

ESSENTIAL HYPERTENSION: INBORN ERROR OF SODIUM METABOLISM?

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THE NATURE of essential hypertension remains largely a matter of controversy and conjecture. The title of this paper is one such conjecture, and it is controversial. Our selection and presentation of material will be tinted by this; readers desiring related but more comprehensive and more impartial reviews might turn to Tobian (1960) or Dahl (1963).

Salt-induced Hypertension in Rats

The history of NaCl-induced hypertension in rats is given by Meneely and Dahl (1961). In our laboratory we now have two strains of white Sprague-Dawley rats, both with fairly predictable prognosis relative to the development of hypertension, (Dahl, Heine and Tassinari, 1962). They are called R (for Resistant) and S (for Sensitive), and if chronically fed the same balanced diet, low in sodium (0.37% as NaCl) their blood pressure (BP) will differ in that while most members of strain S will have a "normal" systolic BP (less than 140 mm. Hg.), the average will be high relative to that of comparable R animals. Among the few S animals that develop hypertension on a low NaCl diet, blood pressures are only moderately elevated and the course is invariably benign. However, if more NaCl is added to the same basic diet, this difference in BP between strains is amplified. All members of S ultimately will become manifestly hypertensive while the BP of the R-rats is hardly affected, and even moderate hypertension in individuals is uncommon. The rate and the degree of BP-increase as well as the malignancy of disease afflicting S-members depend on the amount of salt added and the age at which it is started. The heavier the exposure, and the earlier in life it begins, the more malignant the disease. If these animals are placed on a diet containing 8% NaCl immediately after weaning at 3 weeks of age, they will all rapidly develop hypertension and most will be dead or dying

within two months. Fig. 1 is an illustration of the effect of such an intense loading experiment. Table 1 shows how this response can be modified by a reduction and delay of the salt addition (4% added 3 weeks after weaning). These rats all lived for more than a year without significant changes from the observations at 24 weeks.

The S strain is more susceptible to all other means of producing experimental hypertension that have been tested, including DOCA-salt, unilateral renal artery compression without added salt (Fig. 2), cortisone, and adrenal regeneration (Dahl, Heine and Tassinari, 1963 and 1965).

Perspectives

In these animals hypertensive disease is a predictable and, to a large extent, preventable occurrence. Our interest in them is due to the possibility that they illustrate mechanisms at work in man. While the evidence for such an extrapolation is circumstantial its potential is fascinating: *no matter what the experimental manipulation, pathological condition, or environmental factor responsible, the disease as it is manifested in the individual is markedly affected by the genotype.*

In unselected groups of rats the connection between salt feeding and hypertension is of a statistical nature, and there is a whole scale of individual responses. Our two strains were developed by deliberately selecting and inbreeding individuals from both extremes. (Dahl and others, 1962).

If the same concept is applicable to man, it might serve to explain the statistical nature of all known associations between hypertension and specific diseases. At the extreme ends of the spectrum there are individuals resembling members of our two rat families—on the one hand the young patient in whom hypertension runs a rapidly malignant course and on the other hand the patient with severe renal disease, or other affliction commonly associated with

