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The Rat with Spontaneous Genetic Hypertension is not a Suitable Model of Human Essential Hypertension

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Together let us beat this ample field†

THE general availability of genetically hypertensive rats has provided the opportunity to investigators in diverse disciplines to study the many faces of hypertension and has quickened our appreciation of the complexities of disentangling the snarled hormonal, nervous, functional, and cardiovascular architectural interrelationships required to identify the causes of elevation of blood pressure. The plethora of studies on hypertensive rats has occasioned the remark that essential hypertension, the human disease, may yet prove to be a good model for understanding the disease in the rat (quoted by Simpson, 1976).

In this Controversy, there is an advantage in taking the negative side. Most animal models of human disease are more or less bad approximations of a poorly understood derangement in man. When one considers hypertensive diseases of man and animals, it is patently foolish to compare two unknowns. The fact remains that the causes of human essential hypertension and genetic hypertension in the rat are enigmas. Nonetheless, there are sufficient similarities of a secondary nature to justify comparison of hypertensive diseases in rat and man; studying the disease in the rat may contribute to understanding human essential hypertension. This being the case, then which of the several strains of genetically hypertensive rats do we select as the model of essential hypertension in man? And why is that strain selected for study over the others? Important differences have been shown to exist amongst the strains of genetically hypertensive rats in terms of their sensitivity to salt, the participation of blood pressure-elevating and blood pressure-lowering systems, and the time of onset of hypertension. Some of these differences appear to be fundamental, signifying different genotypes. In addition, an important species difference between the rat and other mammals demands consideration; i.e., a renal prostaglandin mechanism which acts to lower blood pressure in most species including man is not evident in the rat (Malik and McGiff, 1975). This difference constitutes the basis for rejection of the genetically hypertensive rat as a model of human essential hypertension (Vane and McGiff, 1975).

The Japanese strain of spontaneously hypertensive rat (SHR) has received the most attention by scientists worldwide. This can be traced to two events (Geller, 1979), donation of breeder SHR to the National Institutes of Health in 1966 through the cooperation of Drs. Okamoto and Udenfriend and convocation of the first International Symposium in 1971 (Okamoto, 1972). The latter initiated the accelerated phase of new studies on genetically hypertensive rats as it revealed to the scientific world the rich potential of studies using an animal paradigm of a prevalent disease of man.

.... all that rises, rise in due degree‡

Smirk and his colleagues at The Wellcome Medical Research Institute in Dunedin, New Zealand,
were the first to develop a colony of rats with genetic hypertension more than 2 decades ago. After 8 years of selective breeding of ordinary stock Wistar rats with above average blood pressure, Smirk and Hall (1958) reported a rise of systolic blood pressure of almost 20 mm Hg above controls. The rate of rise of blood pressure in the New Zealand strain of genetically hypertensive rat (GH) was about 2 mm Hg per generation. Since 1969, the mean systolic blood pressures, when taken under light ether anesthesia, have been in excess of 170 mm Hg, an increase of 50 mm Hg or more above controls (Smirk, 1973).

In 1963, Okamoto and Aoki in Kyoto reported developing within three generations (F3) a genetically hypertensive rat, the Japanese strain of spontaneously hypertensive rat (SHR). After the F3 generation, the Japanese strain was invariably hypertensive; blood pressure rose to levels which took the New Zealand colony 15 years and as many as 27 generations of inbreeding to attain. In the SHR, elevated blood pressure was detected at birth when measured with the survo-null micropipette transducer system (Bruno et al., 1979). In the GH strain, using a less sensitive method, blood pressures above those of normotensive rats of the same age were recorded by 2 days of age (Jones and Dowd, 1970). It should be recalled that the sympathetic nervous system is neither fully developed (Iversen et al., 1965) nor functional in the perinatal period (Wekstein, 1965). In other strains of genetically hypertensive rats, elevation of blood pressure relative to controls was not apparent until several weeks of age or only after a sufficient period of high salt intake (Bianchi and Baer, 1976; Dahl et al., 1962).

