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HISTOLOGY AND SURVIVAL IN AGE-DELAYED LOW-TRYPTOPHAN-FED RATS

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SUMMARY

Diets containing tryptophan in concentrations 30 and 40 percent of those fed to controls from weaning to 24–30 months or more, can delay aging in Long–Evans female rats. Mortality among low-tryptophan-fed rats was greater in the juvenile period, but substantially less than controls at late ages. Histological biomarkers of aging were also delayed after tryptophan restriction in some organs (liver, heart, uterus, ovary, adrenal and spleen) but not in others (kidney, lung, aorta). Brain serotonin levels were low in tryptophan-deficient rats but showed remarkable capacity for rehabilitation. Effects on early and late mortality and brain levels of serotonin were proportional to the severity of the restriction.

Key words: Biomarkers of aging; Tryptophan restriction; Brain serotonin; Lifespan; Histology.

INTRODUCTION

Severe nutritional restriction is the most reliable known means of delaying aging in the laboratory mammal [1–10]. Low-tryptophan diets, a convenient and effective form of underfeeding, increase maximum lifespan [1,6,7], postpone the onset of tumors [7,11], retard the aging-related loss of temperature homeostasis [9] and slow the senescent deterioration of the coat in female rats [7]. The following results illustrate some age-delaying effects of these low-tryptophan diets at the histological level, and link the magnitude of the age-delay to the severity of the diet.

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Low levels of tryptophan in the diet cause voluntary restriction of food intake [7]. Therefore, some of the observations reported here may be due, at least in part, to food restriction. Tryptophan restriction is relatively easy and less costly to implement than food restriction (e.g. food need not be weighed and aliquoted daily as the rats themselves eat less). Tryptophan restriction has also proven capable of delaying several biomarkers of aging, including age-related cessation of reproductive function [3]. In the present experiment, our major purpose was to compare histological changes, brain serotonin and body growth, under conditions of delayed aging and prolonged survival. To this effect, we have chosen two levels of tryptophan restriction of increasing severity which previous experience had shown capable of satisfying such conditions.

MATERIALS AND METHODS

At 21 days of age, female Long-Evans rats were assigned to groups as described previously [1]:

(1) A control group fed Purina Rat Chow *ad libitum*.
(2) A group fed a low-tryptophan diet with supplemental tryptophan added.
(3) A group fed a low-tryptophan diet containing 40% of the tryptophan fed to rats in Group 2 (T40% diet).
(4) A group fed a low-tryptophan diet containing 30% of the tryptophan fed to rats in group 2 (T30% diet).

At 2, 4, 6, 12 and 24 months of age, 5–7 animals from each group were sacrificed for neurochemical, histological and electron microscopic analysis.

Of the 23 Group 3 rats which survived to 2 years of age and were not then sacrificed, one had been placed on a Purina Rat Chow diet at 23 months of age, five at 28–29 months, and three at approximately 30 months of age. The remaining 14 rats were allowed to finish our their lifespans on this T40% diet.

In Group 4, 20 rats reached 2 years of age; the others either died or had been sacrificed. Of these 20, seven were sacrificed. The remaining 13 were then studied. One of these Group 4 survivors was switched to Purina Rat Chow at 23 months, eight were switched to Rat Chow at 28–29 months, and one was switched at nearly 36 months of age.

The regional (cerebral hemispheres, mesodiencephalon, and pons-medulla) brain neurochemical analyses [1] measured dopamine, norepinephrine and serotonin, as well as levels of several of their related enzymes. Only the results of the serotonin assays are discussed here.

The histological samples were obtained as follows: Dissected organs were fixed in Bouin's solution, a central portion of each organ was embedded in paraffin, and

serially sectioned at a thickness of 6 μm. Sections were stained with Meyer's Hematoxylin and Eosin. The electron microscopy samples are still in preparation.

All data were statistically analyzed. The level of significance (P) between two sets of data was calculated according to Student t-tests.

RESULTS

Control diets

Controls include rats from Group 1 and 2, that is, rats fed a commercial diet (Purina Chow) and those fed the tryptophan-deficient diet supplemented with tryptophan to the same amount as contained in the commercial diet. Inasmuch as no significant differences were found between the two groups with respect to any parameter measured, the data were pooled and the animals henceforth designated as controls.

Body weight

The average body weights of control and low-tryptophan-fed (Groups 3 and 4) rats at ages up to 24 months are shown in Table I. As expected, tryptophan being an essential amino acid for growth, growth is inhibited in these deficient animals and the growth rate corresponds to the level of dietary tryptophan. However, not all animals respond in the same way to tryptophan deficiency. Fig. 1 illustrates the idiosyncratic effect of the low-tryptophan diets on growth. Both 9-month-old animals shown were fed the T40% diet from weaning. One animal was nearly normal size, the other was similar in weight to a 4-week-old rat.

TABLE I

EFFECTS OF DIETARY TRYPTOPHAN-RESTRICTION ON BODY WEIGHTS

	Age in months				
Treatment	*2 Months*	*4 Months*	*6 Months*	*12 Months*	*24 Months*
Control	214.0 ± 4.6[a] $N = 12$	312.8 ± 9.5 $N = 11$	324.8 ± 7.8 $N = 12$	321.0 ± 9.2 $N = 10$	341.2 ± 9.5 $N = 13$
Tryptophan-Restriction T40%	68.2 ± 6.4 $N = 6$	101.2 ± 5.6 $N = 5$	169.2 ± 29.0 $N = 5$	259.2 ≡ 13.0 $N = 5$	270.0 ± 12.2 $N = 6$
Tryptophan-Restriction T30%	51.8 ± 2.6 $N = 6$	73.0 ± 8.0 $N = 5$	85.8 ± 9.0 $N = 5$	159.8 ± 21.7 $N = 5$	249.6 ± 13.1 $N = 5$

[a]Means ± S.E. of body weight in grams. N, number of animals. All differences between controls and experimental rats are statistically (t test) significant.

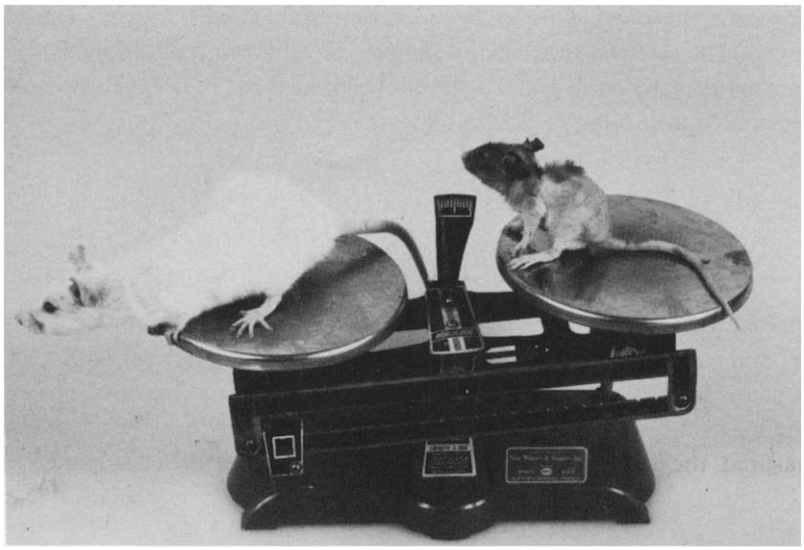


Fig. 1. Idiosyncratic effect of a low-tryptophan diet. Both 10-month-old rats shown here were fed the T40% from weaning. Body weights are: rat on the right: 55 g; rat on the left: 199 g. Controls of the same average 300 g; rats on the T40% diet, average 180 g.

