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Feeding in infancy: Short- and long-term effects on cardiovascular function

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Abstract. Cardiovascular responses of adult organisms to feeding are well characterized and, in general, are understood as acute adaptations required for processing and distributing nutrients. Research over the past several years has shown that infants also have important cardiovascular responses to nutrient intake and that these are regulated by changes in autonomic activity to the heart and vasculature. Recent studies have provided results that suggest these responses in infancy may make an important contribution to the long-term development of cardiovascular function, in particular, adult blood pressure (BP). The purpose of this presentation will be to review the evidence that has led to this conclusion, offer ideas about how this potential early-life shaping of subsequent cardiovascular function may come about, and suggest further studies that will be required in order to characterize the mechanisms responsible for these effects.
Key words. Hypertension; infancy; genetic strains; environmental contributions.

Introduction

Beneath the seeming routine performance of behaviors required for ingestion of water and nutrients is an impressive array of physiologic mechanisms involved in processing this intake. The myriad changes in gastric motility and acid, bile, and hormone secretions which are required for digestion, absorption and cellular uptake of

nutrient are well known. In addition, there are also profound adjustments in autonomic nervous system activity and the circulatory system. Post-prandial changes in peripheral resistance to blood flow and heart rate are generally understood as being cardiovascular adjustments which would aid in the distribution of nutrients to the body. Perhaps less well appreciated are the dramatic responses of the cardiovascular system that occur during feeding. Within a few seconds of the initiation of feeding there are pronounced changes in regional vascular bed resistances and blood flow, and concurrently, increases in arterial blood pressure (BP)[38,41]. Intuitively, these changes in cardiovascular function must also be an important part of the integrated responses to food ingestion and it is not surprising that such changes in cardiovascular function are found in all species studied, including invertebrates[5,14,21,23,34,38,41]. What is of special interest to this current review is that these responses are well developed early in life. The first part of this paper will summarize data collected in our laboratories which demonstrate the pronounced cardiovascular responses infant rats have to nutrient intake which take place over the course of seconds to hours. With this background in hand, the evidence we have accumulated over the past few years, as well as some important new findings, will be presented as support for the hypothesis that physiologic responses to the naturally occurring stimulus of feeding serve not only the immediate needs of the organism for processing food but, during early development, may also be important for shaping subsequent function of the cardiovascular system.

Relationships between nutrient and heart rate in infant rats

The idea that aspects of feeding in neonates might influence development of the cardiovascular system is really a sub-hypothesis that has grown out of the results from studies conducted in our laboratories as well as many others in the field of developmental psychobiology. The recurring inference from this research is that embedded within the normal set of behavioral interactions between mothers and their young are numerous, relatively specific, sources of regulation of infant physiology and behavior. Particularly relevant to the current discussion is the role nutrient plays in the regulation of heart rate. Almost 20 years ago Hofer[16] reported that heart rates of young rat pups were markedly decreased when they were separated from their mothers for several hours. There were also differences in the behavioral responses of the separated pups but, interestingly, behavioral differences induced by separation could be manipulated by changes in environmental temperature. In contrast, the lower heart rates of separated pups remained the same whether cool or at normal nest temperature. Although neither temperature nor behavioral interactions were apparently involved in the effects of separation on heart rate, Hofer and Weiner[20] demonstrated that the decreases in heart rate in these pups were directly related to gastric emptying and that resupply of nutrient of any form resulted in the nearly immediate return of heart rates to normal values. In addition, this regulatory action of nutrient was found to be specific to activation of gastrointestinal interoreceptors because intravenous infusion of nutrient was ineffective in reversing the effects of separation. Ultimately, Hofer provided evidence which suggested that the effects of nutrient loss on heart rate were mediated, at least in part, by changes in peripheral resistance and baroreceptor feedback[18].

These and many other studies have contributed to the notion that interactions between mothers and their young serve as hidden regulators of processes important to the survival of the infant[17]. Moreover, it is clear that these same interactions could serve as forces for shaping the development courses of a wide variety of physiologic and behavioral systems[19]. It is within this context that we began to search for possible linkages between mother/infant interactions and the adult expression of cardiovascular traits.

Relationships between adult BP and mother/infant behavioral interactions

We began our studies of early life correlates of adult BP by characterizing the preweaning environments to which rat pups are exposed. These studies were performed using two inbred strains, spontaneously hypertensive (SHR) and Wistar Kyoto (WKY) rats. At the time we began this work there were a few studies which suggested that the early environment might influence the expression of adult BP. McMurtry, Wright and Wexler[27] had reported that Sprague-Dawley pups that were cross-fostered to SHR dams had increased systolic BPs at 35, 60, and 90 days of age. In contrast, BPs of SHR were not changed when reared by either Sprague-Dawley or WKY dams. Although these particular findings were not replicated in work by other investigators[8], this study did prompt an interest in further examination of potential effects of the maternal environment on adult BP. Additional evidence that adult BP could be altered by manipulation of the early environment came from a study by Tang and Gandelman[39] who reported that daily handling of pups during the preweaning period resulted in decreased adult BP of SHRs. Subsequent to these investigations, several groups of researchers provided convincing data that, indeed, SHR BPs could be reduced if these animals were reared by normotensive mothers[1,8,11].

Although it was apparent that characteristics of the preweaning environment played a role in shaping adult BP, it was not clear exactly what factors were mediating these effects of cross-fostering. A study of maternal behavior by Ciepial, Shasby and McCarty[6] provided important clues as to what mothers might be doing to bring about changes in adult BP of their offspring. Consonant with many reports of behavioral differences between

SHR and WKY[40] they reported that there were significant differences in key behavioral interactions between SHR mothers and their young as compared to WKY. Specifically, they found that SHR mothers spent more time in contact with their offspring, groomed them more, and were seen nursing more often. In a similar study, we made daily observations of naturally occurring activities in the maternal nest environment of SHR and WKY litters using a checklist of mother/infant behavioral interactions[30]. We found, using principal component analyses, that the qualitative 'structure' of maternal behavior was similar for SHR and WKY dams. However, there were several significant quantitative differences between these strains. Prominent among these differences, SHR mothers were seen in the nursing posture most closely associated with milk delivery (arched-nursing) more often, SHR mothers licked and groomed their pups more often than did WKY dams, and SHR mothers were seen in contact with their young more often. These results were strikingly similar to those reported by Cierpial, Shasby and McCarty[8] and provided further support for the hypothesis that differences in maternal behavior might contribute to BP development. Another important finding in our study was the demonstration that, within homozygous strains, the behavior of individual mothers differed significantly from each other. This means that pups from different litters, as well as those from different strains, are exposed to differences in early life experiences. This latter finding suggested a strategy we used in the second part of our study to identify specific behavioral interactions that might be related to adult BP.