Because of the wide distribution of the SHR, leading to variations in breeding techniques within different colonies, genetic change, as revealed by phenotypic dissimilarities, has occurred (Geller, 1979). For example, the blood pressures of mature SHR, purchased from some commercial breeders, are considerably lower than the blood pressures of the SHR obtained either from the original colony in Kyoto or from the colony of SHR maintained at the National Institutes of Health. Further, the inability to demonstrate elevated blood pressure in SHR less than 3 weeks of age may also reflect differences in the genetic makeup of some colonies (Sinaiko and Mirkin, 1978). Indeed, within the original colony in Kyoto, several substrains, having different characteristics, have been classified genealogically. The emergence of substrains has been turned to good advantage by Okamoto et al. (1974), as stroke-prone and stroke-resistant SHR have been made available for studies on cerebrovascular disease in hypertension. However, for the most part, the appearance of substrains has complicated comparison of the SHR with hypertension in man since most studies are based on the assumption that the SHR is a paradigm of human essential hypertension.

In an attempt to prevent further fragmentation of the SHR genotype, the Institute of Laboratory Animal Resources of the National Academy of Sciences has published “Spontaneously Hypertensive (SHR) Rats: Guidelines for Breeding, Care, and Use” (1976). In view of the continued appearance of substrains, a good case can be made for a national registry which authenticates the line and issues a pedigree after submission of the “necessary documents.” The genetically hypertensive rat has become institutionalized, the first step to becoming fossilized.

Because genetic determinants are susceptible to alterations that can fundamentally change the nature of the disease, there are inherent difficulties in comparing hypertension in animals to essential hypertension in man. This factor operates frequently in the hypertensive rat and constantly in hypertensive man whose breeding is more capricious than that of the colonized rat. We are then confronted with a diversity of strains and substrains of genetically hypertensive rats that differ quantitatively and qualitatively in those factors that affect blood pressure.

The proper organs, proper pow'rs assigned; 
Each seeming want compensated of course^
disclosed four proteins not present in the salt-susceptible strain; they were estimated to account for approximately 30% of the blood pressure difference between salt-resistant and -sensitive strains. The remainder of the difference in blood pressure is determined by a renal factor which appears to be the most important, as indicated by renal transplantation experiments (Dahl and Heine, 1975). In the Milan (MHS) hypertensive strain, GFR was found to be low in the pre-hypertensive phase, an abnormality not present in the other strains. This has led to an important finding in the MHS, based on micropuncture techniques, indicating a low glomerular ultrafiltration coefficient as the cause of the depressed GFR. As the glomerular vasculature is a specialized capillary bed, this property of decreased permeability has been shown to be shared by “the entire body capillary” bed of the MHS (Bianchi et al., 1979). The development of hypertension in the MHS, then, is considered to be compensatory because the lower GFR disappears with the onset of elevated blood pressure. The concept that hypertension is a compensatory mechanism to a primary abnormality in the excretory function of the kidney had been advanced almost 2 decades ago by Baldwin et al. (1965) based on a study of salt excretion in human essential hypertension. Within the last decade, genetically determined alterations in renal function as a cause of high blood pressure in rats has received considerable attention in human and experimental hypertension. Adrenergic mechanisms have been suggested to contribute to the elevation of blood pressure in the SHR and GH strains on the basis of augmented sensitivity of pressor responses to central stimulation (Buñag and Takeda, 1979), increased sympathetic nerve activity (Judy et al., 1976), and delayed onset and reduced severity of the hypertension after destruction of sympathetic nerves by pharmacological or immunological means (Phehan et al., 1976; Yamori and Okamoto, 1976). However, interruption of sympathetic nerve activity by ganglionic blockade did not decrease regional vascular resistances more in the conscious SHR than in the normotensive control rat (Brody et al., 1980); a greater decrease in the SHR would have signified heightened sympathetic nerve activity. Nonetheless, even in the absence of increased activity, the sympathetic nervous system may act in concert with one or more blood pressure-elevating factors to cause hypertension. Thus, adrenergic interactions with renal prostaglandins in the rat can increase renal vascular resistance, an initiating factor in the development of hypertension (Coleman et al., 1975). To understand how prostaglandins may modify the activity of a pressor system, the role of renal prostaglandins as modulators of vasoactive polypeptides and the autonomic nervous system will be examined.

