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Transfer of Antibody against *Borrelia duttonii* from Mother to Young in ddY Mice

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The route of transfer of anti-*Borrelia duttonii* antibody subclasses from mother to young and their role in protection against borrelial challenge infection in ddY mice were investigated. Offspring from infected and noninfected mice were segregated and nursed by noninfected or infected mothers. Enzyme-linked immunosorbent assay analysis of antibodies of the cross-suckled offspring revealed that anti-*B. duttonii* immunoglobulin G1 (IgG1) is transferred exclusively in milk and that IgG2a is transferred mainly in milk but also slightly through the yolk sac route. On the other hand, IgG3 is transferred mainly through the yolk sac route but also slightly in milk, whereas IgG2b is transferred through both routes but to a lesser extent. Anti-borrelial IgM was not detected in any offspring. The protective role of transferred IgG subclasses was examined by challenge infection with *B. duttonii*. Offspring from noninfected mice fed by infected mothers had IgG1, IgG2a, and IgG3 at challenge and were completely protected against the challenge infection. On the other hand, offspring from infected mice fed by noninfected mothers had only IgG3, and 8 of 10 were completely protected from challenge infection whereas the other 2 contracted slight and transient spirochetemia. These findings suggested that anti-borrelial IgG3 alone has considerable protective activity and that IgG1, IgG2a, or both, either by themselves or together with IgG3, have a complete protective activity against borrelial infection.

Borrelia duttonii, a causative agent of human relapsing fever, is still prevalent in Africa (10). Mice show a high susceptibility to *B. duttonii* and have long been used as an animal model, allowing scientists to study the immunology of this bacterium (3, 13, 22). Many microbiologists have been interested in the mechanism of the relapse, the characteristic clinical feature of relapsing fever. During this century, it has been established that the humoral immunity plays the most important role in protection against the disease and that the mechanism responsible for the relapse is due to the antigenic variation of the borreliae (4). It is also known that certain humoral immune responses are restricted to particular immunoglobulin G (IgG) subclasses (5, 8, 12, 23, 35) and that each subclass has particular functions in mice (11, 24). Recently several authors demonstrated that particular IgG subclasses are involved in protection against infection by the Lyme disease borrelia, *B. burgdorferi*, in mice and hamsters by artificial passive transfer of monoclonal antibodies (27) or polyclonal antibodies purified by gel permeation chromatography (28). However, the response and protective role of each IgG subclass in mice infected with *B. duttonii* are still unclear.

On the other hand, it has been reported that among Igs, the IgG class is transported from mother to young via the yolk sac and the postnatal intestine (milk) in mice and rats and that certain IgG subclasses are selectively transported (7, 11, 24, 31). However, no data are available regarding the route of transfer and the protective role of Ig subclasses against *B. duttonii*. In the early part of this century, Nohira reported that the offspring of rats immune to relapsing fever had considerable immunity and claimed that the antibodies were transferred through the placenta (22). However, he did not mention the intestinal route. If the anti-*B. duttonii* IgG subclasses are transported selectively through either the yolk sac or the postnatal intestinal route in mice, their role in protection might be determined by observing the immune status of healthy offspring born of mothers or fed by mothers which had had relapsing fever just before or during pregnancy.

In this study, we investigated the response of *B. duttonii*-specific IgM and IgG subclasses in ddY mice, the route of the transfer from mother to young, and the protective role of the transferred antibody.

MATERIALS AND METHODS

Bacteria. *B. duttonii* 406K has been maintained in this laboratory for more than 15 years by mouse passage at intervals of 3 days. One drop of blood from infected mice was obtained by cutting the tail tip and diluted in 0.5 ml of phosphate-buffered saline (pH 7.4) (PBS) containing 0.4% sodium citrate, and 0.2 ml of the diluted sample containing 10^5 to 10^6 borreliae was intraperitoneally injected into mice to cause infection.

Animals. Adult male and female mice (20 to 25 g) of the Sea ddY strain (closed colony; Seiwa Experimental Animals, Ltd., Fukuoka, Japan) were used in the experiments.

Offspring regeneration. We collected 50 μl of blood by cardiac puncture from a mouse 3 days after infection, diluted it in 0.95 ml of PBS–0.4% sodium citrate in a disposable plastic syringe, and counted borreliae in a Thoma hemocytometer with a 0.02-mm-deep chamber (Nichirin, Tokyo, Japan) under dark-field microscopy. The sample was diluted to produce a suspension of 3×10^3 organisms per ml. To obtain offspring from infected mice, five female mice were inoculated intraperitoneally with 0.2 ml of the inocula containing 6×10^2 borreliae. After 5 days of infection, when the first peak of spirochetemia was almost over, male mice were provided for impregnation. At the same time, male mice

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were provided separately to five noninfected female mice for impregnation.