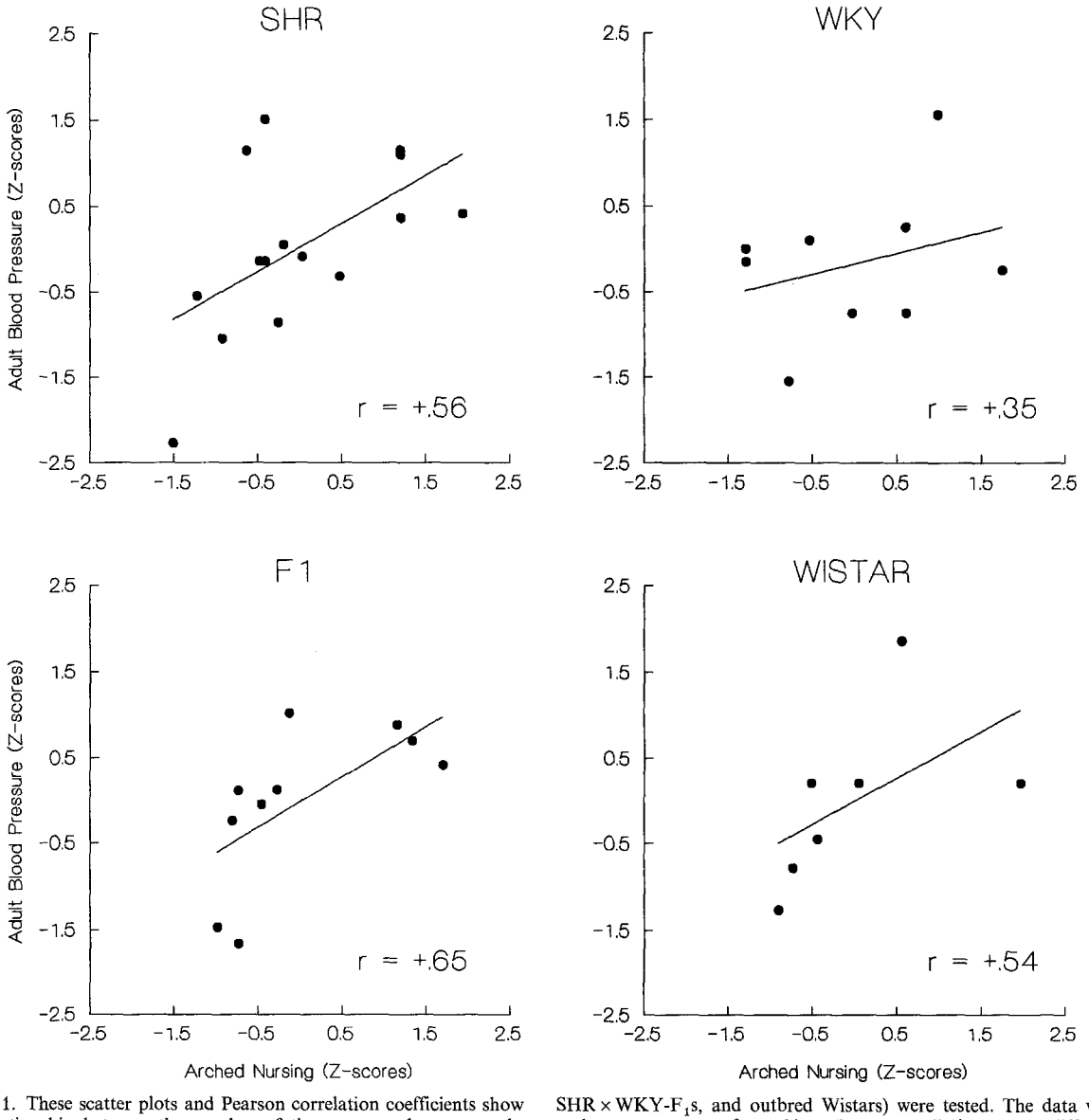

Figure 1. These scatter plots and Pearson correlation coefficients show the relationship between the number of times rat mothers were observed in the arched-nursing posture and the adult blood pressure of their offspring. Four groups of mothers and offspring (SHR, WKY, SHR × WKY-F_1s, and outbred Wistars) were tested. The data within each group were transformed into Z-scores to eliminate mean differences between groups thus allowing all plots to have identical axes. (Data were taken, in part, from Myers et al.[30] and Myers et al.[29]).

The approach we used to extend the observations of strain differences in maternal behavior involved first determining if there were significant correlations between the mother/infant interaction variables and adult tail-cuff BPs of the offspring. We found that within each strain, a combination of three variables; arched-nursing, pup-licking, and mother-in-contact-with-pups, was positively correlated with BPs of the offspring measured at 4 months of age. From these correlations we concluded that a significant portion of the variation in adult blood pressure among individuals was attributable to variation in naturally occurring experiences of early life. Furthermore, because SHR dams engage in more of those activities which are positively correlated with adult BP of the offspring, it seems likely, as is indicated by the cross-fostering studies mentioned previously, that they make an environmental contribution to the severity of hypertension in their pups. In subsequent sections of this review it will become apparent that we believe that the relationship between arched-nursing and adult BP may be the most interesting of these predictive variables. One of the reasons for pursuing this hypothesis is the stable nature of the relationship between this single variable and offspring BPs. We have now observed this relationship in 5 different groups of animals: SHR and WKYs from the experiment just described, two groups of F_1s from SHR♂ × WKY♀ breedings that were cross-fostered to either SHR or WKY dams at birth[29], and in a small group (n = 7) of outbred, heterozygous, Wistar rats (unpublished). By standardizing both BPs and arched-nursing scores using within group Z-transformations, each of these sets of data can be displayed on identical axes (see fig. 1). This figure shows that the regression between frequency of arched-nursing and adult BP is positive in each group. Because there were relatively small numbers of animals in each group, the correlations do not reach significance in every case. However, when all 42 litters are combined, this relationship is highly significant ($r = +0.50$, $p < 0.001$).

