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Strain Differences in Sensitivity of Rats to *Mycoplasma arthritidis* ISR 1 Infection Are Under Multiple Gene Control

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At least 5 female rats from each of 24 inbred (ACI, AS, BDIX, BH, BN, BS, BUF, DA, LE, LEW, MWF, OM, SPRD-Cu_3, W-Krypt, and WKY), *RT1* congenic [BH.1L(LEW), LEW.1A(AVN), LEW.1C(WIST), LEW.1LV3(BH), LEW.1K(SHR), and LEW.1N(BN)], and F_1 hybrid [(LEW × BN)F_1, (LEW.1W × LEW.1A)F_1, and (LEW × LEW.1W)F1] strains, representing eight independent major histocompatibility complex (MHC) haplotypes (*a*, *b*, *c*, *dv1*, *k*, *l*, *n*, and *u*) and five related *RT1* haplotypes (*av1*, *lv1*, *lv3*, *uv2*, and *uv3*), were inoculated intravenously with *Mycoplasma arthritidis*, and the severity of the polyarthritis that developed was determined by estimating arthritis scores and weight reductions. The 24 inbred, congenic, and F_1 hybrid rat strains differed considerably in their sensitivity to infection with *M. arthritidis* and in the severity of the polyarthritis that they developed. Statistical evaluation showed that in the acute phase (days 1 to 42 after infection) as well as in the chronic phase (days 39 to 121 after infection) of the disease, the means of the arthritis scores for the strains form a continuous variation without significant interruptions, with the very sensitive LEW rats, the *RT1* congenic rats on LEW background, the F_1 hybrids with LEW, and the MWF, BS, BH, and DA rats on one end and the resistant WKY, BUF, W-Krypt, LE, and OM rats on the other end. A continuous variation was also observed for the means of the growth rates. There were, however, no significant differences between the sensitive and the resistant rat strains in the antibody titers determined by complement fixation test and enzyme immunoassay. Heritabilities of arthritis scores were calculated for all strains (h^2 = 0.39 to 0.62), for the *RT1* congenic strains (h^2 = 0.04 to 0.14), and for several strains with identical MHC genes (h^2 = 0.61 to 0.93). The results show that non-MHC genes are probably responsible for the sensitivity of rats to infection with *M. arthritidis*.

Mycoplasma arthritidis is a causative agent of spontaneous polyarthritis in rats (2) and induces experimental arthritis in rats, mice, and rabbits (1, 11, 20–22, 29). In rats and mice, polyarthritis can be elicited by intravenous inoculation with *M. arthritidis*. In rabbits, however, polyarthritis develops only after intra-articular injection with the organisms (26, 27). In experiments with inbred and congenic strains of mice, it was demonstrated that toxicity and death induced by *M. arthritidis* were associated with the major histocompatibility complex (MHC) haplotypes expressed. Mice possessing the *H-2*^{k} or *H-2*^{d} haplotype were susceptible, whereas those expressing *H-2*^{b} appeared to be more resistant (10). Further influences asserted by the MHC haplotype were on an ulcerative dermal coagulation necrosis upon subcutaneous injection of *M. arthritidis* (7) and a reactivity of mouse lymphocytes toward *M. arthritidis* supernatants (MAS) acting as a soluble T-cell mitogen (5, 9). Spleen cells from several inbred rat strains also showed a differential response towards MAS, but this was not associated with the rat MHC, *RT1* (6). Rat strains have not been studied for susceptibility or resistance to infection with *M. arthritidis*. The aim of the present study was to determine whether there are differences in the responses of various rat strains to *M. arthritidis* and whether these responses are influenced by the *RT1* haplotype expressed.

