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Genetic Influences on Aspirin-Induced Exencephaly in two Mouse Strains

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ABSTRACT. Inbred adult SWR/J and C57BL/6J mice as well as their reciprocal crosses were used to investigate the teratogenic and other possible effects of Aspirin on foetuses of females treated once each day from day 7 to 12 of pregnancy. The prenatal administration of the drug at a dose level of 400 mg/kg body weight or higher has significantly increased foetal mortality. However, there were no significant differences between the two inbred strains in this respect, except at a dose level of 500 mg/kg, nor between the reciprocal crosses at all dose levels.

The prenatal administration of the drug has also increased exencephaly in foetuses of the C57 inbred strain at a dose level of 100 mg/kg or higher and in foetuses of C57 females x SWR male at a dose level of 500 mg/kg only. Foetuses of SWR inbred strain, as well as those of SWR females x C57 male appeared to be resistant to such inductive effects. Moreover, the prenatal administration of the drug at a dose level of 400 mg/kg or higher has significantly decreased foetal body weight in all mice used.

Salicylates (especially Aspirin or acetylsalicylic acid) have been widely used in human as excellent analgesics for over a century (Collins and Turner 1975). At the lowest doses, they are useful in preventing heart attacks and cerebral thrombosis (Weissmann 1991). They proved to have several other activities such as inhibition of ion transport across cell membranes, as well as the interference with white blood cells activation and the activation of genes that code for heat-shock proteins in the lampbrush chromosomes of *Drosophila* (Weissmann 1991). When administered prenatally during organogenesis, they proved to be teratogenic to several animal species including mice (Larsson *et al.* 1963, Obbink and Dalderup 1964, Trasler 1965, Larsson and Eriksson 1966, Eriksson 1971 and Szaba *et al.* 1971), rats (Warkany and Takacs 1959, Gulienetti *et al.* 1962, Goldman and Yakovac

1964, Baba *et al.* 1966, Takacs and Warkany 1968, Schardein *et al.* 1969, Amels and Sandor 1972, Tanaka *et al.* 1972, Woo and Hoar 1972, Lubawy and Garrett 1977 and Wilson *et al.* 1977), rabbits (Earley and Hayden 1964, McColl *et al.* 1967, Schardein *et al.* 1969 and Szaba *et al.* 1971), monkeys (Wilson 1971, Tanimura 1972 and Wilson *et al.* 1977) and hamsters (Lapointe and Harvey 1964). Nevertheless, comparative studies on teratogenic potentials of salicylates on various mouse strains are virtually non-existing.

Hence, an attempt is being made in the present study to investigate the teratogenic and other possible effects of Aspirin (Acetylsalicylic acid) in two inbred mouse strains as well as in their reciprocal crosses.

Materials and Methods

Normal adult inbred SWR/J (SWR) and C57BL/6J (C57) mice, maintained within a closed colony, were used. They were housed in plastic boxes in an environmentally controlled room with a light/dark cycle of 14/10 hrs. In each box, 3-5 nulliparous females were caged together with a single male in the following combinations: SWR females x SWR male (SWR x SWR), C57 females x C57 male (C57 x C57), SWR females x C57 male (SWR x C57) and C57 females x SWR male (C57 x SWR).

The commencement of pregnancy was determined by the detection of vaginal plugs in mated females, and the day the plug was observed was designated as day 0 of gestation. On day 7 through day 12 of pregnancy, the females were injected once daily intraperitoneally (ip) with 50, 100, 200, 300, 400 or 500 mg/kg Aspro (Aspirin brand of Nicholas Laboratories Ltd., Slough, England) in sterile normal saline. Control mice were injected with corresponding volumes of sterile normal saline alone. On day 17 of pregnancy, the mice were killed by cervical dislocation and the number of live foetuses and resorptions was noted. Each foetus was then examined macroscopically, both externally and internally for gross developmental abnormalities. Ten foetuses from each group were then cleared and stained according to the modification of Abou-Tarboush (1987) of the method of McLeod (1980) for skeletal examinations.

Data were statistically analysed using a student's t-test and a 2 x 2 contingency table (X^2) for the actual numbers obtained (Sokal and Rohlf 1969).

