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Birth and delivery as stress : their relation to adrenocortical function

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BIRTH AND DELIVERY AS STRESS; THEIR RELATION TO ADRENOCORTICAL FUNCTION

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INTRODUCTION

It has long been a generally accepted fact that insult to the body which is sufficient to produce tissue damage calls forth a defense mechanism to enable the body to withstand the insult. It has just been within recent years that Hans Selye formulated the Alarm Reaction and General Adaptation theory in an effort to account for the details of this intricate process.

He defines the General Adaptation Syndrome as "the sum of all non-specific systemic reactions of the body which ensue upon long-continued exposure to systemic stress." A furthur breakdown of the Adaptation Syndrome includes the alarm reaction (subdivided into the shock and counter shock phases), the stage of resistance, and the stage of exhaustion.

The alarm reaction is elicited by any non-specific noxious agent to which the organism is quantitatively or qualitatively not adapted. In the first part of this reaction (called the shock phase) the damaging agent, through adrenalin discharge, or perhaps through a toxic metabolite produced under its influence or by nervous pathways, acts on the anterior lobe of the pituitary and stimulates it to discharge adrenocorticotropic hormone, which acts to raise the

the resistance of the body and elicit the characteristic counter-shock phenomenon. During the counter-shock phase there is an enlargement of the adrenal gland and a reversal of the findings seen in the shock phase.

The stage of resistance occurs when the organism becomes adapted to a prolonged exposure to stress. During this time there is an increased resistance to the stimuli with a decreased resistance to all other stimuli.

The stage of exhaustion represents "the sum of all non-specific reactions which ultimately develop as the result of very prolonged exposure to stimuli to which adaptation has been developed but could no longer be maintained". Even a perfectly adapted organism cannot indefinitely maintain itself in the stage of resistance. Lesions characteristic of the alarm reaction reappear and furthur resistance becomes impossible. (1 and 2)

The stresses, therefore, are an insult to the entire organism. Selye lists a number of different stimuli, morphological, functional, and biochemical, which result in the same morphological response. These include trauma, infection, exposure to cold and heat, irradiation, chemical agents and many others.

At the time of birth, the infant is subjected to sudden, severe, systemic stimuli in the form of changes in temperature, variations in pressure, trauma, anoxia, and an immediate demand for changes in circulation and respiration, as well as being under the influence of sedatives, anesthetics and other drugs in the mother's blood. In like manner, the mother is subjected to similar insults; the physiologic exertion of labor, anesthesia, perhaps surgery, blood loss and emotional changes. Any or all of these are capable of producing a stress which logically would result in the response typical of the alarm reaction.

Since it is known that there is an increased demand for ACTH and the corticoids in response to stress, increases and decreases of these substances in the body have been investigated as an index of the effect of stress. Quantitative assays of urinary 17-ketosteroids have been measured to estimate adrenal cortical function, but were found to be too time consuming and could not always be relied upon. Another method, which has proved to be fairly accurate, is that of determining the level of circulating eosinophiles. Administration of ACTH causes a decrease in the peripheral eosinophiles. Burrell (3) showed that the newborn has an almost total eosinopenia on the day of birth with a sharp rise in the

next few succeeding days and then maintains a stable level.

Robson and Duthie (4) found that capillary resistance is a true indicator of adrenal cortical function, and is a simple and rapid method of following the response to ACTH or to substances which might be expected to have a similar response. That capillary resistance is regulated by cortisone has been shown by Kramar. (5) Adrenalèctomized rats permanently reveal a very low degree of capillary resistance. Adequate doses of cortisone are able to restore it to normal while DOCA or ACTH fail to do so. Furthermore, it has been demonstrated that various forms of stress may elicit a biphasic capillary response in the normal rat; increase of resistance followed by a critical drop. The latter can be prevented by cortisone but not by ACTH. This indicates that the adrenal cortex is primarily responsible for the capillary crisis whether it is on the basis of unresponsiveness or depletion.

It has been found that there is a fair relationship between the eosinophiles in the circulating blood and capillary resistance. Robson and Duthie (6) while studying the effects of ACTH administration to various patients found that in every case as the capillary resistance rose, the eosinophile fell, and vice versa.

PURPOSE

In view of these facts, it was decided to study the capillary resistance in the newborn following delivery and throughout the first week of life in the assumption that the process of delivery as a stress may elicite some typical pattern. In a smaller group, the mothers were tested prior to and after delivery in order to detect the correlation bètween mothers and child's capillary resistance. Another group of babies beyond the neonatal period served for controls.

METHOD OF INVESTIGATION

Capillary resistance was determined in 48 newborn infants. The cases chosen represnt consecutive births in several institutions. The largest consecutive series was collected at the University Hospital over a period of one month and includes 29 cases. Seven cases were observed at the Nebraska Home for Unwed Mothers, six cases at Bryan Memorial Hospital, Lincoln, Nebraska and 5 cases at Booth Memorial Hospital in Omaha. Of these, 44 were full term and 4 were premature, conforming to the international classification whereby the birth weight of 2.500 gms (5.5 lbs.) or less is the criterion of prematurity. Readings were taken every day or every other day from time of delivery until discharged from

the hospital. The average length of time was 5 to 7 days (31 cases). However, it was possible to follow 17 cases over periods varying from 8 days to 39 days who were kept in the hospital longer than normal because of weight under 5½ lbs, delayed discharge of the mother, or because they were kept at the institution for six weeks before discharge.

