R E S U L T S :

Isolated guinea pig ileum :

The antibiotics streptomycin, kanamycin, viomycin, neomycin and paromomycin did not affect the spontaneous contractions of the guinea pig ileum in concentrations upto 1 µg/ml. The spontaneous contractions of the ileum were however, inhibited (Fig.1) by the antibiotics in concentrations of 10 µg/ml and above. The ileum fully regained its spontaneous contractions on changing the bathing fluid.

The responses to histamine (100 ng/ml) were not affected by 10 µg/ml of the antibiotics. In higher concentrations (100 µg/ml and above) the antibiotics inhibited the responses to histamine (100 ng/ml)(Fig.1).

The cumulative dose-response curves to acetylcholine (100, 200 and 400 ng/ml) were shifted to the right by all the antibiotics. It was possible to obtain a maximal response to acetylcholine in the presence of the antibiotics. The logarithm (x-1) was plotted against the negative logarithm of B, where x is the dose ratio and B is the corresponding molar concentration of the antibiotic.

The calculated regression line was fitted and the intercept of line with the abscissa (at zero level) gave the pA_2 values. The mean pA_2 values were calculated from the individual pA_2 values. The data are summarised in Table I.

For competitive antagonism the theoretical value of the slope (b) of the pA plot is -1.0 (Arunlakshana and Schild 1959). The mean slopes given in Table I for the various pA plots are in fair angreement with the theoretical value.

Unlike the antibiotics the degradation products, streptidine and streptamine did not inhibit the spontaneous contractions but potentiated them in concentrations of 1 µg/ml. Streptidine itself induced contractions in higher concentrations (100 µg/ml and above). The responses to histamine (100 ng/ml) were inhibited by streptidine (1 mg/ml and above) and the cumulative dose-response curves of acetylcholine (100,200 and 400 ng/ml) were shifted to the right as in the case of the antibiotics. However, the valuesof slope (b) were less than -1.0 in all experiments (Table I) indicating that the antagonisim was noncompetitive.

Streptamine (1 mg/ml) induced powerful

Table I : Values of mean slopes (b) of pA plots and mean pA_2 of the antibiotics and streptidine obtained with the isolated guinea pig ileum and the frog rectus abdominis muscle. Acetylcholine was the agonist.

Compounds	Guinea pig ileum		Frog rectus abdominis muscle	
	Mean slope 'b' ± S.E.	Mean pA_2 ± S.E.	Mean slope 'b' ± S.E.	Mean pA_2 ± S.E.
Streptomycin	-0.902 ± 0.33	3.56 ± 0.54	-1.032 ± 0.43	2.77 ± 0.56
Kanamycin	-1.145 ± 0.01	3.02 ± 0.04	-1.188 ± 0.34	3.47 ± 0.36
Viomycin	-1.18 ± 0.29	2.79 ± 0.27	-1.12 ± 0.25	3.81 ± 0.17
Neomycin	-0.97 ± 0.29	3.59 ± 0.59	-0.99 ± 0.27	3.20 ± 0.39
Paromomycin	-1.24 ± 0.40	3.11 ± 0.15	-1.03 ± 0.21	3.10 ± 0.17
Streptidine	-0.68 ± 0.17	3.2 ± 0.27	-0.55 ± 0.08	2.75 ± 0.48

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Figure No.2

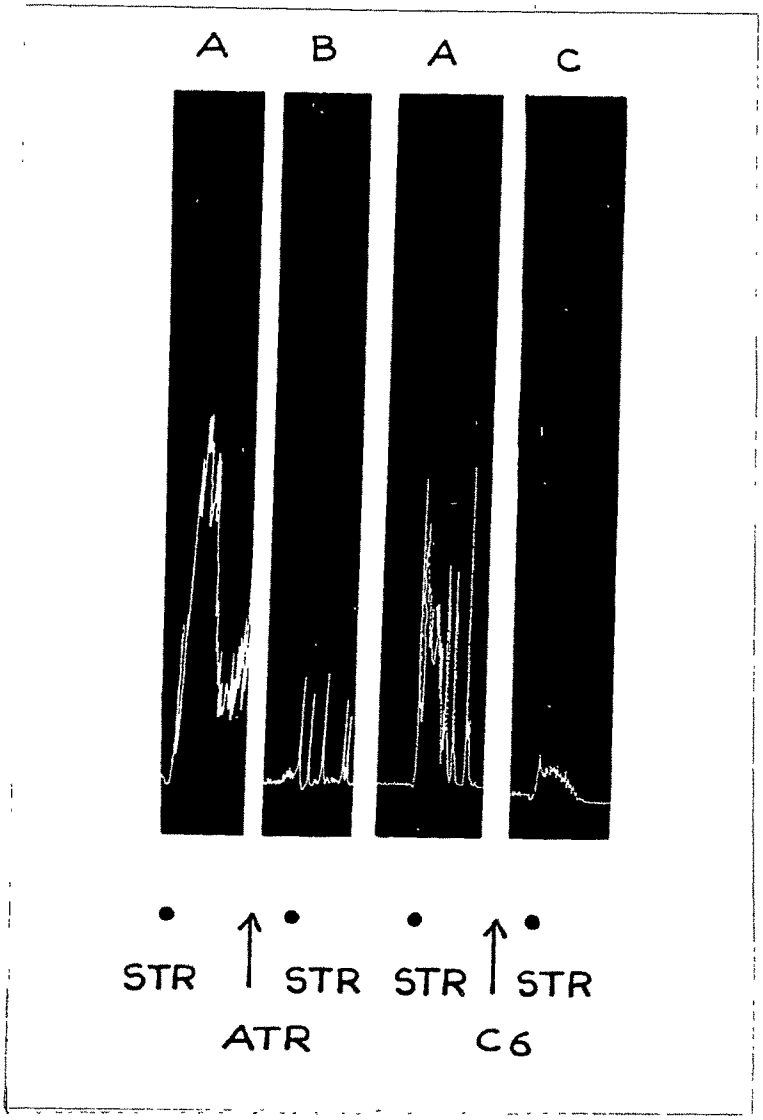

Fig. 2 : Isolated guinea pig ileum suspended in Tyrode solution (5 ml bath, 37°C). Responses streptamine at STR. Panels A show control responses to streptamine (1 mg/ml). Responses shown in panels B and C were obtained after the addition of stropine sulphate (10 ng/ml ATR) and hexamethonium bromide (10 µg/ml C_6) respectively to the bath. Time cycle, 3 min.

contractions of the guinea pig ileum. The spasmogenic action of streptamine (1 mg/ml) and streptidine (1 mg/ml) was completely blocked by atropine (10 ng/ml) and hexamethonium (10 µg/ml) (Fig.2).

Isolated frog rectus abdominis muscle.

All the antibiotics inhibited the contractile response to cumulative doses of acetylcholine (2,3 and 4.5 µg/ml). The analysis of data on antagonism of acetylcholine by the antibiotics was similar to that described under guinea pig ileum. The data are summarised in Table I. The values of slopes of pA plots suggest that the antibiotics antagonised acetylcholine competitively.

Streptidine also inhibited the contractile responses to cumulative doses of acetylcholine (2,3 and 4.5 µg/ml). The cumulative dose-response curves were shifted to the right but the value of slope (b) was less than -1.0 (Table I) indicating that the antagonism was noncompetitive.

Streptamine failed to inhibit the contractile responses to cumulative doses of acetylcholine (2,3 and 4.5 µg/ml) in concentrations of upto 100 µg/ml. In higher concentrations (150 µg/ml and above) the responses to cumulative doses of acetyl-

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Figure No.3

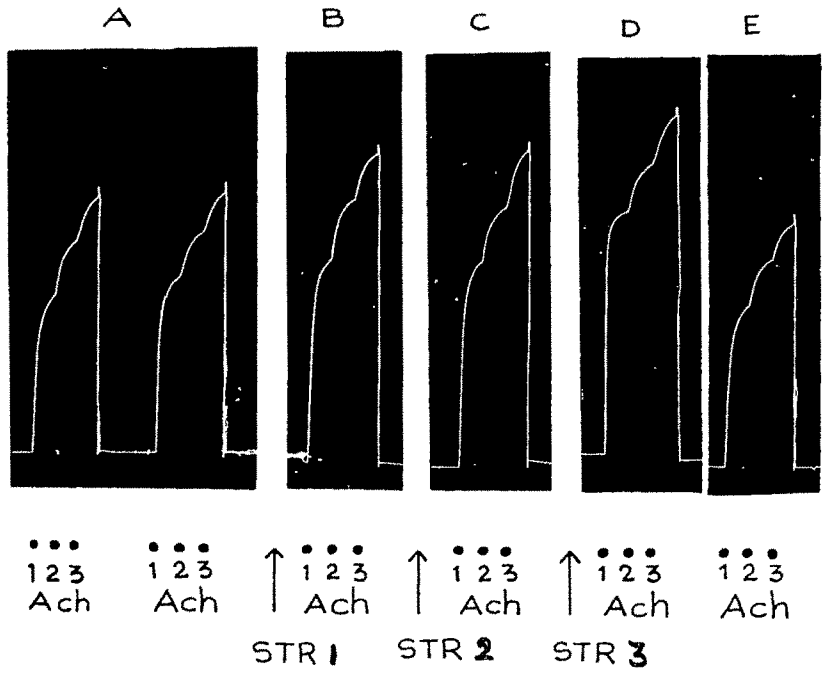

Fig.3: Isolated frog rectus abdominis muscle suspended in frog Riner solution (25 ml bath, 30°C). Cumulative dose responses to acetylcholine (Ach) (2 µg/ml) at 1, (3 µg/ml) at 2 and (4.5 µg/ml) at 3. Panel A shows control responses. Responses shown in panel B, C and D were obtained after the addition of streptamine (180 µg/ml STR1, 720 µg/ml STR2 and 2.9 mg/ml STR3). Panel E shows recovery to acetylcholine responses. Time cycle, 15 min.

