of the compound action potential, whereas in a desheathed preparation (dotted lines) it causes a rapid conduction block. Exposure to the lanthanum saline does not abolish the barrier, as judged from the effect of the subsequent exposure to the high-potassium saline, although in this particular experiment there was some effect on the d.c. potential. In other experiments, however, the effect of the high-potassium saline was apparently normal even after a 1 h incubation in the lanthanum saline (Figure B). In none of these experiments did the lanthanum saline have any detectable effect on nervous conduction in the intact nerve cord, but it had severe and irreversible effects on conduction in desheathed nerve cords (Figure C).

The present experiments are thus in agreement with the ultrastructural observation that lanthanum cannot traverse the blood-brain barrier (the perineurium), but also show that it does not cause the barrier to become significantly more permeable to sodium or potassium ions. This substance does have some effect on the barrier, however, as judged by the complex effect on the d.c. potential (Figure A). The greater depolarization fo the d.c. potential in response to the second exposure to the high-potassium saline suggests that lanthanum decreases the sodium:potassium permeability ratio of the perineurium, although no estimate of absolute permeability changes has been made. By analogy with the effects of lanthanum on other tissues[4–6], it appears likely that there is an overall decrease in the ionic permeability of the perineurium as a result of exposure to lanthanum ions.

Thus, although ionic lanthanum is not totally without effect on the insect blood-brain barrier, it appears that the results of tracer studies using this substance at the low concentrations normally employed can be interpreted with some confidence.

The Effect of Cortisone on the Teratogenic Action of Acetylsalicylic Acid and Diphenylhydantoin in the Mouse

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Summary. Acetylsalicylic acid exerted a potentiating effect on cortisone – induced teratogenicity in the mouse. Diphenylhydantoin remained uneffective in this respect.

Cortisone, when given at a high dose to dams during the sensitive period of embryonic development, is known to produce cleft palate in the mouse foetus[1–15]. The failure of fusion of the embryonic palatal shelves in this species is known to be a non-specific effect occurring after the exposure of the dams to a variety of exogenous influences, including drugs of different chemical structure[16]. The occurrence of cleft palate is considered to result from a complex interaction between extrinsic and intrinsic factors responsible for an increase in maternal plasma corticosterone[17].

The present study was undertaken with a view to determining whether the administration of drugs of known teratogenic potential would alter the teratogenicity of cortisone in the mouse. Acetylsalicyclic acid (ASA) and 5,5-diphenyl-hydantoin (DPH) were selected because these drugs were shown by themselves to induce cleft palate in this species[18–27].

Materials and methods. Albino mice derived from an NMRI-strain and bred on our premises were used. Females aged 2 months were mated with males of proven fertility at the ratio of 1 ♂: 3 ♀♀. The day on which successful mating was verified by the presence of a vaginal plug was taken as 'Day 0' of gestation. Throughout the experiment, the females were kept 5 to a cage in an air-conditioned room at a temperature of 22 ± 0.5 °C and a humidity of 56 ± 3%. The room was illuminated for 12 h daily. A commercial standard diet was fed. Tap water was available ad libitum. The general condition of the dams was checked daily throughout the treatment. The dams were autopsied and the foetuses removed by Caesarean section on Day 18 of pregnancy. The foetuses were submitted to careful inspection with the aid of a dissection lens and were weighed individually.

ASA and DPH (Fluka Ltd., Buchs SG, Switzerland) were given orally by intubation from the 6th until the 15th day of pregnancy, inclusive. The doses were 500 mg/kg/day (ASA) and 100 mg/kg/day (DPH). A 2% aqueous

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Table I. Effects on the mouse embryo of treatment with ASA or DPH alone or in combination with cortisone