Observe how system into system runs ⁵

An anti hypertensive system in most species probably operates in large part through interactions of kinins and prostaglandins, intrarenally and within the vasculature (McGiff et al., 1972; Terragno et al., 1975). The basal release of renal prostaglandins is linked to the level of activity of the renal kallikrein-kinin system (Nasjletti et al., 1978). The released prostaglandins oppose the actions of pressor hormones (McGiff et al., 1970) and the adrenergic nervous system (Malik and McGiff, 1975) and contribute to the blood pressure-lowering effects of kinins by enhancing their vasodilator and diuretic-natriuretic actions (McGiff et al., 1975; Blasingham and Nasjletti, 1979). Moreover, if one assumes tonic activity of the opposing blood pressure-regulating systems, a deficiency of the vasodepressor system may lead to hypertension without any increase in

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⁵ Pope, Alexander, Ibid., p. 16, l. 25.
the basal activity of the blood pressure-elevating system. The evidence thus far obtained indicates that the rat is an exception to this proposal. Indeed, kinins can be shown to constrict the renal vasculature of the rat kidney, an effect probably mediated by a prostaglandin mechanism as indomethacin treatment abolishes it, uncovering a direct renal vasodilator action of bradykinin (Armstrong et al., 1970). Further, an anomalous hypertensive response to bradykinin may be unmasked in the rat after nephrectomy or by treatment with a ganglionic-blocking drug (Croxatto and Belmar, 1961).

Altered activity of the kallikrein-kinin system is only one of several signals to which prostaglandins respond in the regulation of blood pressure. Increased activity of the renin-angiotensin and adrenergic-nervous systems evoked by a variety of stressful stimuli enhances prostaglandin synthesis by the kidney (Terragno et al., 1977) which then protects renal function from excessive effects of angiotensin and catecholamines (McGiff et al., 1970). The importance of this defensive role of prostaglandins is evident after inhibiting prostaglandin synthesis with indomethacin in the surgically stressed dog; renal blood flow declined precipitously and blood pressure increased (Lonigro et al., 1973). In contrast, in the surgically stressed-anesthetized rat, acute inhibition of prostaglandin synthesis with indomethacin was without effect on the renal circulation and actually decreased blood pressure (Roman and Kauker, 1978).

Alterations of prostaglandin synthesis can affect blood pressure differently in the rat than in other species. Because of the limitations inherent in clinical research, differences between the rat and species other than man will be examined. When comparing these species, such as dog and rabbit, with the rat, it is assumed that they resemble man in their circulatory response to those stimuli affecting prostaglandin-dependent mechanisms. Lessening of the severity of hypertension induced by bilateral renal artery constriction has been described in the rat when an inhibitor of prostaglandin synthesis was administered before the hypertension became established (McQueen and Bell, 1976), whereas, in the renovascular hypertensive rabbit, acceleration of the hypertension, resulting in death within days, occurred in response to indomethacin (Romero and Strong, 1977). In normotensive conscious rabbits, chronic elevation of blood pressure has been produced by giving an inhibitor of prostaglandin synthesis (Colina-Chourio et al., 1979), an effect not reported in rats. Long-term administration of a prostaglandin synthesis inhibitor, indomethacin, to the unanesthetized rat with established renovascular hypertension has variable effects. Treatment with either indomethacin or meclofenamate has been reported to increase the severity of the hypertension (Pugsley et al., 1975) or to be without effect (McQueen and Bell, 1976), differences perhaps accounted for by variations in the methods used to induce hypertension.

