Hormonal Influences on Brain Organization in Infant Rats

Hormones present during critical periods of development may exert a direct action on the central nervous system.

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Biological systems are unified and interdependent. The internal and external milieus are equally important interacting systems on which the very nature of the organism's function—whether it be on the cellular or the behavioral level—depends. There now exists an abundance of information which emphasizes the importance of environmental events during sensitive periods in ontogeny as determinants of adult physiological and behavioral processes (*1*). Although we have somewhat arbitrarily separated behavioral and physiological phenomena, the fact remains that behavioral phenomena can and must be viewed in biological perspective. Behavior is as adaptive a process as is the production of glucocorticoids under certain physiological conditions, and the two phenomena can produce equally maladaptive effects. In this article we describe some of the effects of altering the environment of the newborn animal, and we present a model which attempts to account in part for some of the observed results.

In brief, we propose that the presence of hormones (sex, thyroid, or adrenal) during critical periods of development exerts a direct action on the central nervous system, producing profound and permanent changes in the subsequent psychophysiological processes of the organism.

Gonadal Hormones

In the past 10 years many studies have been made of the effects of varying the amounts or kinds of gonadal hormones present in newborn animals. The early research in this area dealt mostly with transplantation of gonads; the more recent work has involved either prenatal or postnatal injections of hormones. Since several recent reviews have dealt with the effects of prenatal injections (*2, 3*), our discussion concerns only studies of animals injected after birth.

Clark (*4*) reported that castration of male and female rats 1 or 2 days after birth abolished the normal sex differences in pituitary gonadotropin. Thus, castrated males exhibited a concentration of gonadotropin in the pituitary which was significantly higher than that of normal males and did not differ from that of females. Pfeiffer (*5*) transplanted gonads of the newborn male rat to litter-mate females, and vice versa. There were numerous other treatments in this monumental study. The principal conclusions were that all rats at birth are physiologically female, but are capable of differentiation into males if testes are present. Testicular transplants into the newborn intact or castrate female led to acyclicity (associated with persistent vaginal cornification) and other permanent changes in reproductive function. In the castrate female these transplants also resulted in overt morphological change. When ovaries were transplanted into the newborn intact male, there was no observable effect. This is in contrast to observations in more recent work (*6–8*) where injection of estrogen into intact newborn male rats did disturb male reproductive function. In this instance the differences were possibly attributable to dose level, since the transplanted ovary may not produce sufficient estrogen to block the action of the endogenous androgens in the intact newborn male. However, in the adult male rat which has been castrated at birth, ovarian transplants develop corpora lutea in a cyclic manner, as in the normal female. More recent work (*9*) has confirmed these observations on the effects of castration of the newborn male. Although Pfeiffer believed it was the pituitary that became sexually differentiated, the evidence (see *10*) indicates that these effects are probably mediated by the hypothalamus and higher central-nervous-system structures.

From 1943 to 1958 this area of research lay dormant, but recently many studies have been reported. There is one major difference between the procedures used in the early work and those used in the more recent studies. Most of the earlier investigators used large multiple doses of hormones, whereas in the later work single injections have been given. Selye (*11*), in 1940, reported that 1 milligram of androgen given daily to female rats from birth through age 30 days markedly impaired ovarian function. Wilson *et al.* (*12*) treated female rats postnatally with testosterone propionate, the injections beginning the day after birth and continuing 3 times a week for 4 weeks. The total doses ranged from 3 to 36 milligrams. This treatment resulted in a loss of spontaneous mating behavior (*13*), acyclicity, sterility, and a lack of a behavioral or uterine response to exogenous estrogen in the mature animal. These data are similar to those of later investigators (*6, 14, 15*) and indicate that postnatal administration of androgen during critical periods markedly and irreversibly affects subsequent reproductive and behavioral functions. Injections given when the rat is more than a week old are superfluous.

There are procedures which suppress ovulation but do not produce a lack of sexual receptivity. Barraclough and Gorski (*16*) report that administration of 10 micrograms of testosterone propionate to newborn female rats blocks ovulation and produces constant vaginal estrus, but that these females are *constantly* sexually receptive. Similar results have been obtained by Mullins and Levine (*17*) with androgen, but these workers found that the degree of sexual receptivity varied inversely with the size of the neonatal dose (Fig. 1). Moreover, although the females were constantly receptive, the sexual behavior was aberrant. Lordosis was maintained for long periods and these females were extremely passive and inactive.