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Figure No. 4

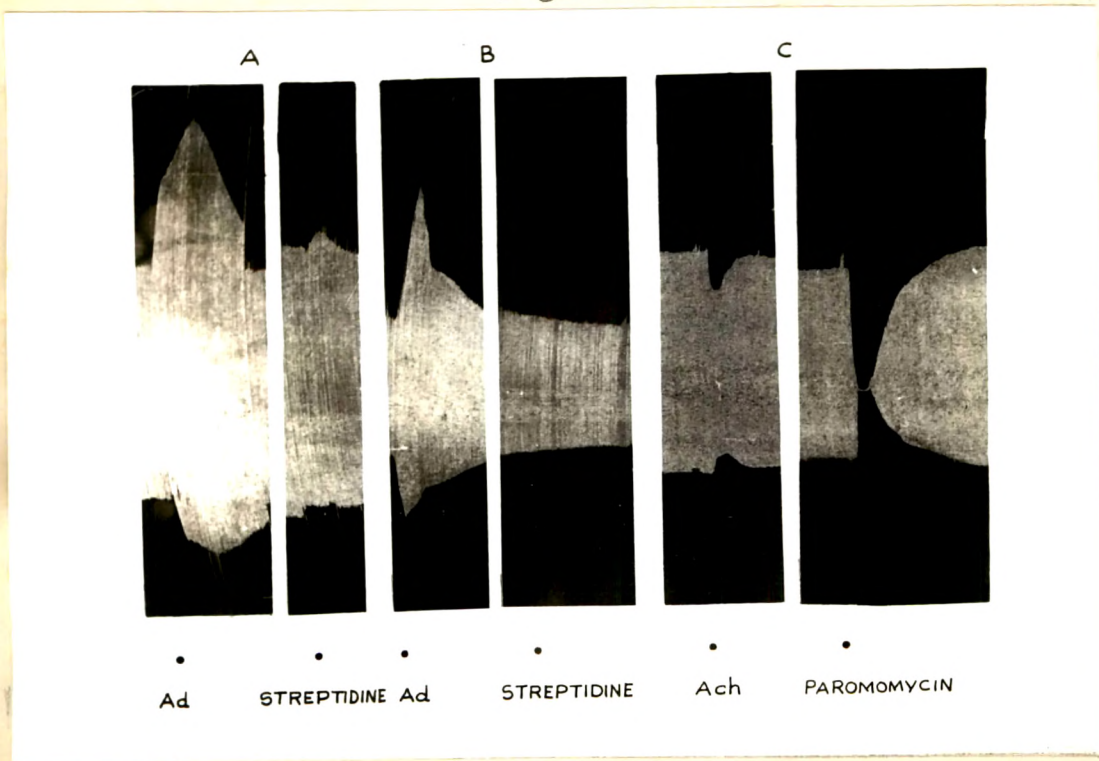

Fig.4 :- Isolated rabbit hearts perfused with oxygenated locke solution (10 ml/min, 37°C). Panel A shows the responses to adrenaline (1 µg Ad) and streptidine (10 mg). Panel B shows responses to adrenaline (1 µg Ad) and streptidine (10 mg) of heart obtained from a reserpine treated rabbit. Panel C shows responses to acetylcholine (3 µg Ach) and paromomycin (10 mg). Time cycle, 5 min.

choline (2,3 and 4.5 µg/ml) were potentiated by streptamine (Fig.3).

Isolated rabbit heart:

The antibiotics did not affect the isolated rabbit heart upto a dose of 1 mg injected in the cannula leading to heart. In higher doses (5 mg and above) the antibiotics elicited negative inotropic action (Fig.4). The recovery was immediate.

The negative inotropic action of the antibiotics was not blocked by atropine (10 ng/ml perfused for 30 min), though the response to acetylcholine was completely blocked.

Streptidine and streptamine (100 µg/ml each) elicited a positive inotropic action (Fig.4). This action was not dose related that is the responses to higher doses (1 mg and above) were not proportionately increased.The stimulant action of these compounds was not observed in hearts obtained from reserpine (5 mg/kg i-p.48 hr before the experiment) treated rabbits (Fig.4).

Rabbit aortic strip and perfused rabbit ear artery:

The contractile responses to adrenaline (10, 20 and 40 ng/ml) and to noradrenaline (10, 20 and 40 ng/ml) of the isolated rabbit aortic strip

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Figure No.5

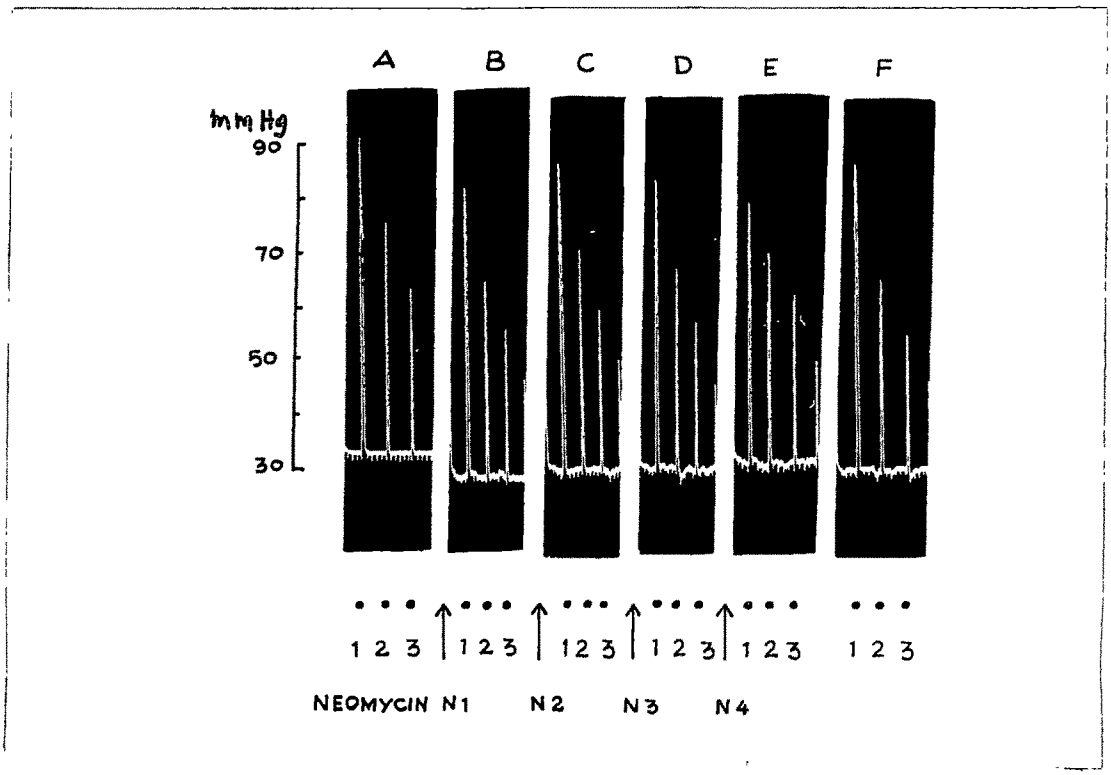

Fig. 5 :- Rabbit ear artery perfused with oxygenated Kreb bicarbonate solution (10 ml/min, 37°C). Responses to 2 ng, 1 ng, and 0.5 ng of adrenaline at 1, 2 and 3 respectively. Panels A and F show control responses. Panels B, C, D and E show responses 30 min after perfusing neomycin 10 ng/ml, 100 ng/ml, 1 µg/ml and 10 µg/ml at N1, N2, N3 and N4 respectively. Time cycle, 2 min.

were not affected by the antibiotics and the degradation products in concentrations ranging between 10 ng/ml to 100 µg/ml.

Similarly the rise in pressure in response to adrenaline (0.5, 1 and 2 ng/ml) and noradrenaline (2, 4 and 8 ng/ml) of the perfused rabbit ear artery was not affected by the antibiotics and the degradation products (10 ng/ml to 10 µg/ml)(Fig.5).

