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Jogging Reduces Obesity and Hypertension in Obese/SHR[1] (41684)

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Abstract. Young Obese/SHR, genetically destined to become obese were made to run three times daily, averaging 2740 ft/day. Siblings of these young Obese/SHR which were allowed to remain sedentary, developed voracious appetites, massive obesity, hyperlipidemia, diabetes, hypertension, hyperadrenocorticism, muscle wasting, kidney stones, thin skin, and accelerated aging. The Obese/SHR that exercised did not become obese, their blood lipid, glucose, BUN, blood pressure, and hyperadrenocorticism were reduced, but their testes and ovaries became prematurely atrophic.

Japanese scientists have provided investigators with (a) the spontaneously hypertensive rat (SHR) which develops naturally occurring high blood pressure that resembles human essential hypertension, and (b) the stroke-prone hypertensive rat (SHR/SP) which develops acute cerebrovascular damage as it occurs in man (1–3). The author has inbred a unique strain of rats which develop massive obesity in addition to spontaneous hypertension, i.e., genetically Obese/SHR (4–8). Breeder Obese/SHR which appear lean but carry the proper genetic constellations will give birth to litters of pups, 75% of which are lean (nonobese/SHR) and 25% of which will become obese (Obese/SHR). At 5 weeks of age, the young that were bequeathed with the gene(s) for obesity develop a voracious appetite concomitant with rapidly rising blood pressure. At 10 months, male and female Obese/SHR weigh 850 and 700 g, respectively. Obese/SHR are extra responsive to even innocuous stress and develop a Cushing's disease-like spectrum of degenerative changes similar to that manifested by humans suffering from hyperadrenocorticism: obesity, fatty liver, hyperlipidemia, hyperinsulinemia, hyperglycemia, kidney stones, "mood swings" (Obese/SHR may be extremely torporous or hyperkinetic and combative when touched), muscle wasting, thin skin, accelerated aging, and premature death (4–7). The Cushingoid spectrum of degenerative changes can be prevented by adrenalectomy (5), by pituitary gland suppression with dexamethasone, or by hypothalamic–pituitary suppression with antiopiates such as naloxone (to be published). Thus, one of the underlying mechanisms of the genetically programmed obesity and hypertension in Obese/SHR is extra activity of the hypothalamic–pituitary–adrenal–gonadal axis.

The Obese/SHR can withstand months of starvation. They lose fat and manifest reduced lipid and glucose levels but little or no reduction of their abnormally elevated blood pressure. Because dexamethasone and naloxone successfully reduce body weight, blood lipid and glucose levels, and blood pressure in Obese/SHR (to be published), the question arose whether prevention of corpulency by daily exercise would also disentrain the genetically programmed obesity and hypertension. Accordingly, Obese/SHR were allowed to remain sedentary, or were made to exercise on a regular basis to determine whether daily exercise would disentrain the genetically programmed obesity and hypertension.

Materials and Methods. *Animals.* In order to fulfill the animal requirements of the experimental protocol, a large number of Obese/SHR breeders were required since only 25% of the litters will develop obesity. (When Obese/SHR become corpulent, they become infertile and their rotundity frustrates copulation.) Eighteen male and 18 female Obese/SHR, 5-week-old siblings were collected. (All of these animals were hyperphagic indicating

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that these animals were destined to become obese.) By random selection, 12 male and 12 female Obese/SHR were assigned to sedentary activity and 6 male and 6 female Obese/SHR called "joggers" were assigned to exercise wheels equipped with revolution counting meters and adjoining metabolic cages to provide direct and constant access to food and exercise. The animals were housed in air-conditioned, humidity-, and light-controlled quarters and were provided with a constant supply of commercial rat chow (Purina) and tap water to drink *ad libitum*.

When Obese/SHR become 10 months old, they begin to die of myocardial infarction (5). Therefore, all animals were killed by instant decapitation at 9 months of age. Forty-eight hours prior to autopsy, the systolic blood pressure of each animal was recorded under quiescent conditions using the Friedman:Freed indirect tail-cuff and microphonic manometer procedure. (Serial blood pressure determinations were deliberately avoided because Obese/SHR are hypersensitive to handling and stress.) Blood ACTH levels were determined by radioimmunoassay kits distributed by CIS Radiopharmaceuticals, Inc., Bedford, Massachusetts; blood lipids, glucose, and BUN were determined using the automated methods prescribed for the Auto-Analyzer (Technicon Instruments, Inc.). Key organs were removed, trimmed, weighed, fixed in 10% neutral formalin, imbedded in paraffin, sectioned at 3 mm, and stained with hematoxylin and eosin. Adrenal glands were frozen, sectioned at 10 mm, and stained for lipids with Sudan black B.

