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DIET AND CALORIE RESTRICTION

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Abstract—Current data suggest that the life spans of commonly held rodent species have decreased and the occurrence of tumors occurs earlier in the lifespan of ad libitum-fed animals. The most likely cause of this change in the life span of barrier-reared genetically defined animals is increased body weight. The effects of caloric restriction on a variety of functional measures and on age-dependent tumors and lesions are the focus of this presentation. Recommendations for caloric restriction, or at least "dietary control," will be discussed. *Copyright © 1997 Elsevier Science Inc.*

Key Words: caloric restriction, mice, rats, life span

INTRODUCTION

MOST DIETS available for laboratory mice and rats were developed for the production of vigorous healthy animals that reproduce early in life and efficiently. The concerns in this diet development are much the same as those in agriculture for the efficient production of hogs and cattle. Diets developed primarily to maximize life span are nonexistent. Dr. Edward Masoro has written several good papers on this topic (e.g., Masoro, 1989, 1993). Portions of this article are drawn from Dr. Masoro's presentation at the last course held in Italy in 1991 (Masoro, 1993).

Dr. Masoro uses the Fischer 344 (F344) rat in much of his research, as do many other American gerontologists. As I indicated in my genotype choices presentation, this model has been controversial, in large part because of the high incidence of renal pathology observed in this rat strain. While there is great interest in the influence of diet on aging processes, dietary induction of pathology, which leads to premature mortality, is generally viewed as a major confounding factor in gerontologic research. Using his standard semisynthetic diet, which used 21% casein as the primary source of protein, Masoro observed that 40% of his rats had severe lesions by 24 months of age (Maeda *et al.*, 1985). Reduction of the casein content to 12.6% reduced the incidence of lesions by about 50%. Replacement of casein as the protein source with soy protein (21%) reduced lesions and increased longevity in these animals (Masoro *et al.*, 1991).

