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Effect of Pregnancy on Resistance to *Listeria monocytogenes* and *Toxoplasma gondii* Infections in Mice

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Studies of the effect of pregnancy on the capacity of mice to resist *Listeria monocytogenes* and *Toxoplasma gondii* infection revealed significantly diminished resistance of pregnant mice to infection by both agents as measured by mortality. The development of immunity to listeria was assessed by studying the kinetics of listeria growth in the livers and spleens of virgin and pregnant mice infected intravenously with a sublethal dose of listeria. In both virgin and pregnant mice there was a rise in the number of listeria colony-forming units per organ during the first 3 days after infection. Thereafter, there was a decline in colony-forming units in these organs in virgin mice but a persistence of listeria in spleens and livers of pregnant mice. Paradoxically, during the first 3 days after infection, listeria counts in spleens of virgin mice were significantly higher than those in pregnant mice. Nonspecific resistance to listeria conferred by chronic infection with *T. gondii* was significantly diminished in pregnant mice when measured by mortality and quantitative cultures of listeria in livers and spleens. These studies demonstrate a remarkably decreased resistance of pregnant mice to two intracellular organisms and a diminished capacity of pregnant mice to develop immunity to listeria. This decrease in resistance may play an important role in congenital transmission of these organisms.

Previous studies have revealed that depression of a number of cellular and humoral immune functions in both laboratory animals and humans is associated with pregnancy. Serum factors (12, 21, 22, 30, 48, 52, 54), lymphokines (1, 35), and various mononuclear cells (9, 28, 52, 58) of the fetus and the pregnant animal or human have been shown to cause depression of maternal mixed leukocyte culture (4, 9, 22, 28, 36, 48), lymphocyte proliferation to mitogens and antigens (3, 40, 59), and in vitro generation of cytotoxic T cells (11, 48) and immunoglobulin production (52). Transfer of spleen cells from multiparous pregnant mice resulted in suppression of rejection of skin (50) and tumor allografts (10).

Because of these findings, we considered it of interest to determine whether suppression of different parameters of the immune response during pregnancy has an effect on resistance to infection during gestation. Our studies have revealed a profound increased susceptibility to certain intracellular pathogens which are important causes of congenital infection.

MATERIALS AND METHODS

Mice. Male and female mice of the Swiss Webster strain (obtained from Simonsen Laboratories, Gilroy, Calif.) were used. Female mice were mated at approximately 7 weeks of age, except in those experiments in which chronically infected mice were used. In the latter case, the mice were mated at approximately 14 to 16 weeks of age. Time of onset of pregnancy was ascertained by mating mice for a maximum of 4 days and examining them for the presence of a postcoital plug after the second day. Pregnant mice were used for experiments at 14 to 16 days of gestation and were age matched with virgin mice. The pregnant mice all had palpable fetuses. All mice that died during an experiment were necropsied to confirm pregnancy. Pregnant mice were evaluated daily for mortality, evidence of abortion, or delivery of viable offspring.

Listeria monocytogenes. The strain of *L. monocytogenes* used, originally obtained from George Mackaness, was grown in Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.). Inocula were prepared by growing cultures for 18 h at 37°C, followed by centrifugation at 9,000 × *g* for 15 min and then resuspension of the organisms in Trypticase soy broth. Samples were frozen in 1-ml aliquots at −70°C until used for inoculation. At different intervals during the study period, it was determined that the number of organisms remained constant in the frozen specimens. Appropriate dilutions of the thawed preparations were made in Hanks balanced salt solution. Mice were infected intravenously (i.v.) with varying doses of listeria in a volume of 0.2 ml. The significance of differences in mortality was evaluated by Fisher's exact test.

