PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 175, 147–157 (1984)

Early Stages in the Organization of Cardiovascular Control[1](41780)

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Abstract. Our studies have revealed a number of unexpected characteristics of the immature cardiovascular system of the infant rat. Sympathetic and parasympathetic divisions of the autonomic system appear to have different timetables for the development of tonic and phasic activities. These different timetables of development result in unusual physiological organizations at particular stages in postnatal life. We have described some of the features of one of these: the infant rat's cardiac rate responses in the second week after birth include a high resting rate, decreased rates in response to several (but not all) forms of activation, and two forms of phasic activity, a bradycardia and a tachycardia, that are related to naturally occurring behavioral states and have not been described in adults. The nature of this age-specific autonomic organization was explored further and found to be embedded in the infant's relationship with its mother and in her role as a supplier of nutrient in particular. The mechanisms by which nutrient intake regulates autonomic cardiovascular control during this stage of life have been partially explored by analytic experiments and the results are described along with the possible adaptive value of this regulatory system.

There is now evidence available that characteristics of adult physiological systems may be shaped by experiences that occur during infancy. In animal experiments where life events can be arranged and precisely controlled, cardiovascular responses of adults can be altered in direction as well as in magnitude by certain interventions occurring during the early postnatal period. For example, by varying the degree of stimulation provided in the neonatal period (1), by early social isolation (1, 2), or by altering early socialization experience (3), cardiac reactivity of rats and dogs in adulthood was consistently altered. More recently, normotensive strains of mice have been made susceptible to hypertension by early maternal separation and social isolation when these were followed by habitat-induced social disorganization (4). Ordinary Sprague–Dawley rat pups consistently developed 20% higher blood pressures when cross-fostered at birth to mothers of the spontaneously hypertensive (SHR) strain (5). And SHR rats, if handled repeatedly by experimenters during infancy (a procedure known to alter mother–pup interactions as well as stimulating pups) showed marked reductions in blood pressure as young adults, even when under anesthesia (6).

These results, impossible to explain or understand according to present knowledge, point out that genetic determinants of cardiovascular system organization depend on relatively subtle aspects of early experience for their final expression. Clearly we need to know more about early autonomic development and about the experiences that affect the infant's cardiovascular regulation, if we are to understand how genes and experience interact in the predisposition to health or disease in the cardiovascular system.

General Methodological Approach. We began our studies with a determination to study the developing cardiovascular system as it functioned in the normally behaving organism, to the extent that this was possible. And we wanted to work with a rapidly growing laboratory animal such as the rat in order to allow experimental interventions in their early life histories. This meant that we had to develop physiological recording techniques that could be applied to unanesthetized and unrestrained rat pups. Furthermore, we would have to find ways to make our observations of the infant in relation to its natural habitat, which includes its mother and its littermates. This seemed to be the best initial approach, since we needed to know how the system

[1] This research was supported by a Research Scientist Award and project grant support from the National Institutes of Mental Health.

0037-9727/84 $1.50

functioned in relation to its environment, before more analytic studies could be done in which attempts would be made to minimize or control environmental effects.

We began with cardiac rate as by far the easiest measure to obtain under these conditions and only recently have begun to work with measures of blood pressure, as our micromethods have improved. We found it was possible to implant five silver wire electrodes under the skin of infant rats at all ages under ether anesthesia, leaving only a tiny connector element protruding. The infants adapted to these so that after 1 or 2 days, lightweight leads could be attached without disturbing pups and an EKG and cardiotachometer tracing could be obtained on a nearby polygraph from undisturbed pups in their home cages (7). Before 3–4 weeks of age, pups appear not to notice lightweight leads attached to them in this way, interact with littermates freely, and nurse from their mother in an entirely normal fashion. A typical tracing taken during nursing is shown in Fig. 1. After a time, mothers and littermates also ignore these leads, at least for 1 to 2-hr recording periods. From the same electrodes, an impedance pneumograph preamplifier permits the recording of respiration. Using the electromyogram from the EKG leads, movement artifacts, and the respiratory training, periods of resting and of activity can be defined in the polygraph recordings and heart rates classified accordingly (see Fig. 1). For pups younger than 16–20 days, a thermostatically controlled heating pad under the home cage floor maintained nest temperature when the mother was removed for recordings.

The Developmental Plan of Heart Rate Regulation. At the outset of our studies, all that we knew about the early development of cardiac regulation came from the work of E. F. Adolph and his colleagues (8, 9). Their work had shown that, with pharmacologic blockade of both sympathetic and parasympathetic systems, the heart rates of infant rats remained essentially unchanged at 250 beats/min from 5 to 45 days to age. By electrical stimulation of sympathetic nerves in the thorax or by using a β-adrenergic agonist, isoproterenol, rates in excess of 600 could be demonstrated throughout the same development time span. Rates between these extremes can thus be interpreted as due to the effects of autonomic regulatory control over cardiac function.

