PART III
GENERAL PHARMACOLOGY
CHAPTER I

EFFECT OF LOCAL ANAESTHETICS ON CARDIOVASCULAR SYSTEM.
PART III

General Pharmacology.

Effect of local anaesthetics on cardiovascular system.

Section 'A': Effect of local anaesthetics on arterial blood pressure of dogs.

Effect of local anaesthetics on the arterial blood pressure has been investigated by different workers. Haggart Woods (1951) observed that intravenous injections of lignocaine, procaine and cocaine produced a severe fall of blood pressure in anaesthetised dogs. Anrep (1880) observed a rise in blood pressure with cocaine. Kimmey et al. (1959) and Larden et al (1956) reported a rise in arterial blood pressure with lignocaine in man and dogs. Edmonds et al (1949) observed a fall in blood pressure with procaine. It is thus obvious that the effect of local anaesthetics on arterial blood pressure in experimental animals and human beings has varied from drug to drug and from worker to worker even with the same drug. The effect of local anaesthetics on the pressure and depressor responses of autonomic drugs has also been investigated by different workers. Bran (1941) and Tischet (1951) reported an increase in pressure responses of epinephrine with cocaine. Nakauchi et al. (1952) observed no change in the pressor response of epinephrine with lignocaine while other workers, Hazard et al. (1951) and Wæedling (1932) have reported a
decreased pressor response to epinephrine. Procaine and cocaine were found to potentiate the pressor response of epinephrine (Nakauchi et al. 1952). The effect on depressor response of acetylcholine with local anaesthetics has also been investigated by several workers. Hazard et al. (1946) found that procaine does not inhibit the hypotensive effect of acetylcholine while lignocaine has been shown to antagonise it (Frommel et al. 1950).

The following experiments were performed to evaluate the effect of the present series of local anaesthetics on the arterial blood pressure of dogs and to find out if any relationship exists between the vascular effects of these drugs and the pressor and depressor responses of autonomic drugs and histamine.

**Procedure for recording Dog's blood pressure.**

Dogs used in these experiments usually weighed between 6 to 8 kg. The dogs were anaesthetised with sodium pentobarbitone 40 mg/kg intraperitoneally. The trachea was exposed and cannulated for inducing artificial respiration when necessary. The right common carotid artery was exposed, cannulated and connected to a mercury manometer through a rubber tubing containing a column of 9% sodium citrate solution, used as an anticoagulant. Blood pressure reading were recorded on a slowly moving kymograph. All the drug solutions were injected through the cannulated femoral vein.

Graded doses ranging from 1 to 5 mg/kg of local
anaesthetics were given and changes in the arterial blood pressure were recorded.

The effect of local anaesthetics was also investigated after atropinisation and after administration of antihistaminic drugs. In certain experiments suitable doses of adrenaline, acetylcholine and histamine were given before and after the administration of local anaesthetics in order to find out if any relationship exists between the effect of local anaesthetics and the autonomic drugs and histamine.


Dogs weighing from 6 to 8 kg were used. They were anaesthetised with ether. Trachea was exposed and cannulated and connected to an ether bottle. A continuous supply of ether was made in order to maintain the anaesthesia. Both the common carotid arteries were exposed in the neck and ligatured so as to minimise the blood loss during the later process. The animal was turned on its belly. The spine of the second cervical vertebra was cleared and cut, and spinal cord exposed. Ether was disconnected at this stage and the artificial respiration started. The cord was then cut, a probe was immediately thrust into foramen magnum and the brain destroyed. Bleeding was checked by inserting a cone of plasticine into the foramen magnum and then plugging it by means of a cork. The muscles and skin were stitched. The animal was then turned on its back. One of the common carotid arteries was cannulated and the blood
pressure recorded on the slowly moving kymograph. The drug solutions were injected through a cannulated femoral vein. In certain experiments blood pressure was elevated by administration of suitable doses of ephedrine hydrochloride and the effect of local anaesthetics was investigated in graded doses.

**RESULTS**

**Effect of local anaesthetics on the arterial pressure of dogs.**

Graded doses of local anaesthetics were given ranging from 1 to 5 mg/kg. All the drugs produced a fall in blood pressure which was approximately proportionate to the doses administered. The most prominent hypotensive effect was observed with lignocaine (L), while the minimum was seen with compound B. The results have been illustrated in fig. 1 to 7.

Effect of these compounds was also studied after complete paralysis of vagal nerve endings to exclude parasympathomimetic action of these drugs. This was achieved by means of atropine sulphate given (0.3mg/kg) intravenously. The hypotensive action produced by the local anaesthetics remained unaltered on atropinisation, this excluded the possibility of their action on the effector cells innervated by parasympathetic autonomic nerve endings. Similarly to exclude the histamine like action of these compounds, a potent antihistaminic drug (Mepyramine maleate) was given prior to local anaesthetic
drugs. The results illustrated in fig. 8 to 14 indicate that the effect has remained unaltered even after full doses of antihistaminic drugs.

The effect of these local anaesthetics on the actions caused by chemical mediators of the body such as adrenaline and acetylcholine on the blood pressure of dogs did not show any marked change. Similarly the actions due to histamine remained unaltered after administration of these compounds. The results have been illustrated in Fig. No. 15 to 21.

Effect of local anaesthetics on the arterial blood pressure of spinal dogs.

The effect of local anaesthetics was studied on the arterial blood pressure of spinal dogs in order to exclude the central nervous influences on the hypotension caused by these compounds. In these very experiments the effect of these drugs was also investigated against the ephedrine (0.5 mg/kg) induced hypertension. The local anaesthetics in graded doses continued to show hypotensive action though the effect was much more marked against ephedrine induced hypertension. The results obtained in these experiments indicate that central nervous system plays little part in causing hypotension by these compounds (Fig 22, 23, 24, 25, 26.).

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SHOWING THE EFFECT OF COMPOUNDS A, B AND C ON ARTERIAL BLOOD PRESSURE OF DOG, BEFORE AND AFTER ATROPINE.

**Fig. 1**

**Fig. 2**

**Fig. 3**

**LEGEND.**

- $A_1$ - 1 mg/kg of compound A.
- $A_2$ - 5 mg/kg of compound A.
- $A_2$ - 5 mg/kg of compound A after atropine.
- $B_1$ - 1 mg/kg of compound B.
- $B_2$ - 5 mg/kg of compound B.
- $B_2$ - 5 mg/kg of compound B after atropine.
- $C_1$ - 1 mg/kg of compound C.
- $C_2$ - 5 mg/kg of compound C.
- $C_2$ - 5 mg/kg of compound C after atropine.
- $T$ - Time - 5 sec. seconds interval.
SHOWING THE EFFECT OF COMPOUNDS D, E AND F ON ARTERIAL BLOOD PRESSURE OF DOG, BEFORE AND AFTER ATROPINE.