Results

The effects of Aspirin on foetuses obtained from pregnant mice are shown in Tables 1-6. The results demonstrated that the treatment of SWR x SWR group at a dose level of 200 mg/kg or higher has significantly increased the proportions of resorptions. At 400 mg/kg or higher, the treatment has also significantly decreased mean live foetal body weight (Table 1). On the other hand, the treatment of C57 x C57 group at 100 mg/kg or higher has resulted in exencephaly that has increased proportionally according to the dose level. At 400 mg/kg or higher doses, the proportions of resorptions have significantly increased, but the mean live foetal body weight has significantly decreased (Table 2).

The treatment of the reciprocal crosses with 400 mg/kg or higher doses has resulted significantly in increased proportions of resorptions. The drug at 300 mg/kg or higher doses has decreased mean live foetal body weight. However, a dose level of 500 mg/kg has increased the proportions of exencephaly in foetuses of C57 x SWR but not in those of the reciprocal cross (Tables 3 and 4). On the other hand, the two inbred strains reacted similarly to the embryotoxic effects of the drug at all dose levels, except at 500 mg/kg dose level where foetuses of C57 inbred strain seemed to be more affected. However, the treatment with 100 mg/kg or higher doses has increased the proportions of exencephaly in foetuses of C57 inbred strain (Table 5).

Table 1. Effect of Aspirin on foetuses taken on day 17 of pregnancy from SWR x SWR matings

Aspro dose (mg/kg)	No. of females	No. of implant. sites	No. of resorption (%)	No. of foetuses (Mean ± SE)	No. of live foetuses (Mean ± SE)	Live foetal body wt. in gms. (Mean ± SE)	Abnormalities observed (%)
Control	25	266	7(2.63)	10.64 ± 0.44	10.36 ± 0.47	0.95 ± 0.01	None
50	15	170	5(2.94)	11.33 ± 0.57	11.00 ± 0.61	0.92 ± 0.02	None
100	15	161	11(6.83)	10.73 ± 0.76	10.00 ± 0.86	0.93 ± 0.03	None
200	15	160	15(9.38)**	10.67 ± 0.67	9.67 ± 0.86	0.92 ± 0.02	None
300	15	163	14(8.59)*	10.87 ± 0.75	9.93 ± 0.61	0.92 ± 0.02	None
400	15	171	16(9.36)**	11.40 ± 0.49	10.33 ± 0.67	0.88 ± 0.03**	None
500	15	175	13(7.43)*	11.67 ± 0.78	10.80 ± 0.80	0.87 ± 0.02**	1 exen. (0.57)

* Statistically different from the control at $P < 0.05$
** Statistically different from the control at $P < 0.01$
exen. = exencephaly

Table 2. Effect of Aspirin on foetuses taken on day 17 of pregnancy from C57 x C57 matings

Aspro dose (mg/kg)	No. of females	No. of implant. sites	No. of resorption (%)	No. of foetuses (Mean ± SE)	No. of live foetuses (Mean ± SE)	Live foetal body wt. in gms. (Mean ± SE)	Abnormalities observed (%)
Control	25	188	10(5.32)	7.52 ± 0.44	7.12 ± 0.46	0.75 ± 0.02	2 exen. (1.06)
50	8	65	3(4.62)	8.13 ± 0.77	7.75 ± 0.86	0.74 ± 0.04	None
100	15	119	7(5.88)	7.93 ± 0.47	7.47 ± 0.44	0.72 ± 0.02	7 exen. (5.88)
200	15	125	8(6.40)	8.33 ± 0.61	7.80 ± 0.63	0.72 ± 0.02	6 exen. (4.80)
300	15	114	8(7.02)	7.60 ± 0.45	7.07 ± 0.53	0.72 ± 0.03	9 exen. (7.89)
400	15	124	15(12.10)*	8.27 ± 0.30	7.27 ± 0.35	0.69 ± 0.02*	13 exen. (10.48)
500	15	121	26(21.49)**	8.07 ± 0.43	6.33 ± 0.63	0.69 ± 0.02*	15 exen. (12.40) 2 abn. tail 3 abn. HL.

