and 0.01). A decrease in urinary PGEs concentration has also been observed (tables 1 and 2, figure 1).
These results provoked by the coadministration of aspirin could be reversed by the infusion of the synthetic PGA_2 (table 1 and figure 1).
Discussion. The data reported here confirm previous findings that aldosterone is able to inhibit (about 50%) the synthesis of PGs in experiments in the skin of the rat[12]. The same result have been obtained by using other anti-inflammatory steroids. In our experiments, aldosterone decreased sodium and increased potassium excretion resulting to a significant decrease of the index (urinary Na/K ratio) in both subgroups, of adrenalectomized and intact animals. These results were accompanied by a significant decrease in renomedullary PGEs release (tables and figure 1). The mechanism by which aldosterone (and other steroids) decreases the synthesis and/or release of PGs is not well-known, but among the suggestions offered is, that: it is a) to prevent the replacement of the synthetase enzyme, b) to interfere with the target organ, and c) to prevent the transport or the release of PG precursors as arachidonic acid[13,14]. Thus the antinatriuretic effect of aldosterone increases by his inhibitory effect on the natriuretic renomedullary PGEs synthesis and/or release. On the other hand, the natriuresis observed by many investigators after long-term administration of aldosterone could be explained by the release of PGEs following extracellular space expansion provoked by the retention of sodium[7,15,16]. The increase of the index (urinary Na/K ratio) following the coadministration of spironolactone observed in these experiments is well-known and the phenomenon could be related to the occupation of the mineralo-corticoid receptors by the substance and/or to the mediation (at least in part) by the simultaneous release of the potent natriuretic PGEs (tables and figure 1). This suggestion is supported by the results obtained when aspirin, a well-known inhibitor of PG synthesis and/or release, was coadministrated[17]. Thus, the index (urinary Na/K ratio) decreased, accompanied by a simultaneous decrease in PGEs concentration in the urine (forth subgroups, tables and figure 1), an effect which could be reversed by the infusion of the synthetic PGA_2 (table 1 and figure 1). The figure 2 shows schematically the possible feed-back between the natriuretic, diuretic and antihypertensive PGEs and their antagonists renin-angiotensin system, aldosterone, noradrenaline and antidiuretic hormone (ADH).

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The effect of methaqualone on prenatal development in the rat

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Summary. Methaqualone treatment of pregnant rats in doses of 100–200 mg/kg day produces resorption and a series of anomalies whose incidence increases with the dose-level employed.

Methaqualone (2-methyl-3-orthotolyl-4-quinazolone) is a nonbarbiturate central nervous system (CNS) depressant which has become frequently abused and is presently highly sought after in the illicit drug market[2–4]. The widespread abuse of methaqualone has created a great deal of interest in, and research on its properties. Surprisingly, there is little information regarding the effect of methaqualone consumption during pregnancy[5,6]. In light of the evidence attesting to the growing number of individuals abusing methaqualone in nontherapeutic doses, we have investigated several dose-levels of methaqualone to assess the full spectrum of its effects on fetal development.
Material and methods. Pregnant Long Evans Hooded rats were administered, as a single daily s.c. injection in a propylene glycol suspension, 100, 125, 150 or 200 mg/kg methaqualone on days 8–15 of gestation or 115 mg/kg methaqualone on days 1–19 of gestation. If maternal deaths occurred, injections were continued until at least 5 mothers per group reached day 20 of gestation, except in the 115 mg/kg group where only 4 mothers were used and the infants were allowed to come to term. 5 females (normal control group) were not injected, but were weighed daily. 5 females (yoke control group) were administered daily s.c. injections of propylene glycol and were administered Purina Lab Chow in quantities just sufficient to maintain their weight at the mean level of the methaqualone groups. On day 20, these animals were sacrificed, their uterine horns exposed and the number of dead and living fetuses and resorption sites counted. The fetuses were weighed, examined for external defects, and their brains removed and weighed. For skeletal examination, the fetuses were placed in alcohol and stained with alizarine red S[7].

