Similarities of Genetic (Spontaneous) Hypertension

Man and Rat

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IN 1963, Okamoto and Aoki introduced a new model of experimental hypertension that required no physiological, pharmacological, or surgical intervention. This spontaneously hypertensive rat (SHR) was developed by meticulous genetic (brother-to-sister) inbreeding that uniformly resulted in 100% of the progeny having naturally occurring hypertensive disease (Okamoto and Aoki, 1963; Okamoto et al., 1966a). Since then, several expert panels have reported that the SHR is an excellent model of experimental hypertension that could serve as a counterpart for clinical essential hypertension (Undenfriend and Spector, 1972; ILAR, 1976).

In this discourse we take the affirmative position that the SHR is, indeed, an excellent model for the study of essential hypertension. We do so, however, with four important caveats. First, we recognize that it is unlikely that both forms of naturally occurring hypertension (man and rat) are identical expressions of genetically determined hypertensive disease. Second, we take the position that both forms of hypertension are polygenic in origin and that both are influenced by environmental factors. Thirdly, since the control of normal arterial pressure in both man and rat is multifactorial, it follows that certain pressor mechanisms might well operate in one form of genetic hypertension that do not necessarily occur in the other (although in both, some similar factors could be involved). This same reasoning also may be applied to hypertensive individuals, although there may be less heterogeneity in SHR because of more rigorously controlled inbreeding. Our fourth clarification is to underscore the well-grounded physiological concept that, as one regulatory factor becomes altered, other homeostatic mechanisms must become involved secondarily. From this last premise, it follows that similar secondary (adaptive) alterations in regulatory mechanisms necessarily will occur in both forms of genetic hypertension. Therefore, it seems reasonable to assume that, until more is learned about initiating mechanisms in genetic hypertension, the study of any model of naturally occurring hypertension should provide useful and important information regarding essential hypertension in humans.

Experimental Genetic Hypertension

Experimental models of genetic (spontaneous) hypertension also have been reported in species other than the rat, but they have not been studied as extensively for practical, financial, and other reasons. In contrast, several forms of murine genetic hypertension, including the SHR, have received a greater interest. The obvious virtues of these rat models are their short life span, small size, and relatively low cost, thereby lending themselves for study of the natural history, genetic determinants, and pathophysiological alterations of the disease.

The New Zealand strain of Smirk seems to be most similar to the Japanese SHR but has not been studied as broadly (Smirk and Hall, 1958; Phelan, 1968). In contrast, the Milan strain, developed by Bianchi et al. (1973, 1974), seems to be different, involving primarily alterations in renal, sodium, and water metabolism (Bianchi et al., 1975); therefore, it may not be analogous to the common clinical problem of essential hypertension. A fourth strain, developed by Dahl, shows a high sensitivity ("S")
Arterial Pressure Development

Depending on which SHR colony is studied, and perhaps on the inbreeding techniques followed, arterial pressure usually is elevated from a very early age in the SHR (Okamoto et al., 1972). In our colony, which has been maintained by strict brother-to-sister mating, the SHR shows an increased arterial pressure (with respect to age- and sex-matched WKY) as early as 3 weeks of age (Trippodo et al., 1978). Further, although the arterial pressure increases with age in both the SHR and WKY, it does so at a faster rate and achieves a maximum level at a later age in the SHR. Thus, arterial pressure in the WKY reaches a maximum by 6–10 weeks of age, whereas it continues to increase in the SHR until approximately age 20–28 weeks. In the conscious, unrestrained male SHR in our colony (age 20–24 weeks) mean arterial pressure (measured directly) averages approximately 190–200 mm Hg as compared with 115–130 mm Hg for the WKY. These pressure differences are similar to those observed under controlled ether anesthesia, although excess ether or pentobarbital will produce much lower pressures (Pfeffer and Frohlich, 1972). In other SHR colonies or laboratories, elevated arterial pressure may be later in onset and achieve a lower maximum (Folkow and Hallback, 1977; Lais et al., 1977). Moreover, environmental factors, in-

