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Influence of the Restriction of Individual Dietary Components on Longevity and Age-Related Disease of Fischer Rats: The Fat Component and the Mineral Component

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The influence of restricting either the fat or the mineral component of the diet to the same extent as they are restricted in the life-prolonging, food-restriction paradigm but without restricting calories was studied in regard to longevity and age-related pathologic lesions of barrier-maintained male Fischer 344 rats. Neither the restriction of fat nor the restriction of mineral influenced the median length of life or maximum life span as indicated by the age of the 10th percentile survivors. Restricting the dietary fat did retard the development of chronic nephropathy and associated lesions, but it also increased the prevalence of lymphoma and leukemia. The development of chronic nephropathy was not significantly affected by restricting the mineral component of the diet.

IT is a generally held belief that food restriction retards aging processes (Masoro, 1985). This belief is based on its effects on life expectancy, maximum life span, physiologic deterioration, and age-related disease processes. Is this action of food restriction due to the reduced intake of food as a whole? Or of calories? Or is it the result of the decreased intake of specific food components?

Little existing research addresses these questions in an unequivocal fashion. Fortunately, however, the design of our food-restriction studies (Yu et al., 1982; Yu et al., 1985), in which a semisynthetic base diet is used, makes it possible to do so. Specifically, dextrin is a major ingredient of the base diet, and therefore, it is possible to restrict components of the diet by replacing the reduced component with dextrin. This does not appreciably influence diet composition except for the component being restricted. Of course, for the interpretation to be unambiguous, it is necessary that the caloric intake and the growth of the rats on the modified diet be the same as that of rats fed the base diet.

This procedure has been used to explore the effects of restricting only casein, the protein component of the diet, to the same extent as in the food-restriction protocol (Yu et al., 1985). The male Fischer 344 rats on this protein-restricted diet had the same caloric intake and growth as those fed the base diet. Protein restriction was found to retard the progression of chronic nephropathy and related disease processes but not to influence neoplastic disease (Maeda et al., 1985). It also did not influence age-related changes in the physiologic processes (Kalu et al., 1983; Kalu et al., 1984; Masoro et al., 1983). It extended the median length of life and the maximum life span as indicated by the age of 10th percentile survivors but marginally compared to food restriction. The median length of life was extended by 16% compared to 51% for food restriction, and the age of the 10th percentile survivors was extended by 14% compared to 49% for food restriction. Moreover, the effect of protein restriction on longevity appears to be related to the retardation of chronic nephropathy, whereas the action of food restriction on longevity appears to involve factors in addition to its effect on chronic nephropathy. The conclusion to be drawn is that protein restriction does not modulate aging processes in the broad fashion that characterizes food restriction.

This approach has been extended to assess the roles that the restriction of the fat and mineral components of the diet may play in the action of food restriction. The work of French et al. (1953) indicates that restriction of dietary fat may play an important part in the effect of food restriction on longevity. They reported that a high-fat diet significantly reduced the length of life of male Wistar strain rats in spite of the fact that it also lowered the caloric intake of these rats. However, contradictory results were reported by Birt et al. (1982), who reported that increasing the fat content of the diet of hamsters increased both caloric intake and longevity. In regard to the effect of mineral restriction, Cheney et al. (1983) showed that the life span of mice can be extended by food restriction in the absence of mineral restriction. However, these findings in no way preclude a role for mineral restriction in those food-restriction regimens in which minerals are restricted. Such is particularly true in studies using rats because of the evidence (Klahr et al., 1983) that minerals are involved in the occurrence of the nephropathy that is commonly found in this species and that progresses in severity with age. It is for these reasons that fat restriction and mineral restriction of the same extent as those used in

our food-restriction studies were evaluated using male Fischer 344 rats. The findings are the subject of this article.

MATERIALS AND METHODS

Rat maintenance and dietary procedures. — The male Fischer 344 rats used in this study were purchased as weanlings (26 to 30 days of age) from the Kingston, NY plant of the Charles River Laboratories. They were maintained in a barrier facility and monitored for virus antibodies and Mycoplasma as described in the accompanying article.

Until 6 weeks of age, all rats were fed a semisynthetic diet (Diet A) *ad libitum;* this is the standard diet that has been used in our laboratory for more than 10 years. (See Table 1 for dietary composition.) At 6 weeks of age, a group of 172 rats (Group A) continued to be fed Diet A *ad libitum* for the rest of their lives; of these, 60 were designated for the longevity study and 112 for the cross-sectional studies. The Group A rats serve as the reference standard to which all other dietary groups were compared. In the accompanying article the data from Group A rats were compared to those of rats fed the soy protein diet (i.e., Group C). In the present article, the data from Group A rats was used as a reference for two other dietary groups (Groups E and F).