LEGEND

\[
\begin{align*}
D_1 & : 1 \text{ mg/kg of compound D} \\
D_2 & : 5 \text{ mg/kg of compound D} \\
D_2^* & : 5 \text{ mg/kg of compound D after atropine}.
\end{align*}
\]

\[
\begin{align*}
E_1 & : 1 \text{ mg/kg of compound E} \\
E_2 & : 5 \text{ mg/kg of compound E} \\
E_2^* & : 5 \text{ mg/kg of compound E after atropine}.
\end{align*}
\]

\[
\begin{align*}
F_1 & : 1 \text{ mg/kg of compound F} \\
F_2 & : 5 \text{ mg/kg of compound F} \\
F_2^* & : 5 \text{ mg/kg of compound F after atropine}.
\end{align*}
\]

\[
\begin{align*}
T & : \text{Time - 5 seconds interval.}
\end{align*}
\]
SHOWING THE EFFECT OF COMPOUNDS A, L, ON ARTERIAL BLOOD PRESSURE OF DOG, BEFORE AND AFTER ATROPINE.

Fig. 7

LEGEND

$L_1$ - 1 mg/kg of compound L.
$L_2$ - 5 mg/kg of compound L.
$L'_2$ - 5 mg/kg of compound L after atropine.

T - Time - 5 seconds interval.
SHOWING THE EFFECT OF COMPOUNDS C AND D ON ATERIAL BLOOD PRESSURE OF DOG, BEFORE AND AFTER MEPYRAMINE MALEATE.

LEGEND

C - 5 mg/kg of compound C
C - 5 mg/kg of compound C after Mepyramine maleate
D - 5 mg/kg of compound D.
D - 5 mg/kg of compound D after Mepyramine maleate
T - Time - 5 at seconds interval.
SHOWING THE EFFECT OF COMPOUNDS E, F AND L
ON ARTERIAL BLOOD PRESSURE OF DOG, BEFORE
AND AFTER Mepyramine maleate.

LEGEND

\[ \begin{align*}
E & \quad - \quad 5 \text{ mg/kg of compound E} \\
E & \quad - \quad 5 \text{ mg/kg of compound E after Mepyramine maleate} \\
F & \quad - \quad 5 \text{ mg/kg of compound F} \\
F & \quad - \quad 5 \text{ mg/kg of compound F after Mepyramine maleate} \\
L & \quad - \quad 5 \text{ mg/kg of compound L} \\
L & \quad - \quad 5 \text{ mg/kg of compound L after Mepyramine maleate} \\
T & \quad - \quad \text{Time - 5 sec seconds interval}
\end{align*} \]
SHOWING THE INTERRELATIONSHIP OF COMPOUNDS C & D WITH ACETYLCHOLINE, ADRENALINE AND HISTAMINE ON ARTERIAL BLOOD PRESSURE OF DOG.

LEGEND

At X, Y and Z 50, 10 and 20 Y respectively of Acetylcholine, Adrenaline and Histamine were given.

At C and D 5 mg/kg respectively of compound C & D were given.

T - indicates time at 5 seconds intervals.
SHOWING THE INTERRELATIONSHIP OF COMPOUNDS E, F & L WITH ACETYLCHOLINE, ADRENALINE AND HISTAMINE ON ARTERIAL BLOOD PRESSURE OF DOG.

LEGEND

At X, Y and Z 50, 10 and 20 respectively of Acetylcholine, Adrenaline and Histamine were given.

At E, F & L 5 mg/kg respectively of compound E, F and L were given.

T: - indicates time at 5 seconds intervals.
SHOWING THE EFFECT OF COMPOUNDS A, C, F, L & E ON DRUG INDUCED HYPERTENSION OF SPINAL DOG.

LEGEND.

At EP 0.5 mg/kg of Ephedrine hydrochloride was given.

At A, C, F, L & E 5 mg/kg respectively of compounds A, C, F, L & E were given.

T - indicates time at 5 seconds interval.
SHOWING THE EFFECT OF COMPOUNDS B and D ON
DRUG INDUCED HYPERTENSION OF SPINAL DOG.

Fig. 25

Fig. 26

LEGEND

At EP 0.5 mg/kg of Ephedrine hydrochloride was
given.

At B and D 5 mg/kg respectively of compounds
B & D were given.

T - indicates time at 5 seconds interval.
Section 'B' - Effect of local anaesthetics on blood vessels.

All the local anaesthetics investigated in the present series including lignocaine have shown a fall in arterial blood pressure (Chapter 1, section A, this thesis). It was therefore considered worthwhile to investigate the mechanism of action of hypotension caused by these drugs. One possible site of action is the peripheral blood vessels. Cocaine, one of the oldest local anaesthetics has been shown to produce prominent vascular effect; in smaller doses it causes peripheral vasoconstriction and larger doses dilatation (Sollmann, 1956). On the other hand local anaesthetics like procaine, stovaine, alypin, eucaine etc. have been shown to produce only dilatation of peripheral blood vessels (Impens, 1905, Behr, 1934). Following experiments were undertaken to evaluate the effect of the present series of local anaesthetics on the blood vessels of experimental animals.

Methods and Materials.

1. Perfused blood vessels of frog:

   Pithed frogs were used. The heart was exposed and cleaned the connective tissues etc. One of the innominate arteries was separated and a ligature was placed under it. A 'V' shaped nick was made into it as near the heart as possible and cannula inserted into the peripheral
end directly away from the heart and tied in situ. The heart was excised or cut into. The cannula was filled with frog's Ringer solution making sure that no air bubbles were present. The frog was now hung by means of a string to a stand. The rubber tubing of the perfusion apparatus was then connected with the cannula, taking special care that the artery was not kinked or twisted. The perfusion was allowed to proceed through the arterial system and back again to the great veins from which it escaped. The rate of the flow was measured by counting the drops falling along the toes of the animals. The rate was adjusted with the help of an adjustable clip so that the number of drops falling per minute was about 20 to 40. When the rate of outflow was constant the respective drug solution in graded doses was injected with the help of hypodermic syringe into the rubber tubing connecting the cannula with the perfusion apparatus and the effect was noted. Special care was taken to make sure that the effect of one single dose had passed out completely before the next dose was injected.

