the question of whether the type of pneumonia produced in animals is the same as that found

in man. Clinically, the two diseases present both resemblances and differences. The animals become definitely ill and show the symptoms already described. The illness, however, is of short duration and apparently reaches its height in the majority of animals in twenty-four to seventy-two hours. Before the expiration of this time, the temperature frequently returns to normal. Many of the infected animals, when they survive, recover in three to five days. The mortality in dogs infected with pneumococci is given by Lamar and Meltzer as 16 per cent. In the present series of twelve infected cats, the mortality was also 16 per cent. These findings differ from human pneumonia in the following particulars: The infection is not so severe; the temperature, though elevated at first, soon falls; the duration of the disease is short; and convalescence is rapid. The mortality is slightly lower. Musser and Norris (12) give the human mortality at 21.06 per cent. Pathologically the two diseases also show differences. The gross appearance of the lungs is not dissimilar, but in the animals the consolidated portions are somewhat dry and they fail to show a stage of gray hepatization (5). The amount of fibrin present is small. There is comparatively slight congestion of the alveolar walls and of the walls of the bronchi.

The relation of experimental pneumonias to the human disease has been discussed by a number of investigators. Almost all believe that the two types are similar, if not identical. Among the first to express this opinion was Sternberg (13); and later Gamaléia (14), Prudden and Northrup (15), Kinyoun and Rosenau (16), Wadsworth (17), Lamar and Meltzer (5), Wollstein and Meltzer (9) coincided with his view. Lamar and Meltzer, especially, have insisted on the identity of the two processes. On the other hand, Welch (18) in his study of experimental pneumonia, says: "Many inoculations of cultures of virulent pneumococci into the trachea and lungs of dogs have been made in my laboratory by Dr. Canfield and myself, but in no instance were we able to produce an inflammation of the lungs which we were willing to identify with acute lobar pneumonia as found in human beings." But he adds that, in the majority of experiments, there was no demonstrable consolidation and that pleurisy and more or less extensive areas of pneumonia were produced only in a few animals.

The inference consequently cannot be drawn that an effect obtained with strophanthin in the experimental disease may be anticipated in man. The striking similarity in action in infected and uninfected animals renders it likely, however, that the usual action of the drug in man may be expected in the presence of pneumonia. We have accumulated evidence, to be published later, which shows that this action actually takes place in the human disease. As far as evidence obtained electrocardiographically is concerned, our experiments show that strophanthin causes the same electrical changes in the heart when the animals are infected as it does under normal conditions.

## CONCLUSIONS.

1. When a like amount of strophanthin is injected intravenously, the mortality is the same in both normal cats and in cats suffering from experimental pneumonia.
2. The minimum lethal dose of strophanthin is the same in normal dogs and in dogs suffering from experimental pneumonia.
3. The presence of an acute infection in these animals does not interfere with the action of strophanthin on the heart.
4. Electrocardiographically the changes occurring in the heart's action when strophanthin is injected are found to be similar in normal and in infected animals.
5. The identity of strophanthin action in infected and normal animals renders it probable that a like similarity may be anticipated in man, under normal conditions and in pneumonia.

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## EXPLANATION OF PLATES.

In the following electrocardiograms leads were taken from the right fore to the left hind leg. In all figures the divisions of the abscissæ equal 0.04 of a second, the divisions of the ordinates equal  $10^{-4}$  millivolts.

## PLATE 74.

FIG. 1, A and B. These curves were taken from Normal Dog B. In A, made immediately before the injection of strophanthin, the P-R interval is 0.07 to 0.08 of a second. The T waves are prominent and upwardly directed. In B, taken 25 minutes after the injection was begun and when 0.43 mg. of strophanthin had been injected, P-R time increased to 0.11 or 0.12 of a second. The T wave is negative. The time since the commencement of the injection and the amount of strophanthin injected are given except in Fig. 3. In the cat curves the time only is indicated.

FIG. 2, A to C. Curves taken from Normal Dog C. Curve A was taken before the injection of strophanthin. The rhythm is regular. The P-R interval is 0.08 to 0.09 of a second. The T waves are negative. Curve B was made 65

minutes after the injection was begun; strophanthin 0.76 mg. had been injected. Complete dissociation between auricles and ventricles is shown. The rate of the auricles is much reduced. Curve C was made 20 minutes later than B; strophanthin 0.85 mg. had been injected. It shows a succession of ectopic ventricular beats. Two distinct types are seen. In the first and last parts of the curve the impulses arose in the wall of the right ventricle; those between, in the wall of the left ventricle. The latter show considerable variation. Auricular complexes cannot be distinguished.