Statistical analyses of the data was performed using one-way analysis, chi-square test, and Student's t test using the methods and tables found in Snedecor and Cochran's text (9).

Results. *General observations.* Both the joggers and the sedentary Obese/SHR consumed the same amount of food, i.e., 30–35 g/day. The joggers were avid exercisers averaging runs of 2740 ft/day for males and 2527 ft/day for females with minor fluctuations in rate of speed or distance. Despite constant exercise, the joggers appeared to gain weight at the same rate as the sedentary Obese/SHR during the first 2 months (Fig. 1). After 3 months, sedentary Obese/SHR were obviously much more corpulent than the joggers. The joggers continued to gain weight but at a reduced rate compared with sedentary Obese/SHR (Fig. 1). By the fifth month, the weight gain of the joggers reached a plateau and body weight held steady until the end of the experiment. The sedentary Obese/SHR became massively obese and their body contour was rounded (Figs. 1 and 2).

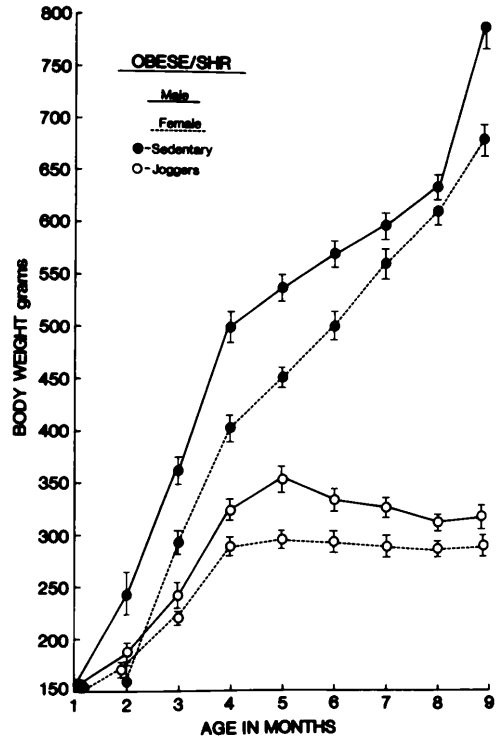

FIG. 1. Average monthly gain in weight of male and female, sedentary Obese/SHR and male and female Obese/SHR which jogged 3 times daily. The animals were provided food and water on an *ad libitum* basis from the time of weaning until they became 9 months old. Each point is the mean ± SE, N = 12 male and 12 female sedentary Obese/SHR, N = 6 male and 6 female Obese/SHR joggers.

Systolic blood pressure. The systolic blood pressure of male and female sedentary Obese/SHR was 166 ± 3 and 159 ± 3 mm Hg, respectively, vs 156 ± 2 and 146 ± 2 mm Hg, respectively, for male and female Obese/SHR joggers (Fig. 3). Although the blood pressures of Obese/SHR joggers were significantly ($P < 0.001$) less than the sedentary Obese/SHR, they remained hypertensive (A systolic blood