Group E rats were fed a diet similar in composition to Diet A but in which the fat content was reduced to provide an intake similar to that of the food-restricted rats of our previous studies (Yu et al., 1982; Yu et al., 1985). The composition of Diet E is described in Table 1. Group E was comprised of 90 rats, 60 for the longevity study and 30 for cross-sectional studies.

The Group F rats were fed a diet similar in composition to Diet A but in which the mineral mix content was reduced to provide an intake similar to that of the food-restricted rats of our previous studies (Yu et al., 1982;.Yu et al., 1985). The composition of Diet F, which contained at least the NRC requirement for each mineral, is described in Table 1. Group F was comprised of 90 rats, 60 for the longevity study and 30 for cross-sectional studies.

The amount of food ingested by each rat was measured as described in the accompanying article. The body weight of each rat was measured at 2-week intervals.

Table 1. Composition of the Diets

Components (grams/100g of diet)	Diet A[a]	Diet E[b]	Diet F[c]
Casein (vitamin-free)	21	21	21
D,L Methionine	0.15	0.15	0.15
Dextrin	43.65	47.65	45.65
Sucrose	15	15	15
Corn oil	10	6	10
Ralstón-Purina vitamin mix	2	2	2
Choline chloride	0.2	0.2	0.2
Ralston-Purina mineral mix	5	5	3
Sōlka-Floc	3	3	3

[a]The physiologic caloric value is 4.10 Kcal/g.
[b]The physiologic caloric value is 3.97 Kcal/g.
[c]The physiologic caloric value is 4.18 Kcal/g.

Procedures for study of sacrificed rats. — Rats at 6, 12, 18, 24, and 27 months of age were sacrificed and assessed pathologically as described in the accompanying article. The organs and tissues also were processed and analyzed histologically as described in that article.

Procedures for study of rats dying spontaneously. — The processing of rats that died spontaneously was carried out as described in the accompanying article. Pathological analyses also were carried out as described in that article.

Grading of lesions. — The severities of chronic nephropathy, cardiomyopathy, hepatic bile duct hyperplasia, and hepatic fatty changes were graded. The grading systems are summarized in the accompanying article.

Statistical methods. — The data were analyzed as described in the accompanying article.

RESULTS

Food intake. — The intake of food expressed as Kcal per rat per day is presented in Figure 1. Through 2 years of age the food intake was similar for Groups A, E, and F and changed little with age. After 2 years of age, the food intake of Groups E and F tended to decrease. However, because after 125 weeks of age the number of rats in the food-consumption measurements was 3 or less from each group, the reliability of food-intake data at the advanced ages is questionable.

Body and organ weights. — Body weights of the rats in Groups A, E, and F are presented in Figure 2. All three groups had similar body weights through 110 weeks of age after which there was a loss in body weight and some difference between groups. The loss in body weight at advanced ages has been reported in almost all life-span studies with rats, and the reason for this has not been clearly

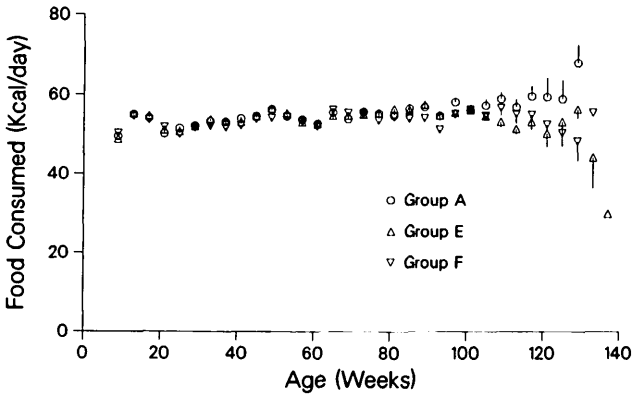

Figure 1. Food intake (Kcal per rat per day) by groups A, E, and F rats of the longevity study. The points are means (bar represents standard errors of the means); the number of rats at the start of this study was 60 for each group, and decreased with age as indicated by the survival curves in Figure 3a and b.

established. In regard to the differences in body weights between the groups observed at advanced ages, it must be kept in mind that the data reported at these ages are for the small number of rats still surviving in each group and, thus, may not be reliable. The changes in organ weight with age noted previously (Yu et al., 1985) for rats fed Diet A were observed in all three groups in the present study. There were no significant differences in the weight of organs between the three groups.

Longevity. — The survival curves for Groups A, E, and F are shown in Figure 3a and b. The curves of Group E and F rats did not differ significantly from that of the Group A rats. The median length of life and the age of the 10th percentile survivors are presented in Table 2. These did not differ significantly between the three dietary groups.