Additional evidence that a prostaglandin mechanism may contribute to elevation of blood pressure in the rat was provided by the use of arachidonic acid, the vascular actions of which are due to its conversion to prostaglandins (Tannenbaum et al., 1975). Laborit and Valette (1975) found that enhancement of prostaglandin synthesis induced by administration of arachidonic acid aggravated hypertension in rats with one kidney, and receiving DOCA and salt. Further, infusion of arachidonic acid into the rat constricted the renal vasculature and prevented natriuresis induced by volume expansion (Weber et al., 1975). In contrast, in the dog, administration of arachidonic acid has been shown to increase renal blood flow and GFR and promote sodium excretion (Chang et al., 1975; Tannenbaum et al., 1975). These studies indicate that a prostaglandin-dependent mechanism has opposite effects on the renal circulation of the rat and the dog. In the rat, activation of renal prostaglandin mechanisms may alter the critical balance between blood pressure-elevating and lowering forces, favoring the former.

Administration of indomethacin also has been shown to increase total peripheral resistance in normotensive man (Wennmalm, 1978); long-term administration of indomethacin increased further the elevated blood pressure in hypertensive man (Ylitalo et al., 1978). These studies, when considered together with recent evidence of prostaglandin deficiency in hypertensive man (Abe et al., 1977; Tan et al., 1978), support the proposal that diminished production of prostaglandins may contribute to blood pressure elevation in all species studied thus far except the rat.

'Tis but a part we see, and not a whole**

The use of the rat as an experimental animal when studying the antihypertensive role of prostaglandins first was challenged because of an unexpected finding; PGE_2, a major renal prostaglandin and potent vasodilator substance, constricted the vasculature of the isolated kidney of the rat, an effect of PGE_2 not found in the rabbit under these experimental conditions (Malik and McGiff, 1975) and not observed in any other species. The principal conclusion of this study, that prostaglandins of the E series could contribute to the elevation of blood pressure in the rat, was based on understanding how renal prostaglandin mechanisms may affect renovascular resistance and, thereby, blood pressure. There were four major findings in this study; together they provide strong support for a prohypertensive action of PGE_2 in the rat and an anti-hypertensive action of PGE_2 in the rabbit. Man and other species, as indicated, resemble the rabbit in

** Pope, Alexander, Ibid., p. 20, l. 60.
terms of prostaglandin-dependent antihypertensive mechanisms. First, infusion of either PGE\(_1\) or PGE\(_2\) constricted the renal blood vessels in the rat but not in the rabbit; in the latter these prostaglandins dilated the renal vasculature. Second, at concentrations 10-fold less, prostaglandins of the E series enhanced the renal vasoconstrictor response of the rat to sympathetic nerve stimulation and attenuated this response in the rabbit (Fig. 1). Third, arachidonic acid, the polyunsaturated fatty acid precursor of PGE\(_2\), when infused in relatively low concentrations into the rat kidney, mimicked the vasoconstrictor effects of infused PGE\(_2\), whereas arachidonic acid dilated the renal vasculature of the rabbit. These effects of arachidonic acid were abolished in both species by inhibiting prostaglandin synthesis with indomethacin, indicating that they were mediated through conversion of arachidonic acid to prostaglandins. Fourth, because of the high levels of PGE\(_2\) in isolated kidneys (Itskovitz et al., 1974) and as PGE\(_2\) was shown to augment the renal vasoconstrictor effect of adrenergic stimulation, inhibition of prostaglandin synthesis with indomethacin reduced the constrictor response of the renal vasculature to nerve stimulation in the rat, whereas, in the rabbit, indomethacin treatment augmented the renal vasoconstriction induced by nerve stimulation. Based on these observations it also was concluded that for "studies in which definition of an antihypertensive role for prostaglandins is the major objective, the use of the rat would not be suitable" (Malik and McGiff, 1975).