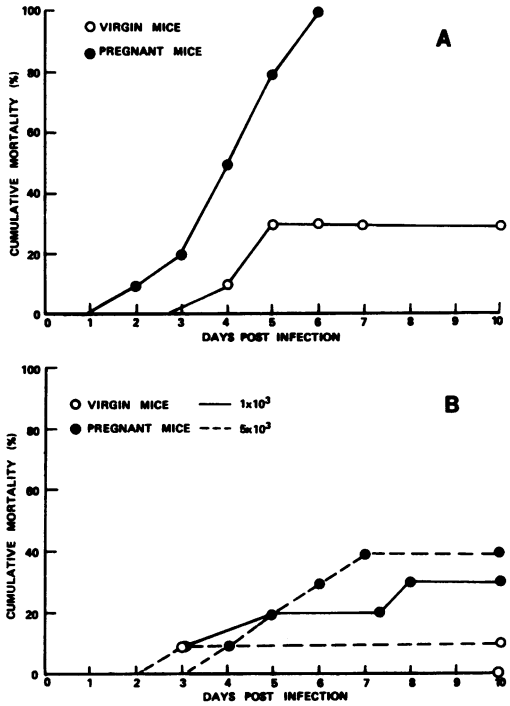

FIG. 1. (A) Increased susceptibility of pregnant (14 to 16 days) mice after i.v. challenge with 5×10^4 listeria (10 mice per group) ($P < 0.002$ at day 6). (B) Susceptibility of pregnant (14 to 16 days) and virgin mice after i.v. challenge with 1×10^4 or 5×10^3 listeria (10 mice per group).

Toxoplasma gondii. Tachyzoites of the C37 strain of *T. gondii* were prepared as previously described (53). Mice were challenged i.v. or subcutaneously with a volume of 0.2 ml of Hanks balanced salt solution containing varying numbers of tachyzoites. Mortality was recorded daily in each group and, the significance of differences in mortality was evaluated by Fisher's exact test.

Determination of listeria CFU in spleen and liver. The method used was essentially that described by Mackaness (26). The significance of differences in colony-forming units (CFU) in livers and spleens was evaluated by using the Student's *t* test.

RESULTS

Effect of pregnancy on susceptibility to listeria. When normal pregnant mice and virgin control mice were infected with listeria, there was significantly greater mortality in the pregnant mice. In Fig. 1A and B are the results obtained in one of two experiments performed. Both experiments yielded similar results. In the experiment in which the i.v. inoculum contained 5×10^4 listeria, 100% of the pregnant mice had died by day 6 whereas only 30% of the virgin mice had died by this time ($P < 0.002$). The first deaths occurred on day 2 in the pregnant mice; virgin mice did not begin dying until day 4. Lower doses (1×10^4 and 5×10^3) of listeria also resulted in greater mortality in the pregnant animals (Fig. 1B), but the differences were not significant ($P > 0.05$). However, when the data