Chronic nephropathy. — The severity of chronic nephropathy in rats sacrificed at 6, 12, 18, 24, and 27 months of age (Table 3) increased with age in all three groups (Group A, $p = .03$; Group E, $p = .03$; Group F, $p = .002$). Data on the severity of chronic nephropathy in all rats that died spontaneously are reported in Table 4; the rats in Group A had more severe lesions than those in Group E ($p = .04$). Indeed, 41% of Group A rats had Grade E lesions compared to 25% for Group E rats. The rats in Group F did not differ significantly from those in Group A with regard to severity of chronic nephropathy.

Cardiomyopathy. — The severity of cardiomyopathy of rats sacrificed at 6, 12, 18, 24, and 27 months of age (Table 5) increased with age in all 3 groups (Group A, $p = .002$; Group E, $p = .0003$; Group F, $p = .02$). Data on the severity in all rats that died spontaneously are reported in Table 6; the rats in Group E had less severe lesions ($p < .05$) than the rats in Group A or F. Only 3% of the rats in Group E had Grade 3 lesions, but 18% of the rats in Group A and 23% of those in Group F had that severity of lesions at death.

Gastrointestinal lesions. — The types and extent of gastrointestinal lesions in rats that died spontaneously are presented in Table 6. The rats in Group E and F had a significantly lower prevalence of gastric hyperkeratosis ($p < .02$) and gastric ulcers ($p < .013$) than the rats in Group A. The rats in Group F exhibited less obstruction of the intestine by hair balls than the rats in Groups A and E ($p = .02$).

Hepatic lesions. — Hepatic lesions were assessed in rats that died spontaneously (Table 6). The rats of all three groups were similar with regard to the occurrence and severity of these lesions to that reported previously for rats fed Diet A (Maeda et al., 1985).

Reproductive lesions. — Reproductive lesions were assessed in rats that were sacrificed or died spontaneously (Tables 5 and 6). The rats of all three groups were similar with regard to occurrence and severity of these lesions to that previously reported for rats fed Diet A (Maeda et al., 1985).

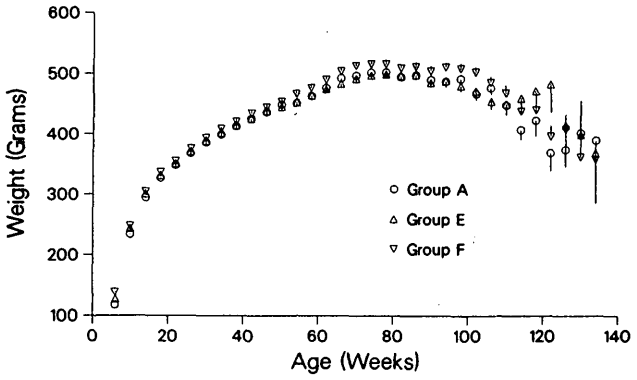

Figure 2. Body weights of Group A, E, and F rats of the longevity study. The points are means (bar represents standard errors of the means); the number of rats at the start of the study was 60 for each group and decreased with age as indicated by the survival curves in Figure 3a and b.