Determination of capillary resistance was done on 16 mothers before labor, during labor, and in the postpartum period. Four of these were tested during labor and every day postpartum until discharge from the hospital. Six mothers were followed during a period of one week before delivery and for a period up to 11 days after delivery, but no readings were taken during labor. Another group of six were checked bi-weekly during the last 2 months of pregnancy, but had not delivered at the termination of the present survey.

In an attempt to determine capillary resistance in infants over 2 weeks of age, readings were taken of 41 children at different ages from 2 weeks to 3 months of age without regard to serial readings or individual patterns.

Capillary resistance was determined by the application of the "negative pressure principle" in which

the surface capillaries under a fixed area of skin are subjected for a limited time to the strain of negative pressure, or suction, applied to their walls through the skin. As a result of the strain, injuries to the capillary walls are produced which become evident as minute petechiae. Although it is not known exactly how the trauma acts on the walls, it is not to be assumed that actual rupture of the capillary walls takes place, since it is possible that the properties of the capillary walls become altered to allow the passage of the red blood cells through the capillary. (7).

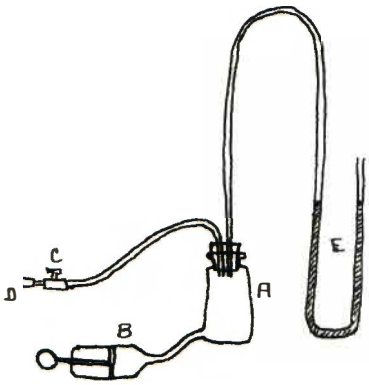


Figure 1.

The apparatus which was used consists of a reservoir (A) in which negative pressure is created by a suction pump (B). A control valve (C) allows suction to be applied to the skin through a small metal cup (D) with an inside diameter of 6 mm. The degree of negative pressure required to produce petechiae is recorded on a mercury manometer (E). The lip of the metal suction cup was lubricated with lanolin or vaseline to insure an airtight seal. The cup was placed firmly on the skin and the stop-cock was opened allowing suction

to be applied for a period of 60 seconds. The infraclavicular region was used as the testing area on the infants, and the antecubital region was tested on the mothers. It has been shown that in a single individual capillary resistance varies in different locations over the body. (8) The infraclavicular area in the infant shows the highest degree of sensitivity to negative pressure. In adults the skin of the antecubital region is easily accessible and is also highly sensitive. The same area was used in each individual each time the testing was done. As nearly as possible, illumination was uniform -- a 60 watt bulb, with reflector, held approxiamtely one foot from the test area. All readings were done in nurseries, therefore the environmental temperature was comparatively constant. It is believed by some that the time readings are taken in relation to feeding may cause a slight variation in capillary resistance. Therefore, in the cases at the University Hospital all readings were taken between 10:30 and 11:30 a.m. The infants were fed at 9:00 a.m. and 1:00 p.m.

The initial reading was taken at an arbitrarily set point. From there alterations in pressure were made at intervals of 2 cm. mercury negative pressure. The "critical pressure" of capillary resistance was