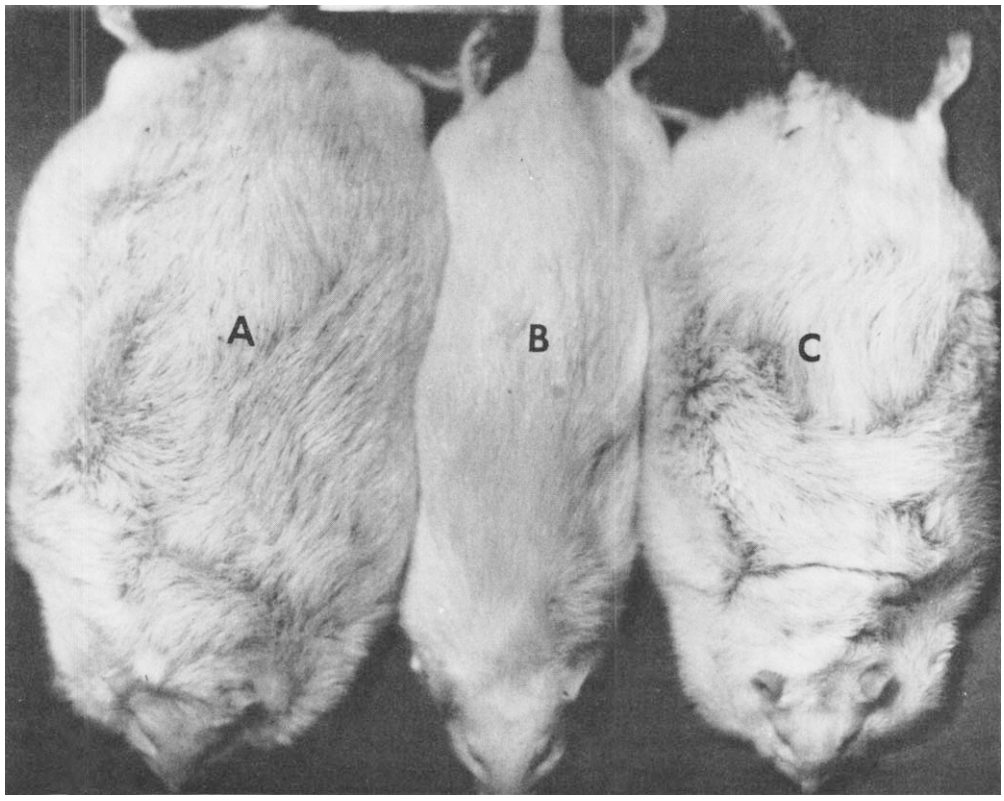

FIG. 2. Photograph of 9-month-old, sedentary male (800 g) and female (670 g) Obese/SHR (A + C) and a male (325 g) Obese/SHR (B) which began jogging 3 times daily at 5 weeks of age prior to the onset of obesity.

pressure above 135 mm Hg is considered to be abnormally high in the rat.)

Blood ACTH. Circulating adrenocorticotrophic hormone (ACTH) levels showed that the sedentary Obese/SHR secreted high levels of ACTH in keeping with their Cushingoid condition whereas ACTH levels were significantly ($P < 0.001$) lower in joggers (Fig. 4).

Blood lipids, glucose, and BUN. Blood lipids, glucose, and BUN levels were reduced in joggers vs sedentary Obese/SHR (Table I).

Gross and microscopic pathology. At necropsy, organ dissection of sedentary Obese/SHR was made difficult by ubiquitous and copious depots of adipose tissue. The thymus glands of the sedentary Obese/SHR were massive (Table I) and free of fatty infiltration; the thymi of joggers were reduced in size but not involuted. Despite their outward appearance of being lean, joggers had considerable periadrenal and retroperitoneal adipose tissue and fatty infiltration of the liver. In keeping with their reduced body weight, the joggers had much smaller pituitary, thymus, adrenal, heart, kidney, and gonad weights (Table I). The atrophy of the testes and ovaries was confirmed by histopathologic examination, e.g., aspermia and atrophic tubules. Joggers did not manifest muscle wasting, thin skin, massive thymi, kidney stones, and accelerated aging. The islets of Langerhans in the sedentary Obese/SHR were giant sized and the number of insulin-secreting beta cells per islet were supranormal; islets of Langerhans in joggers were normal in size with a normal complement of beta cells per islet.

Discussion. Hyperadrenocorticism and the appearance of Cushingoid degenerative changes is commensurate with body surface area and obesity. Clinically, it may be difficult to differentiate the pathogenesis of the Cushingoid habitus of massively obese patients,

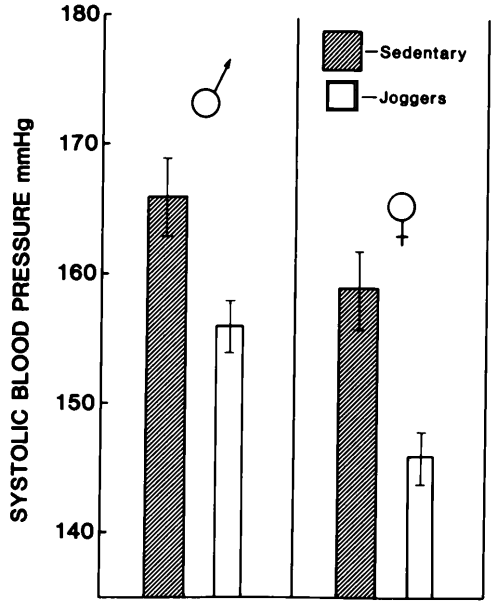

FIG. 3. Terminal blood pressure levels of 9-month-old male and female Obese/SHR. Some of the animals jogged 3 times daily (6 males and 6 females) and some were allowed to remain sedentary (12 males and 12 females) from the time they were weaned until they were autopsied. The height of each column connotes the mean ± SE. The same protocol applies to Fig. 4.