\[ \text{pulmonary diseases (ILAR, 1976). In addition, despite careful inbreeding within the hypertensive and normotensive strains, it is possible that the distinctive characteristics of each strain may change somewhat over the generations or may vary among different colonies (Mullins and Banks, 1976; Sinaiko and Mirkin, 1978). Nevertheless, we still believe that by comparing the regulatory pressor mechanisms that operate in essential hypertension and in various genetic models of experimental hypertension, we eventually will understand more about normal and abnormal control of arterial pressure. Moreover, we also underscore that, to understand adequately the changes in organ function and adaptations that occur in essential hypertension, we must relate the observations made in humans to those made in a slowly progressing and naturally developing hypertension. For example, studies of the performance of the hypertrophied myocardium or of the regression of hypertrophy with antihypertensive therapy are best performed in an experimental model that has developed ventricular hypertrophy in response to slow and progressive elevations in arterial pressure and total peripheral resistance (Sen et al., 1974; Pfeffer et al., 1976; Weiss and Lundgren, 1978; Sen et al., 1980). The same rationale also can be applied to studies of changes in vascular morphology and function (Folkow et al., 1975; Mulvany et al., 1978). The SHR demonstrates these characteristics, and, to date, it is the only model of essential hypertension that has been broadly available.} \]
including excess sodium intake (Louis et al., 1971; Aoki, et al., 1972; Chrysant et al., 1979a; Karr-Dul-lien and Bloomquist, 1979), stress (Yamori et al., 1969), social alterations (Hallback, 1978), and altered light-dark schedule (Lais et al., 1974) also have been shown to influence development of SHR hypertension.

Detailed longitudinal studies involving patients with essential hypertension observed from the early stages of the disease until death are unavailable for obvious clinical and ethical reasons. Thus, the onset and rate of development of arterial pressure in human beings are not as clearly defined as they are in the SHR. However, recent evidence has suggested that some patients with essential hypertension may be identified very early in life (Londe et al., 1971; Loggie, 1971); consequently, the significance of slightly elevated arterial pressure in children is being reassessed (Harlan et al., 1979). Several studies have demonstrated that familial aggregations of arterial pressure exist, even as early as 1 month of age (Kass and Zinner, 1969; Zinner et al., 1971; Klein et al., 1975; Hennekens et al., 1976), and evidence is also accumulating (albeit controversial) suggesting that teenagers and young adults with mildly elevated arterial pressure may be at a greater risk of developing sustained hypertension than those with lower pressures (Levy et al., 1945; Rorbaek and Buch, 1971; Levine et al., 1976). Thus, these and many other studies have indicated that the arterial pressure levels of children may be correlated with those of their parents; and this phenomenon, referred to as tracking, seems to begin in infancy (Lieberman, 1980). Furthermore, cultural, social, behavioral, as well as other environmental factors including dietary sodium, physical work, and obesity also have been implicated as playing a role in essential hypertension (Heyden et al., 1969; Weiner, 1977; Kirkendall and Nottebohm, 1977; Cornoni-Huntley et al., 1979). These findings are similar to the genetic and environmental characteristics of the arterial pressure development in the SHR.

**Hemodynamics**

The elevated arterial pressure of the adult SHR is associated with an increased total peripheral resistance and a normal cardiac output (Pfeffer and Frohlich, 1973; Smith and Hutchins, 1979; Ferrone et al., 1979). This has been observed consistently, regardless of the techniques used to measure cardiac output or the normotensive control strain to which the SHR was compared. However, in the young animals (<12 weeks of age) discrepancies exist, and cardiac output has been reported as increased or normal (Pfeffer and Frohlich, 1973; Pfeffer et al., 1974; Tadepalli et al., 1974; Smith and Hutchins, 1979). Among other factors this has been related to the normotensive strain used for control. Nevertheless, if cardiac output is increased, it does not seem to be essential for the subsequent development of hypertension associated with increased total peripheral resistance (Pfeffer et al., 1974; Pfeffer et al., 1977).

In humans, increased total peripheral resistance and normal cardiac output are also the usual findings in established essential hypertension, and in the milder (earlier) stages of hypertension, cardiac output may be variously increased, normal, or even slightly reduced (Frohlich, 1977a; Messerli et al., 1978). In both the SHR (Sen et al., 1972a; Rippe et al., 1978) and in humans with essential hypertension (Ibsen and Leth, 1973; Tarazi, 1976), blood volume may be either normal or slightly reduced, heart rate may be elevated at all stages, and the left ventricle undergoes progressive hypertrophy (Frohlich, 1977a). However, in the very old SHR (Rippe et al., 1978; Bagby et al., 1979) and in some patients with essential hypertension (Dustan et al., 1972; Tarazi, 1976; Chrysant et al., 1979b), increased arterial pressure may be associated with expanded blood volume. Nevertheless, during the early stages of SHR hypertension (Trippodo et al., 1978) or in the milder forms of essential hypertension (Julius et al., 1971; Messerli et al., 1978) when cardiac output may or may not be elevated, intravascular volume does not seem to be expanded and may be normal or even contracted (Frohlich, 1977a).