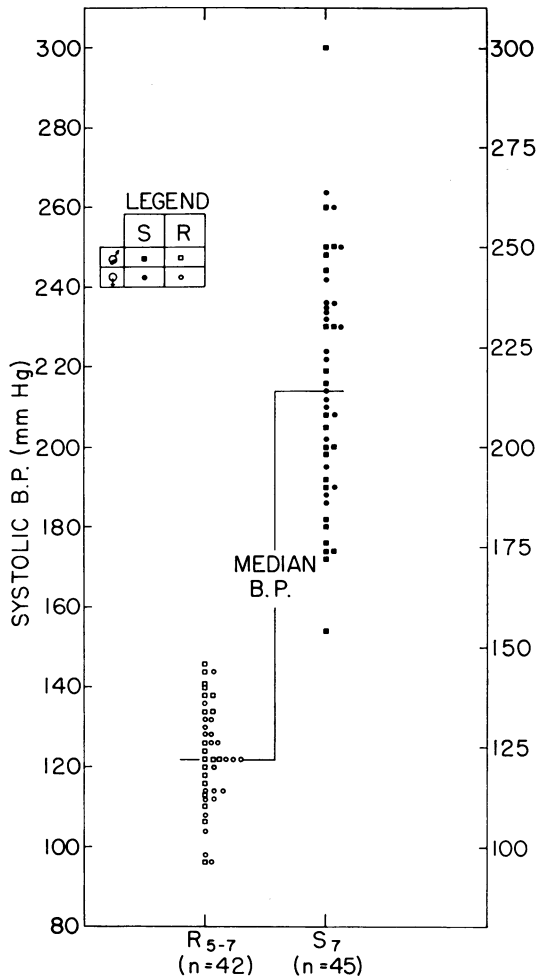


FIG. 1—Genetic influences on B.P. response to high salt diet in Sensitive (S) and Resistant (R) strains of rats. S animals after 1-2 months on salt; R animals after 10-12 months on salt.

hypertension, who remains normotensive. The concept implies that a genetic substrate modifies both the stimuli necessary to elicit a chronic BP elevation and the degree of this response. Fig. 3 is an attempt to illuminate this thesis.

Sodium and Essential Hypertension in Man

If the thesis is valid, essential hypertension in man might be due to a ubiquitous stimulus (or stimuli) acting on a population containing individuals of differing susceptibility. We shall restrict our discussion to the possibility that sodium is such a stimulus.

The first suggestion that salt intake and hypertension in man are connected stems from Ambard and Beaujard (1904) and Allen (1925). Kempner's rice-fruit diet was the first large scale, successful attempt to influence hypertensive disease by diet (Kempner, 1944). It has been shown that its effect was due primarily to its low sodium content (Dole, Dahl, Cotzias, Eder, Krebs, 1950). An epidemiologic survey by Dahl and Love (1954) and Dahl (1960) gave further weight to the thesis that sodium was in some way connected with the pathogenesis of hypertension. This survey was supplemented subsequently by an observation from South Africa on the Bantus (Isaacson, Modlin and Jackson, 1963). (Fig. 4).

Drugs like chlorothiazide and hormones like aldosterone and cortisone which interfere with sodium metabolism, influence the BP. In fact, chlorothiazide is one of the most valuable tools in our therapeutic armamentarium when dealing with essential hypertension.

Genetics and Essential Hypertension in Man

If there has been (and still is) some reluctance in admitting the culpability of sodium in the etiology of hypertensive disease, the thought that hereditary factors are operative is accepted

TABLE 1

AGE weeks	Low Salt (0.37% NaCl)						4% NaCl starting 6th week					
	S			R			S			R		
	n	BP	SD	n	BP	SD	n	BP	SD	n	BP	SD
6	24	113	±12	24	93	±8						
14	6	133	±16	6	109	±12	18	148	±15	18	117	±6
24	6	132	±7	6	96	±12	18	163	±17	18	110	±11
41	6	136	±14	6	112	±5	15	165	±20	18	113	±8

TABLE 1—For explanation see text.
n: Number of animals in group. SD: Standard deviation.