## PLATE 75.

FIG. 3, A to D. These curves were taken from Infected Dog 1. Curve A was made before the injection of strophanthin. The P-R time is 0.10 of a second. The T wave in some of the complexes is flat, in others it is composed of two parts, a low upwardly directed portion and a small negative wave. Curve B was taken 65 minutes after the injection of strophanthin was begun. The P-R time is lengthened to 0.15 of a second. The T waves consist of three parts: first, a gradual upward rise following the S wave; second, a rather sharp downward deflection; and third, an upward rise. Every third auricular impulse is blocked. Curve C was taken 10 minutes after Curve B. The complexes are normal. The P-R time is 0.15 of a second. The ventricular complex is similar to that seen in Fig. 2 B, the principal change being in the T wave. Ventricular extrasystoles occur which are probably of left ventricular origin. The T wave accompanying these is positive. Curve D was taken 25 minutes later than C; strophanthin 1.09 mg. had been injected. No auricular waves appear. In each pair of ectopic ventricular beats the first member has its origin in the left ventricle, and the second in the right ventricle. The third pair forms an exception; here the order is reversed.

FIG. 4, A and B. These curves were taken from Infected Dog 11. Curve A was made before the injection of strophanthin. The P-R time is 0.08 of a second. The T wave is made up of three parts, a small positive wave following directly on the S wave, a small negative, and a small positive wave. Curve B was made 15 minutes after the injection of strophanthin was begun; 0.24 mg. had been injected. The P-R time is unchanged. The T wave is composed of two parts, a negative portion of considerable depth and a small upward part.

## PLATE 76.

FIG. 5, A to D. These curves were taken from Infected Cat 63. The animal survived the injection of strophanthin. Curve A was made before the injection. In the earlier portion of the curve the P wave has a normal relation to the R wave; later it gradually merges into the R wave until it disappears. The excursion of R is now increased and S is decreased. The T wave consists of two portions, a flat or upwardly directed portion and a small negative wave. Curve B was taken 13 minutes after the injection of strophanthin was begun. The P-R time is 0.07 of a second. The T wave consists of two portions, a flat or upwardly directed portion and a negative part of much greater extent than in Curve A. Curves C and D were taken 24 and 48 hours after the injection of strophanthin, respectively. In both curves the P wave is absent and in this



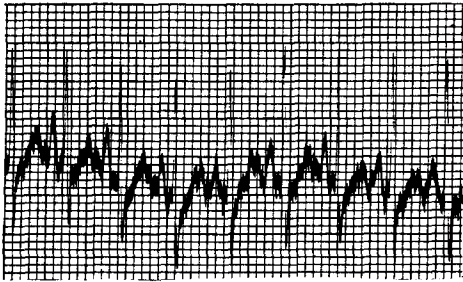


Fig 1A. Dog B.

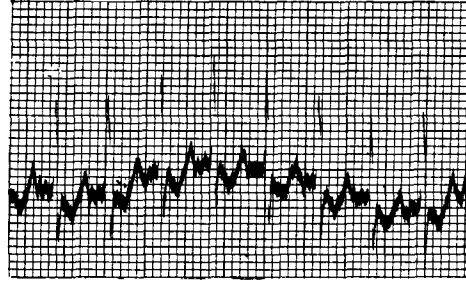


Fig 1B. 25 min. 0.43 mgm.

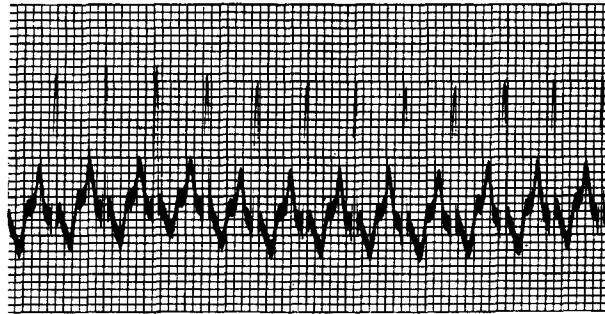


Fig 2A. Dog C.

