PHARMACOLOGICAL STUDIES OF CERTAIN AUTACOIDS IN FOWL

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To

My Parents

CERTIFICATE II

This is to certify that the dissertation entitled "Pharmacological studies of certain autacoids in fowl" submitted by Dr. Shivraj Singh Yadav to the Haryana Agricultural University in partial fulfilment of the requirements for the degree of Ph.D., in the subject of Pharmacology, has been approved by the Student's Advisory Committee after an oral examination on the same, in collaboration with an External Examiner.

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(Shivraj S.Yadav)

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CHAPTER I

INTRODUCTION

INTRODUCTION

Histamine was synthesized as a chemical curiosity in 1907 by Windaus and Vogt. Pharmacological interest in histamine was, however, aroused when it was reported by Barger and Dale (1910) that histamine was responsible for uterine stimulant action of ergot. Since then exhaustive work has been carried out on cardiovascular, smooth muscle, exocrine glands and nervous system, mostly in mammals. Similarly, 5-hydroxytryptamine, after its isolation as a serum vasoconstrictor in a crystalline complex form named as 'serotonin' by Rapport et al. (1948), was studied for its effects on various physiological systems. To date a great deal of information regarding the distribution, pharmacological properties and the role of these amines in inflammatory processes and allergy has been obtained. However, complex physiological functions which are exhibited by these substances are only poorly understood.

Review of literature showed that pharmacological studies of autacoids in fowl have been scanty. Histamine (Akers & Peiss, 1963 and Natoff & Lockett, 1957) and 5-hydroxytryptamine (Bunag & Walaszek, 1961) have been reported to produce effects on cardiovascular system and smooth muscles of fowl similar to those in mammals with slight variations. However, no systematic work with wide

range of doses of these amines and their interactions with antagonists have been conducted in this species.

It is over 40 years since Kurzok & Lieb unwittingly observed activity of prostaglandins in human and sheep semen. Goldblatt (1933) and Von Euler (1934) independently demonstrated the presence of a potent vasodepressor and smooth muscle stimulating material in extracts of human semen, prostate gland and seminal vesicles and sheep vesicular glands. The active principle was called 'prostaglandin' by Von Euler who defined this substance on the basis of its source in some accessory glands of man and sheep and its smooth muscle-stimulating and blood pressure lowering activities. Since then more than a dozen natural prostaglandins have been isolated and characterized in a variety of animal tissues.

Biological effects of pure prostaglandins have been examined in numerous test preparations but no definite physiological role has been ascribed to them. Prostaglandins are remarkably versatile in their biological activities. They affect reproductive, nervous, cardiovascular, respiratory and metabolic functions. These effects are attributable to the broad regulatory powers which the prostaglandins show in respect to smooth muscle activity and their involvement in secretory functions both exocrine and endocrine.

The ubiquity of the prostaglandins, their extreme potency and multiplicity of biological activities has made them logical candidates for implication in important physiological functions. The therapeutic value of prostaglandins is unknown at present, but they could conceivably gain wide spread usage in human and veterinary medicine.

Occurrence, distribution and pharmacological actions of prostaglandins in domestic fowl have not been studied systematically. Only a few reports on the effects of prostaglandins on cardiovascular and on gastrointestinal smooth muscles have appeared. Effects of prostaglandins on fowl blood pressure have been reported to be pressor, pressor-depressor and depressor, depending upon the anaesthesia and animal preparation (spinal or intact). These effects, however, have been reported with single dose of prostaglandins. Effects of prostaglandins only on isolated crop or oesophagus of chick have been reported (Horton & Jones, 1969) and no work seems to have been conducted on the intestine or oviduct of the fowl.

In view of the foregoing facts the present investigation was undertaken to elucidate the actions of histamine, 5-hydroxytryptamine, their antagonists and prostaglandin E_1 on cardiovascular system and isolated intestine & oviduct of WLH fowl with an idea to find out pattern of response, dose response relationship.

threshold concentration and ED_{50} of these agonists. Attempts have also been made to explore the possible mechanisms of effects of these compounds which differed qualitatively as compared to mammals.

CHAPTER II

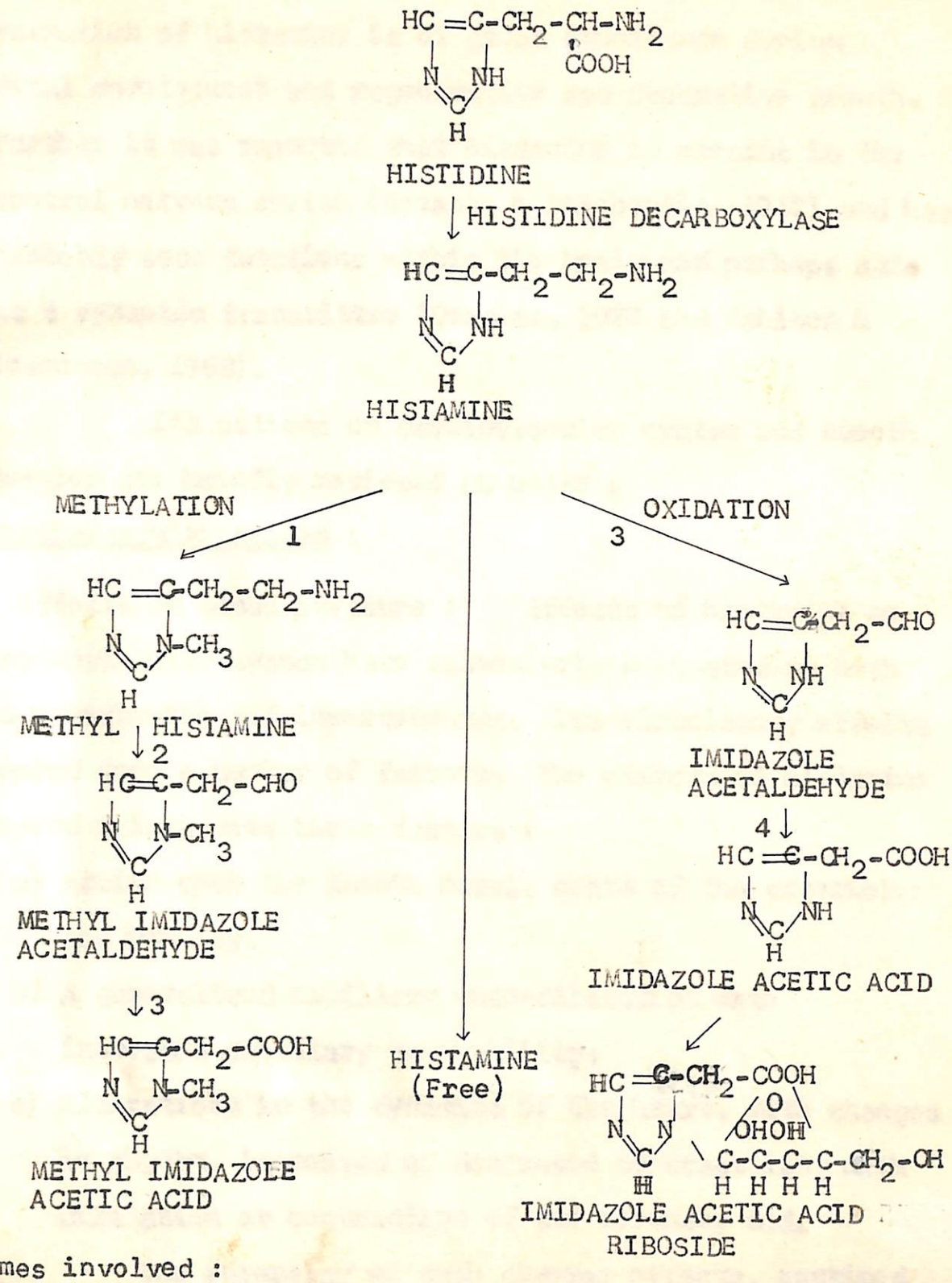
REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTAMINE

Histamine (4-(2-amino ethyl)-imidazole or (β-imidazolylethylamine) is formed by decarboxylation of the aminoacid histidine by the enzyme histidine decarboxylase.(Synthesis and metabolism of histamine is given on page 6).

Histamine was synthesized, before its biological significance was recognised, by Windaus and Vogt (1907). In 1910 Barger and Dale showed that it was present in extracts of ergot. Since that time histamine has been revealed as a widely occuring compound both in plants and animal tissues. The amine is stored in a biologically inactive form in basophilic leukocytes and in mast cells. Later, histamine was subjected to pharmacological studies and it was found that it stimulates a host of smooth muscles and has an intense depressor action. During the first 20 years after the discovery, the main effects of histamine on cardiovascular system (Burn & Dale, 1926;and Dale & Laidlaw, 1910, 1911), on extravascular smooth muscles (Barger & Dale, 1910), in anaphylaxis and allergy (Dale, 1913; Lewis & Grant, 1924 and Dragstedt & Gebauer-Fuelnegg, 1932) and in injury, stress and microcirculation (Schayer, 1963 and Roch E Silva, 1966) have been reported.



Enzymes involved :

1. Imidazole-N-methyl transferase
2. Monoamine oxidase or histaminase
3. Histaminase and diamine oxidase
4. Xanthine oxidase or aldehyde oxidase

MAJOR PATHWAYS OF HISTAMINE SYNTHESIS AND METABOLISM

Kahlson and Rosengren (1968) suggested that histamine stored in tissues may play a minor role, whereas formation of histamine is of great importance during fetal development and regenerative and reparative growth. Further it was reported that histamine is present in the central nervous system (Kataoka & DeRobertis, 1967) and has probably some functions within the brain and perhaps acts as a synaptic transmitter (Douglas, 1970 and Kahlson & Rosengren, 1968).

Its actions on cardiovascular system and smooth muscles are briefly reviewed as under :

Cardiovascular system :

Effects on blood pressure : Effects of histamine on cardiovascular system have extensively been studied both in vertebrates and invertebrates. Its circulatory effects depend upon a number of factors. The effects of histamine depend mainly upon three factors :

a) Action upon the smooth muscle coats of the arterioles and venules.
b) A generalized capillary vaso-dilatation with increased capillary permeability.
c) Alterations in the dynamics of the heart, with changes in rhythm, increased or decreased contractility with dilatation or contraction of the coronary bed.

The interplay of such diverse effects, combined with the fact that different species react differently to the intravenous injection of histamine, might explain a

great deal of the effects of histamine on cardiovascular system. Reite (1969a) reported that intravascularly administered histamine has weak and inconsistent blood pressure effects on hagfish, while no significant effects of histamine were seen in cartilaginous fish. Reite (1969a) recorded the ventral aortic blood pressure in the skate and both the ventral and dorsal aortic blood pressure in dogfish and ratfish and reported that histamine showed no significant effects on blood pressure. Lungfish appeared to be the only fish reported in which histamine unequivocally produced marked changes in blood pressure (Reite, 1970). Dale and Laidlaw (1911) found that in amphibians systemic arterial blood pressure of the frog was slightly increased after intravenous injection of histamine, while Doi (1920) who also studied the effects of histamine on frogs observed a slight decrease after small doses of histamine and a slight increase after higher doses. The effects of histamine in toads and salamanders were insignificant (Reite, 1969b). Contrary to amphibians and most fishes, reptiles usually showed marked changes in systemic arterial blood pressure in response to histamine (Sumbal, 1924 and Reite, 1970).

The blood pressure effects of intravenously injected histamine in most studied mammalian species, including rat, cat, dog and man have been fully recognized as a potent depressor agent and fall of blood pressure

may be transient or lasting depending on the dose (Sollmann & Gilbert, 1938; Burn & Dale, 1926; Dale & Richards, 1918 and Storstein et al., 1959). Rabbits, however, showed a different response. If the rabbit was anaesthetized with ether, the blood pressure effect of histamine was predominantly hypertensive (Dale & Laidlaw, 1910), whereas hypotensive effect was obtained under chloralose or urethane anaesthesia.

In fowl, variable results on blood pressure have been reported particularly in unanaesthetised condition (Akers & Peiss, 1963). The presence of strong depressor effect of intravascularly injected histamine was demonstrated by Dale and Laidlaw (1911). These observations were confirmed by Storm van Leeuwen and Verzar (1921) and Natoff and Lockett (1957).

It is known since long that antihistaminics antagonize in varying degree most, but not all, of the pharmacological effects of histamine. Rapid intravenous injection of an antihistaminic caused a transient fall in blood pressure in mammals. This was assigned to its probable local anaesthetic activity (Douglas, 1970). Antihistaminics such as parabromdylamine, chlorpheniramine and diphenhydramine caused a marked rise (+ 27%) in blood pressure and histamine response to blood pressure was blocked by these drugs (Bunag & Walaszek, 1961).

Effects on heart : Reite (1969a) observed that there was no significant change in heart rate and aortic pulse pressure in jawless vertebrates after intravascular administration of histamine. But histamine in concentrations of 4×10^{-6} to 4×10^{-4} gm/ml caused an augmentation and occasionally a slight acceleration of the heart beats in skates (Huntsman, 1931). It was observed that repeated doses of histamine influenced the heart less than the initial doses, while Mackay (1931) noted that histamine administration in intact skates sometimes produced a slight increase in the force of contraction of the heart, but the response was accompanied by a slightly decreased heart rate.

During studies in intact common eels (Anguilla anguilla) Mott (1951) observed marked but transient slowing of the heart after injection of histamine and this response was probably brought about through vagal stimulation. In studies by Reite (1969b), eels as well as the other species, e.g. teleosts, lungfish and cartilaginous fish failed to reveal any significant influence on the heart after intravascular injections of histamine in intact specimens. Dale and Laidlaw (1911) observed a rise in aortic pulse pressure in intact frogs after administration of histamine. Other workers have also reported that histamine had a negligible effect on chronotropy of isolated heart preparations from frogs (Grant & Jones, 1929), toads (Reite, 1969a), tortoise (Reite, 1970) and in terrapins (Reite, 1965).

In isolated perfused hearts and heart lung preparation, histamine has been shown to have positive inotropic and chronotropic effects. Histamine when applied in large doses had negative inotropic effects, retarded pulse propagation in the conducting system and induced extra systoles and ventricular fibrillation and these effects are suggested to be due to increased sodium conductance (Feigen et al., 1960).

Large doses of histamine injected intravenously or into the heart of dogs, cats, rabbits or guineapigs dilated the right side of the heart, probably through increased resistance in the lung vessels. Repeated hypodermic injections resulted into hypertrophy of the right side of the heart and morphological changes in the heart tissue were produced both by acute and repeated injections (Sollmann, 1957). Studies in intact birds have also failed to reveal significant effects of histamine on the heart but in the isolated perfused heart of the domestic fowl it was found that histamine caused a decrease in contractility (Bartlet, 1963).

Effects on blood vessels : Among lower vertebrates the effect of histamine on the capillaries has been tested in frogs. Based on repeatitive microscopic observations of changes in the microcirculation in the tongue or the web of the frog in response to local mechanical or chemical stimulation. Krogh (1929) concluded that histamine was

entirely without effect on the capillaries of frog, whereas mechanical stimuli and high concentrations of substances like urethane and sodium chloride produced a marked increase in permeability. Philpott (1965) in electron microscopic observations noted that histamine caused damage both to the endothelium and to the basement membrane similar to that induced by 5-HT and snake venom. Histamine was found to be only about $^{1}/_{10}$ as potent as 5-HT in producing local tissue damage.

Ability of histamine to increase the permeability of capillaries in mammals was noticed by Sollmann and Pilcher (1917) and Lewis and Grant (1924) who studied the local wheal formation after intradermal injection of histamine in man and laboratory animals (Dale & Richards, 1918).

Sparrow and Wilhelm (1957) and Miles and Wilhelm (1960) reported that histamine is one of the most potent agent known for increasing capillary permeability. Majno and Palade (1961) reported the mechanism of action of histamine on the capillary wall, as revealed by the electron microscopic studies. Direct action of histamine on arteries varried with the species. In dogs, histamine dilates perfused small arteries whereas in cats it constrict (Burn & Dale, 1926). In birds, it was demonstrated that histamine injected intradermally in the skin of the fowl caused local exudation of a vital dye circulating in the blood (Spector, 1958).

Smooth muscles :

Euler and Ostlund (1957) reported that histamine has negligible effects on intestinal smooth muscle preparations from hagfish and skate. The effects of histamine on amphibian extravascular smooth muscle have been studied in preparations of alimentary tract (Carlson & Luckhardt, 1921), urinary bladder and iris. Kobayasi and Furuya (1960) reported that in isolated lung from toad (Bufovalgaris) low concentrations of histamine caused contraction of the lung while high concentrations caused relaxation. Histamine on smooth muscle preparations from the alimentary tract of the frog caused potentiation of the spontaneous contractions and produced a decrease in the general muscle tone in oesophageal and intestinal preparations, whereas in preparations of the colon, both spontaneous contractions and tone were inhibited. Carlson and Luckhardt (1921) also obtained a weak inhibitory effects of histamine on intestinal smooth muscle preparations of frogs and contraction of smooth muscles of the stomach and lung of the turtle and relaxation of oesophageal smooth muscles.

Storm van Leeuwen and Verzar (1921) studied the effects of histamine on isolated intestine of the domestic fowl (Gallus domesticus) and showed a strong contraction, but the effect was partly inhibited by atropine. Histamine-induced contraction of similar preparations were also observed by Morash and Gibbs (1929). Everett and Mann (1967)

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studied the effect of histamine on isolated intestine of young chicks and reported that histamine either contracted the tissue or produced a biphasic response, depending upon the dose.

Bartlet and Hassan (1968) reported a direct stimulatory action of histamine on the smooth muscles of isolated oesophagus of the chicks, but in addition the drug had indirect stimulatory effects that seemed to be brought about by release of acetylcholine from cholinergic nerves. Mepyramine was reported to antagonise actions of histamine on isolated oesophagus of the chicken. Contractions of the oviduct of domestic fowl in response to histamine has also been demonstrated both directly (McKenney et al., 1932) and indirectly (Weiss & Sturkie, 1952).

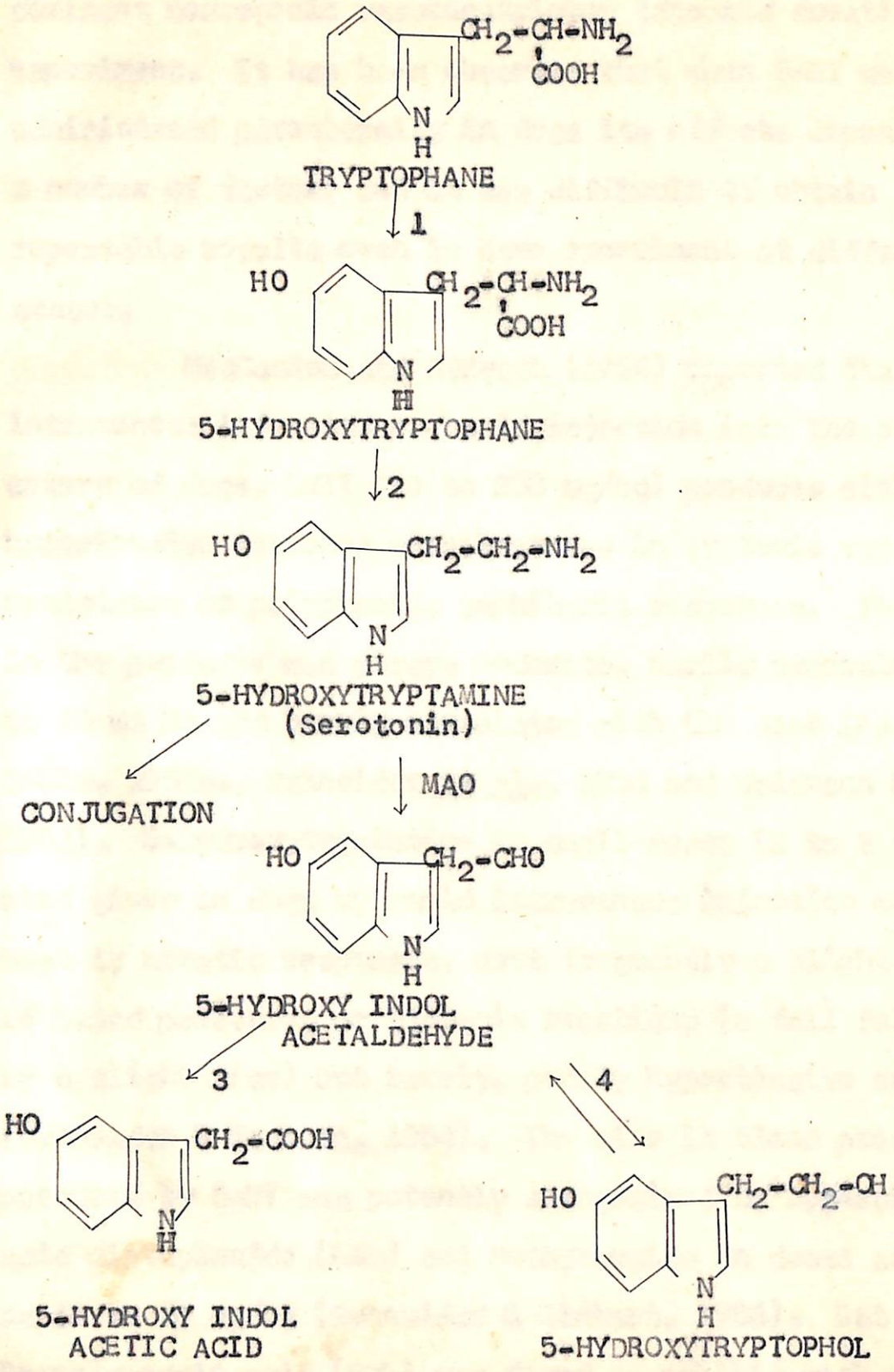
5-HYDROXYTRYPTAMINE

5-hydroxytryptamine (3-(β-amino ethyl)-5-hydroxyindol) is synthesized from dietary tryptophan (synthesis and metabolism shown on page 16). 5-hydroxytryptamine was discovered as a vasoconstrictor material in serum of a blood clot by Rapport et al. (1948) who isolated this serum vasoconstrictor substance in a crystalline form and later Rapport in 1949 named it as 5-HT. Later on Hamlin and Fisher (1951) synthesized this compound. It is widely distributed in animal and plant kingdoms. It occures in vertebrates including mammals, birds, reptiles, amphibians and fishes, mollusks, arthropodes; fruits and nuts and is also present in stings and venoms, including those of common stinging nettle, cowhage, wasps and scorpions.

The various pharmacological properties which 5-HT possesses include its stimulatory effects on smooth muscles, cardiovascular and respiratory systems. Its role in carbohydrate metabolism, as a synaptic transmitter substance and as a precursor of pineal hormone, melatonin, has also been reported (Douglas, 1970).

Cardiovascular system :

Effects on blood pressure : 5-hydroxytryptamine is reported to have variable effects in intact animals, the relative intensity of which depends on number of factors such as species involved, initial blood pressure, type of



MAO Mono amine oxidase
1. Tryptophan 5-hydroxylase
2. 5-hydroxytryptophane decarboxylase
3. Aldehyde dehydrogenase
4. Alcohol dehydrogenase

MAJOR PATHWAYS OF SEROTONIN SYNTHESIS AND METABOLISM

anaesthesia, dose, route, rapidity of drug administration, dominant neurogenic vasoconstrictor tone and duration of experiment. It has been observed that when 5-HT was administered parenterally in dogs its effects depended on a number of factors and it was difficult to obtain repeatable results even in same experiment at different stages.

MacCannon and Horvath (1954) reported that rapid intravenous injection or rapid injection into the pulmonary artery of dogs, 5-HT (10 to 200 ug/kg) produces either a hypertensive response with increase in systemic vascular resistance or polyphasic, amphibaric responses. The rise in the pressure was always moderate, rarely exceeding 40 to 60 mm Hg and barely correlated with the dose (Page, 1952a, 1952b., Schneider et al., 1954 and Weidmann & Cerletti, 1961). 5-hydroxytryptamine in small doses (2 to 8 ug/kg) when given in dogs by rapid intravenous injection caused mostly erratic responses, most frequently a slight fall of blood pressure, or biphasic reactions (a fall followed by a slight rise) but rarely, purely hypertensive one (Schneider & Yonkman, 1954). The rise in blood pressure produced by 5-HT was potently antagonized by Lysergic acid diethylamide (LSD) and methysergide in doses as low as 10 to 20 ug/kg (Schneider & Rinhart, 1956). But Bromolysergic acid (BOL) was found to exhibit weak and inconsistent activity towards the cardiovascular responses to 5-HT(Salmoiraghi et al., 1957).

5-hydroxytryptamine when administered to cats predominantly had a hypotensive response and rarely a mixed response, hypotension followed by a slight pressure increase (Comroe, 1952; Comroe et al., 1953 and Reid, 1952). It was observed that with large doses of 5-HT (20 to 40 ug/kg) a secondry pressure rise occasionally appeared and this has been attributed to stimulation of the suprarenal medulla (Freyburger et al., 1952). The cardiovascular responses to 5-HT in the cat were slightly antagonized by BOL or LSD (Solmoiraghi et al., 1957). Page and McCubbin (1953) reported that ganglionic blockade can abolish the normal depressor action of 5-HT and even reverse it to a presser action in cats. Spies and Stone (1952) reported that intravenous injections of 5-HT constantly elicited a rise in both systolic and diastolic pressures independent of initial blood pressure level i.e. in normal, hypotensive or hypertensive patients. Page and McCubbin (1953), however, found that 5-HT when given to hypertensive persons caused fall in blood pressure with a negligible rise. But most of the workers reported that the effects of 5-HT in man are either biphasic or polyphasic (Hollander & Michelson, 1956).