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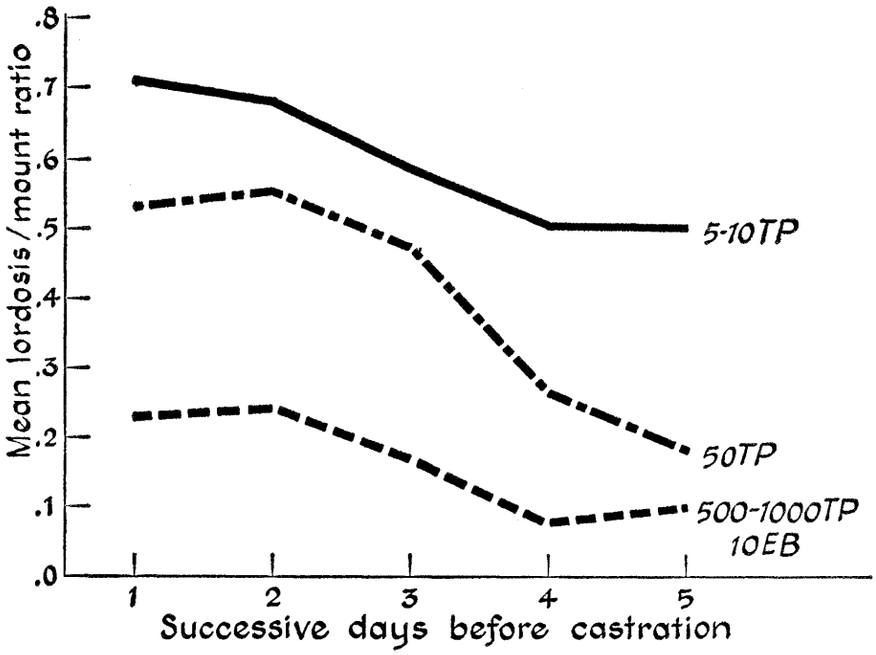

Fig. 1. Mean lordosis-to-mount ratio for female rats given 5, 10, 50, 500, or 1000 micrograms of testosterone propionate (*TP*) or 10 micrograms of estradiol benzoate (*EB*) either 96 or 120 hours after birth. Tests with a sexually vigorous male took place when the animals were 90 days old.

In 1943, two reports were published which bear on the problem of the specificity of hormone treatment (*18*). In these studies it was found that continuous treatment of female rats with estrogen in doses varying from 0.037 milligram to 2.3 milligrams, when started at 1.5 or at 10 days of age, resulted in acyclicity, lack of spontaneous sexual behavior (mating), impaired ovarian function, and failure to respond to administration of exogenous estrogen by changes in the uterus or by "estrous behavior" (after administration of exogenous estrogen the usual copulatory reflex following manual stimulation on the back and pudendal regions could not be elicited).

More recent studies tend to support this earlier work. However, instead of large multiple doses of hormone, single injections of hormones at various dosages have been used. Harris and Levine (*6*) report that a single dose of estrogen administered to females 96 hours after birth resulted in permanent ovarian disfunction, similar in some ways to that produced by androgen. However, the effect of this neonatal estrogen on adult female sexual behavior was to abolish sexual receptivity; this effect was observed at all dose levels from 10 micrograms upward (*7*). By contrast, androgen administered to newborn females has paradoxical effects on sexual receptivity which are dependent on dose level. Although both hormones abolish ovulation, estrogen produces irregular vaginal cyclicity with long periods of estrus (*19*), whereas androgen produces constant vaginal cornification. Thus, it is apparent that the organization of sexual behavior is differentially affected by administration of androgen or estrogen to the newborn female.

Male rats given estrogen in infancy also show marked defects in sexual behavior. These males show a great deal of mounting behavior (although these mounts are often directed to the head or side of the female), they rarely achieve intromission, and they never ejaculate. It is difficult to attribute these effects to an alteration in the central nervous system, since a single injection of estrogen when the rat is 4 days old results in marked atrophy of the reproductive system (Fig. 2) and failure of the os penis to develop. On the basis of sexual behavior alone, no conclusion can be drawn about the central-nervous-system effects of administration of estrogen to the newborn male. Castration of the newborn male rat, however, does markedly alter sexual behavior. Adult males that were castrated in early infancy exhibit complete female sexual behavior if they are given injections of estrogen and progesterone at low dosages (*3, 20*), or if they receive a transplanted ovary (*9*). Males castrated in adulthood show no such behavior after these procedures.

There are data which do indicate that sexual differentiation in the male rat is affected by administration of estrogen to the newborn animal. Throughout the psychological literature there are numerous reports of behavioral differences between males and females. Differences in activity (*21*), avoidance conditioning (*22, 23*), and ulcer formation (*24*) have been reported. The fact that these differences are not solely a function of the gonadal hormones in the circulation is apparent from the work of Anderson (*25*), who reported striking differences between males and females in defecation and ambulation behavior and also in timidity in open-field tests, although the experimental animals, of both sexes, had been castrated long before the open-field testing. An experiment was recently performed (*26*) to determine the effects of administration of sex hormones to the newborn rat on male-female differences in open-field behavior. Untreated female rats are usually more active than males in this test situation. Estrogen was more effective than androgen in reducing this sex difference, but the total amount of open-field activity was reduced in all animals.

It has been suggested (*3, 9*) that gonadal hormones exert a dual influence on the central nervous system—inductive or organizational during development and excitatory or activational in the adult. The studies discussed in this article show that the presence of either androgen or estrogen in the newborn rat causes the sexually undifferentiated brain to be organized so that the acyclic, male pattern of hormone release occurs in the adult. In the absence of gonadal hormones, the basic female (cyclic) hormone-release pattern becomes established. Both of these patterns of hormone release are part of a "hormonostat" whereby the concentration of sex steroids being produced "feeds back" and influences the central nervous system, which, in turn, controls the rate of steroid production or release, or both. Although the altering of steroid concentrations in the newborn permanently alters the functioning of this hormonostat, studies with hormone replacement in adulthood have shown that it is not a deficit in the amount of sex hormones which causes the aberrant neuroendocrine function and behavior that are observed in adult animals given hormones in infancy. A

probable explanation is that this procedure alters the sensitivity of the controlling brain mechanisms with regard to both the type and the temporal sequence of hormones to which they will respond.