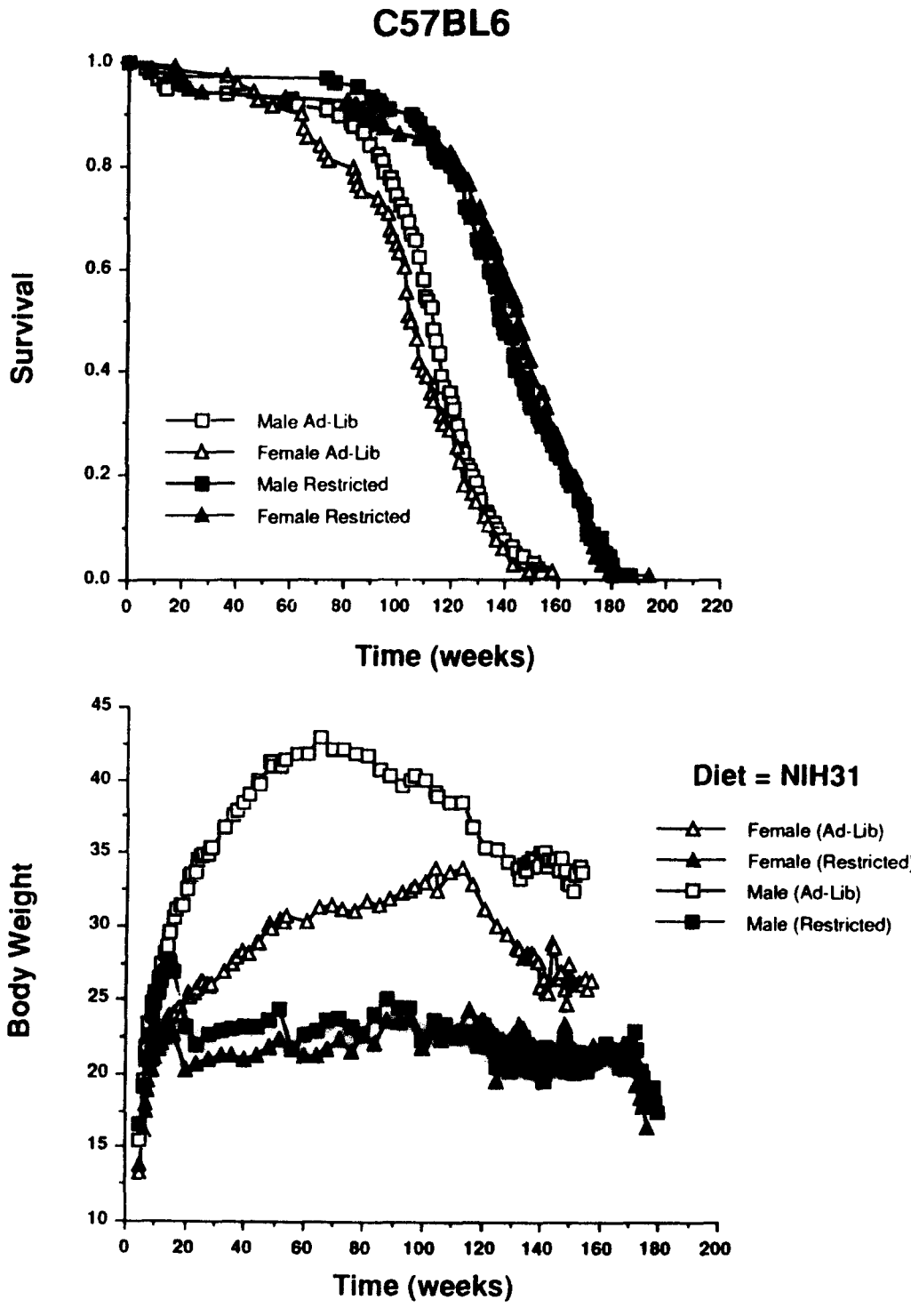

FIG. 1. Probability of survival and mean body weight for C57BL/6N mice in the NIA/NCTR biomarkers of aging colony. All mice were fed NIH31 autoclavable diet. Animals were housed one per side in modified polycarbonate cages that allowed visual and olfactory contact between pairs of animals, but that prevented physical contact (Sprott and Austad, 1996).