These workers had studied rat pups shortly after insertion of wire electrodes while isolated from home cage and littermates, and immobilized by being taped onto a board in a temperature-controlled testing cubicle. "Basal" heart rate was determined after a 0.5-hr adaptation period. Under these conditions, heart rates of infant rats rose from 310 to 380

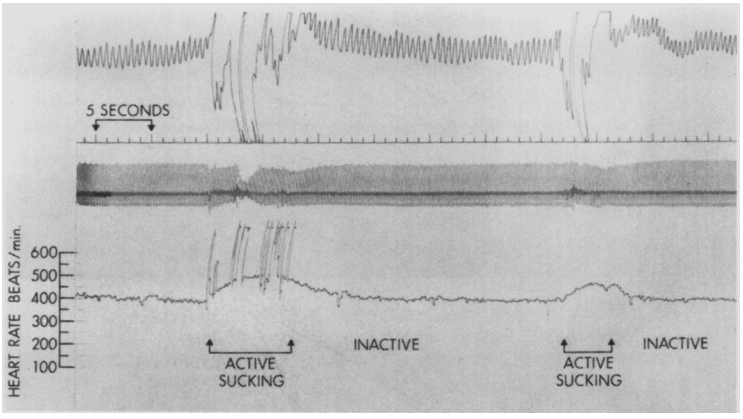

FIG. 1. Sample polygraph page showing, on the top channel, the impedance pneumograph tracing with both regular quiet respiration and activity artifact during sucking. The second is a time channel; the third channel is electrocardiogram and electromyogram, the latter showing characteristic electromyogram bursts during activity. The bottom channel is the cardiotachometer write-out, with its scale given at the left. Two characteristic rises of heart rate during suckling bursts are shown, the first containing a number of movement artifacts. Paper speed is 5 mm/sec. Reproduced, with permission, from Ref. (7).

beats/min over the first week of postnatal life, maintained a plateau of 400 during the second week, and rose again to 500 during the third week.

The data from our initial cross-sectional study (10) is presented in Fig. 2. Under the very different conditions of being asleep with their littermates in their home cages, the heart rates resembled those determined by Adolph over the first 2 weeks of life, but were very different throughout the third week. We found a rapid decline from 16–20 days to levels of 300–350 beats/min, a level comparable to those of resting adult rats. Interestingly, heart rates during spontaneous episodes of activity in the younger pups were no greater than during apparent sleep, until 12 days of age.

The contribution of adrenergic and cholinegic autonomic tone to this developmental pattern was assessed by pharmacologic blockade with propanolol and methylatropine. From 1 to 2 weeks of age, heart rates were not further increased after cholinergic blockade, indicating negligible vagal tone during this period. By 3 weeks of age, when inactive heart rates were much lower, cholinergic blockade reinstated the high levels of inactive heart rate found in 1- to 2-week olds, revealing the rapid development of tonic vagal restraint during this week period. The high rates of 10- to 12-day olds were reduced to 275 beats/min with propanolol, and the increases with activity no longer occurred, showing the primary role of high levels of β-adrenergic tone in the early phases of cardiac autonomic development.

During these recordings, two notable forms of phasic cardiac activity were observed: occasional brief (2- to 3-sec) episodes of precipitous bradycardia, sometimes with apnea, occurring about once every 2 min during periods of active (REM) sleep, and brisk accelerating episodes to the highest levels observed during bouts of the behavioral "face washing" sequence. The sleep bradycardias occurred throughout the first 2 weeks, rising to a peak incidence at 12 days, and were hardly ever observed in 3-week olds. The face washing tachycardias did not occur until 10 days of age and rose thereafter to a peak at 20 days. By the use of autonomic blocking agents, we determined that the sudden bradycardias of sleep were due to phasic bursts of vagal activity and the face washing tachycardias represented the most intense β-adrenergic activation observed.

It is worth emphasizing, that during the period of virtually absent tonic activity of the vagus, episodes of intense phasic vagal activation were nevertheless evident. These episodes became much reduced or masked by the development of tonic vagal restraint in the third postnatal week.

Next we tested the effects of some simple interventions such as picking the pups up and placing them in a novel environment, a plastic test box maintained at nest temperature. The results, shown in Fig. 3, were most unexpected.