* Statistically different from the control at $P < 0.05$
** Statistically different from the control at $P < 0.01$
exen. = exencephaly abn. tail = abnormal tail abn. HL. = abnormal hindlimb

Table 3. Effect of Aspirin on foetuses taken on day 17 of pregnancy from SWR x C57 matings

Aspro dose (mg/kg)	No. of females	No. of implant. sites	No. of resorption (%)	No. of foetuses (Mean ± SE)	No. of live foetuses (Mean ± SE)	Live foetal body wt. in gms. (Mean ± SE)	Abnormalities observed (%)
Control	10	121	2(1.65)	12.10 ± 0.43	11.90 ± 0.43	0.96 ± 0.03	None
300	10	115	6(5.22)	11.50 ± 0.47	10.90 ± 0.44	0.87 ± 0.02**	None
400	10	112	15(13.39)**	11.20 ± 0.59	9.70 ± 0.58**	0.79 ± 0.05**	None
500	10	112	11(9.82)*	11.20 ± 0.63	10.10 ± 0.57*	0.81 ± 0.03*	None

* Statistically different from the control at $P < 0.05$
** Statistically different from the control at $P < 0.01$
exen. = exencephaly

Table 4. Effect of Aspirin on foetuses taken on day 17 of pregnancy from C57 x SWR matings.

Aspro dose (mg/kg)	No. of females	No. of implant. sites	No. of resorption (%)	No. of foetuses (Mean ± SE)	No. of live foetuses (Mean ± SE)	Live foetal body wt. in gms. (Mean ± SE)	Abnormalities observed (%)
Control	11	90	1(1.11)	8.18 ± 0.63	8.09 ± 0.64	0.87 ± 0.03	None
300	10	81	5(6.17)	8.10 ± 0.62	7.60 ± 0.69	0.79 ± 0.02**	None
400	11	90	11(12.22)**	8.18 ± 0.60	7.18 ± 0.97	0.72 ± 0.04**	None
500	12	98	14(14.29)**	8.17 ± 0.63	7.00 ± 0.82	0.75 ± 0.02**	4 exen. (4.08)

* Statistically different from the control at $P < 0.05$
** Statistically different from the control at $P < 0.01$
exen. = exencephaly

Table 5. Effect of Aspirin on foetuses taken on day 17 of pregnanvy from the two inbred strains of mice

Mating	Control	mg / kg Aspro					
		50	100	200	300	400	500
SWR x SWR							
No. of implantation sites	266	170	161	160	163	171	175
Resorptions (%)	7(2.63)	5(2.94)	11(6.83)	15(9.38)	14(8.59)	16(9.36)	13(7.43)
exencephalies (%)	0	0	0	0	0	0	1(0.57)
C57 x C57							
No. of implantation sites	188	65	119	125	114	124	121
Resorptions (%)	10(5.32)	3(4.62)	7(5.88)	8(6.40)	8(7.02)	15(12.10)	26(21.49)**
exencephalies (%)	2(1.06)	0	7(5.88)**	6(4.80)*	9(7.89)**	13(10.48)**	15(12.40)**

* $P < 0.05$ ** $P < 0.01$

Reciprocal crosses of the two strains behaved similarly to the embryotoxic effects of the drug and to the inductive effects of exencephaly at all dose levels used. However, foetuses of the C57 x SWR seemed to be more susceptible to induced exencephaly than those of SWR x C57 only at a dose level of 500 mg/kg (Table 6). The skeletal examinations have shown no abnormalities whatsoever. However, the drug was also observed to have other deleterious effects on 52 of the treated females and their foetuses prior to the killing of the females in the experiment and those females were not included in the tables.

Table 6. Effect of Aspirin on foetuses taken on day 17 of pregnancy from the two reciprocal crosses

Mating female male	Control	mg / kg Aspro		
		300	400	500
SWR x C57				
No. of implantation sites	121	115	112	112
Resorptions (%)	2(1.65)	6(5.22)	15(13.39)	11(9.82)
Exencephalies (%)	0	0	1(0.89)	0
Mean live foetal body wt.	0.96 ± 0.03	0.87 ± 0.02	0.79 = 0.05	0.81 ± 0.03
C57 x SWR				
No. of implantation sites	90	81	90	98
Resorptions (%)	1(1.11)	5(6.17)	11(12.22)	14(14.29)
exencephalies (%)	0	0	0	4(4.08)
Mean live foetal body wt.	0.87 ± 0.03*	0.79 ± 0.02**	0.72 = 0.04	0.75 ± 0.02