2. Perfused hind limb blood vessels of dogs:

Dogs weighing between 6 to 8 kg. were used. They were anaesthetised with sodium pentobarbitone solution 30 mg/kg given intraperitoneally. One of the common carotid arteries was exposed in the neck and cannulated. The animal was bled through this common carotid artery
and the blood collected in a glass jar. The blood was defibrinated by churning vigorously with small pieces of broom sticks tied together. When the white flakes of fibrin had been separated the blood was filtered and mixed with oxygenated Ringer's solution and then used as perfusion fluid. Femoral artery and vein of one side were exposed and cannulated. The cannula in the femoral artery was connected through the rubber tubing to a reservoir placed at a suitable height containing defibrinated and oxygenated blood and a regular flow was maintained. The outflow of blood from the femoral vein was collected in graduated cylinder and measured at regular intervals. The solutions of local anaesthetics in graded doses ranging from 1 to 5 mg/kg were injected into the cannula at the arterial end. The venous outflow was measured at regular intervals until it returned to its original rate.

3. The coronary blood vessels of rabbit (Langendorff's preparation)

Rabbits were killed by a blow on head. The throat was cut and blood drained out. The chest was opened and the heart was removed. It was placed in a basin containing oxygenated Ringer's solution and gently squeezed to remove the blood from the aorta. The cannula was then tied into the aorta.

Assembly for perfusion of the isolated rabbit's heart was kept ready beforehand. Ringer lock solution was oxygenated in a side tube and warmed while passing through a coil immersed in a water bath. The lower end of the coil was connected to the upper end of four way
glass cannula by means of a rubber tubing. The lower most end was tied to the aorta while the remaining two side tubes were fitted with a thermometer and the mercury manometer. The flow of perfusion was adjusted at a constant rate and pressure. The temperature of the perfusion was maintained at 37° C. The ventricle was hooked by means of a curved pin tied with a thread which passes over system of pulleys and finally connected to a long heart lever. The contractions were recorded on a slowly moving drum. The rate of the outflow falling from the heart was noted.

The outflow from the heart was the outflow of fluid which was passed through the coronary arteries to the coronary sinus, and therefore its volume depended on the calibre of the coronary vessels. Graded doses of the drugs were injected through the side arm of the cannula and the effect on outflow and the myocardium was noted.

RESULTS

Effect of local anaesthetics on blood vessels.

A. Effect on perfused blood vessels of frog:- Graded doses of local anaesthetic compounds were given ranging from 0.1 to 1 mg. All the drugs have shown a vasodilatory effect which was approximately proportionate to the doses administered. In small doses (0.1 mg) compound A was found to be the most potent while in higher doses (1 mg) it was compound C which was found
to be the most effective as a vasodilatory agent. Compound B was found to be least potent in this respect. The results have been illustrated in Table No. 6, graph No. 5.

B. Effect on perfused hind limb vessels of dog.
Graded doses of local anaesthetics were given ranging from 1 to 5 mg/kg body weight. Vasodilation was seen with all the drugs which was roughly proportionate to the doses administered. Qualitatively the results were similar as seen in experiments on perfused blood vessels of frog. Compound A & F were found to be the most potent as vasodilatory agents in smaller and higher doses respectively. The least potent were compounds B & E. The results have been illustrated in Table No. 7, graph No. 6.

C. Effect on coronary vessels of rabbit.
Graded doses of local anaesthetics were given ranging from 10.0Y to 1 mg. The effect varied with different compounds. The results may be grouped in 4 categories. Firstly, those which showed an initial increase followed by a decrease in coronary out-flow; this includes compound A. Secondly, those which increase the coronary out flow in all the doses; this includes compound D & F. Thirdly, those which decreased the coronary flow in all the doses which includes compound C. Fourthly, those which have a very little effect on the coronary outflow; these are compounds B, E & L. The
results have been illustrated in Table No.8. It is evident that most of the compounds have little effect on the coronary outflow. However, compound D & F have shown considerable coronary dilator action of which compound F is more potent.
TABLE No. 6

Showing the effect of the local anaesthetics on the perfused blood vessels of frogs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in mg</th>
<th>No. of observations</th>
<th>mean percentages increase in vol.</th>
</tr>
</thead>
<tbody>
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<td>25.5</td>
</tr>
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<td>4</td>
<td>46.0</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>4</td>
<td>68.0</td>
</tr>
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<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>4</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>4</td>
<td>43.0</td>
</tr>
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<td>4</td>
<td>19.0</td>
</tr>
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<td>4</td>
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</tr>
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<td></td>
<td>1.0</td>
<td>4</td>
<td>81.0</td>
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<td>4</td>
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</tr>
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<td>4</td>
<td>34.0</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>4</td>
<td>62.0</td>
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<td>4</td>
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TABLE No. 7

Showing the effect of local anaesthetics on the venous outflow in the perfused leg of dog.

<table>
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<tr>
<th>Drug</th>
<th>Dose in mg/kg</th>
<th>No. of observations</th>
<th>Mean % increase in vol.</th>
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<td>4</td>
<td>49.0</td>
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Graph showing the comparative effect of local anaesthetic compounds on the blood vessels of frog.

GRAPH NO. 5.
Graph showing the comparative effect of local anaesthetic compounds on the venous outflow of the perfused hind limb vessels of dog.

GRAPH - NO. 6.
TABLE No. 8
The effect of local anaesthetics on the coronary blood vessels of isolated perfused heart of rabbit.

<table>
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<tr>
<th>Drug</th>
<th>Dose in micro-grammes</th>
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</table>
Section 'C': Effect of local anaesthetics on the vasomotor centre in dogs.

Local anaesthetics which effect the blood pressure of experimental animals have also been shown to influence the carotid sinus reflex and vasomotor centre. Anrep (1880) demonstrated that rise in blood pressure with cocaine was associated with stimulation of vasomotor centre. Heymans et al. (1933) also observed an effect on the carotid sinus reflex with cocaine and with large doses of procaine. While investigating the effect of the present series of local anaesthetics, cognisance was taken of the possible effect on the carotid sinus reflex mechanism and as such experiments were performed to evaluate the effect of these drugs on it.

