Adrenocortical Response to Stress in Newborn Infants

D. METHVEN CATHRO,* CONSTANCE C. FORSYTH,† and JENNY CAMERON

From the Department of Child Health, University of Dundee

More than half of the deaths occurring under the age of 12 years take place during the first week of life, and the term 'biochemical death' is sometimes used where an adequate pathological explanation cannot be found at necropsy. Following the pioneer work of Selye (1936), which drew attention to the prominent role of the adrenal cortex in the endocrine response to stress, it became established that an increased secretion of corticosteroids occurred in adults under conditions of stress, and that, in some unknown manner, such hormonal activity was essential to the well-being and even to the survival of the subjects in such circumstances.

In paediatric circles, however, it was thought that the adrenocortical response to stress might be relatively deficient in newborn infants, and Bongiovanni (1951) cited several publications which suggested that the excretion of corticosteroids, measured by methods then available, was lower during the first few days of life than at any other age, if the results were compared on the basis of excretion per unit of surface area.

Measurement of corticosteroid excretion in newborn infants by group methods of assay in instances of acute stress has given inconsistent results. Ulstrom and his colleagues (Ulstrom *et al.*, 1959; Colle *et al.*, 1960) found that the urinary excretion of Porter-Silber chromogens by infants undergoing surgery during the first 4 days of life showed no significant increase over the excretion of these compounds in normal controls, though there was a marked increase in the excretion of 17-hydroxycorticosteroids measured in this way when infants were subjected to surgery during the second week of life. Studies of plasma corticosteroids measured as Porter-Silber chromogens by Klein, Fortunato, and Papadatos (1954) showed that the normal newborn infant from the second to the fifth

day of life had a lower level of Porter-Silber chromogens than normal subjects aged 3 weeks to 32 years.

In contrast, Venning, Randall, and Gyorgy (1949) found that premature infants with atelectasis and respiratory embarrassment born to diabetic mothers excreted greater quantities of glucocorticoids than did healthy premature infants. The difference was attributed to the respiratory distress, though the maternal diabetes may have been a factor (Cathro and Forsyth, 1965). Hillman (1961) estimated the Porter-Silber chromogens in the urine of infants born to women with no endocrine disease and found that the urinary excretion of these compounds during the first 3 days of life was, on average, twice as high in infants with the respiratory distress syndrome as it was in normal controls. However, when the position was reviewed in 1963, Bongiovanni considered that it had not yet been ascertained whether a brief period of relative adrenocortical insufficiency occurred about the second or third day of life.

Some of the doubt regarding the adequacy of suprarenal function had arisen from knowledge of the anatomy of the adrenal glands at birth and immediately thereafter, since the large fetal cortex degenerates rapidly after birth, though the small adult cortex gradually increases in thickness. However, recent work has pointed to the fetal zone being concerned essentially with the elaboration of oestrogen precursor Δ^5 -steroids from pregnenolone supplied by the placenta, and it is believed that atrophy of the fetal zone results from the placental connexion being severed. After birth, only the adult zone of the adrenal cortex can synthesize biologically active Δ^4 -corticosteroids, as it possesses the essential Δ^5 - 3β -ol-dehydrogenase activity, whereas the fetal cortex does not. The adult cortex therefore must supply all the needs of the infant for the period of adaptation to extrauterine life. However, the high excretion of Δ^5 -steroids in the urine during the first week of life (Cathro *et al.*, 1963, 1965; Mitchell, 1967) is evidence that there is a relative insufficiency of Δ^5 - 3β -ol-dehydrogenase in the definitive cortex at this period, which does not exist

Received July 1, 1968.

* Present address: INSERM Unité de Recherches Hôpital Debrousse, 29 Chemin Soeur Bouvier, Lyon 5e, France.

† Requests for reprints should be sent to Dr. Constance C. Forsyth, Department of Child Health, University of Dundee, 11 Dudhope Terrace, Dundee. For those interested, data of steroid excretion by individual subjects are available.

in later life. On theoretical grounds, therefore, because of enzyme immaturity, the adrenal glands in the newborn infant might fail to provide as adequate a reserve of function under conditions of stress as is shown by adults.