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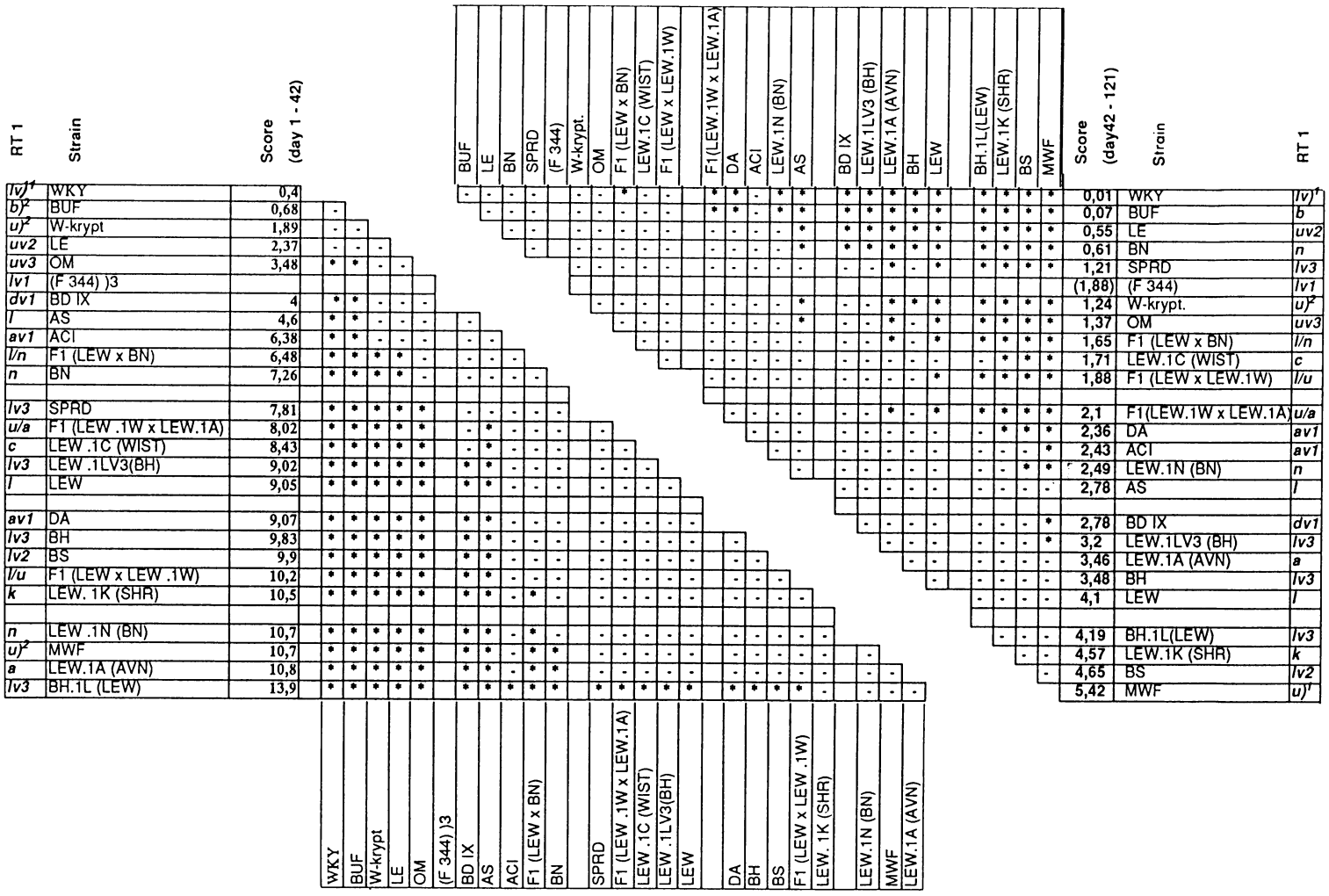
MATERIALS AND METHODS

Mycoplasma. Rats were infected with *M. arthritidis* ISR 1, originally isolated from the internal ear of a rat suffering from labyrinthitis (22). Before being used, this strain was passaged several times in Sprague-Dawley rats to increase its pathogenicity. Then it was cultivated at 37°C in modified Friis medium (15) composed of 50 ml of 10× Hanks balanced salt solution (Flow Laboratories), 1,230 ml of deionized water, 8.2 g of brain heart infusion (Difco Laboratories), 8.7 g of PPLO broth (Difco), 300 ml of swine serum (heated at 56°C for 30 min), 30 ml of fresh yeast extract (50% [wt/vol]), 1.25 ml of phenol red (1% [wt/vol]), and 2,000 IU of penicillin per ml. Agar plates were prepared by adding 1.0% (wt/vol) purified agar (Oxoid Ltd.).