The effect of the antibiotics and the degradation products on the blood pressure of cats :

Antibiotics :. The blood pressure of 72 cats ranged between 110-140 mm Hg. The mean blood pressure was 120.0 ± 8.5 mm Hg. In a few cats the blood pressure was high initially but became steady (120-140 mm Hg) within 30 min.

Ten mg/kg of streptomycin, kanamycin, viomycin, neomycin and paromomycin did not affect the blood pressure of anaesthetised cats. Twenty to thirty mg/kg of streptomycin elicited a sharp and an abrupt fall in blood pressure ranging between 15-20 mm Hg. With 20-30 mg/kg of the other antibiotics the fall ranged between 30-50 mm Hg.(Fig.6). The recovery was complete in 3-4 min in the case of streptomycin and viomycin (3 experiments each).

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Figure No.6

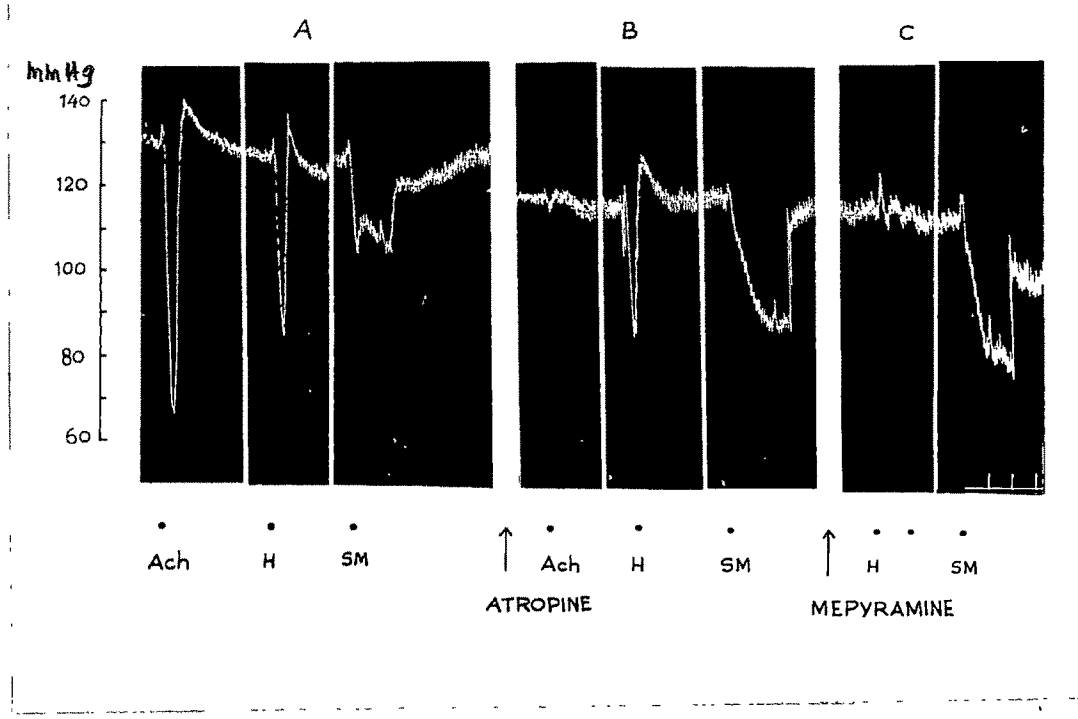

Fig. 6 :- Cat blood pressure (wt. 2.4 kg), chloralose anaesthesia. Responses to acetylcholine (1 µg/kg Ach), histamine (0.4 µg/kg H) and streptomycin (20 mg/kg SM). Panel A shows control responses. Panel B shows responses to acetylcholine (1 µg/kg Ach), histamine (0.4 µg/kg H) and streptomycin (20 mg/kg SM) 30 min after atropine sulphate (1 mg/kg). Panel C shows responses to histamine (0.4 µg/kg H) and streptomycin (20 mg/kg SM) 30 min after mepyramine maleate (1 mg/kg).

However, with kanamycin, neomycin and paromomycin the blood pressure recovered to 80-90 per cent of the control level at the end of 4 min and fluctuated in a wide range of ± 30 mm Hg. Ultimately at the end of about 30 min the blood pressure attained a steady state at about 75-80 per cent of the control level (3 experiments each).

The depressor response to a high dose (20 mg/kg) of these antibiotics were not blocked by atropine (1 mg/kg) or mepyramine (1 mg/kg) injected 30 min before the antibiotics (Fig.6) although those to acetylcholine (1 µg/kg) and histamine (0.4 µg/kg) were blocked by the respective antagonists (3 observations each).

Repeated injections (5-6 for streptomycin and 2-3 for the other antibiotics) of 10 mg/kg of the antibiotics administered at intervals of 10 min affected the blood pressure in a manner similar to higher doses (20-30 mg/kg) injected all at once (3 experiments each). The blood pressure was not affected by the first injection; however subsequent injections elicited an insidious fall in blood pressure which at the end of about 60 min became steady at about 40 per cent of the control level. A similar pattern was observed with repeated

injections (10 min interval) of higher doses (20-30 mg/kg) of the antibiotics. However, the fall in blood pressure was rapid and cumulative. Following the last dose, the basal blood pressure decreased in about 30-40 min to 40 per cent or less of control. Normal saline or adrenaline (10 µg/kg) could not restore the blood pressure and the cats ultimately died (3 experiments each).

Repeated injections (5-6 for streptomycin and 2-3 for the other antibiotics) of 10 mg/kg doses at longer intervals of time (30 min) did not affect the blood pressure upto 3 hr (Table II).

Degradation products : Streptidine and streptamine (10 mg/kg) elicited a rise in blood pressure measuring about 10-20 mm Hg. The pressor response to streptidine commenced after about 1 min whereas that to streptamine was almost instantaneous. The pressor response was sustained for about 3 min with both the compounds and the recovery was complete.

The magnitude of the pressor response to 20 mg/kg dose of streptidine did not differ from that to 10 mg/kg dose, though the duration was longer (7-10 min) than with the former dose. The magnitude of tne response with 20 mg/kg of streptamine was

Table II : Effect of some antibiotics and streptidine and streptamine on the blood pressure of anaesthetised cats. The blood pressure was recorded about 3 hr following the antibiotics.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean blood pressure mm Hg ± S E		P
			Control	Following the compound	
Streptomycin	60.0	18	128.3 ± 9.2	121.1 ± 8.3	<0.02
Kanamycin	30.0	12	121.7 ± 11.1	117.1 ± 9.2	>0.1
Viomycin	30.0	7	129.3 ± 6.1	122.1 ± 9.1	>0.1
Neomycin	20.0	7	121.4 ± 9.0	111.4 ± 6.9	<0.05
Paromomycin	30.0	9	129.4 ± 6.3	122.2 ± 6.7	<0.05
Streptidine	30.0	9	123.3 ± 11.2	119.4 ± 11.1	>0.8
Streptamine	20.0	10	127.0 ± 8.2	121.0 ± 7.0	<0.05

P indicates the probability of significance for the difference between the control mean blood pressure and that following the antibiotics or the degradation products.

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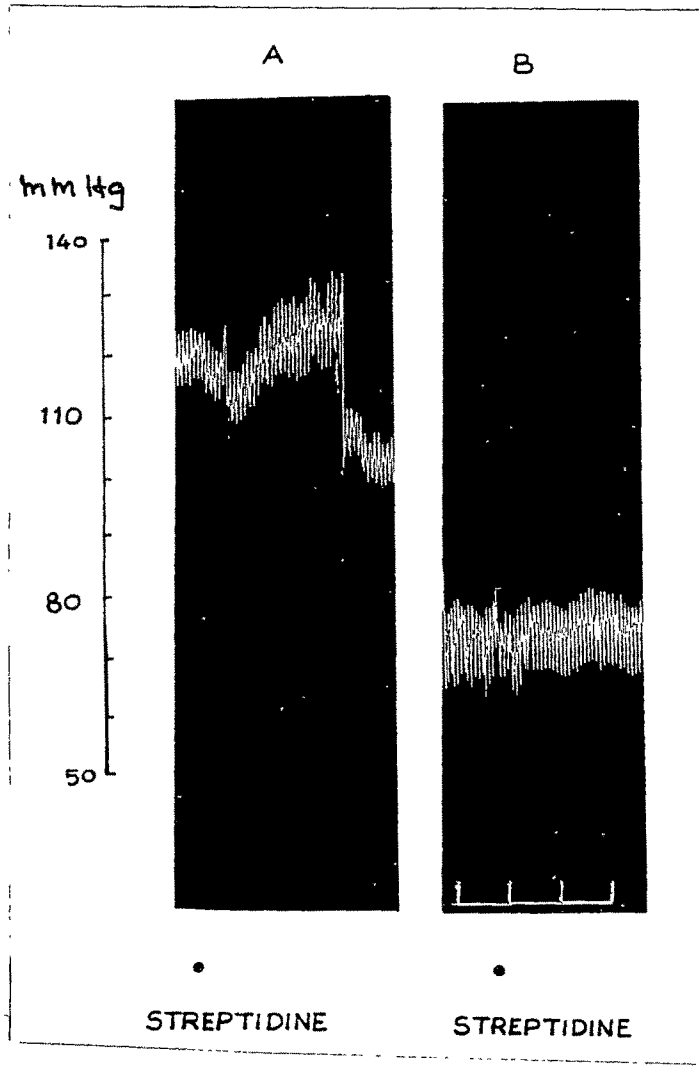

Fig. 7 :- Cat blood pressure (wt. 2.6 kg control and 3.1 kg reserpine treated), chloralose anaesthesia. Control responses to streptidine (10 mg/kg) of a control cat is shown in panel A. Responses to streptidine (10 mg/kg) in reserpine (5 mg/kg i.p. 48 hr before experiment) treated cat is shown in panel B.

comparatively greater (25 mm Hg). Further increase in response was not observed with doses higher than 20 mg/kg. Following the initial rise in blood pressure with 20 mg/kg or higher doses there was an insidious fall in blood pressure which levelled off at 85-90 per cent of the control level in 20-30 min (3 experiments each). The compounds did not affect the blood pressure of reserpine (5 mg/kg i.p., 48 hr before experiment) treated cats (3 experiments each) (Fig.7).