Effects of pup-type on strain differences in maternal behavior

In the study above we found there were significant differences in maternal behavior between SHR and WKY dams. In addition, we noted there were significant differences in the behavior of the pups from these two strains, with SHR pups being consistently more active[30]. In a follow-up cross-fostering study[29] we obtained results which suggest that these strain differences in maternal behavior might result from differences in the characteristics of the pups. In this experiment, we produced populations of pups of uniform genetic background (i.e., F_1 offspring from SHR♂ × WKY♀ breedings), cross-fostered these pups to SHR and WKY lactating females, and then repeated our observation procedures. We found that all of the strain differences in maternal behavior observed in the first study were eliminated when SHR and WKY dams were caring for pups of the same genetic background. Moreover, unlike studies by other workers in which SHR and WKY pups were cross-fostered, in this experiment, where there were no strain differences in maternal behavior, there was also no effect of the strain of the mother on adult BPs of the F_1 offspring. Together, these results suggest that effects of cross-fostering on adult BP, as well as effects of naturally occurring, within-strain differences in maternal behavior, may be dependent upon the behavioral phenotype of pups influencing maternal care patterns.

This conclusion is supported by a study conducted by Cierpial, Murphy and McCarty[7] in which it was found that strain differences (SHR vs WKY) in maternal behavior (e.g. nursing) were reversed when mothers reared cross-fostered pups of the opposite strain. Although results from these two studies are not in complete agreement, with WKY mothers raising F_1 pups being more labile in our study and SHR mothers rearing WKY pups changing the most in the Cierpial, Murphy and McCarty study, the conclusion that the characteristics of the pups being reared is critically involved in determining maternal behavior phenotype is solidly supported in each study.

These studies demonstrate that adult BP is a classic example of a trait which is a product of gene/environment interactions. Differences between SHRs and WKYs, derived by means of selective mating, tell us that genetic factors can influence adult BP, maternal behavior, and pup activity. Significant differences between litters within these homozygous strains with regard to mother/infant behavioral interactions and adult BP tell us there must be important environmental modifiers of each of these variables. The results from between strain cross-fostering studies, in combination with our correlational studies, suggest that specific types of mother/infant interactions shape expression of offspring BP. And finally, the results from cross-fostering of F_1 pups to SHR and WKY dams indicate that certain, as yet unknown, characteristics of pups may influence the very kinds of mother/infant interactions that can alter BP development.

BP responses of infant rats to feeding

During the early phases of our studies we discovered an important relationship between BP and feeding in young rat pups that may be of great relevance to the studies just described. Using procedures developed in our laboratories for cannulating carotid arteries of 2-week-old rats[35], we found that unanesthetized, freely behaving pups exhibit a dramatic surge in BP each time they receive milk from their mothers[34]. In part of this study milk ejections were natural, coming from unanesthetized dams as part of the normal nursing cycle. The magnitude of BP responses in undeprived pups ranged from 10 to 30% above normal resting levels (65–76 mm Hg). When these

pups were studied during reunion after being separated from their mothers for 18 h, the BP increases to milk ejections were even larger, ranging from 20–50% above resting values. These are larger changes in pressure than those associated with even the most vigorous of other pup activities. In the second part of this study BP responses of pups were measured as milk ejections were elicited from anesthetized dams by means of intravenous infusions of oxytocin. Both before and after separation, the BP increases under these conditions were indistinguishable from those observed during normal nursing. Thus, active behavioral interaction between mother and pups is not necessary for eliciting BP increases during feeding. An important note about these responses is that they appear to be specific to oral stimulation. This conclusion is drawn from unpublished studies in which we have found that gastric infusion of nutrient does not elicit these acute increases in BP.

These immediate changes in BP are apparently a component of what has been called the 'pre-adaptive' responses to nutrient intake[32]. These early responses to food, which include rapid increases in insulin, glucose, plasma norepinephrine, and heat production, are dependent on oral stimulation and occur before nutrients reach the digestive tract[25].

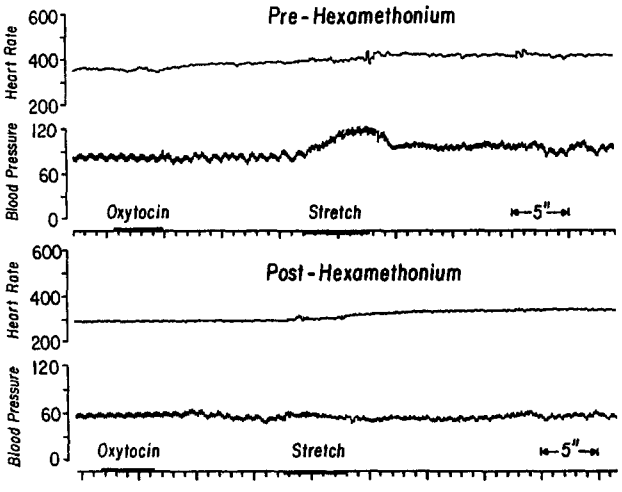

Figure 2. The top two tracings show heart rate and arterial (carotid) BP of a 15-day-old SHR pup while attached to its anesthetized mother. The time tracing indicates when oxytocin was infused into the tail vein of the mother and 'stretch' indicates the occurrence and duration of the pup's behavioral response to milk ejection. The bottom tracings show data from this same animal a few minutes later after injection with hexamethonium. Note that the increase in BP which normally accompanies ingestion of milk from the oxytocin-induced milk let-down is completely abolished by this autonomic ganglionic blocker. (Data are an example taken from Myers and Scalzo[31]).