According to Mary's law a fall in blood pressure in the carotid sinus causes a rise in general arterial pressure. The reason being that a fall of arterial blood pressure in the carotid sinus causes a reflex stimulation of the vasomotor centre which in turn causes a rise in the general arterial blood pressure. Thus the main underlying principle in the experiment to be described is that if any drug depressed the vasomotor centre in the medulla, then clamping of both the common carotid arteries in the neck would result in a lowered rise of blood pressure.

Experimental procedure.

Dogs weighing 6 to 8 kg were used. They were
anaesthetised with 30 mg/kg of pentobarbitone sodium intravenously. Trachea was exposed and cannulated for artificial respiration when necessary. Femoral artery was dissected out in one of the legs and cannulated by means of an arterial cannula. The femoral blood pressure was recorded on a slowly moving kymograph. Common carotid arteries of both the sides were dissected out in the neck, a loose thread was put around the arteries so as to facilitate clamping when required. Both the carotid arteries were clamped simultaneously for half a minute and the rise in femoral arterial pressure was noted. The process was repeated 2 to 3 times till a constant rise in blood pressure was attained. The drug solutions were injected through the cannulated femoral vein and the rise in blood pressure was noted each time on clamping the common carotid arteries.

RESULTS.

Graded doses of local anaesthetics were administered in doses ranging from 1 to 5 mg/kg of body weight, before and after clamping both the common carotid arteries simultaneously for 30 seconds. Results have been illustrated in Fig. 27 to 33. It is evident that the drugs have not in any way altered the rise in blood pressure on clamping the common carotid arteries. This indicates that the hypotension caused by local anaesthetics is not dependent on its effect on carotid sinus or vasomotor centre.
showing the effect of compounds A & B on the vasomotor centre in dogs (carotid sinus reflex)

Fig. 27

LEGEND

At dot occlusion of both the common carotids for half minute.

At A & B 5 mg/kg respectively of compounds A & B were given.

T - indicates time at 5 seconds interval.
showing the effect of compounds C & D on the vasomotor centre in dogs (carotid sinus reflex)

At dot occlusion of both the common carotids for half minute.

At C & D 5 mg/kg respectively of compounds C & D were given.

T - indicates time at 5 seconds interval.
showing the effect of compounds E, F & L on the vasomotor centre in dogs (carotid sinus reflex)

**LEGEND**

At dot occlusion of both the common carotids for half minute.

At E, F & L 5 mg/kg respectively of compound E, F & L were given.

T - indicates time at 5 seconds interval.
Section 'D': Effect of local anaesthetics on autonomic ganglion.

While elucidating the mechanism and sites of hypotensive action of local anaesthetics autonomic ganglion was also thought of as possible site of action. Some of the older local anaesthetics such as cocaine and procaine have been shown to affect the autonomic ganglion by different workers. Hazard (1949) observed depression in transmission of impulses in the synapses of all peripheral ganglion with procaine. Similar observations have been made by Macgregor (1939) and Harvey (1939) with both procaine and cocaine. Following experiments were performed to investigate the effect of the present series of local anaesthetics on the autonomic ganglion.

Experimental Procedure.

The method employed was essentially the same as described by Burn (1952) for cat. In the present experiment dogs weighing between 6 to 8 kg were used. They were anaesthetised with pentobarbitone sodium 40 mg/kg intraperitoneally. Trachea was exposed and cannulated for artificial respiration when needed. The head of the animal was raised on a block and held firmly in position. By means of a silk thread, the edge of the nictitating membrane was tied, the thread was taken onward and forward so as to be an angle of about 30° with axis of the animal, then round a pulley and vertically up to a lever writing on a drum with frontal writing point. The vagosympathetic
chain was dissected in the neck right up to the thorax
where the sympathetic fibers separate out. The
sympathetic fibers were cut sufficiently low in the
thorax so that it can be held on a pair of shielded
platinum electrodes and left in position. The chain was
stimulated with 2 to 3 m.a. current derived from an
electronic stimulator. The drugs were administered
through the cannulated femoral vein and the effects were
noted after pre and post ganglionic stimulation of the
sympathetic chain on the contraction of the nictitating
membrane.

RESULTS

All the local anaesthetics were administered
in a dose of 5 mg/kg of body weight. The effect of
these compounds was observed on the contractions of
nictitating membrane of dogs after stimulation of the
pre and post ganglionic fiber of the cervical sympathetic
chain. The results have been illustrated in Table No.9
and graph No.7 and Figs. No.34-47.

Compound E & F seemed to be the most potent
in reducing the height of contraction of nictitating
membrane after pre-ganglionic stimulation; while compound
A' & L appeared to be the most potent in inhibiting the
contractions of the nictitating membrane after post
ganglionic stimulation. Looking to the effect of local
anaesthetics on the autonomic ganglion, the latter seems
to play an important rôle in causing hypotension.
### TABLE No. 9

**Effect of local anaesthetics on the contractions of nictitating membrane of dogs.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in mg/kg</th>
<th>No. of observation</th>
<th>Mean % reduction in height of contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>F</td>
<td>5</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>L</td>
<td>5</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>II.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>F</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>L</td>
<td>5</td>
<td>3</td>
<td>30</td>
</tr>
</tbody>
</table>

I: Preganglionic stimulation.

II: Post-ganglionic stimulation.

***
Effect on Pre-ganglionic Stimulation  
Effect on Post-ganglionic Stimulation

Graph showing the comparative effect of local anaesthetic compounds on the contractions of nictitating membrane of dog.

GRAPH - NO. 7.
Showing the effect of compounds A, B, C & D on the contractions of nictitating membrane of dog.

Legend

All the contractions are due to preganglionic stimulation.

At A, B, C & D 5 mg/kg respectively of compounds A, B, C & D were given.

T - indicates time at 5 seconds interval.
Showing the effect of compounds E, F & L on the contraction of nictitating membrane of dog.

LEGEND

All the contractions are due to preganglionic stimulation.

At E, F & L 5 mg/kg respectively of compounds E, F & L were given.

T - indicates time at 5 seconds interval.
Showing the effect of compounds A, B, C & D on the contraction of nictitating membrane of dog.

Fig.41
Fig.42

Fig.43
Fig.44

LEGEND

All the contractions are due to postganglionic stimulation.

At A, B, C & D 5 mg/kg respectively of compounds A, B, C & D were given.

T - indicates time at 5 seconds interval.
Showing the effect of compounds E, F & L on the contraction of nictitating membrane of dog.