In rabbits under urethane or pentobarbital anaesthesia, 5-HT caused fall in blood pressure (Page & McCubbin, 1953). This response was attributed largely to pulmonary vasoconstriction and consequent reduction of cardiac output. Erspamer (1952) reported that intravenous

administration of 5-HT in lower doses in guineapigs anaesthetized with pentobarbital usually elicit moderate hypertensive responses while with higher doses hypertension was preceded or followed by a hypotensive phase. Salmoiraghi et al. (1956) reported that intravenous administration of 5-HT in rats caused fall in arterial blood pressure. LSD and BOL in large doses antagonized both pressor and depressor responses to 5-HT in rats (Salmoiraghi et al., 1957). Although the overall effect of intravenous administration of 5-HT in rats was reported to be a depressor one but Oustchoorn and Jacob (1960) reported that the shape of blood pressure response to 5-HT depended both on the dose and the initial level of blood pressure. The depressor effect was less apparent or even absent at low initial blood pressure levels but opposite was the case when the pressor component of 5-HT effect was considered.

Kuida et al. (1961) reported that intravenous infusion of 5-HT (0.2 mg/kg/min.) produces fall in carotid blood pressure in calf. In chicken 5-HT administered intravenously was reported to produce depressor, pressor or polyphasic response in fowl (Bunag & Walaszek, 1961; Eble, 1962 and Yadava & Ahmad, 1970).

Effects on heart : Effects of 5-HT on the heart of intact animals are variable and depend upon animal species and route of administration. In general, 5-HT is reported

to have positive inotropic and the chronotropic effects of varying intensity on isolated heart and atria of various species.

In man (Hollander & Michelson, 1956) intravenous injection of 5-HT is reported to produce an increase in heart rate (5 to 30 beats/min.) by a direct effect on the heart (Lemessurier et al., 1959). Although stroke volume was reduced and cardiac output was increased (Grover et al., 1958 and Bojs, 1961) or remained unchanged (Harris et al., 1960). In dogs rapid intravenous injection of 5-HT usually produced bradycardia or initial bradycardia followed by marked tachycardia (Ben et al., 1962) or sinus tachycardia (McCawley et al., 1952) and the important ECG changes produced by intravenous injection of 200 ug/kg 5-HT consisted of marked negative T-wave during the phase of increased blood pressure, with disappearance of this wave during the phase of hypotension. In cat, 5-HT in doses of 2 to 200 ug/kg showed an increase in heart rate, an increase in coronary flow and an increase in contractile force (Reid, 1952). In rabbits 5-HT produced hypotension accompanied by transient slowing of the heart rate (Schneider & Yonkman, 1954). In chicken, 5-HT (20 to 50 ug/kg) produced a marked diminution in the height of ventricular contraction which was followed by a brief period of myocardial stimulation (Bunag & Walaszek, 1961).

Effects on blood vessels : 5-hydroxytryptamine when given subcutaneously or intradermally produced edema in rats (Rowley & Benditt, 1956). It was 10 to 200 times more potent than tryptamine or histamine in this respect. These results were further confirmed by Sparrow and Wilhelm (1957). It was found that 5-HT increased capillary permeability more effectively than histamine in rodents. However, 5-HT had no prominent effects on capillary permeability in other species, including man (Douglas, 1970).

Smooth muscles :

Euler and Ostlund (1957) reported that 5-HT as low as 0.001 to 0.005 ug/ml was sufficient to stimulate the isolated intestine of fish (Pleuronectes platessa). The isolated small intestine of the land tortoise was not contracted by 0.01 to 0.1 ug/ml of 5-HT but was slightly stimulated by 1 ug/ml and atropine treatment abolished the stimulant effect of 5-HT (Toh & Mohiuddin, 1958). The rat duodenum was also found to be quite sensitive to concentrations as low as 0.001 to 0.01 ug/ml. The stimulant action of 5-HT was reduced by dibenamine (Erspamer, 1953).

The isolated intestine of guineapig was reported to respond to 5-HT but even the most intense spasmogenic effects were transitory and the preparation becomes refractory to further doses (Freyburger et al., 1952; Gaddum, 1953 and Gaddum & Hameed, 1954).

Reppert and Koelle (1953) and Rocha E Silva et al.,

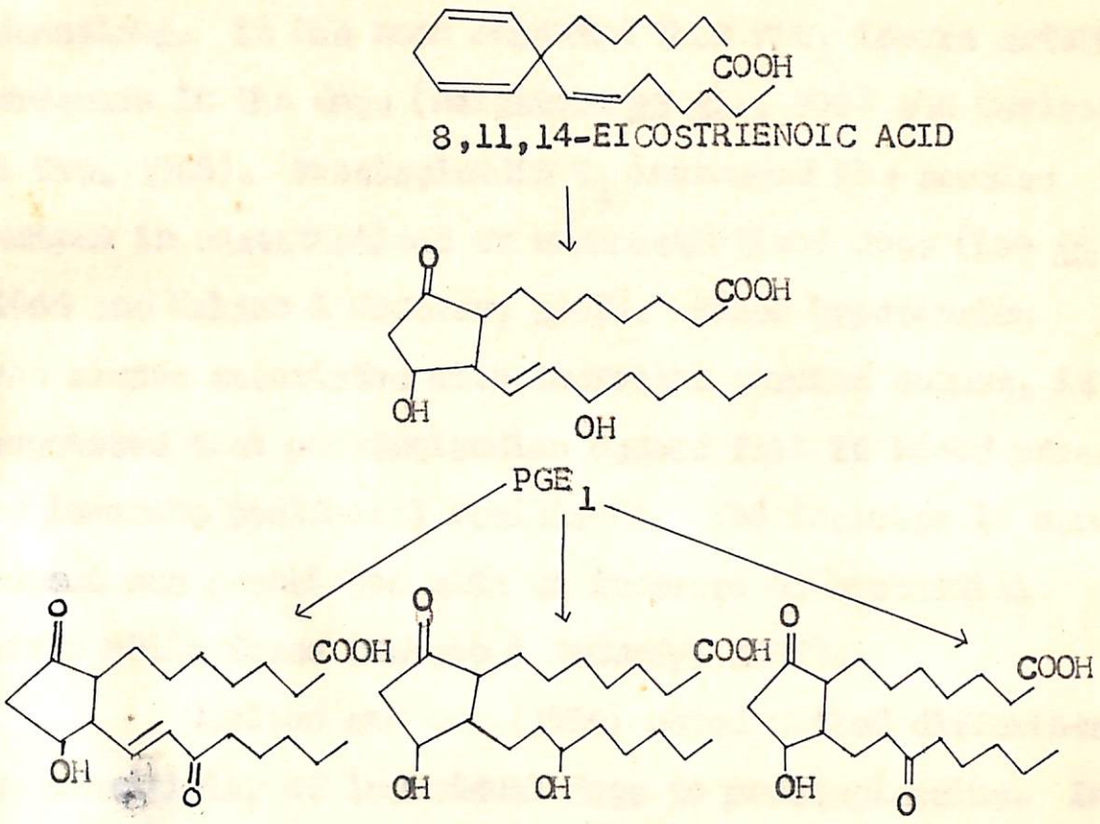
(1953) reported that the spasmogenic action of 5-HT on guineapig ileum was diminished by atropine (0.01 to 1 ug/ml). There was no agreement about the degree of antagonism. Further Robertson (1953) found that atropine (0.01 to 0.1 ug/ml) blocked the action of 2 ng but not that of 20 ng of 5-HT in guineapig isolated small intestine. Harry (1963) reported the contractile action of 5-HT on guineapig isolated ileum. The inhibitory actions of 5-HT on guineapig stomach were reported by Bulbring and Gershon (1968). The threshold concentration of 5-HT in rabbit small intestine was 0.01 to 0.1 ug/ml (Powell, 1955). The 5-HT-induced stimulation of the rabbit intestine was not inhibited by sympatholytic drugs, hexamethonium (10^{-4}M) or atropine (10^{-6}M) (Fingl & Gaddum, 1953). In cat the threshold concentration of 5-HT for isolated small intestine was 10 ug/ml. Sheep reticulum, abomasum and rumen were stimulated by 5-HT in concentrations of 0.2 to 2 ug/ml but no effect was observed on omasum (Sanford, 1958).

In addition to intestine, 5-HT is reported to stimulate the smooth muscles of uterus, urethra and nictitating membrane (Douglas, 1970). Cleugh et al. (1961) reported that many preparations of fowl rectal caecum were insensitive to 5-HT, but a concentration of 0.1 to 2 ug/ml often produced a biphasic contraction.

PROSTAGLANDINS

In 1930 Kurzok and Lieb reported that human uterus could react with either strong contractions or relaxation on instillation of fresh human semen. A few years later Goldblatt (1933) and Von Euler (1934) independently demonstrated the strong smooth muscle stimulating activity of human seminal plasma, extracts of human prostate gland, seminal vesicles and that of sheep vesicular glands. Von Euler named the active principle as 'prostaglandin' on the basis of its source i.e. the prostate glands.

Bergstrom and Sjovall (1960a, 1960b) isolated two prostaglandins (PGE_1 and $PGF_{1\alpha}$) from vesicular glands of sheep and later elucidated their structures and showed them to be derivatives of prostanoic acid (synthesis and metabolism is given on page 24). Biological effects of the pure prostaglandin compounds have been examined in numerous test preparations but no definite physiological role has been assigned to them. Prostaglandins are remarkably versatile in their biological activities and have been reported to affect reproductive, nervous, cardiovascular, respiratory and metabolic functions (Eliasson, 1959; Bergstrom et al., 1968; Horton & Main, 1967b and Weeks, 1972).



SYNTHESIS AND METABOLISM OF PROSTAGLANDIN E_1

Cardiovascular system :

Effects on blood pressure: Prostaglandins have been shown to possess an important role in normal physiological functions. It has been reported that PGE_1 lowers arterial pressure in the dogs (Bergstrom et al., 1964 and Carlson & Oro, 1966). Prostaglandin E_1 increased the cardiac output in anaesthetised or unanaesthetised dogs (Lee et al., 1965 and Nakano & McCurdy, 1967). Since hypotension was always associated with increased cardiac output, it was suggested that prostaglandins caused fall in blood pressure by lowering peripheral resistance. The increase in cardiac output was associated with an increase of myocardial contractile force (Nakano & McCurdy, 1967).

Carlson and Oro (1966) noted marked differences in sensitivity of individual dogs to prostaglandins. In dogs anaesthetised with pentobarbital, the infusion rate of PGE_1 needed to obtain a moderate depressor effect ranged from 0.1 to 1.2 ug/kg/min. In unanaesthetised dogs, the single intravenous dose of PGE_1 required for a 10 to 12 mm Hg fall in blood pressure ranged from 0.56 to 3.2 ug/kg. Holmes et al. (1963) reported that PGE_1 lowers arterial blood pressure in cats. It was also reported to have a similar effects in rabbits (Bergstrom & Euler, 1963 and Horton & Main, 1963), guineapigs, rats (Holmes et al., 1963 and Weeks & Wingerson, 1964) and chicks (Horton & Main, 1965a).

It has been reported that the individual

prostaglandins vary widely in their activities quantitatively and even qualitatively (Horton & Main, 1963). Bergstrom et al.(1964) reported that PGE_2 and PGE_3 are like PGE_1 in their effect on blood pressure but less potent. Depressor activity of PGAs was found greater than that of the corresponding PGEs in dogs but not in rats. Likewise, intravenous infusion of PGA_1 in anaesthetized dogs produced a greater fall in blood pressure than the same dose of PGE_1 (Bergstrom et al., 1967). The cardiovascular actions of PGF_2 were complicated and varied with the species. It was depressor in the cat and rabbit (Anggard & Bergstrom, 1963 and Horton & Main, 1965b) and pressor in the rat and dog (Ducharme & Weeks, 1967).

The route of administration was important for the cardiovascular effects of PGE_1. Intra-aortic infusion produced more pronounced changes than the intravenous route (Bergstrom et al., 1964) and infusion into the thoracic aorta caused severe hypotension than when infused into the lower abdominal aorta (Carlson & Oro, 1966). An antagonism between PGE_1 and catecholamines on blood pressure of dog has also been reported by Bergstrom et al. (1964) and Steinberg et al. (1964).

Effects on heart : Effects of prostaglandins on the heart rate and force of contraction have been reported to be variable. Berti et al. (1965) have reported that PGE_1 had no effect on inotropy or chronotropy of isolated

perfused hearts of cat and rabbit (Euler, 1937). But both the parameters were positively affected in case of rat (Vergroesen et al., 1967) and guineapig (Berti et al., 1965). PGE_1 was found to be without effect on the rabbit heart (Lee et al., 1965). Nakano and McCurdy (1967) reported that intravenously administered PGE_1 had a positive inotropic effect while PGF_2 was without effect in intact dogs while in the dog heart lung preparation, PGE_1 showed typical heart stimulant action i.e. increased force of contraction and cardiac output, a fall in right arterial pressure and no change in heart rate (Katori et al., 1970). Prostaglandin E_1 given intravenously at the rate of 0.1 to 0.2 ug/kg/min. to human beings for 20 minutes increased the heart rate by about 20 beats per minute, while systolic, diastolic and mean arterial pressures remained unchanged (Bergstrom et al., 1968). However, with higher dose a fall in blood pressure was observed. The increase in heart rate was suggested to be due to sympathetic stimulation (Carlson & Oro, 1966). The infusion of doses higher than 0.1 ug/kg/min. further increased the heart rate and decreased the mean arterial pressure and stroke volume. Prostaglandins are reported to exert little or no effect on the locke-perfused chicken heart (Horton & Main, 1967a).

Effects on blood vessels : Hyman (1969) reported that in intact dogs there was active constriction of pulmonary

arteries and veins by injections or infusions of PGF_2. But PGE_1 in contrast dilated these vessels. It was reported that prostaglandins E and A are powerful direct-acting coronary vasodilators in intact dogs (Weeks, 1972). PGE_1 after intraarterial injection was reported to decrease the resistance in the hind limbs of dogs (Lee et al., 1965., Nakano & McCurdy, 1967 and Smith, et al., 1967), cats (Holmes et al., 1963) and rabbits (Beck et al., 1966). The vasodilator effect was not influenced by atropine; the antihistaminic, tripelennamine or the beta-adrenergic blocking agent, propranolol (Nakano & McCurdy, 1967 and Smith et al., 1967).

Smooth muscles :

Effect of prostaglandins on smooth muscles of different species have extensively been studied. The results have, however, been quite variable and controversial. PGFs are reported to be more potent than their corresponding PGEs on rabbit intestine, but they are manifold less potent on guineapig ileum and colon (Bergstrom et al., 1959 and Karim, 1967). Khairallah et al., (1967) reported that PGE_1 in doses of 5 ng/ml relaxes rat duodenum. This relaxation changed to contraction either in the presence of combined alpha and beta-adrenergic blockers (phentolamine plus propranolol) or in reserpinized tissues of the rat. Such contraction was blocked by bromolysergic acid. It was presumed that PGE_1 liberates both

catecholamines and serotonin from the rat duodenum (Khairallah et al., 1967). Prostaglandin E_1 has been reported to inhibit the ureters of dog, monkey and baboon while PGF_1 has stimulatory effects in in vitro studies (Boyarsky et al., 1966 and Strong & Bohr, 1967). Prostaglandins E_1 and F_2 have been reported to cause contraction of isolated uteri of rats and guineapigs (Eliasson, 1959 and Sullivan, 1966). In the guineapig uterus and intestine, smaller doses of PGE_1 are required to produce response than those of the corresponding PGF (Bergstrom et al., 1959). In human uterine strips the three PGE compounds are reported to decrease amplitude of contractions (Bygdeman, 1964 and Bygdeman & Eliasson, 1963a, 1963b). Prostaglandin E_1 was reported to relax the toad intestine acting directly, but PGE_2 caused it to contract (Ng et al., 1970).

Prostaglandin-induced stimulatory and inhibitory actions were reported to be unaffected by anticholinergic agents (Bennett et al., 1968a, 1968b and Ambache & Zar, 1970) adrenergic blocking agents (Turker & Khairallah, 1969 and Sheard, 1968), antihistaminics (Benett, et al., 1968a), tetrodotoxin (Kadar & Sunahara, 1969) or morphine (Turker & Khairallah, 1969). It was reported that in the colon of man and the colon and intestine of the guineapig a host of drugs e.g. tetrodotoxin (a paralysant of intrinsic nerves), anticholinergic and ganglion blocking agents

reduced the prostaglandin-induced contractions which suggested that neural mechanisms are accounted for a part of the contractile action (Bennett et al., 1968a; Bennett & Fleshler, 1969 and Harry, 1968). Horton and Jones (1969) reported that the isolated strip of chick crop is contracted by prostaglandins E_1, F_2 and A_1. The mean thres hold dose for PGE_1 was 2 ng/ml and PGA_1 had approximately 1 percent of the activity of PGE_1. Jones (1970) in his studies observed that PGE_1 initiates or if already present, enhances the rhythmic pendular contractions of the isolated chick oesophagus and also causes potentiation of the contractile response of chick oesophagus longitudinal muscle produced by preganglionic parasympathetic nerve stimulation.

CHAPTER III

MATERIALS AND METHODS

MATERIALS AND METHODS

Pharmacodynamic effects of histamine, 5-hydroxytryptamine and prostaglandin (PGE_1) were studied on cardiovascular system and smooth muscles of WLH birds.

Experimental animals : For cardiovascular studies adult WLH birds of either sex weighing from 1 to 2 kg were employed. For experiments on isolated intestine, chicks (1 to 2 weeks old) and for studies on isolated oviduct, laying birds were taken. Birds were obtained from the Department of Livestock Production and Management, Haryana Agricultural University and from local poultry farms. Birds were housed separately in cages where arrangement for feed and water was made ad lib.

Drugs : Following drugs were used in present investigation:

Histamine dihydrochloride Mol.wt. 184.1

Promethazine hydrochloride Mol.wt. 291.8
(Phenergan)

Diphenhydramine hydrochloride Mol.wt. 291.8
(Benadryl)

Adrenaline hydrochloride Mol.wt. 219.7

Acetylcholine chloride Mol.wt. 181.7

Reserpine Mol.wt. 608.7
(Serpasil)

Tyramine hydrochloride Mol.wt. 173.6

Alpha-methyl-para-tyrosine-methyl ester
hydrochloride Mol.wt. 261.71

5-hydroxytryptamine creatinine sulphate Mol.wt. 405.4

Cyproheptadine hydrochloride Mol.wt. 327.7
(Periactin)

Prostaglandin (PGE_1) Mol.wt. 354

Pronethalol hydrochloride Mol.wt. 265.71

Phentolamine methanesulphonate Mol.wt. 377.3 (Rigitine)

Preparation of solutions : Solutions of the drugs were prepared in double glass distilled water except that of prostaglandin E_1 which was made in 95% ethanol as recommended by M/s Upjohon Company, Michigan (USA). All stock solutions were kept in the refrigerator. Stock solution of PGE_1 was stored in freezer. Solutions for daily use were prepared from the stock solutions.

I. Cardiovascular system :

i. Blood pressure : In the present investigation blood pressure was recorded according to method described by Coon (1939) with slight modification.

Adult WLH birds of either sex weighing 1 to 2 kg were anaesthetised with phenobarbitone sodium (150 to 180 mg/kg, i.m.). Crural vein was cannulated and attached to burette previously filled with saline. Femoral artery was cannulated and attached to the mercury manometer (condon type) through a rubber tubing filled with sodium citrate solution (12 percent). Blood pressure was recorded kymographically and speed of the drum was kept constant at 7.5 mm/min. Drugs were injected through cannulated vein and after each injection 1.5 ml of saline was infused to push the drug into circulation. Effects

of drugs were noted on systolic, diastolic, pulse and mean arterial pressures. Mean arterial pressure = diastolic pressure + $^{1}/_{3}$ of pulse pressure (Duke's, 1955).

Administration of drugs : Histamine in graded doses of 1, 2, 4, 8, 16 and 32 ug/kg was given intravenously. Promethazine (0.31, 1.25, 2.5 and 5.0 mg/kg, i.v.) and diphenhydramine (0.62, 1.25 and 2.5 mg/kg, i.v.) were administered to observe their own effect and also their blocking effect on histamine response on blood pressure.

In order to explore the mechanism of pressor response of promethazine and diphenhydramine in birds, their effect was studied in birds treated with alpha (phentolamine upto 20 mg/kg, i.v.) and beta (pronethalol upto 5 mg/kg, i.v.) adrenergic blockers, reserpine and reserpine plus alpha-methyl para tyrosine.

In order to find a suitable dose of reserpine which could produce adequate catecholamine depletion, different doses of reserpine were tried. In one group, reserpine was administered intraperitoneally at the rate of 1.5 mg/kg, in other group 3 mg/kg and in third group 10 mg/kg. Doses were given for two consecutive days. Birds were mounted for recording the blood pressure after 24 hours of the second dose of reserpine. A few birds from second group were also treated with two doses of alpha-methyl-p-tyrosine (100 mg/kg) given 3 hours and 1 hour before recording the blood pressure.

5-hydroxytryptamine in doses of 10, 30 and 100 ug/kg was given intravenously in phenobarbitone anaesthetised birds and its effect on blood pressure was recorded kymographically. Cyproheptadine in doses of 1.25, 2.5 and 5.0 mg/kg was administered to see its blocking effect on blood pressure response to 5-HT.

Prostaglandin E_1 in doses of 2.5, 5.0 and 10 ug/kg was administered intravenously to observe its effect on blood pressure. Promethazine (5 mg/kg), atropine (3 mg/kg) or cyproheptadine (5 mg/kg) were used to see if they affected the blood pressure response to PGE_1. Response of acetylcholine (1 ug/kg), adrenaline (2 ug/kg) and histamine (4 ug/kg) on blood pressure were noted before and after the administration of PGE_1 (5 and 10 ug/kg).

ii. Electrocardiogram : Electrocardiograms of anaesthetised adult WLH birds of either sex were taken according to method described by Sturkie (1954). Birds were anaesthetized with phenobarbitone sodium (150 to 180 mg/kg, i.m.). Electrodes (hypodermic needles) were inserted below the skin at the appropriate site after removing the feathers. Care was taken that the needle did not enter into the muscle. Electrocardiogram was recorded by Cardiart* at lead II (right wing base and left foot).

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*Transistorized electrocardiograph. Siemens India Ltd.

Histamine (10 ug/kg), promethazine (5 mg/kg), diphenhydramine (5 mg/kg), phentolamine (20 mg/kg), 5-HT (100 ug/kg) or prostaglandin E_1 (10 ug/kg) was injected intravenously in wing vein. Electrocardiograms were taken before and immediately after the injection of drug.

iii. Blood vessels : Angiographic studies were conducted in phenobarbitone anaesthetised birds to see the effect of histamine (10 ug/kg), 5-HT (100 ug/kg) and prostaglandin E_1 (10 ug/kg) on blood vessels. Femoral arteries on both legs were exposed and cannulated with polythene cannula of appropriate size. Contrast media (Conray 420, May & Baker) was injected in one of the femoral arteries (1.5 to 2 ml). Radiograms were taken just after giving the contrast media. In the contralateral artery, the radiogram was taken after the injection of drug and the contrast media. The diameter of 10 mm length of the artery was measured with vernier caliper at three places from the point of origin of the antiria tibialis and the average length of diameter was calculated for finding out the area ($\pi r^2 L$).

II. Smooth muscles :

i. Isolated intestine : Chicks (1 to 2 weeks old) were sacrificed by decapitation and abdomen was opened. Ileum was separated and cleaned gently. A piece of ileum (2 cm) was taken and suspended in Kreb's Henseleit Solution* contained in tissue bath (20 ml).

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*

NaCl	6.95 gm
Kcl	0.34 gm
KH_2PO_4	0.162 gm
$MgSo_4$	0.294 gm
$NaHCo_3$	2.1 gm
Dextrose	2.0 gm
Distilled water ad	1000 ml

Preparations were continuously oxygenated and maintained at 35 ± 1°C. Effects of drugs were recorded on smoked kymograph by means of an isotonic frontal writing lever (Tension 2 gm and magnification 6). A dose of drug was added to the bath and allowed to remain in contact with the tissue. The contact time varied with drugs. Next dose was repeated after 15 minutes interval. During this period 4 to 5 washings were given. Antagonist was added to the bath and allowed to remain in contact with tissue for 15 minutes before agonist was added.

Cumulative dose responses of histamine, 5-hydroxytryptamine and PGE_1 were obtained and ED_{50} were calculated graphically.

ii. Isolated oviduct: Isolated segments of oviduct (isthmus) 2.5 cm in length were taken from laying WLH birds. Preparations were suspended in Ringer Locke Solution*. Bath was continuously oxygenated and kept at 37 ± 1°C. Rest of the procedure was same as described for isolated intestine.