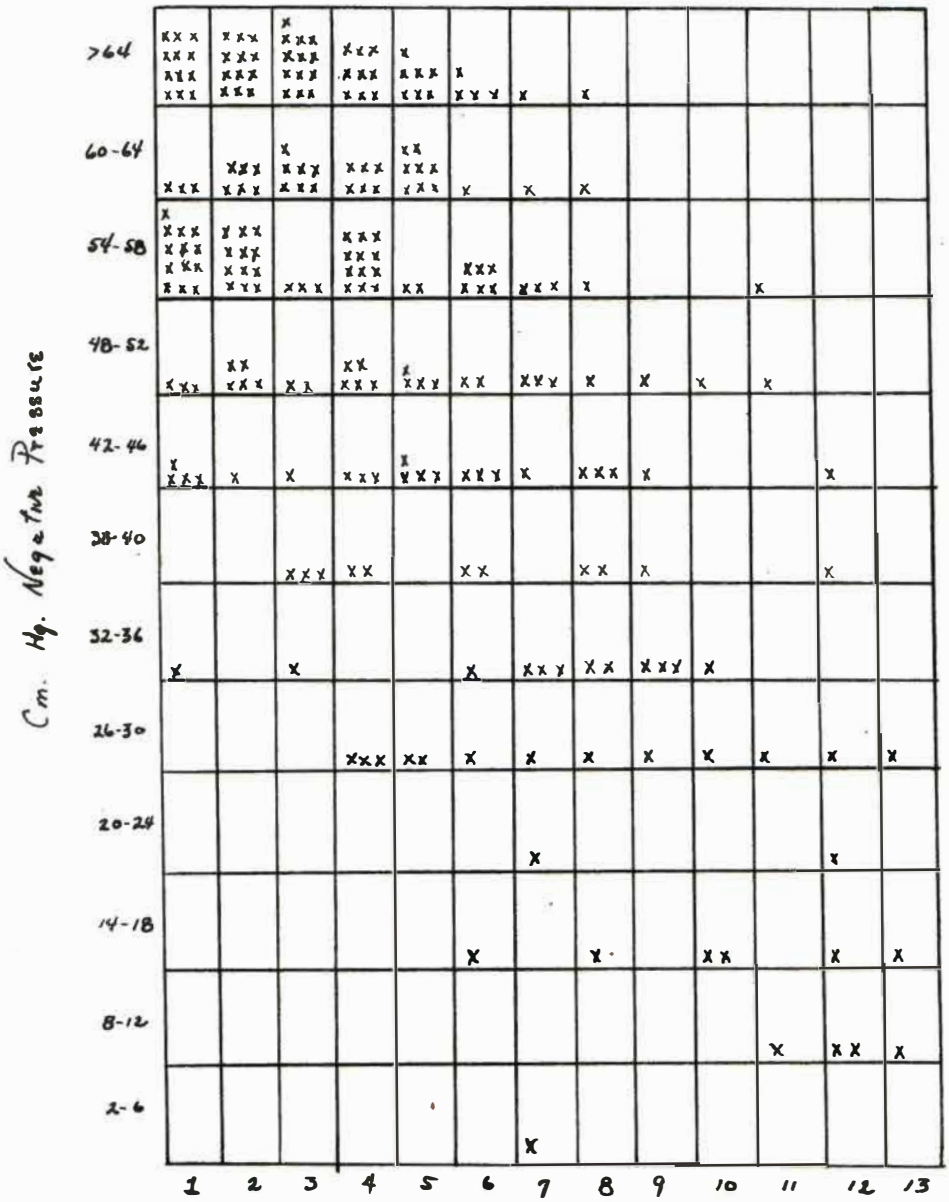
determined as the least negative pressure required to produce petechiae. The upper limit of negative pressure which could be produced by this apparatus was 64 cm. mercury, so that some of the readings are recorded as only 64 plus.

In adults using the technique described, the average range of normal capillary resistance was found to lie between 20 and 30 cm mercury, negative pressure by Duthie and Robson (6), between 20 and 30 cm. mercury by Eliot (9), while Bell, et al. (10) encountered a wider range of normal within a range of 20 to 45 cm. Minkowski and Venes (11) determined in a series of 37 mothers at term that the average capillary resistance during labor was 10 to 15 cm, while those who delivered prematurely (7 to 8 months) had a much wider variation, 20 to 45 cm. They also observed in newborns tested during the first 24 hours, that in 20 term infants capillary resistance was on the average higher than 50 cm mercury negative pressure and in 16 premature infants the average readings were 30 to 35 cm. mercury negative pressure. None of these cases were followed after the first 24 hours of life.

RESULTS

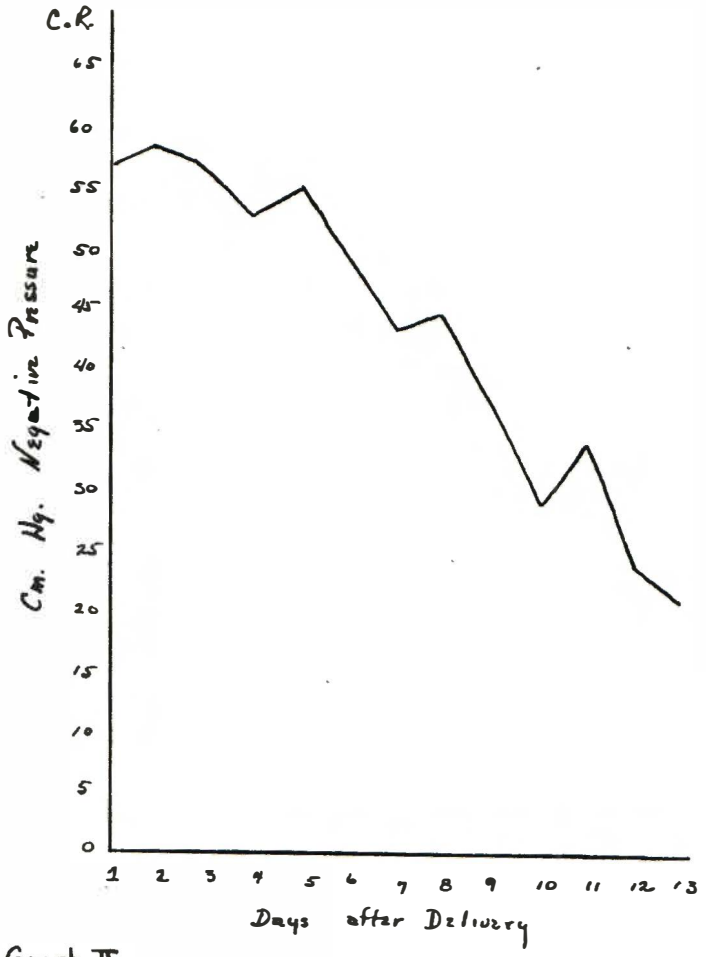
Determination of capillary resistance on 48 apparently healthy newborn infants resulted in a rather

uniform pattern. Graph I demonstrates all individual readings plotted against capillary resistance and days after delivery.