BP responses of SHR and WKY pups to feeding

Following our report of BP increases to feeding in outbred Wistars, a study was conducted to determine if there were strain differences in these responses. In this study we examined the relationships between nutrient delivery and BP responses of 2-week-old SHR and WKY pups[31]. First, BP responses of SHR and WKY pups were measured while they were attached to their own anesthetized mothers and milk delivery was induced by oxytocin infusions into the dams. The responses of pups of both strains were abrupt, reaching a maximum increase in about 10 s, but the increases in SHR pups were nearly 50% larger than those in WKY pups. In the second part of this study we sought to determine if strain differences in BP responses were attributable to differences in constituents of the dams' milk. For this part of the study animals were implanted with posterior tongue cannulas and were given small quantities (50 µl) of cow's milk (Carnation evaporated). These pups were not attached to their mother's nipples but were isolated in a test cage. Under these conditions, BP responses were slower to reach maximum, but were nearly as large as when the pups were attached to their mothers. Moreover, the differences between strains remained highly significant, with SHR pups having larger increases in BP than WKYs. Thus, differences in BP responses between SHRs and WKYs could not be explained by strain differences in milk composition on the behavior of mothers during milk ejection. The larger BP response of SHR pups appears to be a function of amplified physiological response mechanisms and is another of the many traits that distinguish these two strains.

In a recent follow-up study, we investigated the mechanisms involved in the BP responses of SHR and WKY pups[33]. As indicated by the example of responses shown in figure 2, sympathetic ganglionic blockade with hexamethonium completely inhibited the BP responses of both SHR and WKY pups. This finding was independent of the method of milk delivery, i.e. tongue cannula or oxytocin-induced milk ejections from anesthetized dams. These results support the hypothesis that BP responses to oral delivery of milk are mediated by sympathetic activation and that strain differences in these responses are another indication of greater reactivity in SHRs. Furthermore, the results showed that the enhanced sympathetic responses of SHR can be demonstrated very early in life and are elicited by naturally occurring stimuli.

There is one final point to be made about BP responses to feeding in infancy. These responses are not only seen in rat pups but have been observed in the young of many species including lambs[14], calves and kids[5], piglets (F. M. Scalzo, personal communication), and in a case report, human infants[13]. In recent work, we too have shown that BP responses to feeding occur in human infants[9]. In this study infants between 24 and 96 h of age had BPs measured once a minute throughout normal bottle or breast feedings. The results showed that while heart rate appears to respond to sucking, BP increases are more specifically linked to delivery of nutrient. In addition, breast-fed babies were found to have larger

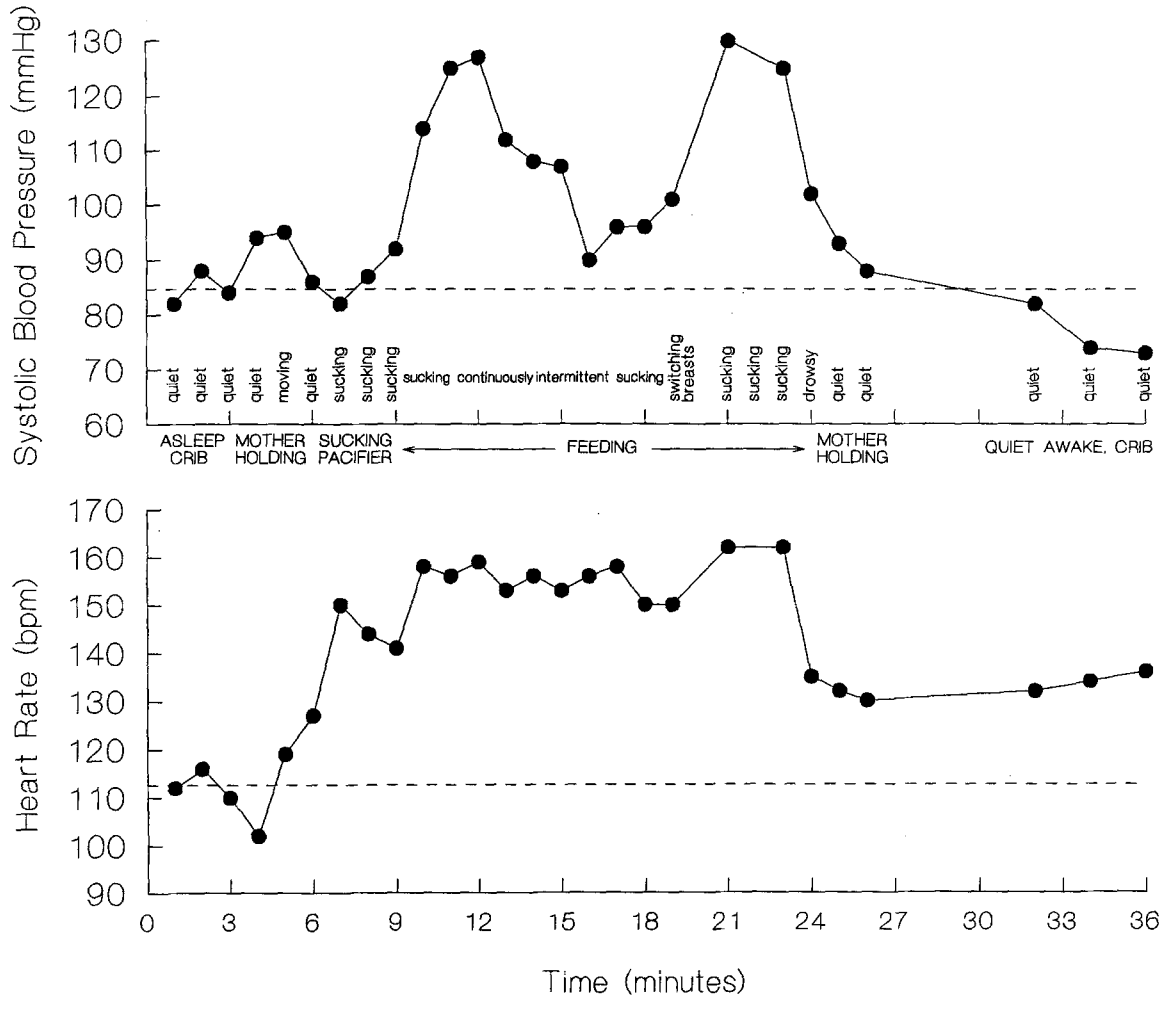

Figure 3. Systolic BP (top) and heart rate (bottom) responses of a 54-h-old baby before, during, and after a normal feed. Measurements were made once each minute along with notes concerning the condition of the experiment and the infant's behavior (see notations on BP graph). Horizontal dashed lines indicate the mean of the first three values taken when the infant was asleep in its crib. Note that heart rate appears to increase when the infant begins to suck on the pacifier but that BP does not increase until the infant starts feeding. Note also the decline in BP (12–18 min) and the second increase (~ 20 min) when the mother spontaneously moves the infant to her other breast. (Data are from one of the infants in the study by Cohen, Myers and Brown [9]).

responses than bottle-fed infants, though the number of subjects in each group was small and this difference needs further study. Figure 3 shows the entire time course of changes in BP and heart rate for one breast-fed baby who had marked responses to feeding. These results are exciting because we now know that repetitive activation of BP responses, which may be involved in shaping cardiovascular system development, occur not only in research animals, but also in human infants.