*P < 0.05 **P < 0.01

Discussion

The present study has clearly demonstrated the teratogenic, toxic and growth suppressing effects of Aspirin on the developing mouse embryos and foetuses whose mothers had been treated with the drug during gestation. The drug has also deleterious effects on some of the treated females, especially at doses of 300 mg/kg or higher. Similar to the observations of Warkany and Takacs (1959), Goldman and Yakovac (1964), Larsson and Eriksson (1966) and Takacs and Warkany (1968), Aspirin has increased the proportions of exencephaly, especially when administered at a dose level of 100 mg/kg or higher in foetuses of the genetically predisposed inbred C57 strain in a dose-response fashion, as well as in those of C57 x SWR but at a dose level of 500 mg/kg. However, foetuses of the other two groups were not affected. The presence of induced exencephaly in foetuses of C57 x SWR compared to those of SWR x C57 might suggest some maternal influences, one of the many factors that affect teratogenicity, since foetuses of the inbred SWR strain, as well as those of the latter group were not affected. Similar observations were made by Fraser *et al.* (1954) and by Goldstein *et al.* (1963) in cortisone-and 6-aminonicotinamide-induced cleft palate in mice, respectively. Furthermore, the present study also indicates that exencephaly in mice is not controlled by a single gene but,

instead there might be an interaction of multiple genetic, as well as environmental factors necessary, for the induction of the condition as has been suggested by Carter (1974).

Similar to the observations of Larsson *et al.* (1963), Goldman and Yakovac (1964), Obbink and Dalderup (1964), Trasler (1965), Larsson and Eriksson (1966), McColl *et al.* (1967), Schardein *et al.* (1969), Eriksson (1971), Collins and Turner (1975), Turner and Collins (1975), Lubawy and Garrett (1977) and Wilson *et al.* (1977), a significant increase in embryonic mortality, as measured by resorption per implantation site, was observed in the Aspirin-treated mice. Such effects were evident in SWR inbred strain at a dose level as low as 200 mg/kg, but doses of 400 mg/kg or more were needed to induce such effects in C57 inbred strain. Though, the differences between the two inbred strains were only significant at a dose of 500 mg/kg. On the other hand. there were no significant differences in the proportions of resorptions between the reciprocal crosses of the two inbred strains.

Moreover, the present results demonstrated that Aspirin exerts growth suppressing effects on surviving foetuses and such effects were more pronounced at a dose rate of 300 mg/kg or higher in inbred strains and the reciprocal crosses used. Though similar observations were already made (Earley and Hayden 1964, Goldman and Yakovac 1964, McColl *et al.* 1965, Larsson and Eriksson 1966, McColl 1966, McColl *et al.* 1967, Woo and Hoar 1972, Lubawy and Garrett 1977 and Wilson *et al.* 1977), yet the present results , demonstrate more clearly the many variations that exist in mouse strains under the influence of the same environmental components.

Among all foetuses examined in the SWR x SWR treated group (Table 1), only one foetus had exencephaly. The exact reasons for this are not completely Known. However, this could be brought about by several environmental factors, including maternal and foetal weights, litter size and the foetal implantation site. Of these, only the implantation site could be responsible. Since, the maternal and foetal weights as well as the litter size of the female were all in the normal range of the group. However, the malformed foetus was situated towards the cervical end of the uterus and such position might be an important factor brining about abnormality observed, as mouse foetuses situated at the ovarian end of the uterus were observed to be less subjected to the effect of teratogens than those situated towards the cervical end (Woollam and Millen 1962).

The teratogenic, toxic and growth suppressing effects observed with the drug could be a result of some of the many biochemical actions of salicylates that includes: altered protein synthesis, uncoupling oxidative phosphorylation, the depression or inhibition of mucopolysaccharides and prostaglandin sytehesis (Larsson *et al.* 1963, Larsson and Bostrom 1965, Larsson and Eriksson 1966, Eriksson 1971, Lubawy and Garrett 1977 and Weismann 1991).

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References

Abou-Tarboush, F.M. (1987) *Effects of Mitomycin-C on the incidence of Neural Tube Defects and Other Malformations in Mice with the Quinky Gene.* Ph.D. Thesis, Colorado State University, 160p. (Unpublished).

Amels, D. and **Sandor, S.** (1972) Multiphasic screening of some known teratogenic drugs. *Rev. Roum. Embryol.* **9:** 123.

Baba, T., Nagahoma, M., Akiyama, N. and **Miki, T.** (1966) Experimental production of malformations due to acetylsalicylate and Phenylsalicylate in rats. *Osaka City Med. J.* **12:** 23.

Carter, C.O. (1974) Clues to the aetiology of neural tube malformations. *Develop. Med. Child Neuro.* **16:** 3-15.