All the contractions are due to postganglionic stimulation.

At E, F & L 5 mg/kg respectively of compounds E, F & L were given.

T - indicates time at 5 seconds interval.
Section 'E': Effect of local anaesthetics on heart.

Older local anaesthetics such as cocaine and procaine have been thoroughly investigated regarding their effect on heart by different workers (Kochmann, 1908, Prus 1913, Kuroda 1915, Bush 1920, Kochmann 1921, and Macgregor, 1939). There is a general agreement regarding the effect of cocaine on heart which is stimulated in smaller doses and depressed in large quantities, while still larger concentrations cause complete arrest of the heart. Similarly procaine has also been shown to stimulate isolated auricles in smaller concentrations and depress the heart in larger doses (Roth 1917, McGregor 1939). The pharmacological effect of procaine on heart has been applied therapeutically in conditions of cardial irregularities (Mautz 1936, Wiggers et al. 1940, Burstein 1940, Hirschfeider et al 1942, Dawes 1946 & Wedd et al 1951).

Following experiments were performed in order to study the effect of local anaesthetics on heart.

**Methods and Materials**

1. **Isolated perfused heart of frog.**

The frog was pithed. The heart was exposed and pericardium removed. A ligature was placed in position under the exposed inferior vena-cava. A 'V' shaped nick
was made into it as much away the heart as possible; a syme's perfusion cannula was inserted and directed towards the heart and tied in situ. The heart along with the cannula was then removed from the thoracic cavity by cutting away the blood vessels coming in and out of the heart. The heart was then suspended to a stand. The side tube of the cannula was connected to a glass reservior containing oxygenated Ringer's solution. Perfusion was started at a rate of 40 drops per minute. A small hook was applied to the ventricular apex and the thread attached to it was connected to the heart lever. The contractions were recorded on a slowly moving drum. Graded doses of local anaesthetics were injected through the side arm of the syme's cannula.

2. **Isolated heart of rabbit (Langendorff's preparation).**

   The method employed was same as described under section B of this chapter, while observing the actions of drugs on coronary circulation. The effect on the rabbit's myocardium was simultaneously recorded on the slowly moving drum.

3. **Isolated auricle of rabbit.**

   The heart was excised from a freshly killed rabbit and placed on a cork mat. The auricles were separated from the rest of the heart very carefully, which ultimately came out in a 'horse shoe' shape. The trimming was carried out with all reasonable speed. The
auricles were dipped from time to time in Ringer's solution to prevent drying. The preparation was then mounted in a bath of 50 cc capacity containing Ringer's solution at 29°C, which was constantly oxygenated. A silk thread was tied to each tip of the 'Horse shoe' shaped auricle. One end was tied to the lower bent end of the oxygen delivery tube, while the other end was attached to a long light straw lever. The rhythmic contractions of the auricles were recorded on a slowly moving drum. The drug solutions were added directly into the bath and the effect recorded.

RESULTS.

Effect of local anaesthetics on isolated perfused heart of frog.

Graded doses of local anaesthetics were administered ranging from 1 to 400μ. The results obtained with these compounds can be grouped under three categories. Firstly, those which cause initial depression of heart followed by stimulation i.e. compounds B & E. Secondly, those which depress the heart in all the doses administered i.e. compounds A, D, F & L. Finally, compounds which produce decrease in the heart rate and marked increase in the force of contraction i.e. compound C. (Fig.48 to 54.).
The results have varied with different doses and there seems to be little relationship between the doses administered and the effects elicited. The most remarkable effects have been seen with compound C which showed a significant increase in the force of contraction and decrease in the heart rate. This effect was seen with all the doses of the drug administered but was more marked with the higher doses (Fig. 50).

Those drugs which showed a negative ionotropic and chronotropic effect were further investigated after atropinisation. The results have remained unaltered in all the cases (Fig. 48 to 54).

**Effect on local anaesthetics on the isolated perfused heart of rabbits.**

Graded doses of local anaesthetics were administered ranging from 10⁻¹ to 1 mg. A negative ionotropic and chronotropic effect was seen to a varied extent with all the compounds and with all the doses administered. The depressant effect was more marked with the higher doses. Compounds A and B were found to be the most and least potent respectively.

The results have been illustrated in Fig. 55 to 61.

**Effect of local anaesthetics on rabbit auricles.**

Graded doses of local anaesthetics were administered ranging from 0.2 to 40⁻¹/cc. The effect produced by these compounds on rabbit auricles can be classified into two categories. Firstly, those which stimulate the
auricles in smaller doses and depress in higher doses i.e. B, C, D and F. Secondly, those which depress the auricles with all the doses administered i.e. A, E & L.

Smaller doses of compound D and F such as $2\gamma/\text{cc}$ caused initial stimulation followed by depression, while higher doses of these very compounds ($40\gamma/\text{cc}$ of D and $20\gamma/\text{cc}$ of F) produced only depression. Compound C in smaller doses ($0.2$ to $2\gamma/\text{cc}$) caused only stimulation but in higher doses ($20\gamma/\text{cc}$) caused depression after an initial marked stimulation. Compound B has shown very little effect in all the doses administered; however, in smaller doses ($2\gamma/\text{cc}$) it has slightly stimulated and in large doses ($4\gamma/\text{cc}$) it has slightly depressed the auricular contractions.

Compound A, E and L have produced uniformly depressant action on the auricular contractions which was roughly proportional to the doses administered (Table No. 10, Fig. 62 to 68.)
### TABLE No. 10