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*

NaCl	9.0	gm
Kcl	0.42	gm
$CaCl_2$	0.24	gm
$NaHCO_3$	0.15	gm
Glucose	1.0	gm
Distilled water ad.	1000	ml

CHAPTER IV

RESULTS

RESULTS

I. CARDIOVASCULAR SYSTEM

Blood pressure :

Histamine and antihistaminics : The mean values of systolic, diastolic, pulse and mean arterial pressures before and after the intravenous administration of histamine in graded doses are given in Table 1. A typical response of histamine on blood pressure was a sharp fall followed by a rise (Fig.1). The effect lasted for about two minutes (Table 2).

The results show that histamine decreased the systolic, diastolic and mean arterial pressures, but had no effect on pulse pressure. Decrease in mean arterial pressure by histamine in doses of 1, 2, 4 and 8 ug/kg were 11.36, 19.66, 27.25 and 34.28 percent, respectively. The intensity of the effect on all the parameters studied, varied directly with log doses of histamine. The percent decrease in mean arterial pressure has been depicted in Fig.2 . It was noted that histamine (0.5 ug/kg) did not elicit a measurable response on blood pressure. With doses higher than 8 ug/kg of histamine, no marked increase in depressor response was observed.

Promethazine hydrochloride in doses of 0.31, 1.25, 2.5 and 5.0 mg/kg given intravenously showed a marked pressor response of its own (Fig.7). Promethazine caused

TABLE -1

EFFECT OF HISTAMINE (i.v.) ON BLOOD PRESSURE OF ADULT WLH FOWLS

(mm Hg)

HISTAMINE ug/kg	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		PULSE PRESSURE		MEAN ARTERIAL PRESSURE (MAP)		PERCENT CHANGE IN MAP
	Before drug	After drug	Before drug	After drug	Before drug	After drug	Before drug	After drug	
1.0	98.9 (10.6)	86.8 (8.9)	95.9 (10.7)	84.6 (9.1)	3.0 (0.22)	2.6 (0.21)	96.8 (10.7)	85.5 (19.0)	-11.36 (1.39)
2.0	99.1 (3.31)	79.5 (8.66)	96.3 (11.53)	76.2 (6.40)	2.8 (0.24)	3.2 (0.26)	97.2 (11.40)	77.2 (8.30)	-19.66 (2.04)
4.0	100.3 (11.35)	73.3 (7.68)	97.2 (11.42)	69.6 (7.87)	3.1 (0.26)	3.6 (0.25)	98.2 (11.40)	70.8 (7.81)	-27.25 (2.14)
8.0	99.9 (10.86)	65.7 (6.92)	96.8 (11.40)	62.5 (7.21)	3.1 (0.49)	3.2 (0.25)	97.8 (11.31)	63.6 (7.14)	-34.28 (1.79)

Values are mean of 16 observations

Figures in parenthesis indicate standard error

TABLE -2

PRESSOR EFFECT OF HISTAMINE ON SYSTOLIC, DIASTOLIC, PULSE AND MEAN ARTERIAL PRESSURES OF ADULT WLH FOWLS

(mmHg)

HISTAMINE ug/kg	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		PULSE PRESSURE		MEAN ARTERIAL PRESSURE (MAP)		PERCENT CHANGE IN MAP
	Before drug	After drug	Before drug	After drug	Before drug	After drug	Before drug	After drug	
1.0	105.2 (1.7)	113.2 (1.3)	103.4 (1.3)	111.1 (1.4)	1.8 (0.17)	2.1 (1.8)	103.9 (1.6)	111.8 (1.4)	+ 7.5 (0.91)
2.0	102.0 (1.1)	110.8 (1.4)	100.4 (1.0)	109.2 (1.3)	1.4 (0.61)	1.4 (0.91)	100.8 (1.6)	109.7 (1.3)	+ 8.7 (1.4)
4.0	102.5 (1.4)	112.8 (1.3)	100.0 (1.4)	111.0 (1.2)	1.7 (0.60)	1.7 (0.43)	101.3 (1.3)	111.5 (1.2)	+10.0 (1.1)
8.0	105.1 (2.8)	120.6 (3.4)	103.4 (2.8)	118.3 (3.5)	1.7 (0.62)	1.7 (0.60)	103.9 (2.8)	118.8 (3.4)	+14.4 (1.7)

Values are mean of 11 observations

Figures in parenthesis indicate standard error

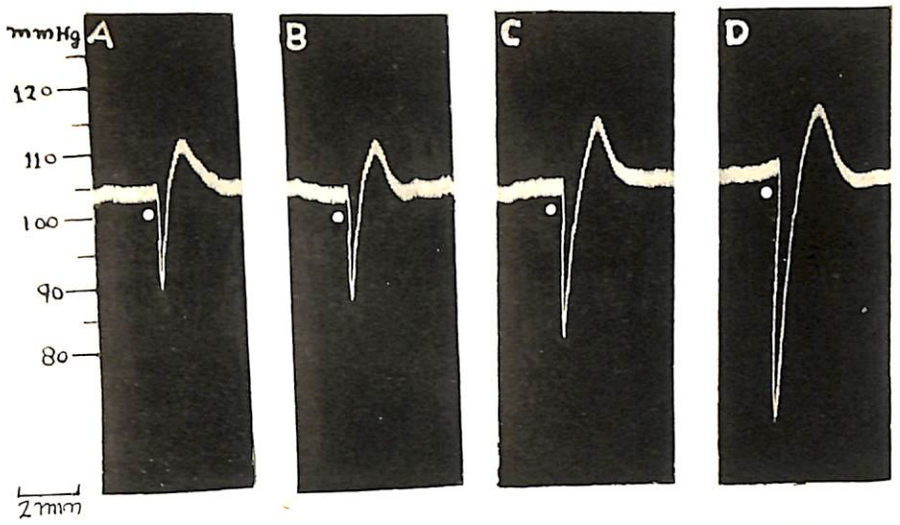


Fig.1. Effect of histamine (i.v.) on arterial blood pressure of fowl in graded doses of (A) 1 ug/kg (B) 2 ug/kg (C) 4 ug/kg and (D) 8 ug/kg.

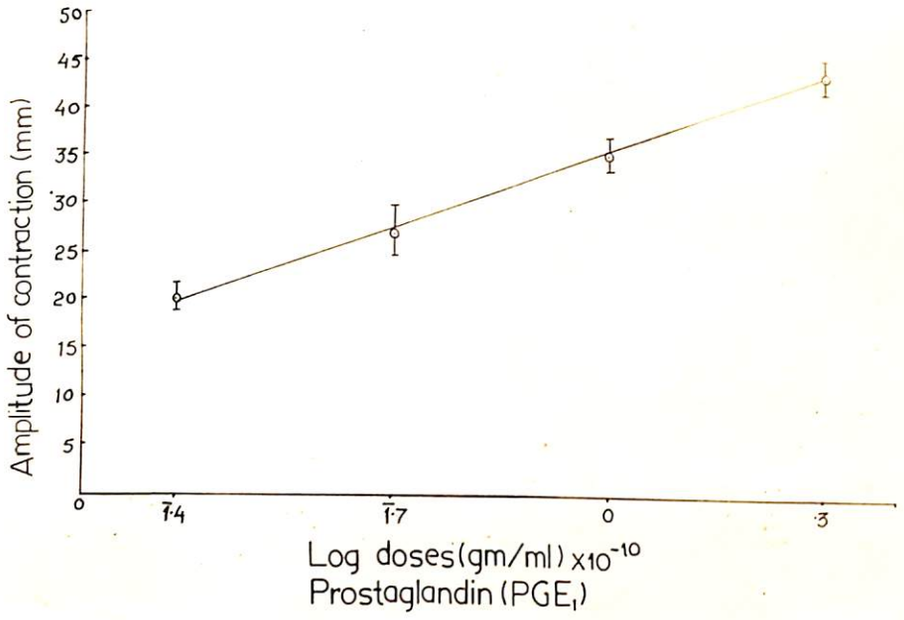


Fig.2. Dose response relationship of histamine on fowl blood pressure. Each value is mean of 16 observations. Vertical bars denote S.E. of mean

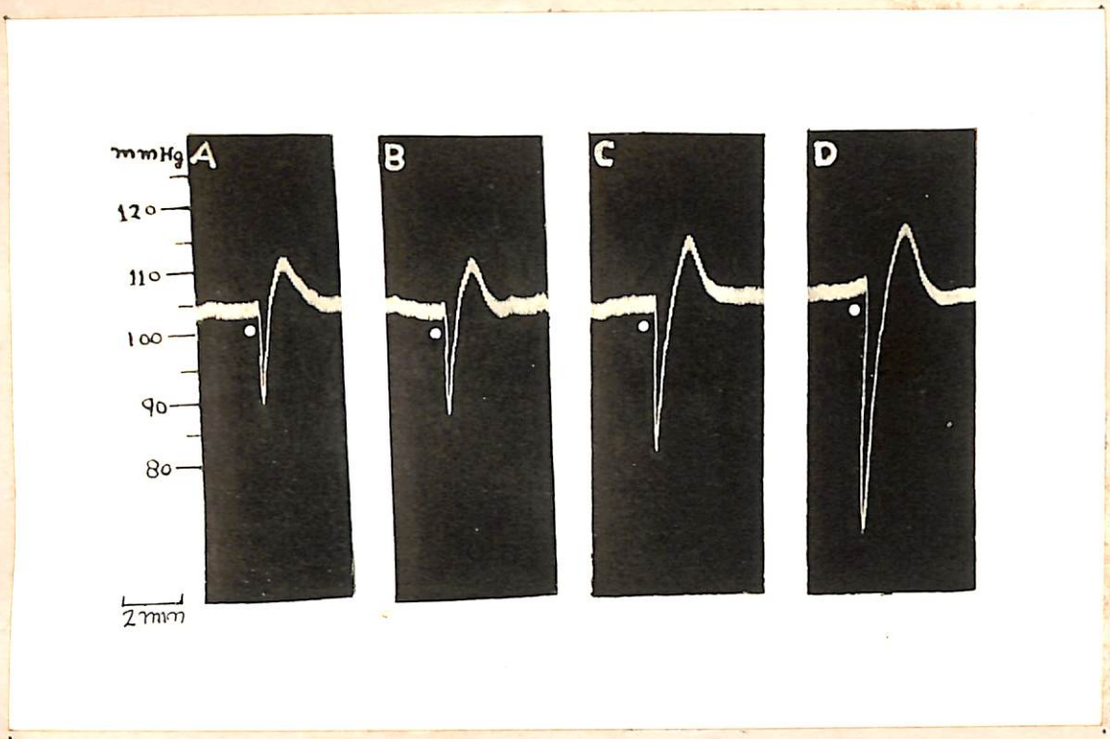


Fig.1. Effect of histamine (i.v.) on arterial blood pressure of fowl in graded doses of (A) 1 ug/kg (B) 2 ug/kg (C) 4 ug/kg and (D) 8 ug/kg.

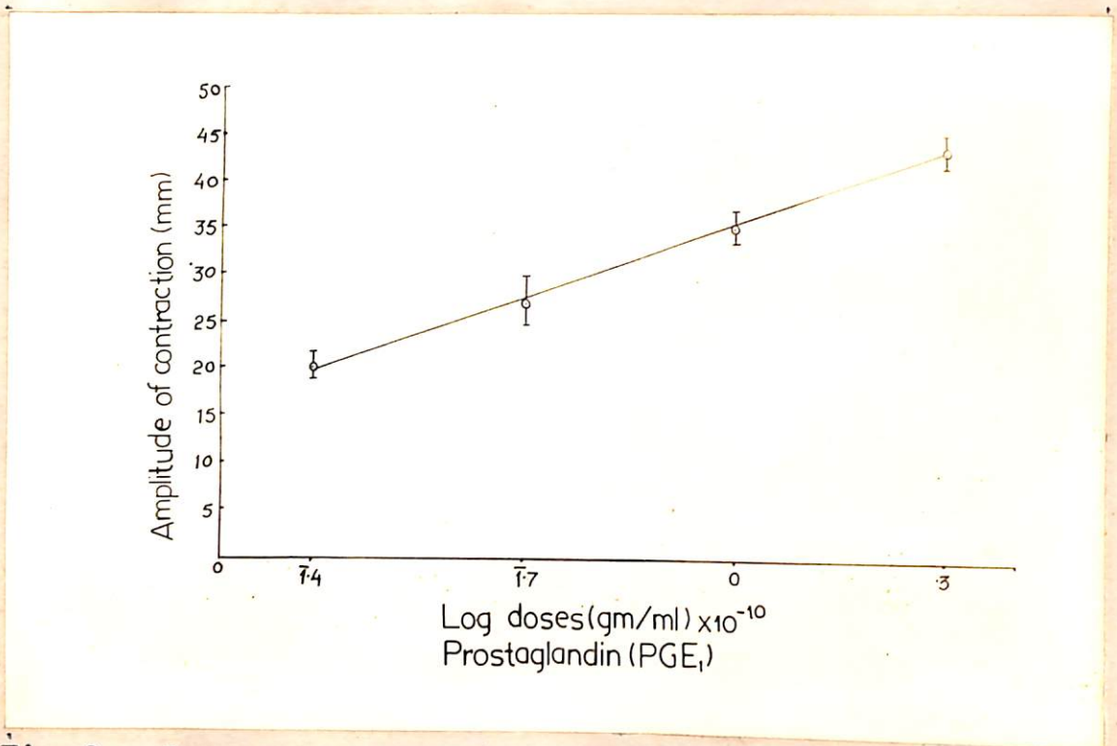


Fig.2. Dose response relationship of histamine on fowl blood pressure. Each value is mean of 16 observations. Vertical bars denote S.E. of mean

a marked increase in systolic, diastolic and mean arterial pressures without producing any change in pulse pressure (Table 3). Increase in mean arterial pressure by promethazine in doses of 0.31, 1.25, 2.5 and 5.0 mg/kg was 3.7, 14.0, 17.0 and 28.0 percent, respectively. Pressor response of promethazine lasted for about 15 to 50 minutes, depending upon the dose. Since all the doses could not be repeated in a single experiment, the result have been taken from different experiments for different doses.

Effect of graded doses of promethazine (0.31, 1.25, 2.5 and 5.0 mg/kg) in blocking the depressor response to histamine (8 ug/kg) has been shown in Fig.3. It was observed that promethazine at all dose levels blocked the depressor response to histamine (8 ug/kg). Percent blockade of histamine response increased with the dose of promethazine. Maximum blockade of 79.3, 67.3, 65.3 and 5.7 percent was observed at first hour of the administration of promethazine in doses of 5.0, 2.5, 1.25 and 0.31 mg/kg, respectively (Fig.4). After administration of promethazine in doses of 0.31, 1.25 and 2.5 mg/kg, response to histamine recovered in about 5 hours, while at 5 mg/kg of promethazine it took about 8 to 10 hours before the histamine response recovered to normal.

Diphenhydramine hydrochloride in doses of 0.31, 0.62, 1.25 and 2.5 mg/kg given intravenously showed a pressor response of its own (Fig.8). Diphenhydramine caused a marked

TABLE -3

EFFECT OF PROMETHAZINE (i.v.) ON BLOOD PRESSURE OF ADULT WLH FOWLS

(mmHg)

PROMETHAZINE ug/kg	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		PULSE PRESSURE		MEAN ARTERIAL PRESSURE (MAP)		PERCENT CHANGE IN MAP
	Before drug	After drug	Before drug	After drug	Before drug	After drug	Before drug	After drug	
0.31	115.4 (7.54)	119.6 (8.0)	112.0 (7.56)	116.2 (8.3)	3.4 (0.40)	3.4 (0.51)	113.0 (8.18)	117.0 (7.54)	+ 3.72 (0.60)
1.25	132.4 (6.08)	151.2 (6.70)	149.6 (5.83)	148.4 (6.78)	3.2 (0.37)	3.4 (0.21)	130.6 (3.16)	149.3 (6.78)	+14.09 (1.6)
2.5	120.8 (15.78)	140.0 (13.63)	118.0 (15.87)	136.8 (13.45)	2.8 (0.37)	3.2 (0.53)	119.0 (15.81)	137.8 (13.49)	+17.26 (3.8)
5.0	112.4 (9.49)	141.0 (5.19)	108.6 (9.49)	137.4 (5.19)	3.8 (0.66)	3.4 (0.67)	109.8 (9.49)	138.5 (5.19)	+28.02 (8.42)

Values are mean of 9 observations

Figures in parenthesis indicate standard error

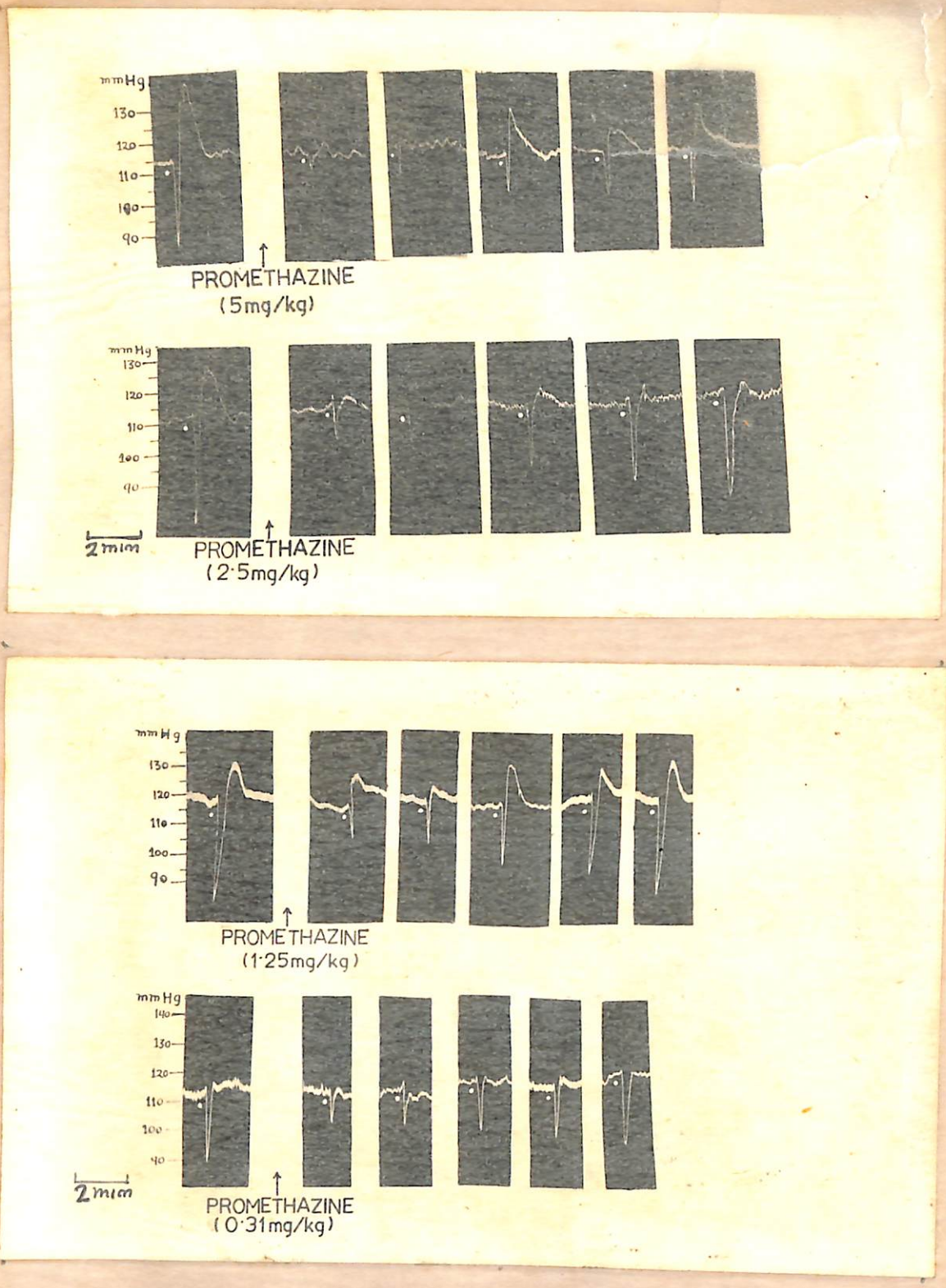


Fig.3. Effect of promethazine in graded doses on fowl blood pressure response to histamine (8 ug/kg) at hourly intervals.

increase in systolic, diastolic and mean arterial pressures without producing any change in pulse pressure (Table 4). Increase in mean arterial pressure by diphenhydramine at 0.31, 0.62, 1.25 and 2.5 mg/kg was 5.5, 6.1, 9.5 and 18.0 percent, respectively. Pressor response of diphenhydramine lasted for about 10 to 40 minutes, depending upon the dose. Since all the doses could not be repeated in a single experiment, the results have been taken from different experiments for different doses.

Effect of diphenhydramine in doses of 0.61, 1.25 and 2.5 mg/kg on the depressor response to histamine (8 ug/kg) has been shown in Fig.5. It was observed that diphenhydramine at all dose levels blocked the depressor response to histamine (8 ug/kg). Percent blockade of histamine response increased with the dose of diphenhydramine. Maximum blockade of 45.4, 42.8 and 11.9 percent was observed at first hour of the administration of diphenhydramine at 2.5, 1.25 and 0.62 mg/kg dose levels, respectively (Fig.6). As compared to the antihistaminic effect of promethazine on fowl blood pressure, the effect of diphenhydramine was less potent and of shorter duration.

Investigation into the mechanism of pressor response to antihistaminics :

Contrary to the observations in mammals, a marked pressor response to promethazine and diphenhydramine was noticed in anaesthetised birds.

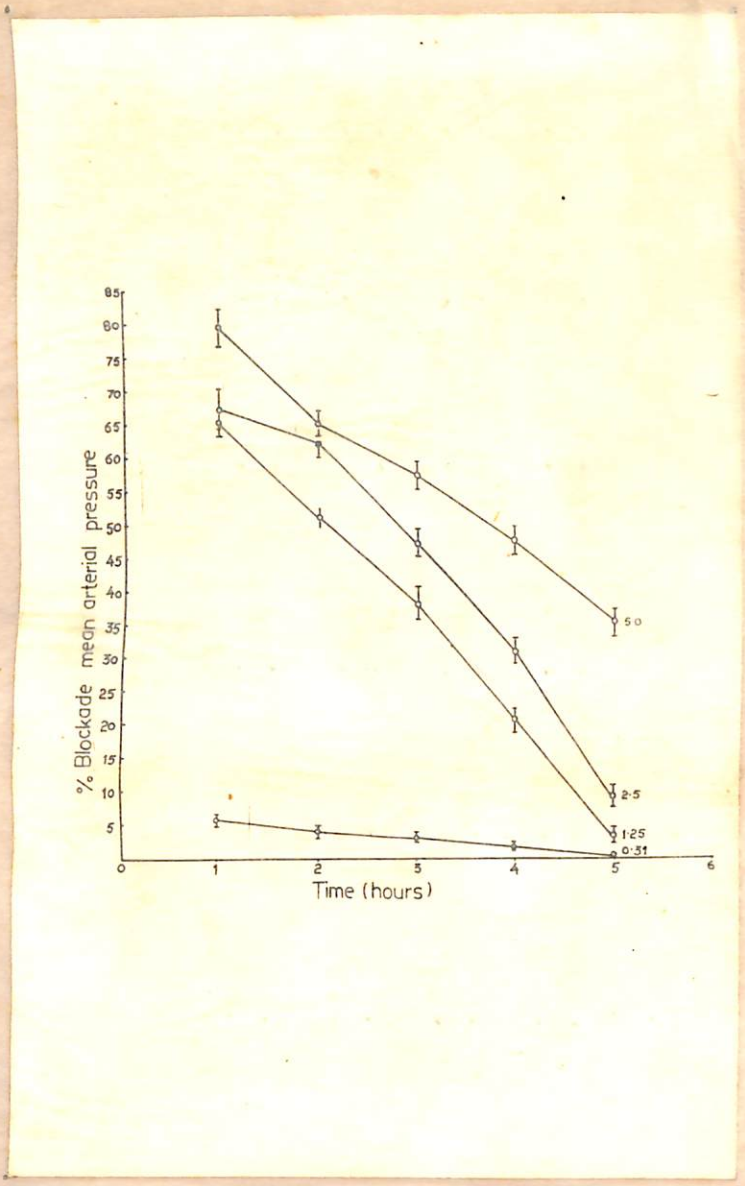


Fig.4. Percent blockade of depressor effect of histamine (8 ug/kg) on fowl blood pressure by promethazine in graded doses (mg/kg) at different times after administration of promethazine. Each observation is a mean of 5 to 7 experiments. Vertical bars denote S.E. of mean.