Animals. Up to 5 female rats from each of 24 inbred (ACI/Ztm, AS/Ztm, BDIX/Han, BH/Ztm, BN/Han, BS/Ztm, BUF/Han, DA/Han, LE/Han, LEW/Han, MWF/Ztm, OM/Han, SPRD-Cu_3/Han, W-Krypt/Ztm, and WKY/Han), *RT1* congenic [BH.1L(LEW)/Ztm, LEW.1A(AVN)/Han, LEW.1C(WIST)/Han, LEW.1LV3(BH)/Ztm, LEW.1K(SHR)/Han, and LEW.1N(BN)], and F_1 hybrid [(LEW × BN)F_1, (LEW × LEW.1W)F_1, and LEW.1W × LEW.1A)F_1] strains, a total of 115 animals, have been used in this study (Table 1). These strains represented eight independent MHC haplotypes, *a*, *b*, *c*, *dv1*, *k*, *l*, *n*, and *u*, and five related *RT1* haplotypes, *av1*, *lv3*, *uv2*, and *uv3*. In addition, six male F344/Han rats (*RT1*^{lv1}) were investigated. All animals were barrier reared and kept in the laboratories of the authors and

TABLE 1. Arthritis scores of and comparisons between rat strains during acute and chronic phases of *M. arthritidis* polyarthritis[a]



[a] *, Significant difference ($P < 0.005$); -, no significant difference. Female animals only, except where noted. Arthritis scores and comparisons are left and below for acute phase and right and above for chronic phase.)[1], MHC classes 1 and 2 identical with standard *l* haplotype but uncertain in the *RT1.C* region;)[2], tested only for MHC class 1 antigens;)[3], only male rats tested.

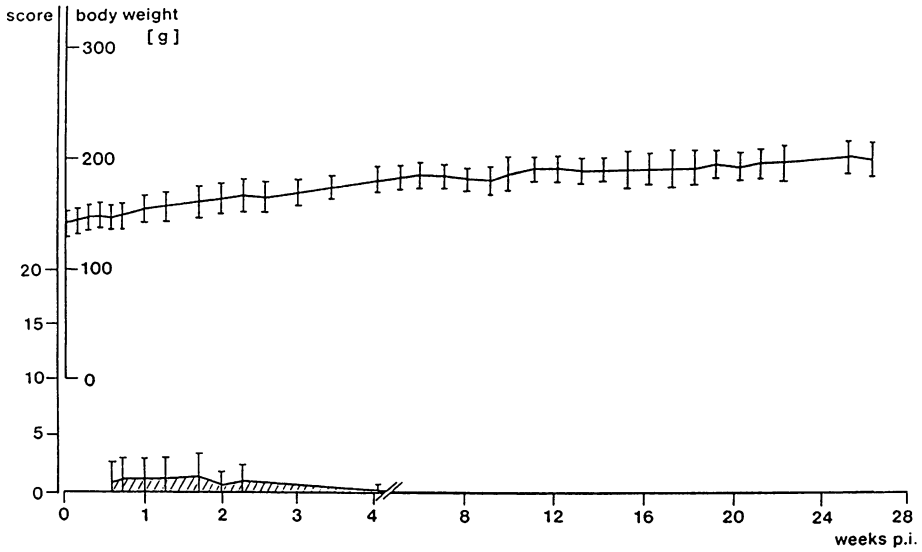


FIG. 1. Mean total arthritis scores and mean body weights of 26 LEW rats until 28 weeks after infection with 10^7 CFU of *M. arthritidis* ISR 1. The area under the arthritis score-time curve is hatched (see Tables 1 and 2). p.i., Postinfection. Error bars indicate standard deviations.

were determined to be free from murine viruses and mycoplasmas.