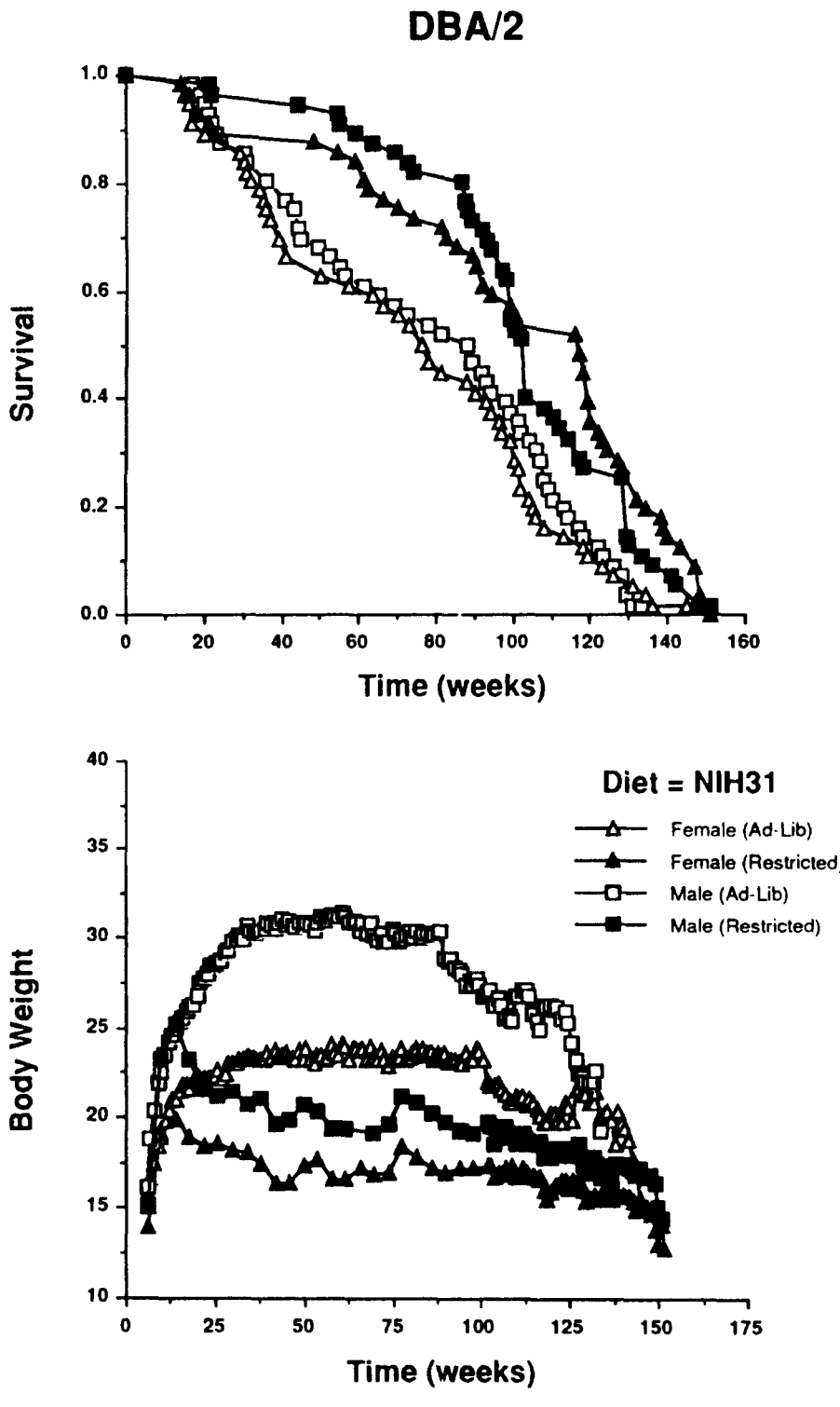

FIG. 2. Probability of survival and mean body weight for DBA/2N mice in the NIA/NCTR biomarkers of aging colony (Sprott and Austad, 1996).