Repeated (2-3) injections of 10 mg/kg of streptidine and streptamine administered every 30 min produced an initial rise in blood pressure which recovered to control level in about 15 min. The control level was maintained for about 3 hr (Table II).

Modification of the responses of cat blood pressure to different drugs by the antibiotics and the degradation products :

Histamine : The control mean depressor responses to 0.1, 0.2 and 0.4 µg/kg of histamine were 33.3 ± 7.6 per cent, (51 observations) 39.4 ± 8.5 per-cent (59 observations) and 49.9 ± 9.4 per cent (50 observations), respectively. The recovery of depressor responses to 0.1, 0.2 and 0.4 µg/kg histamine

Figure No: 8

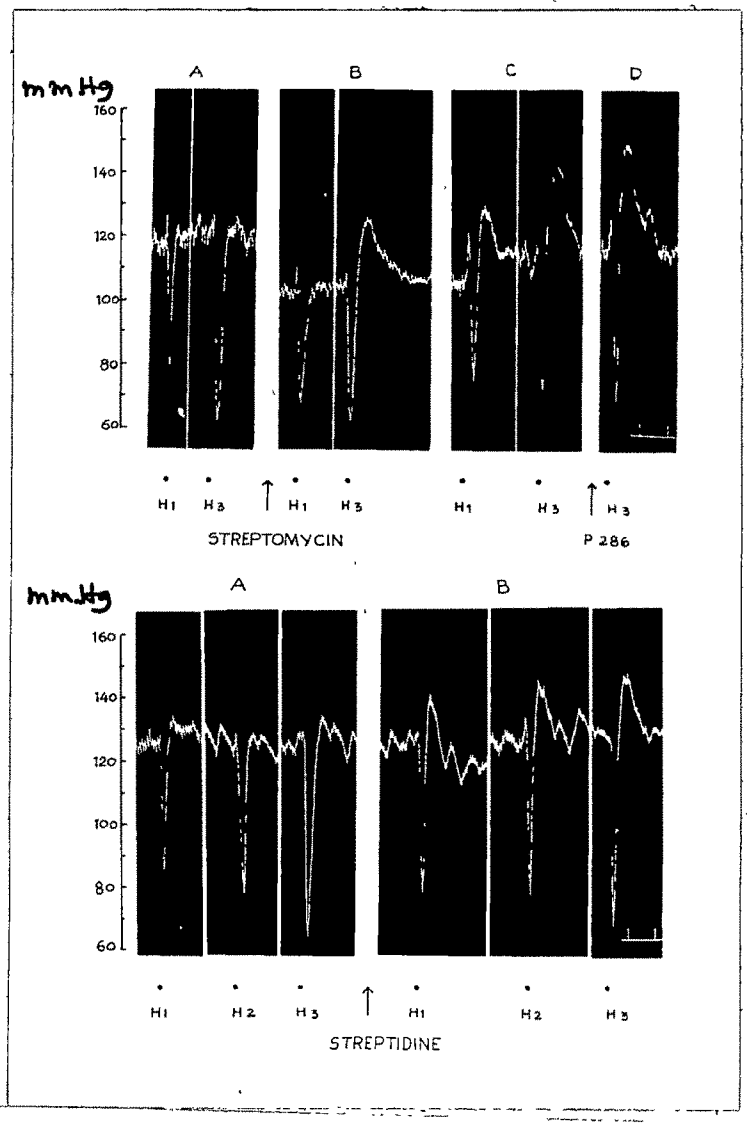

Fig. 8 :- Cat blood pressure (wt. 2.5 kg upper record and wt. 2.8 kg lower record) chloralose anaesthesia. Responses to 0.1 µg/kg, 0.2 µg/kg and 0.4 µg/kg of histamine at H1, H2 and H3 respectively. Streptomycin (10 mg/kg X 6 every 30 min) and streptidine (10 mg/kg X 2 every 30 min) were given cumulatively. Panels A show control responses. Responses shown in panel B were obtained 30 min after the administration of the test compound. Responses in panel C were obtained 60 min after the administration of streptomycin and those shown in panel D were obtained 30 min after the administration of P-286 (1 mg/kg). P-286 was given 3 hr after streptomycin. Time mark, 1 min.

was complete in 1 min. With 0.4 µg/kg of histamine the recovery commenced after a pause of 20-30 sec.

Following the antibiotics or the degradation products, the depressor response to histamine recovered as usual. After the depressor response had returned to normal there was a secondary rise in blood pressure. The secondary pressor response occured gradually over a period of about 30 min following the last instalment of the cumulative dose of the antibiotics or the degradation products.

Thirty minutes after the administration of the last dose of the antibiotics, the vasodepressor response to 0.4 µg/kg of histamine recovered rapidly and culminated into a small secondary rise in blood pressure (Fig.8). The responses to 0.1 and 0.2 µg/kg of histamine were however, only depressor in nature. Subsequently, the vasodepressor responses to 0.1 and 0.2 µg/kg of histamine also culminated into a secondary rise in blood pressure. In the beginning the magnitude of the secondary pressor response was small with all the three doses of histamine, but increased and attained its maximal at 60 min from the last dose of antibiotics (Fig.8). The biphasic response to histamine continued to be elicited upto 3 hr (Tables III,IV,V).

Table III : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to histamine (0.1 µg/kg) in cats of either sex weighing 2.0 - 4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compounds were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean blood pressure response mm Hg ± S.E.				P
			Control response		Responses following the compound		
			depressor	Pressor	depressor	pressor	
Streptomycin	60.0	9	28.8 ± 7.4	-	30.2 ± 7.0	14.8 ± 8.3	} 0.6
Kanamycin	30.0	8	40.1 ± 9.3	-	43.4 ± 7.8	25.4 ±10.5	} 0.4
Viomycin	30.0	7	34.9 ± 6.2	-	39.9 ± 6.4	16.2 ± 9.0	} 0.1
Neomycin	20.0	7	32.5 ±10.2	-	38.5 ±12.2	18.8 ± 5.0	} 0.3
Paromomycin	30.0	8	34.9 ± 9.4	-	36.4 ±10.4	18.4 ±12.0	} 0.8
Streptidine	30.0	6	31.5 ± 3.6	-	35.1 ± 4.4	24.1 ±11.1	} 0.1
Streptamine	20.0	6	29.6 ± 3.8	-	32.8 ± 5.1	19.5 ± 8.6	} 0.2

P indicates the probability for the difference between the control mean depressor responses to histamine and that following the compound.

Table IV : Effect of some antibiotics and streptidine and streptamine on the blood pressure response to histamine (0.2 µg/kg) in cats of either sex, weighing 2.0-4.5 kg, and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean blood pressure responses mm Hg ± S.E.				P
			Control response		Responses following the compound		
			depressor	pressor	depressor	pressor	
Streptomycin	70.0	13	35.8 ± 7.1	-	35.8 ± 7.4	21.3 ±12.1	> 0.9
Kanamycin	30.0	6	45.4 ± 7.4	-	48.9 ± 6.4	30.8 ±11.1	> 0.4
Viomycin	30.0	7	44.2 ± 6.6	-	46.9 ± 5.4	21.4 ± 7.7	> 0.4
Neomycin	20.0	7	40.1 ±10.8	-	45.0 ±13.6	23.1 ± 3.9	> 0.4
Paromomycin	30.0	8	41.3 ±12.4	-	42.5 ±10.6	25.3 ±10.3	> 0.4
Streptidine	30.0	9	38.6 ± 6.2	-	39.5 ± 5.0	28.9 ±11.1	> 0.4
Streptamine	20.0	9	34.7 ± 6.3	-	37.7 ± 8.5	26.7 ±10.9	> 0.4

P indicates the probability for the difference between the control mean depressor response to histamine and that following the compound.