Taken together, the studies presented thus far offer a fascinating sequence of findings. We have learned that offspring of dams that were more often observed to be in a nursing posture closely associated with milk delivery had increased BPs as adults. This was true regardless of whether the offspring were SHR, WKY or F_1 pups. We now also know that each time mothers assume the arched-nursing posture and deliver milk, BPs of the nursing pups rise dramatically and these increases in BP are much larger in SHR pups. Again, these strain differences are not dependent upon unique qualities of SHR mothers' milk or behavior. From these results we suggest there are fundamental linkages between feeding in infancy and BP development, and that these relationships are a clear example of an important principle; adult traits are shaped by the joint actions of environmental events and genetic predisposition. The following sequence of new results provides further evidence that levels of adult BP are linked to feeding in infancy.

Correlations between weight gain in infancy and adult BP of F_2 rats

These next experiments were originally designed as a program of investigations to find physiologic or behavioral traits, measured in infancy, that co-segregate with hypertension in SHR. The major goal was to discover markers that could be used to predict which individuals would develop adult hypertension. The initial study [28]

defined the characteristics of BP development in a segregating population of rats derived from SHR and WKYs. Hybrid offspring (F_1s) were derived from SHR♂ WKY♀ matings and then random matings within this group were used to produce a group of 28 male F_2s who had their BPs measured repeatedly from 2 to 14 weeks of age. The measurements at 14 weeks confirmed the fundamental premise of our strategy. Some F_2s have adult BPs that are similar to WKYs, (i.e. < 135 mm Hg), most have borderline pressures that are characteristic of their F_1 parents (about 150 mm Hg), and about 25% of the animals express hypertensive levels of BPs similar to SHRs (>160 mm Hg). However, as has been noted by Harrap[15], divergence of high versus low BP in F_2s does not occur until after 8 weeks. Also of importance was the finding that while some animals exhibited stability of their rank through development, maintaining either high or low BPs from 4 weeks on, most animals were erratic. Some individuals expressed hypertensive BPs at 8 weeks, but low BPs at 10 and 14 weeks, while others had low BPs at 8 weeks only to become hypertensive later in life. Because clear stratification within the population does not emerge until after 8 weeks, it seems likely that the dynamic hormonal and growth surges associated with puberty contribute to the lack of BP stability in early life. The diversity of developmental trends in F_2 BPs is similar to what has been described in human children[24]. Yet, significant age-to-age correlations in blood pressure during childhood development have been demonstrated by several investigators[2, 3, 24, 44] and this has been taken as evidence that adult hypertension has its origins in early development[3]. We believe this to be a valid conclusion. But, we also believe that the multiplicity of profiles of BP development makes BP measurements through early development a less valuable means of demonstrating the ontogenetic predilection for adult hypertension than might be expected.

Given the marked diversity of patterns in BP development, it is not surprising that tail-cuff BP measurements made in infancy were not predictive of those made later in life. Similarly, heart rates and rectal temperatures taken at any of the ages studied were not related to adult BP. However, one finding that was of potential interest was that F_2s with the highest BPs at 14 weeks of age tended to have greater body weights between 2 and 6 weeks of age. After this time they tended to remain heavier than F_2s with low pressures but differences in adult weights between the high and low BP F_2s were not significant. This unexpected finding had at least two implications. First, low adult body weight, which is characteristic of SHRs from the commercial supplier we use in our research (Taconic Farms) does not appear to be linked genetically to hypertension since the traits of light body weight and high BP showed no evidence of co-segregation. Second, the data suggested there might be some relationship between weight or weight gain early in life and adult BP. Testing this possibility has been pursued in three studies that are summarized in subsequent sections.

The first study involved 50 male F_2 rats from 10 litters. All litters were culled to 5 males and 3 females on day 2 of life. At days 6, 12, 16, and 21 body weights of each animal were taken. At day 21 the males were weaned, 3 per cage, and were left undisturbed except for routine animal care until 20 weeks of age. At this time tail-cuff BPs were measured as reported previously[30] and the median of 5 artifact free readings was taken as the animal's systolic BP. Rectal temperatures and heart rates measured during the tail-cuff procedure, as well as body weights, were also recorded at this age. We have analyzed these data in many ways, but all point to the same conclusion. The most straightforward approach was to divide the population into sub-groups. Specifically, we found that at 20 weeks there were 15 animals with systolic BPs 160 mm Hg or above and 15 animals with pressures less than 135 mm Hg. These groups were designated HIGH and LOW, respectively. With regard to adult measures, there were no significant differences in body weight, temperature, or heart rate between these two groups of animals. However, weight gain in infancy was different. Animals in the HIGH BP group had gained significantly more weight than those in the LOW group, but this difference was restricted to weight gain from days 12–16 of life. These results are shown in figure 4. Although we had not entirely anticipated this result, our previous studies had suggested the outcome of this experiment. High levels of nursing behavior in SHR and WKY dams were associated with higher adult BPs of the offspring. Results from our weight-gain experiment appeared to be consistent with this observation. F_2 pups

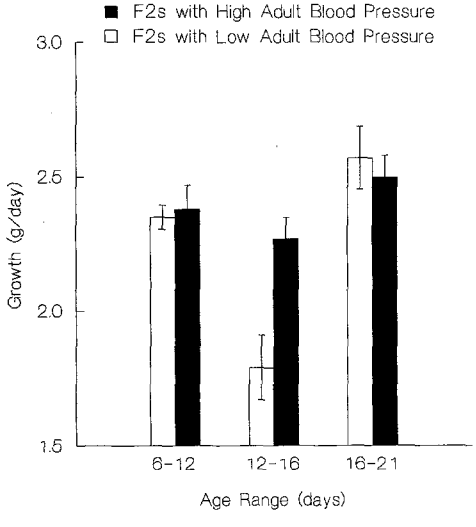

Figure 4. Growth (mean weight gained/day ± SEM) during three preweaning periods for two groups of male F_2 rats. The two groups (N = 15 each group) were formed based on their systolic BPs taken at 20 weeks of age. Animals in the HIGH group all had pressures > 165 mm Hg and the LOW group were all < 135 mm Hg. Note the greater rate of body weight increase in the 12–16-day period in the HIGH BP group. (Data not previously published).

that gained weight rapidly were more likely to have high BPs as adults. Since we had not predicted a specific age range for this effect, a replication of this experiment was conducted.