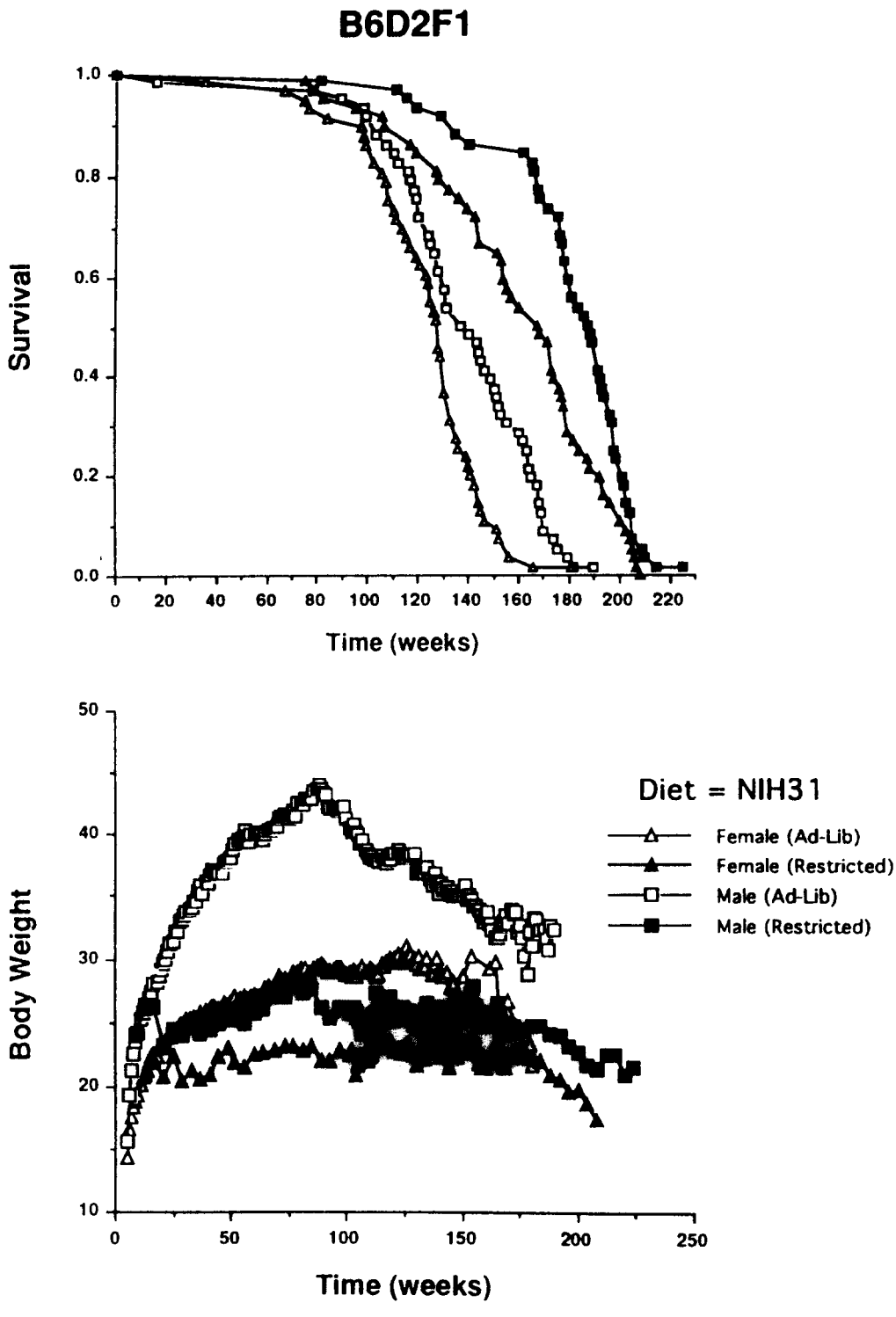

FIG. 3. Probability of survival and mean body weight for B6xD2F1 mice in the NIA/NCTR biomarkers of aging colony (Sprott and Austad, 1996).

