EFFECT OF SOME CHEMICAL COMPOUNDS ON THE DEVELOPMENTAL STAGES OF CHICKS (GALLUS DOMESTICUS)

A Thesis

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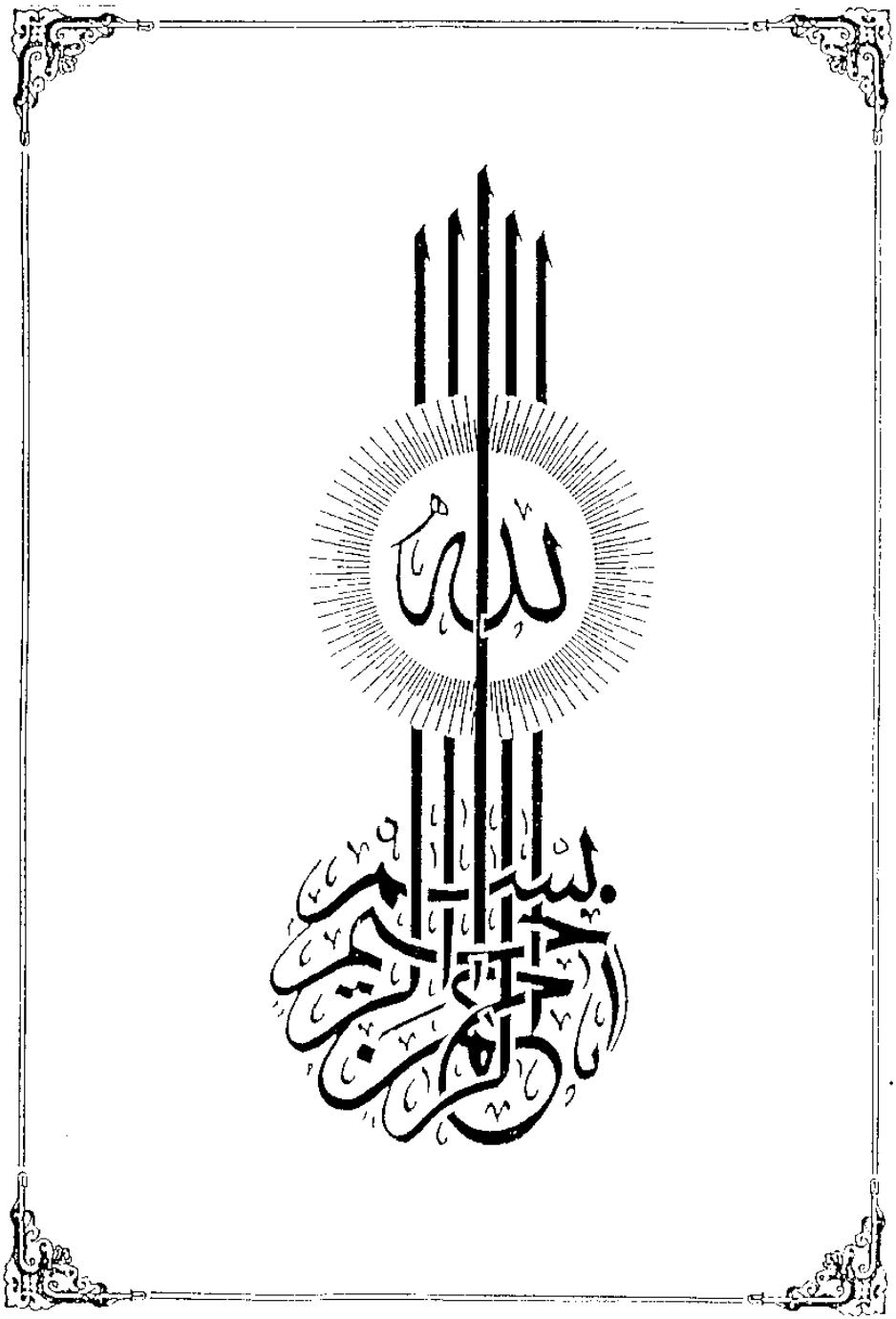
C O N T E N T S



PART II

EFFECT OF RESERPINE AND CHLORPROMAZINE ON THE MOTHER HENS AND THEIR OFFSPRING

P A R T I

EFFECT OF RESERPINE AND CHLORPROMAZINE ON CHICK EMBRYOS

INTRODUCTION

The present work was proposed to examine the effects of two major tranquillizers, namely, reserpine and chlorpromazine on the development and morphology of chick embryos. These two drugs are widely used as sedatives and are prescribed to pregnant women owing to their tranquillizing and relaxing effects. As these drugs are supposed to act mainly on the central nervous system, it seemed to be highly desirable to study their effects on the spinal cord and on the main organelles and inclusions of its nerve cells. The mitochondria, the Golgi apparatus, Nissl substance, neurofibrillae as well as ribo- and deoxyribo-nucleic acids of the spinal cord motor neurones were selected for the present investigation.