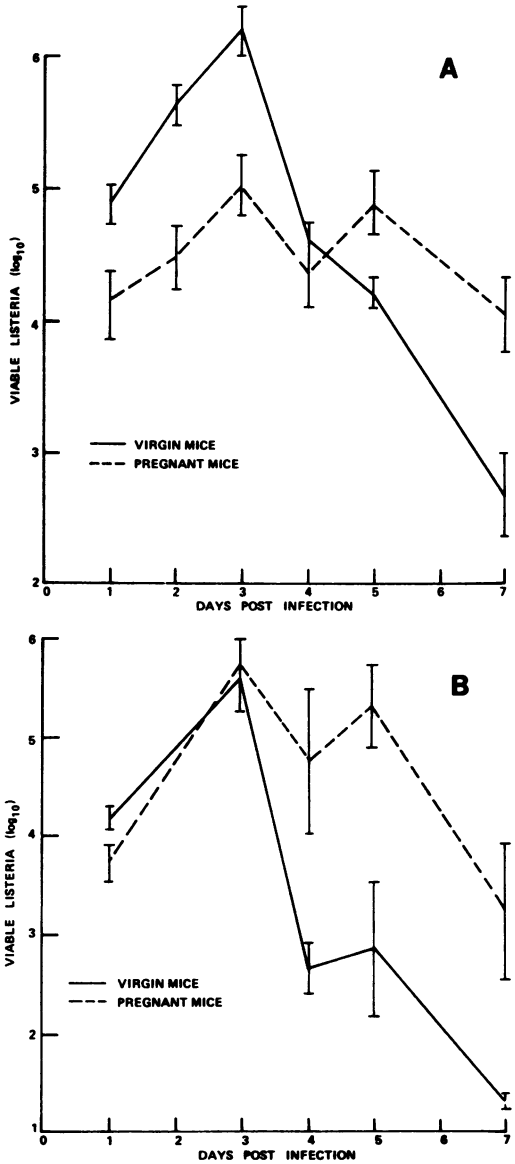

FIG. 2. (A) Growth of listeria in spleens of pregnant mice after i.v. challenge with 2×10^3 listeria. Each point represents the mean and each bar represents the standard error of the mean of the CFU from three mice ($P < 0.05$, day 1; $P < 0.05$, day 3; $P < 0.02$, day 5; and $P < 0.01$, day 7). (B) Growth of listeria in livers of pregnant mice after i.v. challenge with 2×10^3 listeria. Each point represents the mean and the standard error of the mean of the CFU from three mice ($P < 0.05$, day 4; $P < 0.02$, day 5).

TABLE 1. Listeria growth in the spleens and livers of virgin and pregnant mice

Mouse characteristics	Listeria inoculum (CFU)	Organ cultured	Time after infection of organ culture (h)	CFU per organ ± SD[a]		P
				V	P	
Toxoplasma infection	1×10^5	Spleen	240	3	5.32 ± 0.87	0.005
	1×10^5	Liver	240	3	6.92 ± 1.89	0.02
	5×10^5	Spleen	48	5.77 ± 0.14	6.45 ± 0.04	0.001
	5×10^5	Liver	48	5.70 ± 0.07	7.97 ± 0.04	0.0001
Normal	2×10^6	Spleen	4	5.03 ± 0.22	4.62 ± 0.13	0.05
	2×10^6	Liver	4	5.44 ± 0.04	5.48 ± 0.10	NS[b]

[a] For the mice with toxoplasma infection, V is virgin mice and P is pregnant (14 to 16 days) mice chronically infected with strain C37 of *T. gondii* (three mice per group). For the normal mice, V is virgin mice and P is pregnant (14 to 16 days) mice (three mice per group).

[b] NS, Not significant.

obtained with the two lower doses were pooled, the differences were significant ($P = 0.02$).

Pregnant mice that died were necropsied to define the status of their pregnancy. Of the 10 mice that had received 5×10^4 listeria, only 1 had fetuses in utero at the time of death. All of the others had aborted. Similar results, although not as pronounced, were noted in pregnant mice that had received the two lower doses of listeria. The total number of viable offspring of those mice that received the lower inocula was significantly less than the number of offspring we (and the supplier) observed in normal uninfected mice (average of 1.7 pups per live infected pregnant mouse versus an average of 10 pups per uninfected pregnant mouse).

Livers and spleens were obtained from the mice that died on days 3 to 10 after infection. The mice were known to have died within 3 h of necropsy and organ removal. The numbers of organisms in the livers of the pregnant mice did not decrease below that observed in livers of virgin controls necropsied on day 3. In contrast, the numbers of organisms in spleens of 8 of 11 pregnant mice were markedly lower than those of control mice. To study this further, we followed the kinetics of the growth of listeria in livers and spleens of pregnant and virgin mice infected i.v. with 2×10^3 organisms (Fig. 2A and B). This dose was not lethal for virgin mice. Three (15%) of the twenty pregnant mice died during the course of the experiment and are not included in the results. In virgin mice, there was a rise in the number of CFU per organ during the first 3 days after infection and a decline in CFU thereafter. At the different time intervals, the numbers of CFU in the spleens and livers of virgin animals were generally comparable. These results contrast with the rise in the number of CFU per organ observed in pregnant mice during the first 3 days after infection. The rise in CFU in spleens of pregnant mice during the initial 3 days was observed in each of the three experiments performed; in two of the experiments, the rise from day 1 to day 3 was significant ($P < 0.01$), but in the third, it was not. During the first 72 h after infection there was a significantly higher number of CFU in spleens of virgin mice compared with pregnant mice in all three experiments. After 3 days, there was a significant difference between CFU in livers and spleens of pregnant and virgin mice. In pregnant mice, listeria persisted for longer periods than in virgin mice, manifested by a higher number of CFU per spleen at day 5 ($P < 0.02$) and day 7 ($P < 0.01$) and a higher number of CFU per liver at day 4 ($P < 0.05$) and day 5 ($P < 0.02$) in the pregnant mice. At 5 and 7 days, numbers of listeria in the livers of pregnant mice were not significantly lower than the numbers found at days 1 through 4. Similar differences were observed in mice infected i.v. with 5×10^3 organisms.