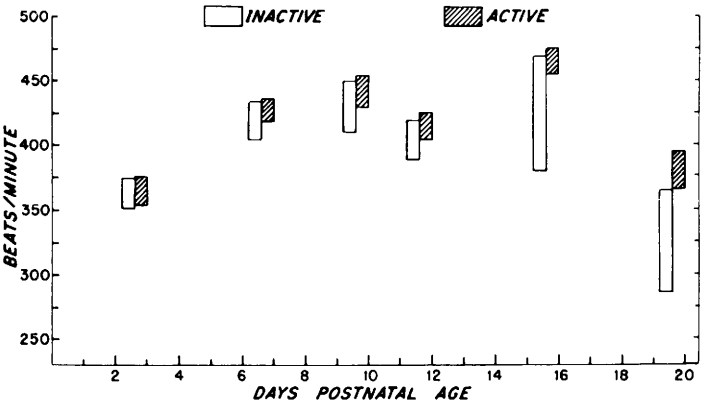

FIG. 2. Ranges of cardiac rates recorded from infant rats during rest and activity in the home cage throughout the preweaning period. Each bar represents the mean range during 10 min of recording for eight infants from four different litters studied only once at each age (cross-sectional design). Reproduced, with permission of the publisher, from Ref. (10). Copyright 1969 by the American Psychosomatic Society, Inc.

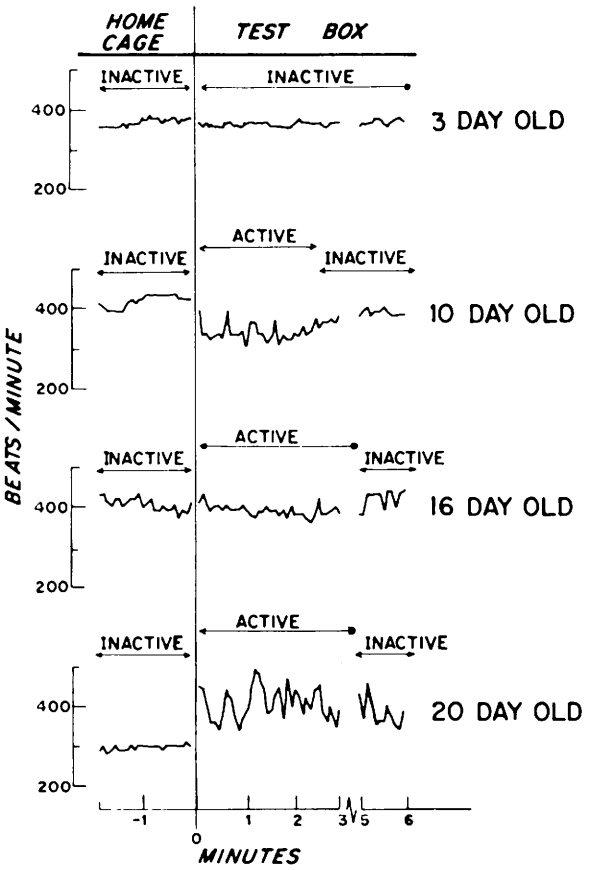

FIG. 3. Examples of typical heart rate recordings at different ages. Lines connect readings made every 5 sec on cardiotachometer tracings of single pups. Reproduced, with permission of the publisher, from Ref. (10). Copyright 1969 by the American Psychosomatic Society, Inc.

After the first week, during which pups showed no consistent cardiac response to this stimulation, 10- to 12-day-old infants began to show steep decelerative responses to being picked up in the experimenter's hand. This bradycardia persisted for 1–2 min as they actively explored the novel environment. These prolonged decelerative responses occurred when the infant was awakened and became increasingly active as a result of our intervention. By 3 weeks of age, the expected pattern was finally seen: pups with low rates while asleep in their home cage and brisk accelerative cardiac responses to the stimulation of being picked up and placed in the novel test box. The deceleratory responses of the 1- to 2-week olds were blocked by atropine and the acceleratory responses of 3-week olds by propranolol, revealing their different autonomic mediation.

At the end of the 6-min test box recordings, pups were given a startle stimulus combining auditory and vibrational components, the forcible sudden opening of their environmental chamber lock. This produced a sudden bradycardia only in 16- and 20-day olds, together with a behavioral freezing response. This was also a phasic parasympathetic event, but not developing during the second week, as had the bradycardias of sleep and of handling, but during the third postnatal week.

We had found a phase in the development of autonomic cardiac regulation, during the second week of postnatal life, when its organization was, so to speak, "upside down." A high level of β-adrenergic tone persisted during rest and the response to stimulation and novelty was primarily parasympathetic, despite behavioral activation. Unstimulated in the home cage, however, spontaneous activity had

begun to be associated with increased β-adrenergic activity and one form of activity, face washing, with very intense β-adrenergic tachycardia.

The discovery of this unexpected phase in the development of autonomic cardiac regulation had many possible implications. We needed to know more about how it fitted into the broader scheme of cardiovascular regulation, and into the infant's general physiological adaptation at that stage in its life.

Cardiac Rate Regulation and the Mother–Infant Relationship. *1. The normal nursing cycle.* We recorded from infants and their mothers from 10 to 19 days postnatal age throughout complete cycles consisting of the nursing bout and the maternal absence from the litter and the nest between bouts (7). Seventeen to 20 of these cycles occur in the course of a day, the mother spending a far greater proportion of each cycle with the pups when they are young, and increasing proportions away from the pups as they approach weaning age of 3–4 weeks, the number of cycles per day remaining nearly constant.