In order to obtain the effects on sexual behavior and physiology that have been discussed, the experimental procedure must be carried out during a certain period of development, often referred to as a "critical period." In the rat, the critical period for affecting sexual development occurs in part after birth. Several experiments (*3, 6, 14*) have shown that the presence of androgen in small amounts (as little as 5 micrograms) in female rats during the first 5 days of postnatal life results in modification of the gonadotropin-releasing mechanism in the central nervous system from a cyclic to an acyclic one. Conversely, absence of androgen in the male rat during the first 48 hours after birth results in establishment of the release mechanism in its basic, cyclic, form. The presence of estrogen in either the intact female or the castrated male during this early period also disrupts the development of normal sexual function.

Although 5 to 6 days after birth is considered the critical period for affecting sexual development, there can be variation of as much as 3 days in this period, depending upon individual differences among the animals and the amount of hormone given. Another important determinant of these effects is the length of time the hormone is or is not present in the newborn animal within the critical period (Fig. 3). Studies now in progress (*27*) indicate that testosterone alone, which is metabolized in about 8 hours in the 1-day-old rat, does not produce the androgen sterilization in female rats that is seen when testosterone propionate, a longer-acting preparation, is used. Work with guinea pigs has shown that intrauterine injections of testosterone propionate must be given for a number of days in order for masculinization of female offspring to occur.

Thyroid Hormone

The number of studies dealing with early thyroid deficiency or excess has been growing. Absence of thyroid hormone in the developing organism has significant consequences for more physiological and behavioral functions than does the absence of androgen (*28, 29*). If thyroidectomy is performed immediately after birth in the rat, cretinism develops. Growth is normal for the first 2 weeks of life, but then it levels off at the animal's normal 3-week size. Opening of the eyes and vagina is retarded, and maturation of many reflex behaviors, such as the righting response, is delayed. In the central nervous system, myelination is retarded, and there is less-than-normal branching and connecting of cell processes in the cortex. Protein synthesis is also impaired in the nervous system, and electroencephalogram patterns are abnormal. Behaviorally, such animals are lethargic and show reduced capacity for learning and

