tion in humans reported here, 19-NET administered prenatally, like testosterone, increased the sensitivity of female mice to the aggression-activating properties of testosterone administered in adulthood and increased the percentage of females that engaged in aggressive behavior (*22*). Zussman *et al.* (*23*) found that boys whose mothers were treated with naturally occurring progesterone during pregnancy were more aggressive in childhood and were more often subjected to disciplinary action in elementary and secondary school than controls. For girls of elementary school age, progesterone administration was associated with a lower incidence of school discipline and tomboyism, but in adolescence the progesterone-exposed girls reported that they got angry more frequently and more intensely than controls (*23*). In another study, 18- to 20-year-old men who had been exposed prenatally to progesterone-based synthetic progestins had elevated hostility scores on the Guilford-Zimmerman Temperament Survey, whereas men exposed to naturally occurring progesterone either alone or in combination with estrogen had lower scores than controls (*24*).

It appears from these and previous data (*5, 17, 19, 20*) that boys and men are more likely than girls and women not only to act aggressively, but also to imagine themselves responding with aggressive behavior to conflict situations. The data presented here suggest that verbal estimates of aggressive response are enhanced in males and females by prenatal exposure to synthetic progestins with androgenic potential. Whether an increased probability of choosing physically aggressive behavior in response to hypothetical conflict situations is related to aggressive action in real life situations has not yet been definitively determined (*17*). Nevertheless, the observation of a relation between augmented prenatal hormone levels and elevated estimates of aggressive response in human females provides additional evidence that many of the principles governing the differentiation of hormone-organized behaviors in laboratory animals may also apply to human behavior. The observed influence of hormones during gestation on later aggressive responses in human subjects suggests that differences in the frequency of aggressive behavior between males and females as well as individual differences may be related to natural variations in hormone levels prior to birth.

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Spontaneous Hypertension in Cross-Suckled Rats

Abstract. *Genetically normotensive Sprague-Dawley rats nursed by spontaneously hypertensive foster mothers develop sustained high blood pressure. Some factor related to the genetically programmed hypertension of the foster mother is probably transmitted to the infant rats through her milk. Alternatively, the hyperkinetic behavior of the mother may activate a hypertensinogen in young having the proper constellation of genes.*

Japanese workers have provided investigators with an intriguing model of genetically programmed hypertension: the spontaneously hypertensive (SH) rat (*1–3*). These rats are of interest to experimentalists and clinicians because they provide close facsimiles of essential hypertension in the human. Although there is no doubt that the spontaneous hypertension in these rats is due to peripheral vasoconstriction and myocardial hemodynamic changes, some investigators believe that nutritional and hormonal alterations may play a conditioning role in the genetic expression of the hypertension (*4*). We and others (*4*) have found that a diet high in calories and fat or a greatly reduced food intake inhibits spontaneous hypertension in SH rats and that hypophysectomy, adrenalectomy, and gonadectomy inhibit the development of high blood pressure if performed shortly after weaning.

The SH rat is born normotensive, but at 4 to 5 weeks of age its blood pressure begins to rise, reaching abnormally high levels by 120 days of age. We attempted to correlate changes in nutritional and hormonal vectors with the pathogenesis of hypertension from the time of weaning and the early steep ascent of blood pressure. The Wistar-Kyoto (WKy) rat is generally purported to be the normotensive counterpart of the SH rat. However, when we transplanted pituitary and adrenal glands from young SH rats into

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young hypophysectomized and adrenalectomized normotensive WKy recipients, the transplants were rejected (*5*); when these transplants were made to normotensive Sprague-Dawley (SD) rats, the transplants were accepted readily. For these and other reasons (*6*), we questioned the appropriateness of the WKy rat as a normotensive counterpart for the SH rat. Therefore, we performed an experiment in which SD, WKy, and SH suckling pups were allowed to remain with their natural mothers or were suckled by foster mothers. We found that weanlings genetically destined to be normotensive developed sustained high blood pressure if they had been nursed by hypertensive foster mothers.