Survival

The percentage of animals surviving in Groups 1, 2, 3 and 4 at yearly intervals is shown in Fig. 2. This figure includes rats sacrificed at yearly intervals, accounting for the decreasing values for "*n*" with time. Thus, while all control rats lived to at least 1 year of age, a number of these survivors were sacrificed, and are not considered in the 2-year survival statistics. While survival was less in the first year for Group 3, and much less in the first year for Group 4, at 3 years of age survival of these low-tryptophan-fed groups was greater than controls. The rats fed the diet lowest in tryptophan (Group 4) are the group most compromised in their first year of life, but, paradoxically, they are also those with the greatest surviving percentage by the third year, and constitute the only group in which survivors reach and exceed 4 years of age.

The survivorship of control and experimental animals, excluding sacrificed animals, also reveals the increase in early mortality with decreasing concentrations of dietary tryptophan (Fig. 3). It, too, highlights the reduced loss of low-tryptophan-fed animals at late ages. Exclusion of rats dying in the first year, clearly demonstrates the lower rate of age-related mortality in the groups fed lower concentrations of tryptophan (Table II).

Neurochemistry

Neurochemical analyses of specific brain regions showed that serotonin levels were significantly lower in tryptophan-deficient animals than controls, especially in the

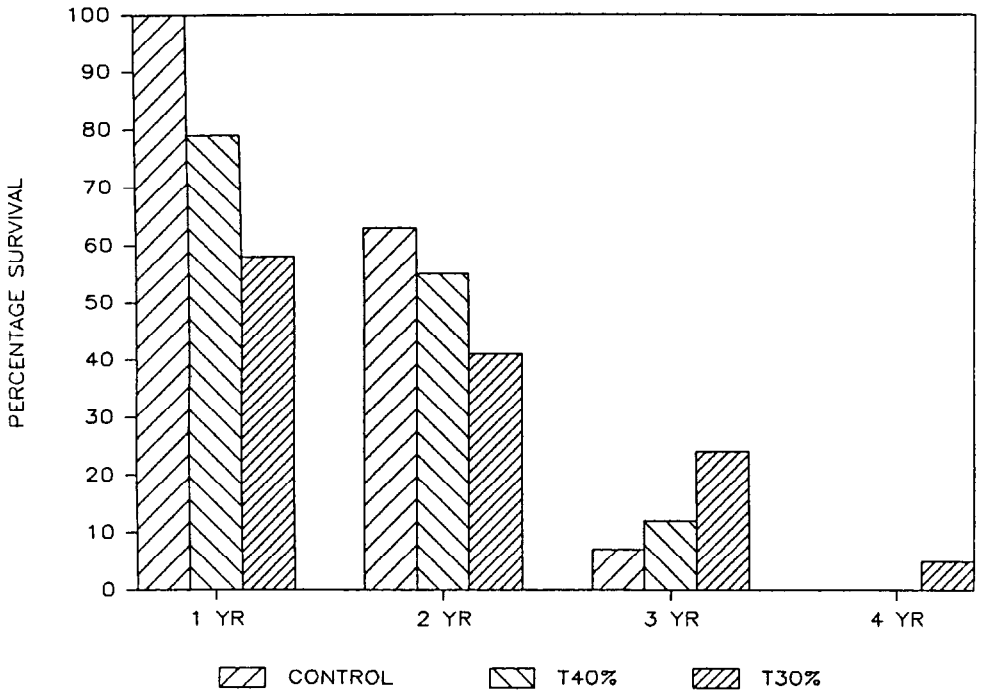


Fig. 2. Fractions of rats surviving in control, T40% and T30% tryptophan-fed rats. Surviving fractions for years 1, 2, 3 and 4, for controls are 72/72, 36/57, 3/43, 0. For T40% they are: 50/63, 30/55, 6/48, 0. For T30% they are: 33/57, 20/49, 10/42, and 2/42.

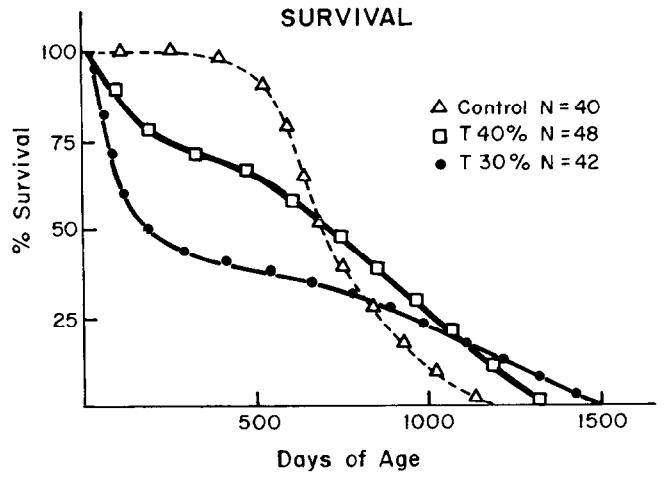


Fig. 3. Unculled rat populations fed control and tryptophan-restricted diets from weaning to adolescence. The highest rate of early mortality is seen in the group (T30%) showing the greatest maximum lifespan and the slowest rate of aging.

