

# TOXIC AND TERATOGENIC EFFECTS OF SOME DRUGS ON CHICK EMBRYO

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## INTRODUCTION

The toxicity and teratogenicity of three commonly used drugs were tested in «Douky 4» chick embryos. Avil (1 - phenyl 2 - pyridyl - 3 - dimethyl aminopropane) is an antihistaminic and antiallergic drug, Nesdonal (a derivative of the acid 2 - ethyl - 5 methyl - 1 - butyl - 5 thio-barbitone) is a general anaesthetic drug, while Revrin (pyrrolidino-methyl tetracycline) is a common antibiotic.

Antihistaminic drugs are generally thought to be safe, Meclozine for instance has been thoroughly investigated and several independent studies in different parts of the world failed to demonstrate any deleterious effect on the embryo or foetus (Wollam, 1966).

On the other hand, Brazelton (1961) showed that heavy barbit-

urate premedication could affect the newborn baby. Botros (1964) stated that «obstetric analgesia may have profound and obvious effects upon the newborn baby». Gupta et al (1980) found that phenobarbital treatment during prenatal development can produce permanent alterations in sexual maturation.

Antibiotics, generally, and tetracycline, in particular, received wide attention and intensive investigations dealing with their side-effects. The Egyptian general organization for pharmaceuticals, chemicals and medical appliances published in 1970 a booklet summarizing the side-effects of tetracyclines. It stated that «chlorotetracycline (Aureomycin) has been proved to have more toxic side-reactions and therefore should be preserved when other tetracyclines fail in the treatment and the organisms are sensitive to it».

Shamikh (1978) found that tetracycline increased the thickness of the epithelial lining of the trachea of the guinea pigs and decreased the pulmonary cell population leading to a decrease in the defence mechanisms of the lungs.

Tetracyclines proved to have certain teratogenic effects. Filippi and Mela (1957), Rendle-Short (1962), Davies et al (1962), Cohlan et al (1963), Walford (1963) and Tubaro (1964) showed that tetracycline deposits in the bone and teeth of experimental animals and human foetus, elevate the percentages of mortalities, exert some congenital malformations of the face and extremities and cause growth inhibition. Klimova et al (1976) found that embryotoxic effects of tetracycline and its derivatives manifested themselves in embryonic chicks by developmental anomalies mainly in the bill, beak, limbs and head. The anomalies produced in the developing chick embryo were analogous to those observed in mammals as rats.

However, in all the previous experiments none dealt with the early structures in the developing embryos. In the present study a detailed investigation dealing with the side-effects of the three drugs in question was made to evaluate their toxic and teratogenic effects on the development of early chick embryos.

## MATERIAL AND METHOD

Fertile «Douky 4» eggs were injected pre-incubation with different doses (including doses equivalent weight to weight to those used therapeutically in man) of Avil, Nesdonal or Revrin. Eggs were then incubated for 72 hours after which they were sacrificed, fixed, stained with borax carmin, dehydrated, cleared and mounted in balsam. The prepared embryos were examined and the relative data were recorded in the table. Some of the embryos were photographed to demonstrate the toxicity and teratogenicity of the drugs under investigation.

## RESULTS

Inspection of the treated embryos after 72 hours of incubation revealed that Avil, in a dose equivalent weight to weight to that used therapeutically in man (0.04mg/egg), and in ten times this dose (0.4 mg/egg) exerted insignificant toxic or teratogenic effects on the treated embryos. In embryos treated with the low dose, only one embryo out of eleven (9.1%) was retarded than the untreated controls (Fig. 1). The retardation was mainly manifested in the circulatory system. The heart was still U-shaped and the vitelline veins were faint and very near to the heart, a phenomenon occurring in the 33-hour normal chick. Also, all the other vitelline vessels were

faint and fewer in number than the controls (Fig. 2). None of the embryos of this group died.

In case of embryos treated with 0.4 mg Avil, only one embryo out of 17 (5.9%) ceased to develop beyond the 33-hour stage and died, but none was abnormal. The above results show that Avil cannot be considered toxic or teratogenic to chick embryos in doses used in this experiment at this particular stage of development.