**Effect of local anaesthetics on the isolated auricles of rabbits.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in /cc</th>
<th>Nos. of Observation.</th>
<th>Mean % reduction in rate/min</th>
<th>Effect on auricular contractions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.0</td>
<td>3</td>
<td>26.0</td>
<td>little depression</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>3</td>
<td>40.0</td>
<td>marked depression.</td>
</tr>
<tr>
<td>B</td>
<td>2.0</td>
<td>3</td>
<td>1.00</td>
<td>little stimulation</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>3</td>
<td>2.00</td>
<td>little stimulation</td>
</tr>
<tr>
<td></td>
<td>40.0</td>
<td>3</td>
<td>2.00</td>
<td>little stimulation followed by little depression.</td>
</tr>
<tr>
<td>C</td>
<td>0.2</td>
<td>3</td>
<td>0.00</td>
<td>little stimulation</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>3</td>
<td>4.00</td>
<td>little stimulation</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>3</td>
<td>29.00</td>
<td>marked stimulation</td>
</tr>
<tr>
<td></td>
<td>40.0</td>
<td>3</td>
<td>20.00</td>
<td>marked stimulation followed by depression.</td>
</tr>
<tr>
<td>D</td>
<td>2.0</td>
<td>3</td>
<td>0.00</td>
<td>little stimulation followed by depression.</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>3</td>
<td>24.00</td>
<td>marked stimulation</td>
</tr>
<tr>
<td></td>
<td>40.0</td>
<td>3</td>
<td>43.00</td>
<td>depression.</td>
</tr>
<tr>
<td>E</td>
<td>2.0</td>
<td>3</td>
<td>0.00</td>
<td>little depression</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>3</td>
<td>11.00</td>
<td>little depression</td>
</tr>
<tr>
<td></td>
<td>40.0</td>
<td>3</td>
<td>29.0</td>
<td>marked depression.</td>
</tr>
<tr>
<td>F</td>
<td>2.0</td>
<td>3</td>
<td>30.0</td>
<td>marked stimulation followed by depression.</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>3</td>
<td>33.0</td>
<td>marked depression.</td>
</tr>
<tr>
<td>L</td>
<td>2.0</td>
<td>3</td>
<td>6.0</td>
<td>little depression</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>3</td>
<td>22.0</td>
<td>marked depression.</td>
</tr>
</tbody>
</table>
Showing the effect of compounds A and B on the isolated perfused heart of frog, before and after atropine. ...

LEGEND

A₁ - 10 ν of compound A
A₂ - 100 ν of compound A
A₃ - 100 ν of compound A after atropine.

B₁ - 1 ν of compound B
B₂ - 10 ν of compound B
B₃ - 100 ν of compound B
B₄ - 100 ν of compound B after atropine.

T - indicates time at 1 second interval.
Showing the effect of compounds C and D on the isolated perfused heart of frog, before and after atropine...

LEGEND.

- $C_1$ - 100 μg of compound C
- $C_2$ - 200 μg of compound C
- $C_3$ - 200 μg of compound C after atropine.

- $D_1$ - 1 μg of compound D
- $D_2$ - 10 μg of compound D
- $D_3$ - 50 μg of compound D
- $D_4$ - 50 μg of compound D after atropine.

$T$ - indicate time at 1 second interval.
Showing the effect of compounds E, F and L on the isolated perfused heart of frog, before and after atropine.

**LEGEND.**

- $E_1$ - 100 $\gamma$ of compound E
- $E_2$ - 200 $\gamma$ of compound E
- $E_3$ - 400 $\gamma$ of compound E
- $E_4$ - 400 $\gamma$ of compound after atropine.
- $F_1$ - 10 $\gamma$ of compound F
- $F_2$ - 100 $\gamma$ of compound F
- $F_3$ - 200 $\gamma$ of compound F
- $F_4$ - 200 $\gamma$ of compound F after atropine.
- $L_1$ - 1 $\gamma$ of compound L
- $L_2$ - 10 $\gamma$ of compound L
- $L_3$ - 100 $\gamma$ of compound L
- $L_4$ - 200 $\gamma$ of compound L
- $L_5$ - 200 $\gamma$ of compound L after atropine.
- $T$ - indicate time at 1 second interval.
Showing the effect of compounds A & B on the rate amplitude and coronary blood vessels of isolated perfused heart of rabbits.

**Fig. 55**

**Fig. 56**

**LEGEND**

Numericals on the top indicate rate of coronary out flow in drops per minutes, before and after the drug.

- $A_1$ - 10 $\gamma$ of compound A
- $A_2$ - 20 $\gamma$ of compound A
- $B_1$ - 10 $\gamma$ of compound B
- $B_2$ - 100 $\gamma$ of compound B
- $B^2$ - 1 $M_1$ of compound B
- $T$ - indicates time at 1 second interval.
Showing the effect of compounds C & D on the rate amplitude and coronary blood vessels of isolated perfused heart of rabbits.

**Fig. 57**

**Fig. 58**

**LEGEND**

Numericals on the top: indicate rate of coronary out flow in drops per minutes, before and after the drug.

| C₁ | 10 γ of compound C |
| C₂ | 100 γ of compound C |
| C₃ | 200 γ of compound C |
| D₁ | 10 γ of compound D |
| D₂ | 100 γ of compound D |
| D₃ | 200 γ of compound D |
| T  | indicate time at 1 second interval. |
Showing the effect of compounds E, F & L on the rate amplitude and coronary blood vessels of isolated perfused heart of rabbits.

LEGEND

Numbericals on the top indicate rate of coronary out flow in drops per minutes, before and after the drug.

- **E**₁ - 10 µ of compound E
- **E**₂ - 100 µ of compound E
- **E**₃ - 200 µ of compound E
- **E**₄ - 1 mg of compound E

- **F**₁ - 10 µ of compound F
- **F**₂ - 100 µ of compound F
- **F**₃ - 1 mg of compound F

- **L**₁ - 10 µ of compound L
- **L**₂ - 100 µ of compound L
- **L**₃ - 1 mg of compound L

T - indicates time at 1 second interval.
Showing the effect of compounds A, B & C on isolated auricle of rabbit.

LEGEND

Numericals on the top indicate rate of auricle beats per minute, before and after the drug.

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2 γ/cc of compound A</td>
</tr>
<tr>
<td>A₂</td>
<td>20 γ/cc of compound A</td>
</tr>
<tr>
<td>B₁</td>
<td>2 γ/cc of compound B</td>
</tr>
<tr>
<td>B₂</td>
<td>20 γ/cc of compound B</td>
</tr>
<tr>
<td>B₃</td>
<td>40 γ/cc of compound B</td>
</tr>
<tr>
<td>C₁</td>
<td>0.2 γ/cc of compound C</td>
</tr>
<tr>
<td>C₂</td>
<td>2 γ/cc of compound C</td>
</tr>
<tr>
<td>C₃</td>
<td>20 γ/cc of compound C</td>
</tr>
<tr>
<td>C₄</td>
<td>40 γ/cc of compound C</td>
</tr>
</tbody>
</table>

T - indicates time at 1 second interval.
Showing the effect of compounds D & E on isolated auricle of rabbit.

**LEGEND**

Numericals on the top indicate rate of auricle beats per minute, before and after the drug.

