THE IMMUNOMODULATORY EFFECTS OF BEHAVIOR

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Evidence is presented indicating that behavioral conditioning techniques can be used to suppress and enhance antibody- and cell-mediated immune responses. Application of conditioning techniques in the pharmacotherapy of autoimmune disease in New Zealand mice resulted in a delay in the onset of lupus using a cumulative dose of immunosuppressive drug that was not, by itself, sufficient to alter the course of the autoimmune disease. Conversely, behavioral studies in lupus-prone Mrl lpr/lpr and Mrl +/+ mice suggest further that immune status can influence behavior and that such behavior may serve to correct an immunologic dysregulation. These data are interpreted to indicate that behavior can serve an immunomodulatory function.

One of the more dramatic lines of research dealing with interactions between the central nervous system and the immune system are the several observations of behaviorally conditioned alterations of immunologic reactivity. The acquisition and extinction of the conditioned suppression and enhancement of antibody- and/or cell-mediated immune responses indicate that behavior can be viewed as another immunomodulatory mechanism. These data will be reviewed briefly and, in keeping with the theme of this conference, data will also be presented indicating that the immunomodulating effects of behavior can be applied therapeutically. Additional, preliminary data will be presented which suggest, further, that the immunomodulating effects of behavior may also serve an immunoregulatory function.

THE EFFECTS OF CONDITIONING ON IMMUNE FUNCTION

The hypothesis that immunologic reactivity could be conditioned and our own studies of conditioning (Ader & Cohen, 1985) derived from serendipitous observations of mortality in an experiment on taste aversion learning. Following consumption of different volumes of a novel, saccharin flavored drinking solution, the conditioned stimulus (CS), rats were injected with cyclophosphamide (CY), an immunosuppressive drug, the unconditioned stimulus (US). After the single conditioning trial, animals were reexposed to the saccharin solution every three days without any further injections of CY. An unexpected mortality rate was found to vary directly with the volume of the saccharin solution consumed on the single conditioning trial. Since the mortality rate paralleled the magnitude of the conditioned aversion to saccharin, it was hypothesized that reexposure to the CS that had been paired with CY had also elicited a conditioned immunosuppressive response that might have made these animals more susceptible to any latent pathogens in the laboratory environment.

In our initial study (Ader & Cohen, 1975), then, similarly conditioned animals were immunized with sheep red blood cells (SRBC). Conditioned animals that were reexposed to the CS (saccharin) at the time of antigenic stimulation (and/or 3 days later) were found to have lower hemagglutinating antibody titers than control groups comprised of: (a) conditioned animals that were not reexposed to the CS, (b) nonconditioned animals that were presented with saccharin, and (c) placebo-treated animals. These data were taken as evidence of a conditioned immunosuppressive response and, as can be seen in Fig. 1, our results have been independently verified by other investigators.

Conditioned immunosuppressive responses have now been observed in mice as well as rats, in response to different antigenic stimuli (Cohen et al., 1979), and using different conditioned stimuli (Ader & Cohen, 1981). Increasing the dose of immunosuppressive drug alters the kinetics of antibody production but does not obviate the phenomenon (Ader & Cohen, 1981).
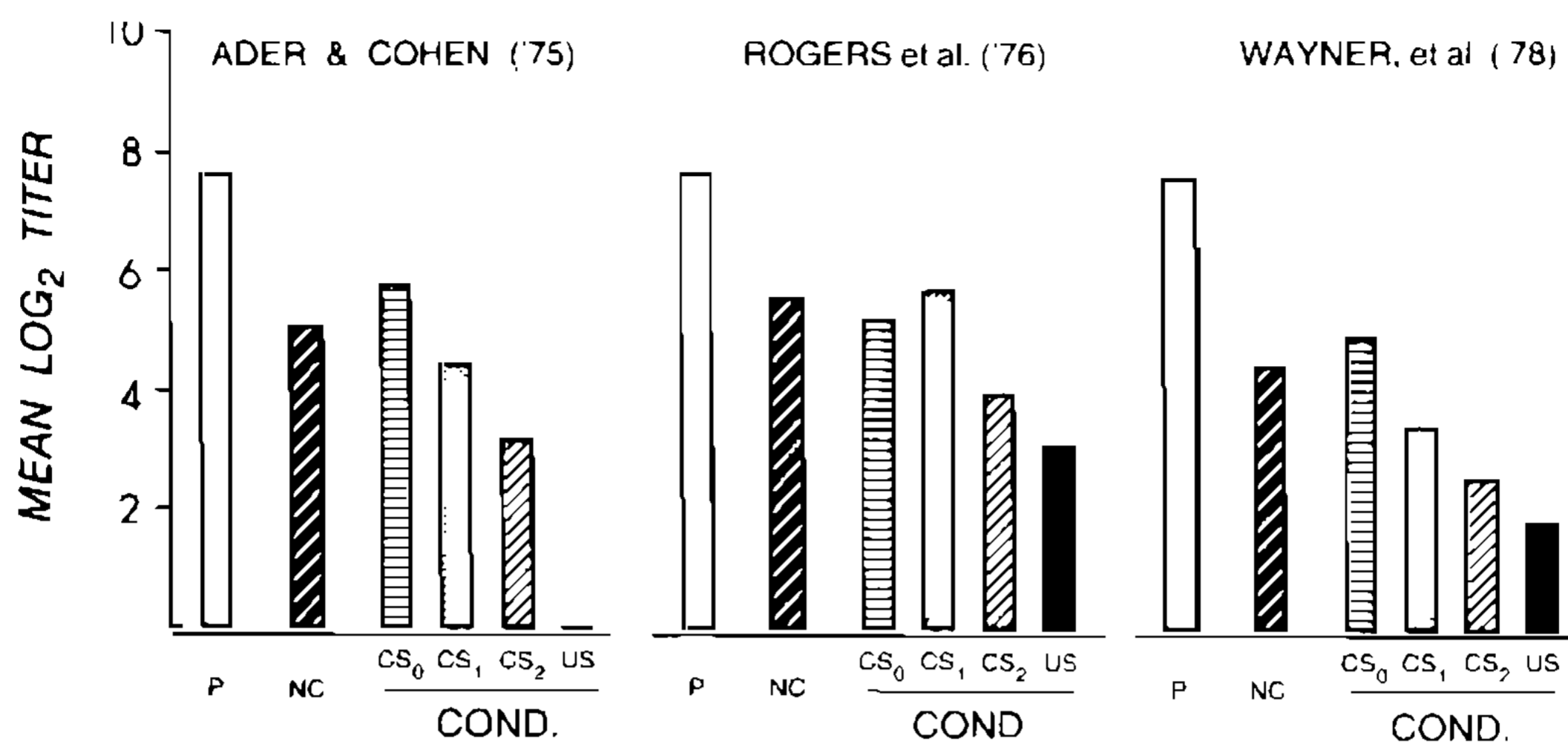
Fig. 1: Hemagglutinating antibody titers (mean ± SE) measured 6 days after the injection of SRBC in placebo-treated rats (P), nonconditioned animals (NC), conditioned animals that were not reexposed to saccharin (CSo), conditioned animals that were reexposed on one (CS_1) or 2 (CS_2) occasions to a saccharin solution previously paired with cyclophosphamide, and conditioned animals injected with cyclophosphamide at the time of immunization with SRBC. Reprinted from Ader (1981) with permission of Pergamon Press.

Also, the effect is observed when behavioral conditioning is assessed in a 2-bottle preference testing procedure that equates total fluid intake among experimental and control groups, and relatively long-term conditioning effects have been observed when reexposure to the CS precedes antigenic stimulation (Ader et al., 1982).

These conditioned immunopharmacologic effects can not be attributed to a stress-induced or conditioned elevation in adrenocortical steroids (Ader & Cohen, 1985). For example, lithium chloride is effective in inducing a conditioned taste aversion and in elevating steroid level, but it is not immunosuppressive under these conditions and does not result in an attenuated atibody response when conditioned animals are reexposed to the CS (Ader & Cohen, 1975). Also, in animals conditioned with CY, injections of LiCl or corticosterone instead of reexposure to the CS does not depress antibody titers (Ader et al., 1979). The role of adrenocortical steroids in the mediation of conditioned alterations of immune responses has been discussed in detail elsewhere (Ader et al., 1987).

