poly C, like that of endotoxins, is enhanced when the mice are pretreated with lead acetate; poly I.poly C and endotoxin cross-protect against death when animals are challenged with homologous or heterologous substance; and poly I.poly C, like endotoxin, can provoke the local Schwartzmann phenomenon. Our results indicate that poly I.poly C further resembles endotoxins in that it is pyrogenic and causes a rapid and short-lived elevation in circulating interferon titre. These properties are dependent on its double-strandedness.

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Embryotoxic Effect of Poly I . Poly C

Polyriboinosinic : polyribocytidylic acid (poly I.poly C), a synthetic double stranded RNA, is an effective inducer of interferon[1]. Recently, poly I.poly C has shown activity against herpetic keratitis in rabbits[2,3] and other viral infections and against both viral and non-viral tumours in mice[4–7] and rats (R. H. Adamson, unpublished). Although the antiviral activity of poly I.poly C is probably due to induction or release of interferon, the mechanism of antitumour activity is not known. Among possible mechanisms are: (1) its ability to induce interferon; (2) its ability to enhance immunological responsiveness; or (3) to act as a synthetic messenger. If poly I.poly C acts via any of these mechanisms and, in particular, the latter two, it is probable that the compound also affects another rapidly growing tissue, the embryo. An additional reason for testing possible effects of poly I.poly C on the embryo is that recently reported effects on human respiratory viruses[8] suggest the possibility of a widespread clinical trial of this agent if other toxicological studies presently under way are not mitigating[7].

Virgin New Zealand white does were mated with proven bucks of the same breed and maintained with Purina rabbit chow and water *ad libitum*. Poly I.poly C was obtained from the Cancer Chemotherapy National Service Center of the National Cancer Institute. Two preparations of poly I.poly C were used in these experiments; the first preparation contained 10 mg of poly I.poly C in 10·8 ml. of 0·01 M buffered phosphate in 0·1 M KCl and the second preparation contained 10 mg in 10 ml. of physiological saline. No difference was noted in the embryotoxic effects of these two preparations. Poly I.poly C was injected subcutaneously in a small portion of the shaved right side of the rabbit at 1 or 2 mg/kg on days 8 and 9 or days 11 and 12 of pregnancy. These doses are equivalent to or less than the systemic doses used to protect against experimental viral infections[2,9] and correspond to one-fifth to one-tenth of the doses used for optimal antitumour activity in mice and rats on an mg/kg basis[4,7,8]. Control rabbits were injected with volumes of saline equivalent to the volumes used for poly I.poly C-treated rabbits. On the 28th day of pregnancy each doe was killed by intravenous injection of an overdose of sodium pentobarbital. The uterus was exposed, carefully opened, and the number of implantations, resorptions and foetuses was recorded. The viable foetuses were examined for external and internal gross abnormalities.

As can be seen from Table 1, poly I.poly C produced 100 per cent resorptions when given subcutaneously at the dose level of 2 mg/kg on days 8 and 9 of pregnancy. An embryotoxic effect was also evident when a dose of 1 mg/kg was used on days 8 and 9 or days 11 and 12. This treatment caused 80 per cent resorptions in the former case and 61 per cent of the implantations ceased to develop in the latter. Three animals out of twenty-six with gross malformations were also seen at the 1 mg/kg dose. In contrast to these results, only 7 per cent resorptions were seen in saline-treated animals, the normal rate of resorption in our colony. Also, two grossly malformed foetuses were seen among seventy-eight foetuses in the control group. Thus although poly I.poly C appears to be extremely embryotoxic in terminating pregnancy, the compound does not have high teratogenic properties at these doses in the rabbit in our experimental conditions.

Table 1. EMBRYOTOXIC ACTIVITY OF POLY I.POLY C IN THE NEW ZEALAND WHITE RABBIT

Treatment (subcutaneous)	Days of pregnancy treated	No. of does	Total No. of implantations	No. of resorptions	No. of normal foetuses	No. of malformed foetuses
Saline	8 and 9	12	84	6 (7%)	76	2
Poly I.poly C						
1 mg/kg	8 and 9	7	55	44 (80%)	9	2
1 mg/kg	11 and 12	5	39	24 (61%)	14	1
2 mg/kg	8 and 9	4	31	31 (100%)	0	0

Until the nature and species specificity of the embryotoxic effect of poly I.poly C are clarified, this compound should not therefore be used in women of child-bearing age. The results indicate that the mechanism of this marked embryotoxic effect is of fundamental importance. If poly I.poly C is embryotoxic by virtue of interferon induction, then rubella and other viruses may exert their known embryotoxic effects by this mechanism. If enhancement of immunological responsiveness by poly I.poly C is responsible for the termination of pregnancy, this compound may be of use in the treatment of choriocarcinoma. The possibility also exists that poly I.poly C or related agents may be of value in population control. A study of the embryotoxic mechanism of poly I.poly C and the effects of related polyanions is under investigation.

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