The second F_2 study was similar to the first with two minor exceptions: adult BPs were determined at 12 weeks of age and infant body weights were taken at 5, 10, 16, and 21 days. From a population of 55 male F_2s from 9 litters, 10 were found to have BPs above 170 mm Hg and were designated as the HIGH group, 10 animals with pressures < 130 mm Hg formed the LOW group, and 10 with pressures ranging from 148 to 155 were denoted as MID. The gains in body weight of these groups during three periods prior to weaning are shown in figure 5. Similar to the previous study, there were no group differences in weight gained between 5 and 10 days of age. However, from 10 to 16 days weight gain of the group of F_2 rats that developed hypertension as adults was significantly greater than that of the LOW BP F_2s. Further, weight gain of the MID group fell virtually midway between. One difference between this study and the last was that the HIGH F_2s gained less weight than the LOW group from 16 to 21 days, but this was not a strong effect and remains to be confirmed in future studies.

The results from these two studies are clear: animals that gain weight rapidly from 10 to 16 days are likely to have higher adult BPs than those gaining less weight. This conclusion raises immediately an important question. Is the relationship between early weight gain and adult BP attributable to the co-segregation of genetically determined traits or, is this an environmental effect? That is, are there genes that influence rates of growth early in life and do these same genes, or ones closely linked, also determine levels of adult BP? Or, do behavioral interactions between mothers and their young lead to different feeding patterns and rates of growth in infancy which in turn modify development of the cardiovascular system? The data collected thus far do not allow an unequivocal dissociation of these two possibilities but, as discussed below, further analysis of these two experiments, in which the data were partitioned into within and between litter effects, does seem to point to the second, environmental, alternative.

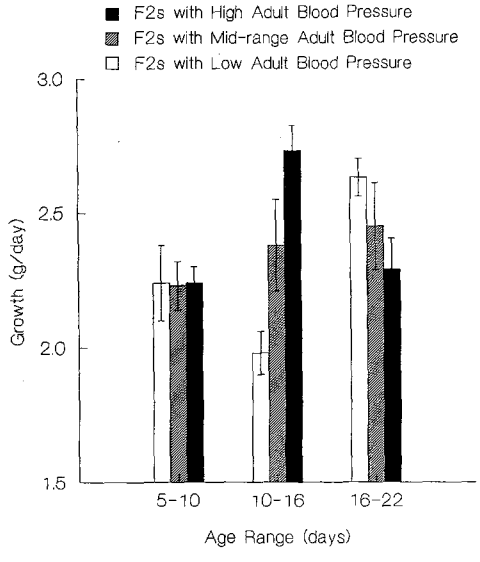

Figure 5. Growth (mean weight gained/day ± SEM) during three preweaning periods for three groups of male F_2 rats. The three groups (N = 10 each group) were formed based on their systolic BPs taken at 12 weeks of age. Animals in HIGH group all had pressures > 170 mm Hg, the MID group all had pressures between 148 and 155 mm Hg, and the LOW group were all < 130 mm Hg. Note the greater rate of body weight increase in the 10–16-day period in the HIGH BP group and that animals with intermediate levels of adult pressure exhibited intermediate rates of growth. (Data not previously published).

Before combining these data sets, which had some differences in ages at which measurements were made, all relevant variables within each study were transformed into Z-scores. The transformed data, which express variability in each measure as standard deviation units from the mean of the study, were then combined into a single data set of 105 animals from 19 litters. The 6–12- and 5–10-day weight gains (studies 1 and 2 respectively) were collapsed into a single period of weight gain noted as 5–12 days. Similarly, the 12–16- and 10–16-day weight gains were combined into a period simply denoted as 10–16 days. Prior to determining the within and between litter correlations between weight gain and adult BP, preliminary analyses were performed to quantify the effect of litters for each of the relevant variables. We found that in these F_2s there were indeed highly significant effects of litter for adult BP and body weight gain over all three of the preweaning intervals. The table summarizes these results.

Summary of litter effects for adult BP and weight gain during three periods of time prior to weaning

Variable	% variance accounted for by litter	Significance
Adult BP	33.7	$p < 0.01$
Body weight gain 5–12 days	37.9	$p < 0.001$
Body weight gain 10–16 days	83.3	$p < 0.001$
Body weight gain 16–21 days	61.9	$p < 0.001$

The interpretation of a significant litter effect is that members of litters are more similar to each other than they are to animals from other litters. In homozygous strains such as SHR and WKY litter effects are clear evidence of environmental effects on the measure of interest. In segregating populations such as F_2s, the interpretation is less clear because it is possible that the distribution of possible genotypes is not random and some clustering of genotypes within certain litters has occurred. Nonetheless, in previous studies using SHR and WKY we found that about 16% of the variance in adult BP is attributable to litters and thus, would expect that a significant part of the variance accounted for by litters in these F_2 populations is a reflection of similar effects of