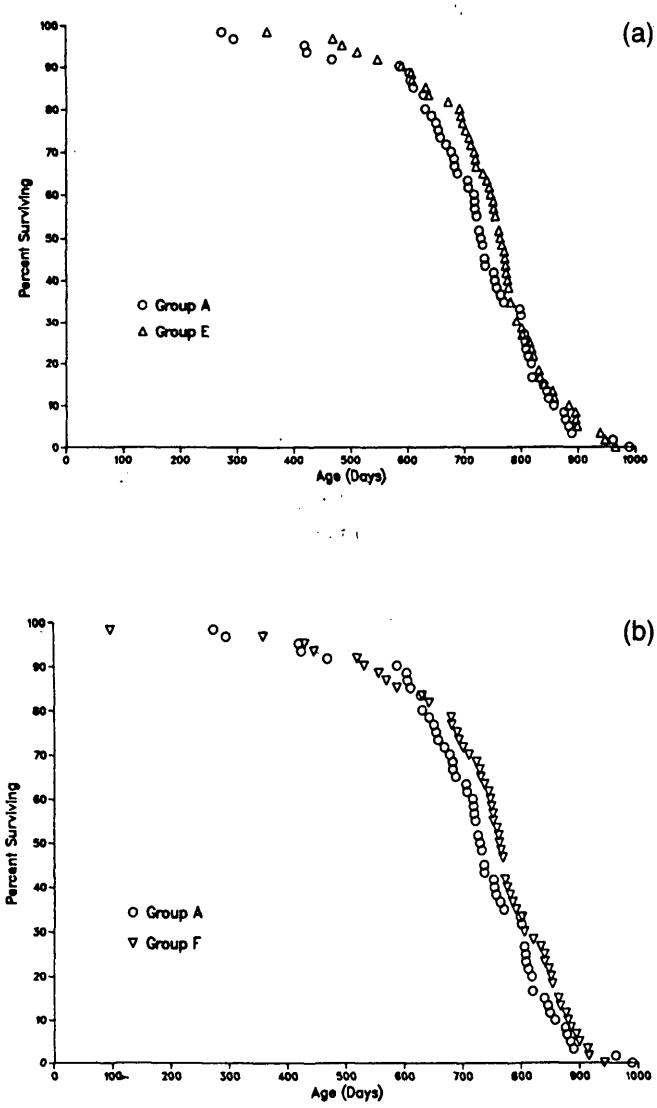

Figure 3. (a) Survival curves for Groups A and E rats; (b) survival curves for Group A and F rats. Each group had 60 rats at the start of the study.

Table 2. Summary of Longevity Findings

Findings	Diet groups		
	Diet A	Diet E	Diet F
Median length of life	730 (708-764)	764 (745-782)	763 (745-785)
Age of 10th percentile	857 (819-961)	884 (833-947)	879 (863-915)
Maximum length of life	989	965	942

Note. Entries are days; 95% Confidence intervals are in parentheses. n = 60 in each diet group.

Table 3. Severity of Chronic Nephropathy in Rats Sacrificed at Various Ages by Diet Group

Ages (in months)	Number examined	Number with lesions of grades					
		0	1	2	3	4	E
Diet Group A							
6	18	3	15	0	0	0	0
12	10	0	2	6	2	0	0
18	15	0	0	2	10	1	2
24	10	0	0	1	5	4	0
27	8	0	0	0	2	4	2
Diet Group E							
18	7	0	0	3	4	0	0
24	10	0	0	1	5	3	1
27	4	0	0	0	2	2	0
Diet Group F							
18	7	0	1	1	4	1	0
24	10	0	0	0	2	7	1
27	4	0	0	0	0	4	0

Note. See accompanying article for description of lesion grades.

Neoplastic lesions. — Neoplastic lesions were not seen in rats before 12 months of age (Tables 5 and 6). For the most part, the age of occurrence, the prevalence, and the nature of neoplastic disease were similar in the three dietary groups. However, some differences were noted in the case of the rats dying spontaneously. Group A rats had less lymphoma or leukemia (p = .043) than rats in Group E and less benign soft tissue mesenchymal tumors (p = .00035) than rats in Groups E and F. Group F rats had less thyroid C-cell tumors (p = .037) than rats in Groups A and E but more pheochromocytoma (p = .05) than rats in Group E.

Miscellaneous nonneoplastic lesions. — Data on the following lesions in rats that died spontaneously are reported in Table 6: osteodystrophy; calcium deposition in heart, kidney, and muscle; pancreatic lobular atrophy; and thyroid C-cell hyperplasia. A smaller percentage of Group E rats had osteodystrophy and calcium deposits in muscles than the rats in Group A ($p < .05$). A higher percentage of the rats in Group F had calcium deposits in the heart than the rats in Group E (p = .03).

DISCUSSION

Restricting the intake of the corn oil component or the mineral component of the semisynthetic diet to the same extent as in our food-restriction studies (Yu et al., 1982; Yu et al., 1985) did not significantly affect the median length of life or the age of the 10th percentile survivors. In contrast, food restriction increased the median length of life by 51% and the age of the 10th percentile survivors by 49% (Yu et al., 1985). Restricting the protein component only did increase longevity but far less markedly than food restriction (Yu et al., 1985). Moreover, protein restriction did not retard the broad spectrum of age-related physiologic changes or pathologic processes that food restriction does (Masoro et al., 1983; Kalu et al., 1983; Kalu et al., 1984; Maeda et al., 1985). Thus, the individual restriction of three of the dietary components — protein or fat or mineral — to the same extent as in the food-restriction paradigm does not markedly affect longevity, neither does it broadly modulate other age-associated events. Because the vitamin component of the diet was not restricted in our food-restriction studies (Yu et al., 1982; Yu et al., 1985), only the carbohydrate and fiber components remain to be investigated individually. Data from such a study, coupled with the data of the present and our earlier studies (Yu et al., 1985; Maeda et al., 1985), would provide, in addition to information on each of the dietary components, unequivocal evidence against the possibility that food restriction extends life by reducing the intake of a toxic contaminant of the diet. Although this possibility is often suggested by gerontologists and others not working in the food-restriction area, it does not seem likely because many studies demonstrating that food restriction extends life and retards the aging processes have used a broad range of food sources (Weindruch, 1985). The data in the present study