As arterial pressure rises and vascular disease progresses with the duration and severity of both forms of hypertension (rat and man), they do so as total peripheral resistance increases (Frohlich, 1977a). This increased vascular resistance seems to be distributed largely uniformly in the various organs of the SHR (Nishiyama et al., 1976; Ferrone et al., 1979) and in humans with milder forms of essential hypertension (Messerli et al., 1978); although earlier reports in man suggested preference for arteriolar constriction in kidney, skin, and the splanchnic circulation (Brod, 1973). In any case, cardiac output in both forms remains normal until the later stages, when myocardial function becomes impaired (Frohlich et al., 1971); then output decreases as congestive heart failure supervenes. Thus, the hemodynamic alterations and cardiac adaptation to the increased vascular resistance in both naturally occurring forms of hypertension seem to follow a very similar course.

**Vascular Factors**

As already indicated, one of the most consistent vascular findings in the adult SHR and in established essential hypertension is an increased total systemic peripheral resistance. Although this may be related to an alteration of the entire vascular system from the aortic arch to the right atrium, the small arteries, arterioles, and perhaps the precapillary sphincters provide the greatest increase in vascular resistance. Many studies in experimental forms of hypertension (including the SHR) and in essential hypertensive man suggest that both active and structural processes are involved in the increased vascular resistance. For example, increased
vasculature reactivity to a variety of stimuli has been demonstrated in most, but not all (Fink and Brody, 1979; Collis et al., 1980) studies of this subject in the SHR (Haeusler and Finch, 1972; Bohr, 1974; Lais and Brody, 1975; Folkow et al., 1975; Hermensmeyer, 1976; Mulvany and Halpern, 1977; Collis and Vanhoutte, 1977; Mulvany et al., 1978; Bohlen, 1979) as well as in humans with essential hypertension (Folkow et al., 1975; Mendlowitz, 1977). In both rats (Ichijma, 1969; Folkow et al., 1975; Collis and Vanhoutte, 1977; Mulvany et al., 1978) and humans (Folkow et al., 1975), there is evidence that the increased vascular reactivity may be related partly to altered vessel design. Likewise, in both forms of hypertension, evidence of increased participation of the adrenergic system may be derived from a variety of studies (see below). Conversely, direct evidence that autoregulation promotes the arteriolar constriction in either form of hypertension is lacking and, at present, arguments in favor of this mechanism are based only on the interpretation of indirect data from other models of hypertension (Coleman et al., 1979). Furthermore, increased vascular smooth muscle reactivity and tone may be related to functional changes in the cellular membrane (Overbeck, 1972; Haddy and Overbeck, 1976; Blaustein, 1977; Lang and Blaustein, 1980), and this concept has received continued interest. Studies designed to examine membrane ionic fluxes and related enzyme activities (Na\(^+\), K\(^+\)-ATPase) in various models of hypertension currently are underway, and any conclusions regarding genetic hypertension would be premature, although several recent reports have shown alterations both in humans with essential hypertension (Garay and Meyer, 1979; Garay et al., 1980) and in the SHR (Jones, 1973; Friedman et al., 1977; Friedman, 1979; Parnami et al., 1979). In addition to the above mechanisms possibly responsible for increased vascular resistance and hyperreactivity, evidence of decreased arteriolar density in skeletal muscle of the SHR (Hutchins and Darnell, 1974; Dusseau and Hutchins, 1979) and in the conjunctiva of humans (Harper et al., 1978) has been reported. However, the extent of this deletion of parallel paths in other tissues is unknown, and its involvement in contributing to the increased total peripheral resistance is uncertain (Holloway and Bohr, 1973; Hallback et al., 1976).