TABLE II

AGING-RELATED MORTALITY

	% *Surviving*[a]			
Treatment	50%	25%	10%	*MAX*
Control	712	869	954	1246
T40%	850	940	1125	1347
T30%	1050	1250	1330	1527

[a]Per cent of population surviving at advancing ages (in days). Includes only rats surviving at least 1 year. MAX, maximum lifespan reached.

first 2–6 months after initiation of the experimental diets (Fig. 4). Low serotonin levels occurred in all regions studied and were slightly lower after the T30% than the T40% diet. Although the animals continued to be fed the tryptophan-deficient diets, serotonin content eventually approached or equalled control levels even in the group most deprived of tryptophan, but this occurred more rapidly in rats fed the less severe diet. In this latter group, which was fed the T40% diet, brain serotonin levels declined

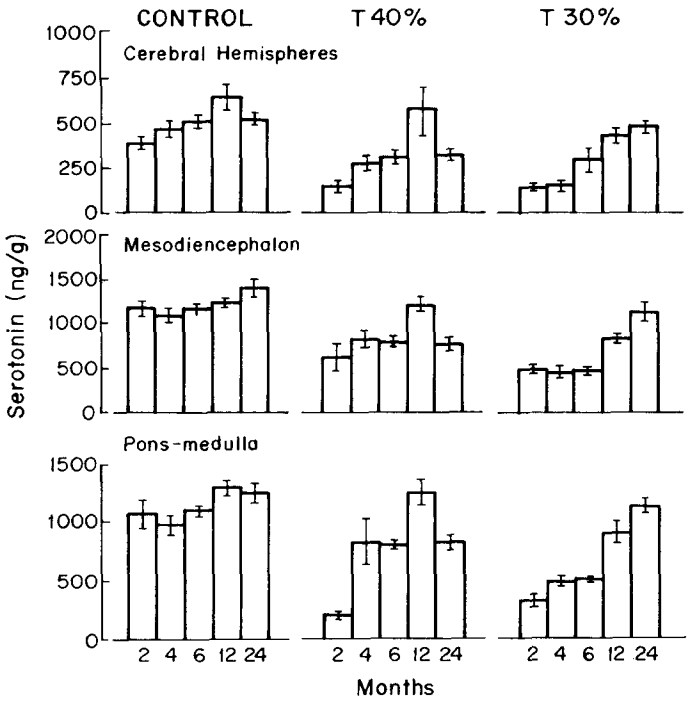


Fig. 4. Serotonin levels in cerebral hemisphere, mesencephalon-diencephalon and pons-medulla in control rats ($N = 8$–13), reach high values early in life, while high values appear only after 1 year in T40%-fed rats ($N = 3$–6) and after 2 years in T30%-fed rats ($N = 4$–5). Note reduction in serotonin levels in late-age T40%-fed rats.

between 1 and 2 years of age. During this time, the increase in mortality was much steeper in these rats than in those fed the T30% diet, suggesting a possible senescence-associated diminished capacity for rehabilitation in the brains of T40% rats as compared to those fed the T30% diet.

Histology

Histological examinations of the tissues and organs of the two control groups show no difference in the age-related changes. Similarly significant differences could not be observed between the T40% and T30% diets, except for a smaller cell size of T30% rats at very young ages. Therefore, most of the following histological descriptions of rats fed the T30% diet apply to those fed the T40% as well.

Liver

The hepatocytes of young rats are identical in size. The nuclei are almost of constant size, except for smaller nuclei in binuclear cells (Fig. 5A). Some hepatocytes of old rats are large with huge nuclei, and the nuclear diameter of mononuclear cells varies more than in the liver of young rats. Some cells contain numerous lipid droplets in the cytoplasm (Fig. 5B). In 3.5-year-old rats, large vacuoles are observed in some cells and regions (Fig. 5C).

The portal triads, (i.e. portal vein, hepatic artery, and bile duct) (Fig. 5D) show remarkable changes in old rats. In 3 and 3.5-year-old rats, the bile canaliculi are hyperplastic (Fig. 5E), as are the interlobular arteries (Fig. 5F). Similar lesions are also found in about half of the 2-year-old rats (6/13).

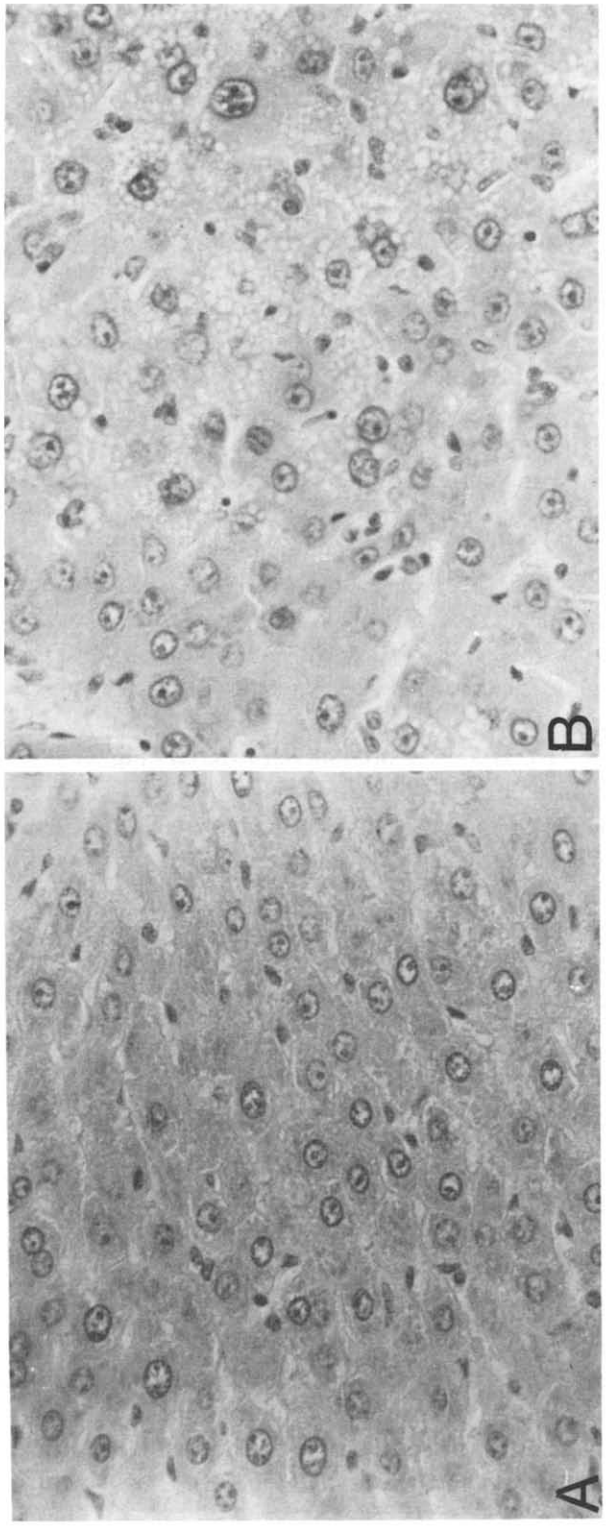
In 2-year-old tryptophan-deficient rats, the hepatocytes are small. In the rats of the oldest group, which were transferred to a normal diet after tryptophan deficiency for 2 years, lipid droplets and vacuoles in the cells are fewer than in cells of controls of the same age. The hyperplastic bile canaliculi and the thickened arteries are not observed in these rats (0/2). Portal triads in the livers of 2-year-old tryptophan-deficient rats showed fewer age-related changes than controls of the same age. No lesions were observed in the livers of rats fed either the T40% or T30% diet (0/11).