women in the advanced stages of pregnancy, or those having true Cushing's disease. Hyperadrenocorticism waxes and wanes with gain and loss of weight in obese patients and when pregnancy is terminated. The author has found the same Cushingoid spectrum of pathophysiologic changes in spawning salmon and in repeatedly bred male and female rats (8). The common *modus operandi* believed to be involved is overstimulation of the hypothalamic–pituitary–adrenal–gonadal axis due to the reproductive effort (8). Hyperadrenocorticism leads to hyperlipidemia and adiposity despite the protein catabolic effects, e.g., muscle wasting, thin skin, etc., of excess glucocorticoids. Although glucocorticoids have marked fat mobilizing effects, hyperadrenocorticism is usually associated with islet hyperplasia, beta cell degranulation, and hyperinsulinemia. Hyperinsulinemia, in turn, causes hyperphagia and enhances fat deposition. Insulin is adipokinetic and can compensate for the catabolic effects of steroids. It is suggested that the introduction of jogging at an early age prevented the development of the genetically programmed corpulency and this reduction of body mass had a dampening effect on the hypothalamic–pituitary–adrenal–gonadal axis. The reduction of ACTH secretion (and lowered glucocorticoid levels) led to reduction of blood lipid, glucose, BUN, and systolic blood pressure levels. Suppression of the hypothalamic–pituitary axis also caused decreased release of gonadotrophic hormones which would account for the severe atrophy of the testes and ovaries in Obese/SHR joggers. The presence of giant-sized thymus glands in sedentary Obese/SHR is an enigma. The reduction in the size of the thymus glands in joggers is paradoxical since the secretion of thymolytic glucocorticoids would be expected to be less in joggers due to their decreased ACTH secretion. Mineralocorticoids are thymotrophic. Obese/SHR secrete extra amounts of the mineralocorticoid, aldosterone (4–7). Perhaps the enlarged thymi of sedentary Obese/SHR was due to their extra production of aldosterone and the smaller thymi of joggers was due to decreased secretion of aldosterone or a change in steroidogenesis permitting the secretion of greater quantities of thymolytic glucocorticoids.

Evidence for salutary effects of exercise or jogging in animals and in man is conflicting

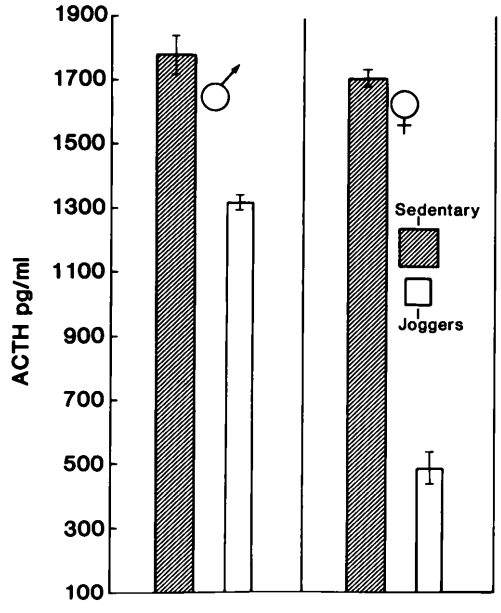

FIG. 4. Blood adrenocorticotrophic hormone levels.