Segregation of offspring. The offspring from infected and noninfected mice were segregated immediately after delivery into the following four groups for feeding for 4 weeks. In group 1, the offspring from the infected mice were fed by their own mothers; in group 2, the offspring from the noninfected mice were fed by infected mothers; in group 3, the offspring from the infected mice were fed by noninfected mothers; and in group 4, the offspring from the noninfected mice were fed by their own mothers.

Challenge infection and determination of spirochetemia. Offspring at the age of 5 weeks, as well as the mother mice, were challenged intraperitoneally with 0.2 ml of inoculum containing 100 borreliae. After the challenge infection, we tested mice for spirochetemia daily for 2 weeks by taking one drop of blood from the tail tip of every mouse, mounting it on a glass slide, and observing it under dark-field microscopy.

Assays of antibody titers in classes and subclasses. To determine antibody titers, duplicate 10-μl samples of blood were collected from the cut tail tip by using a disposable lambda pipette (Becton Dickinson and Co., Parsippany, N.J.) on the first day of the indicated week and diluted in 190 μl of PBS–0.4% sodium citrate. Blood samples from the offspring just after delivery were collected by cardiac puncture.

Antibody titers were measured by the enzyme-linked immunosorbent assay (ELISA) procedure as follows. The antigen used was sonicated cells of *B. duttonii* 406K cultivated in an in vitro system recently developed by the authors (16). Microtiter plates (96 wells; Nunc Inc., Roskilde, Denmark) were coated with the antigen (5 μg of protein per ml) and blocked with 1% bovine serum albumin in PBS. Then serial twofold dilutions of test sera were added to the wells and incubated at room temperature for 4 h for IgM titer determination or at 4°C overnight for IgG subclasses. After the wells had been washed with 0.05% Tween 20 in PBS, diluted rabbit antiserum specific for the mouse IgM or IgG subclass and labeled with peroxidase was added to each well. We used a 1:500 dilution of anti-mouse IgM, IgG1, IgG2a, and IgG3 and a 1:1,000 dilution of anti-mouse IgG2b (Zymed Laboratories Inc., San Francisco, Calif.). Plates incubated for 1 h at room temperature were washed with 0.05% Tween 20 in PBS, and 100 μl of a solution containing 0.1% 2,2′-azino-di-(3-ethylbenzthiazoline sulfonate) and 1 mM H_2O_2 was added to each well. After 1 h at room temperature, the A_{415} was determined by using a microplate reader (no. MTP 32; Corona Electric Co., Katta, Japan). Antibody titers were expressed as the highest final dilution of the sample giving an absorbance twice as high as that of the negative control. Assays with antigen in the absence of sera served as negative controls.

Statistical analysis. All experimental data were analyzed statistically by using a two-sample *t* test and/or Mann-Whitney test (StatFlex; ViewFlex Co., Tokyo, Japan).

RESULTS

Antibody production. We determined the levels of anti-*B. duttonii* immunoglobulins IgM, IgG1, IgG2a, IgG2b, and IgG3 in mother mice infected by *B. duttonii* and their cross-fostered offspring.

In infected mother mice, a low level of antiborrelial IgM was observed at 2 weeks after infection (first borrelial injection) and diminished within 7 weeks (Fig. 1). Although a slight increase in the IgM titer was observed after the challenge (second borrelial injection), the elevation was statistically insignificant ($P > 0.05$). No response of IgM was observed after the challenge in the fostered offspring in groups 1, 2, and 3. However, in the control mothers (those which were used to get normal healthy offspring) and in the group 4 offspring, the IgM response was similar to that in infected mothers after the first injection. The levels of IgG subclasses in infected mother mice all increased, peaking at 7 weeks (Fig. 2). The IgG3 response was the earliest of the four subclass responses. The secondary responses of IgG subclasses were observed at 4 weeks after the challenge. No response of IgG subclasses was observed after the challenge in the fostered group 1, 2, and 3 offspring. However, in the control mothers and offspring (group 4), the production of IgG subclasses was similar to that observed in infected mother mice after the first injection.