In a separate experiment performed to ascertain whether the differences we observed on different days were present earlier postinfection, we examined pregnant and virgin mice at 3 h after an i.v. inoculation of 2×10^6 listeria (Table 1). As was observed on days 1 through 3 postinfection, at 3 h, pregnant mice had lower CFU per spleen than did virgin controls ($P = 0.05$); there was no difference in the counts in the livers between the two groups.

Effect of pregnancy on the nonspecific resistance to infection which is conferred in normal mice by infection with *T. gondii*. Chronic infection with toxoplasma confers upon mice a nonspecific resistance to unrelated intracellular organisms (44–46). Investigation of the effect of pregnancy on this resistance in mice chronically infected with the C37 strain of *T. gondii* revealed that the chronically infected pregnant mice were remarkably more susceptible to infection with listeria than were their chronically infected virgin counterparts. As can be seen in Fig. 3, pregnant mice had a mortality of 100% by day 5

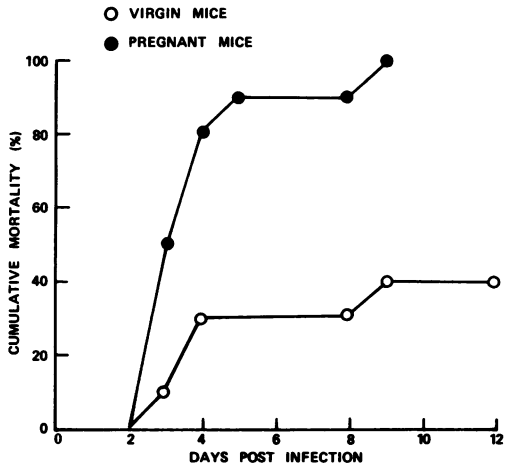

FIG. 3. Increased susceptibility of pregnant (14 to 16 days) mice that had been chronically infected with the C37 strain of *T. gondii* and challenged i.v. with 5×10^5 listeria ($P < 0.001$).

versus a 40% mortality in their virgin counterparts ($P < 0.001$). The time to death was also shorter among the pregnant mice. Results were similar in the two experiments performed.

In Table 1 are the results of quantitative cultures of listeria in livers and spleens of mice chronically infected with toxoplasma which were challenged i.v. with either 1×10^5 or 5×10^5 listeria. In the mice that received 5×10^5 organisms, numbers of CFU were significantly elevated at 48 h in the spleens and livers of pregnant mice compared with virgin controls (spleen, $P < 0.001$; liver, $P < 0.0001$). The mortality of these mice is shown in Fig. 3. Quantitative cultures 240 h after the initial infection with 10^5 listeria revealed marked and significantly elevated CFU in livers and spleens of pregnant mice compared with their virgin counterparts (Table 1) (spleen, $P < 0.005$; liver, $P < 0.02$). From these results, there appears to be a correlation between the higher CFU in livers and spleens of pregnant mice and their higher mortality (among nine pregnant mice that received 10^5 listeria, two died during the experiment. Only one of the seven surviving mice gave birth to viable offspring).