In addition to the direct replications of our initial study (Rogers et al., 1976; Wayner et al., 1978), conditioned suppression of humoral immunity has been observed in studies measuring plaque forming cell responses (Gorczynski et al., 1984; McCoy et al., 1986). Also, Klosterhalfen & Klosterhalfen (1983) confirmed the phenomenon by using conditioning to attenuate arthritic inflammation in rats, and Sato, et al. (1984) reported a depression of the PFC response in mice to a CS previously paired with "stressful" stimulation.

The generality of the phenomenon is further documented by studies indicating that conditioning can influence cell-mediated as well as antibody-mediated responses. In our laboratory, a graft-vs-host (GvH) response was induced in rats seven weeks after they were conditioned by pairing saccharin with CY. Conditioned animals reexposed to the CS showed an attenuated GvH response (Fig. 2), and, when unreinforced CS reexposures were introduced during the interval between conditioning and immunogenic stimulation, extinction of the conditioned immunosuppressive response was found to be a function of the number of unreinforced CS presentations (Bovbjerg et al., 1982; 1984). Gorczynski et al. (1982) described the acquisition and extinction of a conditioned enhancement of a cell-mediated response in an experiment did not involve taste aversion learning; the CS consisted of the procedures and stimulation attending the allogeneic skin grafting of mice.

Other observations of conditioned alterations of cell-mediated responses have involved the conditioned release of histamine (Russel et al., 1984), the use of anti-lymphocyte serum, a biological rather than a pharmacologic immunosuppressant, as the US (Kusnecov et al., 1983), and conditioned enhancement of a delayed-type hypersensitivity (DTH) reaction (Bovbjerg et al., 1987). Other preliminary data obtained by Smith & McDaniels (1983) suggest that conditioning can also modify DTH reactions in human subjects. Nonspecific responses such as changes in white blood cell counts (Klosterhalfen & Klosterhalfen, 1987) and
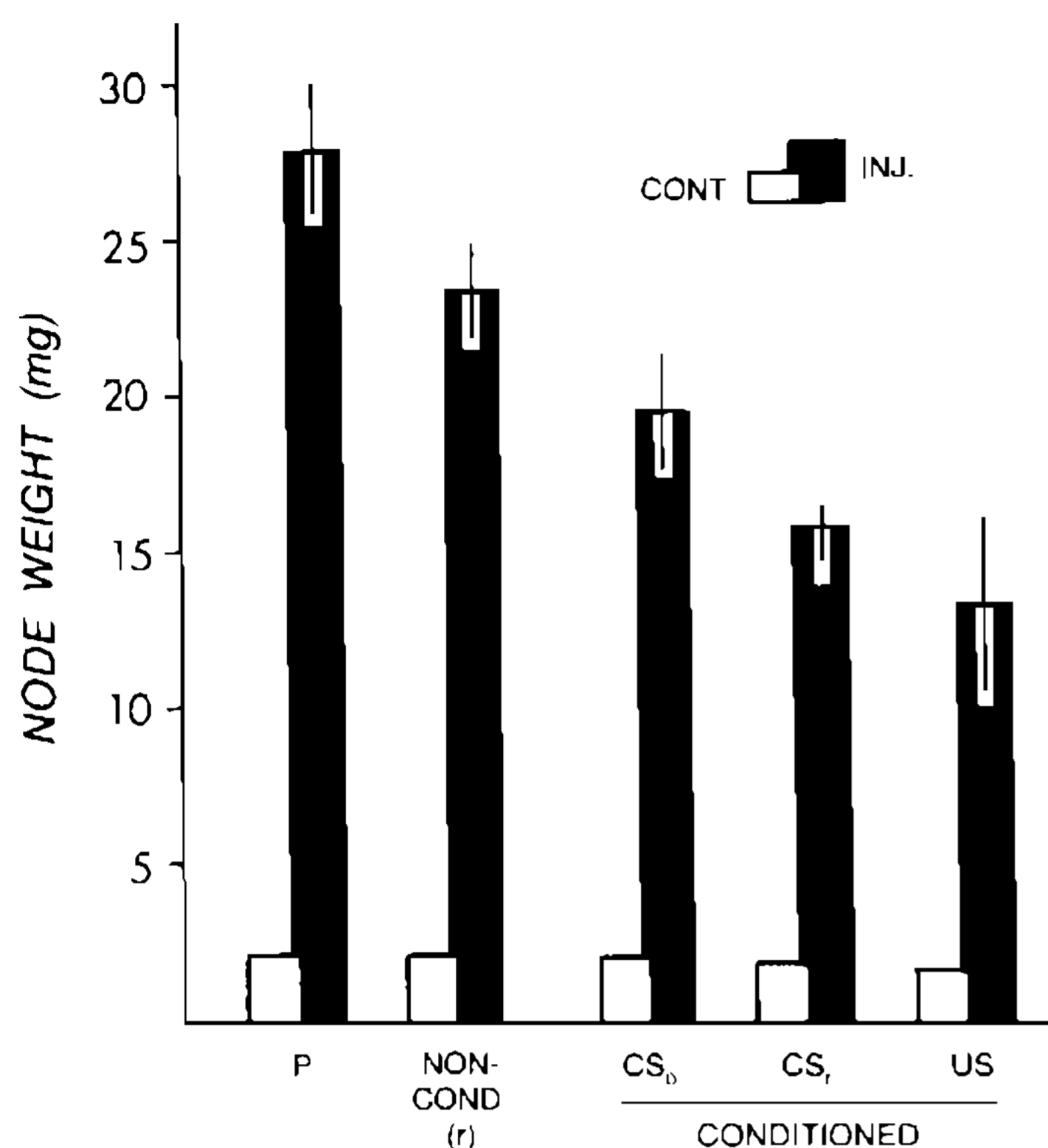
Fig. 2: Popliteal lymph node weights in (Lewis x Brown Norwegian) F_1 rats measured 5 days after inoculation with splenic leukocytes from Lewis donor animals. Mean ($\pm$ SE) for injected and contralateral footpads are shown for placebo-treated rats (P); for nonconditioned animals reexposed to a single low-dose injection of CY (10 mg/kg) administered one day after the cellular graft; and for conditioned animals given a single, low-dose injection of CY and provided with plain water (CSo), conditioned animals given a single, low-dose injection of CY and reexposed to the conditioned stimulus on Days 0, 1 and 2 after the cellular graft (CSr), and conditioned animals given three low-dose injections of CY on Days 0, 1 and 2. Reprinted from Ader & Cohen (1981) with permission from Academic Press.

increases as well as decreases in natural killer cell activity (Hiramoto et al., 1987; O'Reilley & Exon 1986) have also been conditioned.

CONDITIONING IN THE PHARMACOTHERAPY OF AUTOIMMUNE DISEASE

To assess the biologic impact of conditioned immunosuppressive responses, we applied conditioning techniques to the pharmacotherapy of autoimmune desease in New Zealand mice, a disease model in which a suppression of immunologic reactivity would be in the survival interests of the organism. The (NZBx(NZF$_1$) (NZF$_1$) female mouse develops systemic lupus erythematosus and dies with glomerulonephrits within 8-14 months of age (Steinberg et al., 1981; Talal, 1976; Theofilopoulos & Dixon, 1981). The development of disease, however, can be delayed by weekly treatment with the immunosuppressive drug, CY (e.g., Hahn et al., 1975; Russell & Hicks, 1968). Since immunol-

ogic reactivity could evidently be suppressed by conditioning, it was hypothesized that the substitution of conditioned stimuli for some of the active immunosuppressive drug in the treatment of NZF$_1$ mice would result in a greater resistance to the development of lupus in conditioned animals compared to nonconditioned animals treated with the same cumulative amount of drug (Ader & Cohen, 1982).

An 8-week regimen of drug therapy was introduced when female NZF$_1$ mice were four months old. All mice were exposed to a saccharin drinking solution weekly. These animals treated under a "standard" pharmacotherapeutic protocol (Group C 100%) were injected with CY (30 mg/kg) after each exposure to saccharin. As anticipated, the development of proteinuria and mortality was delayed in these animals. Mice in Group C 50% were treated under a partial schedule of pharmacologic reinforcement. That is, the US (CY) followed the CS (saccharin) on only half of the weekly trials (the mice were injected with saline on the remaining trials). Nonconditioned mice (Group NC50%) experienced the same number of exposures to saccharin and the same number of CY and saline injections as animals in Group C 50%, but saccharin and CY or saline were never paired. Pharmacologically, however, there was no difference between Groups C 50% and NC50%.