To recapitulate, in the isolated kidney of the rabbit the effects of PGE\(_2\), arachidonic acid, and indomethacin were opposite those found in the kidney of the rat. In the rabbit, PGE\(_2\) diluted renal blood vessels and inhibited the vasoconstrictor response to renal nerve stimulation; arachidonic acid diluted the renal vasculature and attenuated renal vasoconstriction induced by nerve stimulation whereas indomethacin augmented it. Because of the importance of renal mechanisms to the regulation of blood pressure, the anomalous effects of PGE\(_2\) in the rat probably need occur only in the kidney to cause elevation of blood pressure. Indeed, there is evidence that PGE\(_2\) dilates other vascular beds of the rat (Gerber and Nies, 1979). However, before the proposal that PGE\(_2\) is prohypertensive in the rat could be accepted, it was important to confirm in vivo the effects of PGE\(_2\) in vitro on the renal vasculature of the rat. Isolated blood vessels, such as those of the hindlimb or mesentery, perfused with artificial solutions have been reported to respond differently from the same organ in situ (Phelan et al., 1976). Recently, the observations made in vitro have been confirmed by two studies based on different methods to measure renal blood flow in vivo (Baer and McGiff, 1979; Gerber and Nies, 1979). Infusion of arachidonic acid was shown also by Gerber and Nies (1979) to constrict the renal blood vessels of the rat in vivo, suggesting that the principal product of prostaglandin synthesis of the kidney is PGE\(_2\), as prostacyclin (PGI\(_2\)), also a product of renal arachidonic acid metabolism, is a weak dilator of the renal vasculature of the rat (Baer and McGiff, 1979). Thus, the renal vasoconstrictor action of PGE\(_2\) may be unique in the rat as total vascular resistance decreased during infusion of either PGE\(_2\) or its precursor, arachidonic acid, at a time when renal vascular resistance increased (Gerber and Nies, 1979). Because an increased renal vascular resistance might of itself elevate blood pressure (Tobian, 1974; Norman and Guyton, 1979), enhanced levels of PGE\(_2\) intrarenally could be a sufficient cause of hypertension, a conclusion which led to a study on the possible operation of a renal prostaglandin mechanism as a determinant of elevated blood pressure in the genetically hypertensive rat (Armstrong et al., 1976a).

The anomalous constrictor response of the renal vasculature of the rat to PGE\(_2\) was found to be exaggerated in the GH strain (Fig. 2). Important
interactions of norepinephrine with prostaglandins were shown to contribute to increased tone of renal blood vessels in GH rats. Norepinephrine released prostaglandins in the kidney; these augmented the renal vasoconstrictor response to norepinephrine, an effect which was exaggerated in the GH rat when compared to the normotensive control rat (Fig. 3). Further, indomethacin attenuated the enhanced renal vasoconstrictor effect of norepinephrine, and infusion of PGE$_2$ partially restored the renal vascular action of norepinephrine in the presence of indomethacin in the GH rat. An abnormality in prostaglandin metabolism was found in the GH rat which could account for the elevation of blood pressure in this strain; this defect was not detected in the SHR or in rats made hypertensive by constriction of one renal artery. The major catabolizing enzyme, 15-hydroxyprostaglandin dehydrogenase, was deficient (Fig. 4), a defect leading to higher levels of PGE$_2$ intrarenally. Increased levels of an endogenous inhibitor of 15-hydroxyprostaglandin dehydrogenase have been reported in the GH strain (Wong et al., 1979). As PGE$_2$ constricts renal blood vessels in the rat, elevated levels should depress renal blood flow, a prediction which has been validated in the GH rat by both direct and indirect methods for measuring renal blood flow (Bolli et al., 1976; Baer et al., 1979). Renal blood flows of both adult and weanling GH rats were found to be lower than those of normotensive control rats (Baer et al., 1979).

Abnormalities in prostaglandin metabolism have since been reported in the SHR strain (Dunn, 1976; Pace-Asciak, 1976; Limas and Limas, 1977) which could lead to elevated levels of prostaglandins in this strain as well as in the GH strain. The importance of increased renal prostaglandin levels to hypertensive mechanisms in the GH and SH rats may be understood in terms of prostaglandin-adrenergic interactions, whereby increased levels of a modulator, such as PGE$_2$, will potentiate the effects of the sympathetic nervous system.

\[\text{Vasoconstrictor responses to PGE}_2\]

\[\begin{align*}
\text{GENETIC HYPERTENSIVE} & \quad (n=9) \\
\text{NORMOTENSIVE} & \quad (n=9)
\end{align*}\]

**Figure 2** Mean changes in perfusion pressure produced by PGE$_2$ infused for 8 minutes into isolated kidneys, perfused with Krebs' solution, of normotensive or GH rats. Curves of hypertensives were found to be to the left of normotensives, denoting greater vascular sensitivity to PGE$_2$. [Reprinted from Nature (Armstrong et al., 1976a: Fig. 5, p 585).]