Table V : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to histamine (0.4 µg/kg) in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean blood pressure response mm Hg ± S.E.				P
			Control response		Response following the compound		
			depressor	pressor	depressor	pressor	
Streptomycin	60.0	8	46.3 ± 7.9	-	46.5 ± 8.3	24.3 ±12.2	> 0.9
Kanamycin	30.0	7	53.6 ±10.9	-	54.4 ±13.4	27.0 ±12.7	> 0.9
Viomycin	30.0	7	49.0 ± 6.5	-	53.0 ± 6.1	19.1 ± 9.3	> 0.2
Neomycin	20.0	7	45.8 ±10.5	-	49.5 ±14.0	25.4 ± 7.5	> 0.5
Paromomycin	30.0	7	49.6 ±13.8	-	48.6 ±10.3	27.3 ±11.7	> 0.8
Streptidine	30.0	6	45.6 ± 4.8	-	49.1 ± 4.0	31.1 ± 5.1	> 0.2
Streptamine	20.0	8	39.3 ± 7.9	-	43.6 ± 9.7	24.0 ± 7.7	> 0.3

P indicates the probability for the difference between the control mean depressor response to histamine and that following the compound.

With streptidine and streptamine, the secondary pressor response to all the three doses of histamine could be elicited at 30 min after the last dose (Fig.8). It became maximal by about 15 min later (total time 45 min). The biphasic response continued to be elicited upto 3 hr(Tables III,IV,V).

P-286 (1 mg/kg) was injected 3 hr after the last dose of the antibiotics and their degradation products. Thirty min later, the pressor response to histamine (0.1, 0.2 and 0.4 µg/kg) was not blocked (Fig.8). Similarly, in adrenalectomised cats (adrenalectomy was performed after eliciting a panel of modified responses to histamine), the pressor response to histamine was also not blocked.

McN-A-343 : The response to McN-A-343 (10 and 20 µg/kg) was biphasic in nature in most of the experiments. The response commenced immediately as a sharp fall in blood pressure followed by an equally sharp and rapid recovery culminating into a pressor response. The depressor component of the response lasted for 30 sec and the pressor component for about 1.5 min.

Ten µg/kg of McN-A-343 elicited biphasic response in 27 cats and depressor response in

14 cats while 20 µg/kg of McN-A-343 elicited biphasic response in all the experiments (47 experiments). The control mean depressor response to McN-A-343 (10 µg/kg) was 23.1 ± 7.4 per cent and the control mean pressor response was 8.9 ± 9.2 per cent (mean of 41 observations). The control mean depressor response to 20 µg/kg of McN-A-343 was 28.8 ± 9.1 per cent and the control mean pressor response was 21.4 ± 5.7 per cent.

The response to McN-A-343 (10 µg/kg), following the antibiotics and the degradation products was biphasic in all the experiments including 14 cats which exhibited purely depressor response with 10 µg/kg dose of McN-A-343 in control experiments. The depressor response to both the doses of McN-A-343 was not significantly affected following the antibiotics and the degradation products whereas the pressor component was significantly increased (Tables VI and VII).

Maximal potentiation of the pressor response to both the doses of McN-A-343 (10 and 20 µg/kg) was obtained about 30 min following the last dose of the antibiotics or the degradation product. The increased pressor response was maintained upto 3 hr. The response to McN-A-343 (10 and 20 µg/kg) was

Table VI : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 10 µg/kg of McN-A-343 in cats of either sex weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean blood pressure response mm Hg ± S.E.				P	
			Control response		Response following the compound			
			depressor	pressor	depressor	pressor	depressor	pressor
Streptomycin	60.0	6	18.0 ± 4.8	5.5 ± 6.2	22.1 ± 5.2	21.9 ± 8.3	>0.1	<0.01
kanamycin	30.0	6	25.5 ± 5.3	6.4 ±13.9	29.9 ± 8.7	26.4 ± 4.9	>0.3	<0.01
Viomycin	30.0	7	26.7 ± 4.3	12.1 ± 7.1	31.9 ± 4.2	21.8 ± 7.7	>0.1	<0.01
Neomycin	20.0	7	22.2 ±10.1	9.9 ± 7.8	29.2 ±10.8	24.9 ±10.3	>0.1	<0.01
Paromomycin	30.0	5	26.3 ±10.4	7.7 ± 8.0	28.1 ±10.7	17.3 ± 8.6	>0.7	<0.05
Streptidine	30.0	5	22.5 ± 8.1	12.5 ± 7.7	31.2 ± 3.0	23.2 ± 9.0	>0.05	<0.01
Streptamine	20.0	5	19.9 ± 5.6	15.1 ± 9.3	27.8 ±13.1	24.7 ± 5.8	>0.1	<0.01

P indicates the probability for the difference between the control mean blood pressure response to McN-A-343 and that following the compound.

Table VII : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 20 µg/kg of McN-A-343 in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean blood pressure response mm Hg ± S.E.				P	
			Control response		Response following the compound			
			depressor	pressor	depressor	pressor	depressor	pressor
Streptomycin	60.0	9	21.1 ±10.8	19.2 ±13.8	28.3 ± 6.9	38.4 ± 9.8	> 0.1	< 0.01
Kanamycin	30.0	6	30.9 ± 5.2	26.1 ± 8.3	39.5 ±10.8	36.0 ± 3.3	> 0.1	< 0.01
Viomycin	30.0	7	34.1 ± 5.8	17.8 ± 4.9	39.8 ± 6.2	26.7 ± 6.3	> 0.1	< 0.01
Neomycin	20.0	7	26.6 ± 6.2	18.2 ± 6.6	38.3 ±10.1	33.4 ±11.5	> 0.05	< 0.01
Paromomycin	30.0	5	40.0 ±11.9	22.4 ± 4.2	43.7 ± 7.9	35.9 ± 3.5	> 0.1	< 0.001
Streptidine	30.0	7	30.0 ± 8.1	22.4 ± 2.9	35.3 ± 9.3	35.1 ± 7.8	> 0.2	< 0.001
Streptamine	20.0	6	24.9 ± 6.4	25.6 ± 5.3	37.7 ± 5.1	41.7 ± 5.4	> 0.1	< 0.001

P indicates the probability for the difference between the control mean blood pressure response to McN-A-343 and that following the compound.

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Figure No.9

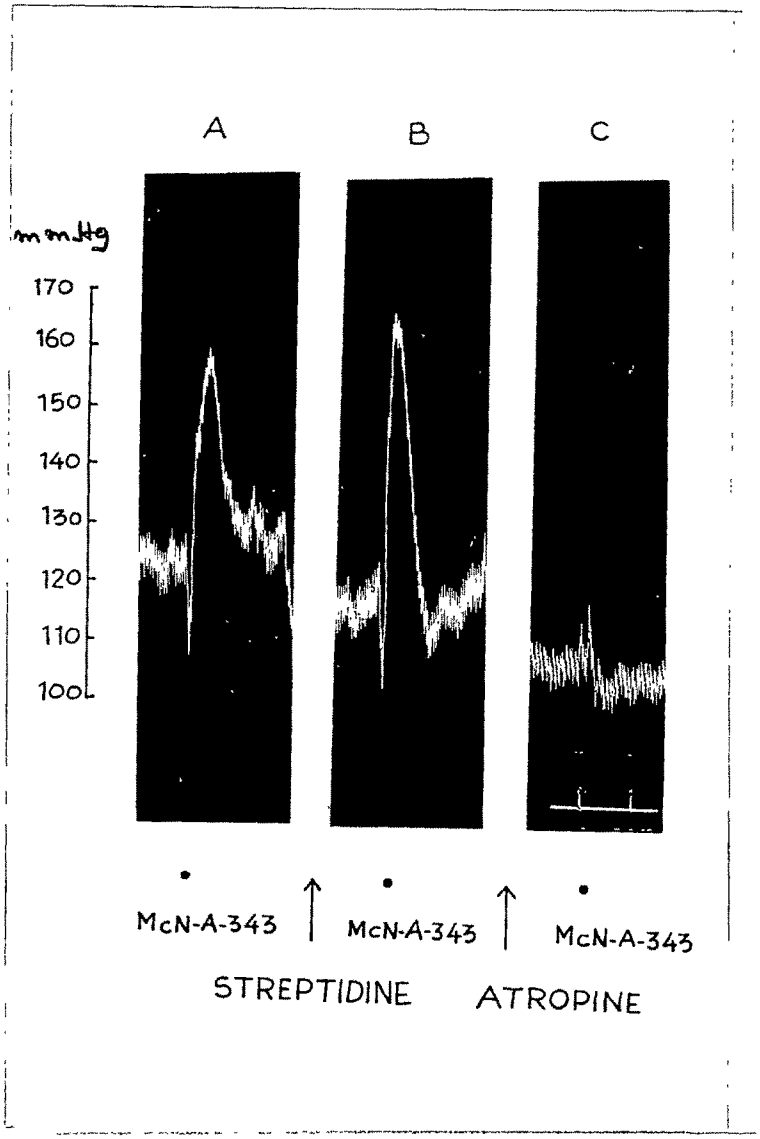

Fig. 9 :- Cat blood pressure (wt. 3 kg), chloralose anaesthesia. Responses to McN-A-343 (20 µg/kg). Panel A shows control responses. Responses shown in panel B was obtained 30 min after giving cumulative doses of streptidine (10 mg/kg X 3 every 30 min). Panel C shows response to McN-A-343 30 min after atropine sulphate (1 mg/kg). Time mark, 1 min.