Regarding the venous side of the circulation, most studies have suggested increased venoconstriction both in humans with essential hypertension (Freis, 1960; Caliva et al., 1963; Walsh et al., 1969; Ulyrcy et al., 1969; Takeshita and Mark, 1979) and in the SHR (Greenberg and Bohr, 1975; Simon, 1976). Although venoconstriction would contribute physically only a small part to the elevated total peripheral resistance in hypertension, it seems to decrease significantly total circulatory capacity, an observation made both in humans with essential hypertension (London et al., 1978; Safar et al., 1979) and in the SHR (Samar and Coleman, 1979; Tripippo et al., 1980). Increased venous capacity could lead to increased filling pressure of the heart; indeed, increased left atrial pressure has been reported in the conscious SHR (Noesson et al., 1979), and this may be important in helping to maintain normal cardiac output in the face of increased total peripheral resistance and decreased cardiac compliance in established hypertension. Alternatively, in the milder forms of hypertension, it could participate in elevating cardiac output (Ulyrcy et al., 1969). Increased venous constriction also could explain the increased capillary filtration and contracted plasma volume that has been observed both in humans with essential hypertension (Tarazi, 1976) and in the SHR (Ripp et al., 1978). The mechanisms responsible for the increased venoconstriction are unknown, but it is conceivable that some of the same factors discussed above which might lead to increased arteriolar constriction could very well be operative on the venules as well. For example, adrenergic mechanisms are known to constrict both pre- and postcapillary vessels as well as to stimulate the heart, and increased sympathetic nerve activity has been implicated as an important pressor mechanism both in humans with essential hypertension and in the SHR (Frohlich and Pfeffer, 1975; Frohlich, 1977b). Also, the structural alterations, which have been observed on the arterial side of the circulation in hypertension, also might occur on the venous side. Indeed, many of the studies cited above suggest that structural changes are responsible in part for the altered venous function in both forms of genetic hypertension, and venular hypertrophy recently has been reported in the adult SHR (Greenberg et al., 1978). On the other hand, Aalkjaer and Mulvany (1979) did not observe any morphological or mechanical differences in the small mesenteric veins between the SHR and the WKY.

Neural Factors

Although it is likely that a major control system of arterial pressure such as the autonomic nervous system must play some part in the initiation or maintenance of elevated arterial pressure in essential hypertension (even if only to be counteract nonneuropressor mechanisms), it has been extremely difficult to understand precisely the extent of the possible neural alterations. The autonomic nervous system is a vastly complex regulatory system that involves impulse generation; neurotransmission; neurotransmitter release and uptake; secretion, excretion, and metabolism of circulating catecholamines; adrenergic receptor interactions; and effector organ reactivity. Furthermore, as in many other aspects of essential hypertension, heterogeneity among subjects adds to the already complicated problem. Hence, as pointed out in a recent discussion of this subject (Kuchel, 1977), the large amount of information regarding neural fac-
tors can be placed in the pathophysiological context of essential hypertension only in conjunction with genetic factors, behavioral patterns, dietary factors, age, duration of hypertension, and the complete spectrum of total autonomic function. We will not undertake such a detailed discussion here, but mention only a few highlights. For example, enhanced adrenergic nerve activity in essential hypertension is suggested by the fact that each of the hemodynamic alterations detailed above can be produced by adrenergic mechanisms. Also, many available potent antihypertensive drugs operate through inhibition of adrenergic function. In addition, some patients with essential hypertension show increased cardiovascular reactivity to catecholamines (Goldenberg et al., 1948, Doyle and Fraser, 1961; Mendlowitz et al., 1965). Regarding the significance of altered catecholamines in essential hypertension, although a complete understanding has not been arrived at yet, studies using recently developed assay methods suggest various degrees of elevated plasma catecholamines and excretion in hypertensive patients under certain conditions (Engelman et al., 1970; DeQuattro and Chan, 1972; Louis et al., 1973; Dechamplain, 1977; Philipp et al., 1978; Eide et al., 1979; Hong Tai Eng et al., 1980; Henry et al., 1980). Also, the hemodynamic and plasma catecholamine responses to mental stress were enhanced in adolescents with labile hypertension or with hypertensive parents (Falkner et al., 1979). Therefore, although the exact nature and extent to which this system participates are presently unclear, a strong body of evidence remains that implicates an important pathogenic role of the adrenergic nervous system, at least in some patients with essential hypertension.