In this study, the effect of these drugs was experimented on early developing chick embryos since the fertilized eggs have the advantage of being available in large numbers irrespective of the season, besides, having quick response to injection (Karnofesky, 1955). According to this author, the chick embryo is a unique system since drugs are retained after injection into the egg and are slowly metabolised.

Hamilton (1952) and Karnofesky (1955) considered the 4th day of incubation to represent the critical stage at which the most severe effects occur. Eggs used in the present study were injected in *vivo* after 48, 72, or 96 hours of incubation, and then they were reincubated to the 13th or 18th day of incubation, after which they were sacrificed. Although Vasudeva (1967) stated that chick embryos cultured in *vitro* offer greater flexibility in terms of experimental embryology, yet it was noticed in a previous study carried out by the present investigator on the effect of salicylates on chick embryos, that injection of the eggs in *vivo* keeps the embryos in a state very close to that occurring in normal development (Abd El-Rahman, 1969).

Since seasonal variations are known to have an effect on the incidence of malformations occurring spontaneously in chick embryos, all the present experiments were designed to be made during the winter season which was suggested by Good Pasture (1938) to be the most favourable period for experimental work. This worker found that the percentage of fertility, vigor and strength of the embryos were highest during this season.

In view of the findings of Landauer (1960), Kamel et al. (1964) and Abd El-Rahman (1969) that the different species of chick embryos differ in their response to the same drugs, only one kind of eggs namely that of White leghorn fowls were used in the present study to avoid any breed differences which might interfere with the obtained results.

In another group of experiments, a trial was made to see if-vitamin B- complex has any useful effect in minimizing the harmful side-effects produced in the chick embryos following injection with the two drugs in question.

HISTORICAL REVIEW

Reserpine:

Reserpine ($C_{33}H_{72}N_2O_9$) is an alkaloid obtained from the roots of certain species of Rauwolfia, or by synthesis. It occurs as odourless, almost tasteless, fine, white to creamy coloured crystals which darken slowly on exposure to light. It is almost insoluble in water but soluble in alcohols and acids.

Injections of reserpine, which are used in the present study, are commercially known as Serpasil (Ciba

limited, Basle, Switzerland). It is prescribed in principle for the treatment of hypertension, and is also useful in nervous irritability and states of anxiety due to its tranquillizing and relaxing effects. This drug is also used as pre- and post-operative sedative and in the treatment of cardiac disorders.

Lazarte et al. (1955), and Kempinsky (1960) used reserpine successfully in the treatment of Huntigton's chorea, and Avol and Vogel (1955) found that injections of this drug were effective in freeing patients from acute hallucinations.

Reserpine was found by Colombati and Benassi (1955), and Noce et al. (1955) to be of value in the treatment of psychiatric and neurological patients, but the good results were noticed to last only while the drug was taken, and relapses occurred after withdrawal of the drug (Barsa and Kline, 1955). Azima (1958) found an increase in dream recall, i.e. awereness of dreams ,when he used reserpine with anxious patients. This was associated with a decrease of the anxious state of the patient. Eskell (1962) reported the successful effect of reserpine in curing acute chilblains.

Reserpine has a relatively low toxicity, but even in minimum therapeutic doses, it may give rise to a number of side-effects, the most common of which are nasal congestion, lethergy, drowsinness, peculiar dreams, gastro-intestinal upsets, diarrhaea, vertige and increase in body weight. Higher doses may cause flushing, infection of conjunctivae, insomnia, brady cardia, occasional perkinsonian-like syndrome and severe depression which may lead to suicide. Sodium retension, oedema, peptic ulceration and epistaxis have also been reported. Intramascular or intravenous injections of reserpinemay cause postural hypotension.