Effect of pregnancy on susceptibility to *T. gondii*. Pregnant mice had strikingly and significantly increased susceptibility to infection with the C37 strain of *T. gondii*. On day 10 post-i.v. challenge with 10^5 organisms (Fig. 4A), 100% of pregnant mice had died versus 20% mortality in the virgin controls. By the 16th day there was 40% mortality among the virgin mice ($P < 0.001$). When pregnant and virgin animals were infected subcutaneously with 5×10^5 organisms (Fig. 4B), at day 9, there was 100% mortality among pregnant mice versus 22% mortality among virgin mice ($P < 0.0001$). Chronically infected pregnant and virgin mice did not die after i.v. or subcutaneous challenge with 10^7 tachyzoites of the virulent RH strain of *T. gondii*. All (100%) of the control uninfected mice died within 5 days after infection with this dosage of the RH strain.

DISCUSSION

The results described above demonstrate that pregnancy results in increased susceptibility to both facultative and obligate intracellular organisms. *L. monocytogenes* and *T. gondii* were chosen for our studies because they can cause congenital infection in humans and animals, because the immune response to both organisms has been well characterized in a murine model, and because we wished to investigate the effect of pregnancy on resistance to infectious agents which are representative of a variety of other intracellular infectious agents of humans. In the case of listeria, cell-mediated immunity has been demonstrated to be the sole mechanism of resistance to the primary infection in the murine

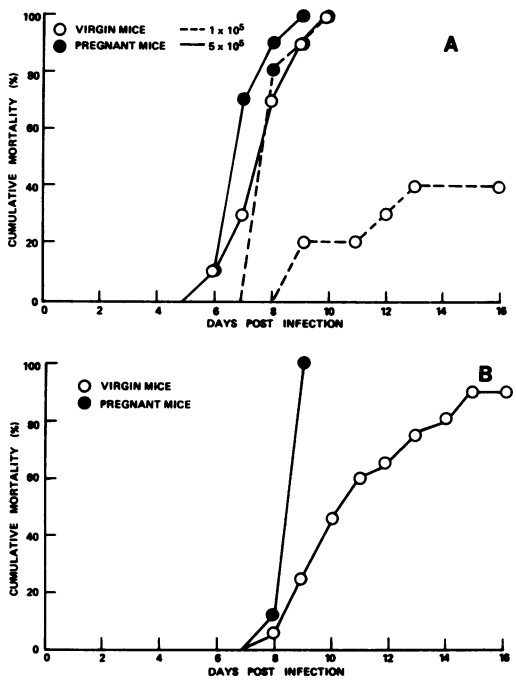

FIG. 4. (A) Increased susceptibility of pregnant (14 to 16 days) mice after i.v. challenge with 5×10^5 or 1×10^5 tachyzoites of the C37 strain of *T. gondii* (10 mice per group) (1×10^5, $P < 0.001$). (B) Increased susceptibility of pregnant (14 to 16 days) mice after subcutaneous challenge with 5×10^5 tachyzoites of the C37 strain of *T. gondii* (18 to 20 mice per group) ($P < 0.0001$ at day 9).

model (5, 25, 26, 33, 34). Recovery from primary infection with toxoplasma, however, appears to depend on both cell-mediated and humoral immunity (41); whereas listeria causes an intracellular infection only in cells of the reticuloendothelial system, toxoplasma infects all mammalian cell types except nonnucleated erythrocytes.

We specifically chose the third trimester to infect the mice because at this time the presence or absence of pregnancy can be established by abdominal palpation. In addition, it is the time during gestation when depression of both cellular (9, 11, 40) and humoral immune parameters (52) has been demonstrated in mice and humans. Suppressor T cells and monocytes, as well as soluble factors, have been identified which modulate this suppression. We considered it important to investigate whether this suppressor activity could affect the host's response to infectious agents which cause maternal and congenital disease. In our studies, the mortality rate in pregnant mice after primary infection with listeria and *T. gondii* was significantly greater and death occurred earlier than in virgin mice. Of interest was the finding of a high rate of abortion in those infected pregnant mice that survived. One may postulate that in such a situation abortion functions to protect the pregnant animal by ridding it of the cause of its immunosuppression. Studies performed in both humans and mice have demonstrated that the fetus and neonate possess suppressor cells which have the capacity to inhibit maternal lymphocytes in mixed leukocyte reactivity (14, 35–38) and B-lymphocyte differentiation and immunoglobulin production (19, 20, 29). It would be of interest to determine whether these suppressor cells play a role in the increased susceptibility to infection that we observed.