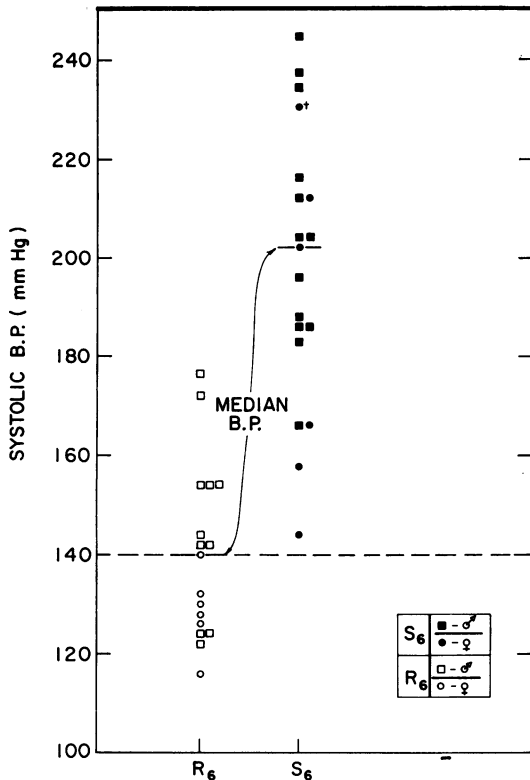


FIG. 2—Effect of genetic factors on development of renal hypertension in rats, 12 weeks after unilateral renal artery compression. R_6 and S_6 = 6th generation inbred for Resistance or Sensitivity to hypertensogenic effect of salt, respectively. † = B.P. at 10 weeks; animal died during 11th week. (Reprinted by permission of the Canadian Medical Association Journal. Dahl and others, 1964).

generally. It is common medical practice to ask a hypertensive patient about a family history of hypertension and more often than not it is found. Careful studies substantiate this impression (Thomas, 1959). Moreover, this is not restricted to essential hypertension. The correlation between pyelonephritis and hypertension is stronger in patients with a family history of high blood pressure than in patients without this background. (Platt, 1961; Cruz-Coke, 1961). The same holds for hypertension in pregnancy (Humphries, 1960, Adams and Finlayson, 1961), and may be true for hypertension associated with chronic renal disease (Hamilton, Pickering, Roberts and Lowry, 1963).

The question then is not whether genetic factors are involved, but rather the mode of inheritance and the relative importance of

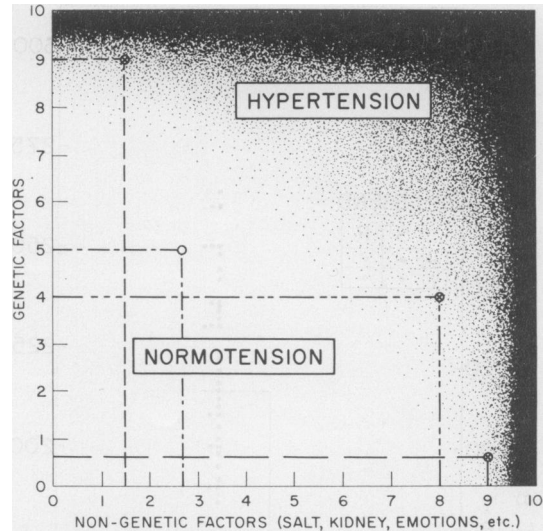


FIG. 3—Diagram to suggest possible relative roles of genetic and non-genetic factors in hypertension. (Reprinted by permission of the Rockefeller Institute Press, from J. exp. Med. Dahl and others, 1965).

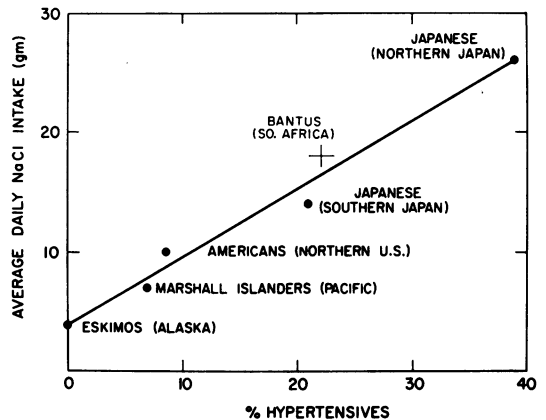


FIG. 4—Correlation of average daily salt (NaCl) intakes with prevalence of hypertension in different geographic areas and among different races. (Adapted from Dahl (1960) and Isaacson and others (1963).)

heredity and environment. Miall and Oldham (1963) concluded that between 55% and 77% of systolic variance and between 70% and 87% of diastolic variance could be explained by environmental factors. Platt (1963) placed the main importance on heredity. He did not rule out a multifactorial inheritance with some superimposed environmental factor, but found that the facts could also be explained by the

action of a single gene, with incomplete dominance and a frequency of about 0.24, which in homozygous form would give rise to severe hypertension, and in heterozygous form to moderate elevation of BP.

The matter is still *sub judice*. In our rats, analysis of the pattern of inheritance is now in progress, but data so far seem to favour the multiple gene hypothesis. A striking feature already apparent from this unpublished study is that the offspring from male S-female R matings are more susceptible to hypertensive stimuli than are rats with male R-female S parents.