Materials and Methods

In 1958, we undertook a study of the urinary excretion of adrenal steroids in 31 male full-term infants and 13 male premature infants, to determine the adrenal response to stress in the newborn period. In 1966, the work was extended to include 18 male dysmature or 'light-for-dates' infants. Complete 24-hour urine samples were collected on the first, second, third, and sixth days of life. Infants were classified as full-term and premature according to well-recognized definitions, but no dysmature infants were included in either of these two groups. The premature group, therefore, was truly immature in that the infants were all of expected weight for the period of gestation. For the dysmature group we used the criteria of Crosse (1957) and Gruenwald (1964).

In Fig. 1 the distribution of the birthweights of the dysmature infants is compared with the data of these authors. Using the Gruenwald criteria, 7 were between 1 and 2 SD below the expected weight for gestational age, and 11 were more than 2 SD below.

Infants were classified as normal or stressed according to the clinical course. The normal ones behaved as healthy infants. The stressed full-term infants included those with asphyxia before or during birth, and also those suffering from Rhesus incompatibility requiring exchange transfusion. The premature and dysmature infants classified as stressed suffered from asphyxia before and during birth or from the respiratory distress syndrome. Death occurred in 1 of the 12 stressed full-term infants, in 1 of the 5 stressed premature infants, and in 3 of the 9 stressed dysmature infants.

Originally, block assay techniques were applied to the urine, but they were found to be unsatisfactory, and paper chromatography as described by Bush and Willoughby (1957) and Bush and Mahesh (1959) was adopted to measure the individual steroids. Considerable modification of Bush's method for adult urine was required before good results were obtained with infant urine. In the method finally adopted (Birchall *et al.*, 1961, 1963), the neutral steroids are extracted from urine after enzyme hydrolysis designed to release both glucuronides and sulphates. It was soon found that the pattern of steroid excretion in newborn infants was quite different from that in adults, and this was reported by Cathro *et al.* (1963, 1965). The present report is concerned only with the corticosteroid fraction as separated by Bush preliminary chromatograms. The individual steroids reducing blue tetrazolium and those giving sodium fluorescence were measured, and the results, expressed as total blue tetrazolium-reducing steroids and as total sodium-fluorescent steroids, were obtained by adding together the quantities of the various individual steroids giving these reactions. Of the blue tetrazolium-reducing

FIG. 1.—Distribution of dysmature infants.

steroids, tetrahydrocortisol and tetrahydrocortisone were found in small amounts. Other reducing steroids included very polar compounds believed to be 6 β -hydroxylated corticosteroids, while compounds apparently preserving the Δ^5 structure of biosynthetic intermediates were also measured in considerable quantities. The steroids giving sodium fluorescence were thought to include 6 β -hydroxycortisol, 6 β -hydroxycorticosterone, cortisol, cortisone, and corticosterone.

Results

From current information on suprarenal metabolism in the newborn period, we think it a reasonable supposition that the blue tetrazolium-reducing and sodium-fluorescent steroids, known and unknown, measured by our method, are largely derived from the infant adrenal glands and are likely to reflect their secretory activity. We have found that the possible contribution from the maternal adrenal glands or the placenta has not been sufficient to lead to an over-all reduction in the excretion of these steroids by healthy infants on the sixth day of life, compared with the excretion on the first three days, suggesting that they are chiefly of infant and not maternal origin. Furthermore, unpublished studies have shown no correlation between the excretion of corticosteroids by infants and by their mothers in the 24 hours after delivery (Cathro, 1964).