Nonconditioned animals did not differ from a control group that received no CY. Group C 50%, however, developed an unremitting proteinuria significantly more slowly than untreated controls and nonconditioned animals (Fig. 4a). Mortality rate yielded the same effects of conditioning. Nonconditioned animals did not differ from untreated controls, whereas conditioned mice survived significantly longer than untreated controls and nonconditioned animals treated with the same amount of the immunosuppressive drug (Fig. 4b).

Preliminary data on extinction (i.e., the effects of unreinforced presentations of the CS) were obtained in a second study. During an inital period of pharmacotherapy, the procedures were the same except that experimental animals received CY after only one third of the weekly saccharin exposures. After the period of drug treatment, the groups were divided into subgroups that: (a) continued to receive saccharin and CY as they had during initial treatment phase of the study, (b) continued to receive saccharin but received no further CY treatment, or (c) received neither saccharin nor
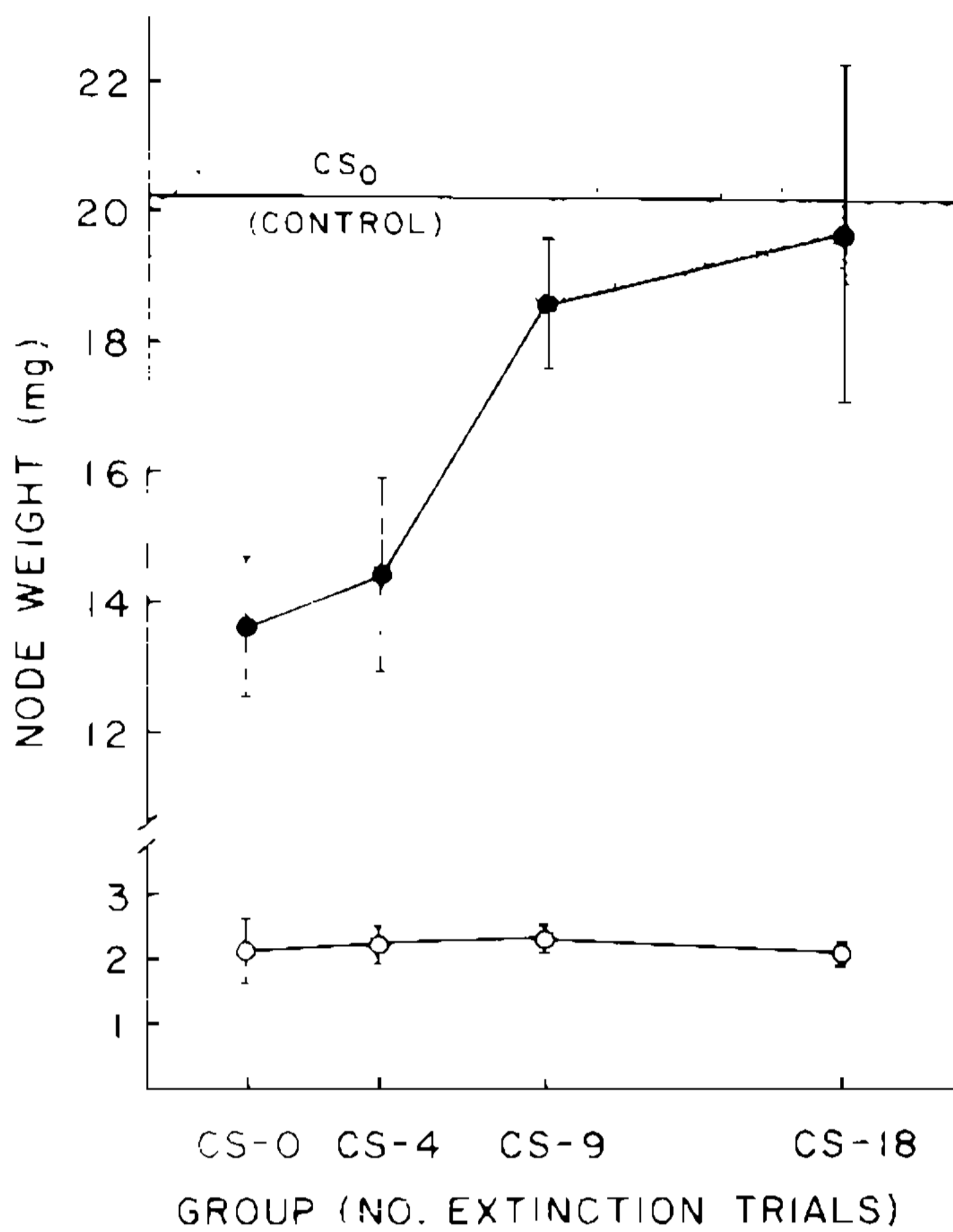
Fig. 3: Popliteal lymph node weights in conditioned animals that were not reexposed to the conditioned stimulus following conditioning (CSo)and in conditioned animals reexposed to the conditioned stimulus following 0, 4, 9 or 18 extinction trials during the 7-weekl interval between conditioning and cellular grafting. Results represent mean (γ SE) weights of draining (●) and unstimulated (O) nodes. Reprinted from Bovbjerg et al. (1984) with permission from the *Journal of Immunology*.

WEEKS (POST-CONDITIONING)

Fig. 4: Rate of development of an unremitting proteinuria (a) and cumulative mortality rate (b) in NZB̅ female mice treated with cyclophosphamide (CY) under different pharmacotherapeutic regimens. Group C 100% received saccharin following by an injection of CY weekly; Group C50% received saccharin weekly and CY on 50% of the saccharin trials; Group NC50% received the same saccharin and CY as Group C50%, but saccharin and CY were never paired; control mice received saccharin but were not treated with CY. Reprinted from Ader & Cohen (1982) with permission of the American Association for the Advancement of Science.

CY. As hypothesized, unreiforced presentations of the CS influenced the progression of disease in conditioned mice but not in nonconditioned animals.

The mortality rate of animals "trained" under a continuous schedule of pharmacologic reinforcement (i.e., mice treated with CY after each exposure to saccharin) are shown in Fig. 5. Those mice that continued to receive CS presentations (saccharin plus injections of saline) after the termination of active drug therapy died more slowly than animals deprived of both saccharin and CY. In fact, conditioned mice that continued to be exposed to the CS after the termination of active drug did not differ from animals that continued to receive CY treatment.

Among the animals originally treated with CY on only 33% of the occasions when saccharin was presented (Fig. 6), conditioned mice that continued to receive exposures to the CS after the termination of active drug therapy
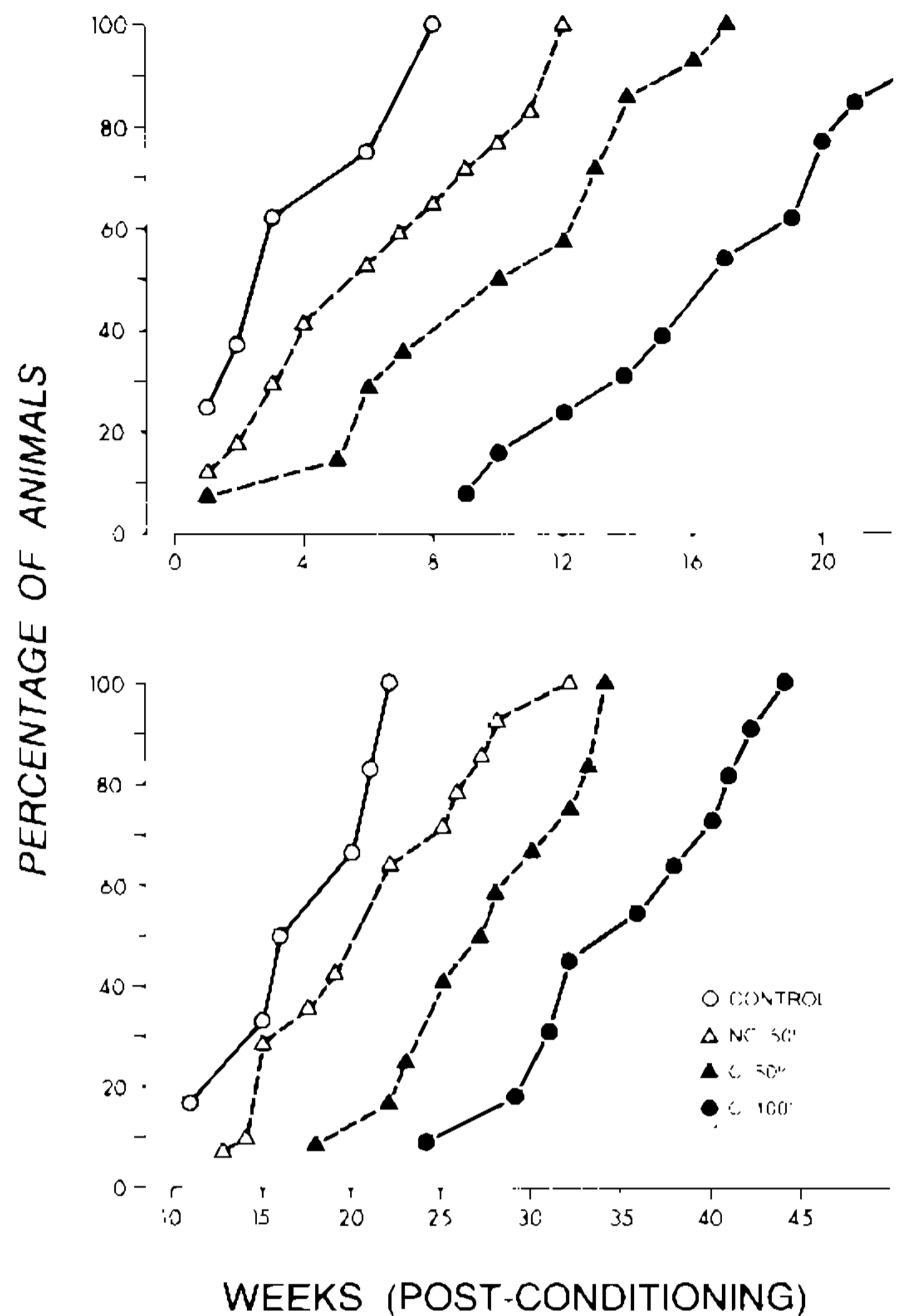
died at a slower rate than mice that were deprived of both saccharin and CY. Moreover, for the initial half of these subgroups, at least, the mortality rate of conditioned mice that received only the CS did not differ from that in mice that continued to receive CY. In nonconditioned mice, however, continued exposure to saccharin had no effect, these animals did not differ from animals that received neither saccharin nor CY.

