

This Week's Citation Classic®

Okamoto K & Aoki K. Development of a strain of spontaneously hypertensive rats. *Jpn. Circ. J.* 27:282-93, 1963.
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This report deals with the discovery, development, and establishment of spontaneously hypertensive rats (Aoki SHR) by the production of a new apparatus for the measurement of rat blood pressure and selective inbreeding of rats with the highest blood pressure.¹ [The *SCI*® indicates that this paper has been cited in more than 1,270 publications, making it the most-cited paper from this journal.]

From a New Apparatus to a New Strain of Rats

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In 1959 I joined the Department of Pathology, School of Medicine, Kyoto University, as a graduate student. Professor K. Okamoto in the department was interested in the production of animal models for the study of diabetes mellitus and hypertension through experimental maneuvers.²

Professor Okamoto kindly gave me a research theme, which was the production of renal hypertension following renal infarction and the mechanisms in renal hypertension. There was no reliable apparatus for measuring blood pressure in rats or rabbits in the laboratories of the department. I attempted to produce a reliable apparatus for measuring blood pressure in rats. I designed

and made a new tail water-plethysmographic device,³ modified from the methods of F.B. Byrom and C. Wilson.⁴

It was found in the testing study that some rats remained normotensive and a few other rats developed hypertension spontaneously, related to age. Such wide variations could be ascribed either to the statistical limits of a homogenous population or to inheritance based on gene differences. If there are gene differences, it should be possible, by selective inbreeding, to separate strains that differ by hypertension genes. The possibility came to mind that selective inbreeding could identify a strain that had hypertension genes. I planned and performed the following experiment to prove this hypothesis.

The discovered hypertensive male rat, with a blood pressure range of 150-175 mmHg, and a normotensive female rat, with a blood pressure range of 130-140 mmHg, were selected for breeding. The first generation obtained consisted of 36 animals. Rats in the first generation with the highest blood pressure were selected for inbreeding to produce the second generation. The third generation was obtained by inbreeding from the rats in the second generation. All of the rats in the third generation developed hypertension; thus, the incidence of hypertension was 100 percent in this generation in both sexes. All of the rats after the third generation by the selective inbreeding from the hypertensive rats (Aoki method) became hypertensive. (See also references 5 and 6.)

I reported and handed my manuscript to Professor Okamoto, who became the first author.

1. Aoki K. Discovery of the spontaneously hypertensive rat. (Aoki K, ed.) *Essential hypertension*. Tokyo: Springer-Verlag, 1986. p. 3-7.
2. Okamoto K. Experimental pathology of diabetes mellitus (report II). III. Studies on rabbits from ancestors diabetic for several successive generations especially on spontaneous occurrence of diabetes in F4 and F5 rabbits. *Tohoku J. Exp. Med.* 61:62-112, 1955. (Cited 5 times.)
3. Aoki K. The spontaneously hypertensive rat: evidence of the genetic hypothesis in essential hypertension. (Aoki K & Frohlich E D, eds.) *Calcium in essential hypertension*. Tokyo: Academic Press, 1989. p. 3-8.
4. Byrom F B & Wilson C. A plethysmographic method for measuring systolic blood pressure in the intact rat. *J. Physiol.—London* 93:301-4, 1938. (Cited 205 times since 1945.)
5. Aoki K. Memories of discovery and development of spontaneously hypertensive rats. The 25th anniversary of the discovery of spontaneously hypertensive rats. (In Japanese.) *Coronary* 2:97-100, 1985.
6. Discovery and development of the spontaneously hypertensive rat. (Aoki K, ed.) *Essential hypertension 2*. Tokyo: Springer-Verlag, 1989. p. 3-8.