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Figure No. 10

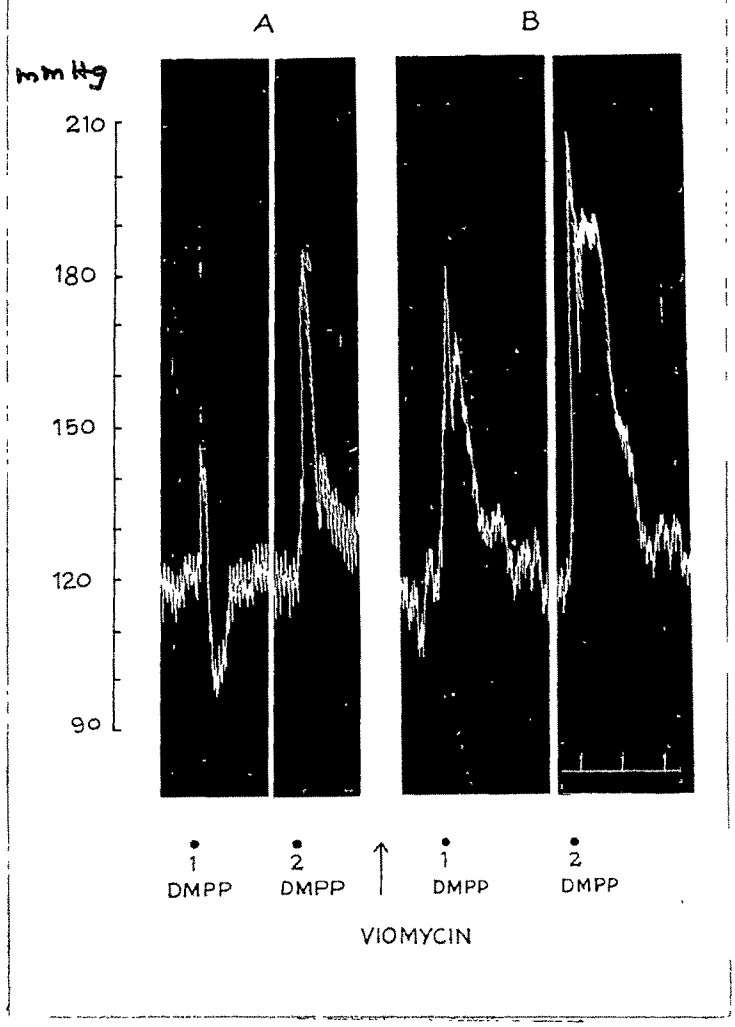

Fig. 10 :- Cat blood pressure (wt. 3 kg), chloralose anaesthesia. Responses to 5 µg/kg and 10 µg/kg of DMPP at 1 and 2 respectively. Panel A shows control responses and panel B shows responses 30 min after the administration of viomycin (10 mg/kg X 2 every 30 min). Time mark, 1 min.

completely blocked by atropine (1.0 mg/kg) injected 30 min before the challenging dose of agonist (Fig.9).

DMPP : In all experiments DMPP (5 and 10 ug/kg) produced a sharp rise in blood pressure commencing after a short latent period of 20-30 sec and lasting for 2 min. The control mean response following 5 µg/kg of DMPP was 21.5 ± 8.3 per cent (45 observations), and that following 10 µg/kg of DMPP was 42.0 ± 9.0 per cent (38 observations).

The pressor response to DMPP following the cumulative doses of the antibiotics and the two degradation products was increased in a manner similar to that following McN-A-343. The increase in the pressor response to both the doses of DMPP (5 and 10 µg/kg) was highly significant (Tables VIII and IX). Maximal increase in the response was observed 30 min after the last dose of the antibiotics or the degradation products and continued tobe elicited upto 3 hr (Fig.10).

P-286 (1 mg/kg) was injected 3 hr after the last dose of the antibiotics or the degradation products. Thirty min later, the pressor response to DMPP (5 and 10 µg/kg) was completely blocked. The pressor response to a higher doses of DMPP

Table VIII : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 5 μg/kg of DMPP in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean rise in blood pressure mm Hg ± S.E.		P
			Control response	Response following the compound	
Streptomycin	60.0	9	20.5 ± 11.2	38.1 ± 10.3	< 0.01
Kanamycin	30.0	6	23.7 ± 7.7	49.05 ± 17.0	< 0.01
Viomycin	30.0	6	26.1 ± 4.8	43.2 ± 12.7	< 0.01
Neomycin	20.0	6	21.8 ± 3.8	40.8 ± 11.8	< 0.01
Paromomycin	30.0	7	16.2 ± 6.2	35.2 ± 9.9	< 0.001
Streptidine	30.0	6	24.7 ± 7.0	44.6 ± 5.8	< 0.001
Streptamine	20.0	5	18.1 ± 6.4	37.3 ± 7.8	< 0.001

P indicates the probability for the difference between the control mean blood pressure response to DMPP and that following the compound.

Table IX : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 10 μg/kg of DMPP in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean rise in blood pressure mm Hg ± S.E.		P
			Control response	Response following the compound	
Streptomycin	60.0	5	40.4 ± 4.3	49.7 ± 3.1	< 0.01
Kanamycin	30.0	6	46.8 ± 9.7	53.0 ± 6.1	< 0.05
Viomycin	30.0	6	38.6 ± 9.2	59.1 ± 14.9	< 0.05
Neomycin	20.0	6	39.3 ± 7.6	64.4 ± 12.2	< 0.001
Paromomycin	30.0	6	36.1 ± 5.9	62.1 ± 11.5	< 0.001
Streptidine	30.0	5	43.9 ± 6.1	74.4 ± 10.1	< 0.001
Streptamine	20.0	4	52.0 ± 4.5	67.4 ± 7.9	< 0.01

P indicates the probability for the difference between the control mean blood pressure response to DMPP and that following the compound.

(50 µg/kg), could, still be elicited (2 experiments). Similarly the pressor responses to 5 µg and 10 µg/kg of DMPP were not elicited in adrenalectomised cats (adrenalectomy performed after eliciting a panel of modified responses to histamine). The pressor response to a higher dose (50 µg/kg) could be elicited in adrenalectomised cats.

Adrenaline and noradrenaline : The response to adrenaline (1 µg/kg) was variable. The response was pressor in 35 experiments, biphasic i.e. pressor followed by depressor in 15 experiments and purely depressor in 7 experiments. The response to 2 µg/kg of adrenaline was, however, pressor in all the experiments (60 observations).

The control mean pressor response to 1 µg/kg of adrenaline was 23.9 ± 8.5 per cent (50 observations) and that to 2 µg/kg was 35.5 ± 10.2 per-cent (60 observations). The recovery was complete in about 1 min.

The cumulative doses of the antibiotics and two degradation products did not affect the pressor response to adrenaline (1 and 2 µg/kg) significantly (Tables X and XI). The depressor response to 1 µg/kg of adrenaline (purely depressor or depressor

Table X : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 1 µg/kg of adrenaline in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean rise in blood pressure mm Hg ± S.E.		P
			Control response	Response following the compound	
Streptomycin	60.0	11	21.7 ± 10.6	26.9 ± 14.8	> 0.1
Kanamycin	30.0	9	25.4 ± 7.0	29.5 ± 12.5	> 0.1
Viomycin	30.0	7	24.8 ± 6.9	27.7 ± 10.1	> 0.1
Neomycin	20.0	7	20.8 ± 6.8	26.3 ± 7.9	> 0.1
Paromomycin	30.0	9	23.7 ± 8.7	27.7 ± 9.2	> 0.1
Streptidine	30.0	7	25.5 ± 11.0	33.7 ± 14.7	> 0.1
Streptamine	20.0	7	25.2 ± 5.8	34.0 ± 12.0	> 0.5

P indicates the probability for the difference between the control mean blood pressure response to adrenaline and that following the compound.

Table XI : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 2 µg/kg of adrenaline in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean rise in blood pressure mm Hg ± S.E.		P
			Control response	Response following the compound	
Streptomycin	60.0	11	29.1 ± 11.8	34.6 ± 12.7	> 0.1
Kanamycin	30.0	8	33.1 ± 8.2	36.6 ± 9.8	> 0.5
Viomycin	30.0	7	37.5 ± 5.4	42.8 ± 8.5	> 0.1
Neomycin	20.0	7	36.9 ± 13.4	53.6 ± 16.4	> 0.1
Paromomycin	30.0	8	34.6 ± 6.9	44.2 ± 12.5	> 0.1
Streptidine	30.0	9	37.5 ± 14.1	48.7 ± 19.4	> 0.1
Streptamine	20.0	10	40.6 ± 8.8	43.3 ± 9.7	> 0.5

component of the biphasic response) was changed to pressor response.