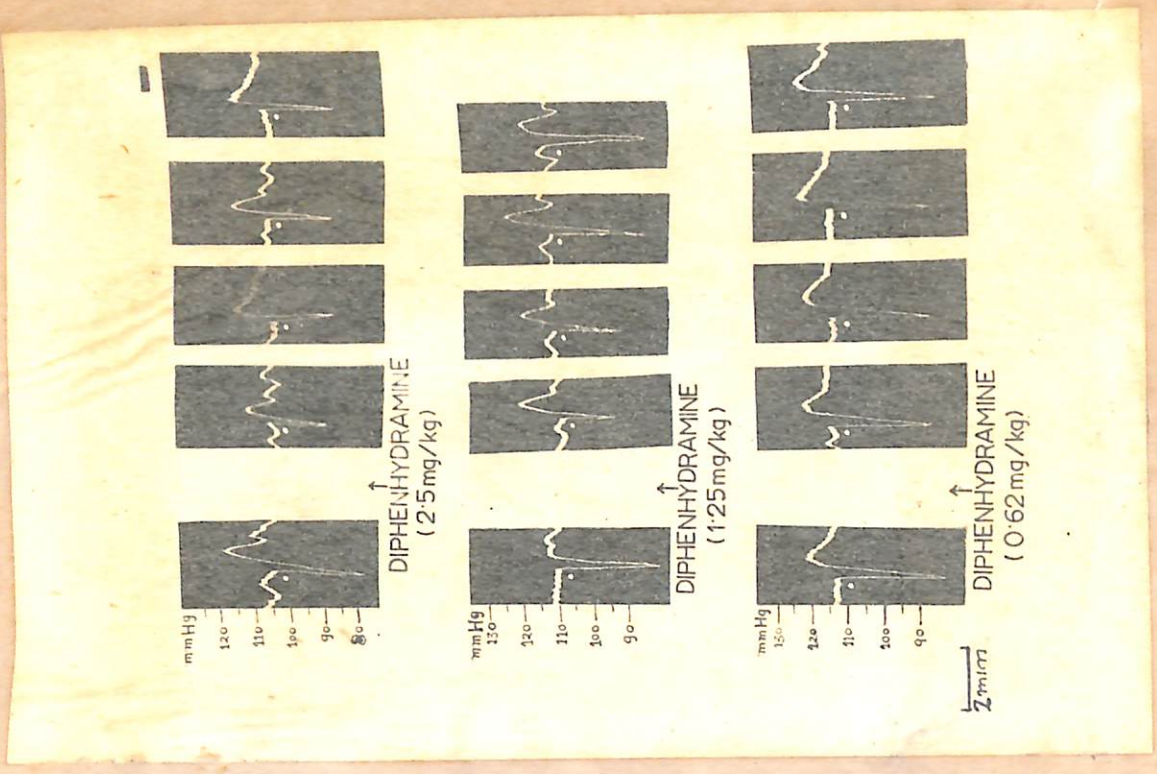


Fig.5. Effect of diphenhydramine in graded doses on fowl blood pressure response to histamine (8 ug/kg) at hourly intervals.

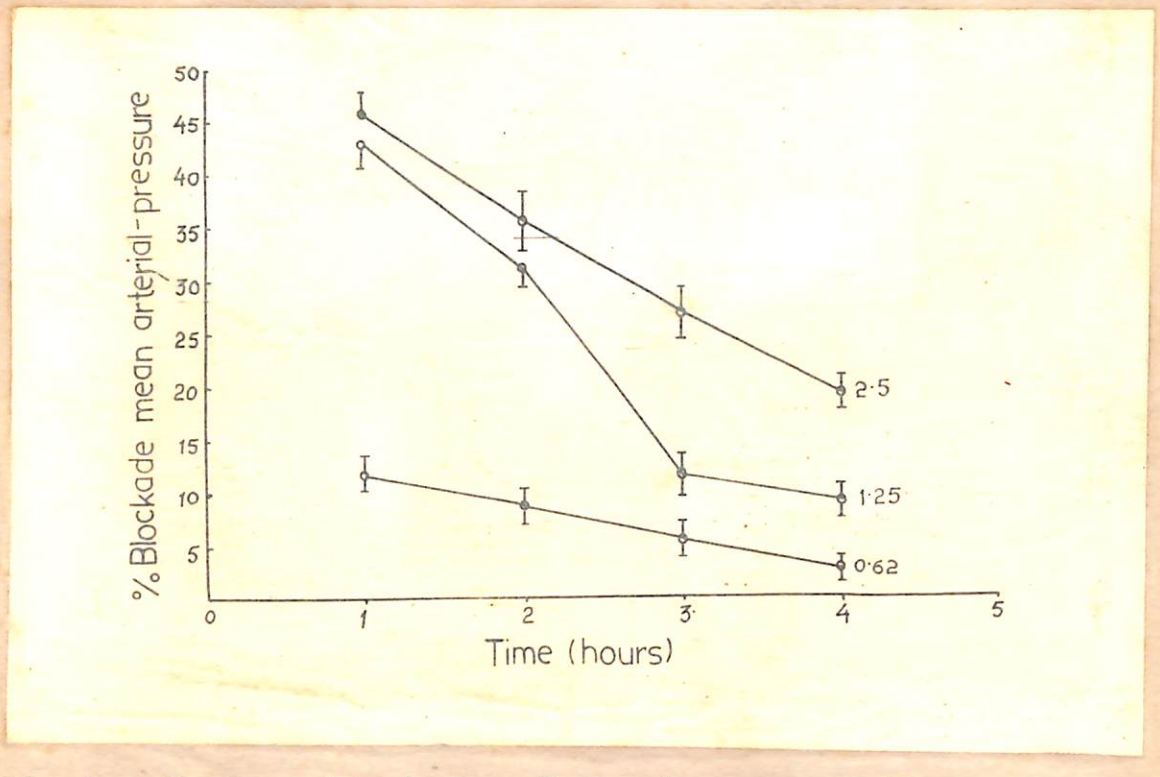


Fig.6. Percent blockade of the depressor effect of histamine (8 ug/kg) on fowl blood pressure by diphenhydramine in graded doses (mg/kg) at different times after administration of diphenhydramine. Each observation is a mean of 5 to 7 experiments. Vertical bars denote S.E. of mean.

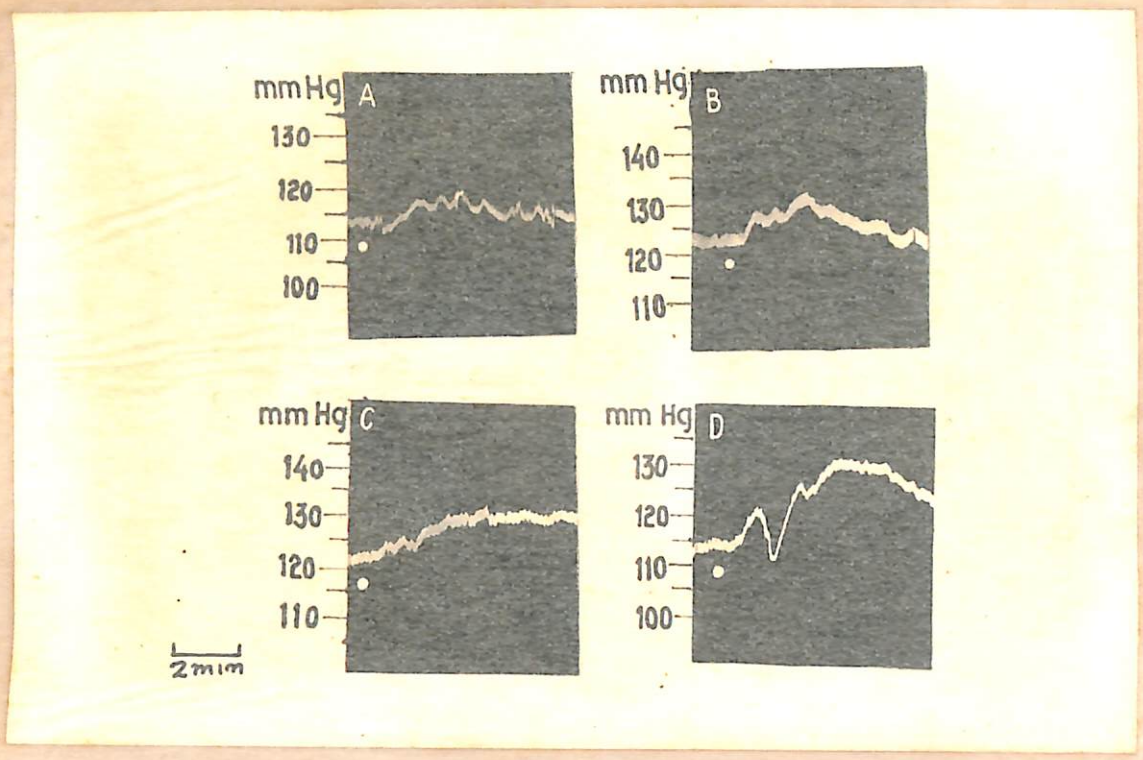


Fig.7. Effect of promethazine (i.v.) on fowl blood pressure in doses of (A) 0.31 mg/kg (B) 1.25 mg/kg (C) 2.5 mg/kg and (D) 5.0 mg/kg.

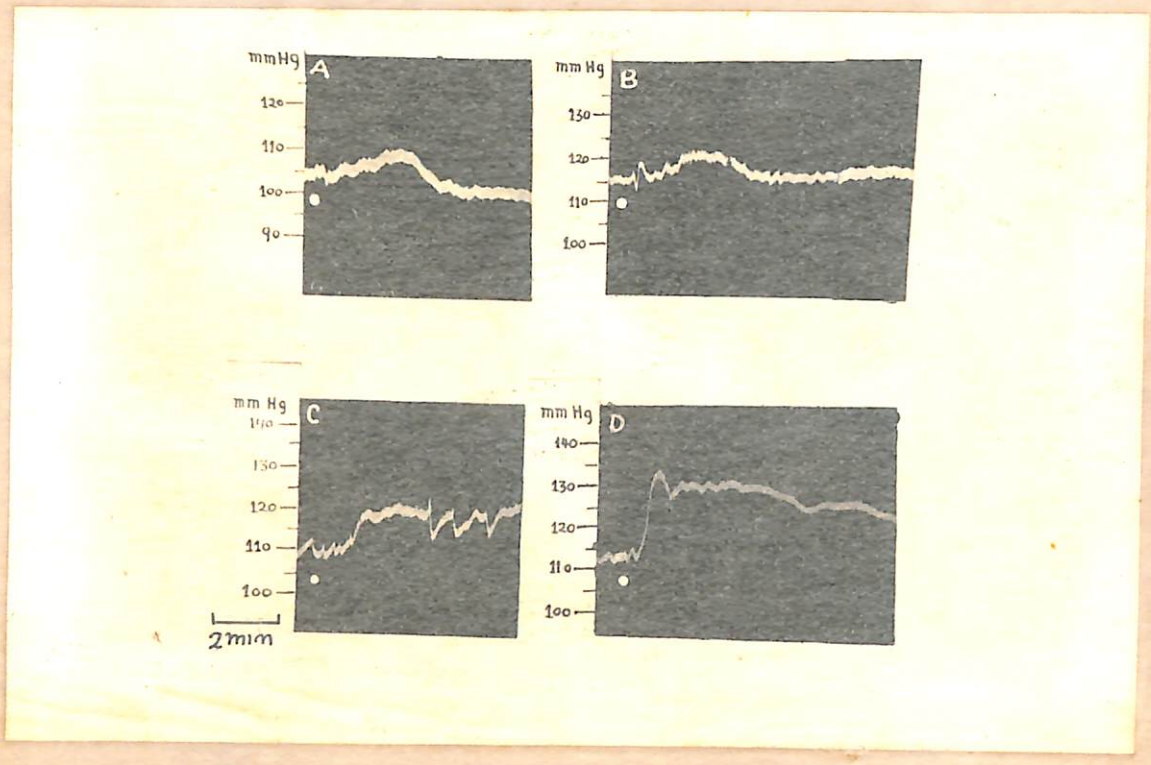


Fig.8. Effect of diphenhydramine (i.v.) on fowl blood pressure in doses of (A) 0.31 mg/kg (B) 0.62 mg/kg (C) 1.25 mg/kg and (D) 2.5 mg/kg.

In order to explore the mechanism of this unusual response the following experiments were conducted.

i. Effect of adrenergic receptor blocking agents :

Pressor responses to promethazine (5 mg/kg) and diphenhydramine (2.5 mg/kg) were not blocked by an alpha-adrenergic receptor blocking agent, phentolamine in doses upto 20 mg/kg, i.v.. While at this dose rate phentolamine blocked about 25 percent response of adrenaline (2 ug/kg). Dose of phentolamine was not increased beyond 20 mg/kg as even this dose was quite toxic. It caused a marked rise in blood pressure (about 55 to 60 percent) and marked electrocardiographic changes. Pronethalol, a beta-adrenergic receptor blocking agent, in doses upto 5 mg/kg did not affect the pressor response to promethazine (5 mg/kg) or diphenhydramine (2.5 mg/kg).

ii. Effect of agents affecting catecholamines stores in sympathetic nerves :

In order to deplete the endogenous nor-epinephrine from the sympathetic nerve endings, reserpine in different doses was administered. In birds pretreated with reserpine (1.5 or 3 mg/kg for two days), the pressor response of promethazine (5 mg/kg,i.v.) remained unaltered (Fig.9A,B) Tyramine (0.5 mg/kg), an indirectly acting sympathomimetic agent which causes release of catecholamines from the adrenergic nerves, usually caused a rise in blood pressure, even in reserpine pretreated birds. This indicates that

anaesthetised fowls is shown in Fig.11.

The effect of 5-HT on blood pressure was not a consistent one. It varied depending upon the initial level of blood pressure. In one set of experiments (11 birds) when the initial blood pressure level was between 125 to 135 mm Hg, 5-HT at all dose levels showed a depressor response.(Fig.11-I). In nine birds with initial blood pressure ranging from 85 to 95 mm Hg, 5-HT at all dose levels showed a pressor response (Fig.11-II). In five birds whose blood pressure ranged between 110 to 115 mm Hg, 5-HT produced a polyphasic response characterised by pressor-depressor-pressor effect (Fig.11-III).

Effect of cyproheptadine, a serotonergic receptor blocking agent in doses of 1.25, 2.5 and 5.0 mg/kg on 5-HT (100 ug/kg) response to blood pressure is shown in Fig.10.

Cyproheptadine at low dose level (1.25 mg/kg) did not block the depressor effect of 5-HT (100 ug/kg) while dose of 2.5 mg/kg blocked the depressor response to 5-HT (100 ug/kg) by about 45 percent. Cyproheptadine at dose rate of 5 mg/kg completely blocked the depressor response to 5-HT (100 ug/kg). Pressor response to 5-HT, however, remained unaltered by cyproheptadine (5 mg/kg). In most of the experiments cyproheptadine alone produced a transitory fall in blood pressure by itself, except in a few experiments where a slight and momentary rise in blood pressure was observed.

doses of reserpine used failed to deplete the catecholamines from sympathetic nerves.

In another set of experiments, the synthesis of endogenous nor-epinephrine was inhibited by administration of alpha-methyl-para-tyrosine, an inhibitor of tyrosine hydroxylase enzyme, in two doses of 100 mg/kg, administered 3 hours and one hour prior to the experiment. In addition, these birds also received reserpine (3 mg/kg) , 24 hours before the experiment. In such birds promethazine (5 mg/kg) still showed a pressor response, indicating that catecholamine depletion was not complete (Fig.9C).

However, the pressor response of promethazine was markedly reduced in birds pretreated with 10 mg/kg of reserpine daily for two days (Fig.9D). In these birds effect of tyramine was also significantly decreased.

Results indicate that adequate depletion of catecholamines could not be achieved with reserpine upto 3 mg/kg alone and reserpine (3 mg/kg) plus alpha-methyl-para-tyrosine, while reserpine in high doses (10 mg/kg daily for two days) could deplete the catecholamines considerably to decrease the pressor response to promethazine (5 mg/kg). It may be mentioned that two out of seven birds treated with reserpine at this dose rate had died during the experiment.

5-hydroxytryptamine : Effect of graded doses of 5-HT (10, 30 and 100 ug/kg, i.v.) on blood pressure of

anaesthetised fowls is shown in Fig.11.

The effect of 5-HT on blood pressure was not a consistent one. It varied depending upon the initial level of blood pressure. In one set of experiments (11 birds) when the initial blood pressure level was between 125 to 135 mm Hg, 5-HT at all dose levels showed a depressor response.(Fig.11-I). In nine birds with initial blood pressure ranging from 85 to 95 mm Hg, 5-HT at all dose levels showed a pressor response (Fig.11-II). In five birds whose blood pressure ranged between 110 to 115 mm Hg, 5-HT produced a polyphasic response characterised by pressor-depressor-pressor effect (Fig.11-III).

Effect of cyproheptadine, a serotonergic receptor blocking agent in doses of 1.25, 2.5 and 5.0 mg/kg on 5-HT (100 ug/kg) response to blood pressure is shown in Fig.10.

Cyproheptadine at low dose level (1.25 mg/kg) did not block the depressor effect of 5-HT (100 ug/kg) while dose of 2.5 mg/kg blocked the depressor response to 5-HT (100 ug/kg) by about 45 percent. Cyproheptadine at dose rate of 5 mg/kg completely blocked the depressor response to 5-HT (100 ug/kg). Pressor response to 5-HT, however, remained unaltered by cyproheptadine (5 mg/kg). In most of the experiments cyproheptadine alone produced a transitory fall in blood pressure by itself, except in a few experiments where a slight and momentary rise in blood pressure was observed.

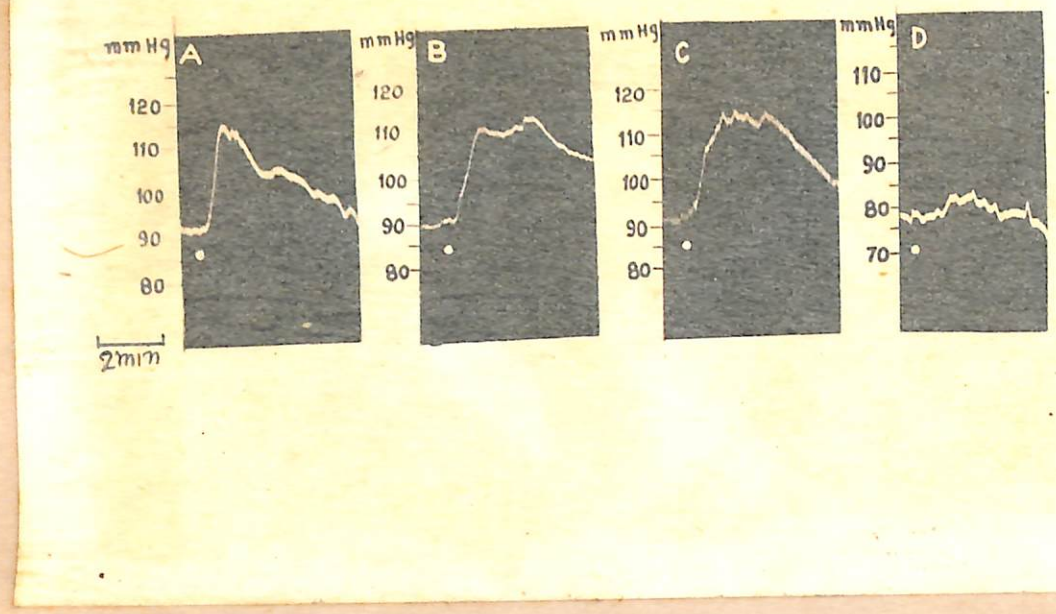


Fig.9. Pressor response of promethazine (5 mg/kg,i.v.) in birds pretreated with reserpine (A) 1.5 mg/kg (B) 3 mg/kg (C) reserpine 3 mg/kg plus alpha-methyl-paratyrosine 100 mg/kg and (D) reserpine 10 mg/kg. Doses of reserpine were repeated after 24 hours. Alpha-methyl-paratyrosine was given 3 hours and 1 hour prior to the experiment. Each response is of different bird.

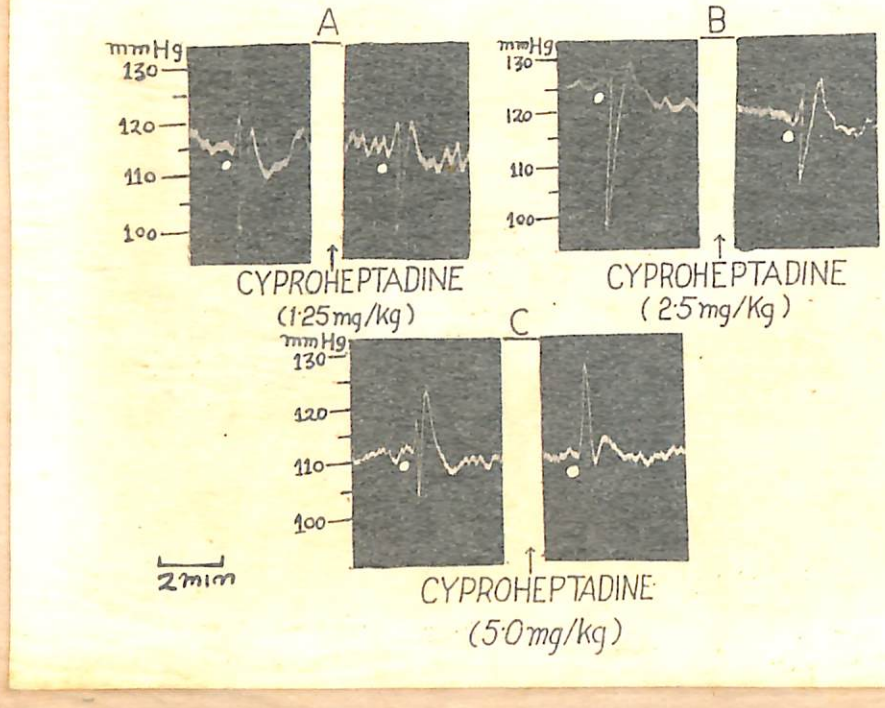


Fig.10. Effect of cyproheptadine in different doses on fowl blood pressure response to 5-HT (100 ug/kg)

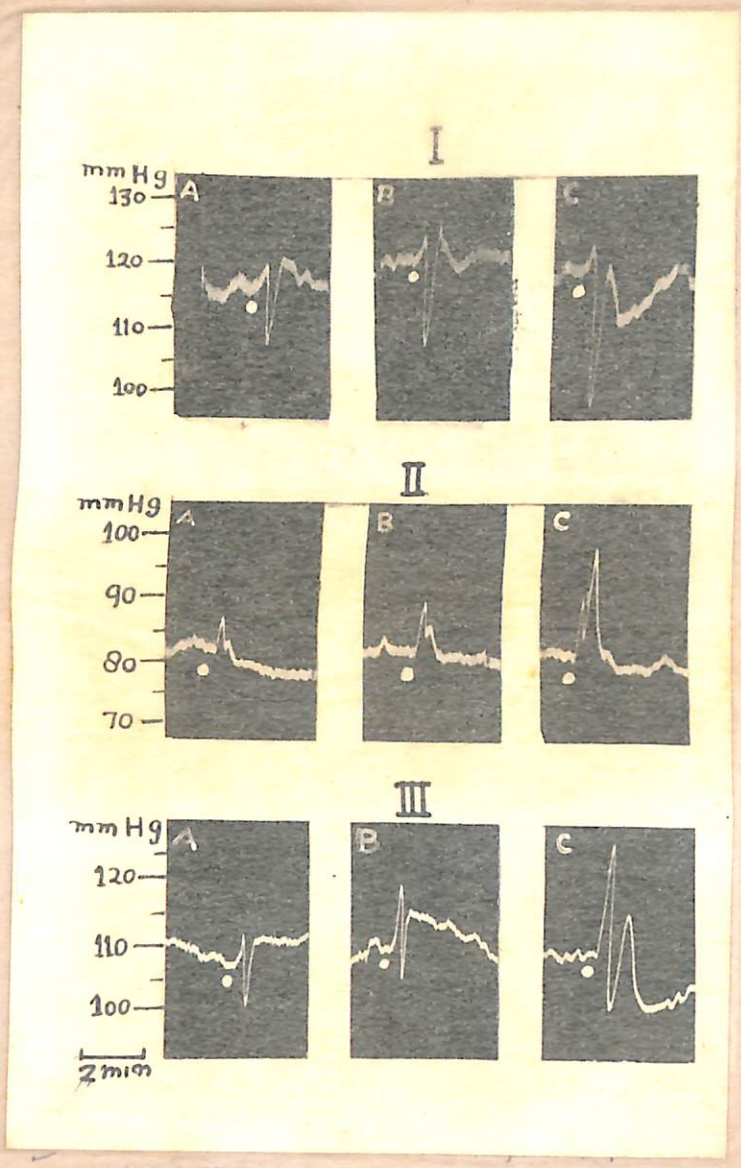


Fig.11. Effect of 5-hydroxytryptamine on fowl blood pressure (i.v.) in doses of (A) 10 ug/kg (B) 30 ug/kg and (C) ug/kg.
I, II and III indicate high, low and intermediate levels of initial blood pressure.

Prostaglandin E_1 : Effect of graded doses of PGE_1 on systolic, diastolic, pulse and mean arterial pressures of phenobarbitone anaesthetised fowls is given in Table 5.

