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Effect of Treatment on Longevity in Spontaneously Hypertensive Rats (39048)

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Previous investigations in this laboratory (1) and by Folkow (2) have demonstrated that continuous treatment with antihypertensive agents of the Kyoto strain of spontaneously hypertensive rats (SHR) will prevent the development of hypertensive target organ disease. Treatment was begun prior to the appearance of secondary pathology and the blood pressure was controlled at low normotensive levels for a 6-month period (1). Pathological changes such as nodular arteritis of the mesenteric arteries, left ventricular hypertrophy and dilatation and nephrosclerosis were found only in control animals and not in the treated group.

As a result of these experiments a second study has been carried out to determine whether continuous control of the blood pressure with antihypertensive drugs will significantly prolong the life-span of the SHR. The previous study had shown that drug treatment did not interfere with normal growth of the animals nor with their ability to reproduce (1). Also, with such treatment it was possible to control the level of blood pressure at rather low levels averaging between 90 and 100 mm Hg systolic without any apparent deleterious effects. These observations raised the possibility that significant prolongation of life might be observed.

Methods. There were 36 SHR in the control or untreated group and 48 in the treated group. The mothers of the treated rats received antihypertensive agents throughout pregnancy and during the period of weaning. Their offspring who became the experimental group of SHR received continuous treatment beginning at the time of weaning. Thus, these animals were exposed to antihypertensive drugs throughout their lives from the time of conception. The drugs were given in the drinking water in the following concentrations: for male rats reserpine 1.4 mg/liter water, hydralazine 80 mg/liter and chlorothiazide 100 mg/liter; for female rats the above concentrations were halved. In occasional rats whose blood pressures were not well controlled the concentration of chlorothiazide was doubled. Control SHR were the offspring of untreated mothers and they received tap water without drugs. These animals came from the same stock as the treated rats and all were bred in this laboratory.

Systolic blood pressure and body weight were measured every 2 weeks beginning at the time when the animals were three months of age. Blood pressure was measured indirectly by the tail cuff method (3) during recovery from light ether anesthesia. Readings were begun when twitchings of the forewhiskers or movement of the eyes were first detected and were continued until the animals began to have gross movements. Immediately preceding anesthesia the rats were warmed for 10 min in a chamber heated to 37°.

Animals were followed until they died of natural causes. Because of cannibalization gross autopsies could be accomplished on only 64 of the 84 animals. No attempt was made to carry out histological examination because of post mortem changes usually present at the time the dead animals were discovered.

Results. Longevity: During the period when the rats were 20–50 weeks of age the percentage of survivors in the treated SHR was essentially the same as in the untreated controls (Fig. 1). The deaths occurring during this period were associated with respiratory infections. Following this period the spread between the percentage surviving in the two groups of rats increased so that at 100 weeks of age the percentage of survivors in the treated group was more than double that of the control animals (50% as compared to 20%). Twenty-two percent of the treated SHR survived to 120 weeks of age while none of the control animals lived to this age. Eleven percent of the treated ani-

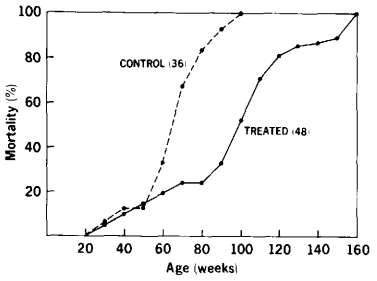

FIG. 1. Mortality rates of control (broken lines) and drug treated (solid lines) SHR. Numerals in parentheses refer to the number of rats in each group.

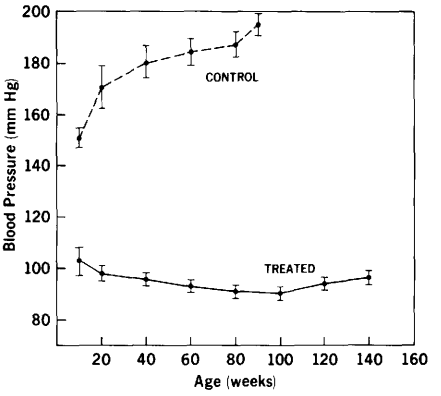

FIG. 2. Average systolic blood pressure of control and drug treated SHR. Vertical lines indicate standard error of the mean. Other relations as in Fig. 1.

mals lived to 152 weeks or approximately 3 yr of age. The mean survival time for the control rats was 73 weeks as compared to 96 weeks for the treated rats ($P < .0005$).