The response to noradrenaline was pressor in all the experiments. The control mean response to 1 and 2 µg/kg of noradrenaline were 39.1 ± 8.6 per cent (51 observations) and 49.4 ± 13.9 per - cent (44 observations) respectively.

The responses to both these doses of noradrenaline were not affected upto 3 hr following the cumulative doses of the antibiotic or the degradation product (Tables XII and XIII).

Modification of the responses of the cat blood pressure to vagal stimulation by the antibiotics and the degradation products :

The blood pressure of cats dropped instantaneously in response to stimulation of the right vagus nerve (10 volts, 0.5 m sec, 20 Hz). Vagal escape did not occur when stimulation was maintained for a period of 10 sec but it occured when the stimulation was continued for 15 sec or more. The blood pressure recovered to basal level on termination of stimulation.

Thirty min after the last dose of cumulative

Table XII : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 1 μg/kg of noradrenaline in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean rise in blood pressure mm Hg ± S.E.		P
			Control response	Response following the compound	
Streptomycin	60.0	8	40.3 ± 12.0	51.1 ± 9.7	> 0.1
Kanamycin	30.0	10	39.1 ± 9.7	47.1 ± 14.9	> 0.1
Viomycin	30.0	7	31.1 ± 9.1	37.0 ± 7.9	> 0.1
Neomycin	20.0	7	32.6 ± 9.9	42.7 ± 11.3	> 0.1
Paromomycin	30.0	7	38.7 ± 11.3	49.7 ± 11.5	> 0.1
Streptadine	30.0	8	42.7 ± 12.5	58.9 ± 13.6	> 0.1
Streptamine	20.0	6	36.3 ± 10.1	45.6 ± 11.8	> 0.1

P indicates the probability for the difference between the control mean blood pressure response to noradrenaline and that following the compound.

Table XIII : Effect of some antibiotics and streptidine and streptamine on the blood pressure responses to 2 µg/kg of noradrenaline in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean rise in blood pressure mm Hg ± S.E.		P
			Control response	Response following the compound	
Streptomycin	60.0	6	49.5 ± 11.8	54.7 ± 12.2	> 0.4
Kanamycin	30.0	6	50.3 ± 9.2	54.2 ± 12.7	> 0.1
Viomycin	30.0	7	44.0 ± 9.4	52.5 ± 12.1	> 0.1
Neomycin	20.0	7	46.7 ± 11.8	58.3 ± 16.5	> 0.1
Paromomycin	30.0	6	52.3 ± 10.6	58.8 ± 15.8	> 0.1
Streptidine	30.0	6	55.4 ± 21.5	71.3 ± 21.7	> 0.1
Streptamine	20.0	6	56.8 ± 17.8	56.2 ± 14.9	> 0.5

P indicates the probability for the difference between the control mean blood pressure response to noradrenaline and that following the compound.

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Figure No.11

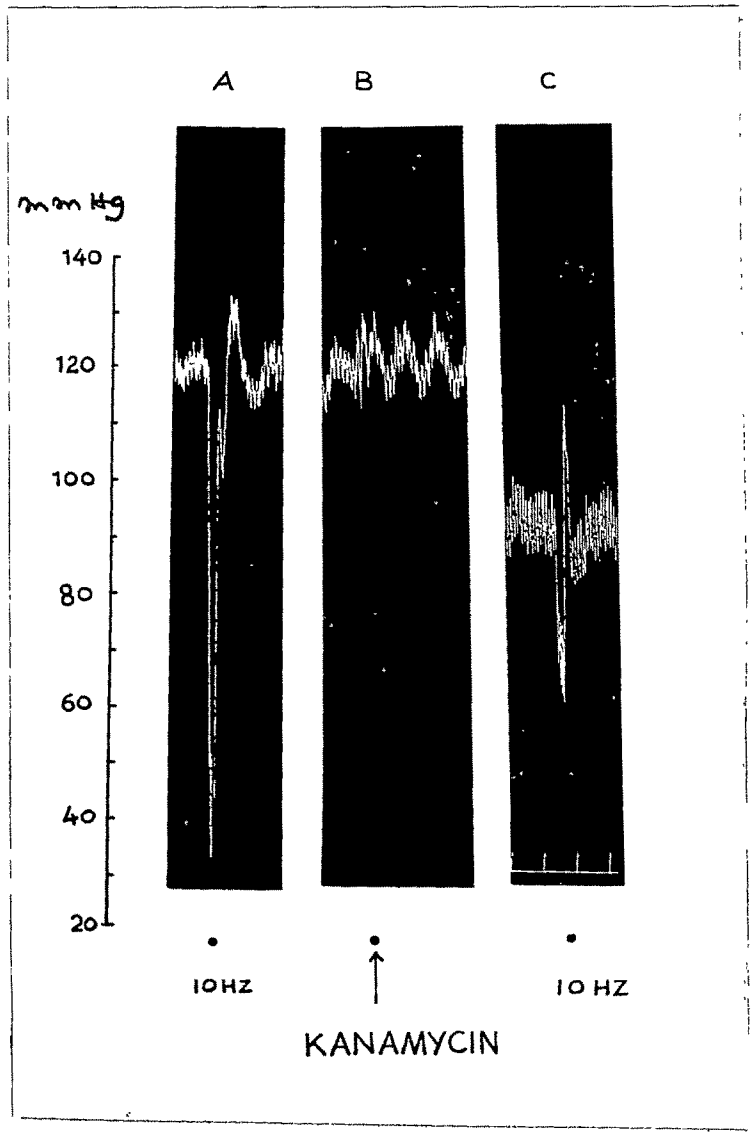

Fig.11 :- Cat blood pressure (wt. 2.5 kg), chloralose anaesthesia. Responses to vagal stimulation (10 Hz) and kanamycin (10 mg/kg). Panel A shows control response to vagal stimulation and panel C shows response 3 hr. after the cumulative administration of kanamycin (10 mg/kg X 2 every 20 min). Time mark, 1 min.

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Figure No.12

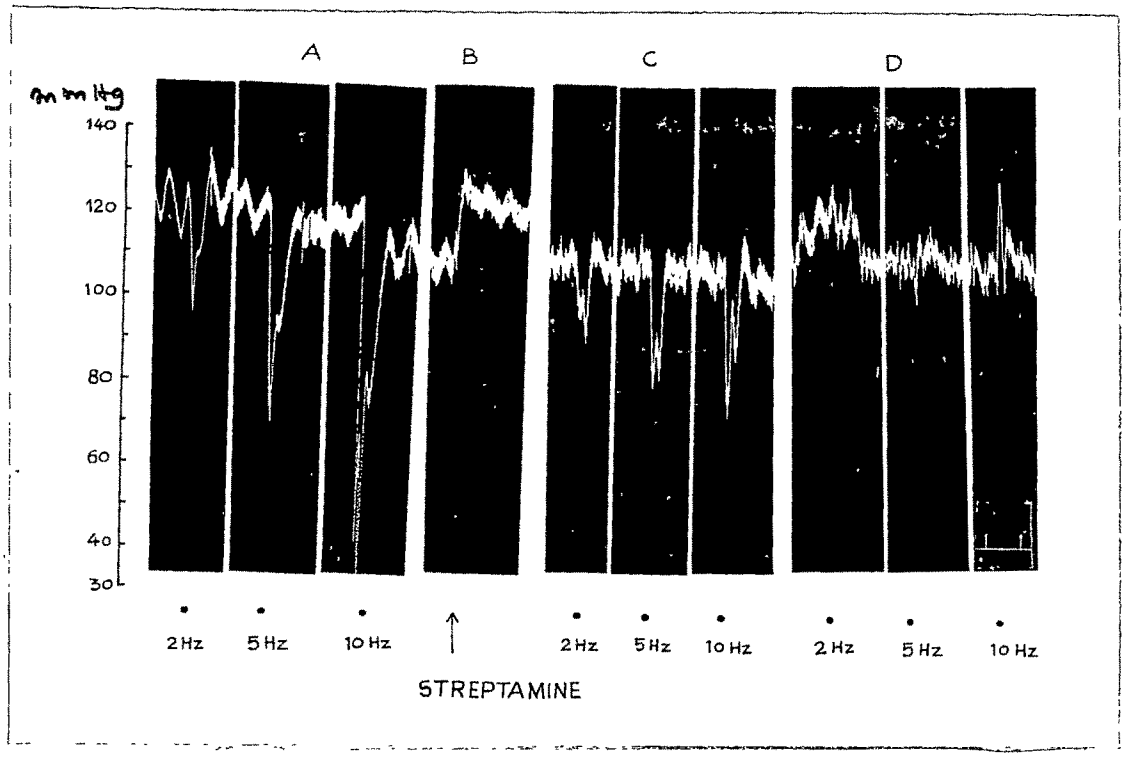

Fig. 12 :- Cat blood pressure (wt. 2.8 kg), chloralose anaesthesia. Responses to vagal stimulation at different frequencies (2,5 and 10 Hz) and to streptamine (10 mg/kg). Panel A shows control responses to vagal stimulation at different frequencies. Panels C and D show responses 30 min and 3 hr respectively after the cumulative administration of streptamine (10 mg/kg X 2 every 30 min). Panel B shows response to streptamine (10 mg/kg)STR). Time mark, 1 min.

administration of streptomycin, kanamycin, viomycin, or paromomycin, the fall in blood pressure in response to stimulation of the vagus (10 v., 0.5 m sec duration, 20 Hz) was inhibited to about 40-50 per cent of the control level (Fig.11). The vagal escape occured by the end of 5-7 sec and the blood pressure completely recovered to the basal level (5 observations).