Heart

The myocardium of 2-year-old rats appears normal, both in control and tryptophan-deficient rats. Severe myocardial degeneration and fibrosis were observed in one of the 3-year-old control rats (Fig. 6A) but they were not detected in the tryptophan-deficient group (Fig. 6B).

Reproductive organs

The uterus of 2-year-old controls has a thin and flat epithelium, and shows diestrus features (Fig. 7A). About half of the tryptophan-deficient rats of the same age show uteri in estrus. Their epithelia are thick and folded, with leucocyte infiltration of the surface surrounding the cavity (Fig. 7B).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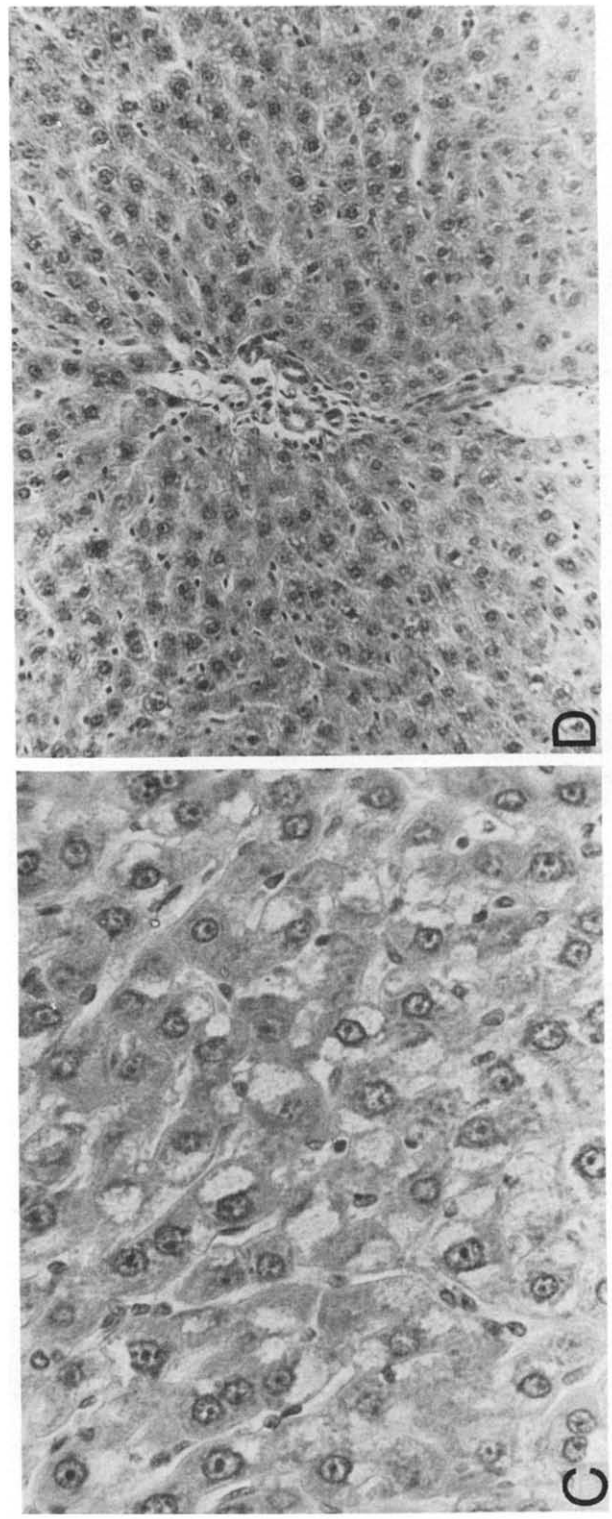
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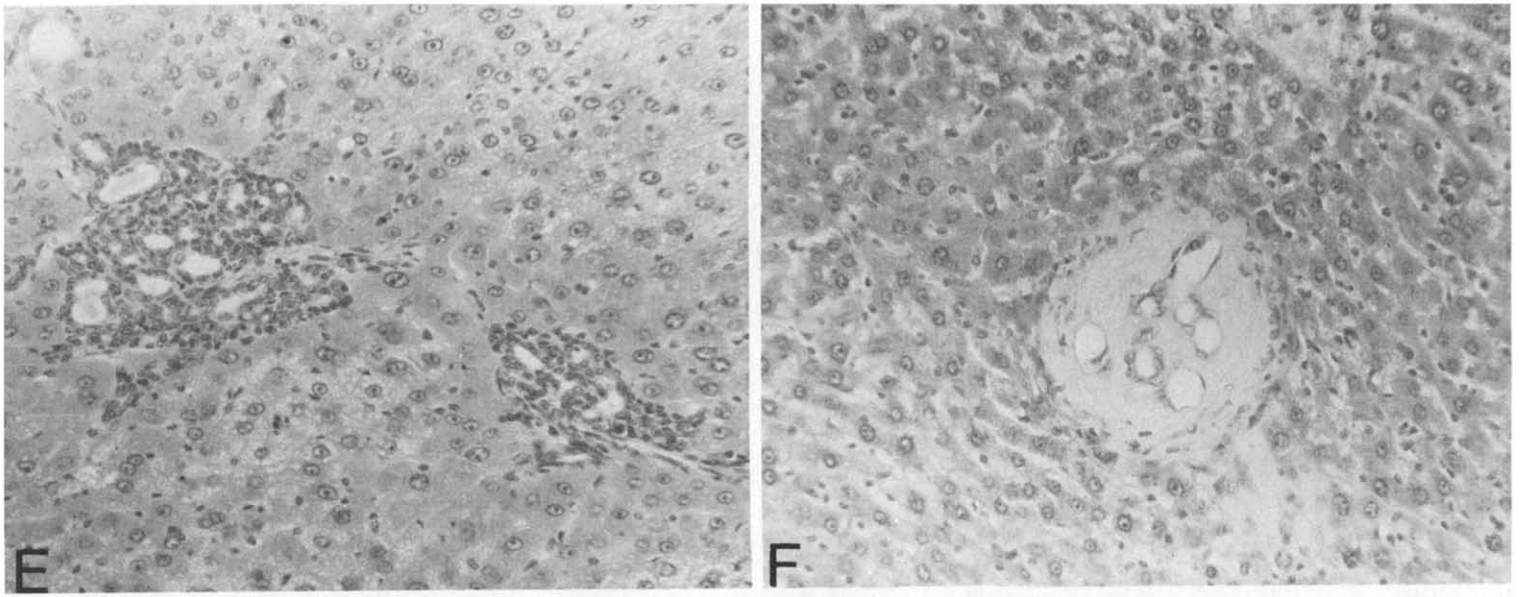


Fig. 5. Histological changes in liver with aging in controls. (A) Hepatocytes from a 6-month-old rat; (B) Hepatocytes from a 3-year-old rat. Some cells are very large and contain numerous lipid droplets; (C) Hepatocytes from a 3.5-year-old rat. Note the large vacuoles in most cells; (D) Portal triad in a 6-month-old rat; (E) Bile duct hyperplasia in a 3-year-old rat; (F) Portal triad with thickening of the bile duct wall in a 3.5-year-old rat.