Fig. 2 gives an over-all picture of the average excretion on days 1, 2, and 3 of the total blue tetrazolium-reducing steroids plotted against the birthweight. The dysmature and premature infants excreted a quantity of steroid falling within the wide normal range for full-term infants, though not unexpectedly the majority of healthy small infants

TABLE
Steroid Excretion

Steroid Assay	Day(s)	Full-term Normal		Full-term Stressed		Premature
		Mean	Range	Mean	Range	Mean
Total blue tetrazolium reducing steroids ..	Average of days 1, 2, 3	386	121-651	641	295-1131	387
Total sodium fluorescent steroids ..	Day 6	322	118-665	523	353-881	426
	Average of days 1, 2, 3	56	19-114	70	41-131	50
	Day 6	51	14-154	79	25-138	43
Cortisol	Average of days 1, 2, 3	7.9	1.2-20.7	6.9	1.5-14.8	5.2
Cortisone	Average of days 1, 2, 3	8.3	2.2-25.0	10.5	4.4-22.0	9.1
Corticosterone	Average of days 1, 2, 3	17.0	3.9-52.3	22.7	10.4-42.6	8.4

gave values in the lower part of the normal range.

Fig. 3 resembles Fig. 2, but here the results are plotted against gestational age. Infants born before term show a steroid excretion falling within the range shown by those born at or near term.

In order to compare the results in infants of low and normal birthweight, we decided to express the excretion in $\mu\text{g./kg.}$ birthweight per 24 hours. The mean excretion and the range of excretion are given numerically in the Table in the Appendix.

Fig. 4 illustrates the tendency towards a higher excretion of blue tetrazolium-reducing steroids in response to stress during the first 3 days of life in full-term and in premature infants. The response is less definite in the dysmature group. Certain stressed infants of all categories show low or normal values.

Fig. 5 shows that on the sixth day of life the tendency to a higher excretion in stressed infants is still apparent, but by that day the number of

FIG. 2.—Average excretion of total blue tetrazolium-reducing steroids on days 1, 2, and 3 related to birthweight.

FIG. 3.—Average excretion of total blue tetrazolium-reducing steroids on days 1, 2, and 3, related to period of gestation.

($\mu\text{g.}/\text{kg. per 24 hr.}$)

Normal		Premature Stressed		Dysmature Normal		Dysmature Stressed	
Range	Mean	Range	Mean	Range	Mean	Range	Mean
204-544	818	343-1195	429	187-1205	444	154-676	
207-766	789	626-952	366	156-509	762	232-1370	
16-93	99	34-195	55	15-107	72	16-143	
16-86	82	74-89	45	26-61	54	13-84	
1.7-11.2	12.9	2.7-22.5	4.7	1.1-9.5	9.5	1.5-26.0	
1.9-29.0	17.9	3.8-66.6	7.8	1.4-19.5	17.8	2.9-46.7	
1.6-18.2	14.9	9.5-22.8	17.6	2.5-49.1	15.6	4.1-33.0	

stressed infants was small, as some had died while others had fully recovered clinically and were therefore classified as normal. The distribution of the results from stressed dysmature infants is of particular interest in that one of these infants gave the lowest value recorded from any stressed infant on this day, though 3 showed a high excretion.

Fig. 6 shows that there is a tendency for an increased excretion of sodium-fluorescent steroids in stressed infants during the first 3 days of life, but the rise is less obvious than with the blue tetrazolium-reducing steroids.

On the sixth day also the average value for the excretion of sodium-fluorescent steroids by stressed infants is higher, though, in parallel with the results for the first 3 days, the difference is less definite than with the blue tetrazolium-reducing steroids (Fig. 7).

The results for urinary cortisol alone are given in Fig. 8, and a rise in some stressed infants of the premature and dysmature group is seen, though no rise is apparent in the stressed full-term infants. This may be because the enzyme system for the conversion of cortisol to tetrahydro-derivatives is more active in full-term than in premature infants.

FIG. 4.—Average excretion of total blue tetrazolium-reducing steroids on days 1, 2, and 3 related to type of infant.

FIG. 5.—Excretion of total blue tetrazolium-reducing steroids on day 6.

FIG. 6.—Average excretion of total sodium-fluorescent steroids on days 1, 2, and 3.

FIG. 7.—Excretion of total sodium-fluorescent steroids on day 6.