Graph I.

Graph II gives the average of all readings.

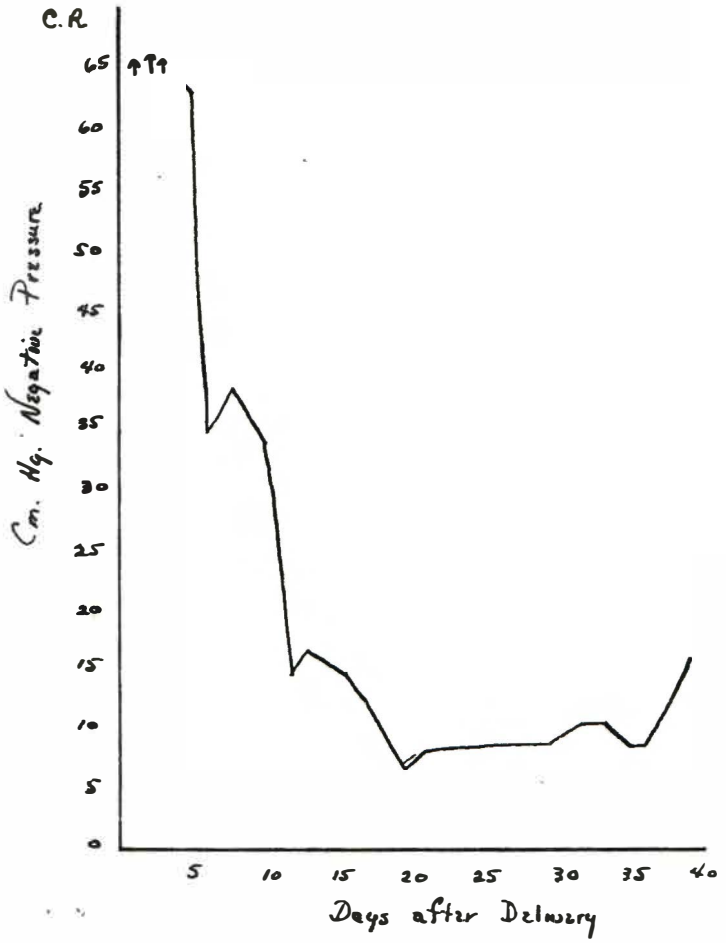


Graph II.

The significant feature is that there is an extremely high level of capillary resistance in the immediate post natal period. There is a slight rise on the first day reaching a peak on the second and third days and gradually decreasing from that time on. It must be remembered that the curve is actually somewhat

flattened because in a large number of cases, a negative pressure of 64 cm mercury did not produce petechia in the first few days and the actual pressure required to produce hemorrhage could not be determined.

Graph III shows a single case, representative of the course followed in all cases, which was observed over a longer period of time (39 days).



Graph III.

This demonstrates the tendency for the capillary resistance to continue decreasing to a level much lower than that seen at birth until about the 20th day and then remain stable for as long as the observations were made.

Several factors were studied to determine if they had any influence on the typical pattern or in the levels of capillary resistance.

Maturity: A very evident variation appears between term infants and prematures. While term infants (44 cases) reached the heighth of capillary resistance within the first 2-3 days and then began a gradual decrease, premature infants (4 cases) showed a definite lag before reaching a maximum resistance and the drop-off was more abrupt. Although the number of premature infants in this series is too small to be significantly compared with the term infants, reference to other author's studies indicate that capillary resistance in prematures is considerably lower than in mature infants of the first day. However, when the peak is reached it is comparable with that of the term infants.

Sex: Female infants consistently showed a higher capillary resistance than males, although the difference was not great. The reason for this is not obvious at this time although is thought that it may be on the basis of hormonal influence from the mother.

in the normal vertex deliveries, and account for 29 cases. Abnormal deliveries included version and breech extraction, precipitate breech delivery, rotation by forceps and manually, and Caesarian section. There was essentially no significant variation due to the type of delivery, with the exception of the Caesarian section which was mentioned previously.

Anesthetic: An attempt was made to determine if the type of anesthetic given to the mother could be expected to have any influence on the infant's response. General inhalation anesthesia using ether, cyclopropane, Trimar, or a conbination of these, saddle block, pudendal block, or no anesthesia were compared. It was found these factors had no effect on the capillary resistance of the infant.