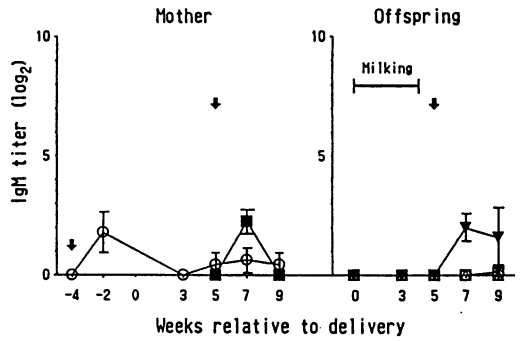

FIG. 1. Profile of IgM titers. Maternal symbols: ○, infected mother ($n = 5$); ■, control mother ($n = 5$). Offspring symbols: ○, offspring born of and fed by infected mother (group 1, $n = 10$); △, offspring born of noninfected mother and fed by infected mother (group 2, $n = 10$); □, offspring born of infected mother and fed by noninfected mother (group 3, $n = 10$); ▼, offspring born of and fed by noninfected mother (group 4, $n = 7$). Arrows indicate injection of *B. duttonii*. Vertical bars show standard deviations.

Transfer of antibody. Anti-borrelial IgM was not detected in the sera of any offspring at birth (Fig. 1). IgG1 was also not detected at birth in any group of offspring (Fig. 2); after 3 weeks of being fed by the infected mother, group 1 and 2 offspring showed a significant increase in this isotype ($P < 0.01$), which then gradually decreased and diminished by 3 weeks after weaning. These findings indicated that IgG1 was transferred only via milk. A low level of IgG2a in the group 1 and 3 offspring was detected at birth. In group 3 offspring, this level decreased gradually; in contrast, it increased significantly in groups 1 and 2, peaked at 3 weeks of feeding ($P < 0.001$), and then decreased after weaning. The results showed that IgG2a was transferred mainly via milk and partially via the yolk sac. The titer of IgG2b in the group 1 and 3 offspring was much lower than that of IgG2a, although the profiles of antibody titers were similar to those of IgG2a. It seemed that IgG2b was also transferred via both milk and the yolk sac. The level of IgG3 in the group 1 and 3 offspring was the highest among the four subclasses at birth. The levels gradually decreased during feeding in the group 1 offspring, although a moderate increase was observed in group 2 offspring after 3 weeks of feeding. These findings showed that a large number of antibodies in this subclass were transferred via the yolk sac but that some of them were also transferred in the milk.

Immunity. The immune status of the mothers and fostered offspring was investigated. Each mouse was challenged with

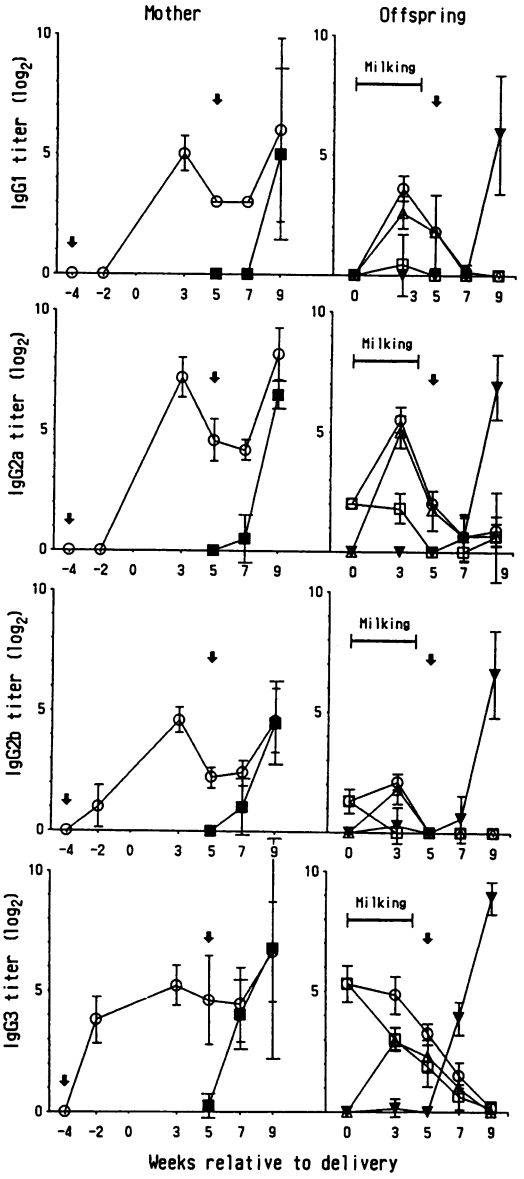

FIG. 2. Profile of IgG subclass titers. Symbols are the same as in Fig. 1. Arrows indicate injection of *B. duttonii*. Vertical bars show standard deviations.