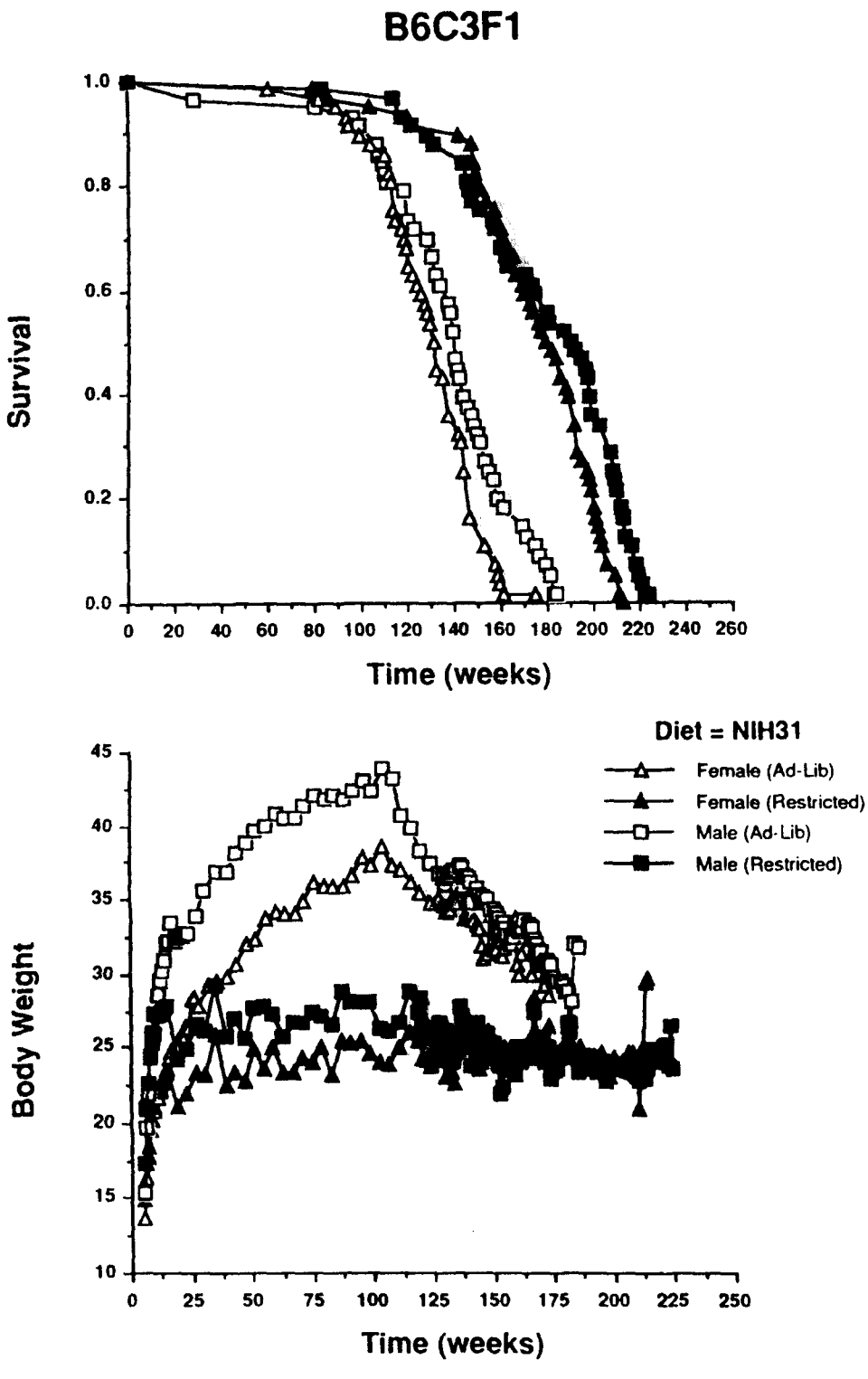

FIG. 4. Probability of survival and mean body weight for B6xC3F1 mice in the NIA/NCTR biomarkers of aging colony (Sprott and Austad, 1996).