Vitamin K: Minkowski (11) noted that Vitamin K given to the mother during labor had no action in preventing hemorrhage in the newborn. In fact, meningeal bleeding in the newborn was found to be more frequent in those whose mothers were given Vitamin K (12). No significant difference could be found in this series when comparison was made between the infants whose mothers received Synkamin prior to delivery and those whose mothers did not.

Age and parity of the mother: The age range of the mothers was 14 years to 37 years. The infant tested was the first born for 16 mothers, 3 mothers had had one previous children, 11 mothers had had 2 previous children, and 18 mothers had born 3 or more children before. Age and parity did not appear to alter the response of capillaries of their children.

Infant feeding: No difference in capillary resistance was noted when babies who were breast fed and those who received stock nursery formulas were compared.

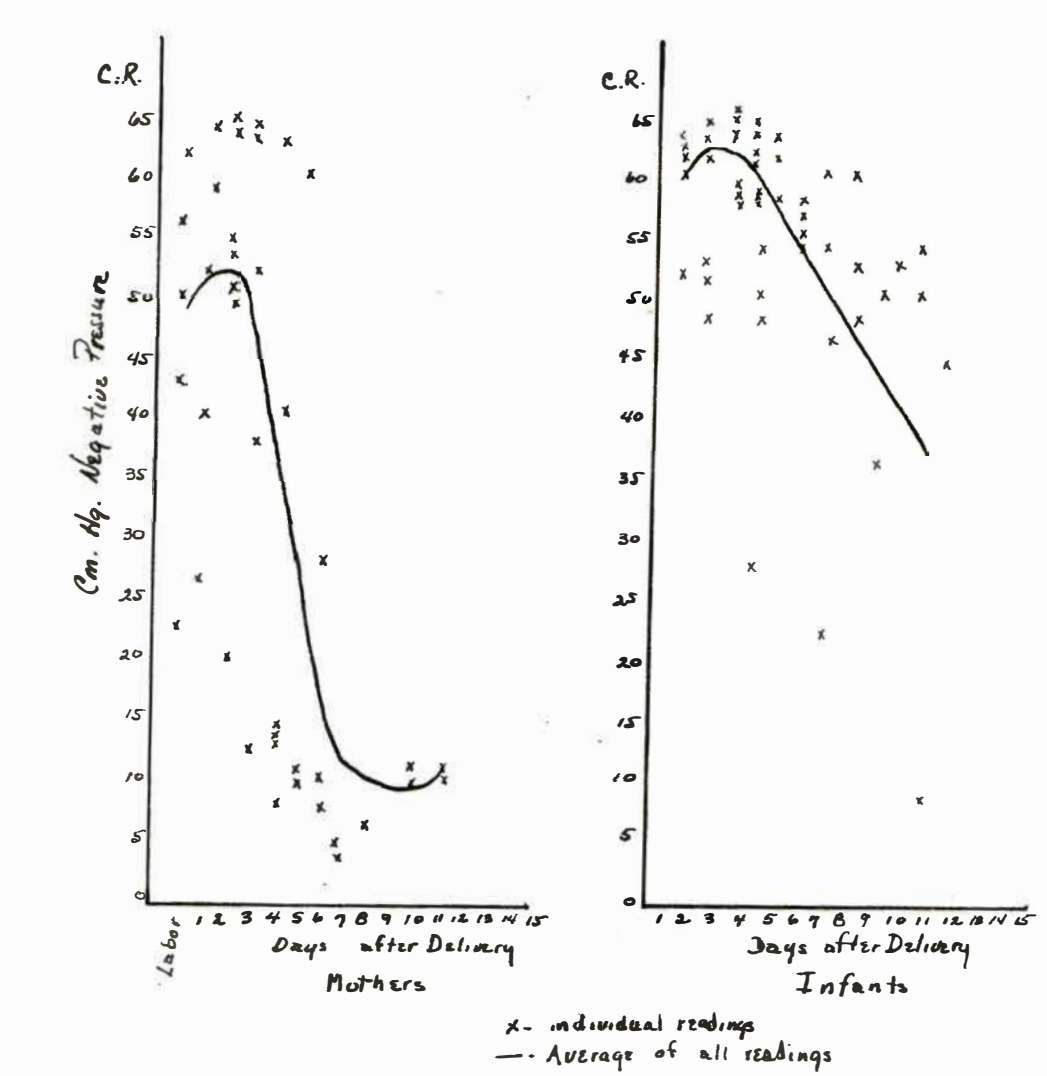
Neonatal complications: All the infants in this series were considered to be normal, that is, there was no gross pathology or serious illness. However, a small number showed minor variations from normal. The variations included jaundice, sluggish response after birth, telangectasia and ecchymosis. The jaundice in all cases were judged to be physiological in nature. The infants who responded sluggishly at time of delivery had no further difficulty as long as they were followed in the hospital. In one infant in whom small teleangiectasia appeared on the face on the fifth day, it was noted that there was no alteration in the capillary resistance from the normal. Scarborough (13) reported that the presence of al little as 4 cc. of extra vascular blood in the tissues or alimentary tract

markedly increased the capillary resistance for several days. For this reason, an infant with a large ecchymotic area around the eye was included in this series. This one case, of course, neither agrees with or refutes his theory, but it was interesting to note that this infants level of capillary resistance falls within the group of prematures with lower readings rather than showing the effect of extra vascular bleeding.