Nesdonal exerted toxic, inhibitory and teratogenic effects on the treated embryos. 42.85% of the embryos treated with a dose equivalent to the human one (0.5 mg/egg), and 28.57% of those treated with double this dose died. Also, 35.1% of those received the high dose were reduced in size and their cardiac movements were feeble and the vitelline vessels were few and faint. The size of the embryonic discs of the reduced embryos was smaller than the normal. Percentages of normal embryos were 57.14 for those treated with the low dose, and 35.1 for those treated with the high one. One of the dead embryos that received a high dose was severely destructed. The head and cardiac regions could not be divided into their respective regions. Only ten pairs of somites were formed. The neural tube was

abnormally dilated posteriorly and the chordal tissue was apparently degenerated inside it. Faint traces of vitelline veins could be traced at both sides of the cardiac region (Fig. 3).

Revrin, on the other hand, showed marked toxic and teratogenic effects on chick embryos. 70% of the embryos treated with a dose equivalent to the human dose (0.22 mg/egg) died early after injection (at about 40-hour stage), and 43.75% of those treated with double the previous dose also died; 31.25% of the latter group were abnormally retarded or malformed. Most of the surviving embryos showed feeble heart beats, faint and fewer vitelline vessels and smaller embryonic discs. Some of them possessed U-shaped hearts similar to those described in Fig. 2. On the other hand, one of the dead embryos that received 0.44 mg Revrin was anidous, its head and cardiac regions were poorly differentiated, in addition to being anisomerous having seven somites at one side and five at the other. Vacuoles were seen caudal to the somites, and the caudal tissues of the embryo and embryonic disc were degenerated and loose (Fig. 4).

The relevant data of the previous treatments are tabulated in the following table.

Toxic and teratogenic effects of Avil, Nesdonal and Revrin on  
early chick embryos

Drug	Dosage mg./egg	Total No. of eggs	Fertile eggs	Normal		Abnormal		Dead	
				No.	%	No.	%	No.	%
Avil	0.04	14	11	10	90.9	1	9.1	—	0.0
	0.4	19	17	16	94.1	—	0.0	1	5.9
	0.5	17	14	8	57.14	—	0.0	6	42.85
Nesdonal	1.00	15	14	5	35.1	5	35.1	4	28.57
	0.22	12	10	2	20.0	1	10.0	7	70.0
Revrin	0.44	16	16	4	25.0	5	31.25	7	43.75
No drug (controls)	—	10	9	9	100.0	—	0.0	—	0.0

### DISCUSSION

In the present study evaluation of the toxicity and teratogenicity of three common drugs, Avil, Nesdonal and Revrin was carried out on the early development of chick embryo.

Antihistaminic drugs have proved to be safe. Their main side-effects are sedation, dizziness, fatigue, insomnia, nervousness; tremors, gastro-intestinal disturbance and dry mouth. Dermatitis and granulocytosis can occur. Severe poisoning due to overdose results in coma and some times in convulsions (Laurence, 1970). Kay (1953) and Correia and De Moura (1963) demonstrated the side-effects of antihistaminic drugs on the gastric mucosa secretion. How-

ever, no available study demonstrated the teratogenic effects of antihistaminic drugs generally and Avil in particular on the embryo or foetus. The present experiment dealing with Avil in the therapeutic dose or in ten times this dose, failed to create significant toxic or teratogenic effects on chick embryos when injected before incubation.

Brazelton (1961), Botros (1964) and Gupta et al (1980) showed that obstetric analgesia in general and barbiturates in particular may cause side-effects on the newborn babies manifested in drowsiness, slowness in gaining weight and alterations in sexual maturation. Laurence (1970) stated that «the unwanted effects of barbiturates are almost those of overdose: coma and respiratory failure, hypersensitivity and rashes and that on the

whole, barbiturates have proved satisfactory drugs». However, in the present study Nesdonal elevated the mortality percentages and caused mild retardation of the treated embryos. It hindered the process of angiogenesis, the heart was retarded and the vitelline vessels became few and faint.