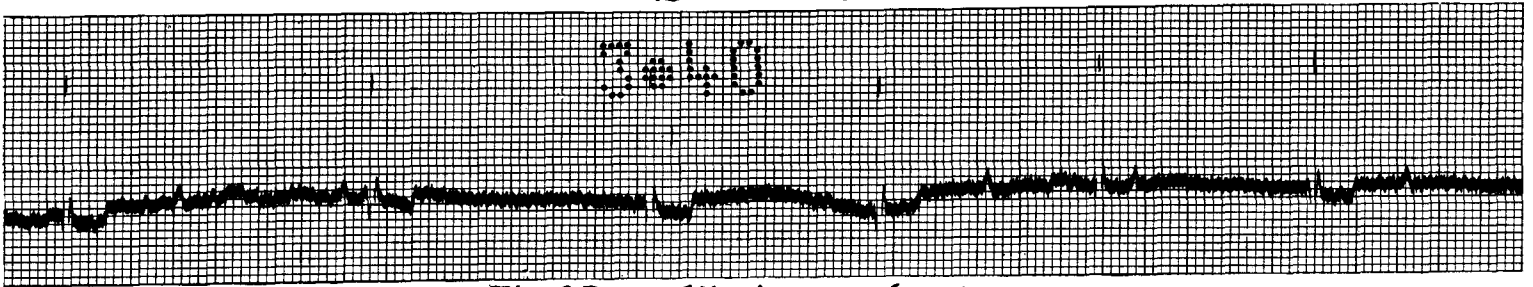


Fig 2B. 65 min. 0.76 mgm.

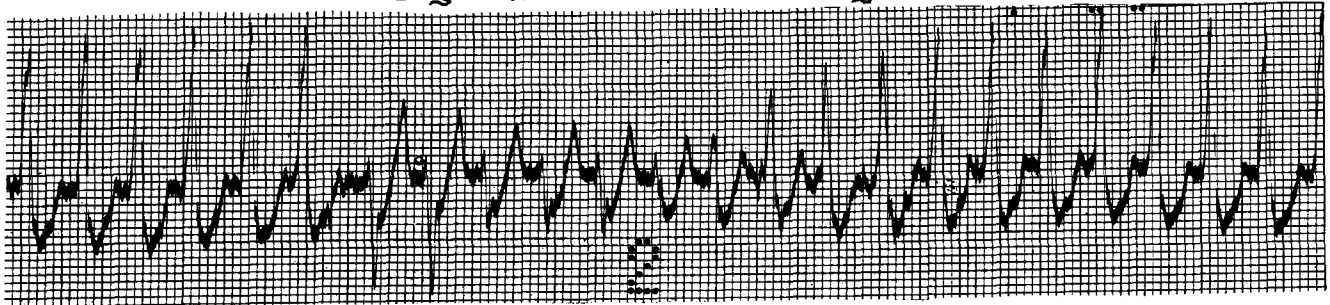


Fig 2C. 85 min. 0.85 mgm.

(Jamieson: Action of Lethal Dose of Strophanthin in Animals.)

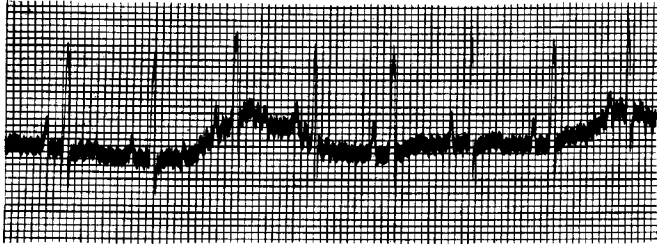


Fig. 3A. Dog 1.

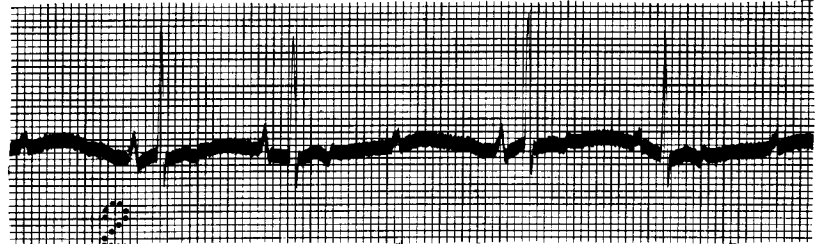


Fig. 3B. 65 min.