100 live borreliae and checked for spirochetemia daily for 2 weeks.

In infected mother mice, no spirochetemia was observed after the challenge infection. The antibodies produced during the course of the first infection ensured complete protection of all mother mice tested. In contrast, all the noninfected mothers showed strong spirochetemia (data not shown).

Group 1, 2, and 3 offspring were protected from the borrelial challenge (Table 1). In group 3, however, the protection was not complete; i.e., one borrelia was found in 50 fields under a dark-field microscope in 2 of 10 offspring 2 days after the challenge, but it was cleared from the blood by the subsequent day. These two mice did not show an increase in antibody titers of any class or subclass after the challenge. The rest of the offspring in these three groups were completely protected and showed no increase in antibody titers. On the other hand, all the offspring of group 4 showed strong spirochetemia.

TABLE 1. Susceptibility of cross-fostered offspring to *B. duttonii*

Group[a]	Status of mother during:		No. of offspring tested	No. of offspring with borrelemia of grade[b]:			
	Delivery	Fostering		−	+	++	+++
1	I	I	10	10	0	0	0
2	N	I	10	10	0	0	0
3	I	N	10	8	2	0	0
4	N	N	7	0	0	0	7

[a] Cross-fostered offspring groups of infected (I) or noninfected (N) mothers.
[b] Defined according to numbers of borreliae in blood samples at a magnification of ×350. Symbols: −, none in 50 optical fields; +, fewer than 50 in 50 optical fields; ++, 1 to 20 in an optical field; +++, more than 20 in an optical field.

The antibody titers of all the fostered offspring just before borrelial challenge are summarized in Table 2. IgG3 was detected in all groups except group 4, and a small amount of IgG1 and IgG2a was detected in groups 1 and 2.

DISCUSSION

We performed our study to find the response of Igs to *B. duttonii* at the IgG subclass level as well as IgM (Fig. 1 and 2). It is well known that borreliae achieve a degree of immortality through multiphasic antigenic variation by responding to the adaptable immune responses of the host (4). We always used borreliae from the first peak of spirochetemia in mice for both routine and experimental purposes. It seemed that there was no major antigenic variation. In a preliminary experiment, we observed that *B. duttonii* harvested from mice at different times bearing different passage numbers showed similar IgM and IgG titers in ddY mice. These findings permit us to rule out the possibility of serotypic changes of the strain used in this study. In fact, mother mice also showed almost the same titers of IgM and IgG subclasses as did other control mice after the first injection of borreliae.

During the course of the primary response in mother mice, significant IgM, IgG2b, and IgG3 titers appeared at 2 weeks after the first borrelial injection and were followed by increases in IgG1 and IgG2a titers. The response of IgM seemed to occur earlier than did those of any IgG subclass. In fact, we observed that the IgM response, but not that of any IgG subclass, increased 3 to 4 days after borrelial injection and peaked at 8 to 10 days (data not shown). Therefore, the titers of anti-borrelial IgM at 2 weeks after the injection were considered to be in the post-peak declining

TABLE 2. Titers of antiborrelial Igs in cross-fostered offspring at challenge

Group[a] (no. tested)	Titer[b] of:				
	IgM	IgG1	IgG2a	IgG2b	IgG3
1 (10)	0	1.8 ± 1.5	2.0 ± 0.0	0	3.2 ± 0.4
2 (10)	0	1.8 ± 1.5	1.7 ± 0.8	0	2.3 ± 0.7
3 (10)	0	0	0	0	1.9 ± 0.9
4 (7)	0	0	0	0	0

[a] See Table 1, footnote *a*.
[b] Expressed as $\log_2$ reciprocal of the highest dilution of the samples that showed an absorbance twice as high as that of the negative control. Results are presented as means ± standard deviations.

phase. In contrast, titers of IgG subclasses continued to increase through week 7. These findings confirmed the previous report by Arimitsu and Akama (3) that the response of IgM to *B. duttonii* in ddY mice was followed by that of IgG. Similarly, in the case of human Lyme acrodermatitis and arthritis, anti-*B. burgdorferi* IgM appears earlier than IgG and is usually not detected in the late manifestations (34). These findings indicate that the responses of IgM and IgG against borrelial infection are similar to those against other bacterial infections (6, 15).