The general outline of our results is presented in Fig. 4. Although heart rates decreased with age and the duration of nursing periods decreased, the general pattern of responsiveness to the nursing experience did not change over that developmental period.

While pups were nursing, cardiac rates rose during the bursts of active treadling and sucking that occurred every few seconds (see Fig. 1) and these were higher than the active heart rates when the mothers were away (see Fig. 4). But the unexpected finding was that inactive heart rates between periods of activity, rose progressively throughout each nursing bout and the increase from the first to last thirds of each nursing episode was highly significant statistically. There were no significant differences between inactive heart rates while mother was away and during the first third of the next nursing bouts. There was a slight tendency for inactive heart rates to decline slowly during the period the mother was away but it was not significant statistically.

What could be increasing resting heart rates during the nursing bout? Our first though was that it might be simply a matter of increasing core temperature, since pups on the average gained 0.4°C during a nursing bout. But we found that artifically raising pup's body temperatures the same amount over the same time period by placing the home cage on a heating pad after a maternal absence generally led to decreases in heart rates instead of increases, so long as pup's temperatures were within normal resting range (34–36°C).

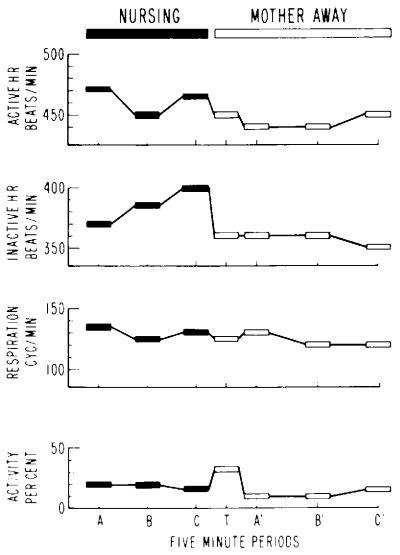

FIG. 4. Mean cardiac rates, respiratory rates, and activity levels of nine infants studied over 14 nursing cycles at 12 to 19 days postnatal age. Nursing phases averaged 26 min in duration and "mother away" phases, 54 min. A–C and A'–C' refer to initial–final thirds of nursing and mother away phases of the cycle. T refers to 5-min period immediately following mothers' departure. Reproduced, with permission, from Ref. (7).

2. Response to maternal separation. Maternal absences from the nest increase as the pups mature but are seldom more than 2 hr in duration. However, if the mother is removed from the home cage of infants in the second week of life, cardiac rates begin to decrease after 4 hr and thereafter fall precipitously to 60% of normal at 24 hr. This response is less pronounced in 1-week-old pups and no longer evident in 3-week olds (11). In 2-week olds, the decline is the same whether the pups' core temperatures are maintained by an external heat source or are allowed to fall 3–4°C as they do when left in the home cage nest without the mother (12).

This marked fall in resting heart rates was most unexpected and its origin and mechanisms have been the subject of considerable research in our laboratories. Pharmacologic

blocking agents demonstrated (11) that the low heart rates of separated pups were due primarily to a fall in β-adrenergic drive, with only a small component of vagal restraint added, since methylatropine raised the rates only slightly. Tail pinch, however, briskly raised rates to preseparation levels, as did the β-adrenergic agonist, isoproterenol, showing that cardiac rates were not fixed and reacted normally to autonomic agents. Apparently the pups responded to the prolonged absence of their mothers by a reduction of the normally high levels of β-adrenergic cardiac drive thereby reducing cardiac rates to levels observed only after β-adrenergic blockade.

What could account for this response? We reasoned that since the mechanism did not appear to be thermoregulatory it must be either sensorimotor or nutritional. Two-week-old rat pups eat small amounts of mash and milk from containers, but lose weight the first 1–2 days after maternal separation. Accordingly, we removed mothers from 2-week-old infants, ligated their mammary ducts under brief ether anesthesia, and replaced the mothers with their litters when fully recovered 2 hr later (13). Their responses were identical to separated infants, as shown in Fig. 5. Nonlactating mothers were observed to spend somewhat more time with their pups than normal mothers and to crouch over their infants in a normal nursing position. Thus, sensorimotor interactions were taking place between infant and nonlactating mother, albeit of an altered quality since nursing and possibly other interactions did not take place. With these negative results we turned our attention to milk.

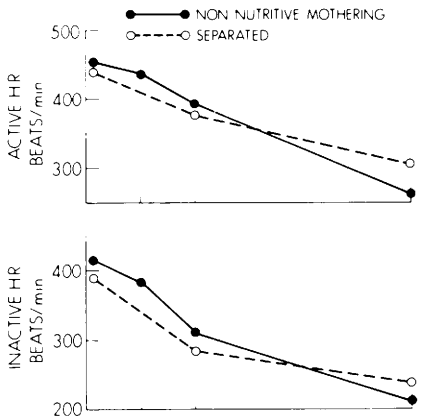

FIG. 5. Active and resting cardiac rates observed in 12 infants from three litters that were housed with their own mothers for 24 hr following mammary duct ligation (solid lines) compared with 6 infants from two litters that were separated from their mothers for 24 hr (dotted lines). Reproduced, with permission of the publisher, from Ref. (11). Copyright 1971 by the American Psychosomatic Society, Inc.