Table 4. Severity of Chronic Nephropathy in Rats Dying Spontaneously by Age and Diet Group

Ages (in months)	Number examined	Number with lesions of grades					
		0	1	2	3	4	E
Diet Group A							
<12	4	0	3	1	0	0	0
12 to 18	9	0	3	6	0	0	0
18 to 24	60	0	0	6	15	14	25
24 to 30	36	0	0	1	4	11	20
>30	2	0	0	0	0	1	1
Total	111	0	6	14	19	26	46
Diet Group E							
<12	2	1	1	0	0	0	0
12 to 18	7	0	4	3	0	0	0
18 to 24	20	0	0	4	7	4	5
24 to 30	39	0	0	6	8	14	11
>30	3	0	0	0	0	1	2
Total	71	1	5	13	15	19	18
Diet Group F							
<12	3	2	1	0	0	0	0
12 to 18	4	0	1	2	0	1	0
18 to 24	21	0	0	8	7	4	2
24 to 30	38	0	0	0	7	11	20
>30	3	0	0	0	1	1	1
Total	69	2	2	10	15	17	23

Note. See accompanying article for description of lesion grades.

Table 5. Lesions Other Than Chronic Nephropathy in Rats Sacrificed at Various Ages by Diet Group

Types of lesions	6 months of age	12 months of age	18 months of age			24 months of age			27 months of age		
	Group A (n = 18)	Group A (n = 10)	Group A (n = 15)	Group E (n = 7)	Group F (n = 7)	Group A (n = 10)	Group E (n = 10)	Group F (n = 10)	Group A (n = 8)	Group E (n = 4)	Group F (n = 4)
Cardiomyopathy											
Number with Grade 0 lesions	11	3	3	2	1	0	2	0	0	0	0
Number with Grade 1 lesions	7	7	10	5	6	6	6	6	2	0	1
Number with Grade 2 lesions	0	0	2	0	0	3	2	3	4	2	2
Number with Grade 3 lesions	0	0	0	0	0	1	0	1	2	2	1
Number with reproductive system lesions											
Testicular interstitial cell											
Hyperplasia	0	0	9	3	3	8	5	8	6	4	4
Tumors	0	0	11	2	7	9	8	10	8	4	4
Atrophy of seminiferous tubules	1	1	3	2	7	9	8	10	8	4	4
Testicular calcium deposits	0	2	2	1	6	3	7	3	6	2	1
Acute or chronic prostatitis	0	0	1	0	1	0	0	1	5	1	0
Number of tumor-bearing rats[a]											
Benign	0	0	8	1	5	7	4	8	5	2	4
Malignant	0	0	0	1	1	1	1	1	3	0	2
Total	0	0	8	2	5	7	4	8	6	2	4
Number with epithelial tumors[b]											
Benign	0	0	2	1	0	0	1	2	2	0	1
Malignant	0	0	0	0	0	0	1	0	0	1	2
Number with mesenchymal tumors[b]											
Benign	0	0	1	0	0	0	0	1	0	0	2
Malignant	0	0	0	0	1	0	0	0	0	0	0
Number with selected non-endocrine-specific tumors											
Preputial gland	0	0	1	0	5	3	2	1	0	0	1
Lymphoma or leukemia	0	0	0	0	0	0	0	0	2	0	0
Mesothelioma	0	0	0	0	0	0	0	1	0	0	0
Number with endocrine tumors											
Pituitary adenoma	0	0	3	0	0	3	1	4	4	0	0
Thyroid C-cell tumors	0	0	0	1	0	2	1	3	2	1	0
Thyroid follicular tumors	0	0	0	0	0	0	0	0	1	1	0
Adrenal cortical tumors	0	0	1	0	0	0	1	0	1	0	0
Pheochromocytoma	0	0	0	0	0	0	1	1	0	0	0
Pancreas islet cell tumors	0	0	1	0	0	4	2	3	1	0	1

[a]Tumors other than testicular interstitial cell tumors.
[b]Other than those listed under the headings of selected nonendocrine-specific tumors or endocrine gland tumors.