Animals weighing 100 to 140 g were intravenously inoculated with 3×10^7 to 5×10^7 CFU of *M. arthritidis* ISR 1 suspended in 1 ml of serum-free medium. The animals were weighed and scored for the development of arthritic symptoms daily for 2 weeks after infection and then twice a week for up to 30 weeks after infection. The severity of arthritis was recorded by scoring the carpal, tarsal, elbow, stifle, and phalangeal joints on a 0 to 3 scale, with 1 representing minimum arthritis (slight redness and slight swelling of the joints, without lameness), 2 representing moderate arthritis (distinct redness and swelling of the joint, combined with slight lameness), and 3 representing maximum arthritis (severe joint swelling and severe lameness). The scores for all joints of each rat were summated for a total score ranging from 0 (no arthritis) to a possible maximum value of 36 (severe arthritis). The highest arthritis score observed in this study was 26.

Samples from joints of the infected rats were cultivated for mycoplasmas. Samples were collected aseptically and inoculated on one plate and in three tubes (undiluted, diluted 10^{-1}, and diluted 10^{-2}) of the medium described above. Subcultivations from the tubes were performed on plates after 3 to 5 and after 8 to 10 days of incubation. Plates not showing mycoplasma colonies after 2 weeks of incubation were considered negative.

Serology. At three and six weeks after infection, the rats were slightly anesthetized with ether and bled by puncturing the periorbital plexus. Antibody titers were measured by an enzyme immunoassay and a complement fixation test as described previously (1, 19).

Histology. Histological examinations were performed on nine LEW, nine OM, three WKY, and three BUF rats. Shoulder, elbow, carpus, stifle, and tarsus samples from each animal were prepared as described elsewhere (18).

Statistics. In order to obtain a better quantitative comparison of the severity of the disease among the individuals, the areas under the total arthritis score-time curve and the body weight-time curve were calculated for each animal (Fig. 1). In other words, for each animal body weight and total arthritis score, deviations from the established state of health before infection (i.e., body weight at the day of infection and total arthritis score of 0) were multiplied by the duration of the deviation. This was performed for the period of the acute stage (days 1 to 42 postinfection) and the period of the chronic stage (days 39 to 121 postinfection) of the disease. By dividing the calculated values by 42 and 82 days, respectively, the mean weight reductions and the mean inflammation scores were computed for each animal and for each period (K. Gärtner, H. Kirchhoff, K. Mensing, and R. Velleuer, J. Behav. Med., in press).

Components of variance and heritability in a broader sense were calculated as described by Weber (28), by the estimation of the components of variance within and between strains (analysis of variance, type II). This was done with an Apple Macintosh II computer and software written by Feldman and Gagnon (14). Differences between strains were determined by the *t* test (28).

RESULTS

Strain comparison. The 24 inbred and F_1 hybrid rat strains investigated differed considerably in their sensitivity to infection with *M. arthritidis* and in the severity of the arthritis that developed. This appears clearly in Tables 1 and 2, which show the arthritis scores and the body weight changes of the rats during the acute phase (days 1 to 42 after infection) and during the chronic phase (days 39 to 121 after infection), and in Fig. 1 and 2, which demonstrate the course of the disease (mean arthritis scores and body weights) in rats sensitive to (Fig. 1) and resistant to (Fig. 2) infection with *M. arthritidis*.

The mean arthritis scores, calculated for each strain from the five arthritis scores per animal, ranged from 0.4 to 13.9 during the acute phase and from 0.01 to 5.4 during the chronic phase (Table 1; rat strains are listed in ascending order of arthritis scores, i.e., according to the severity of clinical disease). All strains were compared with each other, and significant differences ($P < 0.05$) were recorded. For example, during the acute phase, BDIX did not differ from LEW.1C or W-Krypt but differed from LEW.1LV3(BH) and BUF.