3. Milk as regulator of cardiac rate. Our first thoughts were that the cardiac response was due to some aspect of starvation and would be attenuated if we prevented weight loss by intermittent intubation feedings. This was not the case, however, since feedings of small amounts of condensed bovine milk formula every 4 hr (which produced small but consistent gains in weight) did not alter the fall in cardiac rate (14). Thus, it was not a response to starvation.

Two possibilities were then tested: that some substance was secreted in the rat mother's milk that acted on the infant's autonomic system and was not present in our milk formula, or that we were not giving milk frequently enough. After learning how to milk rat mothers "primed" by oxytocin injections, we found that rat milk had no different effects than our bovine formula, but that heart rates of separated infants were transiently raised by intragastric infusions of a sufficient volume of *either* form of milk.

A load–response study was done (see Fig. 6) and showed a sensitive dose-related cardiac response to intragastric milk formula in separated infants, that lasted only 2–3 hr (15). The bradycardia of separation could thus be transiently reversed by the intragastric infusion of milk formula. But could heart rate be maintained for prolonged periods by repeated milk infusions in the absence of the mother? Our next study (16) employed constant infusions of milk formula through chronically implanted gastric cannulas and demonstrated that cardiac rate could be maintained at any desired level over 24 hr, in the absence of the mother, by controlling the rate at which milk was infused.

What this means is that for the rat pup in its second week of life, the mother serves as an external physiological regulatory agent, controlling its cardiac rate by the frequency with which she supplies it with milk.

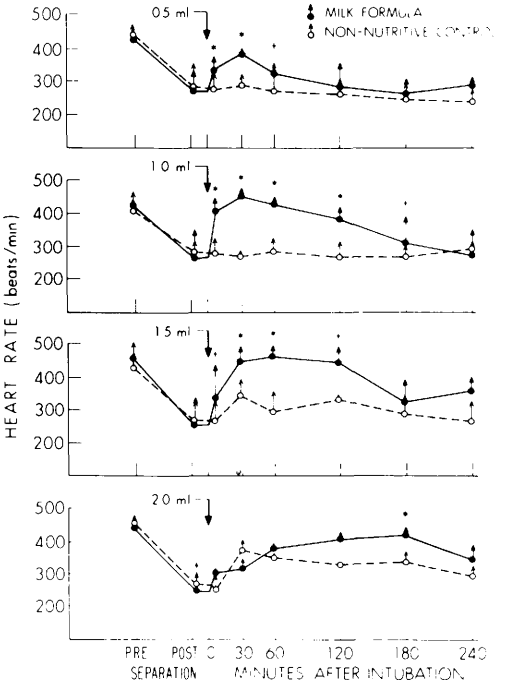

FIG. 6. Cardiac rates of 2-week-old rats separated from their mothers for 16 hr and given feedings of milk or control fluid in four different volumes. The first points after intubation values are at 5 min. Each point represents six pups. Circles indicate median inactive heart rates; arrow points are median active rates. Statistically significant differences between inactive heart rates of milk-fed and control pups are indicated by asterisks ($P < 0.01$) or cross ($P < 0.05$; Wilcoxon–White two-sample ranks test). Reproduced, with permission of the publisher, from Ref. (15). Copyright 1971 by the AAAS.

Nutrient Effects of Autonomic Regulation of the Infant. *1. Efferent limb of the cardiac response.* Since we had evidence that the fall in cardiac rate following nutrient deprivation was the result of the loss of β-adrenergic drive, it seemed reasonable that the milk-induced tachycardia in separated pups might be the result of β-adrenergic stimulation. And in fact we found that it was entirely blocked by doses of propranolol, that alone, had no effect on the heart rates of separated pups (15). The most likely efferent limb then would be the sympathetic cardioaccelerator fibers that leave the spinal cord at T_1–T_3. Spinal cord section at T_1, and not control sections at T_8, were found to reduce immediately the high heart rates of normally mothered pups to post-separation levels and to prevent the tachycardia of milk administration following 24 hr of maternal separation (13). We also found that anesthesia with ether, urethane, or barbiturates interfered with study of the cardiac rate effects of refeeding after deprivation by producing stable midrange heart rates.

These results implicated the central nervous system (CNS) in the mechanism for nutrient regulation of cardiac rate, provided evidence that the active constituents were not specific to rat milk, and suggested the spinal β-adrenergic cardioaccelerator fibers as the efferent limb of the neural control system. Further evidence in support of these conclusions were that adrenalectomized or thyroidectomized pups, maintained on exogenous hormones, showed virtually normal deprivation and milk effects on cardiac rate.