These behavioral modifications of the course of autoimmune disease in lupus-prone mice are consistent with the several studies described above indicating that immunologic reactivity can be influenced by conditioning processes and the hypothesis that conditioned immunosuppressive responses could delay the onset of lu-
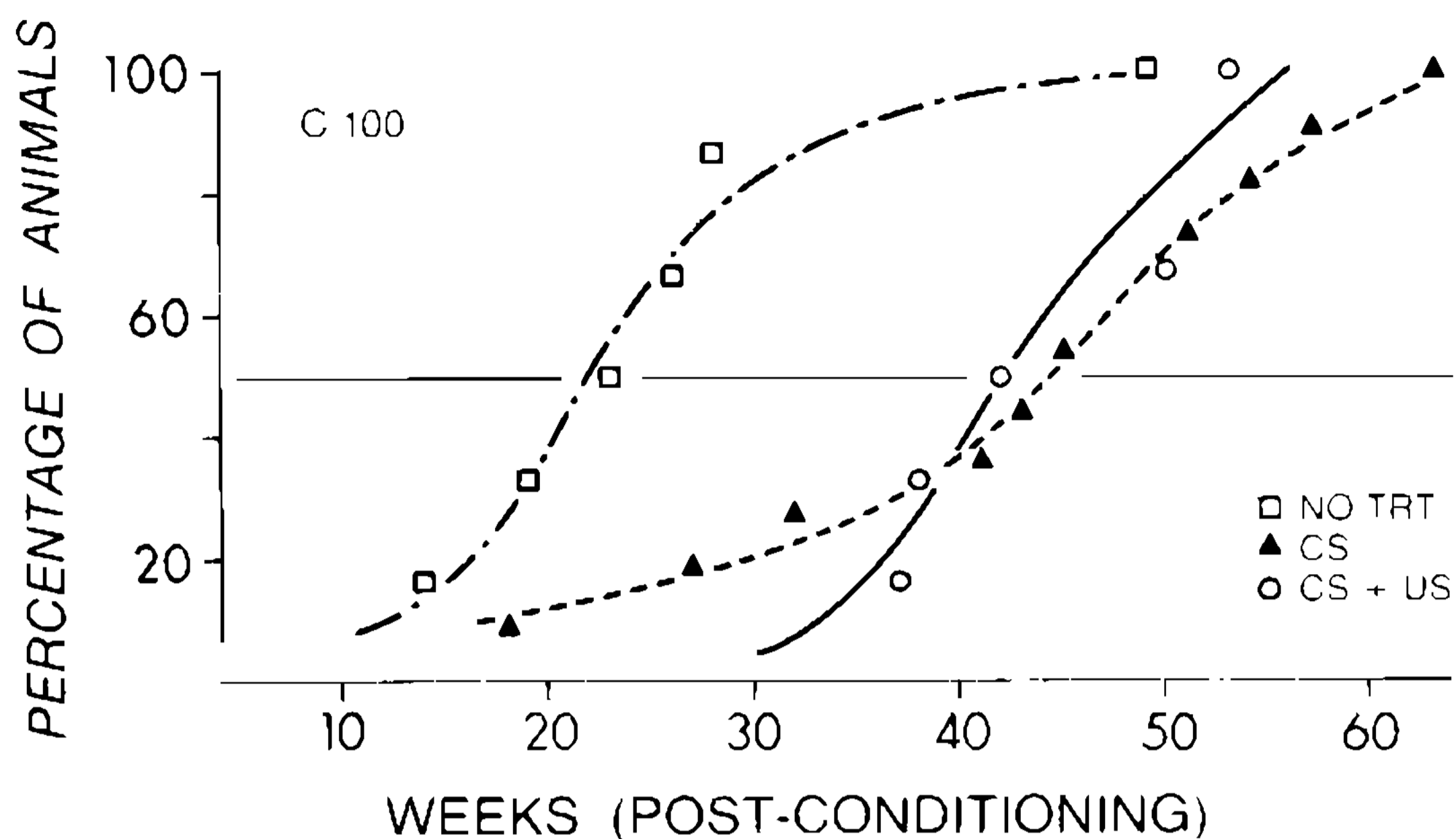
Fig. 5 : Cumulative mortality rate in NZF₁ female mice treated with saccharin, the CS, and cyclophosphamide (CY), the US, weekly and then continued on a regimen of saccharin and CY (CS + US), saccharin alone (CS), or deprived of both saccharin and CY (NO TRT). Reprinted from Ader (1985) with permission from Guilford Press.

pus under a pharmacotherapeutic regimen that was not, by itself, sufficient to influence the development of autoimmune disease.

EFFECTS OF IMMUNE STATUS ON BEHAVIOR (CONDITIONING)

It has been known for some time that lesions or electrical stimulation of certain areas in the brain will alter immunologic reactivity (Stein et al., 1981; Roszman et al., 1985). Conversely, we now know that activation of the immune system results in transient changes within the brain. The firing rate of neurons within the ventromedial hypothalamus, for example, is increased at a time corresponding to the time of peak antibody production (Besedovsky et al., 1977). Similarly, it has long been known that hormones can influence immune responses, and we now know that immune system activity provokes endocrine responses such as changes in corticosterone and norepinephrine levels (Besedovsky et al., 1975, 1983; Shek & Sabiston, 1983). Recent data also indicate that lymphocytes, themselves, are capable of producing ACTH- and endorphinlike peptides (Blalock, 1984; Smith et al., 1982). A review of this literature is beyond the scope of this paper, as is the accumulated literature on the behavioral, electrophysiological, and neuropathological effects of treating animals with anti-brain antibodies (e.g., Jankovic et al., 1968; Mihailovic & Jankovic, 1961).

Similar bidirectional influences appear to characterize the relationship between behavior

and immune function. It is clear from the data reviewed above and from other literature on the effects of "stress", for example, that behavioral factors are capable of influencing immunocompetence. Other data indicate that immune processes are capable of influencing behavior. There is good evidence, for example, that behavioral factors can influence the susceptibility to and/or the progression of infectious disease (Plaut & Friedman, 1981), and there is also evidence that behavior is altered by the induction of or response to a variety of parasitic and infectious diseases (Dolinsky et al., 1985; Hotchin & Seegal, 1977; McFarland & Hotchin, 1983, 1984; McFarland et al., 1981). Bouchon & Will (1982a,b) have described behavioral differences between dwarf and control mice, including a deficit in the maze learning performance of the immunologically compromised dwarf mouse. Hoffman et al. (1978) induced immune complex disease in Sprague-Dawley rats and found that these animals were less resistant to the extinction of a active avoidance response than controls.