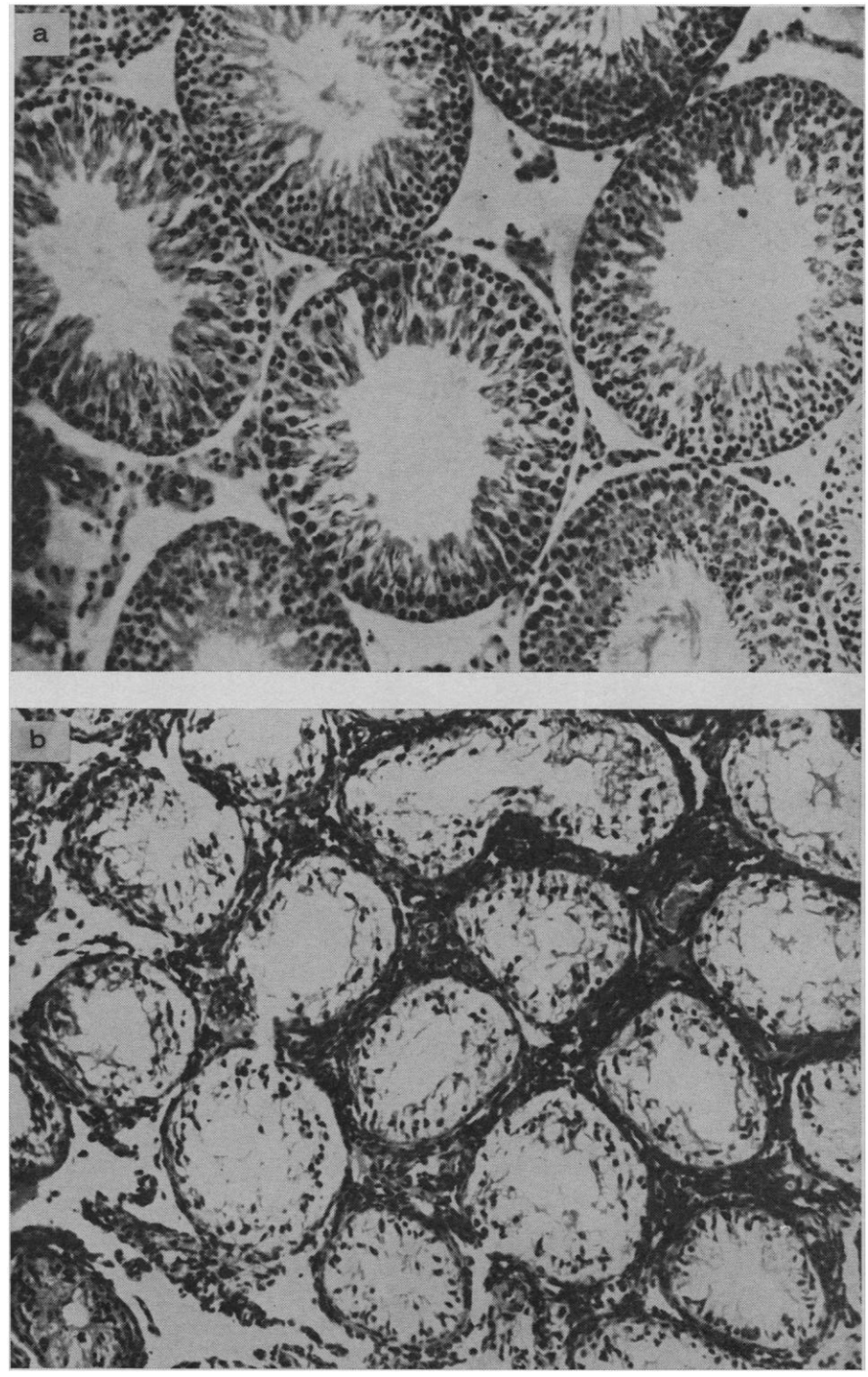

Fig. 2. Sections from the adult testes of (*a*) a normal male rat and (*b*) a male rat given a large dose of estrogen when it was 5 days old; *b* shows degeneration of the seminiferous tubules.

remembering. Thus, the absence of thyroid hormone does not affect any specific class of behaviors but alters the animals' basic ways of interacting with the total environment.

Control of thyroid hormone secretion is partially accomplished by means of a feedback mechanism similar to the "hormonostat" discussed for the gonads (*30*). There is recent evidence (*31*) that administration of thyroid hormone, thyroxin, to a newborn rat will cause permanent hypothyroidism in the animal. It is not known whether this is a result of damage to the thyroid itself or of an alteration in the central-nervous-system control mechanisms, but disruption of the hormonostat is indicated by the fact that pituitary and blood concentrations of thyroid-stimulating hormone are consistently low even though there is a deficit of thyroxin. As is the case in animals subjected to thyroidectomy shortly after birth, there is an impairment in both body growth and thyroid goiter response in these rats which received thyroxin in infancy.

Many of these deficits can be wholly or partially corrected if thyroid hormone replacement is begun within a certain critical period (15 days) following birth. However, once the critical first days of life have passed, many of the effects of hypothyroidism are irreversible and cannot be corrected by thyroid hormone replacement in adulthood (*29*). However, some of the behavioral deficits produced by thyroidectomy in adulthood can be corrected with hormone replacement (*32*).

Adrenal Hormones

We have discussed the effects that the alteration of hormone concentrations in the newborn animal has on the neuroendocrine regulation of gonadotropins and thyrotropin in the adult. There is also evidence that the central-nervous-system regulation of ACTH concentrations in adult rats may be a function of environmental events occurring during critical periods in infancy. Although there is little direct evidence that variation in the concentration of adrenal steroids in the newborn animal can cause permanent alteration in brain mechanisms, in light of the known effects of other hormones given during infancy, this possibility warrants serious consideration.

A number of studies have shown that adult animals given various forms of stimulation during a critical period in infancy differ markedly from nonstimulated animals in the temporal pattern of their steroid response to acute noxious stimulation and the magnitude of their steroid response to novel stimulation or novel experiences. Much of this research has been reviewed elsewhere (*33*), and only a brief summary is given here.

Animals that were stimulated in infancy by being picked up daily, placed in another cage for 3 minutes, and then returned to the nest show a more rapid and greater steroid response to a brief but intensive electric shock in adulthood than is shown by animals not handled in this way (*34*). (The word "handling," as used throughout this article, refers to this procedure.) Animals that have not been handled respond more slowly to the stress, but in such animals the response to stress tends to persist over a much longer period (*35*). However, a recent experiment (*36*) has shown that, at 0, 5, and 15 minutes after the end of a 3-minute period of free activity in an open field, rats that had been handled in infancy secreted significantly *less* adrenal steroids than rats not handled in infancy (Fig. 4). The handled rats do show a response to the novel situation, but a less extreme one. It has also been shown (*22*) that rats handled in infancy explore more freely and defecate less in a novel environment than their nonhandled controls do.

On the basis of these experiments the hypothesis has been developed that one of the major consequences of handling in infancy may be the endowment of the organism with the capacity to make responses more appropriate to the demands of the environment, including appropriate responses to stress. If "adaptiveness" includes the ability to respond according to the demands of the environment, then animals handled in infancy can be said to be more adaptable since they can respond with a moderate steroid output to a novel situation and with a near-maximum output to a physically threatening one, while animals not handled in infancy can only give a near-maximum response to any change in the environment.