Tetracyclines have been the subject of many investigations dealing with their side-effects. The main side-effects are deposition of the drug in the nails, fingers and teeth (Douglas, 1963) and increasing the thickness of the tracheal epithelium and decreasing pulmonary cell population (Shamikh, 1978).

Saxen and Kaitila (1972) found that tetracycline can effect bone formation in vitro. They thought that this effect is not due to the action on proliferative or synthetic activities of the chondroblasts but rather to depend on the deposition of bone minerals in the normally developed matrix.

The teratogenic and toxic actions of tetracyclines have been reported by a number of investigators as mentioned in the introduction. The results obtained by Kerley and Kollar (1978) showed that tetracycline can alter dental development in vitro prior to mineralization. They attributed this inhibition to a disruption of collagen biosynthesis which is thought to play a role in the controlling epithelial-mesenchymal interaction involved in tooth germ morphogenesis. However, in the

present study Revrin proved to be highly toxic to early chick embryos and to inhibit most of the surviving ones. The inhibition was mostly in the circulatory system.

Some of the dead embryos that were treated with Nesdonal or Revrin became highly malformed and were described in the text.

## SUMMARY

The toxicity and teratogenicity of three common drugs, Avil, Nesdonal and Revrin were tested in early chick embryos. Fertile eggs were injected preincubation with doses equivalent weight to weight to those used therapeutically in man, and with double these doses. Embryos were examined after 72 hours of incubation.

Avil proved to be safe since no significant effects were observed in doses up to ten times the human dose. Nesdonal and Revrin, on the other hand, exerted toxic, inhibitory and teratogenic effects on the treated embryos. In this respect Revrin was more powerful than Nesdonal. The teratogenic effects were mainly manifested in inhibiting the process of angiogenesis. Some of the dead embryos were anidous and highly malformed.

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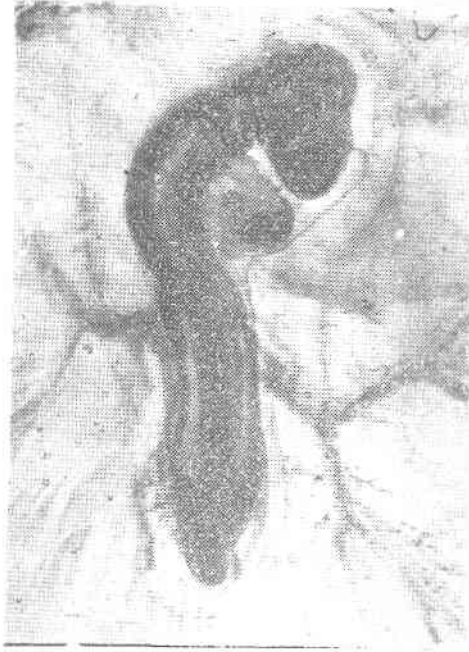
## LEGENDS

Fig. 1 : Normal 72 hour chick embryo (control).

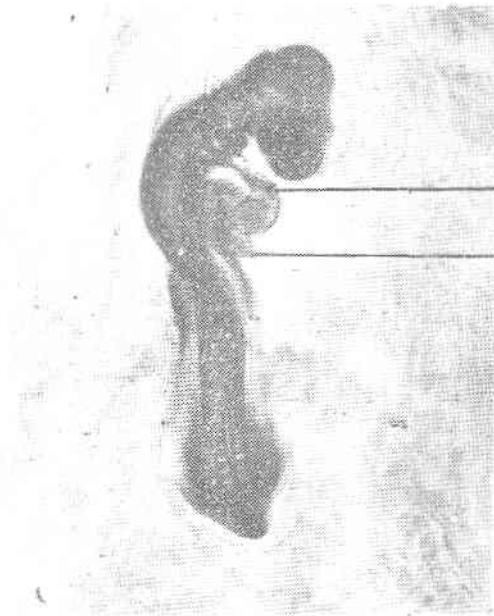
Fig. 2 : A 72 hour chick embryo treated with 0.04 mg Avil. The heart is U-shaped and the vitelline vessels are few and faint.