In our initial studies on the pharmacotherapy of autoimmune disease in female NZF₁ mice (Ader & Cohen, 1982), animals were treated with CY that was paired with the taste of saccharin on a weekly basis. When these mice were subsequently tested, however, we observed no evidence of a conditioned avoidance of the saccharin solution. The most obvious explanation of this failure to observe learning was that the dose of CY (30 mg/kg) was simply too low to
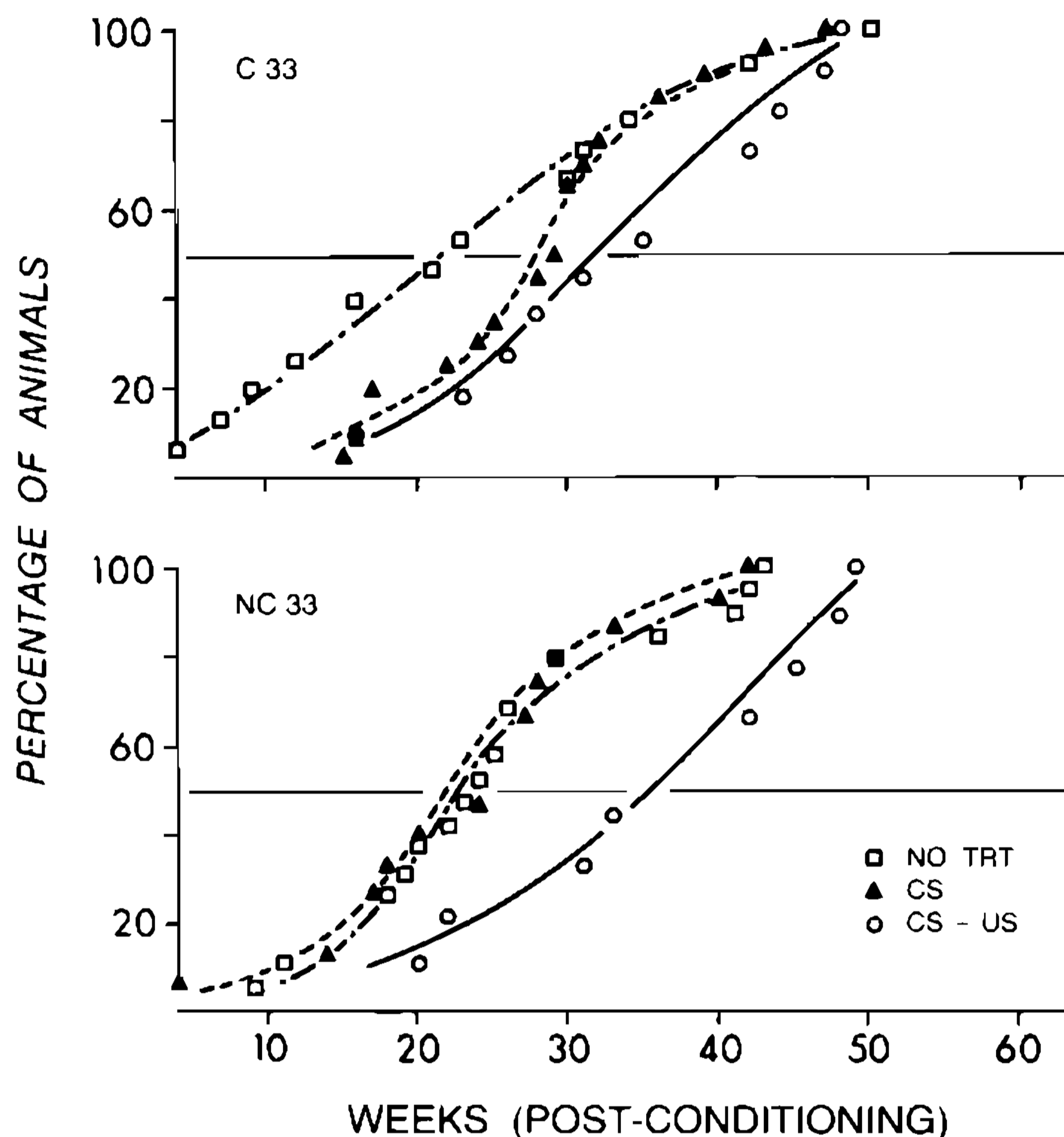
Fig. 6: Cumulative mortality rate in conditioned (C33) and noncondi-
tioned (NC33) NZF₁ mice that continued to receive saccharin and CY
(CS + US), continued to receive only saccharin (CS), or received neither
saccharin nor CY (NO TRT). Reprinted from Ader (1985) with permis-
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elicit the noxious physiological changes re-
quired to induce an aversion in the mouse.
Increasing the dose of CY, however, still yielded
inferior conditioning in NZF₁ mice compared
to normal animals. These latter results prompt-
ed us to ask if the immunologic deficit that
characterizes these lupus-prone NZF₁ mice was
in some way related to a deficit in learning
ability. Nandy et al. (1983) had reported that
NZB mice perform more poorly than C57BL/6
mice in active avoidance conditioning with
electric shock as the US.

In a subsequent study, taste aversion learn-
ing was assessed in C57BL/6 and NZF₁ mice
conditioned with either CY or LiCl as the US.
As shown in Figure 7, C57BL/6 mice acquired
an aversion to saccharin after a single condition-
ing trial with either CY or LiCl. The lupus-
prone animals again showed relatively poor
avoidance performance when saccharin was
paired with CY; but they did show a typical
aversion to saccharin that had been paired
with LiCl. Thus, NZF1 mice do not appear to
have a deficit in learning ability, per se, but

they display little or no aversion to a novel
drinking solution associated with the effects of
a drug which, in suppressing the immune sys-
tem, is acting to promote their ultimate surviv-
al. Based on these preliminary observations, it is
hypothesized that the relatively poor avoidance
performance of NZF₁ mice in a taste aversion
conditioning paradigm with an immunosuppres-
sive drug as the US is a reflection of some "re-
cognition" of their altered immunologic state.

It has long been known that behavioral
means can be used to maintain or restore home-
ostatic balance with respect to a variety of phys-
iologic states such as body temperature (Alberts,
1978; Satinoff & Henderson, 1977) or nutri-
tional requirements (Davis & Levine, 1977;
Peck, 1978). In addition, behavioral mechanisms
(i.e., learning) can be enlisted to correct hor-
monal imbalances. Salt or water loaded normal
or diabetes insipidus rats will differentially learn
a maze reinforced by an injection of antidiuretic
hormone (Miller et al., 1968); hyperglycemic
animals show an aversion to a normally prefer-
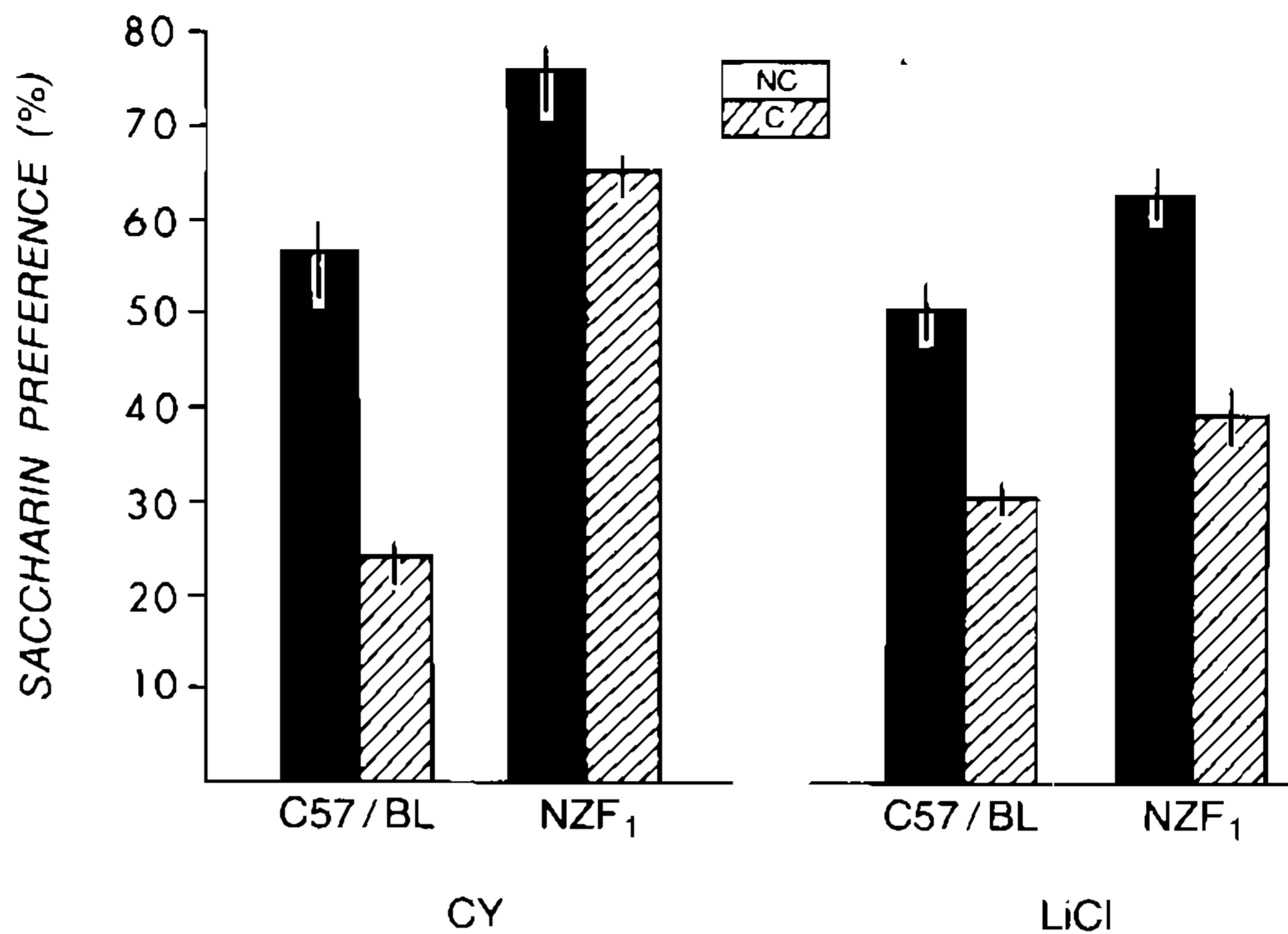red saccharin solution (Brookshire, 1974); pro-