The side-effects are transient and quickly clear up on reduction of dosage or discontinuation of treatment. Tolerance to reserpine does not develop and it does not appear to be habit forming. A survey of the side effects produced by reserpine are tabulated in the following table:

Types of side-effects	Author	
Toxic effects	Philips	(1955)
Asthma	Ferguson	(1955)
Neonatal toxicity	Budnick et al.	(1955)
	Finnerty	(1956)
Oedema.....	Perera	(1955)
	Marely & Bare	(1956)
	Ferguson	(1956)
	Woolman	(1956)
Cardiac failure ----------	Marely & Bare	(1956)
Depressive mental illness------	Muller et al.	(1955)
	Kass & Brown	(1955)
	Wallace	(1955)
	Blote et al.	(1959)
Parkinsonian syndrons----------	Richman & Tyhurst	(1955)
	Groden	(1963)
Gastro-intestinal haemorrhage---	Duncan & Fleeson	(1959)
Hypotension	Fletcher	(1963)
Toxicity of rat foetus	West	(1964)

Chlorpromazine:

Chlorpromazine is a white or cream-like powder with a slight odour and a very bitter taste. It darkens on exposure to light, and is soluble in water. Sterile solution of chlorpromazine hydrochloride in water free from dissolved air is commercially used for injection. The drug used in this study is known as Plegomazin (Egyt, Hungary).

The agent of plegomazin- products is a compound belonging to the group of Phenothiazines: 3-chloro-N(3' dimethyl-amino propyl) phenothiazine hydrochloride.

Chlorpromazine has a wide therapeutic use owing to its various valuable pharmacodynamic properties. It acts equally on the central and the vegetative nervous systems. Through its action exerted on the central nervous system, it relieves certain psychic disturbances, thus promoting mental relaxation. By its influence on the vegetative nervous system, it has a beneficial influence on certain regulating mechanisms (vomiting, thermoregulation, sleep wakefulness, and vascular and muscle tonus).

Chorpromazine also possesses a potent anti-shock effect. It ensures full pre- and post-operative calmness

for the patient. It reduces the efficacy of the heat-regulating centre so that the body acquires the temperature of its surroundings. Some phenothiazine compounds have vasodialator action and reduce blood pressure. Phenothiazine derivatives possess a powerful anti-emetic action which is said to be effective against nausea and vomiting (Martindale, 1957).

The effectiveness of chlorpromazine in the treatment of chizophrania was reported by Fink et al.,(1958) and by Cole et al.,(1964).

Cohen (1956) and Lesse (1959) confirmed that chlorpromazine can stinulate dream recall in patients treated with this tranquillizer. This increased recall or awarness of dreams was associated with reduction of anxiety in the patient.

The effect of chlorpromazine in the treatment of alcoholism was reported by Mitchell(1955).

Laurence et al.,(1958)reported that chlorpromazine is easier to manage, during tetanus convulsions than barbiturates. Packard et al. (1958) showed that chlorpromazine satisfactorily controls convulsions with no

serious side-effects. The effectiveness of chlorpromazine in curing tetanus was also reported by Shanker and Mehrotra (1958).

In spite of all such useful effects, the use of chlorpromazine was accompanied by some side-effects, including occasional disturbances of the haematopoietic system which may be complicated with severe anaemia. Liver damage may occur and certain photosenthitizing effects may be produced by this drug. In the medical or nursing staff, allergic reaction to the drug often appears. Some of the side - effects are common to all members of the group of phenothiazines; symptoms associated with the action of the drug on the autonomic nervous system - dryness of the mouth, tachychardia, pallor, constipation, blurred vision, gain in weight, oedema, and vived dreams-may occur with any of the members of the group. The most common side-effects occurring with the treatment of chlorpromazine are summarized in the following table:

Types of side-effects	Author	
Agranulocytosis	Korst	(1959)
Abnormalities of hepatic-functions	Melrose & Roy	(1959)
	Cupta	(1962)
	Waitzkin & Machmahon	(1962)
	Scheile	(1962)
Dyskinesia	Robinson	(1960)
	Hunter et al.	(1964)
	Heathfield	(1965)
	Morphew & Barber	(1965)
Extrapyranidal symptons	Ayd	(1961)
Poisoning	McKown et al.	(1963)
	Dilworth et al.	(1963)
Blood dyscrasias	Best	(1963)
Gastro-intestinal disturbances	Haden	(1964)
Pigmentation of the skin associated with occular changes	Zelickson & Zeller	(1964)
	Satanove	(1965)
	Cairns et al.	(1965)
Sudden deaths	Hollister & Kosek	(1965)