2. Afferent limb of the cardiac response. The initiating signal did not seem to be simple gastric distention, since in the milk load–response study (Fig. 6), equal amounts of dilute Maalox solution had no effects on cardiac rate. In other studies (13), we found that intragastric lactose, glucose, or amino acid hydrodysate solutions and even corn oil reproduced the cardiac response to milk in deprived pups, whereas equal volumes of distilled water or saline had no such effect.

The effect of sugars, amino acids, and milk on cardiac rate were very rapid, often within the first few minutes after intragastric administration (see Fig. 6). This suggested either very rapid absorption and transport of nutrient to a sensitive receptor site, possibly in the CNS, or a neural or hormonal response triggered by receptors in the gut wall.

Infants were provided with chronic indwelling jugular catheters and high-concentration lactose, glucose, and amino acid solutions were infused after nutrient deprivation with no effects on cardiac rate (13). Clearly there was something crucial about the intragastric route.

Our first thought was the afferent vagus, but subdiaphragmatic vagectomies had no effect either on the resting rates of well-fed pups or the milk response of deprived ones. Next we tried a series of GI hormones in deprived infants. Insulin, glucagon, and histamine were without effect, and gastrin, cholecystokinin, and secretin do not appear to fully reproduce

the milk effect, even when combined with gastric distention by non-nutritive solutions.

Since Sharma and Nasset had reported (17) that firing rates in mesenteric nerves could be altered selectively by sugar and amino acid perfusion of isolated gut loops, we turned our attention next to the splanchnic sympathetic system as a possible afferent pathway. Under an operating microscope I was able to identify and remove the celiac ganglia and both greater splanchnic nerves as well as to cut the paravertebral chain at the level of the diaphragm and to remove at least two paravertebral ganglia at the level of the celiac ganglia and below. Thirty-six hours postoperatively the pups were gaining weight and neither their cardiac response to deprivation or to refeeding was different from normals (13).

These studies ruled out a number of potential afferent pathways and left us with an unanswered question. How does the CNS receive the signal that nutrient is in the gut in order to turn on the spinal cardioaccelerator β-adrenergic efferents? One unexpected result, obtained during the previous studies (13), gave us a clue. When infant rats were adrenalectomized in order to rule out the adrenal medulla as the efferent pathway, we did not maintain all our animals on exogenous corticosteroids. Nursing pups survive and gain weight after total adrenalectomy without replacement corticoids. And we found that these pups failed to show a bradycardia in response to nutrient deprivation until they were given replacement corticosteroid.

This result was puzzling indeed, but finally suggested the following possibility. A permissive level of mineralocorticoid is known to be necessary for α-adrenergic vasoconstriction to take place. In fact, this interaction was originally demonstrated in the mesenteric arteries of the rat (18). It might be that the changes in the β-adrenergic cardiac system are part of a complex cardiovascular response with a major component being α-adrenergic vasoconstriction during nutrient deprivation. After all, it would make sense that the splanchnic circulation should be relatively vasoconstricted during periods when little nutrient was present in the gut and vasodilated when large amounts were to be absorbed. In the absence of corticosteroids, on the other hand, α-adrenergic vasoconstriction would be severely limited and cardiac rate changes would also be limited, if maintenance of blood pressure was a physiological control priority. So we turned our attention to the measurement of blood pressure during the large changes in cardiac rate we could produce experimentally.

3. Blood pressure regulation during nutrient deprivation and refeeding. Again we faced methodological problems, since no one had previously measured the blood pressure of unanesthetized infant rats younger than 4 weeks of age. We eventually developed (19) an indirect tail cuff method utilizing miniaturized inflatable cuffs and a photosensitive microcell detecting the systolic arterial pulse in the transilluminated tail, as well as an indwelling common carotid cannula with a Silastic tip which was capable of recording direct mean blood pressure from freely moving 2-week-old infants. The two measures showed a reasonably high degree of intercorrelation ($r = 0.76$) over six animals studied simultaneously with both methods while blood pressure was raised and lowered pharmacologically.

The results of our experiments were straightforward: blood pressure, measured by either method, did not change during the bradycardia of deprivation or the tachycardia of refeeding (see Fig. 7). An additional group was included, the littermates of the separated pups. Left with their mothers in much reduced numbers, they gained an abnormally large amount of weight during the 24 hr of their littermate's deprivation, had significantly increased heart rates the next day, and again showed no changes in blood pressure.