Fig. 3 : A dead malformed chick embryo treated with 1 mg Nesdonal.

Fig. 4 : A dead malformed chick embryo treated with 0.44 mg Revrin.



**Fig. 1**



→ **Heart**

→ **Vitelline  
vein**

**Fig. 2**

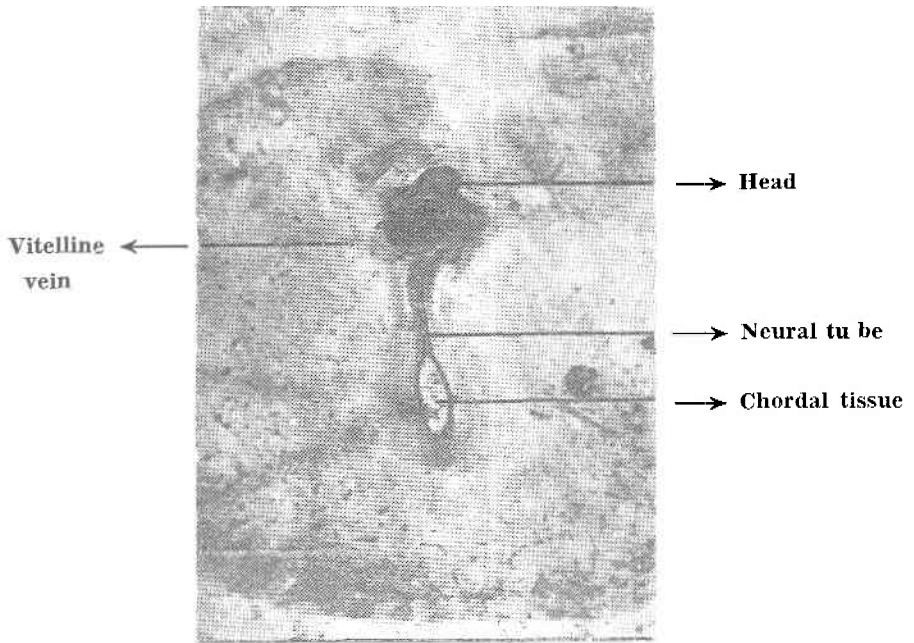


Fig. 3

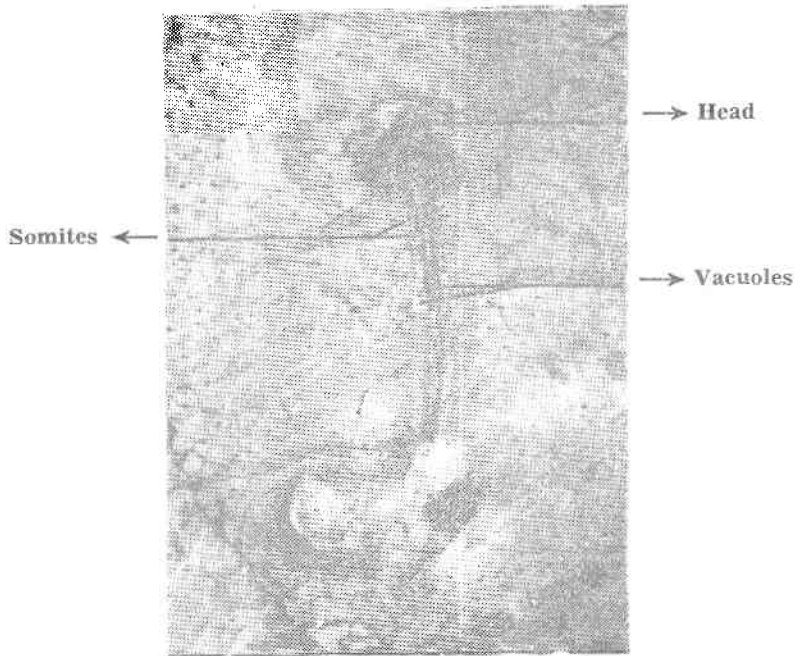


Fig. 4