Discussion

This study indicated that the total serum bilirubin levels of preterm infants during the first 10-day period of postnatal life were lower from March to August than from September to February in an area located far north (latitude 65°1'). The data of Giunta and Rath (1969) showed that infants exposed to environmental light averaging only 90 foot-candles had lower serum bilirubin levels than infants nursed in environmental light averaging 10 foot-candles. Thus, intensity and duration of light in any nursery may play a significant role in explaining the considerable variation in the incidence of hyperbilirubinaemia from one nursery to another (Lucey, 1960).

Compared with the levels of normal daylight, we have been working in relatively dark conditions in our nurseries. Giunta and Rath measured 5000 to 10 000 foot-candles in direct sunlight and 100 to 1000 foot-candles in the shade. According to MacLeod and Stern (1972), the amount of illumination received by an infant varied from 15 to 2500 foot candles, depending upon the location in the nursery, the time of day, and the amount of sunlight.

In this study the babies were treated in incubators, where they were completely exposed except for nappies. In another study we found no seasonal variation in neonatal bilirubin levels of term babies nursed dressed and in cots (unpublished).

In our district (latitude 65°1') the seasonal variation of illumination is extreme. The mean duration of daylight from March to August is twice as long as that from September to February. This difference might explain the lower serum bilirubin levels of the preterm infants born during the light half of the year observed in this study, as well as the seasonal variation in neonatal hyperbilirubinaemia reported by Milby, Mitchell, and Freeman (1969).

This study shows that the natural light in a neonatal ward can have some effect in preventing hyperbilirubinaemia. This should be taken into consideration when designing nurseries.

Summary

The effect of daylight on the serum bilirubin level of preterm infants (birthweight < 2500 g) during the first 10 days of life was studied in a district of Finland (Oulu, latitude 65°1') with large seasonal variations in the length of daylight (range 3 to 22 h). 86 preterm infants born consecutively during one calendar year were studied in incubators where they were completely exposed except for nappies.

A significantly lower bilirubin value from the fifth day of life onwards was recorded in the group of infants born during the light half of the year, compared with the infants born during the dark half of the year. Only 4 infants developed total bilirubin levels higher than 255 µmol/l in the 'light group', as compared with 10 in the 'dark group'. 2 infants in the light group required exchange transfusion, while 4 in the dark group did.

It is concluded that natural light conditions are of importance in the design of wards for newborn infants.

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Sexual precocity associated with a hypothalamic tumour

Effects of sex hormone therapy

The precocious onset of puberty is defined as the appearance of secondary sexual characteristics before the age of 10 years in a boy and 8 years in a girl (Seckel, 1946). The case we describe here is remarkable for its very early age of onset (under one year), its association with a hypothalamic tumour, and the unusual pattern of suppressibility of the greatly raised gonadotrophin and testosterone levels by oestrogen therapy. The results are considered

to be compatible with the hypothesis that this tumour may be acting as an 'irritating' focus on the normal hypothalamic secretory cells.

Case history

The patient was a child of 2 years. His testicles and penis were said to have been large and his muscles thick and strong in the neonatal period. Pubic hair began to appear at 8 months and his voice deepened at about 15 months. Penile erections occurred frequently.

On arrival in our hospital he was a sad and aggressive 'little Hercules', with power behind his punch. He was thick-set and strongly muscular with dark body hair and a distinct moustache. The axillae, however, were free from hair. He had a deep voice and acneiform spots on his chest. The pubic hair was well developed and surmounted a large penis 8.8 cm in length and 6.8 cm in circumference. The testicles were 3 cm in length, with no palpable abnormality. The prostate was large.

His height (94 cm) was the mean for a child of 2 years 10 months, his weight (20.17 kg) the mean for a 5½ year old, and his head circumference (53.5 cm) the mean for a 9–10 year old. Femora and tibiae were markedly bowed and there was a 55° flexion deformity of both knees, without any evidence of rickets.

Neurologically, the only abnormalities found were a slight right internal squint and an inability to see fixed

balls of less than ½" diameter from 3 m distance. It was impossible to exclude adequately a bitemporal hemianopia. His fundi appeared normal.

An air encephalogram revealed a small hypothalamic tumour, and surgery and radiotherapy were considered inadvisable. He received first oral ethinyl oestradiol (25 µg daily for 6 days) and then medroxy-progesterone acetate (MPA) 100 mg intramuscularly weekly. Blood was collected weekly for the estimation of testosterone, luteinizing and follicle stimulating hormones (LH and FSH).

Investigations

Radiology. The bone age was 6 years. The tumour visible on the air encephalogram was 9 mm in diameter and well defined (Fig. 1). It arose from the posterior hypothalamus and was situated in the interpeduncular cistern adjacent to the floor of the anterior part of the third ventricle. The appearance was that of a hamartoma or glioma.

Hormone assays. Testosterone was measured by radioimmunoassay (RIA) using an antiserum to testosterone-3-oxime bovine serum albumin (Collins *et al.*, 1972). The RIA techniques for FSH and LH were based on modifications of the double antibody principle (Munroe, Jaffe, and Midgley, 1972), and the results are expressed in ng of the LER-907 pituitary standard.

FIG. 1.—Air encephalogram of patient.

Urinary pituitary gonadotrophins were measured by a bioassay (Johnsen, 1958), and total 17-ketosteroids by a colorimetric method (Gray *et al.*, 1969).

Results

Plasma testosterone, FSH, and LH were all markedly raised (Fig. 2), being clearly above or at the limit of normal for adult males.

Ethinyl oestradiol produced slight falls in both testosterone and FSH levels which rose after treatment ended; a greater change in LH was observed (Fig. 2b). In the month after MPA was

started all plasma levels were declining steadily to values which were still clearly above normal for a child.