The question which now arises concerns the nature of the physiological processes in the newborn animal whereby handling in infancy can permanently affect the adrenal system so that the adult animal can respond more appropriately. There are differences in the development of the hypothalamo-pituitary-adrenal system in handled and nonhandled rats which may help to provide an answer. The ability of the infant rat to respond to cold with a significant depletion of adrenal ascorbic acid ap-

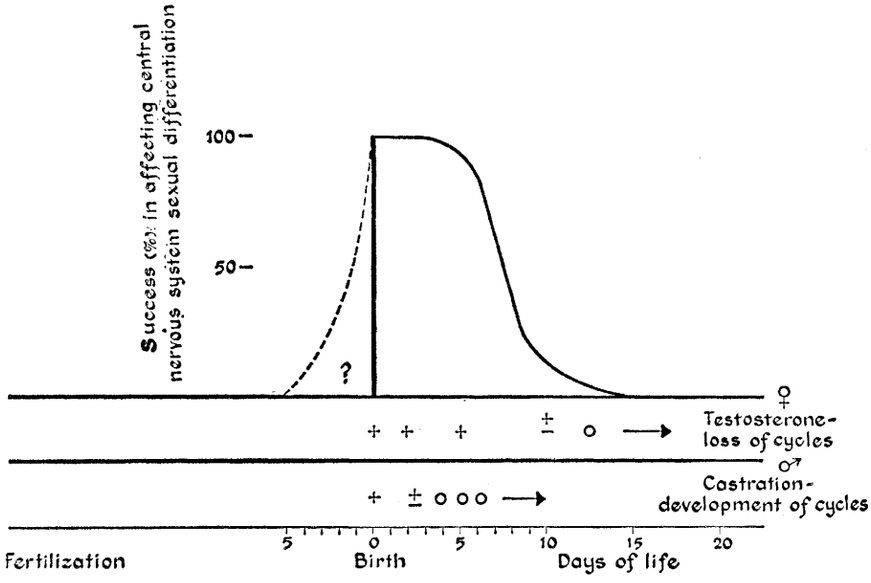

Fig. 3. Diagram summarizing various data concerning the critical period during which the central nervous system of the rat becomes sexually differentiated. The upper line of symbols (+, effective; ±, possibly effective; 0, ineffectual) shows the days after birth when administration of testosterone to the female rat evokes masculinization of the nervous system. The lower line of symbols shows the days when castration of the newborn male rat allows retention of a female type nervous system. The curve shows success in affecting central-nervous-system sexual differentiation. [From Harris (*9*)]

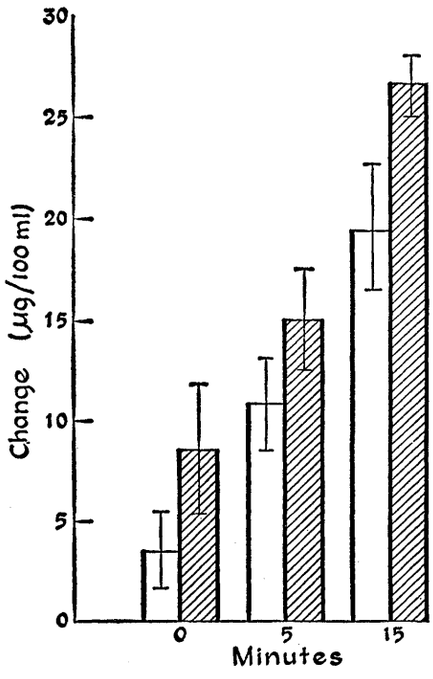

Fig. 4. Mean change in plasma concentrations of corticosteroids at 0-, 5-, and 15-minute intervals after a 3-minute period of open-field testing in adulthood for rats which had either been handled (open columns) or not handled (hatched columns) in infancy. The values for change were derived by subtracting the values obtained for steroid concentrations after the open-field testing from the mean value for base-line control subjects. The small bars represent the standard error of the mean.

pears several days earlier in the animal that has been handled (*37*). Recently in our laboratory (*38*) it has been shown that, in handled animals as young as 3 days old, a significant increase in adrenal steroids occurs following electric shock, while no such increase is seen in nonhandled animals younger than about 9 days old (Fig. 5). In addition, handled animals show a greater steroid response to ACTH injected either 6 or 9 days after birth (Fig. 6). Thus there are changes in the adrenal steroid levels in the handled rat at a time during development when the central-nervous-system mechanisms that control physiological functions in the adult are not yet permanently established.

A Possible Central-Nervous-System Mechanism

In proposing models which partially explain the fact that animals handled during the critical period are able to make more appropriate responses to the environment than nonhandled animals, one can approach the problem either in terms of the animal's ability to make the necessary discriminations among stimuli on the input side or in terms of its ability to make differential responses on the output side. There is no evidence available concerning the effects of early handling on the animal's ability to discriminate among stimuli, but there is a model which might explain the effects of early handling in terms of the responses available to the organism.

It has been postulated that control of adrenal cortical function in adult organisms is partially accomplished by means of a homeostatic feedback mechanism or hormonostat (*39*). In such a system, the concentration of corticosteroids in the blood is monitored in the central nervous system and compared with a controlling set point. If the concentration of circulating steroids is higher than this set point, ACTH secretion and, consequently, adrenal output diminish. If the concentration is below this set point, then ACTH is released and more steroids are produced.

In this hormonostat, moreover, the set point is not fixed at a given level; it can vary to some extent, depending upon the demands of the environment and the inner states of the organism. The sensitivity of the hormonostat is determined by the number of values this set point can have between its minimum value, which corresponds to the concentration of steroids when the animal is resting, and its maximum value, which corresponds to the concentration under conditions of extreme stress. Thus it may be that handling, by causing variation in the concentration of adrenal steroids in the infant animal, modifies the set point during a critical time in development so that it can vary in a graded manner in the adult, with several possible values between the minimum and the maximum. This could explain why handled rats are able to respond to novel but not physically threatening stimuli, such as the open field, with a moderate increase in adrenal steroids, and to shock with a large and rapid increase. In the nonhandled newborn rat there is less variation in adrenal steroid concentration during the critical period, and the set point develops fewer possible values. In these animals the hormonostat tends to operate either at "resting" level, if there is no change in the environment, or at levels close to maximum if there is any change at all, whether or not the change is physiologically threatening.