Prostaglandin E_1 in doses of 2.5, 5.0 and 10.0 ug/kg decreased the systolic, diastolic and mean arterial pressures while no change was observed on pulse pressure. Prostaglandin E_1 in doses of 2.5, 5.0 and 10 ug/kg produced 21, 51 and 54 percent fall in mean arterial pressure, respectively. The hypotensive effect of PGE_1 on blood pressure at dose rate of 2.5 ug/kg lasted for about 5 minutes, while at 5 to 10 ug/kg PGE_1 produced a sharp fall with rapid recovery to about 60 percent and there-after the hypotensive effect lasted for about 5 to 10 minutes (Fig.12).

Depressor response to PGE_1 (2.5 ug/kg) was not blocked by antihistaminic agent, promethazine (5 mg/kg), anticholinergic agent, atropine (3 mg/kg) or by antiserotonergic drug, cyproheptadine (5 mg/kg) (Fig.13 & Table 6).

Effect of PGE_1 in doses of 5 and 10 ug/kg on responses to acetylcholine (1 ug/kg), adrenaline (2 ug/kg) and histamine (4 ug/kg) on mean arterial pressure has been given in Table 7 & 8. Results show that PGE_1 in doses of 5 and 10 ug/kg had no effect on the responses to acetylcholine (1 ug/kg) and histamine (4 ug/kg) on blood pressure while the pressor response to adrenaline

TABLE -5

EFFECT OF PROSTAGLANDIN (PGE_1) (i.v.) ON BLOOD PRESSURE OF ADULT WLH FOWLS

(mmHg)

PROSTAG-LANDIN ug/kg	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		PULSE PRESSURE		MEAN ARTERIAL PRESSURE (MAP)		PERCENT CHANGE IN MAP
	Before drug	After drug	Before drug	After drug	Before drug	After drug	Before drug	After drug	
2.5	115.8 (5.38)	91.7 (3.31)	110.2 (9.49)	86.3 (3.74)	5.1 (0.47)	5.5 (0.69)	111.8 (5.19)	88.1 (4.00)	-21.12 (1.31)
5.0	122.2 (5.19)	59.7 (4.69)	116.1 (5.09)	56.2 (4.99)	6.1 (0.95)	5.8 (0.47)	118.0 (5.08)	56.7 (4.89)	-51.68 (3.10)
10.0	119.0 (10.19)	56.3 (6.16)	114.6 (10.48)	51.6 (6.32)	4.8 (0.68)	4.5 (0.59)	116.2 (10.39)	53.3 (5.31)	-54.51 (3.32)

Values are mean of 7 - 9 observations

Figures in parenthesis indicate standard error

TABLE -6

BLOCKADE EFFECT OF PROMETHAZINE, CYPROHEPTADINE AND ATROPINE ON THE PROSTAGLANDIN (PGE_1) MEAN ARTERIAL PRESSURE (MAP) RESPONSE OF ADULT WLH FOWLS.

(mmHg)

PROSTAGLANDIN (2.5 ug/kg) BEFORE BLOCKER			BLOCKER	PROSTAGLANDIN (2.5 ug/kg) AFTER BLOCKER			PERCENT BLOCKADE
Before drug	After drug	% age change in MAP		Before drug	After drug	% age change in MAP	
99.9 (5.00)	80.9 (2.45)	-18.78 (1.73)	Promethazine 5 mg/kg	106.5 (3.74)	86.8 (2.23)	-18.5 (0.88)	2.1 (0.31)
103.4 (6.24)	86.0 (3.87)	-16.37 (1.21)	Cyproheptadine 5 mg/kg	96.6 (5.65)	80.8 (4.77)	-16.25 (0.11)	1.2 (0.22)
102.0 (5.43)	82.7 (3.12)	-19.0 (1.50)	Atropine 3 mg/kg	96.9 (4.25)	78.9 (3.39)	-18.51 (1.00)	2.6 (0.28)

Values are mean of 5 - 8 observations

Figures in parenthesis indicate standard error

TABLE -8

EFFECT OF PROSTAGLANDIN (PGE_1) (10 ug/kg) ON ACETYLCHOLINE, ADRENALINE AND HISTAMINE MEAN ARTERIAL PRESSURE RESPONSE IN ADULT WLH FOWLS.

(mmHg)

DRUGS	BEFORE PROSTAGLANDIN (10 ug/kg)			AFTER PROSTAGLANDIN (10 ug/kg)			PERCENT BLOCKADE
	Before drug	After drug	% age change in MAP	Before drug	After drug	% age change in MAP	
Acetylcholine 1.0 ug/kg	117.2 (3.16)	69.8 (5.38)	-40.7 (2.14)	115.5 (7.93)	70.1 (10.5)	-39.5 (6.2)	3.94 (0.64)
Adrenaline 2.0 ug/kg	113.7 (3.6)	156.4 (10.4)	+37.39 (5.14)	111.3 (7.61)	147.5 (10.5)	+28.1 (2.23)	24.8 (1.56)
Histamine 4.0 ug/kg	118.5 (5.09)	76.5 (5.09)	-35.39 (2.82)	111.7 (6.24)	78.0 (10.81)	-30.42 (3.74)	1.28 (0.31)

Values are mean of 5 - 7 observations

Figures in parenthesis indicate standard error

TABLE -7

EFFECT OF PROSTAGLANDIN (PGE_1) (5 ug/kg) ON ACETYLCHOLINE, ADRENALINE AND HISTAMINE MEAN ARTERIAL PRESSURE RESPONSE IN ADULT WLH FOWLS.

(mmHg)

DRUGS	BEFORE PROSTAGLANDIN (5 ug/kg)			AFTER PROSTAGLANDIN (5 ug/kg)			PERCENT BLOCKADE
	Before drug	After drug	% age change in MAP	Before drug	After drug	% age change in MAP	
Acetylcholine 1.0 ug/kg	114.5 (15.12)	66.6 (9.64)	-41.5 (1.42)	108.4 (16.31)	60.7 (3.87)	-41.00 (5.74)	1.2 (0.44)
Adrenaline 2.0 ug/kg	102.6 (18.00)	129.8 (16.16)	+25.47 (6.16)	106.0 (18.11)	131.4 (19.21)	+23.46 (10.34)	7.8 (1.82)
Histamine 4.0 ug/kg	112.3 (13.52)	66.6 (11.91)	-40.6 (8.00)	109.6 (15.36)	72.2 (7.54)	-40.0 (5.65)	1.4 (0.73)

Values are mean of 5 - 7 observations

Figures in parenthesis indicate standard error

TABLE -8

EFFECT OF PROSTAGLANDIN (PGE_1) (10 ug/kg) ON ACETYLCHOLINE, ADRENALINE AND HISTAMINE MEAN ARTERIAL PRESSURE RESPONSE IN ADULT WLH FOWLS.

(mmHg)

DRUGS	BEFORE PROSTAGLANDIN (10 ug/kg)			AFTER PROSTAGLANDIN (10 ug/kg)			PERCENT BLOCKADE
	Before drug	After drug	% age change in MAP	Before drug	After drug	% age change in MAP	
Acetylcholine 1.0 ug/kg	117.2 (3.16)	69.8 (5.38)	-40.7 (2.14)	115.5 (7.93)	70.1 (10.5)	-39.5 (6.2)	3.94 (0.64)
Adrenaline 2.0 ug/kg	113.7 (3.6)	156.4 (10.4)	+37.39 (5.14)	111.3 (7.61)	147.5 (10.5)	+28.1 (2.23)	24.8 (1.56)
Histamine 4.0 ug/kg	118.5 (5.09)	76.5 (5.09)	-35.39 (2.82)	111.7 (6.24)	78.0 (10.81)	-30.42 (3.74)	1.28 (0.31)

Values are mean of 5 - 7 observations

Figures in parenthesis indicate standard error

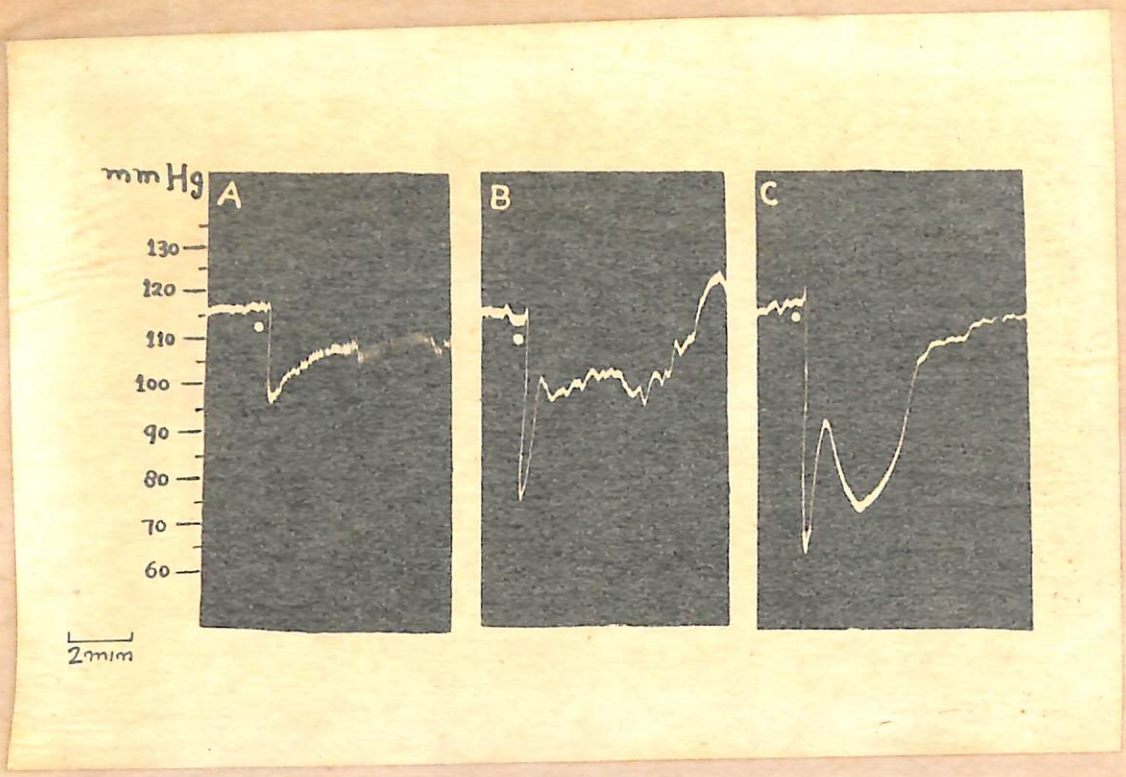


Fig.12. Effect of PGE_1 (i.v.) on fowl blood pressure in doses of (A) 2.5 ug/kg (B) 5.0 ug/kg and (C) 10 ug/kg.

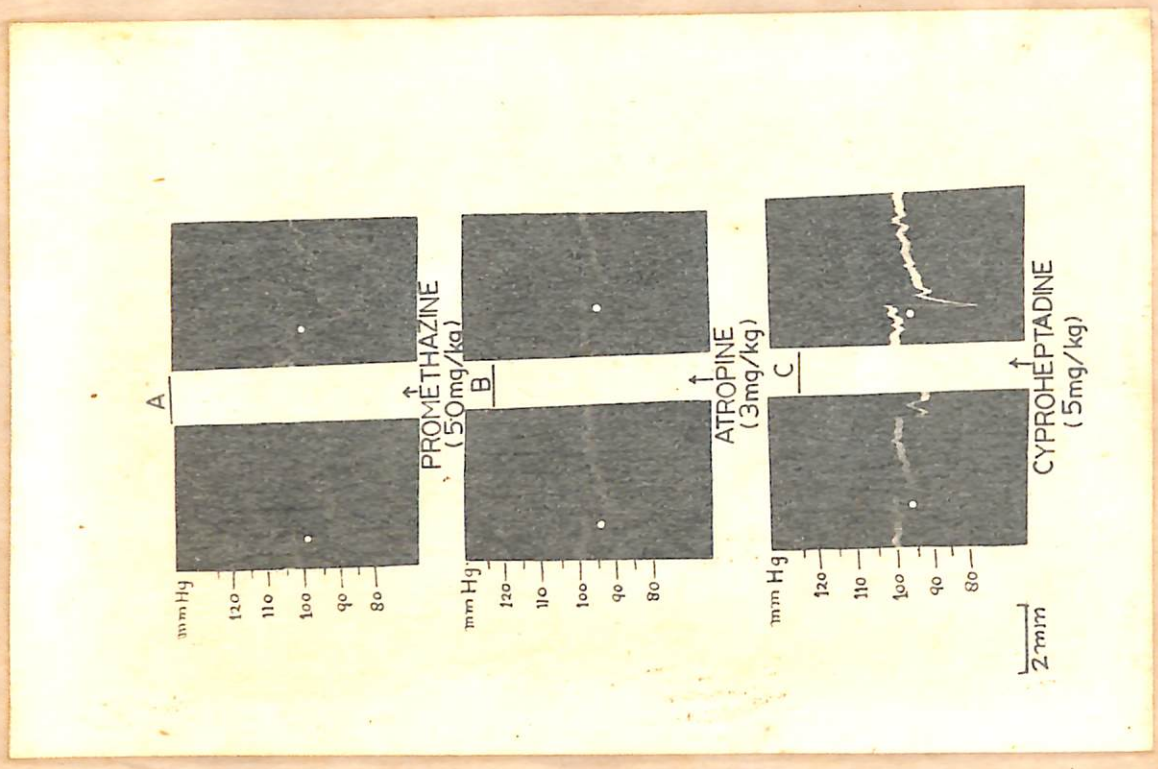


Fig.13. Depressor response of PGE_1 (2.5 ug/kg) in anaesthetized fowls before and after (A) promethazine, 5 mg/kg (B) atropine, 3 mg/kg and (C) cyproheptadine, 5 mg/kg. Drugs were injected intravenously.

(2 ug/kg) was reduced by 8 and 25 percent at 5 and 10 ug/kg of PGE_1, respectively (Fig.14). Such reduction in pressor response to adrenaline by PGE_1 was observed in 10 out of 13 experiments while there was no change in other three experiments.

Electrocardiogram :

Effect of intravenous administration of histamine (8 ug/kg), promethazine (5 mg/kg), diphenhydramine (5 mg/kg), 5-HT (100 ug/kg), PGE_1 (5 ug/kg) and phentolamine (20 mg/kg) on electrocardiograms of phenobarbitone anaesthetised fowls is given in Table 9 & 10 (see also Fig.15). The data show that histamine in dose of 8 ug/kg did not produce any significant effect on electrocardiographic pattern. PGE_1 (5 ug/kg) caused a slight reduction in S-T interval. A slight decrease in heart rate was observed with promethazine (5 mg/kg) and diphenhydramine (5 mg/kg) without affecting other components significantly. Heart rate was slightly increased with 5-HT (100 ug/kg) without altering any other component. Phentolamine (20 mg/kg) increased heart rate by 60 beats/min. and reduced the amplitude of P-wave while amplitude and duration of S-wave were increased.

Blood vessels (Angiographic studies) :

The effect of histamine 10 ug/kg (Fig.16), 5-HT 100 ug/kg (Fig.17) and PGE_1 10 ug/kg (Fig.18) on blood

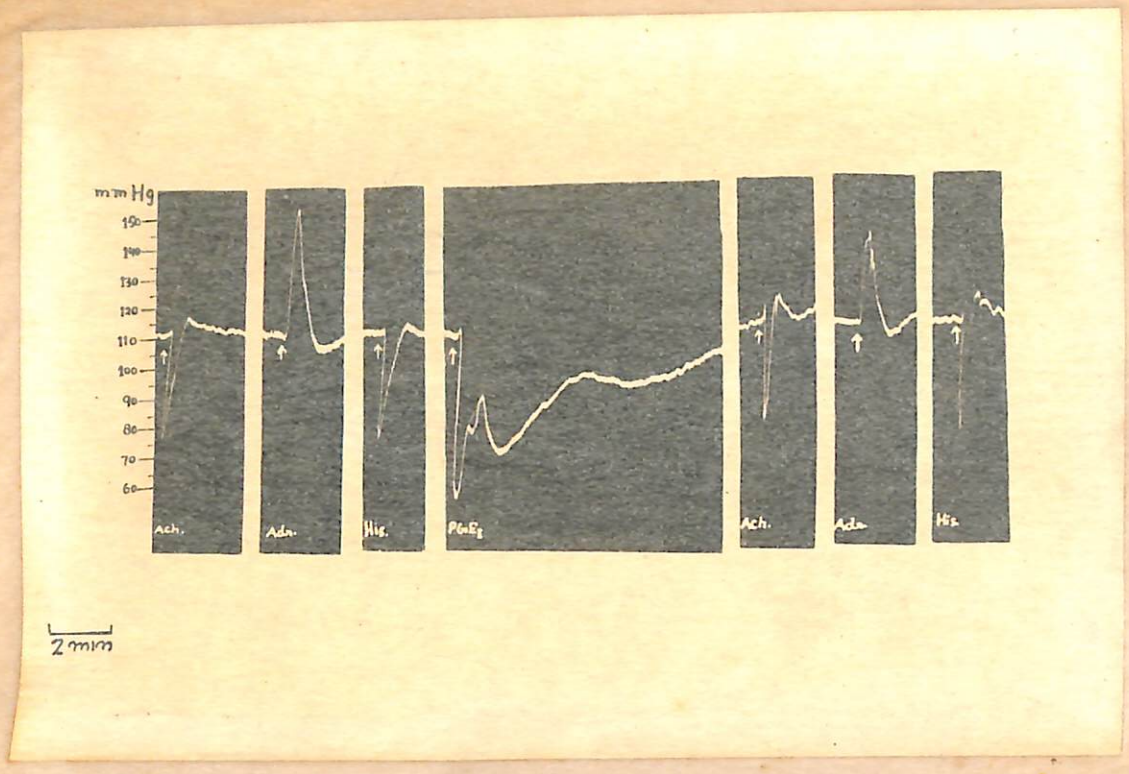


Fig.14. Effect of PGE_1 10 ug/kg (i.v.) on fowl blood pressure responses to acetylcholine 1.0 ug/kg (Ach.), adrenaline 2.0 ug/kg (Adr.) and histamine 4.0 ug/kg (His.) in anaesthetised fowls. Drugs were given intravenously.

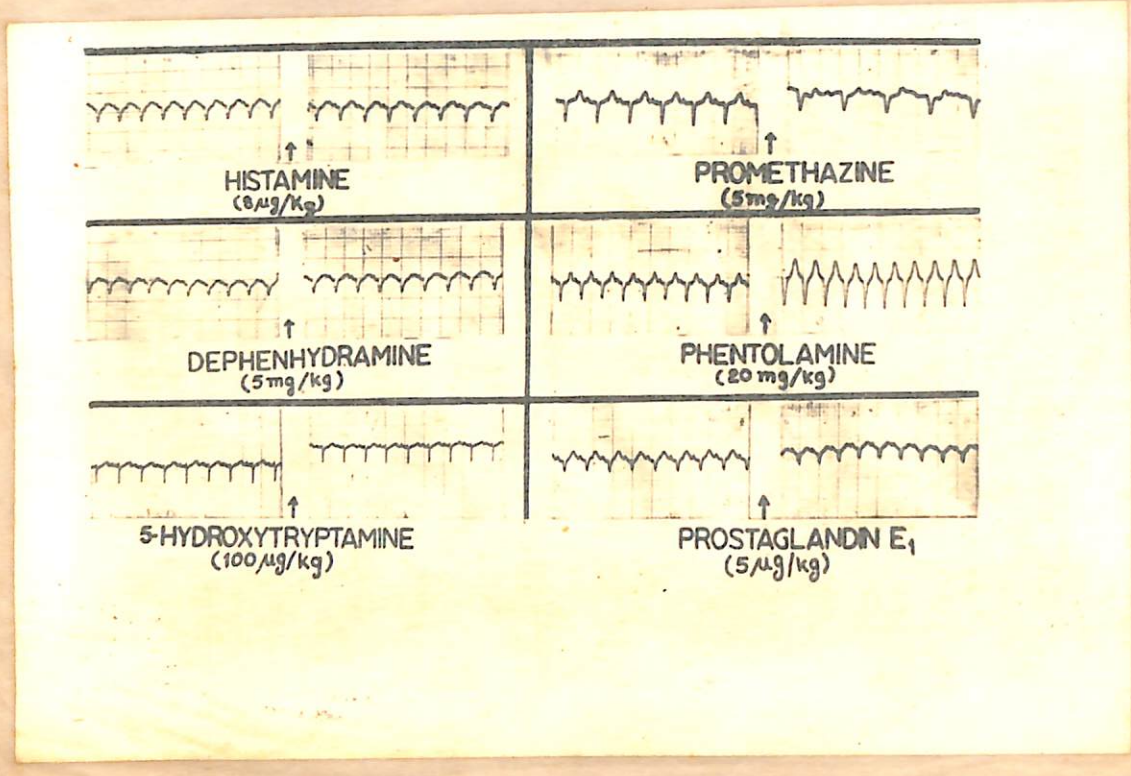


Fig.15. Electrocardiograms (lead II) of phenobarbitone anaesthetised fowls before and just after the intravenous administration of drugs.

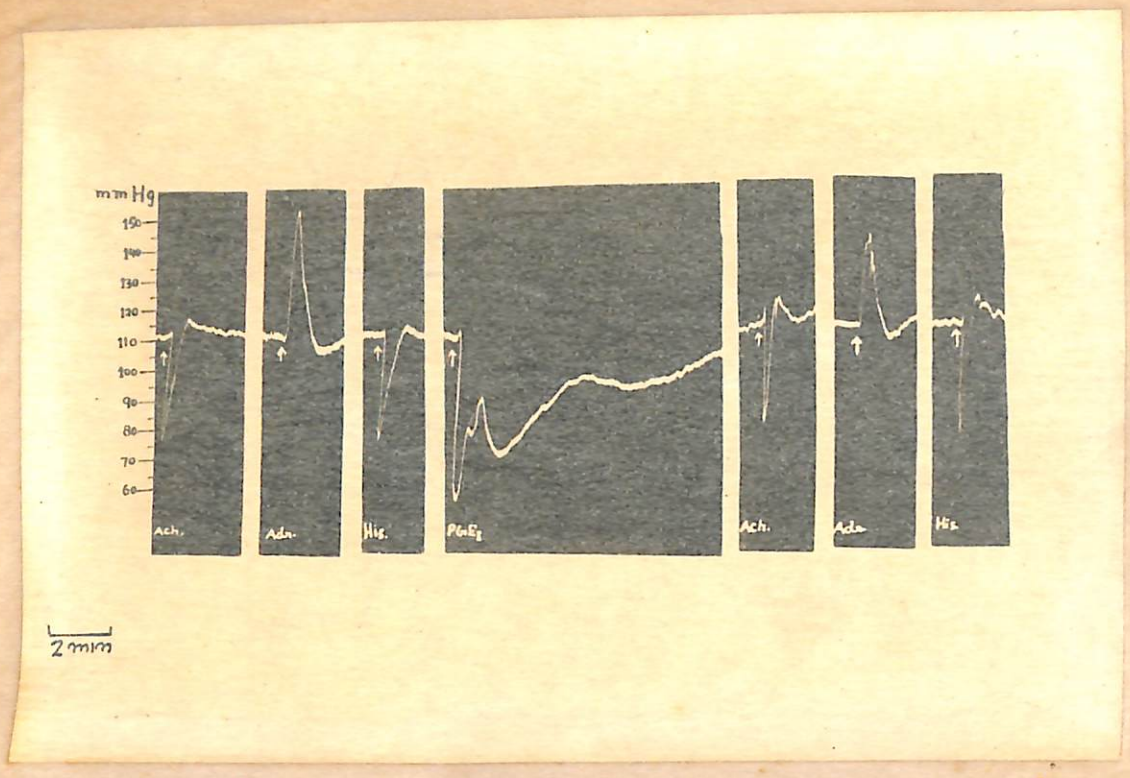


Fig.14. Effect of PGE_1 10 ug/kg (i.v.) on fowl blood pressure responses to acetylcholine 1.0 ug/kg (Ach.), adrenaline 2.0 ug/kg (Adr.) and histamine 4.0 ug/kg (His.) in anaesthetised fowls. Drugs were given intravenously.