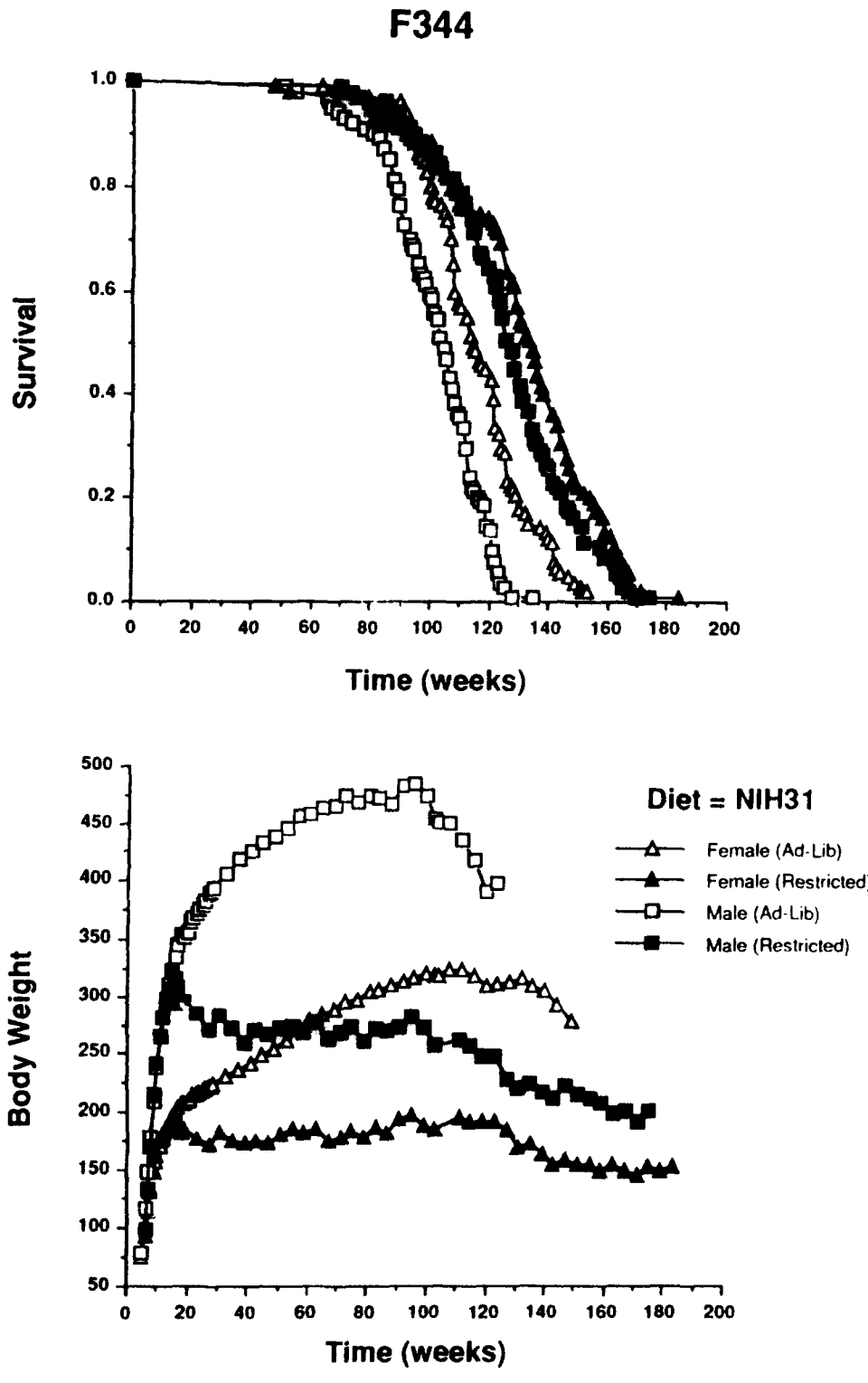

FIG. 5. Probability of survival and mean body weight for F344 rats in the NIA/NCTR biomarkers of aging colony (Sprott and Austad, 1996).