Fig. 9 shows that certain infants show a rise in cortisone excretion in response to stress.

Fig. 10 illustrates that several full-term infants show a rise in corticosterone excretion in response to stress, and 2 premature and 2 dysmature infants also show high readings. It might be emphasized

at this point that in full-term normal infants the excretion of corticosterone as estimated by our method, which measures urinary corticosterone sulphate as well as the free steroid, was double that of cortisol or cortisone, suggesting a greater relative importance of corticosterone or of corticosterone

FIG. 8.—Average excretion of urinary cortisol on days 1, 2, and 3.

FIG. 9.—Average excretion of urinary cortisone on days 1, 2, and 3.

FIG. 10.—Average excretion of urinary corticosterone on days 1, 2, and 3.

sulphate in the steroid metabolism of the newborn infant than in the older child or adult.

Discussion

It is well recognized in the older child or the adult that the urinary excretion of unmetabolized 'cortisol' is a much better guide to adrenocortical production of cortisol than is the urinary excretion of cortisol metabolites as measured by block assays. The present study shows that measurement of cortisol excretion by our method is not a satisfactory guide to adrenocortical activity in the newborn infant, and the same applies to measurement of the other primary steroids that are excreted in urine, namely cortisone and corticosterone. However, the quantities of these three steroids excreted by newborn infants were small, and it is not surprising that measurement of the total sodium-fluorescent steroid excretion has given a clearer picture of the adrenocortical response to stress.

The blue tetrazolium-reducing steroids gave the best indication that stress provoked an increased excretion of steroids in several infants in each of the three categories studied. These steroids are present in the urine of infants in approximately 8 times the quantity of the sodium-fluorescent steroids and the results are therefore less liable to error. In addition, by the nature of our method, the measurement of blue tetrazolium-reducing steroids is more accurate. Nevertheless, it has been our experience that the excretion levels of the two groups

of compounds in any one infant tend to be in parallel.

When the values for the excretion of blue tetrazolium-reducing steroids/kg. per 24 hours, averaged for the first 3 days of life, in full-term normal infants and clinically satisfactory premature and dysmature infants, were compared statistically, no difference between the groups was apparent. Likewise, results based on the measurement of sodium-fluorescent steroids did not show any statistically significant difference between the groups. The resting level of excretion in our series was thus of the same order in full-term, premature, and dysmature infants. Our work, therefore, does not support the concept of frank hypo-adrenocorticism in premature or dysmature infants compared to full-term infants.

When the results suggesting an increased output of blue tetrazolium-reducing steroids in the first 3 days of life in response to stress were submitted to statistical analysis by the *t*-test, the full-term group as a whole showed a response which was statistically significant, the probability of error being 0.001 or 1/1000. The response in the premature group was also statistically significant though less definitely so, the probability of error being 0.01 or 1/100. The response in the dysmature group was not statistically significant. From Fig. 4 it will be noted that one normal dysmature infant showed a very high output and as he became ill on the 4th day of life the figures were also submitted to analysis after classifying him as stressed, but the results again showed no significant difference for the dysmature group. Thus, the dysmature group of infants considered as a whole showed no significant response to stress during the first 3 days of life.

When the blue tetrazolium-reducing steroid output on the sixth day (Fig. 5) was submitted to statistical analysis, the stressed full-term group of infants showed a rise in excretion which was just statistically significant, the probability of error being 0.05 or 1/20. The number of premature infants studied on the sixth day was too small for statistical analysis; the dysmature group of infants showed no significant difference.

In summary, our results have shown that certain infants of the full-term, premature, and dysmature categories have shown an increased excretion of blue tetrazolium-reducing and sodium-fluorescent steroids in response to stress, but that other infants in all 3 categories have not. When the excretion of blue tetrazolium-reducing steroids has been considered in each group as a whole, the full-term group has shown a statistically significant response to stress on days 1, 2, and 3 and on day 6, and the

premature group has shown a statistically significant response on days 1, 2, and 3, the numbers on day 6 being too small for statistical analysis. The dysmature group has shown no statistically significant response to stress either on days 1, 2, and 3 or on day 6.