Blood pressure. The mean blood pressure levels for the groups of SHR are shown in Fig. 2. At 12 weeks of age the average systolic blood pressure was 150 mm Hg in the control animals and 103 mm Hg in the treated rats. Blood pressure rose gradually in the control SHR to an average value of 185 mm Hg at 60 weeks of age. Because of the death and hence selective removal of the animals with the highest levels of blood pressure the average level among the surviving controls changed little with the further passage of time. For example, only 10 control animals survived beyond 84 weeks and their average blood pressure at that time was 190 mm Hg. Their blood pressure over subsequent weeks until death averaged between 192 and 220 mm Hg. By contrast the blood pressures of the treated animals fell during the experiment from 103 to a range of 90–95 mm Hg at 116 weeks of age when there were only 13 survivors. Measurements in subsequent weeks preceding death showed no further significant change in blood pressure.

Gross pathology. Nodular arteritis of the mesenteric arteries was present in 27 of the control group and was extensive in 16 of the animals. A few small nodules which were limited to the pancreatico-duodenal artery were seen in eight of the treated animals. Left ventricular hypertrophy and enlargement were observed in 24 of the control and none of the treated SHR. Granularity and pitting of the kidneys were seen in 23 of the untreated rats. None of the treated animals showed this change.

Body weight. The body weights of the treated SHR remained somewhat below that of the controls until the animals were 62 weeks of age. The difference was small averaging between 5 and 10 g or about 1.5–3% less than the body weight of the controls. From the ages of 58–86 weeks the body weights of the control animals declined steadily from an average of 332–268 g. This average reduction was the result of both individual weight loss particularly in the males and to the fact that the longest survivors were predominantly females who weigh less than males. On the other hand, the body weights of the treated rats remained relatively constant at an average of 320 g from 56 to 102 weeks of age. Subsequent to this time the majority of the survivors were females which accounted for the lower average body weights observed up to 114 weeks of age.

Discussion. The life span of the albino rat is said to be about three years which is considered to be equivalent to 90 years of human life (3). The life span of the SHR is considerably less than this averaging about 1.5 yr (4). The average survival time for the untreated SHR in the present series was 73 weeks or about 1.4 yr and only one animal survived to 2 yr. By contrast, in the drug treated SHR the average longevity was 96 weeks or 1.9 yr and 11% of the animals survived to about 3 yr of age. Thus, it would

appear the control of blood pressure with antihypertensive drugs prolonged the lives of the SHR approximately to that of the normal albino rat.

The significant prolongation of life was accomplished without any apparent deleterious effects of the SHR. The animals gained weight normally throughout the growth phase and then maintained their weight throughout the remainder of their lives. There were no difficulties in breeding and the rats bore normal healthy litters. The animals appeared healthy and active with normal behavior in all respects.

The lack of evidence of hypertensive changes in the heart and kidneys in the treated animals is consistent with prior observations that long-term treatment has such a protective effect (1). Nodular arteritis of the mesenteric arteries also was reduced in incidence, severity and extent but was not completely prevented. Nodular arteritis was found in all of the control animals examined post mortem and in 60% of these the lesions were extensive and severe. In the treated rats only eight of 37 animals examined postmortem exhibited such lesions which were few in number and limited to the pancreatico-duodenal artery. The average age at death of these animals was 109 weeks. Nodular arteritis of the mesenteric arteries can occur with aging in normal rats. Wilens and Sproul found that 15% of an Osborn–Mendel strain living for 128 weeks or longer exhibited such lesions (5).

A mixture of antihypertensive agents was used in the present experiment since previous experience indicated that the blood pressure was more effectively lowered with a combination of drugs than with a single agent. It is possible that one of the components may have a vascular protective effect which is independent of the blood pressure reduction. This possibility seems unlikely, however, in that prolonged treatment with a different mode of action than those used in the present study also was found to prevent vascular changes in the SHR (2).

Summary. Continuous control of the pressure of spontaneously hypertensive rats at systolic levels of 90–100 mm Hg with antihypertensive agents significantly prolonged their life span. The mean survival time in control animals was 73 weeks as compared to 96 weeks in treated SHR ($P < .0005$) with 11% of the latter surviving to approximately 3 yr of age. Cardiovascular lesions were limited almost exclusively to the control rats. The general health, body weight and reproductive functions of the experimental animals remained normal throughout the drug treatment. These results indicate that by preventing the rise in blood pressure and consequent cardiovascular complications the life span of the SHR may be prolonged to that of the normal albino rat.

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