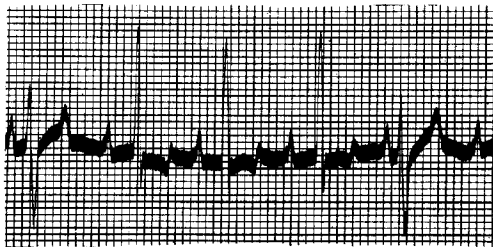


Fig. 3C. 75 min.

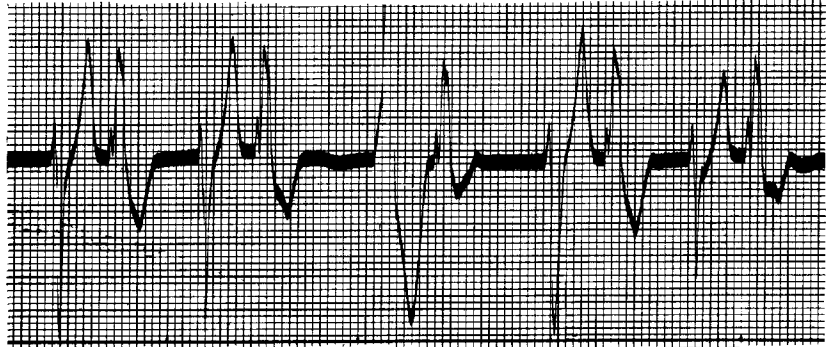


Fig. 3D. 100 min.

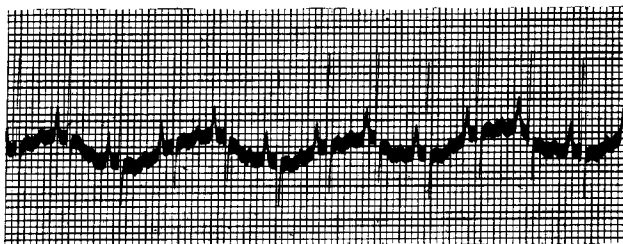


Fig. 4A. Dog 2.

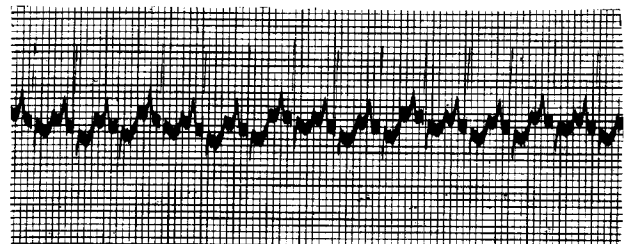


Fig. 4B. 15 min. 0.24 mgm.

(Jamieson: Action of Lethal Dose of Strophanthin in Animals.)

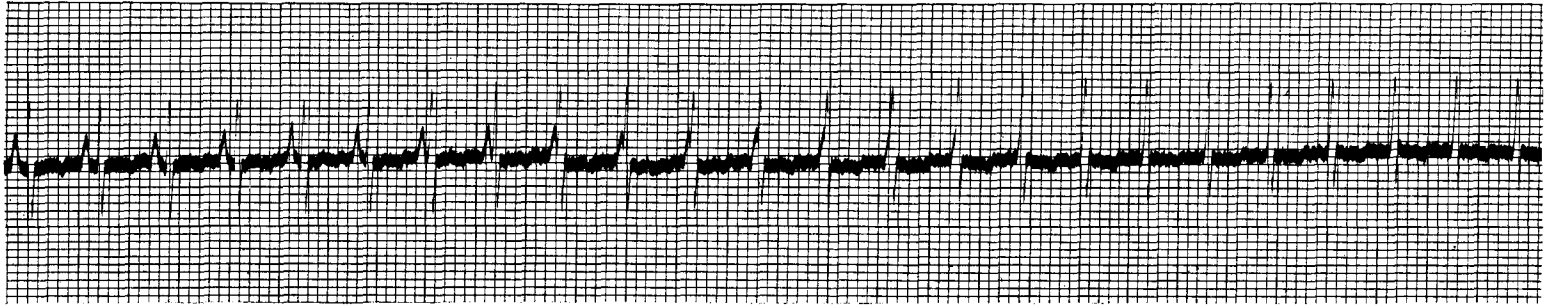


Fig. 5A. Cat 63.