Male and female SD and SH rats were raised in our animal research colony. The SH rats were derived from the original breeder stock of the Okamoto-Aoki strain. WKy rats were purchased from Harlan Laboratories, Indianapolis. All the animals were given unrestricted access to Purina Lab Chow and tap water. On days 21 and 22 of pregnancy, the females were observed closely for signs of impending parturition. Immediately after birth, pups destined to be presented to a foster mother were removed from the natural mother (before she could nurse them). If milk was found in the stomach of the pups or if several hours had elapsed since their birth, the litters and dams were designated as natural. Foster pups were placed with a dam of another strain or a dam of the same strain. Litter size was adjusted to eight to ten pups per litter for all groups. Blood pressure for each pup was recorded at days 35, 60, and 90 by the Friedman-Freed microphonic manometer (indirect tail-cuff method without the use of ether or restraint). Analyses of variance and Student's *t*-test were used to determine significant differences in the data.

The mean blood pressure of male and female SD pups suckled by SH foster mothers was significantly higher at 35, 60, and 90 days of age than that of SD pups suckled by their natural, normotensive mothers ($P < .001$) (Fig. 1). The mean blood pressure of male and female SD pups suckled by an SD foster mother was slightly (but not significantly) higher than that of pups suckled by their natural mothers. In general, the blood pressure of SD rats was lower than that of WKy rats at 35, 60, and 90 days of age whether they were suckled by their natural or foster mother (Figs. 1 and 2). The SH pups developed abnormally high blood pressure whether they were suckled by their natural or foster mother. The female (but not the male) SH pups suckled by SD foster mothers developed significantly higher blood pressures than SH pups suckled by their natural mothers ($P < .05$) (Fig. 1). This finding did not hold true for female SH pups nursed by WKy dams, but higher blood pressures were found in male SH pups that had been suckled by WKy dams (Fig. 2). Unlike the SD pups, WKy pups did not develop increased blood pressure when suckled by SH dams. Although SH pups developed hypertension whether they

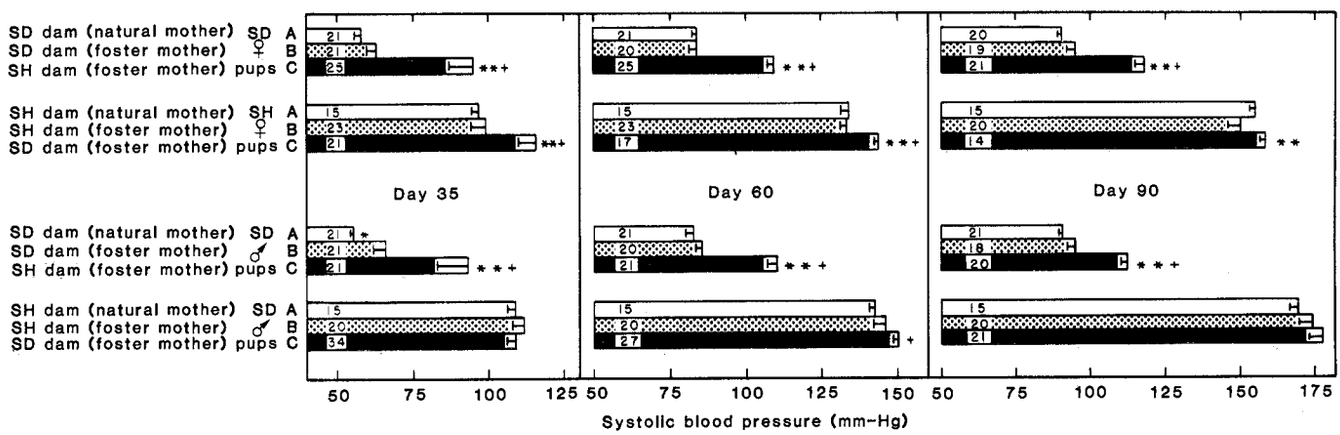

Fig. 1. Systolic blood pressure in SD pups that were nursed by natural or foster SD dams or by foster SH dams and in SH pups that are nursed by natural or foster mothers. Values are means ± standard errors; the number within each bar indicates the number of weanlings sampled in that group (A, B, or C). Symbols: (*) group A blood pressure is significantly different from that of B; (**) group C blood pressure is significantly different from that of B; and (+) group C blood pressure is significantly different from that of A—all at $P < .05$.