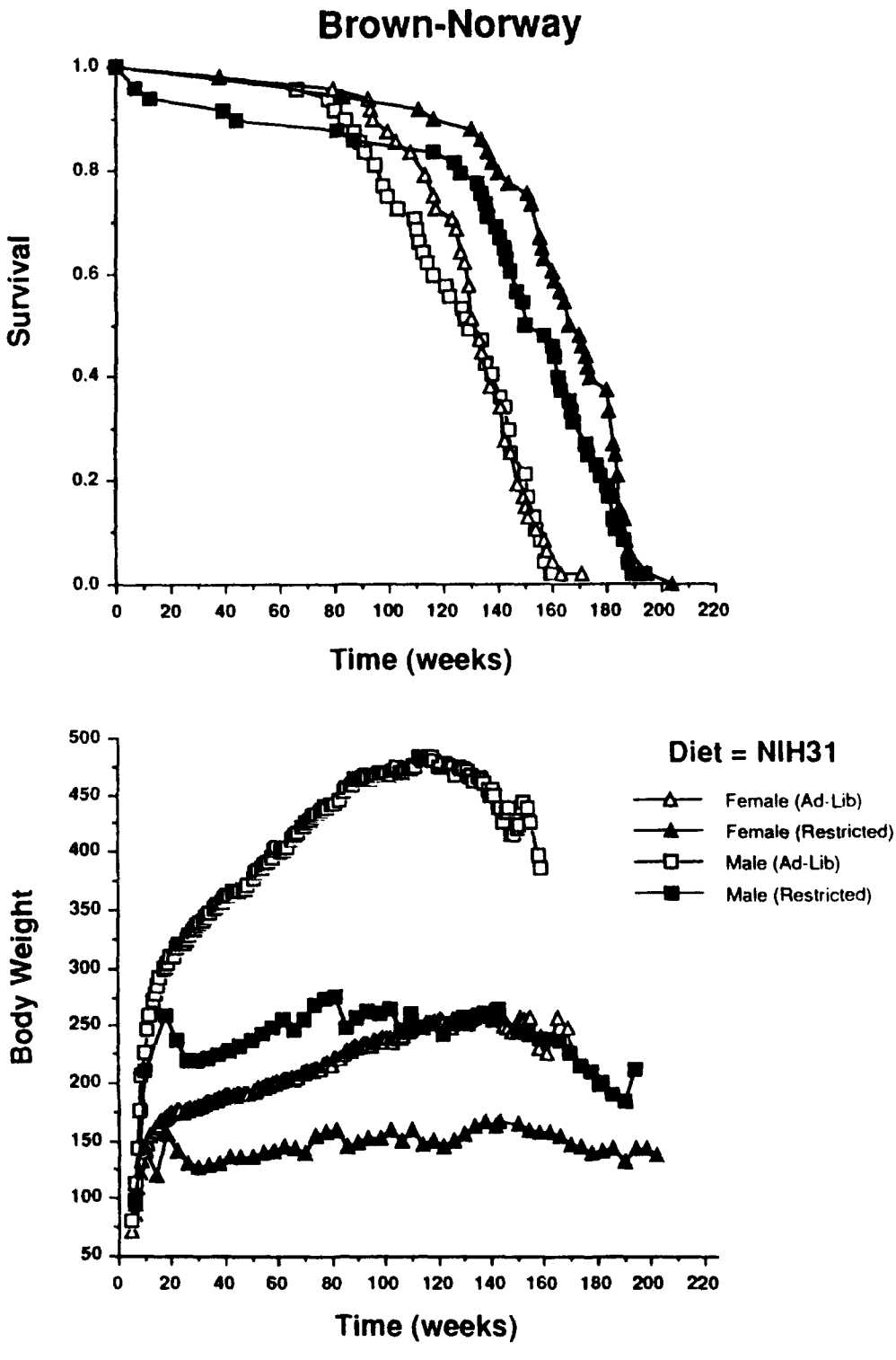

FIG. 6. Probability of survival and mean body weight for Brown Norway rats in the NIA/NCTR biomarkers of aging colony (Sprott and Austad, 1996).

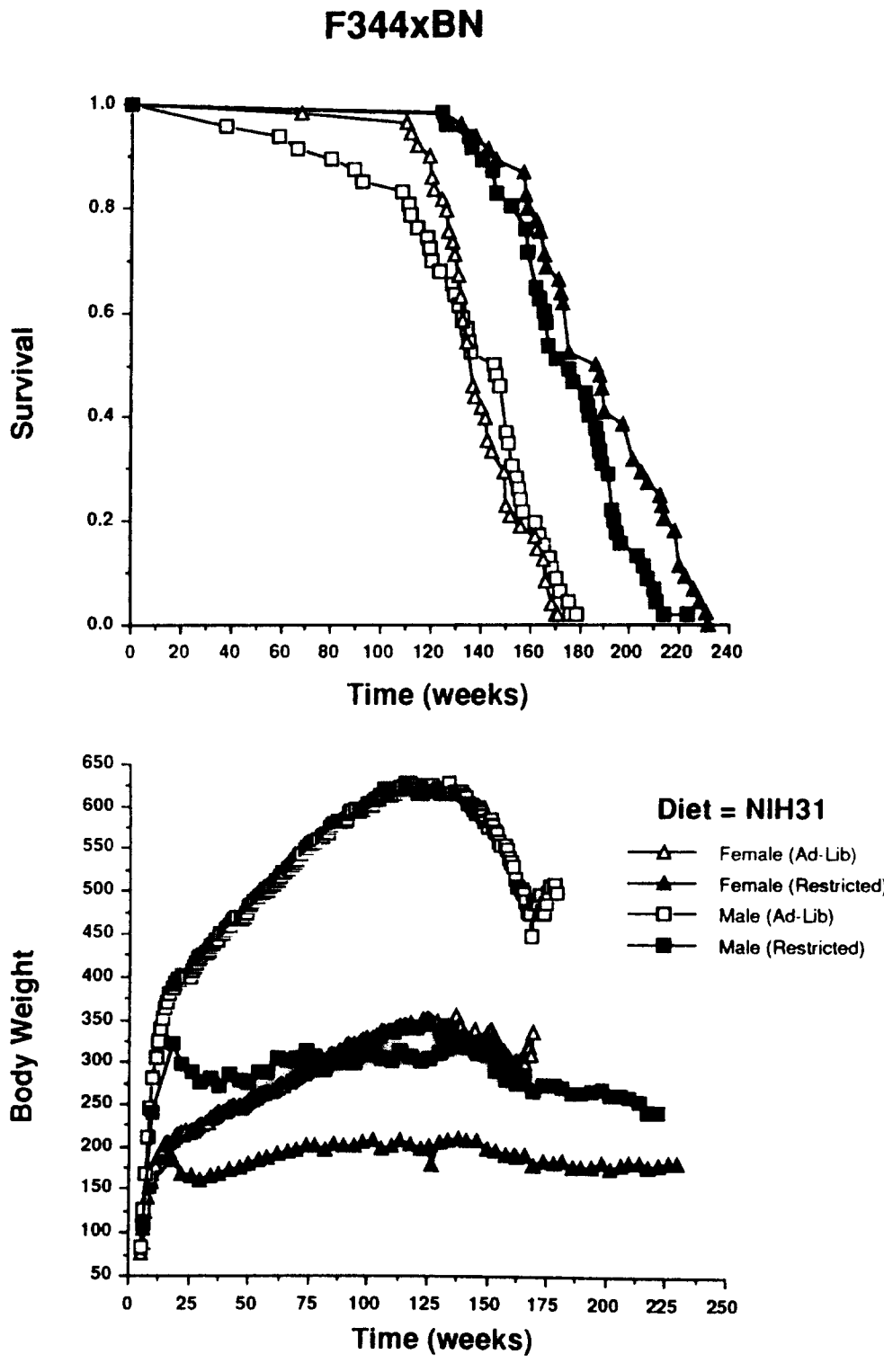

FIG. 7. Probability of survival and mean body weight for F344xBN rats in the NIA/NCTR biomarkers of aging colony (Sprott and Austad, 1996).