The importance of neural factors in SHR hypertension likewise has been demonstrated by hemodynamic findings similar to those in humans with essential hypertension discussed above and by many experimental (SHR) studies showing a greater than normal reduction of arterial pressure by surgical or pharmacological abolition of sympathetic nerve activity (Okamoto et al., 1966b; Folkow et al., 1972; Numao and Iriuchijima, 1974; Yamori, 1976), prevention of the development of hypertension by immunosympathectomy (Cutilletta et al., 1977) or chemical sympathectomy (Provost and DeJong, 1978) or by depletion of central catecholamines (Erinoff et al., 1975), slowing of the development of increased arterial pressure by renal denervation (Liard, 1977; Kline et al., 1978), increased sympathetic nerve activity by direct recordings (Okamoto et al., 1967; Judy et al., 1976; Schramm et al., 1979), enhanced release of catecholamines during brief immobilization (Kvetnansky et al., 1979), and a positive correlation between renal sympathetic nerve activity and mean arterial pressure in hybrid SHR/WKY (Judy et al., 1979). Furthermore, there may be a greater participation of the sympathetic nervous system in the initiation or early stages of elevated arterial pressure in the SHR than in the later phase when other pressor and adaptive mechanisms also may contribute to the high vascular resistance and elevated arterial pressure (Folkow and Hallback, 1977). Thus, in both rats and persons with genetic hypertension, there is ample evidence documenting high sympathetic nerve activity at least in some stages of the disease and in some individuals. Such activity could participate, along with other possible mechanisms, in the pathogenesis of the hypertension.

**Renal Factors**

The interaction of renal function and arterial pressure is well known, and participation of renal factors (either as primary or secondary events) which might initiate and/or maintain elevated arterial pressure, continues to be studied. In comparing overall renal function in essential hypertensive humans with that in the SHR, several similarities are evident. Hence, in most patients with uncomplicated essential hypertension, renal blood flow usually is reported as normal or decreased with normal or slightly reduced glomerular filtration rate and increased filtration fraction (Brod, 1973; Coleman et al., 1975; Hollenberg and Adams, 1976; Messerli et al., 1978). Similarly, in the SHR, renal blood flow has been reported normal or decreased with a normal glomerular filtration rate and increased filtration fraction (Nishiyama et al., 1976; Beierwaltes and Arendshorst, 1978; Stee1 and Underwood, 1978; Arendshorst and Beierwaltes, 1979; DeChamplain, 1977; Philipp et al., 1978; Eide et al., 1979; Hong Tai Eng et al., 1980). Similarly, in the SHR, renal blood flow has been reported normal or decreased with a normal glomerular filtration rate and increased filtration fraction (Nishiyama et al., 1976; Beierwaltes and Arendshorst, 1978; Stee1 and Underwood, 1978; Arendshorst and Beierwaltes, 1979; DeChamplain, 1977; Philipp et al., 1978; Eide et al., 1979; Hong Tai Eng et al., 1980). In addition, some patients with essential hypertension show increased cardiovascular reactivity to catecholamines (Goldenberg et al., 1948, Doyle and Fraser, 1961; Mendlowitz et al., 1965). Regarding the significance of altered catecholamines in essential hypertension, although a complete understanding has not been arrived at yet, studies using recently developed assay methods suggest various degrees of elevated plasma catecholamines and excretion in hypertensive patients under certain conditions (Engelman et al., 1970; DeQuattro and Chan, 1972; Louis et al., 1973; DeChamplain, 1977; Philipp et al., 1978; Eide et al., 1979; Hong Tai Eng et al., 1980; Henry et al., 1980). Also, the hemodynamic and plasma catecholamine responses to mental stress were enhanced in adolescents with labile hypertension or with hypertensive parents (Falkner et al., 1979). Therefore, although the exact nature and extent to which this system participates are presently unclear, a strong body of evidence remains that implicates an important pathogenic role of the adrenergic nervous system, at least in some patients with essential hypertension.

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(Okamoto et al., 1967; Judy et al., 1979). Despite, or perhaps as a result of the increased renal vasoconstriction, the overall renal handling of electrolytes and water appears to be largely normal in the SHR (Beierwaltes and Arendshorst, 1978; Norman et al., 1978) except for the unexplained phenomenon of enhanced natriuresis, which has been reported inconsistently (Kraoff et al., 1970; Mullins and Banks, 1976; Vandewalle et al., 1978; Beierwaltes and Arendshorst, 1978) in both man (Farnsworth, 1946) and rat (DiBona and Rios, 1978; Willis and Bauer, 1978; Willis, 1979). Furthermore, both extracellular fluid volume and plasma sodium concentration seem to be normal in these two genetic hypertensions, man (Frohlich, 1964; Tarazi, 1976) and rat (Trippodo et al., 1978; Baer et al., 1972; Willis and Bauer, 1978). Parenthetically, one current theory holds that the renal excretion of normal amounts of sodium and water in the presence of elevated arterial pressure represents an altered functional state of the kidney (shift of the renal pressure-diuresis relationship), which itself underlies the pathogenesis of elevated arterial pressure (Guyton et al., 1974; Guyton, 1977). However, this theory has been neither refuted nor confirmed.