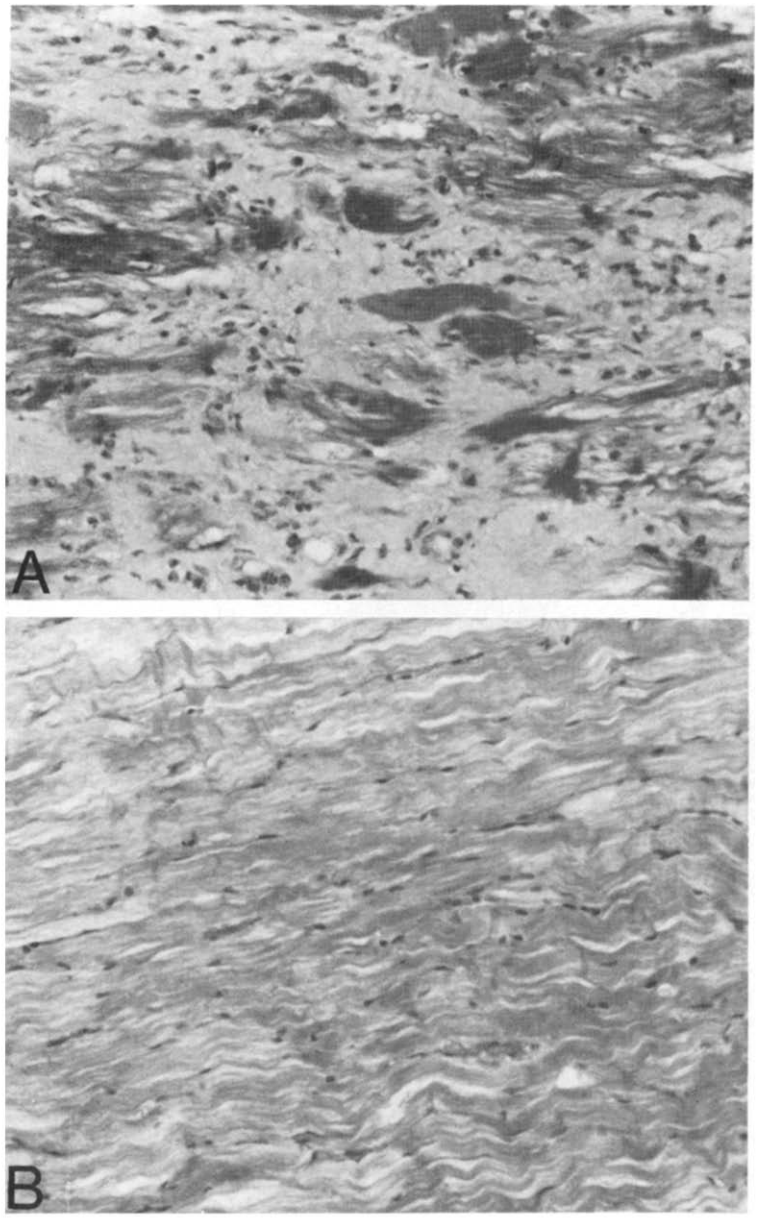


Fig. 6. Myocardial changes with aging and tryptophan-deficient diet. (A) Myocardial degeneration with fibrosis in a 3-year-old control rat; (B) Myocardium of a 3-year-old rat fed a tryptophan-deficient diet. Note the absence of degenerative changes.

Although the normal estrous cycles have ceased in 2-year-old rats, the ovarian follicles of both control and tryptophan-deficient rats contain many oocytes, and appear to be still active. All the ovarian follicles of normal 3 and 3.5-year-old rats are atretic and devoid of oocytes (Fig. 8A). In contrast, in the ovaries of a 3-year-old rat

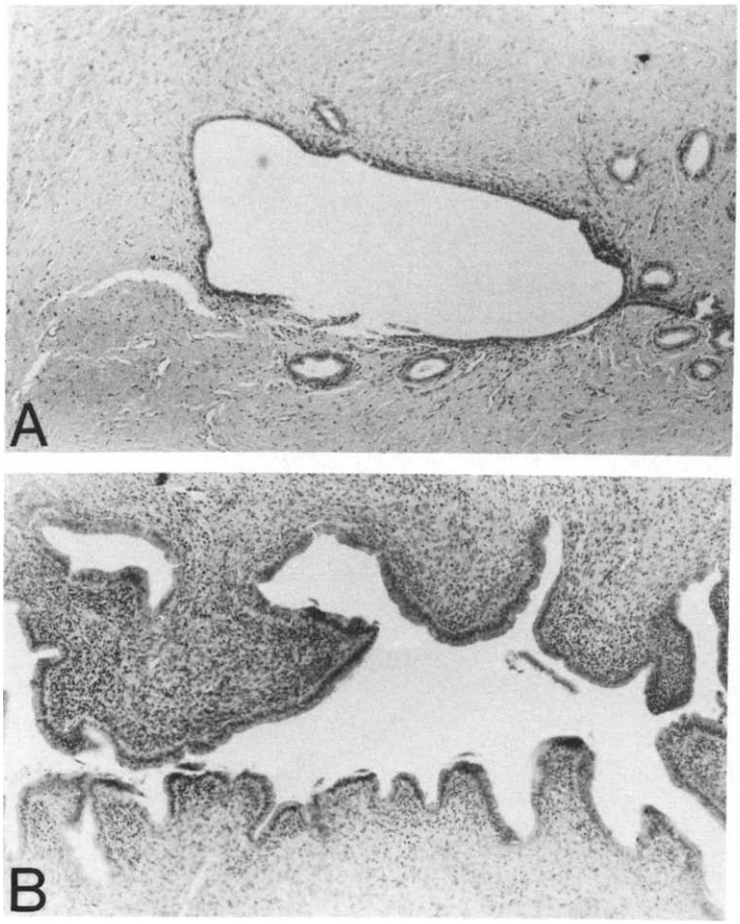


Fig. 7. Uterine changes with aging and tryptophan-deficient diet. (A) Uterus of a 2-year-old control rat in diestrus showing flat and thin epithelium; (B) Uterus of a 2-year-old rat fed a tryptophan-deficient diet shows thick and folded epithelium and leucocyte infiltration (estrus).

fed the tryptophan-deficient diet until 24 months of age, some follicles contain healthy looking oocytes (Fig. 8B).