Since it was impossible to follow all these infants over a long enough period of time to see if the level of capillary resistance would remain low in comparison to that immediately following delivery, 41 individual readings were taken on infants from 2 weeks to 13 weeks of age. It was found that with only a few exceptions the capillary resistance was far below the average obtained in the newborn period. The readings ranged from 6 to 52 with the average being 24 cm. mercury negative pressure. The distribution was as follows:

Cm. mercury	No. cases	
6-12	12	
13-18	5	
19-24	6	24 cm. Hg. average
25-30		
31-36		
37-42	7	
Over 42	2	

The results of the comparative study made on mothers and infants are given in Graph IV.

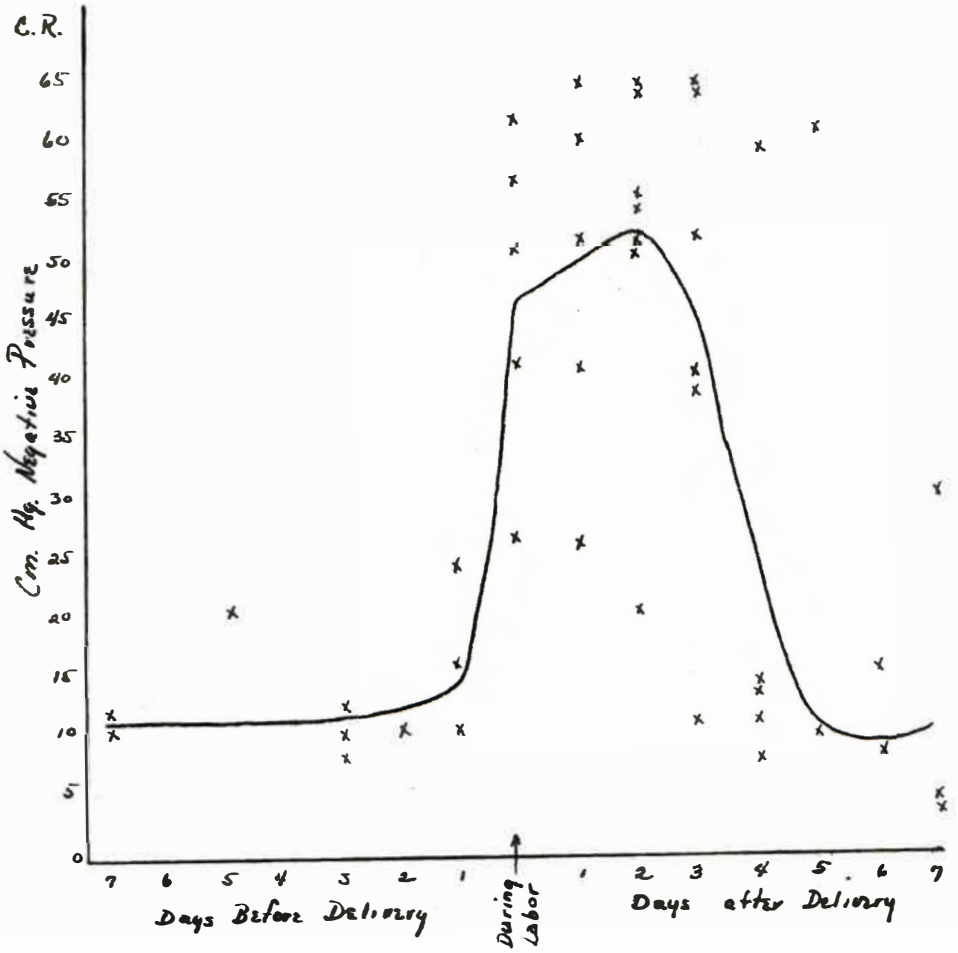


Graph IV.

There is again a definite pattern in both mothers and babies. Both have high capillary values the day after delivery. There was, however, a difference in the decrease of the capillary resistance thereafter.

Whereas all the mothers' resistances dropped to normal or subnormal between the fifth and tenth day, that of the infants still remained high at this time.

Graph V gives us information on our observations on the mothers that we were able to follow about one week prior to delivery and following delivery.



Graph V.

This graph clearly indicates that the rise in

capillary resistance sets in only after the onset of labor.

A comparison of the values of capillary resistance of the individual mothers with that of their babies shows no significant correlation. In six

Table 1

No.		Del Day	1	2	3	4	5	6	7	Relation
17	M	62	64	64	64	58				High
	I			48	58	64	62			High
15	M	56	59	64	64		60			High
	I		62	64	64		58			High
26	M	50	52	54	52	14				High
	I		52	62	64	62				High
28	M	22	26		12		10			Low
	I		62		64	64	64			High
46	M			50		14		16		High
	I			52		54		58		High
48	M		40			12		10		Low
	I		60			62		54		High
50	M			20				10		Low
	I			62		50			56	High
51	M			54		40			28	High
	I			62		48			22	High
52	M			50		8			4	High
	I			52		28			46	High

cases the capillary resistance was high in both mother and child, and in three cases the babies' resistance was high while that of the mothers' was low, even below the average of normal persons.