Thus, blood pressure remained constant during normal overfeeding provided by the mother, the deprivation of maternal separation and refeeding by the experimenters, while cardiac rate varied consistently in all three conditions. Since we are dealing with large (150 beats/min) changes in cardiac rate, it is most likely that cardiac output is changing in the direction of the rate changes in these experiments. And this in turn means that total peripheral resistance must be changing in an opposite direction to the changes in cardiac output, in order to maintain blood pressure so constant. This provided us with further evidence that changes in adrenergic vasoconstrictor tone might be an important part of

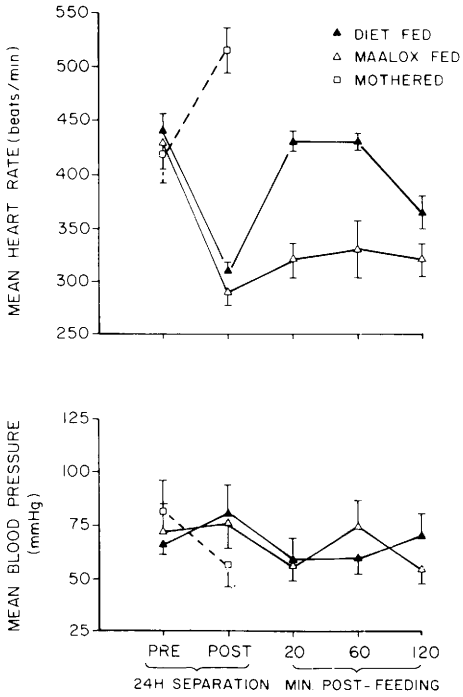

FIG. 7. Mean heart rates (top) and indirect blood pressure (bottom) in three groups of rat pups. Two groups were separated for 24 hr (solid lines) and compared with mothered controls (broken lines). The separated pups were then fed either an artifical rat milk formula (diet fed, 1.2 ml) by gastric intubation or an equal volume of dilute aluminum hydroxide gel (Maalox fed). Heart rate and blood pressure were recorded at intervals following this refeeding. Brackets indicate standard errors of the means. Diet fed, N = nine pups from four litters; Maalox fed, N = six pups from four litters; mothered, N = four pups from two litters. Reproduced, with permission of the publisher, from Ref. (19). Copyright 1983 by the American Psychosomatic Society, Inc.

the cardiovascular response to nutrient in these young animals.

4. Integration of α-adrenergic and β-adrenergic mechanisms. If blood pressure was being maintained constant by reciprocal and interrelated changes in arterial resistance and cardiac output during variations in nutrient intake in 2-week-old infants, and if the resistance changes were mediated by changes in α-adrenergic tone, then when the α-adrenergic system was blocked pharmacologically, β-adrenergic cardiac rate regulation should be altered in a predictable manner.

In recent unpublished experiments we explored this possibility by giving the α_1, and α_2 blocking agent, phenoxybenzamine, intraperitoneally to both deprived and normally fed infants. We hypothesized that the deprived infant had greatly increased α-adrenergic vasoconstrictor tone, necessitating the much lowered cardiac rate (output) in order to keep blood pressure normal in the face of the incresed peripheral resistance. Giving phenoxybenzamine should raise the heart rates of deprived pups and prevent the development of bradycardia if given prior to deprivation. Normally fed pups, in contrast, should have very low α-adrenergic vasoconstrictor tone and therefore little or no change in cardiac rate when given phenoxybenzamine.

The results supported this line of reasoning. Separated pups showed a brisk tachycardia in response to phenoxybenzamine that mimicked precisely the rapid rise following intragastric milk and was similarly blocked by the β-adrenergic blocker, propranolol, indicating its reflex nature. A clear dose–response relationship was found in deprived infants, whereas the same dose range of phenoxybenzamine given to normally mothered pups produced no significant tachycardia at any dosage. This was not a "ceiling" effect in the reflex effector system, since the β-agonist isoproterenol consistently increased the heart rates of similarly treated infants.

5. The role of carotid and aortic baroreceptors. The results of the previous experiments suggested that the β-adrenergic cardiac rate changes we had been so assiduously studying were actually secondary or compensatory adjustments to changes in α-adrenergic vasoconstriction induced by intragastric nutrient. The most likely mechanism for such compensatory adjustments is the baroreceptor system. And the most approachable part of this system, the carotid sinus and aortic nerves, are thought to carry a major portion of the afferent signal.

A way to test the concept that was beginning to form in our minds as a result of these experiments would be to interrupt the baroreceptor feedback. If the autonomic system of the infant rat really worked the way we thought it did, the cardiac rate response to nutrient deprivation should be blunted or diminished by sectioning both the carotid and aortic baroreceptor nerves (sinoaortic denervation).

In current unpublished studies, we have de-

veloped a microsurgical method for cutting these afferent nerves in pups as young as 4–5 days of age. And in 2-week-old infants we have been able to test for abolition of baroreceptor function. We used a chronically implanted fine plastic loop snare around the abdominal aorta, which produced a brisk and readily reversible 30% increase in common carotid blood pressure in the unanesthetized and unrestrained infant, and the expected precipitous drop in cardiac rate of 100 beats/min. This reflex was prevented by our surgical procedure, cardiac rates changing only 10–15 beats/min. Cutting just the aortic nerves accounted for the majority of this effect. These results showed that our microsurgical denervation produced the expected results on a standard test of baroreceptor function.