Adrenal

Adrenals of the rat older than 2 years have many large blood-filled sinuses in the medulla (Fig. 9A). Lipofuscin pigment accumulates in the cells of the zona reticularis. In 3-year-old rats, the zona reticularis contains many cystic spaces and cells with vacuoles (Fig. 9B).

In the 3-year-old rats fed the tryptophan-deficient diet for the first 24 months of life, cells of the zona reticularis retained their youthful appearance, although they have some lipofuscin pigment (Fig. 9C).

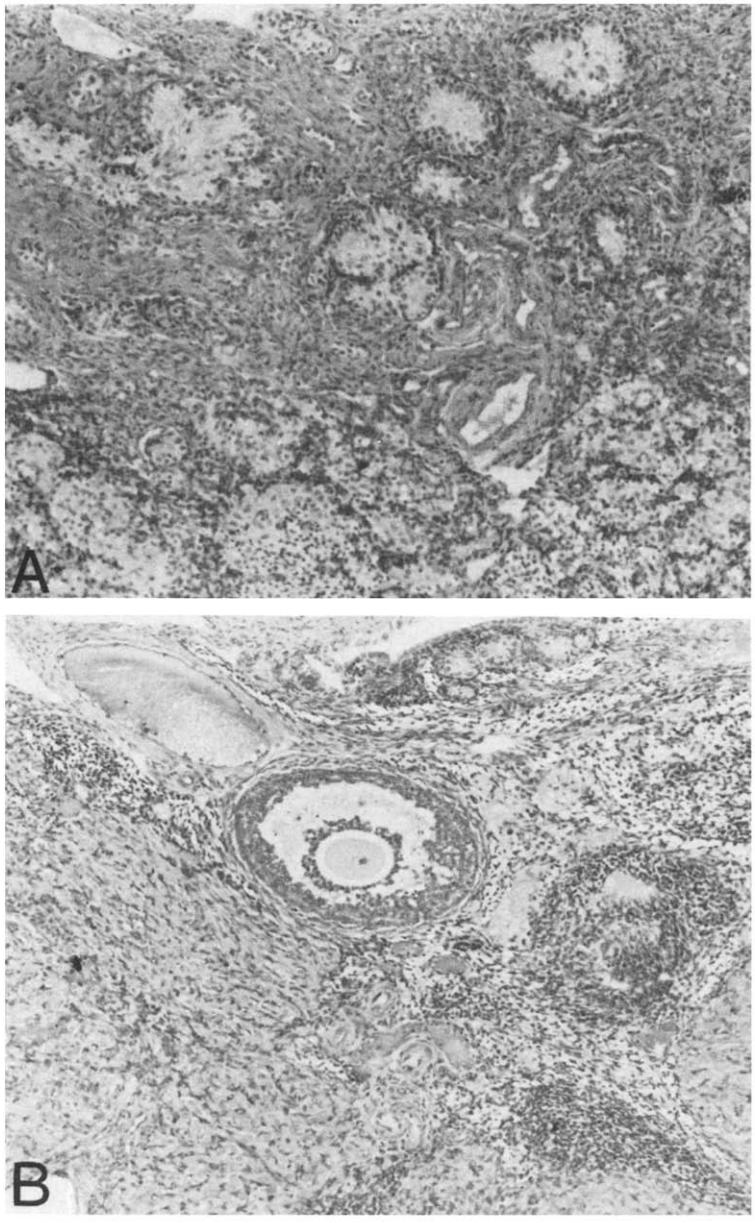


Fig. 8. Ovarian changes with aging and tryptophan-deficient diet. (A) Ovary of a 3-year-old control rat with atretic follicles; (B) Ovary from a rat of the same age as in (A) but fed a tryptophan-deficient diet for the first 2 years of life. Note the numerous active follicles.

Spleen

The spleens of 2 and 2.5 year-old rats contain a large amount of hemosiderin pigment. In the spleen of the older rats, hemosiderin pigment is further reduced, and trabeculae are more frequently observed (Fig. 10A). White pulp surrounding arteries

is atrophic. In tryptophan-deficient 3-year-old rats, the spleen has more white pulp than control (Fig. 10B).

Kidney

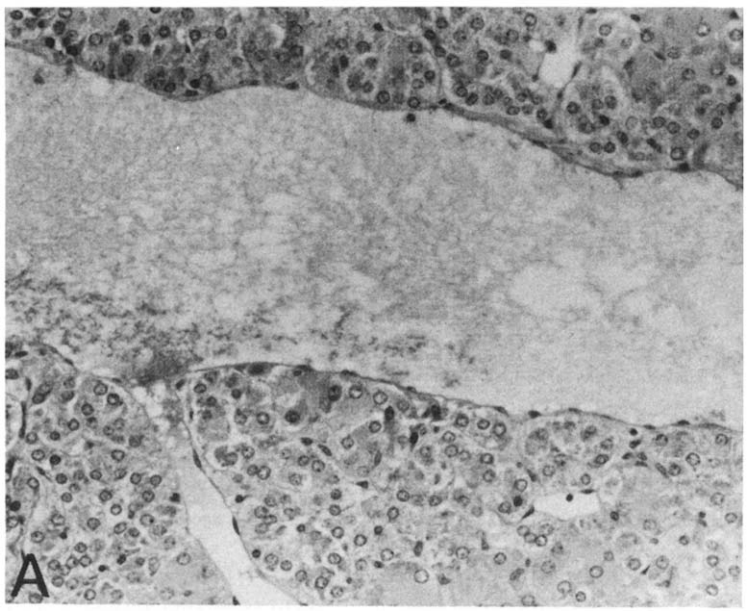
In the kidneys of rats older than 3 years, many cells in the distal and proximal tubules degenerate and these tubules develop cysts (Fig. 11A), that are also found in tryptophan-deficient rats. Edema was observed in some 2-year-old rats which were fed the commercial diet (Fig. 11B).

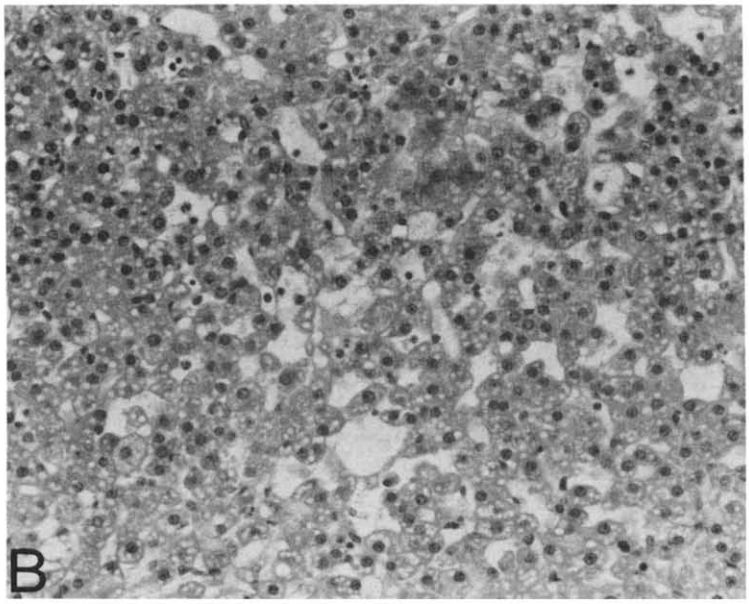
Lung

In the lung of 2-year-old rats, perivascular aggregation of lymphocytes is common. In 3-year-old rats, partial thickening of the alveoli and infiltration of leukocytes are observed. These lesions are present to the same extent also in tryptophan-deficient animals.