The kinetics of listeria growth in primary listeria infection in mice has been well delineated (5, 25, 26, 33, 34). After initial i.v. inoculation of the organism, the liver clears approximately 90% of the organisms, and remaining bacteria are cleared by the spleen. Within 12 h after the inoculation, approximately 50% of the organisms are destroyed, principally by the Kupffer's cells of the liver. This initial resistance is T-cell independent and represents innate resistance of the animal to listeria. After this initial killing of the organisms, the remaining bacteria proliferate in macrophages of the livers and the spleens of infected mice for 48 to 72 h. During this time, the host develops T-cell-dependent acquired immunity, with activation of macrophages and, thereby, control of the infection.

In our experiments on the kinetics of growth of listeria in the livers and spleens of virgin and pregnant mice, we noted an increase in listeria CFU during the first 3 days after infection in both groups of mice. Thereafter, listeria persisted in significantly higher numbers in the spleens and livers of the pregnant mice than of virgin mice. This persistence most likely indicates that pregnancy causes a decrease in the ability to develop the T-cell-dependent activation of enhanced macrophage antibacterial function so essential for resistance to listeria infection. Paradoxically, during the first 3 days of infection, there were significantly fewer listeria in spleens of pregnant mice than in spleens of virgin mice. This difference was demonstrable as early as 3 h after infection and for 72 h thereafter. One possible reason for this decreased number of listeria CFU in the spleens of pregnant mice compared with virgin mice during the first 72 h of infection, followed by persistence of the organisms in the livers and spleens of pregnant animals during the latter course of the infection, might be that the bactericidal activity of the splenic macrophage is non-specifically heightened in order to compensate for a diminished T-cell-mediated immune responsiveness. Splenic macrophages may be partially activated as a result of hormonal changes which occur during pregnancy or as a result of a persistent low-grade immunogenic stimulation from the presence of the fetus. It is well established that during pregnancy a cell-mediated immune response develops which is directed against embryonic and paternally inherited fetal histocompatibility antigens (42, 49). There have also been reports of maternal development of antibodies to fetal histocompatibility antigens as well as reports of circulating immune complexes containing a presumed placental or fetal antigen (2, 27). An alternative explanation might be that during pregnancy the capacity of splenic macrophages to phagocytose this organism decreases. Support for this concept comes from observations of a serum factor described in pregnant women which has the capacity to inhibit phagocytosis of *Staphylococcus aureus* by normal polymorphonuclear leukocytes (39). Data pertaining to macrophage activity in the reticuloendothelial system of pregnant mice are scant and conflicting, with some authors claiming increased phagocytosis (47) and others decreased phagocytosis (31) by the reticuloendothelial system. Another possible explanation for the decrease in listeria CFU during the initial period of infection in pregnant mice may be that during pregnancy there is a decreased blood flow to the spleen as a result of shunting of the blood away from the spleen or as a result of impingement on the spleen by the enlarging uterus.

Mice chronically infected with toxoplasma are remarkably resistant to infection with listeria

and other phylogenetically unrelated organisms (44–46), due to the fact that the infection results in populations of macrophages which have markedly enhanced (45), but nonspecific (46), microbicidal activity. In the present study, pregnant mice chronically infected with *T. gondii* had a significantly diminished capacity to resist infection with listeria when compared with age-matched chronically infected virgin mice. This may reflect that during gestation there is a generalized suppression of the cell-mediated immune system which might depress the activity of the lymphocyte population necessary to maintain macrophages in an activated state. Reports which demonstrate significant depression of lymphocyte transformation in response to various antigens during the latter part of pregnancy (3) support this suggestion. Alternatively, the pregnant state may directly affect macrophage function independent of any effect on T cells.