Recent work in our laboratory suggests that the variation in concentration of steroids that is seen in the handled animal may come about not only as a result of the handling of the infant but also as a result of disturbance of the

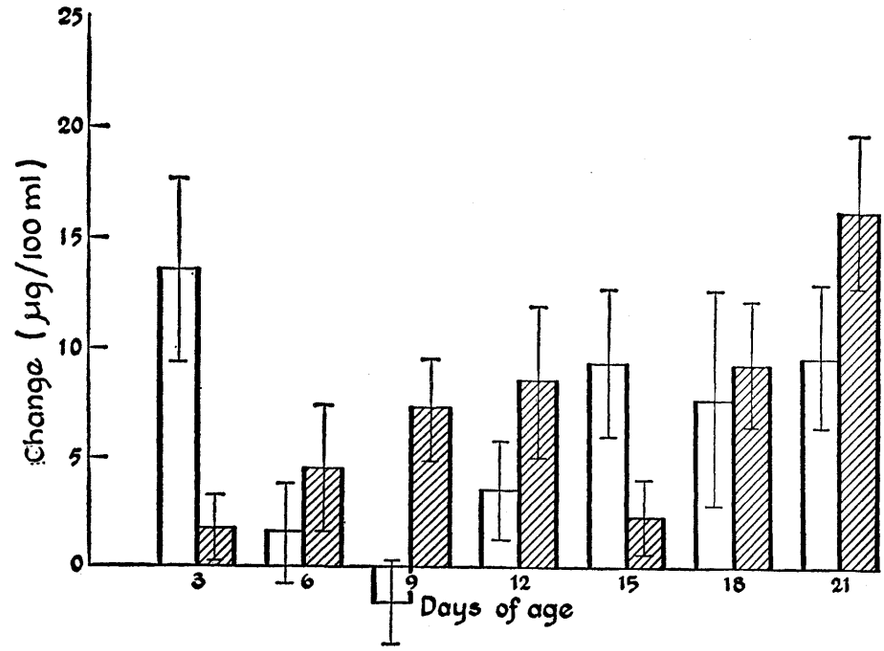

Fig. 5. Mean change in plasma concentrations of corticosteroids following electric shock (0.1 milliampere) in previously handled (open columns) and nonhandled (hatched columns) infant rats, at various ages. The small bars represent the standard error.

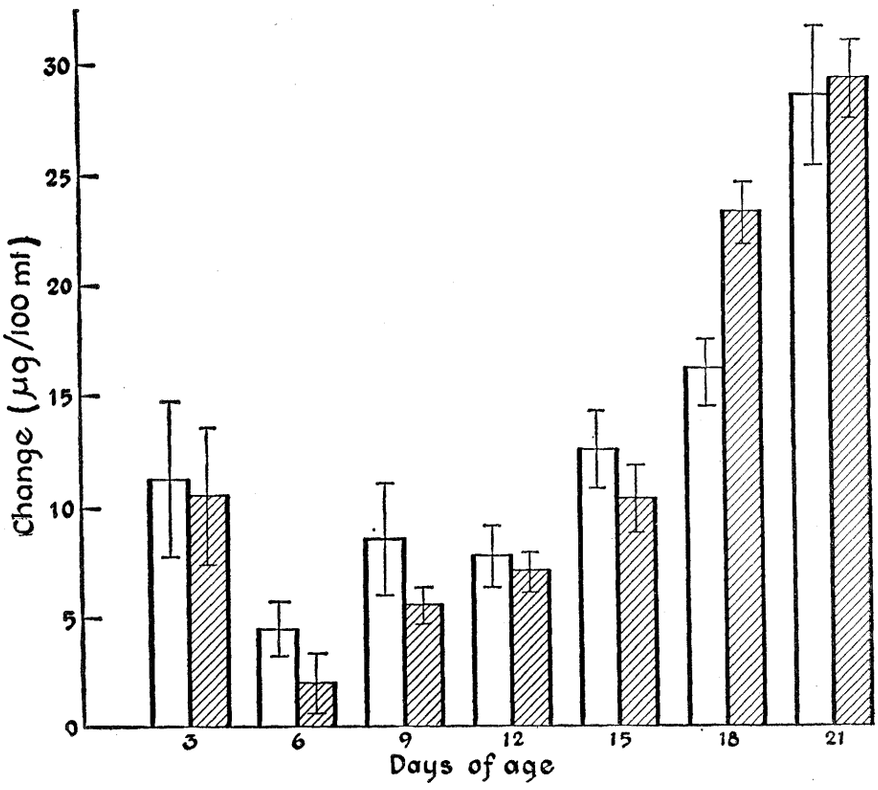

Fig. 6. Mean change in plasma concentrations of corticosteroids following an intravenous injection of ACTH (10 milliunits per 100 grams) in previously handled (open columns) and nonhandled (hatched columns) rats, at various ages. The small bars represent the standard error.

mother during the handling process. The resulting variation in the mother's steroids could be communicated to the young, possibly through the milk. This idea is supported by findings which indicate that the circulatory portal system between the median eminence of the hypothalamus and the pituitary is not developed before the animal is 5 days old (*40*), and that feedback mechanisms of the type found in the adult thus would not be operating in the newborn animal.