Aorta

The walls of the aorta in old rats (older than 2 years) thicken and elastic fibers are fewer than in young rats. These changes are observed also in the tryptophan-deficient rats.





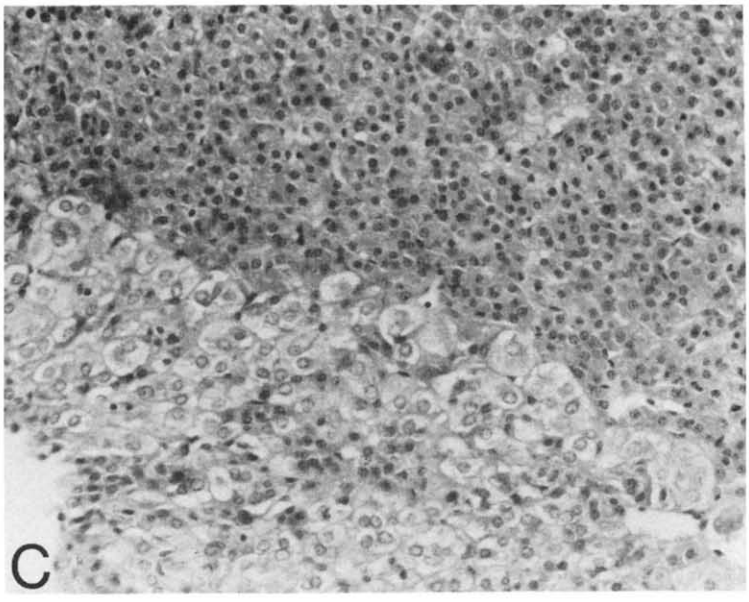


Fig. 9. Adrenal changes with aging and tryptophan-deficient diet. (A) Medulla of a 3-year-old control rat with a large, blood filled sinus; (B) Zona reticularis of the cortex in a 3-year-old control rat. Note numerous vacuoles and lipid droplets; (C) Medulla and cortex of a 3-year-old rat fed a tryptophan-deficient diet for the first 2 years of life. The medulla contains some sinuses, but the zona reticularis resembles that of young adult rats.

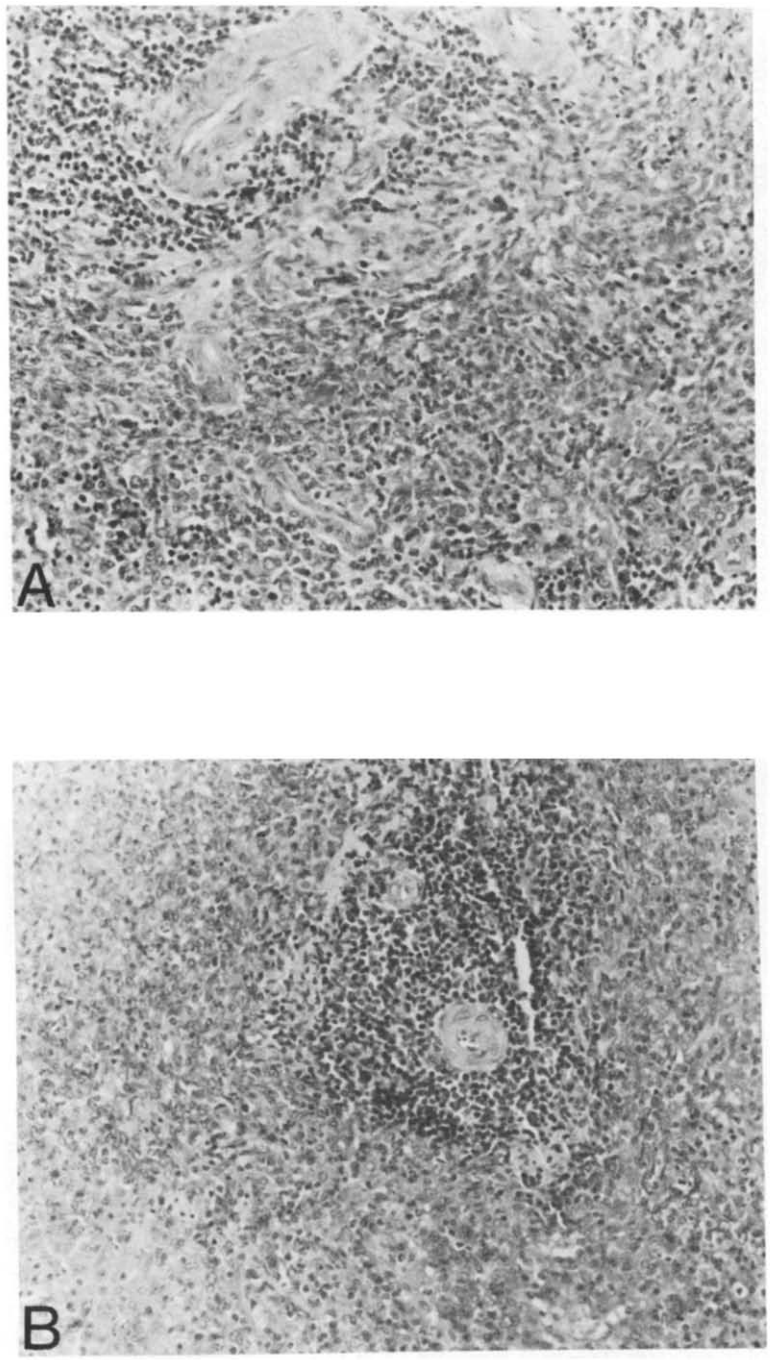


Fig. 10. Splenic changes with aging and tryptophan-deficient diet. (A) Spleen of a 3-year-old control rat; (B) Spleen of a 3-year-old rat fed a tryptophan-deficient diet for the first 2 years. The white pulp is better defined than in control rats of the same age.