Measurement of cortisol production rates in newborn infants by other workers has supported the concept of adequate adrenocortical function in infants of normal birthweight born at term. Aarskog (1965) found a mean cortisol production rate of 22 mg./sq. m. per 24 hours in 5 full-term infants studied on the third day of life. For comparison, an approximate figure for the cortisol production rate in adult males is of the order of 13–14 mg./sq. m. per 24 hours (Dorfman and Ungar, 1965). Bertrand *et al.* (1963a, b) have also found the cortisol production rate of newborn infants to be above that of adults, their infant values averaging 22·2 mg./sq. m. per 24 hours in the first 5 days of life. Their level for 5 healthy subjects between the ages of 5 and 52 years was 12·4 mg./sq. m. per 24 hours. Similar results from a number of studies by Kenny, Malvaux, and Migeon (1963), Kenny, Preeyasombat, and Migeon (1966b), and Kenny *et al.* (1966a, 1966c) have also shown that newborn infants less than 5 days of age secrete more cortisol per sq. m. body surface than do older infants, children, or adults. It may be postulated that the raised cortisol production rate of healthy normal infants during the first few days of life signifies an adrenocortical response to normal adaptation to life.

The low birthweight infant, prematurely born, but of expected weight for gestational age, also appears to have a satisfactory cortisol production rate (Kenny *et al.*, 1963, 1966a, c), and recent work based on the urinary excretion of corticosteroids has suggested that the hypothalamo-hypophysial-adrenal axis of the premature infant can respond to metyrapone administration (Klein *et al.*, 1962).

No cortisol production rate studies have been carried out on full-term and premature newborn infants undergoing physical stress more severe than that imposed by an uneventful delivery and neonatal course. Our assessment of the capacity of the adrenal cortex to respond to pathological stresses in the first week of life provides evidence that the full-term and premature groups of infants show a response that is statistically significant, whereas the dysmature group does not.

The results in the group of dysmature infants are not unexpected on theoretical grounds. It is well established that the function of the fetal zone of the adrenal cortex *in utero* may be depressed in pre-eclamptic toxemia, and that the resultant low

oestriol excretion in the mother's urine provides an early indication of fetal deprivation. It is believed that the enzymes in the fetal zone of the adrenal cortex are particularly sensitive to oxygen lack, and this deficit may be rectified on delivery. These infants are also generally undernourished *in utero*. This is a further possible cause for underactivity of the fetal zone and, in all probability, for an associated hypofunction in the definitive or adult cortex, the zone required for the adaptation response after birth. It is tempting to postulate that those dysmature infants showing a response to postnatal stress have been less deprived than others in whom prolonged adrenocortical hypofunction *in utero* may have given rise to a situation in which the adrenocortical response to postnatal asphyxia or other stress may be suboptimal.

Recently, Kenny and Preeyasombat (1967) have published cortisol production rate studies on 8 dysmature infants, all of whom had symptomatic hypoglycaemia during the first 4 days of life. These workers found the cortisol production rate per kg. body weight to be more than 2 SD below the normal mean in 3 of the infants, between 1 and 2 SD below in a fourth, and significantly above the mean in only 1 infant. In our series of dysmature infants only 2 had symptomatic hypoglycaemia: 1 of these infants had the lowest steroid excretion of any stressed baby studied, while the other showed an above average steroid excretion.

In conclusion, our results indicate that there is no evidence of frank hypoadrenocorticism in premature and dysmature infants pursuing a normal clinical course compared to full-term infants. The majority of full-term and premature infants show an above average excretion of corticosteroids in response to stress. However, certain infants in all three categories may fail to show a response to a stressful situation, while the dysmature group of infants shows an inadequate response more frequently than the other two groups to the extent that, taking the group as a whole, there is no statistically significant response to stress.