Table 6. Lesions Other Than Chronic Nephropathy in Rats Dying Spontaneously at Various Ages by Diet Group

Types of lesions	< 12 months of age			12 to 18 months of age			18 to 24 months of age			24 to 30 months of age			> 30 months of age			Total		
	Group A (n = 4)	Group E (n = 2)	Group F (n = 3)	Group A (n = 9)	Group E (n = 7)	Group F (n = 4)	Group A (n = 60)	Group E (n = 20)	Group F (n = 21)	Group A (n = 36)	Group E (n = 39)	Group F (n = 38)	Group A (n = 2)	Group E (n = 3)	Group F (n = 3)	Group A (n = 111)	Group E (n = 71)	Group F (n = 69)
Cardiomyopathy																		
Number with Grade 0 lesions	2	1	2	2	1	2	3	0	0	0	2	1	0	0	0	7	4	5
Number with Grade 1 lesions	2	1	0	7	6	2	23	15	11	8	15	4	0	0	0	40	37	17
Number with Grade 2 lesions	0	0	1	0	0	0	25	5	10	18	20	18	1	3	2	44	28	31
Number with Grade 3 lesions	0	0	0	0	0	0	9	0	0	10	2	15	1	0	1	20	2	16
Number with lesions of gastrointestinal tract																		
Esophageal hyperkeratosis	0	1	0	5	2	2	31	13	17	24	23	26	2	3	3	62	42	48
Gastric hyperkeratosis	1	0	0	0	1	2	28	4	3	22	14	12	1	2	0	52	21	17
Gastric ulcer	0	0	0	0	0	0	21	2	2	19	10	10	1	2	1	41	14	13
Intestinal obstruction by hair balls	3	1	0	6	5	1	2	1	0	0	0	0	0	0	0	11	7	1
Number with hepatic lesions																		
Bile duct hyperplasia																		
Number with Grade 0 lesions	4	2	3	3	3	2	0	0	1	0	2	1	0	0	0	7	7	7
Number with Grade 1 lesions	0	0	0	5	2	2	28	11	11	14	24	15	0	0	2	47	37	30
Number with Grade 2 lesions	0	0	0	1	2	0	21	6	7	15	8	15	2	3	0	39	19	22
Number with Grade 3 lesions	0	0	0	0	0	0	11	3	2	7	5	7	0	0	1	18	8	10
Fatty change																		
Number with Grade 0 lesions	1	1	1	2	2	1	14	2	4	8	10	8	1	1	2	26	16	16
Number with Grade 1 lesions	3	1	2	6	4	3	32	14	12	20	18	24	0	2	0	61	39	41
Number with Grade 2 lesions	0	0	0	1	1	0	8	3	5	5	7	4	0	0	1	14	11	10
Number with Grade 3 lesions	0	0	0	0	0	0	6	1	0	3	4	2	1	0	0	10	5	2
Periductal fibrosis	0	0	0	0	3	0	38	8	5	31	19	27	1	2	3	70	32	35
Cystic space	1	0	0	0	0	0	6	1	3	8	11	9	1	3	0	16	15	12
Number with reproductive system lesions																		
Testicular interstitial cell																		
Hyperplasia	0	0	0	1	1	0	28	9	9	14	17	17	0	0	1	43	27	27
Tumors	0	0	0	0	0	0	46	17	17	35	33	37	2	3	3	83	53	57
Atrophy of seminiferous tubules	0	0	1	1	1	1	35	14	12	32	34	35	2	3	3	70	52	52
Testicular calcium deposits	0	0	0	0	2	0	23	8	9	18	20	21	1	3	3	42	33	33
Acute or chronic prostatitis	3	2	1	1	2	0	14	3	2	10	10	14	2	0	1	30	17	18

(continued)

Table 6. Lesions Other Than Chronic Nephropathy in Rats Dying Spontaneously at Various Ages by Diet Group (continued)