During the acute phase (days 1 to 42 after infection), the

TABLE 2. Weight increase during acute and chronic phases of *M. arthritidis* polyarthritis in rat strains (female animals)

Strain	Weight increase (g/day), acute phase	Strain	Weight increase (g/day), chronic phase
OM	2.18	WKY	1.01
SPRD	1.99	DA	1.07
W-Krypt	1.83	OM	1.09
BUF	1.79	LE	1.09
BD9	1.76	LEW.1L	1.11
LE	1.76	ACI	1.11
WKY	1.71	LEW.1A	1.12
(LEW.1L × BN)F_1	1.67	(LEW.1L × BN)F_1	1.12
LEW.1A	1.66	BN	1.13
MWF	1.64	W-Krypt	1.13
LEW.1LV3(BH)	1.64	MWF	1.13
LEW.1L	1.59	(LEW.1W × LEW.1A)F_1	1.14
BH1L(LEW)	1.57	LEW.1N	1.14
(LEW.1W × LEW.1A)F_1	1.54	LEW.1K	1.14
BH	1.50	BS	1.15
BS	1.48	SPRD	1.16
(LEW × LEW.1W)F_1	1.47	LEW.1C	1.17
AS	1.44	LEW.1LV3	1.17
LEW.1N	1.41	(LEW × LEW.1W)F_1	1.18
LEW.1K	1.40	AS	1.18
ACI	1.38	BD9	1.19
DA	1.33	BH	1.21
BN	1.30	BUF	1.22
LEW.1C	1.29	BH.1L(LEW)	1.25

strain means of arthritis scores formed a continuous variation without significant interruptions. Heritability (h^2) in a broader sense was calculated by taking into account the 89 individual mean arthritis scores of the female rats from 24 different genotypes ($h^2 = 0.62$ [$P < 0.001$]) (Table 3).

For the chronic phase (days 39 to 121 after infection), strain means of the arthritis scores also show a continuous variation ranging from 0.01 to 5.42 (Table 1). Heritability was calculated as $h^2 = 0.39$ ($P < 0.001$). Both strain comparisons (acute phase and chronic phase) correlate significantly in their rank orders ($r^2 = 0.55$, $P > 0.1$).

For strain F344, only males were tested. The results are integrated into Table 1. Because of the different sex of the F344 rats, however, these results were not compared statistically with the results for the other strains. Other investigations showed that male rats in general develop more severe symptoms than do females of the same strain (unpublished data). In spite of this, the F344 rats are grouped with the more resistant genotypes.

Considering LEW (*RT1*^{l}) and the four LEW congenic strains (LEW.1A, LEW.1C, LEW.1K, LEW.1N), it appears that all are heavily diseased. During the acute phase, differ-

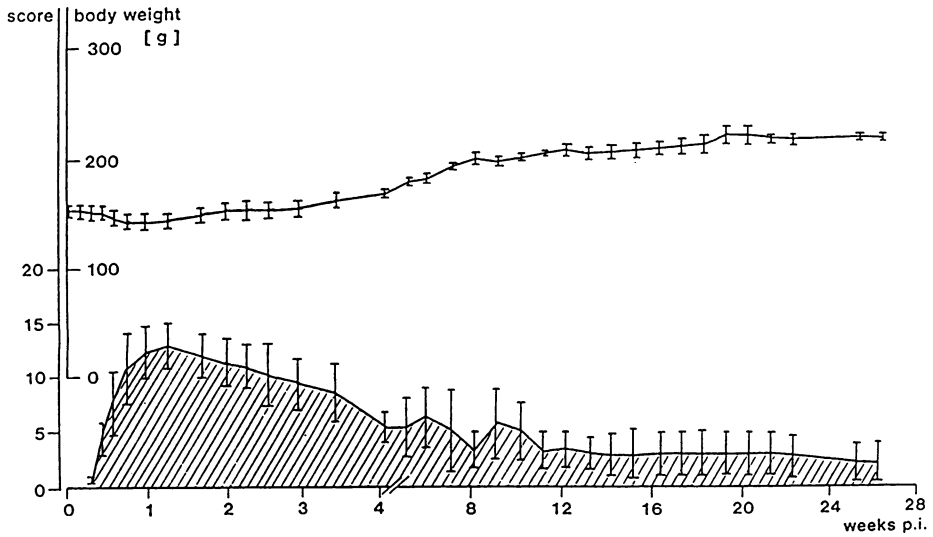


FIG. 2. Mean total arthritis scores and mean body weights of five WKY rats until 28 weeks after infection with 10^7 CFU of *M. arthritidis* ISR 1. The area under the arthritis score-time curve is hatched (see Tables 1 and 2). p.i., Postinfection. Error bars indicate standard deviations.