In therapy, therefore, while physiological doses of cortisol of the order of 5–7½ mg. daily might occasionally be of value in situations of stress in full-term and premature infants, such therapy might be indicated more often in the management of dysmature infants whose response to stress is more likely to be suboptimal.

Summary

The excretion of individual corticosteroids in the urine of male newborn infants averaged for the first, second, and third days of life and for the sixth day

of life has been studied by the method described by Birchall *et al.* (1963). 31 full-term, 13 premature, and 18 dysmature infants have been included, and the results compared in those pursuing a normal clinical course and in those undergoing various types of stress. The steroids have been measured individually and then summed to give the total blue tetrazolium-reducing steroids and the total sodium-fluorescent steroids.

Results showed a wide range of steroid excretion by normal infants. Associated with stress, an increased steroid output was apparent in some infants of all 3 groups, indicating a response of the adrenal glands in the first few days of life. When the groups were considered as a whole, this response, measured in terms of the blue tetrazolium-reducing steroids, was statistically significant in the full-term and premature infants, but not in the dysmature infants.

This research programme has been supported by a grant from the Scottish Hospital Endowments Research Trust, and more recently by a grant from the Medical Research Council.

We wish to thank Dr. Kathleen Birchall and Dr. F. L. Mitchell, the biochemists concerned with the methodology; Professor J. L. Henderson and Dr. C. H. M. Walker for access to patients under their care; and the nursing staffs of the nurseries in the Maternity Units at Maryfield Hospital and at Dundee Royal Infirmary for their sustained co-operation. Technical assistance was provided by Miss G. F. Halley, Miss J. Peters, Miss M. Philp, Mr. I. Roberts, Mr. B. Mitchell, Miss A. Brand, and Mrs. M. Marnie. We are grateful to Mr. J. C. G. Pearson of the Department of Social and Occupational Medicine for advice on statistical analysis, and to Mr. R. Fawkes for photography.