Fig. 7: Mean (± SE) preference for saccharin in NZF_1 and C57BL/6 mice following a single conditioning trial on which saccharin was paired with either CY or LiCl. NC = nonconditioned mice. Reprinted from Ader et al. (1987) with permission from the New York Academy of Sciences.

tein deficient animals prefer odors assoacited with balanced protein food (Booth & Simson, 1971); and adrenalectomized animals self-select saline solutions containing corticosterone in preference to plain saline (Castonguay et al., 1985). A great deal of attention has been devoted to the instrumental conditioning of autonomic and visceral responses previously thought to be involuntary (Miller, 1969); and there is a large literature indicating that pharmacologic responses can be conditioned (Eikelboom & Stewart, 1982). With respect to learned associations between gustatory stimuli and drug-induced gastrointestinal consequences, distinctively flavored but non-preferred solutions can become preferred substances as a result of their association with recovery from illness or the reinstatement of homeostatic balance (Garcia et al., 1974; Rozin & Kalat, 1971; Zahorik et al., 1974).

Miller et al. (1968) advanced the hypothesis that, "at least in cases where homeostasis is mediated via the central nervous system, deviations in any direction, if large enough, can function as a drive and the prompt restoration to normal levels by any means can function as a reward." (p. 686). Such phenomena have never been reported in the case of immune responses.

Sufficiently large deviations from homeostasis may occur only under abnormal circumstances, as these authors point out, but considering our ability to influence the onset of

autoimmune disease in lupus-prone mice by conditioning (Ader & Cohen, 1982) and the disruption of immunoregulatory circuits that characterizes autoimmune disorders (Smith & Steinberg, 1983), a predisposition to autoimmune disease may constitute a sensitive model in which to examine the role of learning in the maintenance of homeostasis and the impact of the immunologic status of the organism on behavior.

In view of the above speculations, it is possible that the relatively poor avoidance bahavior of lupus prone animals in response to a stimulus associated with the effects of an immunosuppressive drug may reflect the immunorestorative effects of that drug in this particular strain of mice. Because CY unconditionally elicits noxious gastrointestinal effects, this hypothesis would, operationally, translate into the hypothesis that the dose of CY and the degree of immunologic dysregulation would interact to influence the acquisition of a conditioned avoidance response based on the pairing of a distinctive taste with an immunosuppressive drug. That is, it would require higher doses of an immunosuppressive drug or more conditioning trials at a constant dose of drug to induce a taste aversion in lupus-prone than in control mice. Conversely, animals with an autoimmune disease would acquire a taste aversion more rapidly or at a lower dose of an immunoenhancing drug than a strain of animals that was not sus-

ceptible to autoimmune disease. The reverse might be true in the case of animals with other kinds of immunologic dysregulations.

In order to evaluate this hypothesis, preliminary studies have been initiated with Mrl mice. These animals were derived from the LG (75%), AKR (12.6%), C3H (12.1%), and the C57BL/6 (0.3%) strains (Murphy & Roths, 1978). A spontaneous autosomal recessive mutation divided the Mrl mice into two congenic inbred strains. One substrain possesses the lpr (lymphoproliferative) gene (Mrl-lpr/lpr) and the other does not (Mrl +/+), but the two strains share at least 89% of their genomes. In contrast to New Zealand hybrid animals, Mrl-lpr/lpr mice develop symptoms of SLE relatively early in life and there is a 50% mortality in males and females at approximately 5-6 months of age. Females are only slightly more susceptible than males. Mrl +/+ mice also develop autoimmune disease, but desease is delayed and a 50% mortality is not reached until 17 months in females and 23 months in males. Both NZF$_1$ and Mrl mice develop immune complex glomerulonephritis, the principal cause of death. The degree of lymph node hyperplasia, however, varies considerably; there is, maximally, a 2- to 3-fold enlargement in NZF$_1$ females and as much as a 100-fold enlargement in Mrl-lpr/lpr mice (Theofilopoulos & Dixon, 1981). From the perspective of behavioral studies, the advantages of Mrl mice are: (a) the availability of a congenic control strain, (b) the relatively rapid development of disease, and (c) an external marker of disease, lymphadenopathy.

Our initial experiments were intended to define a dose or doses of CY that would be sufficient to induce a taste aversion in Mrl mice and discriminate between the performance of Mrl-lpr/lpr and +/+ mice. Animals were obtained from The Jackson Laboratories (Bar Harbor, ME) and, in our first study, male and female Mrl-lpr/lpr and +/+ mice 26 weeks of age (when lpr mice had already developed manifest lymphadenopathy) were provided with a distinctively flavored solution (chocolate milk) instead of plain water during their 1-hr. scheduled drinking period. After drinking, mice were injected ip with saline or with 150 or 250 mg/kg CY. Every three days after the single conditioning trial mice were reexposed to chocolate milk, alone. The results (Fig. 8) were consistent with the hypothesis that the performance of Mrl-lpr/lpr mice would be inferior to that of Mrl +/+ animals. The differences were seen primarily in

extinction of the avoidance response. Among females, extinction was significantly more rapid in lpr mice at the higher dose of CY; among males, more rapid extinction in lpr relative to +/+ mice was observed only at the lower dose of CY.

An independent population of animals was similarly tested when they were 10 weeks old, i.e., before lymphadenopathy was evident in Mrl-lpr/lpr mice. In the absence of overt disease, there were no differences in taste aversion conditioning between Mrl-lpr/lpr and +/+ animals (Fig. 9).

We next examined the effects of two conditioning trials using lower doses of CY. We also attempted to hold constant the status of the Mrl-lpr mice by initiating conditioning after palpable lymphadenopathy had been evident for a constant period of time, two weeks. Mrl-lpr/lpr and +/+ animals of comparable age were conditioned as above by pairing consumption of chocolate milk with either 50 or 100 mg/kg CY. One week later, a second conditioning trial with CY was administered. There were no strain differences in the rate extinction, but the initial avoidance behavior of lpr mice was not as great as that of +/+ animals.