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Effect of methaqualone on development of rat fetuses

Group	Gestational days injected	No. of litters	Total No. of implantation sites	Fetal body weight (g) (mean ± SE)	Fetal brain[a] weight (g) (mean ± SE)	Resorbed or dead fetuses (%)	Anomalies (%)
Normal control (uninjected)	–	5	59	4.408 ± 0.085[b]	0.1909 ± 0.002	0	0
Yoked control (propylene glycol)	8–15	5	53	4.100 ± 0.045	0.1862 ± 0.002	5.7	0
Methaqualone:							
100 mg/kg	8–15	5	59	3.52 ± 0.57[b]	0.1533 ± 0.004[b]	23.7[b]	0
125 mg/kg	8–15	5	53	3.03 ± 0.069[b]	0.1381 ± 0.002[b]	52.8[b]	1.9
150 mg/kg	8–15	5	48	2.70 ± 0.102[b]	0.1363 ± 0.007[b]	87.5[b]	8.3[b]
200 mg/kg	8–15	5	48	1.80 ± 0.235[b,c]	0.1336 ± 0.002[b]	64.6[b]	18.8[b]
115 mg/kg	1–19	4	48	ND[d]	ND[d]	14.6	12.5[b]

[a] Brain weights not taken on exencephalic or dome headed fetuses.

[b] $p<0.05$ compared with the yoked control group.

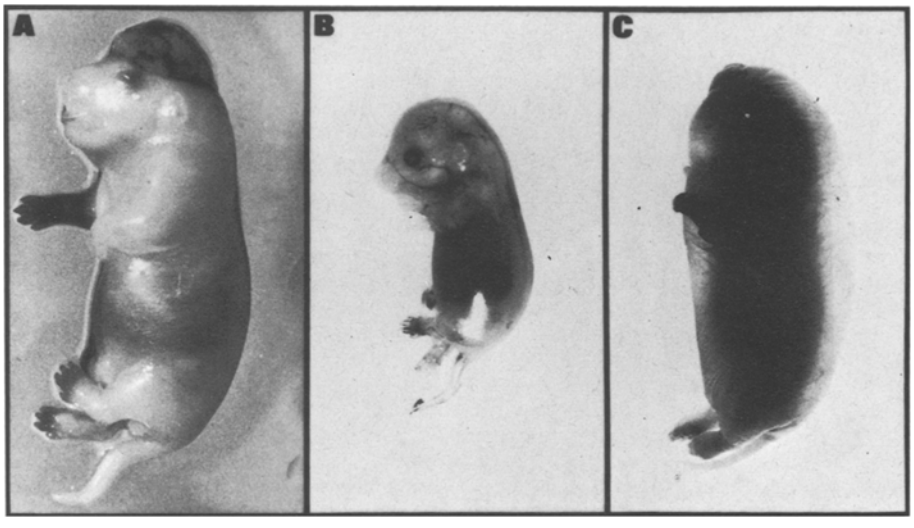
[c] Omitting litter with $\bar{X} = 0.82 \pm 0.041$ g, remaining fetuses $\bar{X} = 2.57 \pm 0.082$ g.

[d] Not determined.

Results. Maternal weight gain was depressed in all methaqualone treated mothers. As the dose-level increased, mothers spent more time sleeping, and maternal death rate increased.

Fetal body and brain weight was reduced in a dose-level fashion (figure, B; table). These reductions in brain and body weights were not likely due to insufficient maternal food consumption alone, since body and brain weights were significantly below those of yoke weight control animals. The percent of resorptions and external anomalies increased with the dose of methaqualone administered. Although there were no anomalies in either of the control groups, and the normal control group had no resorptions, the yoked control group had a 5.7% resorption rate. At 100 mg/kg methaqualone, although there was a 23.7% resorption rate, no physical anomalies were observed. In the 125 mg/kg methaqualone group, facial hypoplasia and absence of skull roof were seen. In the 150 mg/kg group, exencephaly (figure, A) and anophthalmia were observed. At the highest dose-level employed, 200 mg/kg methaqualone, fetuses were observed with anophthalmia and domed heads. In the group receiving continuous injections of 115 mg/kg methaqualone on days 1–19 of gestation and allowed to come to term, infants were born with facial hypoplasia and massive s.c. edema (figure, C). Deficient ossification of the sternum and double vertebral centra were observed in all methaqualone treated groups.

Discussion. These findings indicate that maternal administration of methaqualone can cause defects in the developing fetus, and that the probability of these defects rapidly increases with the dose-level employed. A dose of 25 mg/kg day, or less, has no apparent anatomical effect on the fetus[6]. Doses of 50 mg/kg day and higher cause a deficiency of ossification of certain skeletal centers[5]. At 100 mg/kg day fetal resorption rate increases, and at doses of 115 mg/kg day or higher, anomalies, including exencephaly and anophthalmia, are observed with increasing frequency. At these dose-levels, however, the incidence of maternal fatalities increases.



Fetuses from mothers treated with *A* 150 mg/kg day, or *B* 200 mg/kg day methaqualone on embryonic days 8–15, or *C* 115 mg/kg day methaqualone on embryonic days 1–19. Note: *A* exencephaly, *B* reduced fetal body size and *C* s.c. edema.