When sinoaortic denervated pups were nutrient-deprived, they showed a significantly attenuated cardiac rate response, about half of normal. And here again, aortic nerve-sectioned pups showed greater attentuation than carotid sinus nerve-sectioned ones. These recent findings have given us a further conceptual building block in our understanding of how gastrointestinal nutrient level regulates autonomic cardiovascular function in the infant rat.

6. Current model for nutrient cardiovascular regulation in infancy and its adaptive significance. Infant mammals must process large quantities of milk during early stages of rapid growth. The 2-week-old infant rat ingests about 20% of its weight in milk every day. Given these nutritional demands, a maximally vasodilated cardiovascular system with high cardiac output (rate) would be appropriate for the absorption, transport, and utilization of relatively large amounts of nutrient to a rapidly growing organ systems. A high resting cardiac output would maintain normal blood pressure and support the high levels of metabolic activity. When the nutrient supply decreased, however, such a wide-open system would only act as an energy drain when conservation was needed. The deprived pup apparently solves this problem by vasoconstricting peripherally and decreasing cardiac output while maintaining blood pressure within the narrow range necessary for vital organ function.

Our experiments thus far suggest that young rats' autonomic cardiovascular control systems are regulated through the physiological processes outlined in Fig. 8. Milk, acting at sites in the upper gastrointestinal tract that respond to chemical stimulation rather than distention, sets in motion a complex shift in autonomic neural integration over afferent pathways (dotted lines) probably involving the abdominal mesenteric sympathetic nerves and/or mesenteric blood vessel resistance. Arterial vasocontrictor tone is reduced over spinal (α-adrenergic) pathways, lowering peripheral resistance, while cardiac pumping rate is increased over β-adrenergic pathways, maintaining blood pressure (B.P.) constant in response to feedback from arterial baroreceptors. Adrenal cortical hormones play a permissive role in these shifts of adrenergic regulation, but thyroidectomy was found to have only minor effects. Although the abdominal vagus plays no afferent role in the milk effect, decreases in the heart rate with deprivation are supported to a minor extent by the appearance of a slight degree of tonic vagal cardiac activity.

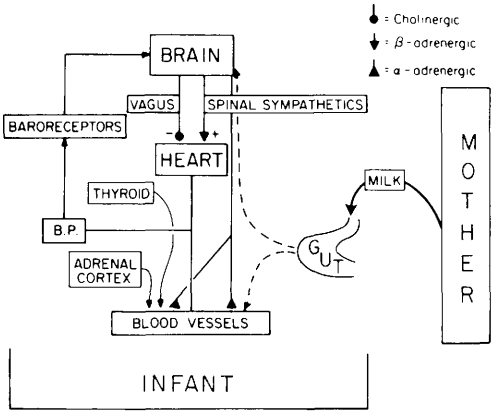

FIG. 8. Schematic representation of inferred mechanisms for cardiovascular regulation by nutrient intake in 1 to 2-week-old rats.

There is some evidence that the nutrient-controlled autonomic mechanisms described for 2-week-old rats do not entirely disappear with maturation. Landsberg and co-workers (20) have shown that in adult rat hearts, norepinephrine turnover was significantly reduced by 2 days of starvation and increased again within a few hours of refeeding. Results after ganglionic blockade suggested centrally mediated changes in sympathetic activity. Ap-

parently, circulatory changes have become limited to regional beds in the adult and large-scale changes in cardiac rate are no longer necessary.

Conclusion. In our first studies on cardiac control, we found that tonic vagal activity was delayed in its development, compared to tonic adrenergic cardiac drive. This divergence in developmental timetables would appear to form the basis for the occurrence of other age-specific phenomena: unusual types of phasic cardiac activity and nutrient regulation of cardiac rate.

In the 1 to 2-week-old infant, the presence of high levels of tonic adrenergic cardiac tone sets a baseline from which phasic vagal bradycardias and deceleratory responses to handling and novelty become evident. And the absence of tonic vagal restraint makes it possible for cardiac pumping rate to be controlled sensitively and powerfully by changes in nutrient intake. As tonic cardiac vagal restraint develops, in the third and fourth weeks, it is no longer possible for infants to show these responses in their original form. Instead, a delicate balance develops between tonic adrenergic and cholinergic cardiac activity that forms the basis for the variable and environmentally sensitive cardiac responses of the adult.

It seems possible that alterations in the timetables or course of early development in the two systems may underlie individual differences in autonomic balance and aberrant cardiac responses in adulthood. The fact that the tonic autonomic regulation of the infant rat comes under maternal control, through the sensitive nutrient-dependent mechanism we have described, provides a means by which early social relationships might affect the expression of genetic programs for the development of autonomic balance and by which early social experience may exert some of the long-term effects on cardiovascular development described in the introductory section of this paper.

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