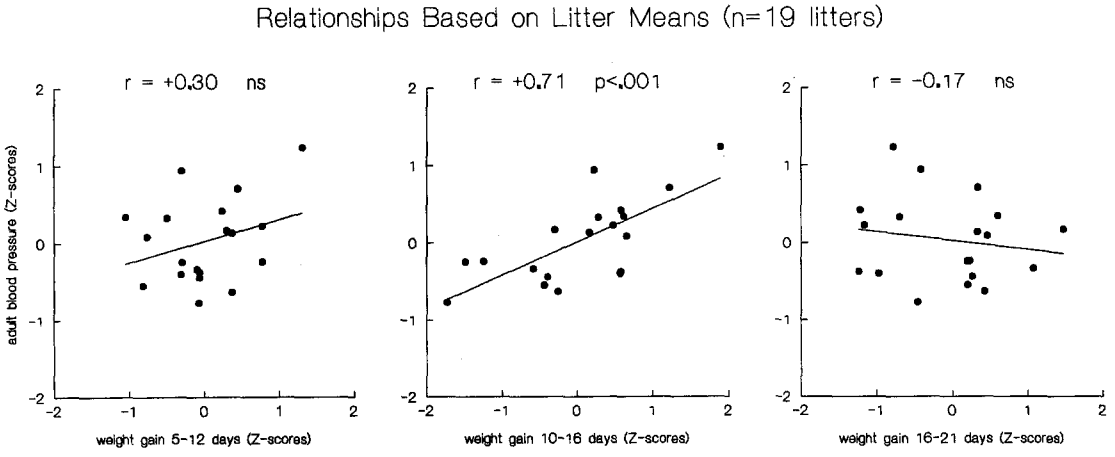

Figure 6. These three scatter plots show the relationships between adult BP and weight over three age ranges during the preweaning period. The points on each plot are based on the mean values of males from 19 F_2 litters. The data were standardized using Z-score transformations. Note that the correlation between infant weight gain and adult BP is significant only during the 10–16-day period of development. (Data not previously published).

the early environment. It is also interesting to note that litters account for more of the variance in weight gain during infancy than for BP, with this difference being particularly marked for the 10–16-day growth period.

Having shown these significant litter effects, we sought evidence to support the hypothesis that the correlation between infant weight gain and adult BP was the result of an environmental effect, not genetic co-segregation. There were two analyses conducted. In the first, we asked if the variance in adult BP that was due to litters was accounted for by the variance due to litters in infant weight gain. Figure 6 reveals the answer to this question. We found that for weight gain from 10 to 16 days, but not for the other two periods, there was a strong correlation between litter-mean weight gain and litter-mean adult BP ($r = +0.71$, $p < 0.001$).

A second analysis of these data involved computing correlations between infant weight gain and adult BP based not on litter means, but on individual differences from litter means. The reasoning behind this analysis is a continuation of the logic for the litter-mean analysis. If significant litter effects are attributable in large part to differences in mother/litter environment, the degree to which individuals differ from the mean of their litter is largely a measure of genetic differences. Thus, significant correlations between individual differences in infant weight gain and individual differences in adult BP would be very strong evidence of some type of genetic coupling. The results from these analyses were clear. Whereas there was a highly significant correlation between weight gain from 10 days to 16 days and adult BP when litter means were used, no such correlation could be demonstrated using residuals from litter means. This lack of correlation with adult BP was found for each of the three weight gain periods (days 5–12, $r = +0.05$; days 10–16, $r = +0.08$; days 16–21, $r = +0.04$).

Although these analyses suggest that the effect of weight gain in infancy is unlikely to be attributable to genetic co-segregation of traits, they are not conclusive proof. Additional studies using data from homozygous strains would be required to converge on this conclusion. Nonetheless, we felt these results were sufficiently indicative of an environmental effect to warrant another type of experiment designed to test further this hypothesis.

Effects of litter size on adult BP

The previous two studies demonstrate that naturally occurring differences in body weight gain during a specific period of early development are linked to individual differences in adult BP. The strong dependence of this relationship on differences between litters, and not within litter differences, suggested that the effect was due to environmental factors influencing infant weight gain which, in turn, were linked to alterations in cardiovascular system development. If this tentative conclusion was correct, we reasoned that manipulations of the early environment which modify weight gain should also alter adult BP. To test this hypothesis we performed an half of the litters were fostered to dams of the other half, thus forming experiment in which weight gain from 10 to 16 days of age was manipulated by altering litter size. In this experiment, we studied females as well as males. F_2 litters were culled to 4 males, 4 females on day 2 and left undisturbed until day 10. At that time, 2 males and 2 females from half of the litters were fostered to dam of the other half, thus forming litters of either 4 or 12 pups. At day 16 the fostered pups were returned to their natural mother thereby reconstituting litters of 8. Weight gain of these pups from 10 to 16 days was exactly what we had hoped, pups in the small litters gained nearly twice the weight of the 12/litter F_2s. After being returned to their natural mothers, the F_2s that had been in litters of 12 exhibited considerable 'catch-up growth' from 16–21 days but were still lighter than their 4/litter counterparts at 21 days. As young adults (12 weeks of age), F_2s reared for

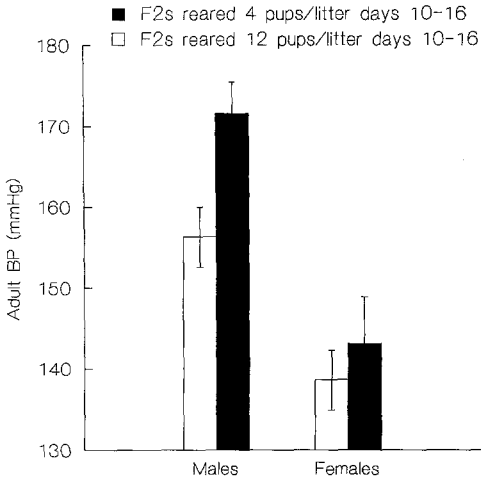

Figure 7. Adult (12 weeks of age) systolic BP of male and female F_2 rats which were reared in litters of either 4 animals or 12 animals from 10 to 16 days of age. Prior to 10 days and after 16 days litter size was maintained at 8/litter. The males in the 4/litter group, which gained weight more rapidly from 10 to 16 days, had higher adult BPs than the animals in the 12/litter condition. There was no effect of litter size on BP in the females. (Data not previously published).

6 days in litters of 4 were heavier than those reared at the same time in large litters, and this difference was more pronounced in males than in females. The main purpose of this experiment was to determine if the litter-size manipulation would alter adult BP. Results of these analyses are depicted in figure 7. Male F_2s that had gained weight rapidly, due to being in small litters from 10 to 16 days, had significantly higher adult BPs than males in the slower growth 12/litter group. However, females did not express this effect.