We next attempted to use the number of trials to an arbitrary acquisition criterion as a measure of differences in learning between Mrl-lpr/lpr and +/+ animals. Animals of both strains were conditioned at approximately 22 weeks of age using 50, 100, or 200 mg/kg CY. The arbitrary criterion was established as a $\leqslant 50\%$ preference for chocolate milk since all the mice conditioned with 200 mg/kg CY had exceeded this level of avoidance after two conditioning trials. This procedure was not especially effective; asymptotic performance at a wide range of preference scores was usually reached after only a few trials. We were, however, able to extract from the data the level of performance achieved under conditions that were constant for all animals, i.e., three test trials. These data are shown in Fig. 10. Preference for chocolate milk remained high in nonconditioned (placebo-treated) animals. At 50 mg/kg CY, there was an attenuation of the preference for chocolate milk but preference scores were not consistently below 50% in either strain and there were no strain differences. Using a dose of 100 mg/kg, two conditioning trials resulted in a significant difference in the performance of Mrl-lpr/lpr and +/+ mice. On the second and third preference tests, chocolate milk comprised bet-
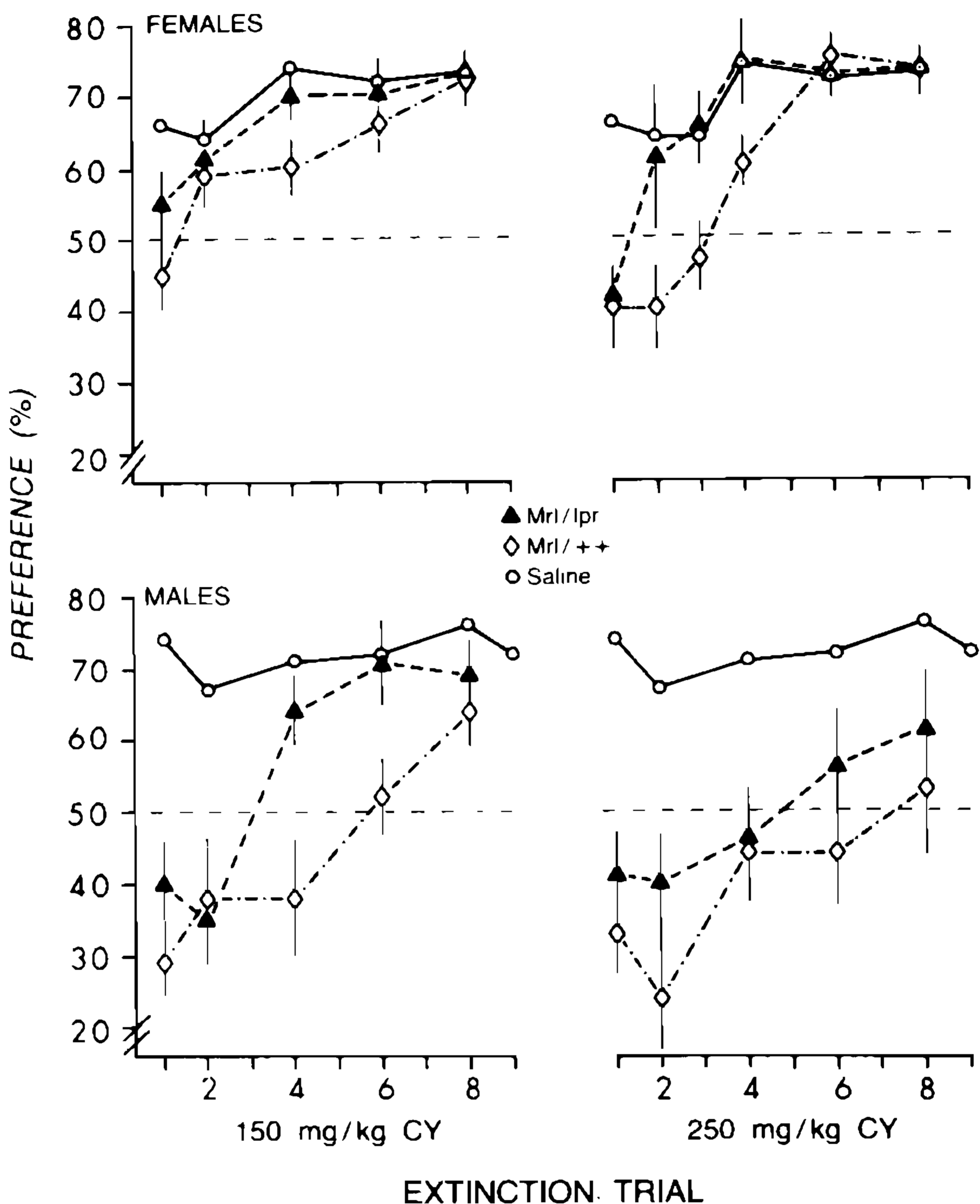
Fig. 8: Preference for chocolate milk (mean ± SE) previously paired with either 150 or 250 mg/kg CY in Mrl-lpr/lpr and Mrl +/+ mice. Reprinted from Ader et al. (1987) with permission from the New York Academy of Sciences.

ween 55 and 60% of the total fluid consumed by lpr animals; in contrast, chocolate milk comprised approximately 38% and 25%, respectivelly, of the total fluid consumption of +/+ mice. Using a dose of 200 mg/kg, the preference for chocolate milk was well below 50% in both Mrl-lpr/lpr and +/+ animals.