- $D_1 = 2 \gamma/\text{cc}$ of compound D
- $D_2 = 20 \gamma/\text{cc}$ of compound D
- $D_3 = 40 \gamma/\text{cc}$ of compound D
- $E_1 = 2 \gamma/\text{cc}$ of compound E
- $E_2 = 20 \gamma/\text{cc}$ of compound E
- $E_3 = 40 \gamma/\text{cc}$ of compound E

$T$ - indicates time at 1 second interval.
Showing the effect of compound F & L on isolated auricle of rabbit.

LEGEND

Numericals on the top indicate rate of auricle beats per minute, before and after the drug.

- $F_1$ - 2 $\gamma$/cc of compound F
- $F_2$ - 20 $\gamma$/cc of compound F
- L - 2 $\gamma$/cc of compound L
- L - 20 $\gamma$/cc of compound L
- T - indicate time at 1 second interval
Section 'F': Electrocardiographic study of local anaesthetics with special reference to their antiarrhythmic effect.

During the course of study with present series of local anaesthetics on the amphibian heart, it was observed that the hearts showing atrial beats and an irregular rhythm were immediately brought to normal after administration of these compounds. This led to suggest that these compounds might be exerting some antifibrillating and antiarrhythmic activity. Anti-fibrillatory and antiarrhythmic property of local anaesthetics, particularly procaine has been investigated by different workers. (Hirschfelder et al. 1942, Bostein 1946, Schlachman et al. 1951, Woske et al. 1952, Van Dongen 1953, Arora et al. 1961, Singh et al. 1961). The following experiments were performed to evaluate the effect of the present series of local anaesthetics on the E.C.G. recordings of the normal and against the artificially induced fibrillation in the intact heart of dog.

Experimental Procedure.


The dogs used in these experiments usually weighed between 6 to 8 kg. The dogs were anaesthetised with 30 mg/kg of pentobarbitone administered intraperitoneally. The effect of these compounds was recorded electrocardiographically with bipolar limb leads and
conventional leads, followed by unipolar chest leads up to v5. Later on the E.C.G. observations were also made after opening the chest and exposing the heart with only bipolar conventional leads, so as to see the difference if any.

2. Acetylcholine induced auricular fibrillation in dogs.

The method employed to induce auricular fibrillation was similar to the one described by Scherf and Chick (1951). Adult mongrel dogs weighing 6 to 8 kg. were used. They were anaesthetised with pentobarbitone sodium solution 30 mg/kg given intravenously. Artificial respiration was instituted through tracheal cannula. A midline incision was made and parts of sternum and ribs directly over the right auricle were removed. A pericardial cradle was made. E.C.G. was recorded with a direct recording G.E.C. electrocardiograph using conventional bipolar lead III. The preference given to record lead III here was merely due to the fact that there was some mechanical disturbance present in lead II which could not be corrected. A small pledget of cotton wool soaked in 5% acetylcholine was placed over the region of S.A. node for one minute and then removed. The auricle was then pinched and fibrillation was induced almost immediately as confirmed by E.C.G. recording. If the fibrillation was short-lived, say, for less than 20 minutes, the pledget was allowed to remain at S.A. node for longer
time. Rest period of 10 minutes was allowed between each test. Two control were taken, subsequent to which the procedure was repeated third time. After allowing the auricle to fibrillate for about a minute, the drug under test was injected intravenously through the cannulated femoral vein and continuous record of E.C.G. was obtained.

RESULTS.

The observations made after the detailed study of E.C.G., first with normal anaesthetised dog's heart, then with open chest and lastly after inducing the auricular fibrillation followed by the administration of the drugs, are presented in the tabular form in Table No. 11 & 12. Also the relevant E.C.G. tracing's photo prints are shown in Fig. No. 69 to 79.

For convenience the observations are classified in three different groups:

1. Effect on normal heart with closed chest.
2. Effect on normal heart with open chest.
3. Effect on fibrillating heart with open chest.

1. Effect on normal heart with closed chest.

The local anaesthetics studied were A, B, C, F & L only because it was suspected from other animal experiments, that the above drugs might be having same digitalis like action. However, E.C.G. recordings did not reveal any such effect with any of the above drugs. Only.
compound A reduced the heart rate from 187 (normal) to 150/min, also slight reduction in rate was observed with F and L when the rate was reduced to 168 to 163 respectively. No alteration was found in rhythm and no significant changes were noted in P, QRS & T waves, PR, ST and QT interval after administration of different drugs, when compared to a normal tracing taken before in at least 3 dogs. (Table No. 11 and Fig. 69 to 77.)

2. Effect on normal heart with open chest.

In this only bipolar leads were studied before and after the opening of the chest, so as to observe the changes occurring in E.C.G. tracings. There was practically no change after administration of the drugs except that the normal rate here was 120/min. as compared to group one where it was 187, but the dogs used were different and the variations may be individual.

3. Effect on fibrillating heart with open chest.

The drugs studied were A, B, C, D, E, F, L and quinidine. Quinidine was included as the standard. Fibrillation was induced according to the method described above. The drugs were given intravenously in a dosage of 5 mg/kg and the effects were observed with a continuous tracing. Each drug was tested separately. The observations were made as regards rate, rhythm, P, PR interval, Q, RS waves, QT interval, T and ST
segments in each E.C.G. before and after administration of drug in fibrillating heart.

The significant changes observed were as follows:-

(a) Rate - During fibrillation, ventricular rate varied between 225 to 300 / mint, with an average of 261 / mint; on administration of the above drugs it was reduced significantly, varying from 109 to 150 / mint with an average of 120 / mint.

(b) Rhythm - The previously irregular ventricular rhythm was restored to perfectly regular rhythm within few seconds after administration of each drug (T.V.) and persisted for at least half an hour during which period another attempt to induce fibrillation did not succeed. The regular rhythm persisted for nearly 1½ hour with compound C during which fibrillation could not be induced. If the fibrillation was not induced for the second time, the regular rhythm restored by the above drugs persisted for several hours.

(c) P wave - The absent P wave during fibrillation made its appearance again soon after the regular rhythm was restored with the above drugs and were regularly placed in front of QRS complex. Well formed P waves were seen in normal rhythms restored by compounds A, C and D while they were very small and inconspicuous after the normal rhythm restored by compounds B, E, L and quinidine. They were not seen after administration of compound F.
(d) PR interval - This was restored to normal (0.08) in the regular rhythm induced by compounds A, C, D, F, L and Q while it was slightly reduced (0.06) after compounds B and E.