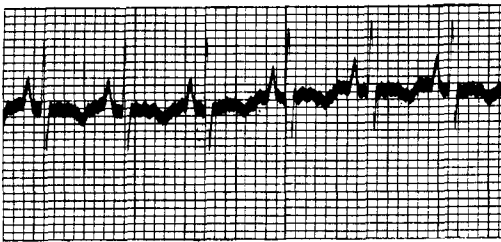


Fig. 5B. 13min.

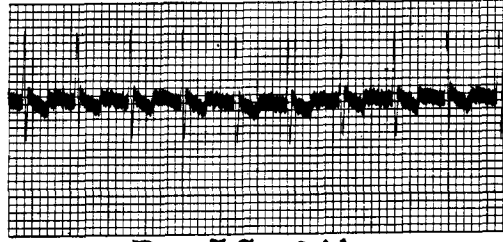


Fig. 5C. 24hrs.

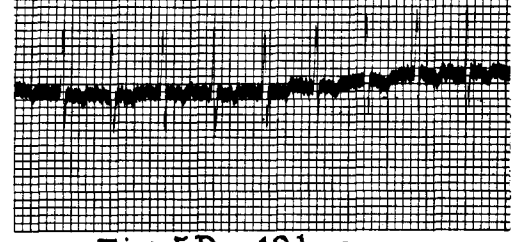


Fig. 5D. 48hrs.

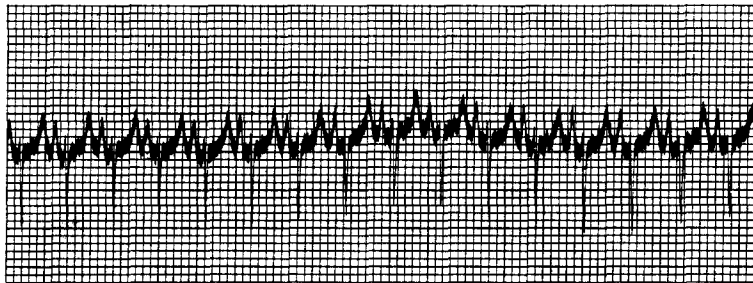


Fig. 6A. Cat 64.

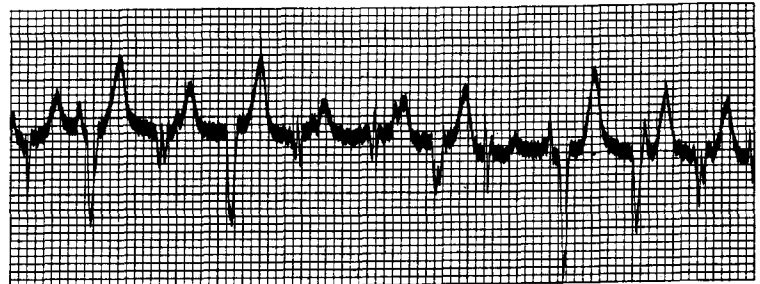


Fig. 6B. 33min.

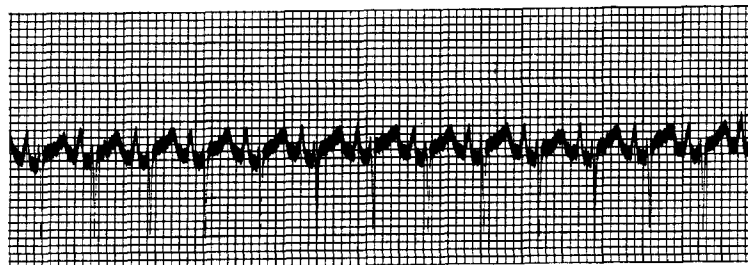


Fig. 6C. 24hrs.

(Jamieson: Action of Lethal Dose of Strophanthin in Animals.)

respect they resemble the last portion of Curve A. A negative T wave has persisted in C and D, though in the latter T wave is more like the form seen in Curve A.

FIG. 6, A to C. These curves were taken from Infected Cat 64. This animal survived the injection of strophanthin. Curve A was made before the injection. The heart rhythm is normal. The P-R time is 0.07 of a second. The T wave is positive. Curve B was taken 33 minutes after the injection of strophanthin was begun. It shows a completely irregular heart action. No P waves are discernible. The ventricular complexes are ectopic, have various forms, and have their origin at several points in the walls of the right and left ventricles. Curve C was taken 24 hours later and shows the return of the heart to a normal rhythm. The P-R time is the same as in Curve A. The T waves are positive.