No studies have been carried out on the response of each IgG isotype in mice during bacterial infections, including relapsing fever. However, there are some reports on the response against protozoal infection (1, 33). Albright and Albright (1) reported that, of the IgG isotypes, both IgG2b and IgG3 appeared earliest and increased most rapidly in C57BL/6 and C3H strains of mice during *Trypanosoma musculi* infection; C57BL/6 mice produced the antibodies earlier than C3H mice did. In our investigation, similar findings were obtained with borrelial infection in that IgG2b and IgG3 appeared earlier than IgG1 and IgG2a.

With respect to the magnitude of the response of IgG isotypes against *T. musculi*, Albright et al. (1, 2) reported that the highest response of IgG2a and the lowest response of IgG3 occurred in BC3F1 mice, whereas the highest response of IgG3 and the lowest response of IgG1 occurred in C57BL/6 and C3H mice. On the other hand, Wechsler and Kongshavn (33) observed the highest response of IgG2b and the lowest response of IgG3 in C57BL/6 mice infected with *T. musculi*. The variation of the IgG subclass responses against the same pathogen in these studies might be due to differences in mouse strains as well as assay procedures. In the present study, the titer of IgG2a was the highest and that of IgG2b was the lowest in mother mice (Fig. 2), indicating that the response of IgG isotypes to *B. duttonii* in ddY mice is different from that to *T. musculi*. It has been reported that certain humoral immune responses against bacterial infection are restricted to particular IgG subclasses (8, 23). In the present study, however, titers of all of the IgG isotypes increased significantly ($P < 0.01$) after borrelial injection, as observed during the protozoal infection (1, 2). These results might reflect a resemblance of the antigenic complexity of *B. duttonii* to that of *T. musculi*.

It has been reported that the antibody response varies depending on mouse strains (11, 20, 21, 30). We used ddY mice (closed colony) in this experiment because an inbred strain, BALB/c, which we tried to use initially, did not produce sufficient numbers of offspring from infected mother mice for statistical analysis as a result of their low fertility, small litter size, and high susceptibility to *B. duttonii*. Recently Masuzawa et al. (18) reported on the usefulness of ddY outbred mice for passive and active immunization experiments with *B. burgdorferi*. They reported that the sensitivity of ddY mice to infection is very similar to that of hamsters and Lewis rats. However, further studies with inbred strains of mice and purified antigens are necessary to clarify the significance of IgG isotypes during *B. duttonii* infection in mice.

When the infected mothers and the cross-fostered offspring in groups 1, 2, and 3 were challenged with 10^2 borreliae, all the mice were completely protected from the borrelial infection except 2 of 10 offspring in group 3, and none produced detectable levels of IgM and IgG subclasses. It appeared that most of the injected borreliae were eliminated from mice by the action of antibodies transferred to the fostered offspring and that the remaining borreliae could not stimulate any antibody responses, since the protective immunity was passively transferred and had no positive memory. In contrast, the results of the IgG responses in infected mothers indicated that 10^2 borreliae were enough to produce the secondary responses of all IgG subclasses in mice, since the protective immunity of the infected mothers was actively acquired and had positive memory.

TABLE 3. Route of antibody transfer

Route	Titer[a] of:				
	IgM	IgG1	IgG2a	IgG2b	IgG3
Milk[b] ($n = 10$)	0	2.6 ± 0.7	5.0 ± 0.7	1.8 ± 0.6	2.9 ± 0.3
Yolk sac[c] ($n = 7$)	0	0	2.0 ± 0.0	1.3 ± 0.5	5.3 ± 0.8

[a] See Table 2, footnote *b*.
[b] Titers in the offspring born of noninfected mothers after 3 weeks of being fed by infected mothers.
[c] Titers in the offspring, born of infected mothers, just after delivery.

One of the aims of this study was to elucidate the transfer route of Igs specific to *B. duttonii* from mother to young in ddY mice. One would assume that embryonal mice were infected with a relapse of the original infecting isolate. However, there was little likelihood of transplacental infection, since IgM was not detected in any offspring born to infected mothers. IgM against a relapse strain may also be detectable because of common antigens in the ELISA system even if transplacental infection occurs. Moreover, even if it occurs, it would not affect the interpretation of the results, because it has been reported that specific antibodies to the relapse strain have no ability to protect offspring from infection by the original isolates (4).