Thus, although questions remain as to whether the kidney provides the causative mechanisms or bears the brunt of the vascular disease, data from the SHR and from humans with essential hypertension seem to be similar. Hypertensive vascular disease, as it involves the renal circulation and parenchymal function, seems to parallel the involvement of the systemic disease. Moreover, additional renal factors complicating the problem (including nephrosclerosis and exaggerated natriuresis) are similar in both genetic diseases.

**Humoral Factors**

In general, strong evidence directly linking excessive circulating pressor agents or decreased levels of depressor substances to the pathogenesis of SHR or essential hypertension currently is lacking. For example, in studies of the SHR in parabiosis with the WKY (in which humoral agents may be free to diffuse between the circulations of the rat pairs), arterial pressure did not increase in the WKY partners, and there was no interference with the normal progression of hypertension in the SHR partners (Ebihara, 1972). Regarding the renin-angiotensin system, despite extensive study, it still is uncertain whether or not this regulatory system plays an important pathogenic role in either form of genetic hypertension. Indeed, most patients with essential hypertension have normal or decreased plasma renin activity (Doyle, 1977); and in the SHR, studies on plasma renin activity are conflicting (Sen et al., 1972b; DeJong et al., 1972; Freeman et al., 1975; Bagby et al., 1979). Nevertheless, inhibition of the conversion of angiotensin I to angiotensin II (using the orally effective, converting enzyme inhibitor, captopril) has been found to lower arterial pressure in both humans with essential hypertension (Atlas et al., 1979; Bravo and Tarazi, 1979; Sullivan et al., 1979) and in the SHR (Crofton et al., 1979; Koike et al., 1980). However, this drug also lowers arterial pressure in an experimental hypertensive model which is believed to be volume expanded and renin suppressed (Murhead et al., 1979), and the mechanism of action of captopril may involve effects other than inhibition of the circulating renin-angiotensin system in both humans (Waeber et al., 1980) and the rat (Hutchinson et al., 1980).

Steroids, such as aldosterone and 18-hydroxy-11-deoxy-corticosterone, also have been studied, and although they may participate importantly in other types of hypertension, they do not seem to be important in the SHR (Melby, 1977). However, conclusive evidence presently is lacking regarding the participation of these and other mineralocorticoids in the pathogenesis of essential hypertension (Melby, 1977; Nowaczynski et al., 1977). Other possible humoral factors, such as prostaglandins, kalikrein-kinins and vasopressin currently are under investigation. Thus far it has been found that urinary kalikrein excretion was decreased in patients with essential hypertension (Margolius et al., 1971), and also decreased in the SHR when compared with the WKY (Geller et al., 1975); but the implications of these observations currently are unknown (Croxatto, 1977). Thus, whereas humoral factors are important in the multifactorial regulation of arterial pressure, at this point it has not been demonstrated clearly that they participate importantly in the pathogenesis of the arterial pressure elevation in the SHR or essential hypertensive human being.

In conclusion, genetic (essential) hypertension is one of the major clinical problems to afflict mankind. One line of current thinking holds that this condition is polygenetically inherited, environmentally influenced, involves a number of physiological factors, and is, hence, multifactorial. It follows that a logical approach to study the pathophysiological alterations and natural history of the disease would be to produce hypertension naturally, through genetic inbreeding. It is clear that the likelihood of totally mimicking essential hypertension by genetic inbreeding is highly improbable. Nevertheless, by the predictable production of hypertension in a laboratory animal with a short enough life span to evaluate the natural history of the disease, it is possible to derive certain similarities. The SHR is such an experimental model and, “clinically,” the disease is very similar to essential hypertension in man. Both have their apparent onsets very early in life. Their elevated arterial pressure is mediated through a slow and progressively increased total peripheral resistance which demands cardiac and vascular adaptation. Eventually, cardiac failure, strokes, and renal lesions result in a shortened life span by about one-third in both forms of hypertension. In both genetic diseases (especially in SHR
hypertension) neural mechanisms seem to predominate in the early stages, whereas in the later and more complicated phases structural, renal, endocrine, humoral, and metabolic mechanisms, including certain less well-studied mechanisms (such as kallikrein–kinin, prostaglandins, and vasopressin) also may participate. In both forms of hypertension there seems to be susceptibility for aggravation of the disease by excess dietary sodium, stress, and other environmental factors. Also, both naturally occurring diseases are responsive to antihypertensive agents. Thus, until a better experimental model is made generally available, we feel justified to take the affirmative position that the SHR is indeed an excellent laboratory counterpart of essential hypertension.

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