Although there is no direct evidence that the more varied steroid output of the adrenal system in the handled animals causes the permanent changes in the central-nervous-system mechanisms that have been hypothesized, it seems reasonable to assume that adrenal steroids in the newborn animal play an important role in determining the sensitivity of the brain areas which control adrenal functioning in the adult.

Implicit in the foregoing discussion is the notion that there are specific time periods in development during which particular types of stimulation will have profound and irreversible effects upon the physiology and behavior of the adult organism. Here again is the idea of a critical period before or after which stimulation will have little or no effect. Although there has been controversy concerning this hypothesis (*41*), data do exist which indicate that handling during the first 5 days of life is critical for subsequent physiological changes in both developing and adult organisms. Levine and Lewis (*42*) handled infant rats on days 2 to 5, 6 to 9, 10 to 13, or 2 to 13 after birth; control animals were not disturbed. When the animals were 14 days old, studies were made to determine whether adrenal ascorbic acid was depleted following exposure to cold. The groups handled on days 2 to 5 or 2 to 13 exhibited significant depletion of adrenal ascorbic acid, but the other groups did not. Bell, Reisner, and Linn (*35*) handled rats on days 2 to 5, 6 to 9, and 10 to 13, and they also used undisturbed controls. When the rats were 46 days old, half the animals in each group received electroconvulsive shock. Twenty-four hours later blood samples were obtained from all the animals, and the glucose concentration was measured. Those rats which had been handled on days 2 to 5 showed no significant increase in glucose levels following shock; the blood sugar concentrations of the shocked animals in the other groups were significantly higher than those of their controls.

These results appear somewhat paradoxical, but it should be noted that, whereas in the Levine and Lewis study (*42*) the depletion in adrenal ascorbic acid was measured 90 minutes after the onset of stress, in the experiment of Bell and his co-workers (*35*) the blood glucose concentrations were determined after an interval of 24 hours. In addition to demonstrating that there is a critical period for handling of newborn animals, these data also indicate a difference between the time course of the stress response in adult animals that were handled during the critical period and those that were not.

Thus we have an instance where the same treatment of the newborn has an effect for two different stresses, two physiological measures, and two test ages. Much more evidence concerning critical periods has been reported, but it is by no means as clear as that just presented. Denenberg (*43*) has pointed out that the intensity of the infantile experience may be an important determinant of the critical period. He has demonstrated (*44*) that rats handled from days 1 to 3, 3 to 5, and 1 to 5 of life did not differ from controls in avoidance learning (no physiological measures were taken), whereas animals shocked on those days did differ from the controls (*45*). More recently, in our laboratory we have found that a single exposure to extreme cold within the first 12 hours after birth improves avoidance conditioning in adulthood. In contrast, a single handling experience during the same period is without effect. Inasmuch as we are hypothesizing that the effects of handling in infancy are attributable to an increase in adrenal steroids and the action of these steroids on the central nervous system during a critical period in development, it seems reasonable to assume that the intensity of the stimuli to which the newborn animal is exposed is an important determinant of the magnitude and duration of its steroid response.

Unfortunately, the evidence for a critical period for early stimulation which affects later adrenal response and central-nervous-system organization is not nearly as definitive as the evidence which has been presented for the effects of gonadal hormones in the newborn on

sexual differentiation of brain mechanisms. However, it seems reasonable to postulate at this time that changes in the central nervous system occur when stimulation is applied during critical periods of development.

Discussion

All the experimental evidence presented here supports the view that alterations in the hormonal status of the newborn animal have profound and permanent effects on the animal's subsequent biological functioning. More specifically, we hypothesize that hormones in the newborn are partially responsible for the organization of some of the central-nervous-system control mechanisms which will control the activation of these hormones in the adult. For the three hormone systems discussed above, the effects of varying the hormone concentrations in newborn animals have differed slightly.

In the gonadal system, we have postulated that the action of steroids in the newborn animal alters the patterns, and probably also the amounts, of hormone secretion in the adult. In addition, the steroids present in the infant also determine to what hormones the brain centers controlling sex behavior in the adult will be responsive. If testosterone is removed from the male rat immediately after birth, through castration, the animal will show complete female receptive behavior in response to administration of estrogen or progesterone in adulthood. This is not the case in animals which are castrated after the first 5 days of life. Similarly, administration of testosterone or estrogen, in large doses, to female rats during the first 120 hours after birth renders them incapable of responding normally to female sex hormones in adulthood. Paradoxically, females given estrogen in infancy sometimes show complete male sex behavior patterns in response to testosterone in adulthood, while adult animals not given estrogen in infancy only show mounting behavior when given the same amount of testosterone.