The results from the males of this study are consistent with our prior studies. Nursing frequency was shown to be correlated with adult BP of SHR and WKY offspring, male F_2 pups that gained weight more rapidly from 10 to 16 days of age had higher adult BPs, and now, male F_2s that were made to gain weight rapidly during this period by means of a litter size manipulation had higher adult BPs. However, the results also added a new dimension not explored in our prior studies; females appear to be resistant to the effects of early weight gain on adult BP.

Is the relationship between infant weight gain and adult BP dependent on changes in adult body weight?

Thus far, we have concentrated on relationships between neonatal weight gain and adult BP. A necessary question to ask is whether these effects might be explained by early life determination of adult body weight and if it is really the relationship between adult body weight and BP which is at the heart of our observations. To test this hypothesis, we have examined relationships between adult body weight and adult BP, and relationships between adult body weight and weight gain in infancy. Using the data from our first two F_2 studies ($n = 105$), the correlation between adult body weight and adult BP was positive but not very robust ($r = +0.19$, $p = 0.06$). Body weights of animals at 10, 16, and 21 days were all significantly correlated with adult body weight ($r = +0.38$, $r = +0.53$, $r = +0.48$; all $p < 0.001$). Weight gain from 10 to 16 days was also positively correlated with adult body weight ($r = +0.30$, $p < 0.01$), but this relationship was not as strong as those obtained using any of the three preweaning weights. Thus, weight gain during a sensitive period is positively correlated with adult BP and adult body weight, but adult body weight and adult BP are only weakly correlated. From these correlations it appeared that the relationships between infant weight gain and adult weight and BP were likely independent effects. This conclusion is supported by results of analyses of covariance in the first two F_2 studies. These analyses showed that the relationship between early weight gain and adult BP is highly significantly even when adult body weight is used as a covariate.

In the case of the litter-size study, we also have good reason to believe that changes in adult body weight do not account for the effects of this manipulation. When animals were divided, based on their adult weights, into heaviest and lightest within each litter size group (4/litter and 12/litter), we found that there was considerable overlap in adult body weights between the 5 heaviest from the 12/litter group and the 5 lightest from the 4/litter group. When we reanalyzed the data from these subsets of the two-litter size groups, which had virtually identical mean adult body weights, we found that adult BPs were still significantly higher in the 4/litter group ($p < 0.01$). These analyses should not be taken as evidence that adult weight is unimportant with regard to cardiovascular function. But, they are strong support for the conclusion that the relationship between rapid weight gain in infancy, either naturally occurring or experimentally induced via litter size manipulation, and adult BP is not purely a function of these animals having increased adult weight.

Conclusion

Taken together, we believe that the studies summarized in this review offer strong support for the contention that feeding patterns during critical periods of early life play an important role in shaping cardiovascular system development and act, along with genetic predisposition, as a co-determinant of levels of adult BP. In male F_2s, the effect appears to be a major contributing factor to high BP. This conclusion is perhaps best demonstrated when the impact of weight gain in infancy is expressed in terms of risk. In the two F_2 studies, in which naturally occurring differences in weight gain were recorded, the incidence of adult BPs greater than 160 mm Hg was increased four-fold in animals in the top quintile of early life weight gain versus those in the lowest quintile (65% vs 15%).

It is interesting to note that our effects of litter size manipulation are consistent with observations made over 25 years ago. Widdowson and colleagues reported that rats reared in small litters (rapidly grown) had larger hearts and double the incidence of kidney lesions at the time of death when compared with animals from large litters[42,43]. However, this effect was specific to males. In light of our data, it is interesting to speculate that their rapidly grown males may have had more kidney disease and larger hearts due to a greater incidence of hypertension. The potential impact of variations in early growth were also apparent in a study by Blizard and Adams[4] in which it was found that rats with low body weights at 35 days of age were more susceptable to the adverse effects of high salt diet and had increased mortality. This suggests there may be an inverted U-shaped function whereby either rapid or slow growth early in life renders animals at risk for adult pathologies.

Our results indicate there is a very interesting relationship between early weight gain and adult BP and they form the basis for future studies which will be concerned with elucidating the mechanisms involved in this effect. For example, we need to know whether the mechanisms are embedded in some aspect of increased frequency of feeding. Accompanying increased feeding in infancy there is increased close physical contact with the mother, greater volumes of nutrient intake and growth acceleration, and repetitive sympathetic discharges. Each might play a role in the effect. Weight gain itself might only be a co-variate of the actual mechanisms responsible for the effect. Moreover, although we have presented results that support an environmental hypothesis for this relationship, genetic co-segregation of the two traits can not yet be ruled out. Several experiments will be required to address this issue. Many good examples of these types of experiments, which would involve further use of homozygous strains, cross-fostering strategies, and manipulations of diets, are summarized by the other investigators contributing to this series of articles.

Another issue we must examine is why these effects of weight gain are isolated to a narrow period of development. Slotkin and colleagues find an increased rate of sympathetic nervous system activity during this period and have suggested that these surges are instrumental for shaping development of target organs[36,37]. Furthermore, litter size and growth have been shown to affect growth and differentiation of the heart during this period of development[42,43]. The results of McCarty and colleagues[26], in which the effects of cross-fostering on SHR adult BP were confined to the first two weeks of life clearly support the notion that it is during this period when environmental events can have a great impact on BP development. Studies such as those reported by Kirby and Johnson[22] in which selective pharmacologic blockers were administered during specific periods of development affords a powerful approach to the identification of which regulatory systems are key mediators of the observed effects.

Finally, it is not clear why the weight gain effects we have observed should be selective to males. Because male and female gonadal hormones are known to play important roles in BP development[10,12], it seems possible that these hormones may modulate the effects of early weight gain. Here the experimental approaches would be straight forward and would make use of lesion/hormone replacement strategies common to the field of hormones and behavior.

There is much work to be done in the area of how genetic and environmental factors act in concert to determine adult traits. This is not an easy task. Indeed, the goal of simply defining more specifically what is meant by gene/environment interaction often seems unattainable. However, we believe that the studies presented in this review show that such questions can be pursued.

Answering the challenge of providing increased understanding of how genes and the environment interact will necessarily involve providing detailed, well worked out examples of how such interactions mold specific physiologic and behavioral processes. We are certain that the relationship between the mother/infant environment and adult cardiovascular function is one such area in which this challenge can be met.

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