Group	No. of dams	Mean number of implantations ($\bar{x}$)	Embryonic deaths (%)	Foetal deaths (%)	Live foetuses		Malformation rate		
					total	%	Litters		Foetuses
							total	%	%
CMC (control)	27	11.48	6.1	1.9	285	92.0	1	3.7	0.4
ASA	13	10.38	6.7	2.9	122	90.4	5	38.5[b]	5.7[b]
DPH	17	12.06	10.2	1.0	182	88.8	4	23.5	7.7[b]
Cortisone, 20 mg/kg									
+ CMC	22	11.09	7.4	2.0	221	90.6	12	54.6	13.6
+ ASA	20	11.80	19.1[a]	3.8	182	77.1	14	70.0	25.3[b]
+ DPH	21	11.95	15.1	0.8	211	84.1	9	42.9	10.9
Cortisone, 60 mg/kg									
+ CMC	21	11.33	7.1	1.3	218	91.6	21	100	52.3
+ ASA	19	12.11	12.6[a]	0.4	200	87.0	19	100	88.5[b]
+ DPH	19	11.79	8.0	0.5	205	91.5	17	89.5	48.3
Cumulative control	415	11.24	7.6	0.7	4,278	91.7	17	4.1	0.4

[a] Significantly greater than in corresponding ASA-group (χ^2 test, $p < 0.01$). [b] Significantly greater than in CMC-groups (Fisher's exact test, $p < 0.01$ or 99% confidence limits).

solution of sodium carboxymethylcellulose (CMC) was used as the vehicle. The amount of fluid administered was 0.1 ml per 10 g of body weight.

Cortisone acetate (Fluka Ltd.) was prepared for s.c. injection by homogenizing it in a solution of 1% CMC dissolved in saline (0.9% NaCl); of this suspension 0.05 ml per 10 g of body weight was injected into each animal 2 h after the other drugs, or in the case of the controls, the vehicle alone was injected. The treatment with cortisone was confined to days 11 to 13 of gestation. The treated groups and number of animals are indicated in Table I.

Results and discussion. Dams treated with ASA showed sedation and dyspnoea. 4 of the 17 animals in group 1 died spontaneously, and at necropsy damage to the gastric mucosa was observed. The administration of DPH was tolerated except that feed intake was slightly reduced.

The data on the progeny (Table I) revealed that the incidence of embryonic deaths was significantly higher in the animals that had received cortisone in combination with ASA, than in those having received ASA alone.

Both ASA and DPH exerted a definite teratogenic action (Tables I and II). Following the administration of cortisone at a dose of 20 mg/kg, the percentage of malformations was higher in the group receiving cortisone and ASA combined than in the group injected with cortisone alone. When the dose of cortisone was raised to 60 mg/kg, an even greater number of malformed foetuses was observed when combined with ASA. By contrast, no influence of DPH on the teratogenicity of cortisone was noted even at this high dose-level.

The seemingly potentiating effect of cortisone and ASA given combined to the dams is particularly evident by recording the number of individual foetuses affected. With regard to the numbers of litters affected, i.e. of litters containing at least 1 malformed foetus, numerical differences were less marked and the only significant difference ($p < 0.01$) from the corresponding control group receiving CMC was found after the administration of ASA.

A particular feature of the malformations produced by ASA was missing or short mandible in a number of foetuses (Table II). However, the incidence of these mandibular malformations remained unaffected by cortisone. It seems noteworthy that the cortisone-induced increase in the number of malformed foetuses concerned only cleft palate.

The two drugs (ASA and DPH) whose teratogenic activity in the mouse was confirmed in these experiments differed in their effects on the dams and progeny. ASA was moderately toxic to the dams at doses that exerted a slight to moderate teratogenic action. DPH proved teratogenic to a comparable degree, but the dams were almost unaffected by treatment. Furthermore, ASA induced some degree of embryolethality that was attributed to the maternal toxicity. The teratogenic action of this drug and its potentiation by cortisone appeared to be independent of this type of non-specific toxicity.

No interaction was apparent between the teratogenic actions of DPH and cortisone under the conditions of this experiment.

Table II. Malformations of live foetuses

Group	Cleft palate (%)	Malformations of jaws[b] (%)
CMC (control)	0	0.35
ASA	4.10[a]	2.46
DPH	7.69[a]	0
Cortisone, 20 mg/kg		
+ CMC	13.12	0.45
+ ASA	21.98[a]	3.85[a]
+ DPH	10.43	0
Cortisone, 60 mg/kg		
+ CMC	52.29	0
+ ASA	86.50[a]	2.00
+ DPH	48.29	0.49
Cumulative control	0.12	0.21

[a] Outside the 99% confidence limits of CMC-groups. [b] Particularly mandibular aplasia or hypoplasia.