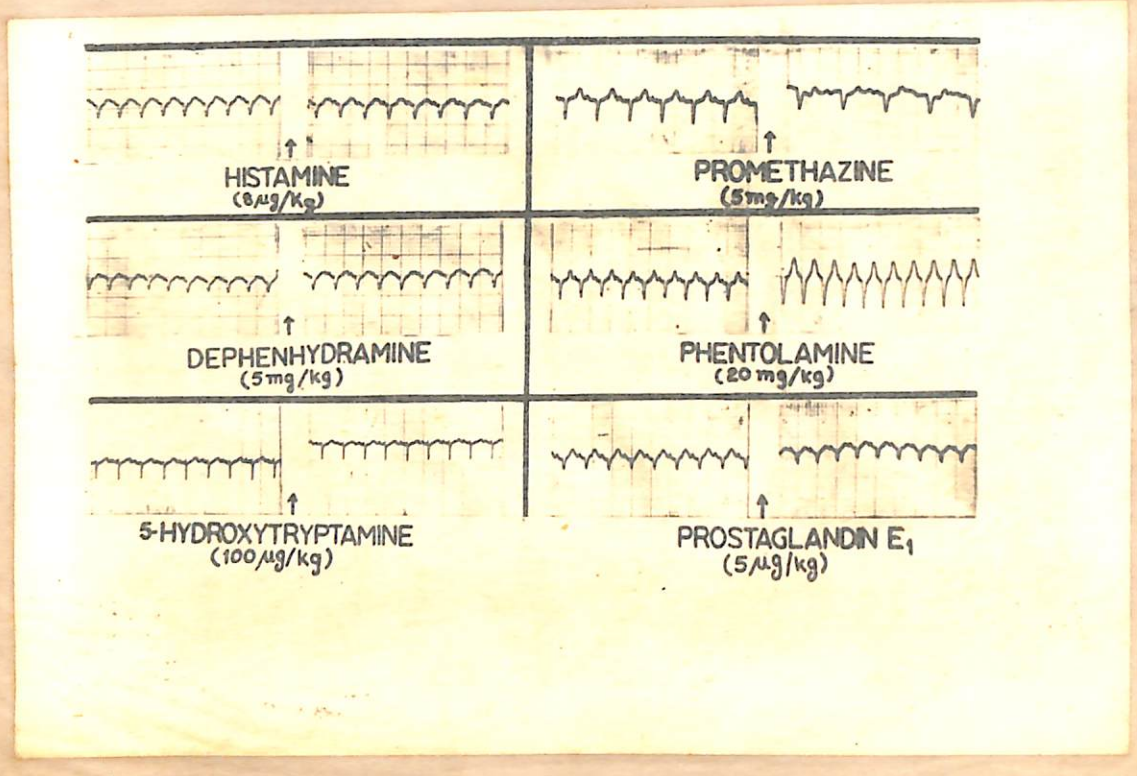


Fig.15. Electrocardiograms (lead II) of phenobarbitone anaesthetised fowls before and just after the intravenous administration of drugs.

TABLE -9

EFFECT OF INTRAVENOUS ADMINISTRATION OF DRUGS ON ELECTROCARDIOGRAM OF PHENOBARBITONE ANAESTHETIZED ADULT WLH FOWLS.

PARAMETERS	HISTAMINE (8 ug/kg)		PROMETHAZINE (5 mg/kg)		DIPHENHYDRAMINE (5 mg/kg)	
	Before drug	After drug	Before drug	After drug	Before drug	After drug
Heart rate/min.	185	190	220	198	200	186
P - wave						
Amplitude (mm)	1.12	1.12	0.83	0.66	0.83	1.0
Duration (sec)	0.035	0.047	0.02	0.03	0.02	0.03
P-S interval (Sec)	0.09	0.10	0.12	0.15	0.12	0.14
S - wave						
Amplitude (mm)	1.7	2.0	3.0	2.8	2.5	2.3
Duration (sec)	0.04	0.04	0.07	0.07	0.04	0.06
S-T interval (sec)	0.18	0.19	2.0	2.2	0.78	1.38
T - wave						
Amplitude (mm)	1.7	1.8	2.5	1.5	2.3	1.8
Duration (sec)	0.12	0.12	0.12	0.14	0.12	0.14

Values are mean of 4 - 6 observations

TABLE -10

EFFECT OF INTRAVENOUS ADMINISTRATION OF DRUGS ON ELECTROCARDIOGRAM OF PHENOBARBITONE ANAESTHETIZED ADULT WLH FOWLS.

PARAMETERS	5-HYDROXYTRYPTAMINE (8 ug/kg)		PROSTAGLANDINS (5 ug/kg)		PHENTOLAMINE (20 mg/kg)	
	Before drug	After drug	Before drug	After drug	Before drug	After drug
Heart rate/min.	293	326	273	260	220	280
P - wave						
Amplitude (mm)	1.1	1.25	1.0	1.1	0.83	0.16
Duration (sec)	0.02	0.01	0.02	0.02	0.02	0.03
P-S interval (sec)	0.04	0.03	0.08	0.08	0.13	0.02
S - wave						
Amplitude (mm)	3.7	2.5	2.1	2.8	3.5	6.8
Duration (sec)	0.02	0.02	0.04	0.04	0.04	0.73
S-T interval (sec)	0.20	0.15	0.78	0.16	2.2	2.4
T - wave						
Amplitude (mm)	1.1	1.0	1.8	1.8	2.0	4.6
Duration (sec)	0.10	0.10	0.13	0.10	0.14	0.14

Values are mean of 4 - 6 observations

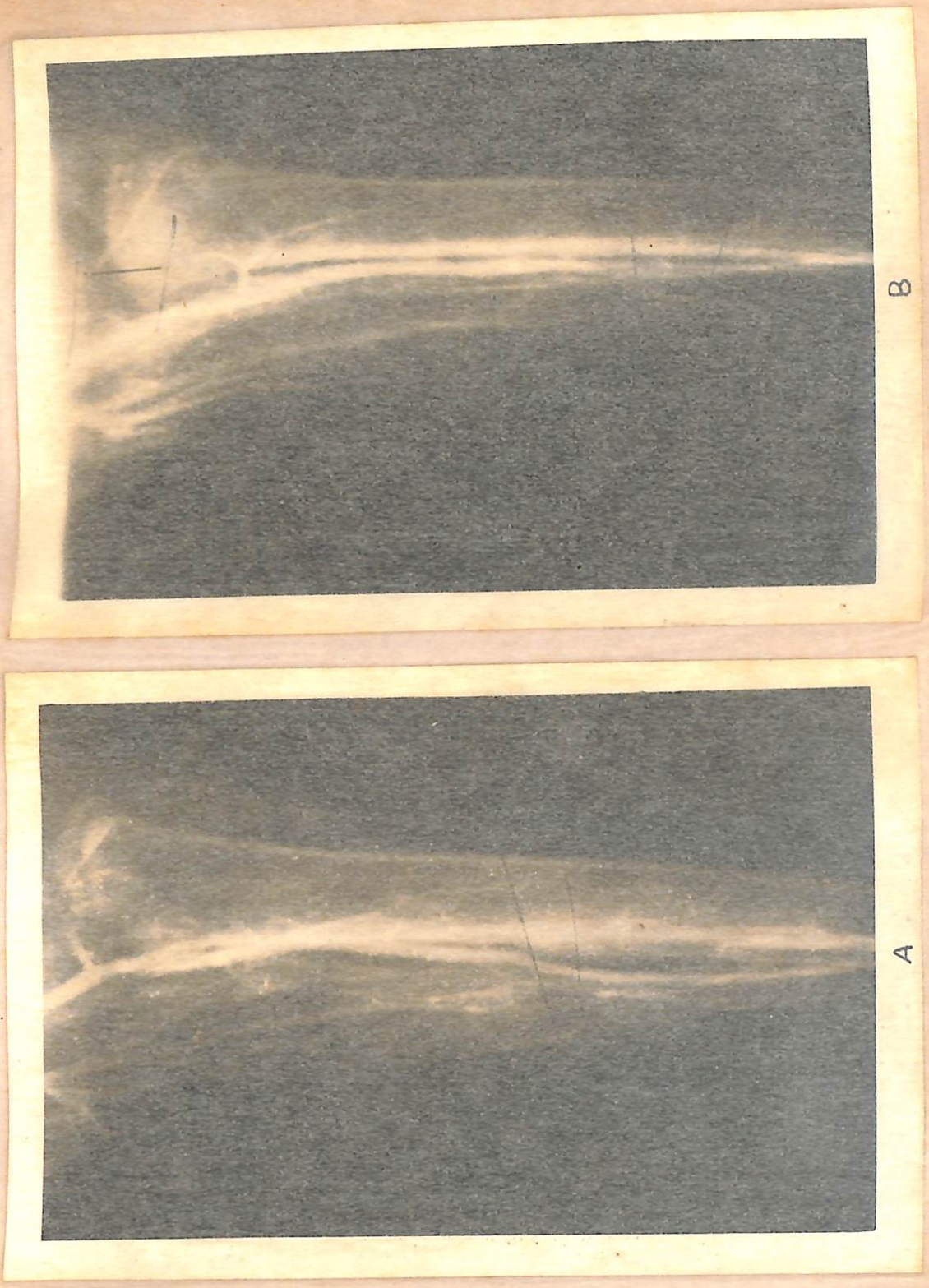


Fig.16. Angiograms of branches of femoral artery in phenobarbitone anaesthetised fowls (A) left leg, control (B) right leg, just after histamine (8 ug/kg) intraarterially.

Fig.17. Angiograms of branches of femoral artery in phenobarbitone anaesthetized fowls (A) left leg, control (B) right leg, just after 5-HT (100 ug/kg) intraarterially.

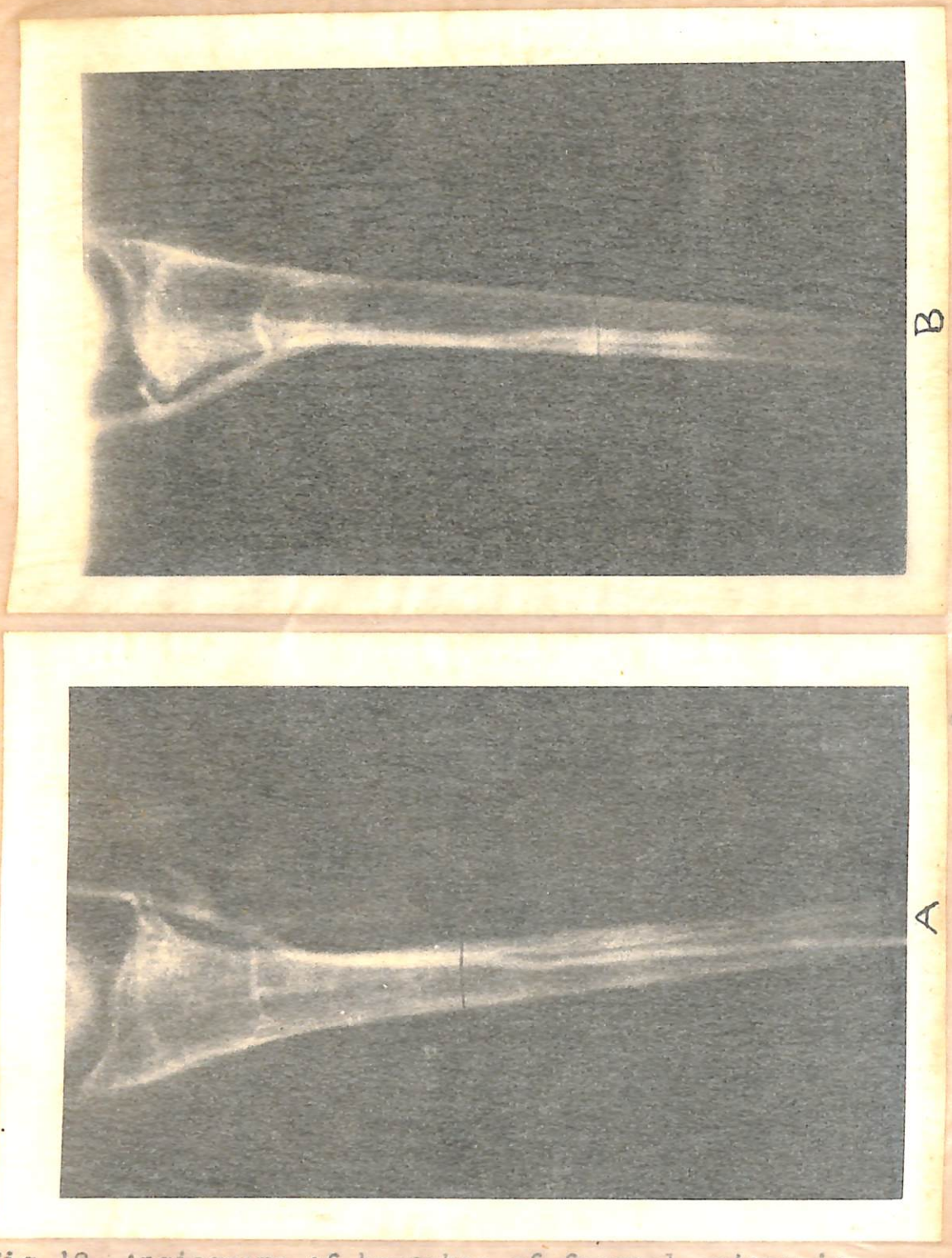


Fig.18. Angiograms of branches of femoral artery in phenobarbitone anaesthetized fowls (A) left leg, control (B) right leg, just after PGE_1 (10 ug/kg) intraarterially.

vessels of anaesthetised fowls have been shown in Fig. 16, 17 and 18, respectively. Histamine, 5-HT and PGE_1 dilated the branches of femoral artery by 22.2, 13.7 and 38.2 percent, respectively. This indicates that the dilatory effects are in following order: PGE_1 > histamine > 5-HT

II. SMOOTH MUSCLES

Histamine dihydrochloride :

Isolated intestine : Effect of histamine on isolated ileum of chicks (1 to 2 weeks old) in graded concentrations of 2.5×10^{-8}, 5×10^{-8}, 10^{-7}, 2×10^{-7}, 4×10^{-7} and 8×10^{-7} gm/ml is shown in Fig.19.

Results show that histamine in concentrations lower than 2.5×10^{-8} gm/ml did not produce any measurable effect on isolated chick ileum. Concentrations ranging from 2.5×10^{-8} to 2×10^{-7} gm/ml relaxed the intestine in almost all the experiments. This response increased in magnitude with increase in concentration upto maximum of 2×10^{-7} gm/ml, after which further increase in concentration (4×10^{-7} gm/ml) produced contractile response except in one or two experiments where 4×10^{-7} gm/ml concentration showed relaxation. With further increase in concentration of histamine to 8×10^{-7} gm/ml a marked contractile response (55 mm) was obtained in all the experiments. Histamine in lower concentrations (2.5×10^{-8} to 2×10^{-7} gm/ml) which produced relaxation of chick ileum did not cause this effect on preparations from adult

birds.

Relaxant effect of histamine at lower concentrations on isolated ileum has been reported to be due to indirect release of catecholamines from the intestinal musculature of chicks (Everett & Mann, 1967). Therefore, a beta-adrenergic receptor blocking agent pronethalol was used to block the relaxant effect of histamine in concentrations of 2.5×10^{-8}, 5×10^{-8}, 10^{-7} and 2×10^{-7} gm/ml. Effect of pronethalol in concentrations of 10^{-6} and 2×10^{-6} gm/ml on histamine-induced relaxation is shown in Fig.19. Results show that pronethalol in concentration of 10^{-6} gm/ml blocked the histamine (2×10^{-7} gm/ml) induced relaxation by 20 to 25 percent. Further, it was noticed that at higher concentration (2×10^{-6} gm/ml), pronethalol completly abolished the relaxant effect of histamine and even reversed to a contractile response (Fig.19). The ED_{50} of histamine calculated on isolated ileum was found to be 10^{-6}M (Fig.20).

Effect of promethazine on histamine-induced (8×10^{-7} gm/ml) contractile response of isolated ileum of chicks is shown in Fig.21.

Results show that promethazine in concentrations of 10^{-8}, 2×10^{-8} and 4×10^{-8} gm/ml blocked the histamine (8×10^{-7} gm/ml) contractile response by 9.8, 34 and 58 percent, respectively. It may be mentioned here that after washing the normal contractile response of the

tissue to histamine (8×10^{-7} gm/ml) returned to its original height in about 30 to 40 minutes.

Effect of diphenhydramine on histamine (8×10^{-7} gm/ml) contractile response of isolated chick ileum is shown in Fig.22.

Results show that diphenhydramine in concentrations of 10^{-8}, 2×10^{-8} and 4×10^{-8} gm/ml blocked the histamine (8×10^{-7} gm/ml) contractile response by 25, 53 and 70 percent, respectively. Contractile response to histamine (8×10^{-7} gm/ml) after blocking with diphenhydramine in doses of 10^{-8}, 2×10^{-8}, 4×10^{-8} returned to its original height within the duration of 40 to 60 minutes.

While comparing the antihistaminic action of promethazine and diphenhydramine on isolated intestine of chick it was evident that diphenhydramine as histamine blocker was more potent than promethazine.

Isolated oviduct : Effect of histamine on isolated terminal portion of oviduct (isthmus) of laying birds was studied. It was observed that isolated segments of oviduct taken from the non-laying birds failed to elicit the contractile response to histamine. ED_{50} of histamine calculated on isolated oviduct of laying hens was 5×10^{-8}M (Fig.23).

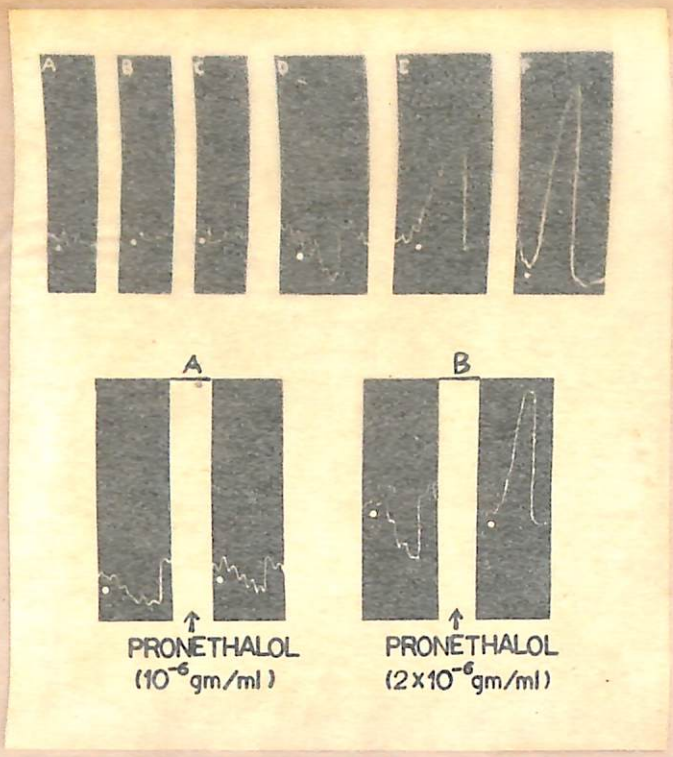


Fig.19. Upper tracing : Effect of histamine on isolated ileum of chick in concentrations of (A) 2.5 x 10^{-8} gm/ml (B) 5 x 10^{-8} gm/ml (C) 10^{-7} gm/ml (D) 2 x 10^{-7} gm/ml (E) 4 x 10^{-7} gm/ml (F) 8 x 10^{-7} gm/ml. Lower tracing : Effect of histamine (2 x 10^{-7} gm/ml) on isolated ileum of chick before and after two doses of pronethalol (A) 10^{-6} gm/ml and (B) 2 x 10^{-6} gm/ml.

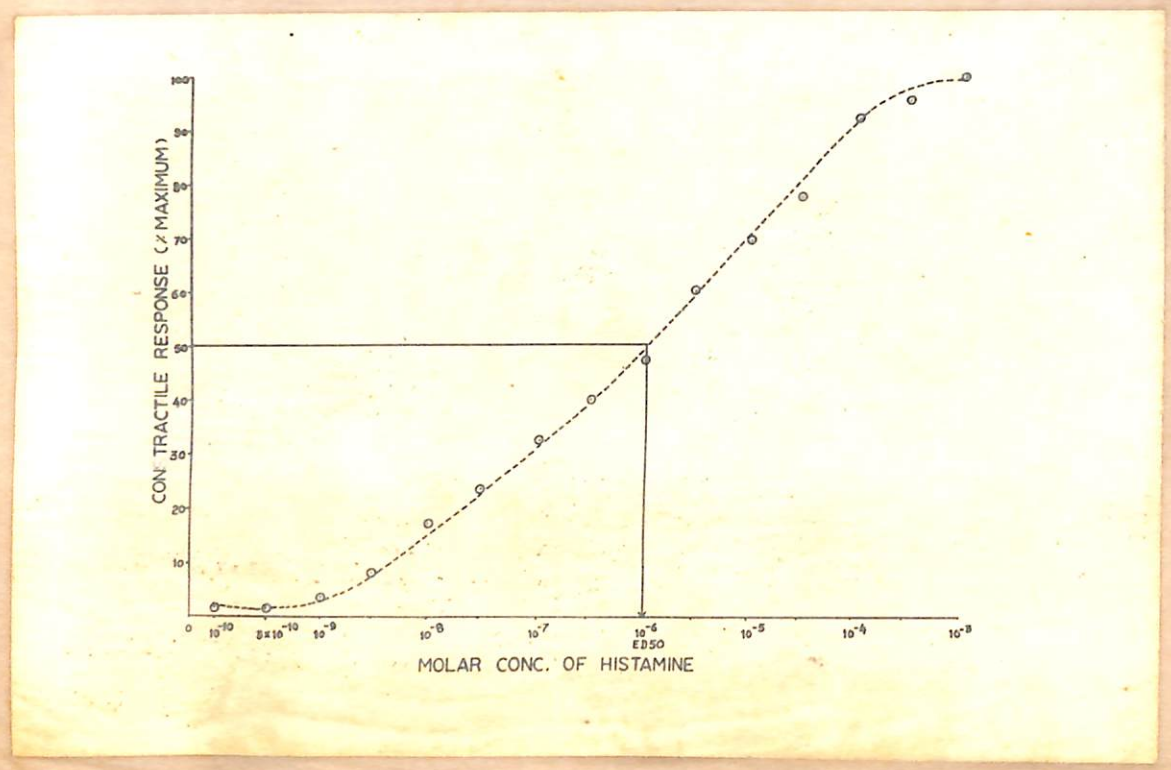


Fig.20. Dose response curve of histamine on isolated ileum of chick. Each observation is mean of 8 to 9 experiments.

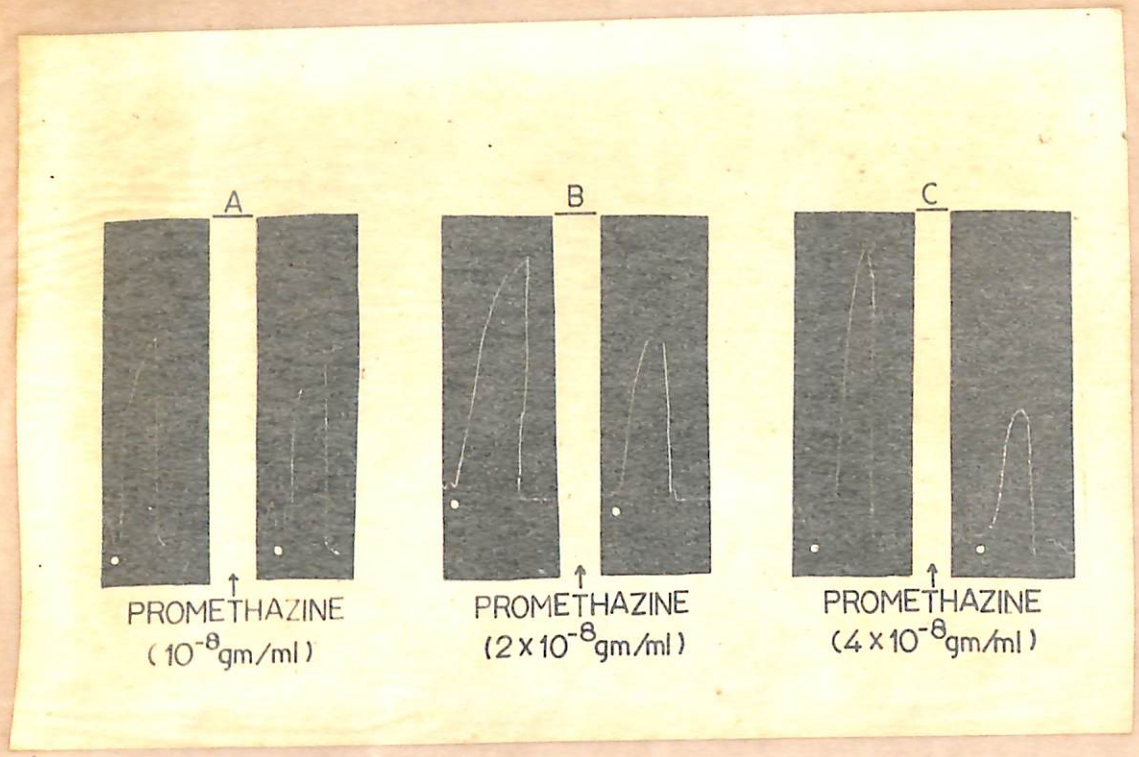


Fig.21. Effect of histamine (8×10^{-7} gm/ml) on isolated chick ileum before and after different concentrations of promethazine.