The response to vagus stimulation following neomycin was similar to that with other antibiotics except that the secondary rise in blood pressure was observed in 2 out of 6 experiments.

The fall in blood pressure in response to vagus stimulation following streptidine was not inhibited. However, the vagal escape occured 2-3 sec after the start of stimulation. The secondary rise in blood pressure was observed (5 observations). The response to vagal stimulation was completely blocked (Fig.12) following streptamine (6 observations).

<u>The effect of the antibiotics and the degradation products on the superior cervical ganglion of cat:</u>

The heights of control mean contractile responses of the nictitating membrane to preganglio-

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Figure No. 13

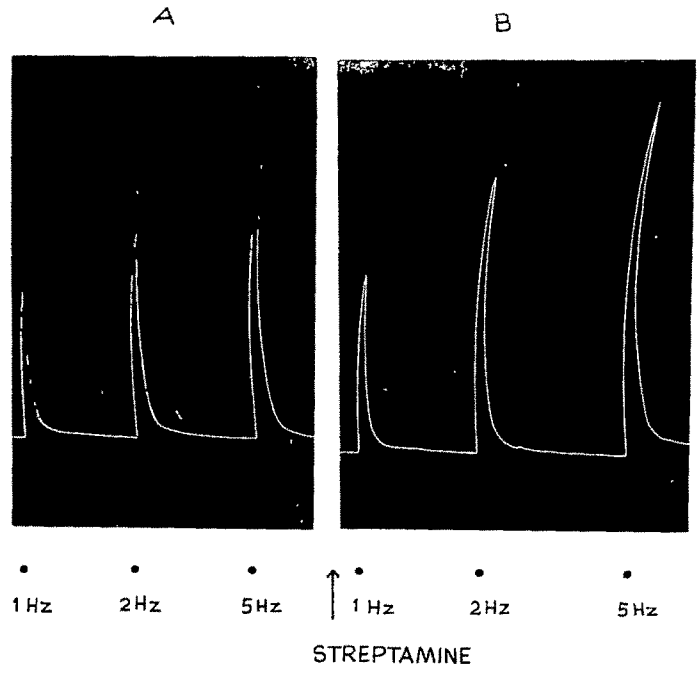

Fig.13 :- Cat nictitating membrane (wt. 2.3 kg), chloralose anaesthesia. Responses to stimulation of preganglionic sympathetic fibres of superior cervical ganglion at different frequencies (1, 2 and 5 Hz). Panel A shows control responses and panel B shows responses 3 hr after the administration of streptamine (10 mg/kg X 2 every 30 min). Time mark, 1 min.

nic stimulation of the superior cervical ganglion at 2, 5 and 10 Hz were 38.7 ± 7.4 mm (35 observations), 45.3 ± 8.3 mm (38 observations) and 49.4 ± 6.2 mm (30 observations) respectively. The contractions commenced immediately following tne stimulus and attained maximum height in about 6-7 sec. The response lasted for about 2 min.

Streptomycin, kanamycin, viomycin, neomycin and paromomycin (20 - 60 mg/kg) did not affect the ganglionic transmission since the contraction heights to stimuli following the antibiotics were not significantly different than the control heights (Tables XIV, XV and XVI).

The sensitivity of the nictitating membrane was more in cats used for experiments with streptamine; hence frequencies of 1, 2 and 5 Hz were employed. The results indicated that the responses of the nictitating membrane were significantly increased with all the frequencies (1, 2 and 5 Hz) (Fig.13). The contractions in response to 5 Hz and 10 Hz following streptidine were potentiated while those in response to 2 Hz were not potentiated. The potentiation lasted for 3 hr from the last dose of these compounds (Tables XIV, XV, XVI).

Table XIV : Effect of some antibiotics and streptidine and streptamine on the responses of nicititating membrane to preganglione stimulation of the superior cervical ganglion at 2 Hz in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean response of nictating membrane mm contraction ± S.E.		P
			Control response	Responses following the compound	
Streptomycin	60.0	9	36.7 ± 10.0	44.2 ± 8.0	> 0.1
Kanamycin	30.0	6	32.0 ± 8.2	37.5 ± 6.1	> 0.4
Viomycin	30.0	4	40.5 ± 3.9	41.2 ± 3.9	> 0.8
Neomycin	20.0	4	30.2 ± 3.9	37.0 ± 10.7	> 0.3
Paromomycin	30.0	4	28.0 ± 5.7	31.0 ± 3.5	> 0.4
Streptidine	30.0	4	39.7 ± 6.8	48.2 ± 5.4	> 0.1
Streptamine	20.0	4	50.2 ± 4.1	57.7 ± 3.0	< 0.05

P indicates the probability of significance for the difference between the control mean response to preganglionic stimulation of superior cervical ganglion and that following the compounds.

Table XV : Effect of some antibiotics and streptidine and streptamine on the responses of nictating membrane to preganglionic stimulation of the superior cervical ganglion at 5 Hz in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean response of nictating membrane mm contraction ± S.E.		P
			Control response	Responses following the compound	
Streptomycin	60.0	8	48.3 ± 4.3	54.9 ± 5.9	> 0.3
Kanamycin	30.0	7	40.4 ± 8.1	44.6 ± 9.2	> 0.8
Viomycin	30.0	4	40.5 ± 3.8	41.2 ± 3.9	> 0.8
Neomycin	20.0	6	37.3 ± 5.3	41.5 ± 6.7	> 0.3
Paromomycin	30.0	5	40.4 ± 2.7	40.8 ± 3.1	> 0.8
Streptidine	30.0	4	52.5 ± 3.3	57.8 ± 2.2	< 0.05
Streptamine	20.0	4	63.5 ± 4.0	71.0 ± 4.8	< 0.05

P indicates the probability of significance for the difference between the control mean responses to preganglionic stimulation of superior cervical ganglion and that following the compounds.

Table XVI : Effect of some antibiotics and streptidine on the responses of nictating membrane to superior cervical ganglion stimulation at 10 Hz in cats of either sex, weighing 2.0-4.5 kg and anaesthetised with chloralose (80 mg/kg). Responses following the test compound were elicited 3 hr after its last dose.

Compound	Cumulative dose mg/kg (10 mg/kg every 30 min)	Number of observations	Mean response of nictating membrane mm contracting Hg ± S.E.		P
			Control response	Response following the compound	
Streptomycin	60.0	7	61.0 ± 7.0	69.3 ± 7.2	> 0.05
Kanamycin	30.0	5	41.6 ± 8.5	42.8 ± 8.1	> 0.8
Viomycin	30.0	4	48.2 ± 4.3	48.7 ± 4.8	> 0.9
Neomycin	20.0	5	46.8 ± 5.4	48.6 ± 6.9	> 0.6
Paromomycin	30.0	5	49.6 ± 4.8	52.8 ± 5.5	> 0.4
Streptidine	30.0	4	68.0 ± 5.1	74.5 ± 2.2	< 0.05

P indicates the probability of significance for the difference between the control mean response to preganglionic stimulation of superior cervical ganglion and that following the compound.

Modification of the responses of the dog blood pressure to different procedures and drugs by the antibiotics and the degradation products :

Blood pressure : The antibiotics (10 and 20 mg/kg each) did not affect the blood pressure of dogs. Streptidine (10 mg/kg) and streptamine (10 mg/kg) however raised the blood pressure of the dogs in a manner similar to that in cats. The magnitude of the rise in response to streptidine was not dose-related, though the response to higher doses (20 mg/kg) was sustained for longer duration (10-15 min). The responses to 10 and 20 mg/kg of streptamine were dose related though higher doses (30 mg/kg) did not show a proportionate increase.

The responses to histamine (1 and 2 µg/kg), McN-A-343 (10 and 20 µg/kg), DMPP (5 and 10 µg/kg), adrenaline (1 and 2 µg/kg), and noradrenaline (1 and 2 µg/kg) were not modified by the antibiotics and the degradation products. However, if the initial responses to adrenaline (1 µg/kg) were depressor or biphasic, they were converted to completely pressor responses as was observed in cats.

The vagal effect on blood pressure was modified in a manner similar to that described for the cat blood pressure.

The contraction of the nictating membrane in response to preganglionic stimulation of superior cervical ganglion was not affected by the antibiotics and the degradation products.