TABLE 3. Comparison of genetic and nongenetic components of variance of the arthritis scores for the acute and chronic phases

Phases and strains compared	DF	s^2 (%)			P
		Total	Genetic[a]	Nongenetic[b]	
Acute					
All 24 strains listed in Table 1	88/23	34,645 (100)	21,588 (62)	13,057 (38)	<0.001
LEW and MHC congenic strains on LEW background	19/4	8,814 (100)	338 (4)	8,473 (96)	>0.25
All strains except MHC congenic strains	69/18	37,709 (100)	23,390 (62)	14,319 (38)	<0.001
Strains expressing identical MHC haplotypes					
W-Krypt; MWF (*RT1^u*)	9/1	41,248 (100)	38,561 (93)	2,687 (7)	<0.001
AS; LEW (*RT1^l*)	9/1	12,400 (100)	9,363 (76)	3,037 (24)	<0.005
SPRD; LEW.1LV3; BH (*RT1^{lv3}*)	13/2	4,622 (100)	−0.1 (0)	4,622 (100)	>0.25
BN; LEW.1N (*RT1^n*)	8/1	7,720 (100)	5,438 (70)	2,282 (30)	<0.05
Chronic					
All 24 strains listed in Table 1	88/23	28,568 (100)	11,095 (39)	17,473 (61)	<0.001
LEW and MHC congenic strains on LEW background	18/4	27,121 (100)	3,873 (14)	23,248 (86)	<0.05
All strains except MHC congenic strains	69/18	27,858 (100)	11,975 (43)	15,883 (57)	<0.001
W-Krypt; MWF (*RT1^u*)	9/1	9,895 (100)	8,472 (85)	1,423 (15)	<0.01
AS; LEW (*RT1^l*)	9/1	4,375 (100)	−0.1 (0)	4,375 (100)	>0.25
SPRD; LEW; BH (*RT1^{lv3}*)	13/2	2,271 (100)	1,380 (61)	891 (39)	<0.01
BN; LEW.1N (*RT1^n*)	8/1	2,129 (100)	1,683 (79)	446 (21)	<0.01

[a] Attributable to genetic factors.
[b] Attributable to nongenetic factors.

ences between the congenic strains could not be verified ($0.05 < P < 0.1$; Table 1). During the chronic phase, strain LEW.1C showed more severe arthritis than did LEW and LEW.1K ($P < 0.05$). Heritability of the arthritis scores caused only by the different *RT1* haplotypes was calculated by a separate comparison of the five congenic LEW strains. The result was compared with the heritability calculated from the remaining 19 scores (Table 3). The influence of the different MHC haplotypes on the scores differs between the acute and chronic periods. During the acute period, an influence by the different *RT1* haplotypes could not be verified. Among the five congenic strains, heritability accounted for less than 4% of the total variance. On the other hand, the total variability was caused by remarkable genetic sources ($h^2 = 0.62$).

During the chronic phase the different *RT1* haplotypes accounted for about 14% of the total variance. They accounted for about one-third or one-half of the overall heritability of the arthritis score ($h^2 = 0.39$). Hence, the non-MHC genes are thought to be the predominant influence on the severity of the arthritis.

This was also shown by comparing heritability between different strains expressing identical MHC haplotypes. Table 3 shows the results for strains identical in *RT1^u*, in *RT1^l*, in *RT1^{lv3}*, and in *RT1^n*. Heritability of the arthritis score was most frequently high ($h^2 = 0.61$ to 0.93) for acute and chronic phases.

Furthermore, arthritis scores for particular strains were compared. The (LEW × BN)F_1 hybrids were compared with their parental strains. During the acute phase, there was no significant difference between that hybrid strain and its parental strains. During the chronic phase, the mean scores differed significantly between the two parental strains (mean scores, 0.61 and 4.10) ($P < 0.05$) and between the hybrid strain (mean score, 1.65) and LEW. The F_1 hybrid score was between the scores for its two parental strains.