These data suggest that when the dose of immunosuppressive drug is "low", there are no differences in the avoidance performance of Mrl-lpr/lpr and Mrl +/+ mice; neither strain acquires a strong taste aversion. At "high" doses of CY, both Mrl-lpr/lpr and +/+ mice display taste aversion behavior and, again, there are no strain differences. There are intermediate doses of CY, however, that are sufficient to induce taste aversions in Mrl +/+ mice but are ineffective in inducing the avoidance behavior in lupus prone Mrl-lpr/lpr animals. These data, then, are consistent with the hypothesis that there would be an interaction between the noxious and immunosupressive effects of CY and the immune status of the organism that influences the performance of animals in a taste aversion conditioning paradigm in which CY is used as the unconditioned stimulus.
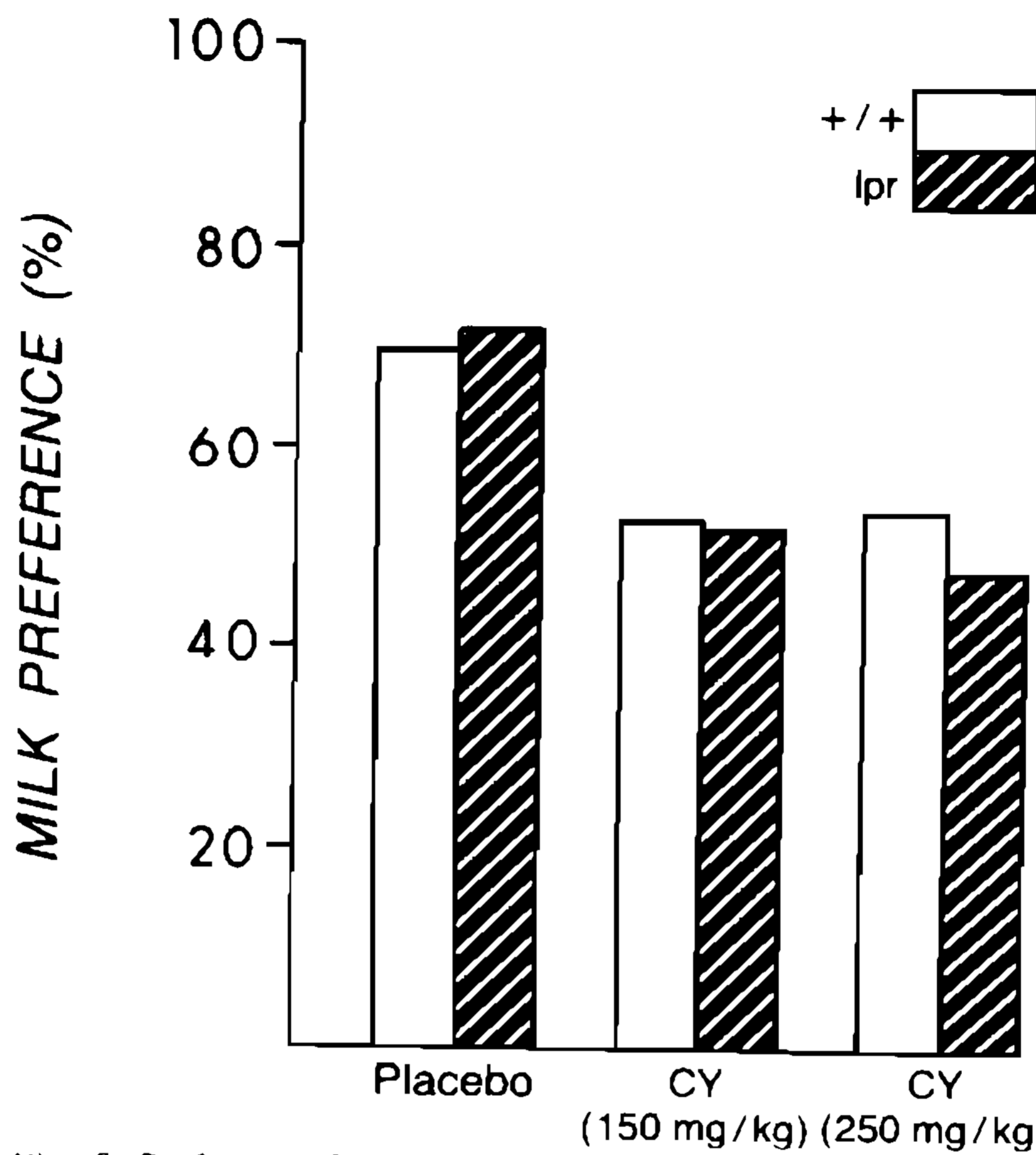
Fig. 9: Preference for chocolate milk (mean ± SE) previously paired with CY in 10-week old Mrl-1pr/1pr (prior to the development of lymphadenopathy) and Mrl +/+ mice. Reprinted from Ader et al. (1987) with permission from the New York Academy of Sciences.
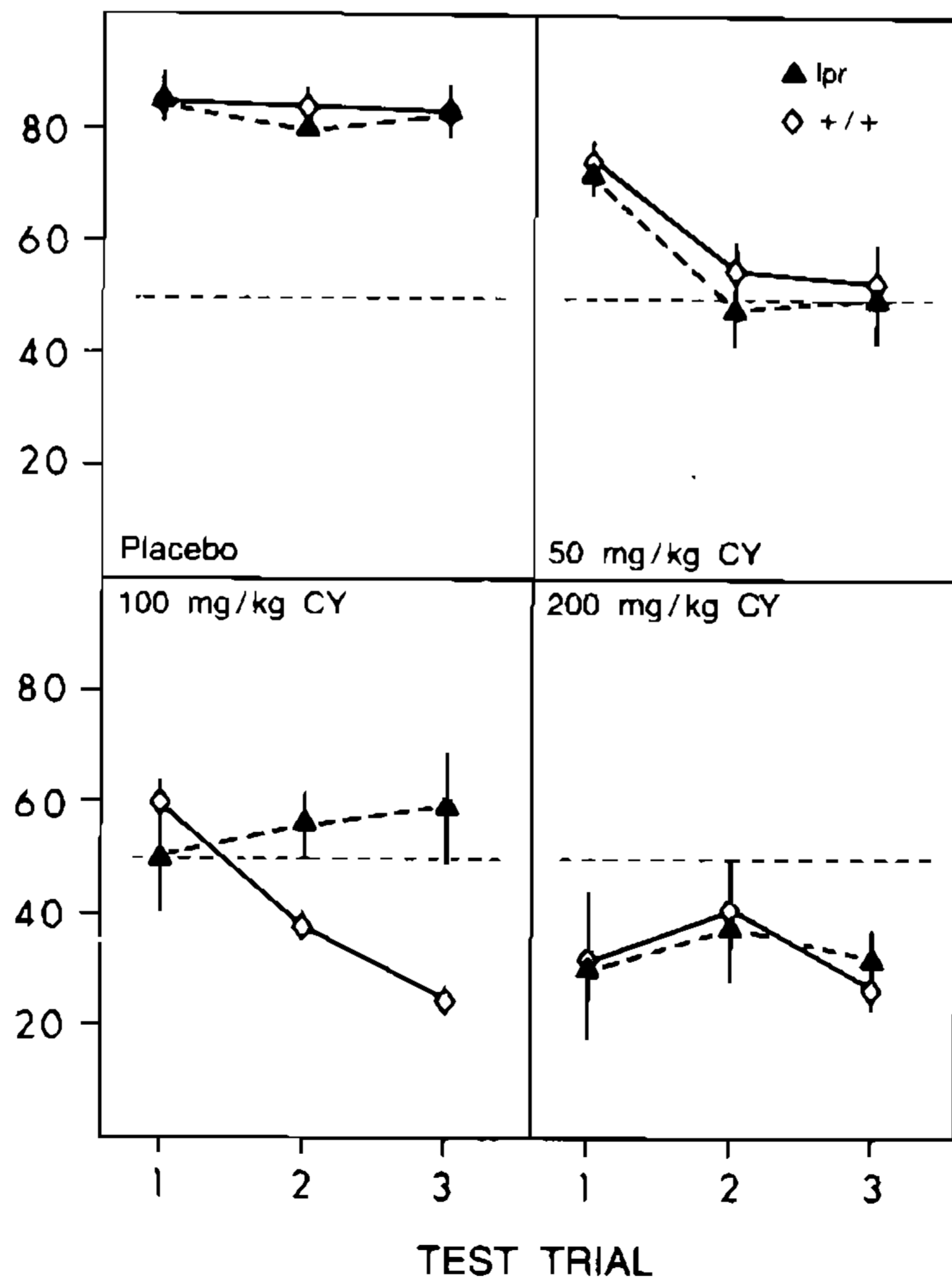

Fig. 10: Preference for chocolate milk (mean ± SE) following each of two conditioning trials (Test Trials 1 and 2) and one subsequent test trial (Test Trial 3) in Mrl-1pr/1pr and Mrl +/+. Reprinted from Ader et al. (1987) with permission from the New York Academy of Sciences.

DISCUSSION

The several reports describing conditioned alterations of antibody-and cell-mediated immune responses provides dramatic evidence of an intimate relationship between central nervous system function and immune function. Indeed, if one thinks of immune function as part of an integrated physiological system operating to maintain or restore homeostatic balance, conditioned changes in immunologic reactivity can be viewed as extensions of a large literature on conditioned physiologic effects. The available literature has not yet provided a complete description or experimental analysis of the circumstances under which conditioning can attenuate or potentiate nonspecific defensive reactions and specific immune responses — or the mechanisms mediating conditioned alterations in immunologic reactivity. The available data do provide compelling evidence that behavioral processes can serve to modulate immunity and therefore raise innumerable questions about the normal operation and modifiability of the immune system. Moreover, the ability to apply conditioning techniques to the pharmacologic modification of autoimmune disease in lupus-prone animals attests to the biological impact of conditioned alterations in immune function. While admittedly speculative, the application of conditioning techniques could lead to the development of innovative pharmacotherapeutic regimens for the treatment of immunologic dysregulations and other pathophysiological processes (Ader, 1985).

Our observations of differences in the avoidance conditioning of lupus-prone animals and the observations of others on the behavioral sequelae of infectious diseases are also interesting and worthy of more thorough investigation. It would appear that, although lupus-prone animals do not show a deficit in learning ability, per se, animals with autoimmune disease perform more poorly than controls in acquiring a taste aversion to a neutral taste stimulus that has been associated with an immunosuppressive drug. There are, to be sure, methodological issues that need to be resolved. Nonetheless, these preliminary data suggest that immune function has implications for the behavior of organisms and that such behavior may even serve to correct a deviation from homeostasis within the immune system. These results, too, are consistent with a large literature on the effectiveness of behavior in the maintenance or restoration of homeostasis within other physiologic systems.

In order for changes or differences in the state of immune system to influence behavior, particularly adaptive processes such as learning, we must assume that: (a) there are neural and endocrine correlates and/or peripheral effects of experimentally-induced or naturally occuring differences in immune function that are capable of influencing learning, and/or (b) the central nervous system is capable of receiving and processing information provided by the immune system and, in particular, deviations from homeostasis within the immune system. It is already known that neural and endocrine changes are initiated by activation of the immune system (e.g., Besedovsky et al., 1975, 1977) and that there are common channels of communication between the nervous and immune systems (e.g., Blalock, 1984). Assuming that the brain is capable of acting on the information provided by the immune system, we can speculate further that behavioral processes can function as an adaptive mechanism through which *in vivo* regulation of the immune system can occur. Whether the performance of lupus-prone animals in acquiring a taste aversion based on the immunosuppressive effects of a pharmacologic agent reflects the operation of such a mechanism remains to be determined.

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