REFERENCES

- Aarskog, D. (1965). Cortisol in the newborn infant. *Acta paediat. (Uppsala)*, suppl. 158.
- Bertrand, J., Loras, B., Gilly, R., and Cautenet, B. (1963a). Contribution à l'étude de la sécrétion et du métabolisme du cortisol chez le nouveau-né et le nourrisson de moins de trois mois. *Path. et Biol.*, **11**, 997.
- , —, Roux, Mme, Saez, J. M., and Frederich, A. (1963b). Détermination de la sécrétion surrénale en cortisol par dilution isotopique. Intérêt clinique. *Ann. Endocr. (Paris)*, **24**, 598.
- Birchall, K., Cathro, D. M., Forsyth, C. C., and Mitchell, F. L. (1961). Separation and estimation of adrenal steroids in the urine of newborn infants. *Lancet*, **1**, 26.
- , —, and — (1963). A method for the separation and estimation of neutral steroids in the urine of newborn infants. *J. Endocr.*, **27**, 31.
- Bongiovanni, A. M. (1951). Physiology of the adrenal cortex in infancy and childhood. *Amer. J. med. Sci.*, **222**, 710.
- Bush, I. E. (1963). The adrenal gland in infancy. *Pediatrics*, **31**, 357.
- , and Mahesh, V. B. (1959). Adrenocortical hyperfunction with sudden onset of hirsutism. *J. Endocr.*, **18**, 1.
- , and Willoughby (1957). The excretion of allotetrahydrocortisol in human urine. *Biochem. J.*, **67**, 689.
- Cathro, D. M. (1964). A study of adrenocortical function in newborn infants. M.D. Thesis, University of Edinburgh.
- , Birchall, K., Mitchell, F. L., and Forsyth, C. C. (1963). The excretion of neutral steroids in the urine of newborn infants. *J. Endocr.*, **27**, 53.
- , —, and — (1965). 3β : 21-dihydroxypregn-5-ene-20-one in urine of normal newborn infants and in third day urine of child with deficiency of 3β -hydroxysteroid-dehydrogenase. *Arch. Dis. Childh.*, **40**, 251.
- , and Forsyth, C. C. (1965). Excretion of corticosteroids by infants of diabetic and pre-diabetic mothers. *ibid.*, **40**, 583.
- Colle, E., Ulstrom, R. A., Burley, J., and Gunville, R. (1960). Adrenocortical steroid metabolism in newborn infants. III. Urinary excretion of 17-hydroxycorticosteroids following major surgery and stimulation with adrenocorticotropin. *J. clin. Endocr.*, **20**, 1215.
- Crosse, V. M. (1957). *The Premature Baby*, 4th ed., p. 72. Churchill, London.
- Dorfman, R. I., and Ungar, F. (1965). *Metabolism of Steroid Hormones*. Academic Press, New York.
- Gruenewald, P. (1964). Infants of low birthweight among 5,000 deliveries. *Pediatrics*, **34**, 157.
- Hillman, D. A. (1961). Urinary 17-hydroxycorticosteroid excretion in newborn infants with respiratory distress syndrome. *Amer. J. Dis. Child.*, **102**, 569.
- Kenny, F. M., Malvaux, P., and Migeon, C. J. (1963). Cortisol production rate in newborn babies, older infants and children. *Pediatrics*, **31**, 360.
- , —, Preeyasombat, C., Spaulding, J., and Migeon, C. J. (1966a). Cortisol production rate in the perinatal period: normal newborns and abnormal conditions. (In Proc. 2nd int. Congr. Hormonal Steroids.) *Excerpta Med. (Amst.) int. Cong. Ser.*, **111**, 175.
- , and Preeyasombat, C. (1967). Cortisol production rate. VI. Hypoglycemia in the neonatal and postnatal period, and in association with dwarfism. *J. Pediat.*, **70**, 65.
- , —, and Migeon, C. J. (1966b). Cortisol production rate. II. Normal infants, children, and adults. *Pediatrics*, **37**, 34.
- , —, Spaulding, J. S., and Migeon, C. J. (1966c). Cortisol production rate. IV. Infants born of steroid-treated mothers and of diabetic mothers. Infants with trisomy syndrome and with anencephaly. *ibid.*, **37**, 960.
- Klein, R., Fortunato, J., and Papadatos, C. (1954). Free blood corticoids in the newborn infant. *J. clin. Invest.*, **33**, 35.
- , Taylor, P. M., Hays, P., and Masquelier, U. (1962). Response of female premature newborn infants to SU-4885. *J. Pediat.*, **61**, 79.
- Mitchell, F. L. (1967). Steroid metabolism in the fetoplenal unit and in early childhood. *Vitam. and Horm.*, **25**, 191.
- Selye, H. (1936). Thymus and adrenals in the response of the organism to injuries and intoxications. *Brit. J. exp. Path.*, **17**, 234.
- Ulstrom, R. A., Colle, E., Burley, J., Gunville, R., and Reynolds, J. (1959). Neonatal adrenal function. *Med. Bull. Univ. Minn.*, **30**, 495.
- Venning, E. H., Randall, J. P., and Gyorgy, P. (1949). Excretion of glucocorticoids in the newborn. *Endocrinology*, **45**, 430.

Appendix

The following terms have been used in the text.

Trivial Name	Compound
Cortisol	11 β : 17 α : 21-trihydroxypregn-4-ene-3: 20-dione
Cortisone	17 α : 21-dihydroxypregn-4-ene-3: 11: 20-trione
Corticosterone	11 β : 21-dihydroxypregn-4-ene-3: 20-dione
Tetrahydrocortisol	3 α : 11 β : 17 α : 21-tetrahydroxy-5 β -pregnan-20-one
Tetrahydrocortisone	3 α : 17 α : 21-trihydroxy-5 β -pregnan-11: 20-dione
6 β -hydroxycortisol	6 β : 11 β : 17 α : 21-tetrahydroxypregn-4-ene-3: 20-dione
6 β -hydroxycorticosterone	6 β : 11 β : 21-trihydroxypregn-4-ene-3: 20-dione