Urinary pituitary gonadotrophin titres were 3.2 mg/day (normal range for adult men 0.5–3.0 mg), and 17-ketosteroids 2 mg/day (normal for age <1 mg).

Discussion

The manner in which a hypothalamic tumour promotes sexual development is unknown. In the course of normal puberty it has been suggested that the hypothalamic sensitivity to the sex hormones is diminished so that FSH and LH levels rise (Kelch, Kaplan, and Grumbach, 1973). Therefore, relatively larger doses of oestrogen would be required to suppress the secretion of gonadotrophins after adolescence than in childhood. In this respect, the child's hypothalamus is exquisitely sensitive so that a daily dose of 2 to 3 $\mu\text{g}/\text{m}^2$ ethinyl oestradiol has been shown to suppress promptly FSH and LH titres (Kelch *et al.*, 1973).

In adults serum FSH can be suppressed within one week after administration of 25 to 50 μg ethinyl oestradiol daily, though the fall in LH is delayed (Kulin and Reiter, 1972; Franchimont, Legros, and Meurice, 1972). Thus the effect of oestrogen therapy on our patient's hormonal pattern is abnormal, as suggested by the persistently high levels of FSH, LH, and testosterone which are unusual even for a normal adult. These levels, however, did show a steady decline by the end of the study period (Fig. 2), under the influence first of ethinyl oestradiol, then of MPA. In the long run suppression to normal levels might have been achieved.

The mechanism producing the change in hypothalamic sensitivity at puberty may be mimicked or stimulated by a tumour, but its mode of action remains obscure. It is likely that the tumour is acting as an 'irritating' focus causing increased secretion of LH-releasing hormone from normal hypothalamic cells. These cells retain a sensitivity to sex hormone, albeit a diminished one, permitting large doses of MPA to dampen their activity. It is of interest that after 6 days of oestradiol therapy the fall in FSH was only 20%, whereas that in LH was 57%. This appears to be a reversal of trend expected in the sexually mature adult (Franchimont *et al.*, 1972).

Summary

A case of sexual precocity of unusually early onset and associated with a hypothalamic tumour is described. The effects of ethinyl oestradiol and

FIG. 2.—Effects of ethinyl oestradiol (OE) and medroxyprogesterone acetate (MPA) on plasma testosterone, FSH, and LH levels.

medroxyprogesterone acetate treatment have been monitored by plasma testosterone, FSH, and LH estimations. The results suggested a partial suppression of the tumour's influence, the mechanism of which is discussed.

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Bone changes in congenital cytomegalic inclusion disease

We report the case of a female infant born with cytomegalic inclusion disease, in whom bone changes were present in x-rays of the tibiae and femora. She was the mother's first child and was born 8 days postmature after a normal delivery; birthweight 2.52 kg. Many infarcts were seen in the placenta. The mother had had a feverish illness at the 7th month of gestation, diagnosed by the family doctor as influenza. No drugs had been given.

Case report

The infant became jaundiced on the second day, serum bilirubin was 6.1 mg/100 ml, Hb 25 g/dl and the

Coombs's test was negative. The liver was palpable 2 cm below the costal margin and the tip of the spleen was palpable. During the following days the jaundice became deeper and greenish in colour and the stools became pale. She was transferred to this hospital on the 9th day.

On admission the jaundice was marked, the liver palpable 3 cm below the costal margin, and the tip of the spleen palpable. Total serum bilirubin was 13.5 (unconjugated 6.8) mg/100 ml, serum alkaline phosphatase 10 units, thymol flocculation positive, thymol turbidity 4.0 units, zinc turbidity 4.5 units, SGOT 110 K units/ml, SGPT 73 K units/ml. The urine contained no pus cells or reducing substances, but bile, urobilin, and urobilinogen were present. Repeated specimens were examined for cytomegalic inclusion bodies with a negative result. The blood culture and Wassermann reaction were both negative. Serum immunoglobulins—IgG 1109 mg/100 ml (normal), IgA 10 mg/100 ml, and IgM 32 mg/100 ml. X-rays of chest and skull normal. X-rays of the legs showed oval translucencies at the distal ends of both tibiae and faint longitudinal striations at the distal ends of both femora (see Fig.). At the age of 2 months the appearance had returned to normal.

Blood was collected from mother and infant for viral studies and to exclude toxoplasmosis. At 12 days cytomegaly titre was 1/512 (mother and infant); at 11 weeks 1/128 (infant); at 7 months 1/64 (infant).

Many specimens of urine were cultured for viral infections and were negative until the infant was 8 months old, when cytomegalovirus was cultured.

Progress. The jaundice gradually disappeared and by the age of 3 months the total serum bilirubin was less than 1 mg/100 ml. The liver, however, was still enlarged and firm and could be felt 3 cm below the costal margin; the spleen was still palpable. A liver biopsy showed that 'a giant cell hepatitis was present with minimal fibrosis' (Dr. J. M. Bouton).

Steady improvement followed and by the age of 3 years the liver and spleen were normal in size and the liver function tests were also normal. Examination of the central nervous system showed minimal cerebral dysfunction with slight clumsiness of movement of the limbs. Intellectual assessment at the age of 5 years was satisfactory, the IQ being 102 on the Stanford-Binet Scale.

Discussion

There have been numerous reports of bone changes in newborn infants with congenital rubella syndrome. The principal changes described are alternative dense and radiolucent striations in the metaphysis of long bones, particularly at the distal ends of the femora (Singleton *et al.*, 1966). More recently similar changes were found in a patient with cytomegalic inclusion disease (Graham, Thal,