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# FREE BLOOD CORTICOIDS IN THE NEWBORN INFANT<sup>1</sup>

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Infants in the first week of life respond to ACTH administration with a smaller fall in circulating eosinophils and a smaller increase in urinary corticosteroids than these same or other infants do when they are older (1, 2). Since these findings seem to validate the suggestions that certain infants suffer from transient adrenal failure and that others are unable to withstand the stress of surgery in the newborn period because of a lack of adrenal cortical hormones (3, 4), the logical inference is that these infants should be treated with adrenal cortical hormones. The administration of these hormones to infants is dangerous. In this period particularly, in addition to all the potential dangers they possess in older children and adults, they inhibit growth, increase susceptibility to infection, and are associated with a high mortality (5, 6).

It is important, therefore, that two questions be answered. Do newborn infants have a period of transient adrenal hypofunction and if so, does this have any clinical significance? This study attempts to answer the first question.

Up to this time the evidence that the newborn infant has a period of depressed adrenal function for approximately a week has been indirect. Corticosteroid excretion is affected by urinary clearance rates and methods and rates of hormonal degradation, etc. Recently, Bergstrand, Hillström, and Jonsson have challenged the validity of the eosinophil measurements as evidence (7). The present study was undertaken to make direct measurements of adrenal corticoids in the serum of normal newborn infants.

## MATERIALS AND METHODS

The method of Nelson and Samuels for measuring blood 17 hydroxycorticoids utilizing florisol as the chromato-

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graphic agent was used throughout (8)<sup>3</sup>. The only change in the method as published was the use of serum instead of plasma for most of the measurements in the present study. The serum or plasma of 41 children and adults considered normal for the purpose of this study was analyzed for control measurements. The ages of these subjects ranged from 3 weeks to 32 years. The group included 13 infants under one year of age. The adults were laboratory workers in apparent health. The children either were in the hospital for elective surgery, for the investigation of chronic neurologic disorders or behavior problems, or had recovered from minor respiratory infections. Fourteen specimens obtained from newborn infants from two days to five days of age were analyzed. The deliveries of these infants were normal, and the infants were considered healthy by the examining pediatricians. Since the method requires 10 ml. of serum or plasma, it was necessary to pool sera from two infants in eight instances. In addition, serum was obtained from each of six children with erythroblastosis fetalis before exchange transfusion was carried out. One specimen of 10 ml. of serum was obtained from a seven-day old normal newborn infant. Sera were also obtained from 23 cord bloods of normal children born of normal deliveries.

## RESULTS

The mean level of circulating compound F-like substance in the blood of normal children and adults was 13 micrograms per 100 milliliters of serum. The standard error of the mean was  $\pm 1.21$ . This agrees with the mean of 13  $\mu\text{g}$ . per 100 ml. reported by Nelson for normal adults and by Kelley and Ely for normal children (9). There was no discernible difference in the various age groups within this overall group of 41 normal individuals, 3 weeks to 32 years of age. Figure 1 graphically shows the results found in the control subjects, the cord bloods and the normal newborn infants. The mean level in the 23 cord bloods was 21.4 micrograms per 100 milliliters of serum. If the two unusually high results of 100 and 57 micrograms per cent are excluded, the mean level is 16.0. In any event, these results are not significantly different from those found in the normal

<sup>3</sup> Standard compound F was kindly supplied by Dr. W. J. Haines, Upjohn Company.