The least confusion but in one, not all That system only, but the whole must fall***

The capacity of PGE$_2$ to act as a modulator of blood pressure regulatory systems should be distinguished from a direct vascular action; the former may be evident at concentrations as much as 200-fold less than those which have a direct effect (Malik and McGiff, 1975). Because of the ability of PGE$_2$ to potentiate adrenergic nerve-mediated constriction of the renal vasculature of the rat, there need not be any increased intrinsic activity of renal adrenergic mechanisms for initiating the sequence of events leading to elevated renal vascular resistance and, finally, hypertension. Thus, increased renal levels of the modulator itself could elevate...

* Pope, Alexander, Ibid., p. 46, 11. 249-250.
blood pressure in the absence of increased activity of pressor systems, such as the adrenergic nervous system. What is required is increased levels of PGE2 at sites in proximity to the adrenergic neuroeffector of the renal vasculature. In the GH and SHR strains, this requirement appears to be fulfilled by either decreased degradation or increased synthesis of PGE2 and biologically related agents within the kidney. This interaction of PGE2 with the renal sympathetic nerves can explain the increased sensitivity of the renal vasculature to sympathetic nerve stimulation in weanling rats and the elevated renal vascular resistance in adult rats (Baer, personal communication). The latter correlates with gradually increasing sympathetic nervous activity with maturation (Iversen et al., 1967). Further, prostaglandin-adrenergic interactions provide an explanation for attenuation of the development of hypertension through interruption of sympathetic nervous activity (Clark, 1971; Clark and Phelan, 1976).

There is evidence for prostaglandin-mediated vasodilatation in the rat kidney evoked by volume expansion (Dusting et al., 1977) and infusion of angiotensin II (Finn and Arendshorst, 1976). This vasodilator mechanism probably is subserved by prostacyclin or its active metabolite, 6-keto-PGE1 (Wong et al., 1980), as PGF2 and 6-keto-PGE1, unlike PGE2, can dilate the renal vasculature of the rat (Quilley et al., 1979). PGF1α has been shown to subserve some prostaglandin-related vasodilator mechanisms in several species (Dusting et al., 1979). Second, the possibility should be considered that thromboxane A2, which has been shown to constrict blood vessels (Dusting et al., 1979), may be generated in increased amounts in some forms of genetically hypertensive rats. These considerations are advanced as qualifications to the proposal that a mechanism operating through one or more renal prostaglandins, primarily PGB2, can elevate blood pressure in the rat.

and reasoning but to err****

In conclusion, the major strains of hypertensive rats, as well as some of the substrains, demonstrate fundamental differences which indicate the operation of different genetic determinants and ultimately different biochemical and molecular mechanisms, no matter the final common pathway; viz., end organ damage to the cardiovascular system, kidney, and brain due to elevated blood pressure. However, it is not for this reason that the rat is the subject of this polemic: to be resolved “that the rat with spontaneous genetic hypertension is not a suitable model of human essential hypertension.” In fact, there is ample justification for pursuing most of the studies cited, as they contribute importantly to our understanding of the operation of genetic, renal, and cardiovascular determinants of hypertension, both experimental and human. The major objection to the assumption that the spontaneously hypertensive rat is the animal model “closest to essential hypertension in man,” allowing that it is not “a precise counterpart” (Tobian, 1977), rests on the potential importance of a blood pressure-lowering mechanism intimately related to renal prostaglandins, a mechanism which in the rat, rather than being antihypertensive, may contribute to elevation of blood pressure.

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**** Pope, Alexander, Ibid., p. 53, 1. 2.
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