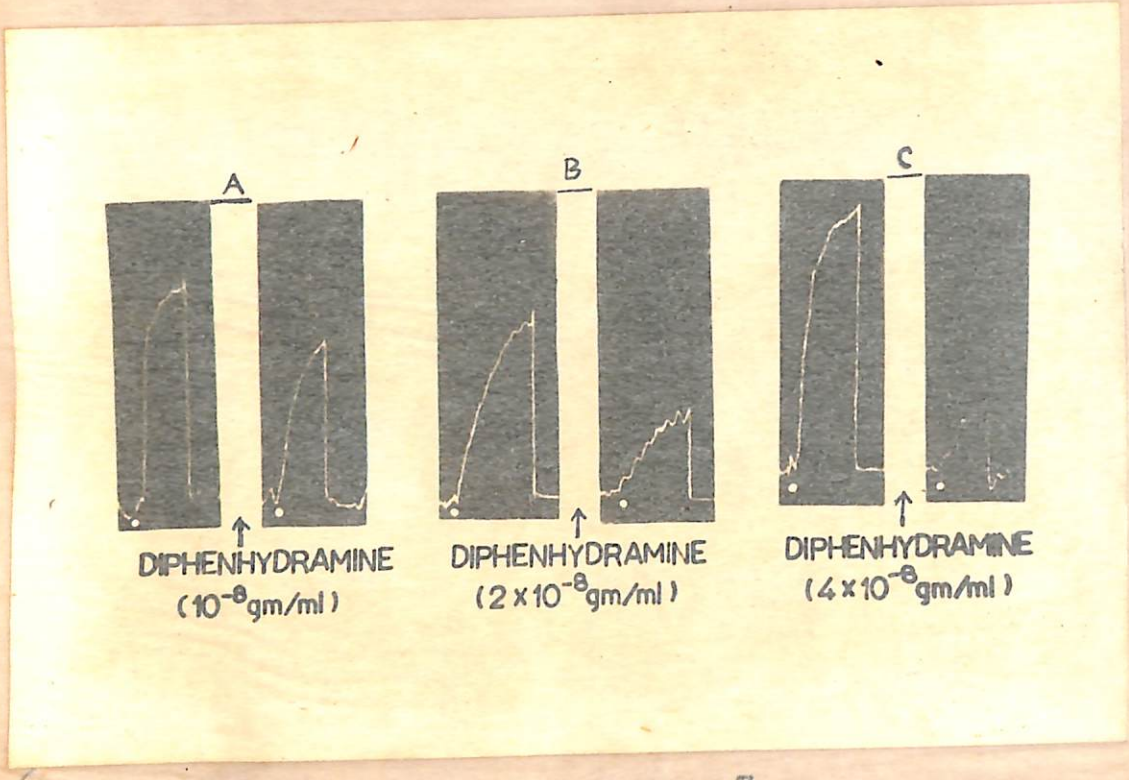


Fig.22. Effect of histamine (8×10^{-7} gm/ml) on isolated chick ileum before and after different concentrations of diphenhydramine.

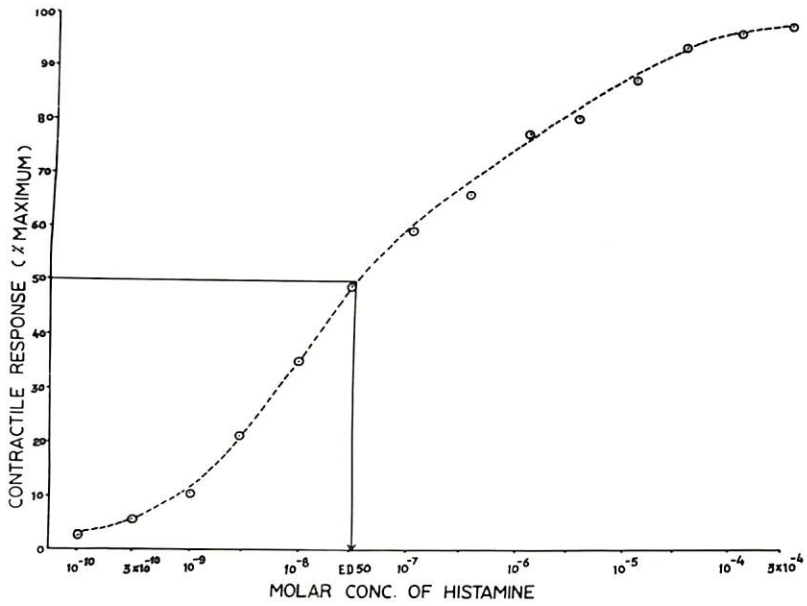


Fig.23. Dose response curve of histamine on isolated oviduct of laying birds. Each observation is mean of 8 experiments.

5-hydroxytryptamine :

Isolated intestine: Effect of 5-HT on isolated intestine of fowl in graded concentrations is shown in Fig.24. Results show that 5-HT in concentrations of 1.25×10^{-8}, 2.5×10^{-8} and 5×10^{-8} gm/ml showed a contractile response (fig.24). ED_{50} of 5-HT calculated on isolated intestine was 3.4×10^{-8}M (Fig.25).

Blocking effect of cyproheptadine on 5-HT induced contraction of isolated chick ileum was studied. The results show that cyproheptadine in concentrations of 2.5×10^{-9}, 5×10^{-9} and 10^{-8} gm/ml blocked the contractile response produced by 5-HT (5×10^{-8} gm/ml) by 19.1, 38.3 and 50.34 percent, respectively (Fig.26 & Table 11).

Isolated oviduct : Effect of 5-HT on isolated terminal portion of oviduct of laying birds was studied. ED_{50} of 5-HT calculated on this tissue was found to be 7×10^{-8}M. (Fig.27). It may be mentioned here that segments of oviduct taken from non-laying birds were much less sensitive to 5-HT than the laying one as was observed in case of histamine.

Prostaglandin E_1:

Isolated intestine : Effect of PGE_1 on isolated ileum of chick in graded concentrations is shown in Fig.28. Results show that PGE_1 in concentrations of 2.5×10^{-11}, 5×10^{-11}, 10^{-10} and 2×10^{-10} gm/ml produced an average contraction of 20.3, 26.5, 34.0 and 42.1 mm, respectively (Table 12).

TABLE -12

EFFECT OF PROSTAGLANDIN (PGE_1) ON ISOLATED INTESTINE OF FOWL

PROSTAGLANDIN gm/ml	AMPLITUDE OF CONTRACTION (mm)						MEAN*
	1	2	3	4	5	6	
2.5×10^{-11}	21	20	23	18	22	18	20.3 (1.31)
5×10^{-11}	27	22	35	20	29	26	26.5 (2.17)
1×10^{-10}	33	32	40	31	36	32	34.0 (1.38)
2×10^{-10}	45	43	44	41	44	36	42.1 (1.35)

*Values are mean of 6 observations

Figures in parenthesis indicate standard error

TABLE -11

EFFECT OF CYPROHEPTADINE ON 5-HYDROXYTRYPTAMINE (5×10^{-8} gm/ml) RESPONSE ON ISOLATED INTESTINE OF FOWLS.

CYPROHEPTADINE gm/ml	AMPLITUDE OF CONTRACTION (mm)		PERCENT BLOCKADE
	Before drug	After drug	
2.5×10^{-9}	60.2 (7.7	50.0 (6.3)	19.1 (1.5)
5×10^{-9}	53.2 (6.2)	32.8 (3.8)	38.2 (5.0)
1×10^{-8}	57.8 (2.7)	28.8 (3.1)	50.3 (9.7)

Values are mean of 5 observations

Figures in parenthesis indicate standard error

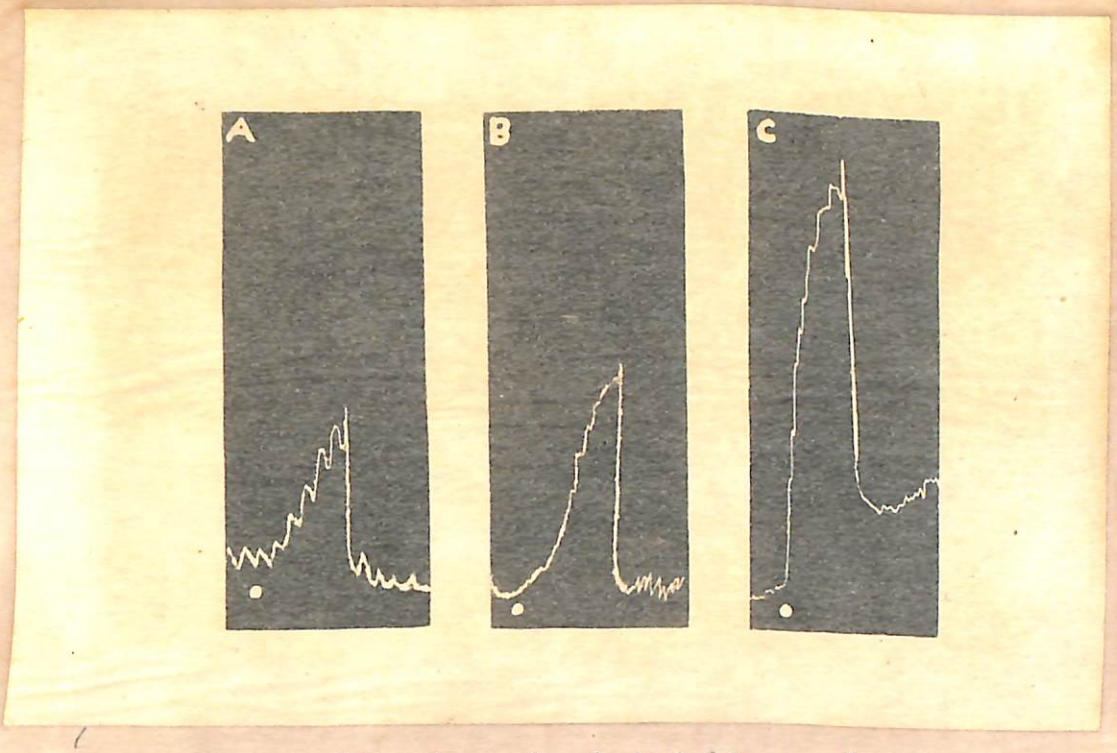


Fig.24. Effect of 5-HT on isolated ileum of chick in concentrations of (A) 1.25 x 10^{-8} gm/ml (B) 2.5 x 10^{-8} gm/ml and (C) 5 x 10^{-8} gm/ml.

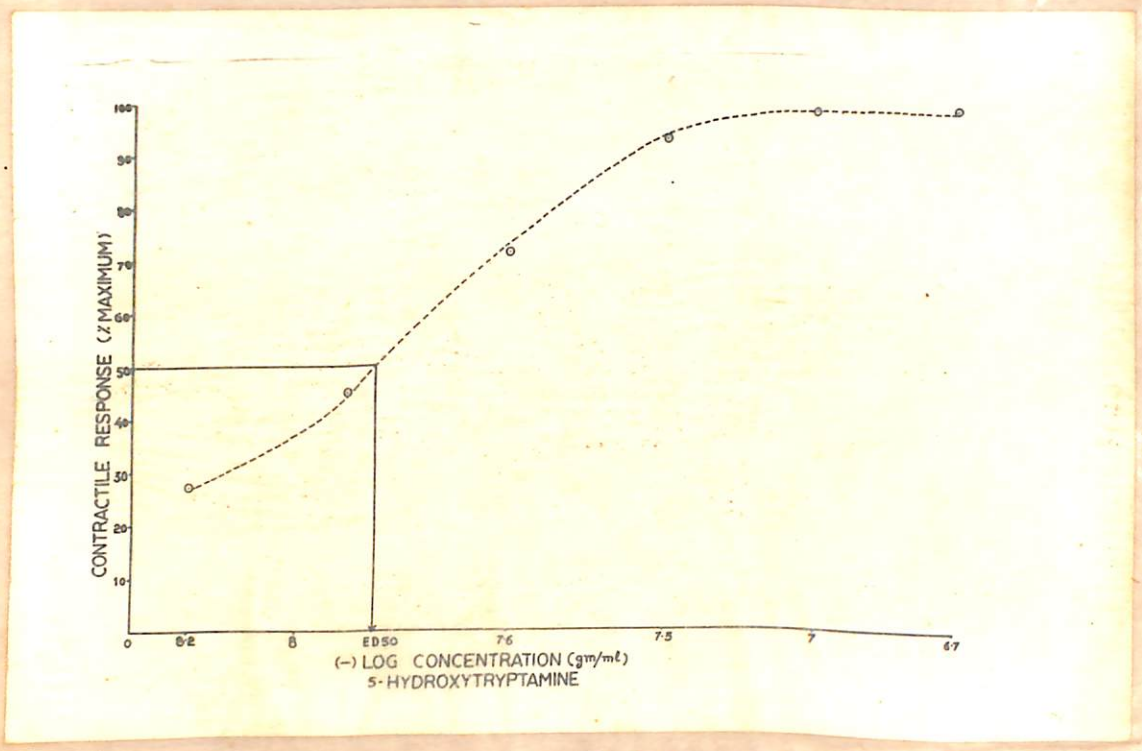
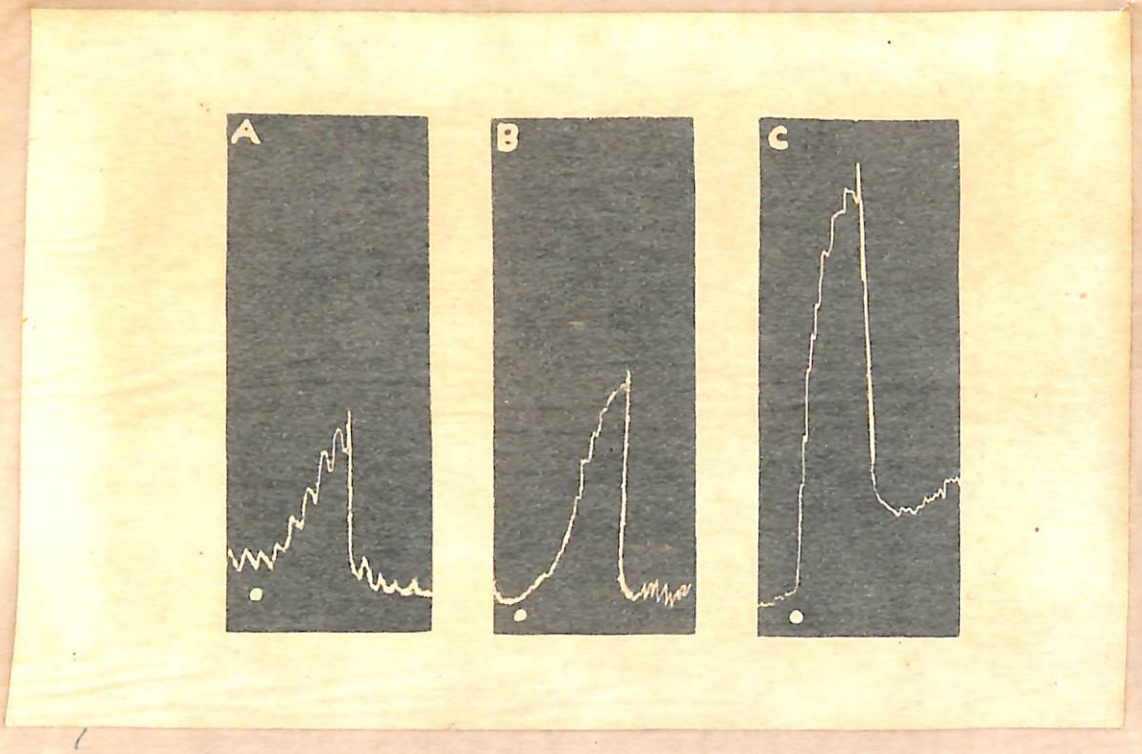


Fig.25. Dose response curve of 5-HT on isolated ileum of chick. Each observation is mean of 5 experiments.



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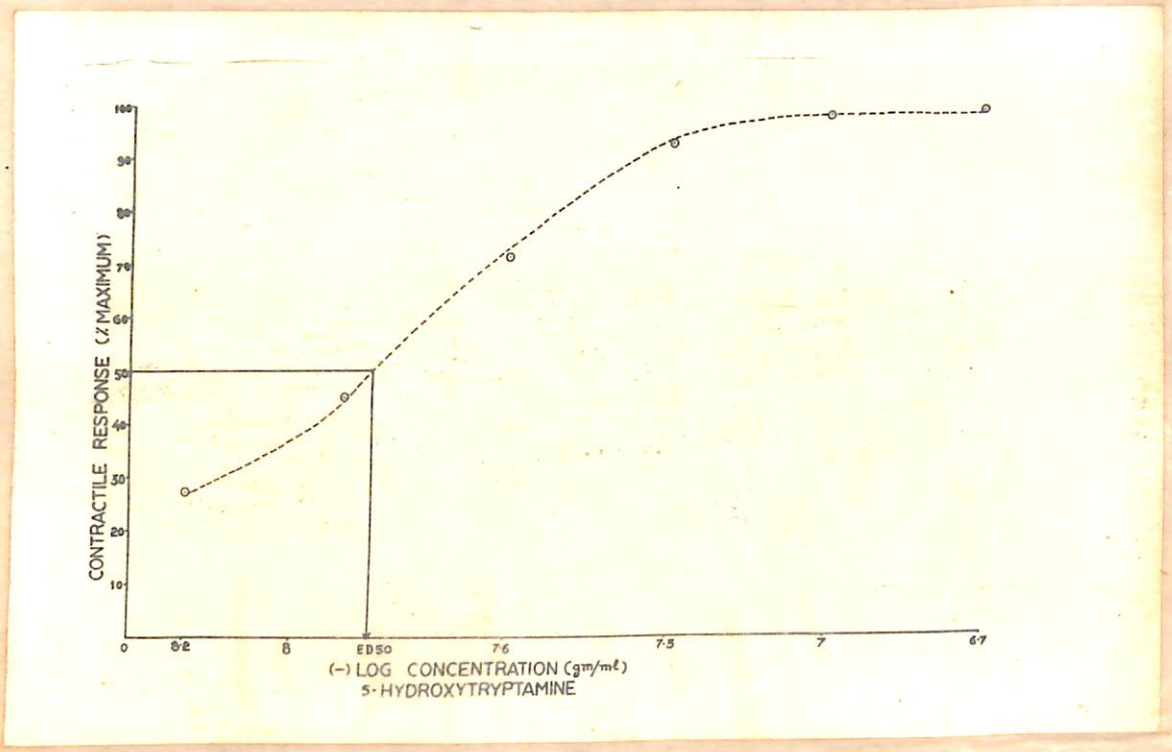

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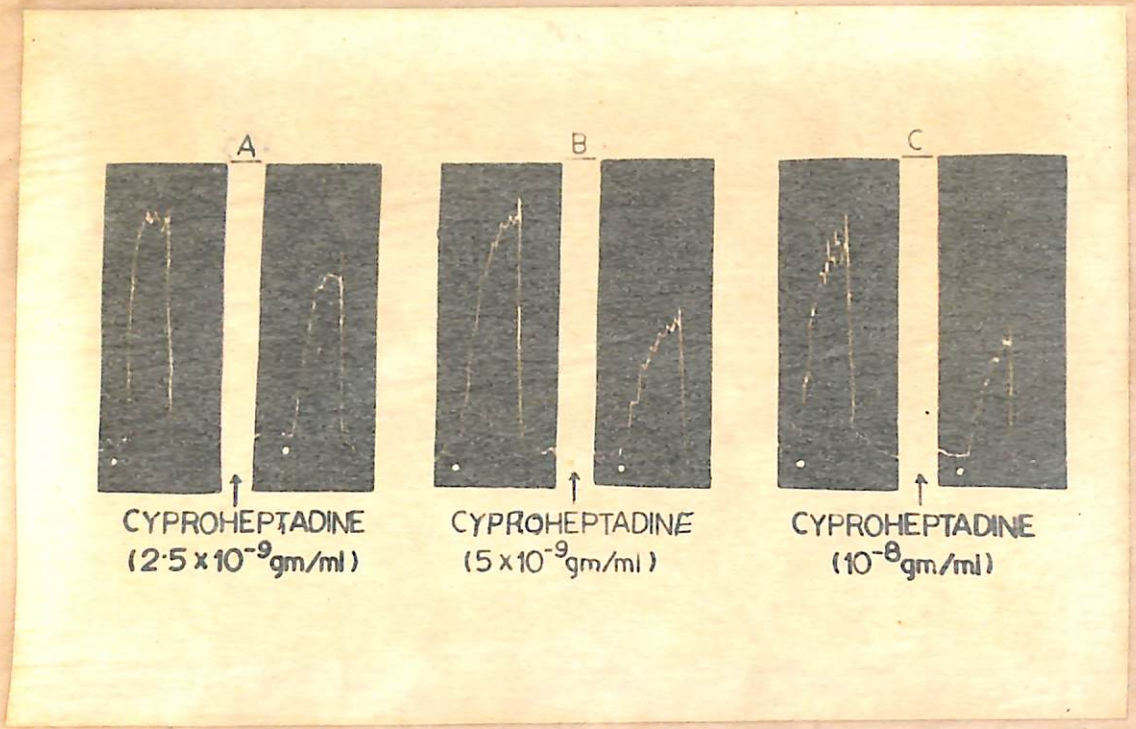

Fig.26. Effect of 5-HT (5×10^{-8} gm/ml) on isolated ileum of chick before and after different concentrations of cyproheptadine.

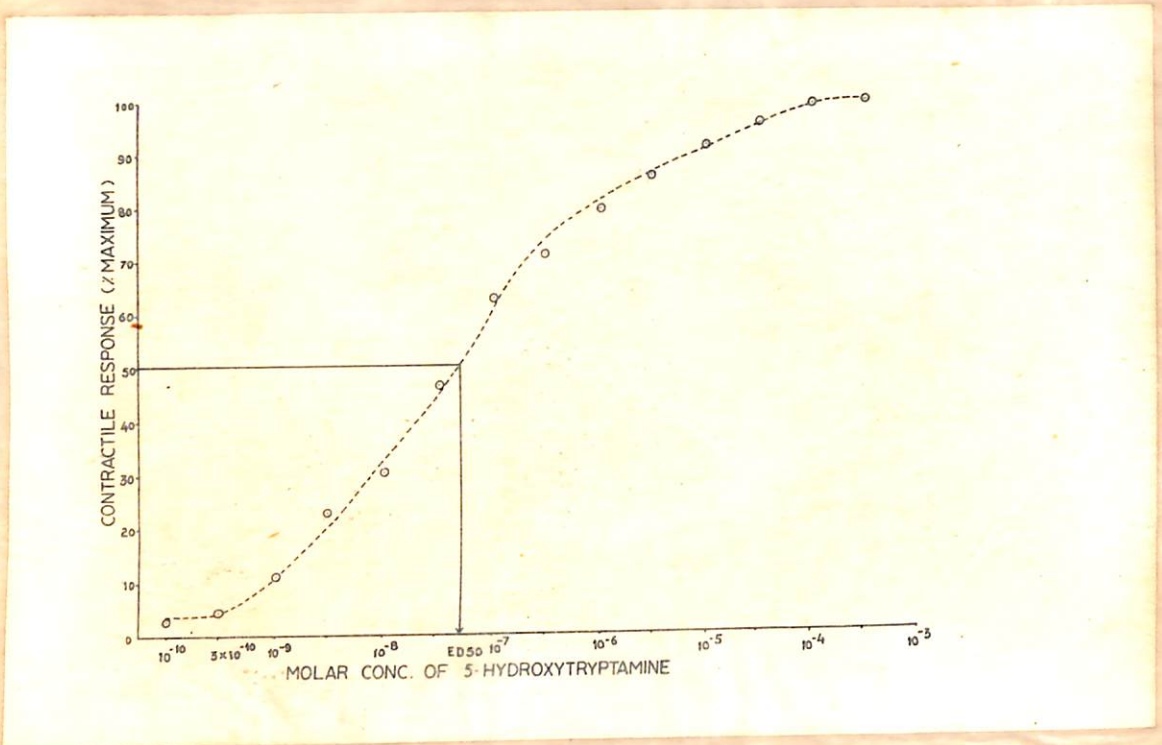

Fig.27. Dose response curve of 5-HT on isolated oviduct of laying birds. Each observation is mean of 9 experiments.

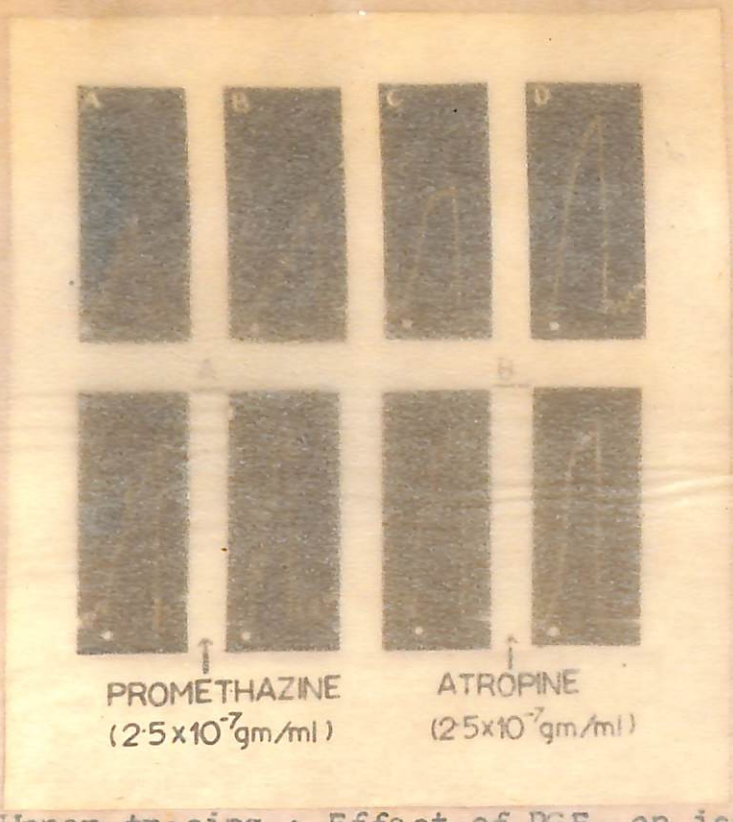

Fig.28. Upper tracing : Effect of PGE_1 on isolated ileum of chick in concentrations of (A) 2.5 x 10-11 gm/ml (B) 5 x 10-11 gm/ml (C) 10-10 gm/ml and (D) 2 x 10-10 gm/ml.
Lower tracing : Effect of promethazine and atropine on isolated ileum of chick on PGE_1 (2 x 10-10 gm/ml) induced contractile response.