DISCUSSION

That there is a uniform change in the function of the pituitary-adrenal axis following delivery is clearly shown by the uniform pattern of capillary resistance in newborns. The increased capillary resistance during the first days indicates that there is an increased concentration of cortisone present. A gradual decrease in concentration of cortisone through depletion or unresponsiveness of the adrenal cortex is shown by the gradual decrease in capillary resistance. The final average situation that prevails throughout infancy is reached at about three to four weeks.

The uniform behavior of the mother's capillary resistance indicates that there is an increased production of cortisone with the onset of labor. This is followed by a rapid drop after three to four days to the levels found before labor begins.

The situation of the mother is quite clear and is readily explained by Selye's stress theory. Systemic stress (in this case, delivery) stimulates an increased discharge of ACTH which in turn causes hyperfunction of the adrenal cortex as indicated by the response of the capillary resistance. However the findings in the newborn can be interpreted in

several ways. The first possibility is that the stimulus of birth may elicit an active production of cortisone by the infant's adrenal cortex. A second possibility is that the excess of cortisone produced by the mother at the onset of labor is transferred to her infant before delivery and the high capillary resistance found at birth in the newborn is merely a passive response to increased cortisone concentration. A still further possibility is that a combination of these two may be present.

Investigation by several authors gives a basis for the belief that the adrenal cortex is capable of functioning at birth and that cortisone is actively produced at birth.

Developmentally, the adrenal cortex becomes the most advanced structure of either the thoracic or abdominal cavity during the first four and one-half months of pregnancy. The outer cortex is composed of small cells which, after birth, form the definitive cortex. The inner provisional or fetal cortex is made up of large cells separated into cords one cell thick by endothelium-lined vascular channels. As long as the fetus remains in the uterus, the provisional cortex continues to grow. At birth the adrenal cortex is quite large in proportion to the total body weight

in comparison to its size from one month on. Within the first few days after birth the cells in the provisional cortex become pale and vacuolated and gradually disappear, causing a general shrinkage of the gland(14). The hypertrophy and extreme vascularity of the fetal adrenal gland suggests that endocrine production is possible; however, it has not been definitely proved as yet whether androgen or cortisone is produced. If it is assumed that cortisone is produced actively by the cortex, the involution of the provisional cortex after birth would lead to a gradual diminution of cortisone concentration. The gradual decrease in capillary resistance that is seen in the newborn infant is the normal "physiologic" decrease which could be expected after increased activity of the gland had ceased.

It is known that the fetus manufactures its own corticoids as early as the third month. Gravid patients with Addison's disease appeared to improve during the latter months of pregnancy, but in the post partum period, the symptoms returned, and in most cases were more severe(15). Animals adrenalectomized in the last stages of pregnancy showed no deleterious effects after the operation (16), and the adrenal glands of the fetus were found to be larger than

normal (17). However, these findings are complicated by the fact that the placenta produces large amounts of corticoids quite independently of any reaction to stress (18). It may be that the remission of symptoms in these patients with surgical or pathologic adrenalectomy may be due to the corticoids produced by the placenta rather than to increased adrenal activity of of the fetus, although the increase in the size of the fetal glands would indicate that they are producing the corticoids.

In newborns, Wolman (19) studied the urinary excretion of adrenal cortical metabolites and found that small amounts of 17-ketosteroids were present in the urine in the first few days of life and increased significantly in the second week. Day (20) reports values of 0.13 - 3.25 micrograms in 24 hours in 12 newborns.

Jailer, Wong and Engle (21) also suggest that the pituitary-adrenal axis is capable of normal function on the first day. They administered epinephrine to newborns and measured the results with the eosinophile response. They found, however, that prematures do not respond before the ninth day. In general, the less the birth weight, the greater the interval before the result of epinephrine becomes positive. This finding

is compatible with our observations; newborn premature infants had a delay of several days before reaching the maximum levels of capillary resistance. Using ACTH as a stimulus, Wolman gave daily injections to newborns and followed the course of the response by fluctuations in the eosinophile count. He also found that the majority of term infants responded on the first or second day with a decrease in circulating eosinophiles and that prematures respond a few days later in proportion to their birth weight.

Another point in favor of active production by the newborn is suggested by the results obtained in comparison of mothers with their infants (Table 1). Unfortunately, the number of cases is too small to allow a definite conclusion to be drawn. It will be observed that in three of the cases, the infants have a high capillary resistance at birth while the resistance of the mothers is comparatively lower. It does not appear that the mothers in these cases have produced enough cortisone to raise their capillary resistance and therefore could not have had an excess to transfer to their babies. In this event, the infant in order to show the typical behavior of capillary resistance would have to produce its own cortisone.