Infection with *M. arthritidis* may cause retardation of growth and may influence the growth rate. For an accurate estimate of how strain type influences the retardation in growth caused by the infection, comparisons should be made between the growth rates of healthy and infected rats within each strain, but the growth rates were only measured in the present investigation. The growth results shown in Table 2, therefore, are helpful only for general information.

Individual growth rates were estimated by repeated weighing of the animals during the acute and chronic phases. For each animal, an individual mean growth rate was calculated. Between days 4 and 15 after infection, the body weights of most of the rats investigated decreased or at least stabilized. After that time, the body weights increased again at different rates. The growth rate of each rat for the period between days 1 and 42 after infection was expressed as weight change in grams per day. From these individual means ($n = 89$), the means for the 24 strains were calculated (Table 1). The strains varied in their growth rates between 1.29 and 2.18 g/day in the acute phase and 1.0 and 1.25 g/day in the chronic phase. The differences between the rat strains show a continuous variation in the range from 2.18 g/day (OM) to 1.2 g/day (LEW.1C). A special cluster of scores was formed only by the strain OM. Its growth rate was higher than those of the other strains tested. There is no correlation between the strain means from each period ($r^2 = 0.01$). On the other hand, the strain-related growth rates estimated during the acute period correlate with the strain-related arthritis scores ($r^2 = 0.23$, $P < 0.05$). Because of the lack of sufficient controls, further evaluations are omitted.

The six F344 rats could not be included in the statistical evaluation because of their sex. Nevertheless, the results obtained with these rats are very interesting, especially in comparison with the sensitivity of these rats to other microbial agents. The F344 rats were very resistant to infection with *M. arthritidis*, with total mean arthritis scores of only 3.5 and no significant loss of weight.

Reisolation of mycoplasmas and histology. All nine LEW rats histologically investigated showed the characteristic signs of mycoplasmal arthritis (18). Of the 45 joints investigated, 12 were affected. *M. arthritidis* was isolated from 8 of 34 joints. The nine OM, three WKY, and three BUF rats analyzed did not show histological signs of arthritis, and it was not possible to isolate *M. arthritidis* from the joints of these rats 7 to 45 days after infection.

Serology. In rats infected with *M. arthritidis* ISR 1, ho-

mologous antibodies which could be demonstrated by complement fixation testing and enzyme immunoassay developed. Maximum antibody titers (up to 1:4,096 by complement fixation testing) were already reached by 3 weeks after infection and stayed at these levels or decreased for up to 6 weeks after infection. Only about half of the rat strains tested by enzyme immunoassay reached maximum antibody titers (up to 1:640) within 3 weeks. The other rat strains showed an increase of antibody titers 6 weeks after infection. The differences in the levels of the antibody titers, however, did not correlate with the severity of the disease and the sensitivity of the rat strains to infection with *M. arthritidis*.

DISCUSSION

The present study shows marked differences in the susceptibilities of the 24 rat strains to infection with *M. arthritidis* ISR 1. The majority of the strains investigated were highly susceptible. All of the LEW rats showed high sensitivity to infection with *M. arthritidis*. LEW rats appear to be more sensitive to this type of disease than other rat strains. For example, LEW rats are more susceptible than BN rats to collagen II-inducible arthritis (16, 17, 25); react more strongly than BUF, WKY, and F344 rats to the inoculation of streptococcal cell walls (3, 23, 24, 27); and are much more sensitive than F344 rats to infection with *Mycoplasma pulmonis* (13). Our investigations with *M. arthritidis* infections show the same results: BUF, WKY, and F344 rats were more resistant than LEW rats. In contrast, BN rats shown to be resistant to inoculation with collagen II were highly sensitive to infection with *M. arthritidis* (almost to the same degree as LEW rats) (Tables 1 and 2). Obviously, there are different mechanisms involved in the induction of these two arthritic diseases.

