anism is not likely since detectable amounts of erythropoietin activity in the plasma and urine at any time post-infection were not observed. Moreover, there is no evidence to date that a virus can influence the production and/or release of a hormone.

Another possible mechanism is that the polycythemic virus *per se* initiates erythropoiesis independently of erythropoietin. If this be so, the polycythemic virus, like erythropoietin, is capable of enzyme induction in the stem cells, causing them to differentiate into proerythroblasts(9). The fact that the polycythemic virus caused an increase in proerythroblasts, erythroblasts, and reticulocytes, an increase in Fe_{59} uptake of the spleen, blood and, initially, in the bone marrow, without detectable erythropoietin activity in the plasma and urine, implies more favorably that the polycythemic virus acts directly upon hemopoietic precursor or stem cells independently of erythropoietin. The best way to resolve which postulation is correct is through the use of an anti-erythropoietin(10); however, our attempts to solve the problem in this way have been unsuccessful to date.

Summary. Like erythropoietin, a murine polycythemic virus can initiate erythropoiesis in a hypertransfused-polycythemic state. The mechanism by which this virus is able to do this is not known.

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Sensitization of the Mouse to Bradykinin.* (32147)

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Mice inoculated with a *Bordetella pertussis* phase I vaccine develop an enhanced susceptibility to a variety of agents and conditions such as histamine(1), serotonin(2), anaphylaxis(3), endotoxin(4), peptone(5), etc. The possible interrelationship of histamine and serotonin(6) and the suggestion that a plasma kinin(7) might play a role in systemic anaphylaxis prompted the following study of the sensitivity of the pertussis-treated mouse to bradykinin.

Materials and methods. Female Carworth Farm mice (CFW) of about 20 g weight were maintained on Purina Laboratory Chow with drinking water allowed *ad lib. B. pertussis* phase I cells, 6×10^9, in 0.5 ml volume were injected intraperitoneally (i.p.) into each mouse followed on the fourth subsequent day by intravenous (i.v.) inoculation of 0.4 mg of synthetic bradykinin† dissolved in 0.5 ml of saline solution.

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A second group of mice received 1 mg of the β-receptor adrenergic blockader, propanolol,‡ i.p. in 0.5 ml volume 10 minutes prior to the challenge with bradykinin. Groups of untreated mice serving as controls received an i.v. dose of either 0.4 mg or 0.8 mg bradykinin. The number of deaths was recorded after an additional 24 hours.

Results. The mortality rate of pertussis-treated mice was 8/12; there were no deaths in the control group at 0.4 mg and 2/10 at the 0.8 mg dose level. Calculated according to the method of Finney(8), the difference between the vaccinated and the control animals is highly significant, $p = <0.01$, whereas the difference between the 2 dose levels for the control mice is not significant, $p = >0.05$.

At the 0.4 mg level, bradykinin was 100% lethal to mice pre-treated with propanolol. The results then indicate that both the pertussis- and propanolol-treated mouse show an enhanced sensitivity to the lethal effects of bradykinin.

Discussion. The entire phenomenon of anaphylaxis in the mouse is very complex undoubtedly involving the participation of a number of pharmacologically active agents. Of these, the evidence implicating serotonin seems to be largely circumstantial(9,10,11); no increase in blood or lung serotonin was detected during systemic anaphylaxis(12). On the other hand, although the blood histamine level was significantly increased(9), its role in the reaction has been questioned(13). The concept has been advanced that the reaction is a result of the simultaneous release of histamine and serotonin with each strengthening the pharmacological effects of the other (6). A recent publication would appear to substantiate this suggestion(14).

The possibility that a plasma kinin might play a significant role in systemic anaphylaxis was suggested by the finding of a bradykinin-like activity in blood obtained during shock (7). The striking correlation between the circulatory collapse characterized by dilation of blood vessels and increased permeability of capillaries in anaphylaxis in the mouse(15) and the similar pharmacological effects of bradykinin(16) seems to point to an interrelationship. The above reported findings that pertussis-treatment, which enhances anaphylactic sensitization(3), and the ability of the β-adrenergic blocking agent, propanolol, to mimic the action of pertussis vaccine in the enhancement of sensitivity to bradykinin indicate such a relationship.

It is interesting to note that although histamine and serotonin are said to be released from degranulating mast cells which may be involved in the anaphylactic reaction(17), bradykinin is the result of the action of a kinin-forming enzyme(18) possibly released from lung tissue as a result of an antibody-antigen reaction on a plasma fraction(19). For the mouse, at least, the participation of plasma kinin as a mediator in systemic anaphylaxis needs to be considered further(20).

Summary. Pertussis-inoculation enhances the sensitivity of the white mouse to the lethal effects of bradykinin. The β-adrenergic blocking agent, propanolol, mimics the action of pertussis. The role of bradykinin in anaphylaxis is discussed.

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Effect of Maternal Administration of Dimethyl Sulfoxide on the Development of Rat Fetuses. (32148)

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Dimethyl sulfoxide (DMSO) has been widely used for inherent medicinal properties (1,2,3), and for enhancement of drug penetration through the skin(4); however, its embryocidal and teratologic properties have not been fully explored. Caujolle *et al*(5) did not provide data but reported that oral administration of DMSO to rats of both sexes at 5 g/kg/day for 4 days before coitus and then continued in the pregnant females throughout gestation did not noticeably interfere with fertility or development of the young. Abortions were subsequently obtained following administration of undefined doses of DMSO throughout pregnancy(6). Single intravenous injections of up to 12 g/kg to mice on undefined days of gestation significantly increased numbers of resorptions. Subcutaneous administration of 2 and 4 g/kg/day to the rabbit throughout gestation did not alter normal reproductive processes. Malformations were not observed in any of the above studies.

To test a possible teratogen in a given species an agent should be administered during the period of organogenesis at doses which do not affect the maternal organism but which would ideally result in partial loss of young (*e.g.*, fetal LD 50). If under these conditions no malformations result among the surviving offspring the agent is not likely to be teratogenic in the species tested(7).

The doses used to date in the rat were not large enough to be embryocidal and since the mammal may be able to adapt to the continued presence of a teratogen if administered in low dosage prior to the period of organogenesis(8) this study was initiated to determine whether malformations would result following an embryocidal dose of DMSO administered to the rat only during the period of organogenesis.

Methods. Forty mature Sprague-Dawley (C-D) female rats obtained from Charles River Laboratories were mated to males of the same strain. The controls received subcutaneous injections of distilled water (10 ml/kg/day) on Days 8, 9 and 10 of gestation (Day 1 being the day sperm were observed in the vaginal lavage). The remaining rats were administered DMSO† as a 90% aqueous solution on Day 8, Days 8 and 9, or on Days 8, 9 and 10 at 10.25 g/kg/day; one-half of the maternal LD 50 per injection as determined previously for the subcutaneous route(9). Body weights were recorded on Days 1, 8 and 19 of gestation. All female rats were killed on Day 19 by cervical dislocation and the reproductive status was determined. All live, dead and resorbed fetuses were weighed and the young examined for gross developmental abnormalities. The fetuses were then fixed in 70% ethanol prior to clearing to allow skeletal examination(10). A multiple range test(11) was applied for group comparisons.

Results. DMSO did not significantly alter maternal body weight gain, nor the weight of the live fetuses obtained on Day 19. No

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