The observations of our series and the findings of other authors point to the conclusion that active production of cortisone by the newborn infant is possible.

There are several points in favor of a transfer of cortisone from the mother to her baby at the time of delivery.

It is well known that estrogens are transferred from the mother to her infant. The enlargement of the breasts and uterine enlargement with menstrual-type bleeding in the newborn are evidences of the withdrawl of the estrogen at the time of birth. If estrogens are able to pass the placental barrier, it seems logical to believe that cortisone can also be transferred.

The precipitous drop of capillary resistance occurring three to four days after delivery in the mother in contrast to the gradual decrease which would be expected if activity of the gland had ceased suggests that there is a "drainage" phenomenon present.

Venning (22) investigated the adrenal response during the neonatal period using as criteria, the excretion of cortical and 17-keto-steroids, changes in the uric acid ratio, and eosinophile fall. The urinary corticoid output during the first three days of life

was found to be on the average 0.71mgm. A definite increase was found by the fourth week. When ACTH was administered an increase in urinary corticoids during the second day of life was found, but this increase was not as marked as when the hormone was readministered after the ninth day of life. Also there was a decrease in eosinophiles noted on the second day but there was a lag in the response. She suggests that the reason for this sluggish response is that the adrenal might not be capable of responding to stress at this time. Racher (23) believes that the cause of this non-response of the cortex is that the infant had been subjected to stress during the intra-uterine period and in the neonatal period is in the adaptive phase and is not able to respond to further ACTH stimulation.

Considering that the cortex may be unable to respond because of immaturity or because of depletion, the high capillary resistance found in the newborns at birth may be on the basis of transfer of cortisone to the infant from the mother.

There is a third possibility that a combination of these two mechanisms may be responsible for the behavior of the infant after birth. The mother responds to the onset of labor with an increased production of ACTH

and cortisone. It seems quite possible that this excess of ACTH and cortisone could be transferred to the infant before delivery. Evidence points to the belief that the term newborn infant is capable of producing its own corticoids. The rise in capillary resistance would then be an indication of both an active production of cortisone by the mature adrenal cortex of the infant in response to stress and an increased concentration of cortisone transferred from the mother.

In further support of this theory is the behavior of the premature infants. Their capillary resistance is high at the time of birth, but lower than term infants, and there is a definite lag up to five or six days before the peak of resistance is reached. A delayed response is also seen in reaction to epinephrine and ACTH administration. Anatomically, the adrenal gland is smaller in premature infants than in mature infants. The cortisone derived for the mother would account for the initial high level of capillary resistance. The peak is then reached after the adrenal cortex has developed in maturity to the point where it can produce its own corticoids in response to the stress of birth.

SUMMARY

We have seen that birth and delivery behave as a stress by the response of the capillary resistance. How the response of the newborn is to be interpreted is debatable. The possibilities arise that either the infant actively produces adrenal corticoids in response to the stimulation of the stress of birth or that the objective findings observed following birth are due to a passive response to cortisone transferred from the mother to the infant at the time of delivery.

Evidence has been presented which indicates that either of these theories is plausable. The infant's cortex is apparently capable of responding to several types of exogenous experimental stimuli and is developmentally mature at the time of birth. However, it is suggested that since the mother shows such a precipitous drop of capillary resistance within a few days following delivery she may have transferred her excess cortisone to her baby.

That these two mechanisms are together responsible seems to be the most logical answer to the problem. It is known that estrogens can pass the placental barrier; therefore, it can be assumed that cortisone can effect the same transfer. This fact, together with the knowledge that the neonatal cortex is capable of response

to stimuli suggest that the mother transfers cortisone produced during labor to her child and that the infant also actively produces cortisone in response to the stress of birth. The increased capillary resistance observed, then, would be due to a combination of both factors. Further investigation is necessary before a definite conclusion can be drawn.

CONCLUSION

It was felt that if systemic stimuli could elicit the alarm reaction, delivery and birth would act as a similar stress and provoke a typical pattern which could be correlated with Selye's alarm reaction and General Adaptation Syndrome. With this purpose in mind, the capillary resistance in 48 newborns following delivery and throughout the first week of life was studied. Several infants were followed for longer periods. Fourteen mothers were tested prior to and after delivery to detect any relationship between the mother's and the infant's capillary resistance. Forty one infants between the ages of two and fourteen weeks were used as controls. It was found that there is a v very high capillary resistance in newborns in the first week of the neonatal period with gradually decreasing resistance reaching a low level within three to four weeks which remains comparatively stable throughout infancy. The mothers show a low capillary resistance during the latter periods of pregnancy and an increase with the onset of labor continuing after delivery until the fourth or fifth day when there is a precipitous drop to antepartum levels. The response of the mother is explained as a response to the stress of delivery. The interpretation of the infants response

is found to be controversial. The response of the capillary resistance may be due to either an active production of cortisone by the infant's adrenal cortex in response to birth stress or to an increased cortisone concentration present from a transfer of the mother's excess cortisone to her infant. It is suggested that the basic mechanism may be a combination of the two.

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