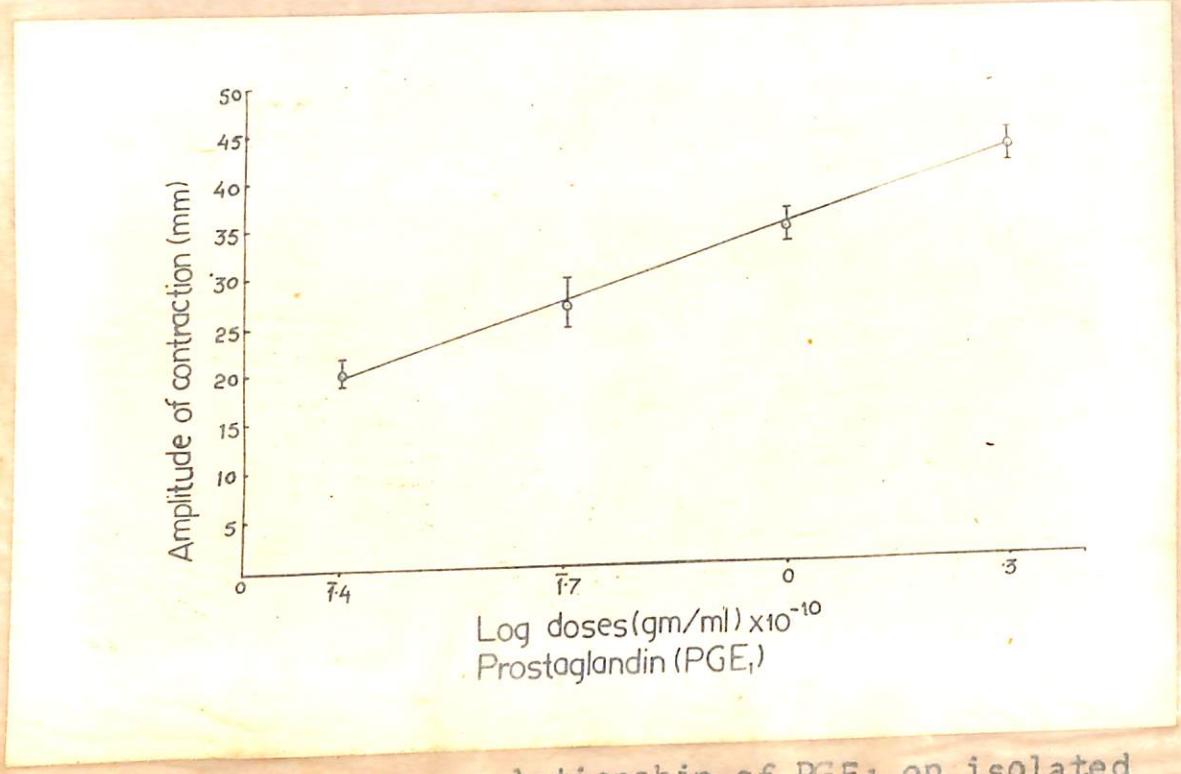

Fig.29. Dose response relationship of PGE_1 on isolated ileum of chick. Each observation is a mean of 8-9 experiments. Vertical bars denote S.E. of mean.

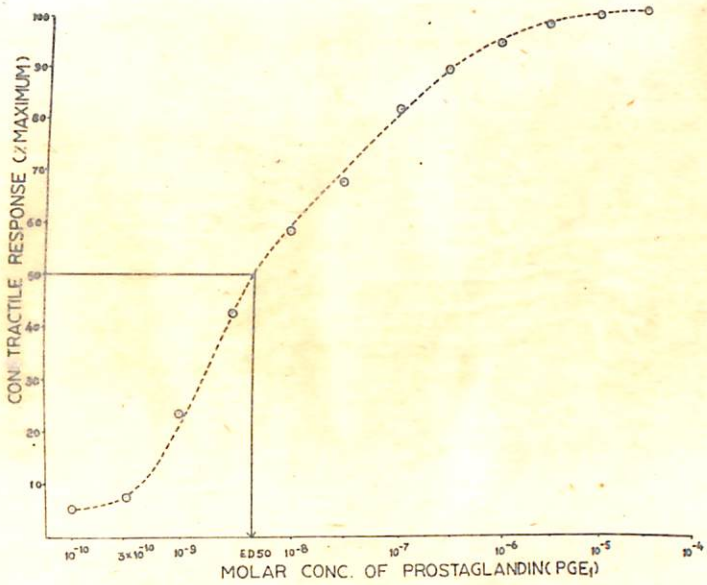

Fig.30. Dose response curve of PGE_1 on isolated oviduct of laying birds. Each observation is a mean of 7 experiments.

It is evident from the graph (Fig.29) that there was a linear relationship between the amplitude of contraction and log concentration of PGE_1 in the range of concentrations studied. It may be mentioned here that PGE_1 in concentrations lower than 1.25×10^{-11} gm/ml did not produce any measurable response on the isolated ileum of chicks. Thus the minimum thres hold concentration was 1.25×10^{-11} gm/ml. During the experiment it was also observed that in quiscent tissues, spontaneous activity appeared after instillation of PGE_1 in the bath.

Effect of promethazine and atropine on PGE_1 (2×10^{-10} gm/ml)-induced contractile response on isolated ileum of chick is shown in Fig.28. It is evident that promethazine in concentration of 2.5×10^{-7} gm/ml did not influence the contractile response to PGE_1. Atropine (2.5×10^{-7} gm/ml), however, reduced the response to PGE_1 by 15 to 20 percent in three out of twelve experiments.

Isolated oviduct : Effect of PGE_1 on isolated oviduct (isthmus) of laying birds was studied. EC_{50} calculated on this tissue was found to be 6.25×10^{-9} M (Fig.30). Promethazine or atropine in concentration of 2.5×10^{-7} gm/ml did not affect the PGE_1-induced contractile response on the isolated oviduct of laying birds.

CHAPTER V

DISCUSSION

DISCUSSION

I. CARDIOVASCULAR EFFECTS :

Histamine : In the present investigation histamine dihydrochloride in graded doses decreased the systolic, diastolic and mean arterial pressures in anaesthetized fowls. A typical response of histamine on blood pressure of fowl was characterised by a sharp fall followed by a rise. The intensity of the effect of histamine in doses ranging from 1 to 8 ug/kg on blood pressure was linearly related with log doses of histamine. This response could be used for bioassay of histamine.

Effect of histamine on blood pressure in different species of animals has been reported to vary qualitatively and quantitatively. In cats and dogs it produces a sharp fall in arterial blood pressure while in rabbits and guineapigs a hypertensive effect is observed. It has been shown that a predominance of the capillary dilatation over the spasmogenic action of histamine upon arterioles and venules is a major contributing factor in the production of the fall in blood pressure (Rocha E.Silva, 1966). While it was shown by Dale and Laidlaw (1919) that in addition to its constrictor action on larger blood vessels, histamine has powerful dilator action on the minute blood vessels, capillaries and venules. It was suggested that the effect of histamine on vascular resistance and blood

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pressure resulted from a balance between the two opposed actions. Where the constrictor actions on the larger resistance vessels are comparatively feeble, the overall effect is fall in vascular resistance (Douglas, 1970). On the analogy of mammals the effect of histamine in birds seems to be due principally to capillary dilatation.

Hypotensive effect of histamine in fowl as observed in present investigation has also been reported by Bunag and Walaszek (1961). They did not report the secondary rise in blood pressure which, however, could be noticed from the examination of their observations. In present studies the rise in blood pressure was quite marked and was observed at all dose levels of histamine. Such an effect of histamine has also been observed in cats and dogs though only at higher dose levels (Slater & Dresel, 1952; Trendelenburg, 1961 and Robinson & Jochim, 1960). This rise due to histamine has been suggested to be mediated, at least in part, through the release of catecholamines, either from the adrenal medulla or terminals of the sympathetic nervous system or both (Robinson & Jochim, 1960 and Rocha E.Silva, 1966).

Antihistaminics, promethazine hydrochloride (Phenergan) and diphenhydramine hydrochloride (Benadryl), blocked the depressor response to histamine but the effect of diphenhydramine was less potent and of shorter duration as compared to that of promethazine.

Antihistaminics are known to antagonize in varying degree most, but not all, of the pharmacological effects of histamine in mammals and their effects are due to thier ability to compete with histamine for the receptor sites on the effector cells. In fowls, as well, blockade of histamine response on blood pressure by both the antihistaminics is through such a mechanism.

It was observed in this study that promethazine and diphenhydramine produced a marked pressor response of their own, at all dose levels. Bunag and Walaszek (1961) have also reported such a pressor effect of diphenhydramine on fowl blood pressure. The effect of antihistaminics in fowl is opposite to that observed in mammals since these drugs cause a fall in blood pressure in mammals. This effect is probably related to their local anaesthetic activity (Douglas, 1970). It is likely that the action of antihistaminics in the fowl may be operating through a different mechanism or these drugs may be lacking the local anaesthetic activity in this species.

In order to find out the mechanism of pressor response of antihistaminics, it was explored whether or not these drugs act through the release of catecholamines from tissue stores. The following experiments were planned with this point of view :

(i) An alpha-adrenergic receptor blocking agent (Phentolamine) and beta-adrenergic receptor blocking agent

(pronethalol) did not effect the presser response to antihistaminics.

(ii) Pressor effect of antihistaminics was not affected by alpha-methyl-para-tyrosine, an inhibitor of tyrosine hydroxylase enzyme, which is responsible for conversion of tyrosine to DOPA, the first step in the synthesis of catecholamines.

(iii) Reserpine in lower doses failed to deplete the catecholamines adequately since tyramine could still show its pressor effect which is due to the release of catecholamines.

However, in experiments where birds were pretreated with reserpine 10 mg/kg daily for two days, a marked reduction in pressor response to promethazine was observed and in such a experiment the tyramine effect was also decreased. It is, however, possible that due to species variation, very large doses of reserpine are needed to deplete the catecholamine stores in fowl. Everett & Mann (1967) have also used such high doses of reserpine in chicks in order to deplete the catecholamine stores from the intestine.

It was also reported earlier by Thompson and Coon (1948) that very large doses of adrenergic blocking agents are needed to block the receptors in vivo. Phentolamine in doses of 20 mg/kg as used in the present study caused hypertension by itself and also produced some other toxic

symptoms. Doses higher than these could not be administered for these reasons.

This experiment could not provide a conclusive evident whether or not the pressor action of promethazine was due to the release of catecholamines. Further work in adrenalectomized animals and in which chemical sympathectomy of adrenergic nerves by antiserum, 6-hydroxy-dopamine or guanethidine has been carried out, will conclusively settle this issue.

5-hydroxytryptamine : 5-hydroxytryptamine produced fall in blood pressure in anaesthetised fowls. Effect of 5-HT on blood pressure was not consistent. It varied depending upon the initial blood pressure level.

When the initial blood pressure was high, 5-HT always showed a depressor response. When the initial blood pressure was low, 5-HT caused a pressor response and when the blood pressure was in an intermediate range, 5-HT produced a polyphasic response characterised by pressor-depressor-pressor effect. Page and McCubbin (1953) introduced the term 'amphibaric' to describe the highly variable effects of serotonin on arterial pressure in mammals. The fall in fowl blood pressure induced by 5-HT may be through the coronay chemoreflex (Bezold-Jarisch reflex) as described in mammals (Douglas, 1970). The rise followed by a fall in blood pressure may probably be due to increased cardiac output and peripheral vasoconstriction.

The variable and often unpredictable effects due to serotonin in intact animals have been described partly due to variations in (1) species; (2) the initial blood pressure levels; (3) dose; (4) anaesthetic used; (5) pattern of innervation; (6) route of administration; and (7) speed of injection. In this investigation, when most of other variables were controlled, it seems that the initial level of blood pressure is major factor in determining the effect of 5-HT on fowl blood pressure.

Cyproheptadine at low dose (1.25 mg/kg) did not block the depressor effect of 5-HT while dose of 2.5 mg/kg blocked the depressor response to 5-HT by about 47 percent. Cyproheptadine at dose rate of 5 mg/kg, completely blocked the depressor response to 5-HT (100 ug/kg). Pressor response to 5-HT, however, remained unaltered by cyproheptadine at any dose level.

Cyproheptadine is a non-specific serotonergic receptor blocking agent. It may be competing with 5-HT for sites where 5-HT acts to produce a vasodepressor effect. The sites where 5-HT acts to produce a pressor response may be different and may not be accessible or responsive to the action of cyproheptadine. The indirect action of 5-HT in producing this pressor effect is, however, not ruled out.

Prostaglandin E_1: In the present study, PGE_1 lowered the arterial blood pressure. It was observed that PGE_1 at higher doses produced a sharp fall which recovered rapidly to about 60 percent and thereafter the hypotensive effect lasted for about 5 to 10 minutes.

Prostaglandin E_1 exerted little effect on the ECG of intact animals. Hypotensive response of PGE_1 was not blocked by promethazine, atropine or cyproheptadine, thereby excluding the possibility of PGE_1 response being mediated through histaminergic, cholinergic or serotonergic receptors or through release of these transmitters. The fall in blood pressure of fowl produced by PGE_1 may be due to the direct effect on the peripheral blood vessels as in case of mammals, where PGE_1 is reported to decrease systemic arterial blood pressure in rats (Weeks & Wingerson, 1964) and dogs (Lee et al., 1965 and Nakano & McCurdy, 1967). In addition, it could also produce this effect by interfering with or modifying the synthesis, release or action of other neurohumoral agents (Bergstrom, 1966).

It was also observed in this study that PGE_1 had no effect on responses of blood pressure to acetylcholine or histamine while the pressor response to adrenaline was significantly reduced by PGE_1 in 10 out of 13 experiments. Such anti-adrenergic effect of PGE_1 on fowl blood pressure has not been reported earlier, however, such an effect has been shown in rabbits (Holmes et al., 1963).

Prostaglandins are known to inhibit adenylcyclase which is stimulated by catecholamines (Butcher et al., 1967). It is possible, therefore, that PGE_1 may be having anti-adrenergic effect in fowl through the adenylcyclase-cyclic AMP system.

Electrocardiographic studies in intact birds anaesthetised with phenobarbitone indicated that histamine and PGE_1 did not produce any significant effect on electrocardiogram while promethazine and diphenhydramine slightly decreased heart rate without affecting other components. Phentolamine increased heart rate and reduced the amplitude of P-wave while amplitude and duration of S-wave were increased.

In intact mammals report indicate that histamine did not produce any direct cardiac actions, but barosensory reflexes evoked by the falling blood pressure, stimulate heart rate and tend to augment cardiac output and ECG may also show minor changes. PGE_1 is reported to produce variable effects on heart rate and force of contraction (Douglas, 1970). Findings of the present study are in accordance with Bartlet (1963) who failed to show any significant effect of histamine on ECG of intact birds, however, he found a decreased contractility with histamine in isolated perfused heart of domestic fowl. Marked changes by phentolamine, an alpha-receptor blocking agent, on electrocardiographic pattern may be attributed to its

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cardiac stimulant and vasodilatory effects as suggested by Nickerson (1970). The blood pressure, therefore, varied with the relative contributions of the two effects. Therefore, it is likely that in the present experiments in birds, phentolamine produced more cardiac stimulation rather than vasodialtion as phentolamine raised blood pressure when injected intravenously.

Histamine, 5-HT and PGE_1 caused vasodilation as evident from angiographic studies and their dilatory effects were in the following order : PGE_1 > Histamine > 5-HT. These drugs exert their effect on blood vessels and cause vasodilation and hence produce a hypotensive response. Whether the vasodilatory effect of these drugs is due to their direct actions on blood vessels or through the release of some other transmitter can not be ascertained in the light of present findings. The results suggest that these drugs are vasodilators in case of fowls and this action may contribute as one of the important factors in lowering the blood pressure in this species.

II. SMOOTH MUSCLES :

Histamine : The results indicate that histamine in concentrations lower than 2.5×10^{-8} gm/ml did not produce any measurable effect on isolated chick ileum. Concentrations from 2.5×10^{-8} to 2×10^{-7} gm/ml of histamine relaxed the intestine in almost all the experiments and further increase in concentration produced a contractile response.

The relaxation induced by histamine in lower concentrations was blocked by pronethalol. This indicates that the relaxation caused by histamine is either due to release of catecholamines or by direct stimulation of beta-adrenergic receptors. There is no report so far to suggest that histamine acts directly on the beta-adrenergic receptors. So it may be acting through the release of catecholamines. Everett and Mann (1967) reported similar findings in chick ileum. The present investigation shows that histamine in higher concentrations produced contractile response and such a response may be due to direct action of histamine on smooth muscle. Action of histamine on the cell membrane to facilitate the calcium entry has been reported. Thus the influx of calcium ions provides the immediate intracellular stimulus for activation of the action of the actin -myosin system in smooth muscles. Histamine is reported to promote calcium influx and thus produce contraction by action on the membrane that result in increased permeability to ions, depolarization and increased 'spike' (impulse) frequency (Douglas, 1970).

In the present study histamine in lower concentrations relaxed the ileum in young chicks (1 to 2 weeks old) but not in adults. This indicates that age is one of the important factors in determining the action of histamine on isolated ileum. This difference with age may

merely reflect the development of diffusion barriers to the site of action of histamine in releasing catecholamines. Histamine, therefore, may be effective in releasing catecholamines only in young chicks.

Antihistaminics, promethazine and diphenhydramine blocked the contractile response to histamine by a competitive antagonism on chick ileum. Similar findings were reported by Everett and Mann (1967) with mepyramine.

Therefore, present investigation reveals that inhibitory response to histamine in the chick intestine may be the result of an adrenergic mechanisms while stimulatory responses involve histaminergic receptors directly as the contractile response of histamine was competitively antagonized by promethazine and diphenhydramine. Diphenhydramine was, however, more potent as histamine blocker than promethazine.

5-hydroxytryptamine : 5-hydroxytryptamine in different concentrations showed a marked contractile response and intensity of effect on amplitude of contraction was dose - dependent. Its action on the isolated ileum was direct and was blocked by cyproheptadine. Cleugh et al. (1961) have also observed a biphasic contraction on fowl rectal caecum with 5-HT (0.1 to 2 ug/kg) while higher doses (5 ug/ml) produced prolonged contractions.

Prostaglandin E_1: Prostaglandin E_1 produced marked contractile response. A linear relationship between the amplitude of contraction and log doses of PGE_1 was observed. Horton and Jones (1969) also reported the contractile response to isolated chicken crop by PGE_1.

In present work it was noticed that in quiscent tisssues spontaneous activity appeared after instillation of PGE_1 in bath. Such findings are in agreement with Jones (1970) who observed that PGE_1 initiates or if already present, enhances the rhythmic pendular contractions of the isolated chick oesophagus.

Promethazine and atropine did not block the contractile response induced by PGE_1 either on isolated ileum or oviduct. However, in very few experiments atropine did show a slight reduction in contractile response to PGE_1 on isolated ileum. Such reduction in response of PGE_1 by atropine was also observed by Harry (1968) on guineapig isolated intestine.

It was noticed that oviduct taken from the laying birds were responsive to histamine, 5-HT and PGE_1 while preparations from the non-laying birds were insensitive to the action of these drugs. This suggests that hormonal status during the laying stage of birds may have important impact in determining the effect of these drugs on oviduct of fowl.

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CHAPTER VI

SUMMARY AND CONCLUSIONS

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In the present investigation effects of histamine, 5-hydroxytryptamine, their antagonists and prostaglandin E_1 were observed on (i) cardiovascular system (blood pressure, electrocardiogram and blood vessels) in phenobarbitone anaesthetised adult WLH fowls, (ii) isolated small intestine of chicks, and (iii) isolated oviduct of laying WLH birds. The following effects were observed.

Effects on blood pressure :

1. Histamine dihydrochloride in doses of 1 to 8 ug/kg, i.v. decreased arterial blood pressure. Depressor response to histamine was linear when plotted against its log doses. A typical response of histamine on blood pressure was characterised with a sharp fall followed by a rise.

Blockade of histamine response on blood pressure with diphenhydramine was less in intensity and duration when compared with that of promethazine. Promethazine or diphenhydramine alone showed a marked and sustained rise in fowl blood pressure which was not blocked by phentolamine (20 mg/kg, i.v.), pronethalol (5 mg/kg, i.v.), pretreatment with two doses each of alpha-methyl-para-tyrosine (100 mg/kg) and reserpine (1.5 & 3 mg/kg). However, birds pretreated with reserpine at the dose rate of 10 mg/kg daily for two days showed a marked

decrease in pressor response to promethazine.

2. 5-hydroxytryptamine (10, 30 and 100 ug/kg) showed a variable response on fowl blood pressure (depressor, pressor or polyphasic) which mainly depended upon the initial level of blood pressure.

Cyproheptadine, an antiserotonergic drug, blocked only the depressor phase of response while pressor phase remained unaffected.

3. Prostaglandin E_1 (2.5, 5 and 10 ug/kg) decreased the arterial blood pressure of fowl and such a depressor response was not blocked by histaminergic, cholinergic and serotonergic receptor blocking agents. Prostaglandin E_1 in doses of 5 and 10 ug/kg reduced the pressor response to adrenaline (2 ug/kg) while responses to acetylcholine (1 ug/kg) and histamine (4 ug/kg) remained unaltered.

Effects on electrocardiogram :

Histamine, 5-HT, PGE_1 and antihistaminics did not produce any significant effect on electrocardiographic pattern in phenobarbitone anaesthetised fowls. Phentolamine (20 mg/kg) increased heart rate as well as the amplitude and duration of S-wave while the amplitude of P-wave was reduced.

Effects on blood vessels (Angiographic studies) :

Histamine, 5-HT and PGE_1 produced dilatation of branches of femoral artery by 22.2, 13.7 and 38.2 percent.

respectively in phenobarbitone anaesthetised fowls.

Effects on isolated smooth muscle preparations :

Histamine in lower concentrations (2.5×10^{-8} to 2×10^{-7} gm/ml) relaxed the isolated ileum of chick and this relaxation was blocked by pronethalol. Histamine in higher concentration (4×10^{-7} gm/ml) produced contractile response and this response was blocked both by promethazine and diphenhydramine. Diphenhydramine was more potent than promethazine. Mean effective concentrations (ED_{50}) of histamine on chick ileum and oviduct were found to be 10^{-6}M and 5×10^{-8}M, respectively.

5-hydroxytryptamine and prostaglandin E_1 produced a marked contractile response on chick ileum and the response of 5-HT was blocked by cyproheptadine but PGE_1 induced-contractile response was not blocked by anticholinergic or antihistaminergic receptor blocking agents. ED_{50} of 5-HT on chick ileum and oviduct were 3.4×10^{-8}M and 7×10^{-8}M, respectively. ED_{50} of PGE_1 on oviduct was found to be 6.25×10^{-9}M.

The following conclusions may be derived from the results of the present investigation :

(a) Histamine produced a dose dependent fall on blood pressure and this effect could be used for bioassay of histamine.

(b) Histamine caused a secondary rise on fowl blood pressure as in cats and dogs. However, this effect

was observed in fowl at much lower doses than in mammals.

(c) Antihistaminics-induced pressore response in fowl was opposite to that seen in mammals and this may be mediated through catecholamine release.

(d) As in mammals the effect of 5-HT on fowl blood pressure was variable. Cyproheptadine blocked the depressor phase of reasponse while pressor phase remained unaffected. This suggests that cyproheptadine acts only on sites where 5-HT acts to produce a vasodepressor response but fails to act on those sites where 5-HT acts to produce a vasopressor response.

(e) Little blockade of epinephrine pressor response by phentolamine is difficult to explain. This probably indicates that (i) phentolamine does not gain access to the receptors, (ii) the adrenergic receptors are of different type and not easily blocked by phentolamine or (iii) the receptors are altogether absent in the blood vessels of this species.

(f) The order of dilatory effects of the autacoids, used in this study, was : PGE_1 > histamine > 5-HT.

(g) Inhibitory responses to histamine in chick ileum seem to be due to the release of catecholamines, while stimulatory responses involve direct activation of histaminergic receptors.

(h) Promethazine was more potent antihistamine <u>in vivo</u> as compared with diphenhydramine while <u>in vitro</u> the reverse case was found to be true.

CHAPTER VII

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REFERENCES

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