When pregnant mice chronically infected with toxoplasma were reinfected with a high dose of virulent toxoplasma, there was no mortality. In contrast, chronically infected pregnant mice all died after challenge with an inoculum of listeria that was a 20% lethal dose for chronically infected virgin mice and a 100% lethal dose in normal mice. Thus, pregnancy profoundly altered the nonspecific resistance to listeria conferred by toxoplasma infection but did not appear to suppress resistance to the homologous infecting organism, *T. gondii*. These results suggest that specific immunity is more important than nonspecific resistance against intracellular pathogens during pregnancy.

In studies designed to define the mechanism(s) underlying the increased susceptibility to infection which we observed in pregnant mice, we have recently demonstrated that peritoneal macrophages from pregnant mice have a diminished capacity to become fully activated when stimulated by an intraperitoneal injection of *Corynebacterium parvum* (Luft and Remington, manuscript in preparation). This was assessed in assays which measure the ability of the macrophage to kill or inhibit the intracellular replication of *T. gondii* (53). We found that macrophages from pregnant animals activated with *C. parvum* had the ability to inhibit intracellular multiplication of *T. gondii*, but a strikingly and significantly diminished capacity to kill the organism. This represents an intermediate level of macrophage activation.

Of interest in this regard is the observation that estrogens and corticosteroids, which are elevated during pregnancy, may suppress resistance to infection. Mice treated with high doses of hexoestrol and thereafter infected with toxoplasma had evidence of more severe infection than did control mice. This was reflected in increasing numbers of cysts in the brains and other organs (23). High doses of cortisone have been shown to provoke a necrotizing encephalitis in mice chronically infected with toxoplasma (16) and can prolong parasitemia in these animals (51).

Previous studies of the effect of pregnancy on the resistance to infection demonstrated that pregnancy results in an increased susceptibility to *Plasmodium berghii* and to certain viruses. Studies of the effect of pregnancy on chronic *P. berghii* infection revealed that during gestation there was a significant increase in recrudescence of the infection. The proportion of animals in which recrudescence of malaria was observed was dependent on the strain of mice employed, as was the mortality due to recrudescence (56). In experiments with viral agents, Knox noted a greater susceptibility in pregnant mice to poliovirus, and this susceptibility increased as gestation progressed (24). In another study, Byrd noted that the incubation period of the Lansing strain of poliovirus was shorter in pregnant than in nonpregnant animals (6). Similarly, increased susceptibility has been reported in pregnant mice infected with coxsackievirus (13), foot-and-mouth disease virus (7), and encephalomyocarditis virus (15). In humans, pregnancy has been associated with an enhanced susceptibility to poliomyelitis (57). During the influenza epidemics of 1918–1919 and 1957, pregnancy was associated with a higher mortality (18). However, increased severity of influenza infection in pregnant women has not been documented in recent influenza outbreaks (8). Pregnancy has also been associated with an increased incidence of asymptomatic excretion of cytomegalovirus from the cervix as well as depressed lymphocyte responsiveness to cytomegalovirus in women who had serological evidence of previous infection with cytomegalovirus (43). This was particularly evident in women who gave birth to congenitally infected children. Diminished lymphocyte responsiveness persisted for up to 1 year postpregnancy (17). Depression of lymphocytotoxic activity against rubella-infected target cells was found in pregnant patients with serological evidence of previous rubella infection compared with nonpregnant controls (55).

Our findings in mice reported here, along with the results of other investigators discussed above, raise the question as to whether a defect in cell-mediated immunity associated with pregnancy may decrease the resistance of the pregnant individual and serve as a significant factor in determining the incidence, severity, and outcome of maternal and congenital infection. Further studies are now in progress in our laboratory to compare the phagocytic and microbicidal activity of nonactivated and activated macro-

phages in pregnant and virgin mice. In particular, attempts to study lymphocyte function of pregnant mice and the ability of lymphocytes to activate macrophages will be important to understand the defect in immunity which may affect congenital transmission of intracellular pathogens.

ACKNOWLEDGMENTS

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