TABLE I. COMPARISON OF BLOOD LIPIDS, GLUCOSE, BUN, AND ORGAN WEIGHTS OF 9-MONTH-OLD, MALE AND FEMALE, OBESE/SHR, SEDENTARY VS JOGGERS

	Free fatty acids (mEq/liter)	Trigly (mg %)	Chol (mg %)	Glucose (mg %)	BUN (mg %)	Pituitary (mg)	Thymus (mg)	Adrenal (mg)	Heart (mg)	Kidney (mg)	Testis/ovary (mg)
Male											
Sedentary	389 ± 21	197 ± 16	142 ± 10	205 ± 6	30 ± 1	11.0 ± 0.6	750 ± 61	28 ± 2	1861 ± 39	1461 ± 26	1534 ± 41
Joggers	221 ± 18*	162 ± 11†	121 ± 3†	108 ± 3*	18 ± 1*	8.3 ± 0.4*	457 ± 30*	21 ± 1*	933 ± 24*	828 ± 13*	335 ± 21*
Female											
Sedentary	447 ± 9	251 ± 13	137 ± 14	186 ± 17	32 ± 1	17.6 ± 0.5	681 ± 24	43 ± 2	1442 ± 61	1371 ± 70	38 ± 4
Joggers	207 ± 12*	139 ± 8*	117 ± 4	92 ± 3*	19 ± 1*	8.0 ± 0.3†	362 ± 16*	21 ± 1*	836 ± 31*	702 ± 12*	14 ± 2*

Note. The data represent the mean ± SE; sedentary, $N = 12$, joggers, $N = 6$. Trigly = triglyceride; Chol = cholesterol; BUN = blood urea nitrogen.
* $P < 0.001$, joggers vs sedentary.
† $P < 0.05$, joggers vs sedentary.

(10–14). Although some view with alarm the increasing number of automobile fatalities, orthopedic and reproductive dyscrasias associated with the internationally burgeoning fad of jogging, others claim that jogging is an excellent preventive means against cardiovascular disease and it affords a feeling of well being and even euphoria (12, 14). The premature involution of the reproductive organs of these male and female Obese/SHR serves as a caveat and hopefully will stimulate others to investigate the effect of chronic exercise on the reproductive system.

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1. Okamoto K, Aoki K. Development of a strain of spontaneously hypertensive rats. Japan Circ J **27**:282–293, 1963.
2. Okamoto K, Yamori Y, Nagaoka T. Establishment of the stroke-prone spontaneously hypertensive rat (SHR). Circ Res (Suppl 1) **34–35**:143–153, 1974.
3. Yamori Y, Horie R, Handa H. Pathogenetic similarity of strokes in stroke-prone spontaneously hypertensive rats and humans. Stroke **7**:46–53, 1976.
4. Wexler BC, Iams SG, McMurtry JP. Pathophysiologic differences between obese and non-obese spontaneously hypertensive rats. Brit J Exp Pathol **61**:195–207, 1980.
5. Wexler BC, McMurtry JP. Ameliorative effects of adrenalectomy on the hyperphagia, hyperglycaemia and hypertension of obese, spontaneously hypertensive rats (Obese/SHR). Brit J Exp Pathol **62**:146–157, 1981.
6. Wexler BC, McMurtry JP. Kidney and bladder calculi in spontaneously hypertensive rats. Brit J Exp Pathol **62**:369–374, 1981.
7. Wexler BC, McMurtry JP. Cushingoid pathophysiology of massively obese, spontaneously hypertensive rats (SHR). J Gerontol. **38**:148–154, 1983.
8. Wexler BC. Comparative aspects of hyperadrenocorticism and aging. In: Everitt AV, Burgess JA, eds. Hypothalamus, Pituitary, and Aging. Springfield, Ill, Thomas, p 333, 1976.
9. Snedecor GW, Cochran WG. Statistical Methods, 6th ed. Ames, Iowa State Univ Press, 1967.
10. Kramsch DM, Aspen AJ, Abramowitz BM, Krei-

nendahl T, Hood WB. Reduction of coronary atherosclerosis by moderate conditioning exercise in monkeys or on atherogenic diet. N Engl J Med **305**:1483–1489, 1981.

11. Reaven GM, Reaven EP. Prevention of age-related hypertriglyceridemia by caloric restriction and exercise training in the rat. Metabolism **30**:982–986, 1981.
12. Stern MJ, Cleary P. The national exercise and heart disease project. Arch Intern Med **142**:1093–1097, 1982.
13. Virmani R, Robinowitz M, McAllister H. Nontraumatic death in joggers. Amer J Med **72**:874–882, 1982.
14. Carr DB, Bullen BA, Skrinar GS, Arnold MA, Rosenblatt M, Beitins IZ, Martin JB, McArthur J. Physical conditioning facilitates the exercise-induced secretion of beta-endorphin and beta-lipoprotein in women. N Engl J Med **305**:560–563, 1981.

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