Collins, E. and **Turner, G.** (1975) Maternal effects of regular salicylate ingestion in pregnancy. *The Lancet.* **2:** 335-337.

Earley, P.A. and **Hayden, J.** (1964) Effects of acetylsalicylic acid on fetal rabbits. *The Lancet*, **1:** 763.

Eriksson, M. (1971) Salicylate-induced foetal damage during late pregnancy in mice: A comparison between sodium salicylate, acetylsalicylic acid and salicylsalicylic acid. *Acta Pharmacol. Toxicol.* **29:** 250-255.

Fraser, F.C., Kalter, H., Walker, B.E. and **Fainstat, T.D.** (1954) The experimental production of cleft palate with cortisone and other hormones. *J. Cell Comp. Physiol.* **43:** 237-259.

Goldman, A.S. and **Yakovac, W.C.** (1963) The enhancement of salicylate teratogenicity of maternal immobilizatlon in the rat. *J. Pharmacol. Exp. Therap.* **142:** 347-351.

Goldman, A.S. and **Yakovac, W.C.** (1964) Salicylate intoxication and congenital anomalies. *Arch. Envir. Hlth.* **8:** 648-656.

Goldstein, M., Pinsky, M.F. and **Fraser, F.C.** (1963) Genetically determined organ specific responses to the teratogenic action of 6-aminonicotinamide in the mouse. *Genet. Res. Camb.* **4:** 258-265.

Gulienetti, R., Kalter, H. and **Davis, N.C.** (1962) Amniotic fluid volume and experimentally-induced congenital malformations. *Biol. Neonate*, **3:** 300.

Lapointe, R. and **Harvey, E.B.** (1964) Salicylamide-induced anomalies in hamster embryos. *J. Exp. Zool.* **156:** 197-200.

Larsson, K.S. and **Bostrom, H.** (1965) Teratogenic action of salicylcates related to the inhibition of mucopolysaccharide synthesis. Acta Paediat. Scand. 54: 43-48.

Larsson, K.S., Bostrom, H. and **Ericson, B.** (1963) Salicylate-induced malformations in mouse embryos. *Acta Paediat. Scand.* **52:** 36-40.

Larsson, K.S. and **Eriksson, M.** (1966) Salicylate-induced fetal death and malformations in two mouse strains. *Acta Paediat. Scand.* **55:** 569-576.

Lubawy, W.C. and **Garrett, R.J.** (1977) Effects of aspirin and acetaminophen on fetal and placental growth in rats. *J. Pharmacol. Sci.* **66:** 111-113.

McColl, J.D. (1966) Teratogenicity studies. *Appl. Therap.* **8:** 48-52.

McColl, J.D., Globus, M. and **Robinson, S.** (1965) Effect of some therapeutic agents on the developing rat fetus. *Toxicol. Appl. Pharmacol.* **7:** 409-417.

McColl, J.D., Robinson, S. and **Globus, M.** (1967) Effect of some therapentic agents on the rabbit foetus. *Toxical. Appl. Pharmacol.* **10:** 244-252.

McLeod, M.J. (1980) Differential staining of cartilage and bone in whole mouse fetuses by Alcian Blue and Alizarin Red S. *Teratology*, **22:** 38-39.

Obbink, H.J.K. and **Dalderup, L.M.** (1964) Effect of acetylsalicylic acid on foetal mice and rats. *The Lancet*, **1:** 565.

Schardein, J.L., Blatz, A.T., Woosley, E.T. and **Kaump, D.H.** (1969) Reproduction studies on sodium meclofenamate In comparison to aspirin and phenylbutazone. *Toxicol. Appl. Pharmacol.* **15:** 46-55.

Sokal, R.R. and Rohlf, F.J. (1969) *Biometry: The Principles and Practice of Statistics In Biological Research.* W.F. Freeman and Company, San Francisco, 776p.

Szabo, K.T., Free, S.M., Birkhead, H.A., Kang, Y.J., Alston, E. and **Henry, M.** (1971) The embryotoxic and teratogenic effects of various agents in the foetal mouse and rabbit. *Toxicol. Appl. Pharmacol* **19:**371.

Takacs, E. and Warkany, J. (1968) Experimental production of congenital cardiovascular malformations in rats by salicylate poisoning. *Teratology* **1:** 109-118.