There are two approaches for ascertaining the underlying causes of the differences in the susceptibilities of LEW and F344 rats to arthritogenic agents. The differences between LEW and F344 rats in the severity and chronicity of *M. pulmonis* respiratory disease were found to be associated with differences in numbers and subpopulation distributions of lung lymphoid cells (13). LEW lymphocytes had a significantly higher response to mitogenic stimulation than did F344 lymphocytes. High numbers of T-helper cells (W 3/25 T) were found in LEW lymphoid populations, whereas no change could be observed in the number of cytotoxic T-suppressor cells (Ox-8^+) (12). A high response by LEW lymphocytes to mitogenic stimulation (stimulation by MAS) was also observed by Cole et al. (6). In their investigation, splenic cells from DA, BUF, AUG, WF, and (LEW × BN)F_1 rats also responded well to MAS, whereas lymphocytes from BN and MAXX rats showed only very weak responsiveness or nonresponsiveness. Recent studies (23, 24) indicate that the susceptibility of LEW rats to streptococcal cell walls is due in part to defective inflammatory and stress-mediator-induced activation of the hypothalamic-pituitary-adrenal axis as a consequence of a hypothalamic defect in the biosynthesis and secretion of corticotropin-releasing hormone. This defect could not be detected in the relatively arthritis-resistant F344 rats.

The different susceptibilities of the rat strains to *M. arthritidis* were further supported by histological analysis of the joints during the acute and chronic stages of the arthritis. Acute arthritis started with vascular changes and alterations in the cell layer lining the synovium and then passed into an acute exudative phase with deposits of fibrin and infiltration of polymorphonuclear granulocytes accompanied by joint destruction and the occurrence of pannuslike granulation tissue. The chronic phase was characterized by destruction of cartilage and bone, ankylosis, and chronic inflammation. In about 25% of the joints investigated, acute recurrences were observed (18). Histological signs of arthritis were observed in LEW rats but not in BUF, WKY, or OM rats. Moreover, reisolation of *M. arthritidis* was possible from LEW rats only.

There were no significant differences between the antibody titers in susceptible and resistant rat strains. This shows that a humoral influence can be excluded. It may be an indication that cellular reactions are involved in the differential sensitivity of the rat strains to infection with *M. arthritidis*.

Forty to sixty percent of the large variability observed between the arthritis scores of the different rat strains is caused by differences in genotype. The 24 genotypes form a continuous range of arthritic severity without conspicuous clusters of scores. We therefore conclude that the genetic disposition for polyarthritis is of polygenetic origin. Comparison of the F_1 hybrids (LEW × BN) with their parental strains supports this conclusion. The hybrid animals show intermediate arthritis scores and differ significantly from their parental strains in the chronic phase of the disease.

Multiple-gene control was also observed for the responses of rats to collagen II (16, 17) and streptococcal cell walls (3, 29), as well as for the reactivity of rat lymphocytes to MAS (6). In contrast, in mice, toxicity, death (10), and ulcerative dermal coagulation necrosis (7) induced by *M. arthritidis*, as well as the mitogenic response of the lymphocytes to MAS (4, 5, 8), are associated with the haplotype expressed at the H-2 complex.

The present study indicates that the sensitivities of the different rat strains to *M. arthritidis* infection in vivo cannot be controlled by a single autosomal gene, as has been proposed by others (12), that causes the high responsiveness of LEW rats to mycoplasmas. The question is whether the MHC plays any role in the severity of arthritis caused by *M. arthritidis* in rats. No relationship between the MHC and the arthritis scores was determined for the acute phase of the disease. An influence of MHC on arthritis scores can be supposed, however, for the chronic phase. Our results allow an estimate of the influence of the polyallely of the MHC locus on one hand and the remaining genome on the other hand on the total variance of the arthritis scores. The different *RT1* haplotypes cause about one-third or one-half of the overall heritability of the arthritis scores. The non-MHC genes are thought to be the predominant influence on the severity of the arthritis.

In order to determine the number of genes involved and to ascertain the possible role of the MHC on *M. arthritidis* infection, further studies with defined cross and backcross populations are required.

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