It has been reported that mouse IgGs are transported from mother to young via the yolk sac, milk, or both (7, 17, 31). We demonstrated that IgG1 is transferred only through the postnatal intestinal route (via milk), IgG2a is transferred through both the prenatal (via the yolk sac) and postnatal routes but mainly through the postnatal route, IgG2b is transferred through both routes but to a lesser extent, and IgG3 is transferred through both routes but mainly through the prenatal route, as summarized in Table 3. The Fc receptor (FcRγ) involved in transport mechanisms has been considered to be specific for the IgG subclass in humans (32). However, the specificity of IgG-isotype binding to the FcR in mice has not been clear, although the isolation and characterization of the Fc receptors from the fetal yolk sac of the rat and on the intestinal epithelial cells of the neonatal rat have been reported (26, 29). Grey et al. (11) reported that the total nonspecific IgG3 level in neonates is higher than that in the maternal circulation and that the concentration of IgG1 and IgG2 in neonates was less than 30% of that in the maternal serum, indicating that IgG3 is preferentially transferred via the yolk sac. Although we measured only the levels of antibody specific to *B. duttonii* in this study, the transfer ratio of a specific antibody of a given isotype seems to be proportional to that of the total nonspecific antibody of that isotype. Indeed, the titer of IgG3 in the serum of neonates seemed to be similar to that in the maternal circulation, and the titers of IgG2a and IgG2b in the serum of neonates were much lower than in the maternal circulation (Fig. 2). These findings suggest that the affinity of IgG3 for FcR is much higher than those of IgG2a and IgG2b and that there is not a remarkable difference between the affinities of a specific and a nonspecific antibody of a given isotype in ddY mice. Although mouse IgG2a has been considered to be

the predominant subclass capable of yolk sac transport by virtue of its relatively strong affinity for FcRγ on the human placental plasma membrane (24, 32), our result was coincident with the finding of Grey et al. (11) indicating that IgG3 which responds to specific antigens also is preferentially transferred via the yolk sac to the fetus in mice.

The protective roles of the transferred antibodies specific to *B. duttonii* are also of interest in the present study. Nohira (22) showed that the offspring of mice immune to relapsing fever borreliae had considerable immunity and claimed that the antibodies were transferred via the placenta. However, data regarding antibody transfer during spirochetal infection are not available except for Nohira's report, although similar studies of other bacterial and viral infections have been reported (14, 19, 25). In the case of type III group B streptococcal infection in suckling rats, the pups born to immunized mothers and fostered on nonimmunized mothers had a higher survival rate (98%) than those born to nonimmunized mothers and fostered on immunized mothers (66%) (13). These data indicate that the protective antibodies specific to type III group B streptococci transferred via the yolk sac play a more important role than those transferred via milk. In contrast, it was shown by using cross-fostered infants that the maternal-fetal-neonatal transfer of influenza virus immunity was most probably mediated by breast milk antibodies (19, 25). In the present study, the group 1 and 2 fostered offspring were completely protected against borrelial challenge (Table 2) but 2 of 10 mice in group 3 showed incomplete immunity. The group 2 offspring were born to noninfected mothers and fostered on infected mothers, and the group 3 offspring were born to infected mothers and fostered on noninfected mothers. These findings suggest that the transfer of antibodies via milk is more important than that via the yolk sac for borrelial immunity in mice.

Recently, Fikrig et al. (9) reported that IgG3 monoclonal antibody to outer surface protein A from *B. burgdorferi* N 40 was protective against Lyme disease in mice, whereas IgG1 did not show such a role. Schaible et al. (27) reported that protection was most efficient with outer surface protein A-specific monoclonal antibodies of the IgG2b isotypes. In the case of *T. musculi* infection, IgG2a has been recognized as the curative antibody in mice (33). In the present study, anti-borrelial IgG3 showed some protective activity, since the fostered group 3 offspring, which acquired only IgG3 from infected mothers, were partially protected against borrelial challenge. On the other hand, all of the group 2 offspring showed complete protection. This group was born to noninfected mothers but acquired considerable levels of IgG1, IgG2a, and IgG3 through milk from the infected mothers. These results suggest that IgG1, IgG2a, or both also play an important role in the protection. However, it is still unclear which subclass is more important in the protection against relapsing fever in mice. Currently we are purifying the Ig subclasses specific to *B. duttonii* from the immune sera to clarify this point.

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