Tanaka, S., Kuwamura, T., Kawashima, K., Nakaura, S., Nagao, S. and **Omori, Y.** (1972) Effects of salicylic acid and acetylsalicylic acid on the foetus and offspring of rats. *Teratology* **6:** 121.

Tanimura, T. (1972) Effects of macaque embryos of drugs reproted or suspected to be teratogenic to humans. *Acta Endocrinol.* **166:** 293.

Trasler, D.G. (1965) Aspirin-induced cleft lip and other malformations in mice. *The Lancet* **1:** 606-607.

Turner, G. and **Collins, E.** (1975) Foetal effects of regular salicylate ingestion in pregnancy. *The Lancet* **2:** 338-339.

Warkany, J. and **Takacs, E.** (1959) Experimental productin of congenital malformations in rats by salicylate poisoning. *Amer. J. Pathol.* **35:** 315-331.

Weissmann, G. (1991) Aspirin: After more than 200 years, the mechanisms by which this venerable drug and its relatives achieve their wide range of effects have yet to be fully elucidated. *Scient. Amer.* **265:** 58-64.

Wilson, J.G. (1971) Use of rhesus monkeys in teratological studies. *Fed. Proc. Fed. Amer. Soc. Exp. Biol.* **30:** 104-109.

Wilson, J.G., Ritter, E.J., Scott, W.J. and **Fradkin, R.** (1977) Comparative distribution and embryotoxicity of acetylsalicylic acid in pregnant rats ,and rhesus monkeys. *Toxicol. Appl. Pharmacol.* **41:** 67-78.

Woo, D.C. and **Hoar, R.M.** (1972) Apparent hydronephrosis as a normal aspect of renal development in late gestation of rats: The effect of methlysalicylate. *Teratology* **6:** 191-196.

Woollam, D.H.M. and **Millen, J.W.** (1962) Influence of uterine position on the response of the mouse embryo to anoxia. *Nature* **194:** 990-991.

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التأثيرات الوراثية على تعرية المخ (Exencephaly) المستحدثة بواسطة الأسبرين في سلالتين من فئران التجارب

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استعملت في هذه الدراسة السلالتان النقيتان C57/BL/6J, و SWR/J من فئران التجارب وتزاوجاتهما العكسية لدراسة التشوهات الخلقية والتأثيرات السامة لعقار الأسبرين على الأجنة التي عولجت امهاتها بجرعات مختلفة من هذا العقار يومياً منذ اليوم السابع الى اليوم الثاني عشر من الحمل. ولقد كانت المعالجة مرة واحدة في اليوم. هذا وقد أوضحت الدراسة أن حقن العقار للأمهات خلال فترة الحمل وخاصة بالجرعتين ٤٠٠ و٥٠٠ مغم/كجم من وزن الجسم قد أدى إلى زيادة ذات دلالة معنوية في معدلات موت الأجنة في كل الفئرن المستخدمة، إلا أنه لا توجد اختلافات ذات دلالة معنوية بين السلالتين النقيتين (فيما عدا الجرعة ٥٠٠ مغم/كجم) أو بين التزاوجات العكسية المستخدمة فيما يتعلق بهذا التأثير. كما وأوضحت الدراسة أيضاً أن هذا العقار قد أدى الى زيادة ملحوظة في نسب تشوهات تعرية المخ (Exencephaly) في أجنة السلالة النقية C57 باستخدام الجرعات ١٠٠، ٢٠٠، ٣٠٠، ٤٠٠ و٥٠٠ مغم/كجم وفي أجنة التزاوج (ذكور X SWR إناث C57) عند الجرعة ٥٠٠ مغم/كجم فقط. إلا أن أجنة السلالة النقية الأخرى (SWR) وأجنة التزاوج (ذكور X C57 أناث SWR) يبدو انها مقاومة لمثل ذلك التأثير. وبالاضافة إلى ذلك فإن هناك انخفاضاً ذا دلالة معنوية في معدلات أوزان الأجنة في كل الفئران المستخدمة عند الجرعتين ٤٠٠ و٥٠٠ كغم/كجم. ان التأثيرات المشوهة والسامة والمثبطة للنمو المشاهدة في هذه الدراسة قد تكون نتيجة للتأثيرات الكيميائية الحيوية العديدة للأسبرين والتي منها تغيير عملية تصنيع

البروتينات وخفض أو ايقاف عمليتي تصنيع كلا من السكريات المخاطية المركبة والبروستاجلاندين.