Studies of Pathogenesis

An analysis of the current concepts concerning the pathogenesis of hypertension would carry us far off the present path. Of the many factors known to be operative, sodium is remarkable in that it is involved in a number of interactions. Genetic factors evidently might influence any or all.

What information we have permits brief analyses of several possibilities, but no final conclusions. Three large areas are offered for scrutiny: the cardiovascular system, the kidney, and the endocrine organs regulating electrolytes and water. The central role of sodium in the two latter fields is well known and need not be documented. Yet, sodium metabolism and genetics must be connected with the cardiovascular system to achieve a satisfactory and straightforward story.

There is very little evidence connecting hypertension with sodium metabolism of the heart, but this possibility should be considered. Ledingham (1954) found that in three forms of experimental hypertension in rats—renal, adrenal steroid, and renoprival—a disturbance common to all might be present in the sodium distribution in the heart, in which the extracellular concentration was raised relative to the intracellular.

There is more to build a case on when we look at the arterioles. Tobian, Janeczek, Tomboulian and Ferreira (1961) analyzed the arteriolar walls in hypertension produced by renal clamping in rats. They found the sodium concentration to be 16% higher than in control groups of untreated and "cured" animals. Friedman and Allardyce (1962) working with arterial segments *in vitro* concluded that NASHIFTS were directly correlated with changes of vascular wall tension.

It is also worth noting that intake patterns of salt and water may be modified by such

factors as disease, ethnic background, or the inherent composition of food. It borders on a platitude to say that a high salt diet always implies a high water intake as well. In our feeding experiments the effect of salt and of water were not studied separately. However, there are experiments indicating that increased water intake without added salt does not produce hypertension in susceptible animals (Hall and Hall, 1964). And there are clinical studies indicating that decreasing the water intake of hypertensive patients maintained on a high NaCl intake, failed to result in a fall in BP (Dole and others, 1950). When young rats from our two strains are given a free choice of both water and saline, those from the S-Strain (hypertension-prone) drink more water and less saline than do those from the R-Strain. It is tempting to speculate that this is a "feedback" mechanism acting on the intake (Wolf, Dahl and Miller, 1965).

Conclusion and Summary

It is generally accepted that genetic factors play a decisive role in the development of essential hypertension in man. There are good reasons for believing that sodium participates directly in the pathogenesis of the disease. In some rats these two factors unquestionably interact to produce hypertension. The important question is whether the latter is equivalent to essential hypertension in man.

The clinical course in these rats and in man has many similar features. The epidemiologic studies in man and the result of salt feeding to unselected batches of animals show additional resemblances. Furthermore, the observation that among young, untreated animals, those from the R-Strain have a lower average BP than the S's, even in absence of frank disease has its counterpart in man: individuals with a lower-than-average BP run a lesser risk of developing hypertension later in life, than do members from the average population (Smirk, 1957). The susceptibility of our S-rats to several "kinds" of experimental hypertension, could mirror the correlation between "secondary" hypertension in man and familial disposition to "essential" hypertension.

Apart from the possible extrapolations, what may be the derangement responsible for the disease in our rats? "Inborn errors of metabolism" is an established concept in medicine. In the prototype of these diseases, phenylketonuria, it is known that the oligophrenia which is the dominant clinical end-result can be modified if phenylalanine is

restricted in the diet of the very young patients. Further, it is a characteristic of such diseases that the clinical syndrome may vary, depending on the susceptibility to the deranged metabolism of the organs in the affected individual. Presence of manifestations at birth is not critical to the diagnosis: although the genetic defect is present at that time, appearance of overt disease may be delayed for decades, as in gout. Precipitation of symptoms in an inherited disease may occur from non-genetic factors, as in the onset of diabetes in association with pregnancy, infection, trauma, or over-nutrition.

The similarities between those diseases known to result from inborn errors of metabolism and the types of hypertension discussed here are so many that it appears permissible and possibly fruitful as a working hypothesis to consider hypertension as another inborn error of metabolism.

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