(e) Q Wave - These were absent in all the E.C.G. tracings either before or after induction of fibrillation and therefore no significance could be attached.

(f) RS waves - Both normal (control) and after the induction of normal rhythm with drugs showed RS, rS or RS patterns. During fibrillation they were variable and irregular in height and shape.

(g) QT interval: This was found to be normal in all tracings after induction of normal rhythm with above drugs.

(h) T: - All the waves were upright and no significant change was observed.

(i) ST segment - remained unchanged in control as well as in the regular rhythms restored after the drugs.

The results have been illustrated in Table No.12 and Fig. No.78 & 79.

***
<table>
<thead>
<tr>
<th>Rate</th>
<th>Rhythm</th>
<th>Normal</th>
<th>0.26 mm</th>
<th>Slightly bigger &amp; wider</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Q 0.12 mm</td>
<td>0.09 sec.</td>
<td>0.22 sec.</td>
<td>Normal upright</td>
<td>upright</td>
</tr>
<tr>
<td>S</td>
<td>QT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE No. 11**

Effect of local anaesthetics on normal E.C.G. recordings on dogs closed chest.

<table>
<thead>
<tr>
<th>After drug</th>
<th>Rate</th>
<th>Rhythm</th>
<th>Normal</th>
<th>0.26 mm</th>
<th>Slightly bigger &amp; wider</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>150</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>B</td>
<td>184</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>C</td>
<td>180</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>D</td>
<td>168</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>E</td>
<td>163</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

* = mean of three observations.
Figure 69 - shows the normal E.C.G. of drug.

Figure 70 - shows the E.C.G. of the same drug after 5 mg/kg of compound A (I.V.) administration.
Figure 70 - shows the normal E.C.G. of drug.

Figure 71 - shows the E.C.G. of the same drug
after 5 mg/kg of compound B (I.V.) administration.
LEGEND.

Figure 72 - shows the normal E.C.G. of drug.
Figure 73 - shows the E.C.G. of the same drug
after 5 mg/kg of compound C (I.V.)
administration.
Figure 74 - shows the normal E.C.G. of drug.

Figure 75 - shows the E.C.G. of the same drug after 5 mg/kg of compound F (I.V.) administration.

**LEGEND**

Figure 74 - shows the normal E.C.G. of drug.

Figure 75 - shows the E.C.G. of the same drug after 5 mg/kg of compound F (I.V.) administration.
LEGEND.

Figure 76 - shows the normal E.C.G. of drug.

Figure 77 - shows the E.C.G. of the same drug after 5 mg/kg of compound L (I.V.) administration.
### TABLE No. 12.

**Effect of Local anaesthetics on artificially induced fibrillation in dog's heart.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate</strong></td>
<td>120</td>
<td>261</td>
<td>After A</td>
</tr>
<tr>
<td><strong>Rhythm</strong></td>
<td>Regular</td>
<td>Irregular</td>
<td>Regular</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>Present normal</td>
<td>Absent</td>
<td>Present small</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>-</td>
<td>-</td>
<td>0.08 normal</td>
</tr>
<tr>
<td><strong>Q</strong></td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>R</strong></td>
<td>RS pattern variable</td>
<td>Upright</td>
<td>rs &amp; RS</td>
</tr>
<tr>
<td><strong>S</strong></td>
<td>Upright normal</td>
<td>Upright normal</td>
<td>Upright normal</td>
</tr>
<tr>
<td><strong>QT</strong></td>
<td>Upright normal</td>
<td>Upright normal</td>
<td>Upright normal</td>
</tr>
<tr>
<td><strong>T</strong></td>
<td>Upright normal</td>
<td>Upright normal</td>
<td>Upright normal</td>
</tr>
<tr>
<td><strong>ST</strong></td>
<td>Slightly depressed.</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

* Mean of three observations.
EFFECT OF LOCAL ANAESTHETICS ON RESPIRATION.

Local anaesthetics in general have been shown to affect the respiratory centre and respiration after systemic administration or after absorption from the site of intradermal injection (Goodman & Gilman, 1956). Roth et al. (1947) observed that cocaine stimulated the respiration initially and finally paralysed in larger doses. Similar observations have been made with procaine. During the course of toxicity experiments with the present series of local anaesthetics in mice and rats, it was observed that respiration is stimulated with smaller doses and in the initial stages with larger doses, while in the later stages with toxic doses there is depression of respiration culminating in failure. Following experiments were performed to evaluate the effect of these drugs on the respiration of dogs and compared with the standard drug lignocaine.

Experimental procedure.

Dogs weighing from 8 to 10 kg. were used. They were anaesthetised with sodium pentobarbitone solution 30 mg/kg intravenously. The trachea was exposed and cannulated. One limb of the cannula was connected to a respiratory tambour by means of pressure rubber tubing. The respiratory excursions were recorded on
the slowly moving kymograph. The common carotid artery of one side was also dissected out and cannulated. The blood pressure tracings were also simultaneously recorded on a kymograph. The solutions of the drugs were injected through the cannulated femoral vein.

RESULTS.

Effect of local anaesthetics on respiration.

Initially with all the compounds an increase in rate and amplitude of respiratory movements have been observed which was followed by a slight diminution in the amplitude but a marked decrease in the rate of respiratory movements. Compound F and C have shown proved most marked stimulating action on respiration as compared to other compounds in equivalent doses and at the same time the after effects of depression of respiration are also more prominent. Compound E and lignocaine have produced very little effect in respiratory movements. The results have been illustrated in Fig. 80 - 86.

***
Showing the effect of compounds A, B, C & D on artificially induced fibrillation in dog's heart.

Legend:

N - normal rhythm.
Fib - fibrillation induced by acetylcholine.
A - 5 mg/kg of compound A immediately after fibrillation.
B - 5 mg/kg of compound B immediately after fibrillation.
C - 5 mg/kg of compound C immediately after fibrillation.
D - 5 mg/kg of compound D immediately after fibrillation.
Showing the effect of compounds E, F, L & Q (Quinidine) artificially induced fibrillation in dog's heart...

**LEGEND.**

- **N** - normal rhythm.
- **Fib** - fibrillation induced by acetylcholine.
- **E** - 5 mg/kg of compound E immediately after fibrillation.
- **F** - 5 mg/kg of compound F immediately after fibrillation.
- **L** - 5 mg/kg of compound L immediately after fibrillation.
- **Q** - 5 mg/kg of compound Q immediately after fibrillation.