Types of lesions	< 12 months of age			12 to 18 months of age			18 to 24 months of age			24 to 30 months of age			> 30 months of age			Total		
	Group A (n = 4)	Group E (n = 2)	Group F (n = 3)	Group A (n = 9)	Group E (n = 7)	Group F (n = 4)	Group A (n = 60)	Group E (n = 20)	Group F (n = 21)	Group A (n = 36)	Group E (n = 39)	Group F (n = 38)	Group A (n = 2)	Group E (n = 3)	Group F (n = 3)	Group A (n = 111)	Group E (n = 71)	Group F (n = 69)
Number of tumor-bearing rats[a]																		
Benign	0	0	0	2	0	2	34	9	13	24	29	30	2	3	2	62	41	47
Malignant	0	0	0	1	2	1	24	11	12	16	17	12	0	2	2	41	32	27
Total	0	0	0	3	2	3	46	17	20	31	33	32	2	3	3	82	55	58
Number with epithelial tumors[b]																		
Benign	0	0	0	0	0	0	4	0	0	3	4	3	1	0	0	8	4	3
Malignant	0	0	0	0	1	0	5	1	1	3	1	0	0	1	1	8	3	2
Number with mesenchymal tumors[b]																		
Benign	0	0	0	0	0	0	2	2	3	0	8	8	0	1	0	2	11	11
Malignant	0	0	0	1	0	0	4	1	2	0	3	2	0	1	0	5	5	4
Number with selected nonendocrine-specific tumors																		
Preputial gland	0	0	0	0	0	0	11	5	6	3	7	7	0	2	1	14	14	14
Lymphoma or leukemia	0	0	0	0	0	1	5	5	3	2	6	5	0	0	0	7	11	9
Mesothelioma	0	0	0	0	0	0	4	2	2	0	0	1	0	0	0	4	2	3
Number with endocrine tumors																		
Pituitary adenoma	0	0	0	1	0	1	15	3	3	10	9	13	1	1	1	27	13	18
Thyroid C-cell tumors	0	0	0	1	0	0	8	3	1	8	11	4	0	1	1	17	15	6
Thyroid follicular tumors	0	0	0	0	0	0	2	0	0	2	2	1	0	0	0	4	2	1
Adrenal cortical tumors	0	0	0	0	0	0	3	0	0	1	4	2	0	0	1	4	4	3
Pheochromocytoma	0	0	0	0	0	1	2	0	3	5	3	7	1	1	0	8	4	11
Pancreas islet cell tumors	0	0	0	0	0	0	5	1	0	6	9	8	1	0	0	12	10	8
Number with selected nonneoplastic lesions																		
Osteodystrophy	0	0	0	0	0	0	16	1	1	16	10	17	1	1	2	33	12	20
Calcium deposits in																		
Heart	0	0	0	0	0	0	12	5	3	13	8	20	1	1	2	26	14	25
Kidneys	4	0	1	2	3	1	34	13	11	29	21	30	1	3	1	70	40	44
Muscles	0	0	0	0	0	0	21	1	3	20	11	17	2	3	2	43	15	22
Pancreatic lobular atrophy	0	0	0	2	2	0	18	5	7	7	9	8	0	1	0	27	17	15
Thyroid C-cell hyperplasia	0	0	0	0	0	0	21	3	3	15	14	14	0	0	1	36	17	18

[a]Tumors other than testicular interstitial cell tumors.
[b]Other than those listed under the headings of selected nonendocrine-specific tumors or endocrine gland tumors.

and those of our earlier study (Yu et al., 1985) provide further evidence that such contaminants are not the basis for the life-prolonging effects of food restriction.

Of course, it is possible that the restriction of individual dietary components may provide little information on the action of food restriction on the aging processes because such action may depend on synergistic interactions between restricted components or because the reduction of caloric intake rather than specific nutrients is the basis of the antiaging effects. Other research from our laboratory (Masoro et al., 1982) provides further insight into these issues. Specifically, the intake of calories and other nutrients per unit of lean body mass was found not to be reduced by food restriction; that is, lean body mass was reduced in proportion to the decrease in caloric intake. Subsequent work by McCarter et al. (1985) on metabolic rate per unit of lean body mass or of "metabolic mass" is in accord with this view. On the basis of these findings, our conclusion is that food restriction does not modulate aging processes by reducing the intake per unit of protoplasmic mass of either calories or a specific nutrient or a combination of nutrients. Our working hypothesis is that food restriction acts on the total organism by modulating its endocrine or neural regulatory systems or both. It is further hypothesized that these regulatory systems couple food restriction with the aging process of the tissues and organs of the body and that a direct action of a reduced nutrient flux to those tissues and organs is not involved. The data in this paper are consistent with this view.

Although longevity was not influenced, the rats in Group E (the corn oil-restricted group) had less severe chronic nephropathy at death than the rats in Group A (fed the standard diet). There is a considerable literature on the effects of dietary lipid on renal disease, but much of it is contradictory, and nothing is conclusive (Klahr et al., 1983). Our data clearly show that the age-related progression of chronic nephropathy in the rat is decreased by reducing the dietary fat component of the diet. Brenner et al. (1982) believe that the chronic nephropathy occurring in rats is similar to the progression of chronic renal failure to end-stage disease in humans who previously have had their kidneys damaged by an acute disease. If so, in managing such patients, attention should probably be paid to dietary fat.