It has been found that administration of thyroid hormone to the newborn rat permanently suppresses thyroid function. It may be that the set point for the thyroid hormonostat is set so low by the early treatment that very small amounts of thyroid hormone are able to shut down the thyrotropin-releasing mechanisms in the brain. For the adrenal system, we have proposed that the increased variation of concentrations of adrenal steroids in the infant animal following handling allows the controlling set point of the brain hormonostat to elicit, in the adult, graded adrenal responses appropriate to the demands of the environment. The smaller amount of variation in the nonhandled animals means that, in the adult, the adrenal system will respond in a more "all-or-none" manner, and that any change in the environmental demands on the animal will elicit a near-maximum response.

Another indication that hormones may have different actions at different stages of development comes from evidence that endocrine systems are active during the first few days after birth, cease functioning for a week or more, and then assume adult functioning. With regard to the production of male sex hormone, two distinct generations of Leydig cells have been described in rat testes (*46*), one occurring in the fetus and infant and the other appearing at puberty. In the rat, a change in concentration of corticosteroids can be elicited in the first 3 to 4 days after birth by an injection of ACTH, but a response of the same magnitude cannot be obtained again until the rat is about 15 days old (Fig. 6). In the two cases, there is a similar ontogenetic pattern of hormone activity, with two active periods of endocrine function separated by a period of little hormone secretion. Further evidence regarding a unique role for hormones in newborn animals is given by the data on critical periods. Unless handling is begun shortly after birth, sex hormone treatment within 4 to 5 days of birth, and thyroid replacement in thyroid-deficient animals within 2 weeks of birth, irreversible changes in physiology and behavior occur.

Perhaps most indicative and exciting for future research are the interrelationships which have been found among the endocrine systems. It has been shown that manipulation, in infancy, of either the adrenal, gonadal, or thyroid systems can affect the functioning of another of these systems.

The common biochemical derivation of the adrenal and gonadal steroids may in part explain some of the interactions which have been found. Male rats given estrogen in infancy show a greater adrenal-steroid response to the stress of ether anesthesia than do injected controls (*27*). Injection of sex hormones into newborn animals also affects later emotional behavior (*26*) and thyroid function (*6*). Simply injecting female rats with saline right after birth reduces the amount of male mounting observed when they are given testosterone after castration in adulthood, as shown by recent work in our laboratory. Conversely, handling in infancy advances the onset of puberty in rats, an event which is partially controlled by the sex and thyroid hormones (*47*), and also affects thyroid response to cold (*48*). Further, it has been shown that both emotional and physical stress can markedly alter thyroid function (*49*). These results are only the beginning of what will eventually be a long list of interactions among the neuroendocrine systems at all stages of development.

It appears that the effects of variations of both the external and the internal environment are mediated through basic, but as yet undetermined, biochemical processes. The elucidation of these processes should bring us much closer to an understanding of the intimate relationship between physiology and behavior.

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Archeology in an Emergency

The federal government's Inter-Agency Archaeological Salvage Program is 20 years old.

Frederick Johnson

Salvage archeology as a basic national policy has been spreading into numerous countries, especially during the past three decades or more. Everyone is familiar with the spectacular salvage archeology now in progress on the upper Nile in areas where a reservoir is to be created by the Aswan dam. Here, whole temples are being moved to higher levels and even more importantly archeologists are recording the long prehistory of the Nile River Valley before it goes under water. It was not common knowledge, prior to this emergency, that the prehistory of the region extends back into Paleolithic times.

Probably less well known, or at least less dramatically publicized, is the fact that, within the United States, the federal government has been conducting, since 1947, an "Inter-Agency Archaeological Salvage Program." This was designed initially to salvage materials to be destroyed by the construction of multipurpose dams in all parts of the nation. The results may not be as spectacular as those coming from work in the Old World but they are fully as valuable, for they document a significant part of the long human occupation of the New World. This program has also been supported by numerous state and local institutions. The expansion of the population and the need for services such as oil pipelines, private dams to produce power, real estate developments, airfields, and other modifications of the landscape complicate the emergency and have given rise to nongovernment projects designed to assist in the preservation of archeological data which otherwise would have been destroyed. The whole endeavor has efficiently preserved, in many parts of the United States, a wealth of evidence contributing to our knowledge of the past 9000 years. This article is a brief description of the salient aspects of the unprecedented development and accomplishment of the federal program.

The rapid expansion of the program has two aspects, the administrative and the scholarly. These are very closely related. However, for purposes of clarity I treat them separately, discussing on the one hand the administrative problems and, on the other, the features of the scholarly research which are controlled by the emergency situation and which to a large extent are still with us. An indispensable characteristic of the whole broad federal program has been the successful cooperation between these two aspects which, under other circumstances, often hold themselves aloof. One of the mechanisms which aided in the establishment of and promoted this essential cooperation was creation of a free-wheeling committee, the Committee for the Recovery of Archaeological Remains (CRAR).

I have much to say about river basins, for the reason that people have always been dependent upon the resources of these specialized regions for their main source of food, for transportation, and, in fact, for most of the things which are vital to human existence. The significance of the river valleys to human life increases as we go back of the time when our present mechanized culture began to extend our horizons. Early historic and particularly prehistoric peoples built their houses and tilled their fields close to the rivers. The remains of such human occupation are the basic data of archeology.

Federal-government plans for the development of water resources for construction of dams to form reservoirs, irrigation canals, and other public works in river valleys threatened to destroy the archeological evidence for

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