TABLE 1. MEDIAN LIFE SPAN

	Male		*Female*	
	Ad libitum	*Rest*	*Ad libitum*	*Rest*
Mouse				
B6D2F1	138	187	128	168
DBA2/N	88	104	77	117
B6C3F1	140	191	131	180
C57BL/6N	120	138	116	145
Rat				
BN	129	153	133	168
F344BNF1	145	175	137	187
F-344	103	125	116	132

Sprott and Austad, 1996.

CALORIE RESTRICTION AND INCREASED LIFE SPAN IN RODENTS

Clearly, diet can have a significant effect on life span and pathology. Of more interest is the question of whether more subtle diet effects have impact on basic aging processes. So far, the NIA has been unable to stimulate significant research on a diet to maximize life span. An experiment to do so was initiated at the Fruili Animal Research (FRAR) facility in northern Italy after the last of these courses. This experiment was unfortunately interrupted when funding for FRAR terminated due to the financial difficulties of The Fidia Pharmaceutical Company. It is our hope that the acquisition of this facility by Harlan-Italy and the creation of new research institute, the International Biogerontology Resource Institute (IBRI) at this facility will lead to a return to research of this type.

Meanwhile, the most striking demonstrations of the importance of diet and nutrition come from research on calorie restriction (CR). NIA, together with The National Center for Toxicological Research (NCTR) in Jefferson, AR, has carried out an assessment of the effects of CR

TABLE 2. MAXIMAL LIFE SPAN

	Male		*Female*	
	Ad libitum	*Rest*	*Ad libitum*	*Rest*
Mouse				
B6D2F1	180	215	163	207
DBA2/N	130	144	130	148
B6C3F1	180	221	164	208
C57BL/6N	150	178	147	174
Rat				
BN	158	190	163	194
F344BNF1	174	214	168	227
F-344	124	161	148	171

Sprott and Austad, 1996.

in four mouse and three rat genotypes for the last eight years. Dr. Lipman describes many of the pathology findings for these experiments elsewhere in this issue. Figures 1–7 from the NIA/NCTR Biomarker colonies show mortality curves for these animals, while Tables 1 and 2 give the median and maximal life spans (calculated by the mean of the last decile of survivors) of these animals in the colonies. Experiments with Masoro Diet, Emory Mouse 911, and NIH31 showed similar effects with all 3 diets. This data is from groups fed NIH31.

As you can see, calorie restriction extended life spans in all genotypes of mice and rats. This is true even in the F1 hybrids, which are longer lived than either of the parental types. CR studies show the magnitude of the effects that could be obtained by optimizing diets. Turturro and Hart (1992) have shown that C57BL/6 mice consuming the same total calorie intake ad libitum with different diets have different growth curves. Higher fat, isocaloric diets result in decreased survival. Given the magnitude of these effects, it is surprising that little interest in developing a "longevity diet" has been shown. The need has been obvious for more than 25 years, but such research is not appealing to reviewing groups and the market has been too small to attract commercial interest. The fact that the commonly used paradigms for toxicological assessments of drugs in the U.S. have become difficult to carry out due to body weight gain and early mortality led to a conference sponsored by the International Life Sciences Institute (ILSI) recently to consider whether CR should become the standard maintenance condition for all toxicity and carcinogenicity research (Hart *et al.*, 1995). NIA now makes CR animals available to all of its grantees. With the increase in use of the animals that will follow their greater availability, we expect that CR maintained animals will become the model of choice for investigators concerned about disease incidence or about modeling very late life phenomena. The development of an optimum, ad libitum-fed diet could save the large cost in resources and effort now needed to impose a CR regimen in a large rodent colony.

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