It is striking that although the rats in Group E had less severe chronic nephropathy than those in Group A, there was not a significant increase in median length of life or age of the 10th percentile survivors of Group E rats compared to Group A rats. Moreover, the rats in Group E had less severe cardiomyopathy, a lower prevalence of gastric ulcers and osteoporosis than the rats in Group A. A possible reason for the lack of effect on longevity may be found in the data on neoplastic disease. At death, the rats in Group E had a higher prevalence of lymphoma or leukemia than the rats in Group A. These findings suggest that differences in diet may explain the discrepancy between the results of Maeda et al. (1985), indicating that chronic nephropathy is the major disease process contributing to the death of *ad libitum* fed Fischer 344 rats, and the results of Maloney et al. (1970) and Stromberg and Vogtsberger (1983), indicating that large granular lymphocyte leukemia is the major contributing disease in the death of this strain.

In summary, the restriction of the fat component of the diet to the same extent as it is restricted in life-prolonging, food-restriction regimens did not influence the median length of life or the maximum life-span potential (as indicated by the age of the 10th percentile survivors). However, the restriction of the fat did retard the development of chronic nephropathy and associated lesions, such as gastric ulcers, osteodystrophy, and calcium deposits in muscle. In regard to longevity, these beneficial actions may be counterbalanced by the higher prevalence of lymphoma and leukemia in the fat-restricted rats. Restricting the mineral component of the diet also did not influence longevity, neither did it significantly affect the development of chronic nephropathy. The latter is of particular interest because most rat diets are rich in minerals (including our standard diet), and minerals have been implicated in the development of nephropathy (Klahr et al., 1983).

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REFERENCES

Birt, D. F.; Higginbotham, S. M.; Patel, K.; Pour, P. Nutritional effects on the lifespan of Syrian hamsters. Age 5:11–19; 1982.

Brenner, B. M.; Meyer, T. W.; Hostetter, T. H. Dietary protein intake and progressive nature of kidney disease. N. Engl. J. Med. 307:652–657; 1982.

Cheney, K. E.; Liu, R. K.; Smith, G. S.; Meredith, P. J.; Mickey, M. R.; Walford, R. L. The effect of dietary restriction of varying duration on survival, tumor patterns, immune function, and body temperature in B10C3F$_1$ female mice. J. Gerontol. 38:420–430; 1983.

French, C. E.; Ingram, R. H.; Uram, J. A.; Barron, G. P.; Swift, R. W. Influence of dietary fat and carbohydrate on growth and longevity in rats. J. Nutr. 51:329–339; 1953.

Kalu, D. N.; Cockerham, R.; Yu, B. P.; Rose, B. A. Lifelong dietary modulation of calcitonin levels in rats. Endocrinology 113:2010–2016; 1983.

Kalu, D. N.; Hardin, R. R.; Cockerham, R.; Yu, B. P. Aging and dietary modulation of rat skeleton and parathyroid hormone. Endocrinology 115:1239–1247; 1984.

Klahr, S.; Buerkert, J.; Purkerson, M. L. Role of dietary factors in the progression of chronic renal disease. Kidney Int. 24:579–587; 1983.

Maeda, H.; Gleiser, C. A.; Masoro, E. J.; Murata, I.; McMahan, C. A.; Yu, B. P. Nutritional influences on aging of Fischer 344 rats: II. Pathology. J. Gerontol. 40:671–688; 1985.

Maloney, B. C.; Boschetti, A. E.; King, V. P. Spontaneous leukemia in Fischer rats. Cancer Res. 30:41–43; 1970.

Masoro, E. J. Nutrition and aging — A current assessment. J. Nutr. 115:842–848; 1985.

Masoro, E. J.; Compton, C.; Yu, B. P.; Bertrand, H. Temporal and compositional dietary restrictions modulate age-related changes in serum lipids. J. Nutr. 113:880–892; 1983.

Masoro, E. J.; Yu, B. P.; Bertrand, H. A. Action of food restriction in delaying the aging process. Proc. Natl. Acad. Sci. USA 79:4239–4241; 1982.

McCarter, R.; Masoro, E. J.; Yu, B. P. Does food restriction retard aging by reducing metabolic rate? Am. J. Physiol. 248:E488–E490; 1985.

Stromberg, P. C.; Vogtsberger, L. M. Pathology of mononuclear cell leukemia of Fischer rats. I. Morphologic studies. Vet. Pathol. 20:698–708; 1983.

Weindruch, R. Aging in rodents fed restricted diets. J. Am. Geriatr. Soc. 33:125–132; 1985.

Yu, B. P.; Masoro, E. J.; McMahan, C. A. Nutritional influences on aging of Fischer 344 rats: I. Physical, metabolic, and longevity characteristics. J. Gerontol. 40:657–670; 1985.

Yu, B. P.; Masoro, E. J.; Murata, I.; Bertrand, H. A.; Lynd, F. T. Life span study of SPF Fischer 344 male rats fed ad libitum or restricted diets: Longevity, growth, lean body mass and disease. J. Gerontol. 37:130–141; 1982.

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