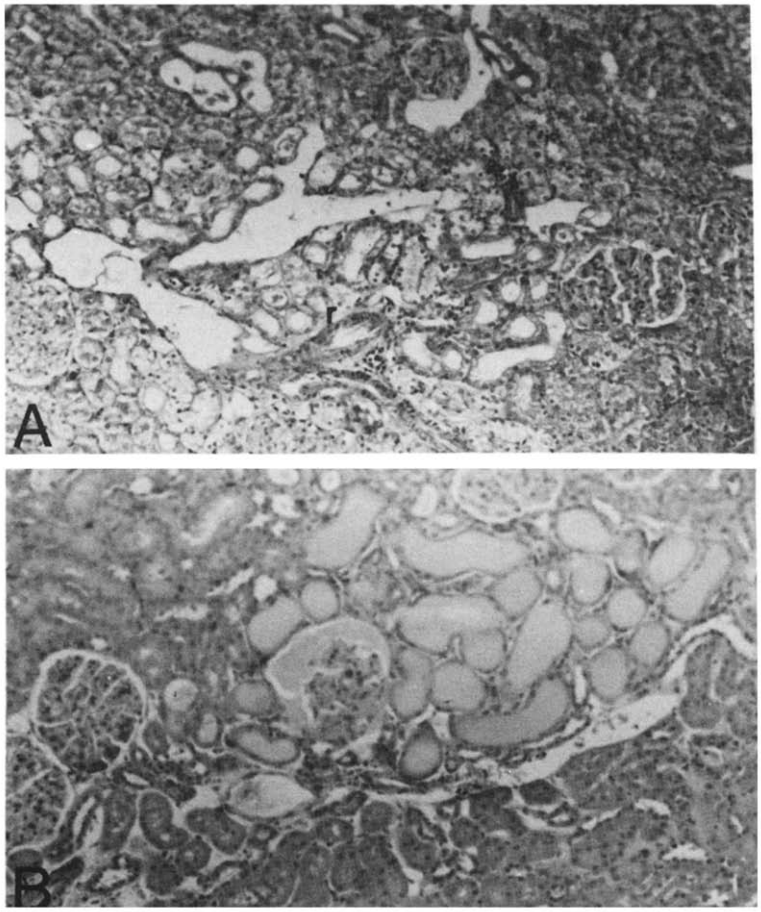


Fig. 11. (A) Renal changes with aging and tryptophan-deficient diet. The renal cortex with degenerating tubules in a 3-year-old control rat; (B) Kidney of 2-year-old control rat showing edema.

DISCUSSION

Our previous work has shown that tryptophan-deficient diets retard the rate of aging in the rat [1,3,6,7,9]. Whether this action is specific to the restriction of tryptophan and its consequent effects on serotonin metabolism or is dependent upon concomitant food restriction remains to be clarified. Long-term treatment with pharmacologic antagonists of serotonin, while markedly decreasing brain serotonin did not affect growth to the same extent as tryptophan restriction. Also, the pharmacological treatment could not be carried beyond 2–3 months due to the side effects of the drug [12,13]. However, alterations in brain serotonin markedly influenced the reproductive timetable in the rat [14]. The low serotonin levels reported here in all three brain areas studied, represent an expected consequence of the dietary-restriction

in tryptophan, the precursor amino acid. Although serotonin reduction was more marked with the more severe restriction, brain metabolism appears capable of significant adaptation and recovery. Serotonin levels rise to control levels in the tryptophan-deficient rats, 12 months after the initiation of the diet in T40% rats and 24 months in T30% rats. Despite the capacity for rehabilitation, reduction of brain serotonin levels at an early age induce irreversible changes, for example it delays the timetable of ovarian maturation and aging [14]. Thus, despite the possibility of long-term rehabilitation, the persistence of low serotonin levels in young animals for a relatively long period of time, may induce neurochemical changes capable of altering the aging process.

Histological examination in the present work indicates that aging-related changes in various tissues are reduced in the rats fed tryptophan-deficient diets. Differences between normal and tryptophan-deficient rats are especially remarkable in the oldest group which includes 3-year-old rats. In this group, the experimental rats, which were tryptophan-deficient for the first 2 years of life, and then fed a normal diet for 1 year, exhibited retardation of aging compared with control rats of the same age. The delay of aging was supported by the histological observation of fewer or no lesions in tissues of tryptophan-restricted rats.

All tissues studied showed well-defined aging changes by 2 years of age and these changes progress over time. Feeding the tryptophan-deficient diet prevents some of the age-related changes in the liver, heart, uterus, ovary, adrenal and spleen. No clear effect of dietary regimen on senescent degeneration was recognized in the kidney, lung and aorta. This differential suggests tissue-specific differences in the aging delaying effects of tryptophan deficiency.

A conspicuous difference between the normal and tryptophan-deficient animals is the frequency of portal triad hyperplasia in the liver, which develops in the rat older than 1 year but is not present in tryptophan-deficiency. Despite several studies on the hepatic structure of senescent rats, the frequent development of this lesion was not reported. Burek [15] described a high incidence of biliary cysts in the liver of old BN/Bi rats. The strain difference may be important in the development of senescent bile-duct lesions.

Organs other than liver also showed retardation of age-changes in tryptophan-deficient 3-year-old rats, although no distinct difference was detected between the 2-year-old groups. Among these organs the most remarkable effects of tryptophan-deficiency were observed in the adrenals and the ovaries. This result suggests that the tryptophan-deficient rats acquire more resistance to stress in the senescent period. It is also consistent with the previous observation that tryptophan-deficient rats preserve reproductive ability until very old [3].

As none of the control rats died in the first year of life, we can assume that deaths prior to 1 year of age were caused by the failure of some animals to adapt to the low-tryptophan diet, and are not due to aging. Additionally, the greatest percentage of these first deaths occurred in the first half of the first year, rather than later, thus further suggesting that they were not related to aging.

The Long–Evans rat is a polygenic animal and different rats respond differently to the low-tryptophan diets (Fig. 1). The use of a polygenic strain has the advantage that some animals exhibit greater growth deficits than others, and are more drastically affected by the diet. Although early mortality is high, once those animals not adaptable to the low-tryptophan levels are lost, the remaining population is more stable than controls. The surviving animals can then be studied to sort out the factors responsible for their more "successful" aging [16]. Biomarkers of aging, such as the onset of breast tumors [7], the loss of reproductive competence [3], and the appearance of some of the age-related histological features noted above are significantly delayed in this selected sub-population.

The paradoxical increase in the maximum lifespan seen in those animals fed diets lowest in tryptophan, which grew most slowly, showed the highest rates of early mortality and the slowest accumulation of CNS serotonin, suggests that delayed aging may originate in the drastic nature of the intervention itself. One possible explanation is that severe nutritional restriction, started early, may delay or prevent programmed events in the CNS [17–19]. Thus, severe nutritional restriction, as it engenders a scarcity of both energy and building blocks, may alter the neuroendocrine signal crucial to maturation. Then maturation might be delayed. If aging was due to a cascade of events subsequent to maturation, then too, aging would slow.

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