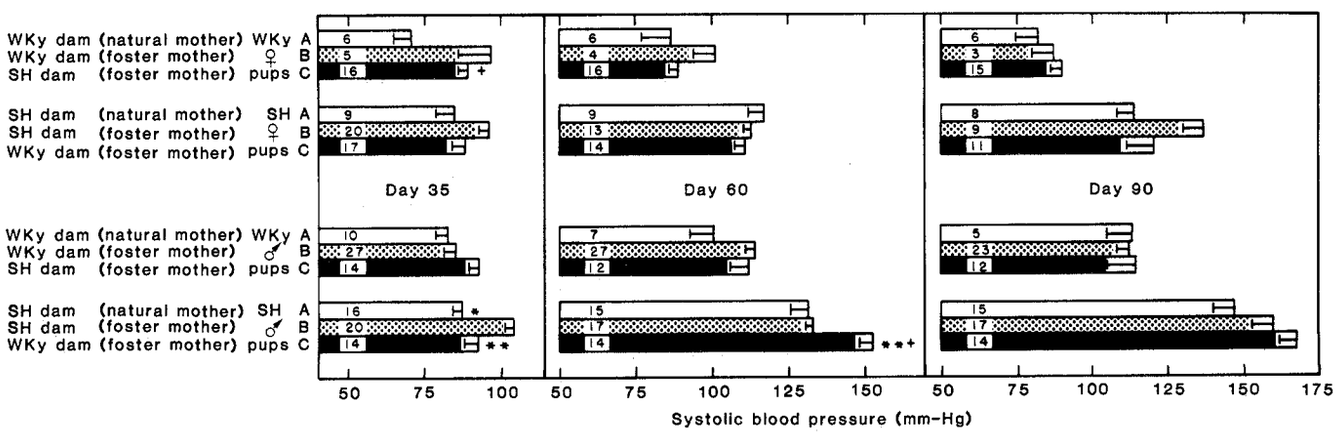

Fig. 2. Systolic blood pressure in WKy and SH rats nursed by their natural or foster mothers.

were nursed by a hypertensive or a normotensive mother, only male SH pups developed severe hypertension when nursed by WKy dams.

These findings suggest that an animal genetically programmed to be normotensive can become hypertensive if it is nursed by a hypertensive mother. Some factor may be transmitted through the milk, triggering the pathogenesis of progressively increasing blood pressure. This factor or factors appear to be specific in genetic transcription, since not all genetically normotensive weanlings nursed by hypertensive dams respond by developing hypertension. SH offspring become inordinately sensitive to extra dietary salt if they are nursed by mothers that were provided with extra salt during gestation (*7*). Cholesterol metabolism in weanling rats favors atherogenesis if they were suckled by mothers who were fed a diet high in cholesterol and fat (*7*).

Alternatively, the hypertension in the offspring may be attributable to the mother's behavior during the 21 days of lactation. SH rats are extremely sensitive to stress; even mild disturbances can cause inappropriate hyperkinetic behavior and marked stimulation of the pituitary-adrenal axis (*4*). If disturbed, SH mothers may eat their young.

A hypertensinogen, a factor that will induce high blood pressure de novo, has been sought in hypertensive humans and animals (*8*). Although this factor causes increased aldosterone secretion, sodium retention, blood volume expansion, and sustained hypertension—all reduced by adrenalectomy—it is not adrenocorticotropic hormone, renin, or angiotensin (*8*). Our investigations of cerebrohypothalamic-pituitary function in various substrains of SH rats (*4*, *9*) direct attention to the possibility that the hypersensitivity of SH rats to stress is mediated by endogenous opiates or cerebropeptides (β-endorphin, enkephalins, and so forth) (*10*). The factor transmitted through the mother's milk or activated by her hyperkinetic behavior may be such a cerebrohypothalamic neurotransmitter. The fact that SD offspring, rather than WKy, were more susceptible to the purported hypertensinogen activated or transmitted by SH dams underscores the belief that individuals genetically destined to become hypertensive will do so eventually if they are exposed to hypertension-inducing conditions.