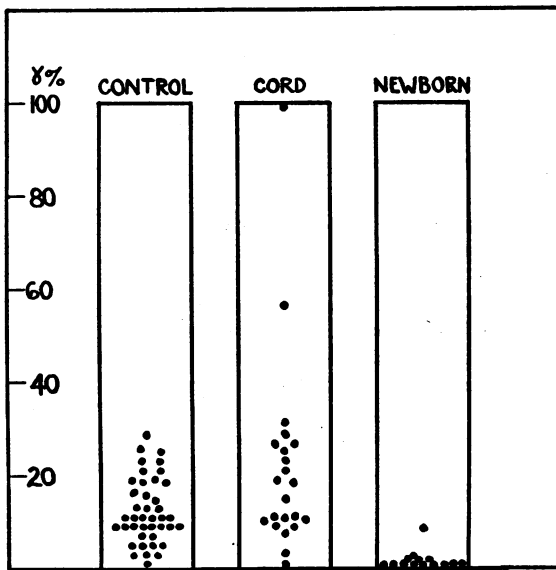


FIG. 1. FREE CORTICOIDS IN SERA OF 41 NORMAL CHILDREN AND ADULTS, THREE WEEKS TO 32 YEARS OF AGE: 23 CORD BLOOD OBTAINED FROM NORMAL INFANTS BORN OF NORMAL DELIVERIES: 14 NORMAL NEWBORN INFANTS TWO TO FIVE DAYS OF AGE

control subjects. The mean level found in the 14 normal infants was 0.9 with a standard error of the mean of  $\pm 0.6$ . As may be seen by inspection there is only one level above 2 micrograms per cent. Actually any level below 2 micrograms per cent probably should be considered a zero measurement (10). The one specimen obtained from a one week old child contained 15 micrograms per 100 milliliters of serum. The results obtained from six patients with erythroblastosis were as follows: 16, 12, 2.5, 1, 0, 0 micrograms per 100 milliliters. The age and weight of these patients are shown in Table I. Acid hydrolysis of the sera from four normal newborn infants showed no sig-

TABLE I

Age, sex, birth weight, and level of free serum compound F of six children with erythroblastosis fetalis before exchange transfusions

Pt.	Sex	Age	Birth wt.	"F"
		Hrs.	Kg.	%
TH	M	12	2.80	12.0
JA	F	30	2.95	15.9
JO	M	4	2.95	0
HA	M	23	2.60	1.0
WI	M	8	3.15	0
BA	F	5	2.60	2.5

nificant increase in the amount of compound F-like substance measurable.

#### DISCUSSION

The uniform finding of absent or very small amounts of compound F-like substance in the serum of normal newborn children bears out previous indirect evidence of a period of lowered adrenal function in the newborn period. The normal levels in the cord blood samples probably represent maternal hormone. The more variable results obtained from the sera of children with erythroblastosis were to be expected and presumably represent different rates of degradation or excretion of the maternal hormone. It was surprising to the authors that so many low levels were obtained so soon. The obvious difficulties in obtaining specimens have made it impossible to determine the time at which the average newborn infant first has a normal circulating level of free 17 hydroxycorticoids but from previous indirect evidence it might be assumed that this would happen sometime in the second week of life.

Jailer has shown that the newborn rat pituitary produces very little ACTH (11). ACTH increased in the newborn rat pituitary with the passage of time and simultaneously with this the adrenal becomes more responsive.

The excretion of 17-ketosteroids in the urine of the normal newborn infant is high in the first day or two and then gradually drops to the low levels of later infancy (12). Gardner has shown similar changes in blood ketosteroids (13).

From the work of Gardner, the present work and the urinary excretion studies it is apparent that maternal steroids are passed to the fetus and that these rapidly disappear in the neonatal period. This fact coupled with the logical inferences from Jailer's work would seem to strengthen the original hypothesis advanced by one of the authors in 1950 that the period of lowered adrenal responsiveness in the newborn is due to suppression of pituitary production of ACTH by the excess maternal corticoids passed transplacentally (1).

It must be emphasized, however, that it has not been demonstrated, as yet, that this period of relative adrenal hypofunction does the child any harm. The hypofunction is relative and the adrenal can respond to sufficient stimulus (2, 3).

## SUMMARY

Sera have been analyzed for free compound F-like material from normal infants and adults, from cord bloods from normal children born of normal deliveries, from 14 normal newborn infants and from five infants in the first day of life with erythroblastosis. It has been shown that the normal newborn infant from two to five days of age has a significantly lower level of circulating free compound F-like substance than have normals from the age of three weeks to 32 years. Indeed most of the newborn infants have no measurable levels. Cord bloods have amounts of free compound F-like substances that approximate the amount circulating in normal adults. The levels obtained from children with erythroblastosis in the first day of life vary greatly and are intermediate between the values found in cord bloods and in normal newborns of two to five days of age.

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