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6. The disbursement of Okamoto-Aoki SH strain and the WKy rat, its purported normotensive counterpart, has resulted in the dilution of strains. Use of the WKy rat as the only suitable control for SH rats is no longer justifiable. Other investigators encounter loss of elevated blood pressure in their SH strain, but blood pressure in our strain has remained elevated. Other investigators complain that their SH rats are susceptible to respiratory disease, but our strain is resistant. Most SH substrains are short-lived; ours is unusually long-lived. Other investigators report comparatively low aldosterone and corticosterone concentrations and decreased responsiveness to stress in their SH rats; we find high concentrations of these hormones and hypersensitivity to stress. Okamoto and Aoki (*1*) claim that early gonadectomy does not inhibit the pathogenesis of hypertension in SH rats, but we find it to be an effective retardant of hypertension. Okamoto *et al.* (*2*) describe a stroke-prone SH substrain; our descendants of their stroke-prone rats develop exceptionally high blood pressure but do not have strokes. Yamori *et al.* (*3*) describe ringlike fatty deposits in fat-fed SH rats; the same diet caused complete inhibition of hypertension, severe hyperlipidemia, but no atherosclerosis in our SH strain.
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Trisomic Hemopoietic Stem Cells of Fetal Origin Restore Hemopoiesis in Lethally Irradiated Mice

Abstract. *Autosomal trisomy in the mouse is invariably associated with fetal or early postnatal death. Hemopoietic stem cells from fetuses trisomic for chromosome 12 or 19 can be rescued by transplantation into lethally irradiated mice. These trisomic cells restore hemopoiesis, including lymphopoiesis, in the irradiated mice and establish a permanent and almost complete engraftment. There is no evidence that hemopoietic cells with trisomy 12 or 19 are cytogenetically unstable.*

The life-span of mice with autosomal trisomies is limited. Developmental failure occurs during the second or final third of fetal development, depending on the chromosome involved (*1*, *2*). Short postnatal survival is observed only in mice with trisomies 13, 16, and 19 (*3*). In this report, we examine whether hemopoietic stem cells from the liver of trisomic fetuses can reconstitute hemopoiesis in hosts given a lethal dose of radiation, thus enabling trisomic cells to survive in the hosts. Such radiation chimeras provide a tool for studying the stability of chromosomally unbalanced donor cell lines and for analyzing the biological effects of trisomy in hemopoietic cells. It can be shown that a permanent and almost complete reestablishment of hemopoiesis, including lymphopoiesis, is obtained with cells trisomic for chromosome 12 or 19.

We induced trisomy by crossing males heterozygous for two Robertsonian (Rb) translocation metacentrics showing homology of one of their arms with females with acrocentric chromosomes only (Fig. 1) (*1*). To induce trisomy 12, Rb(8.12)5Bnr/Rb(4.12)9Bnr males were mated with NMRI females, and to induce trisomy 19, Rb(9,19)163H/Rb(8.19)-1Ct males were mated with C3H/He females. Since the life expectancy of trisomic individuals is limited, it seemed appropriate to remove the fetuses with trisomy 12 on day 14 or 15 and the fetuses with trisomy 19 on days 16 to 19 (day 1 being the day on which the vaginal plug appeared).

To distinguish between trisomic and normal fetuses, we performed cytogenetic analyses on extraembryonic membranes (days 14 and 15) or small pieces of liver (after day 15). The samples were incubated for 45 minutes in tissue culture medium (TCM) 199 containing 20 percent fetal calf serum and 0.05 μg of Colcemid per milliliter. Further processing involved standard techniques. Trisomic fetuses (cytologic marker: two metacentric chromosomes) and control fetuses (cytologic marker: one metacentric chromosome) were chosen from the same litter whenever possible, and suspensions of single cells were made separately from each liver. Adult C3H/He females were irradiated with 1000 R (55 R/min) (*4*), and 1 to 4 hours later were in-

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