The mortality rate from exchange transfusions even in healthy babies is real, and probably stands around 1% in most centres (Jablonski, 1962; Kitchen, 1970). As rhesus incompatibility becomes a preventable disease, it seems likely that most other causes of neonatal hyperbilirubinaemia could be managed on a multifaceted conservative approach, i.e. using phenobarbitone, phototherapy, early feeding regimens, and perhaps oral agar to interrupt the neonatal enterohepatic circulation of bilirubin (Lucey, 1971). It has recently been shown that early clamping of the cord can significantly decrease the need for exchange transfusion in the premature infant by reducing placental transfusion and consequent hyperbilirubinaemia (Saigal et al., 1972). Together these factors could make a significant reduction in the need for exchange transfusion. The category of babies in which these advances are likely to make the least impression would have findings similar to this case report. This is the fairly unusual group of babies who develop severe neonatal jaundice without it being anticipated in the antenatal period. They may thus have the added disadvantage of being born at home, or in a small hospital, where the necessary paediatric care is some distance away. It is suggested that where there is delay in obtaining compatible blood, a ‘mini plasma exchange’ is a satisfactory holding procedure. Previous workers have been concerned largely with albumin priming in an effort to increase the efficiency of an exchange blood transfusion. It has recently been pointed out that albumin priming can also be useful in severe neonatal hyperbilirubinaemia when blood is not immediately available for an exchange transfusion (Tsao and Yu, 1972). The decision to proceed to a ‘mini exchange’ rather than albumin priming depends on the Hb level.

**Summary**

A small exchange plasma transfusion of 12 ml/kg is a feasible and instantly available alternative to an exchange blood transfusion in the management of neonatal hyperbilirubinaemia when there is delay in obtaining compatible blood. The infant must have an adequate Hb for the procedure, and a minimum level of 14 g/100 ml is suggested. In the case described there was no significant rebound in the serum bilirubin after the plasma exchange, unlike that commonly observed after an exchange blood transfusion.

I thank Dr. B. McDonagh for permission to publish this case, and Dr. E. Tempany for helpful advice and criticism.

**Nephrotic syndrome in congenital syphilis**

The nephrotic syndrome is an uncommon complication of both congenital and acquired secondary syphilis. The case described below is the first in which the signs of the nephrotic syndrome developed after a patient had been treated with adequate penicillin therapy for congenital syphilis. The findings of a renal biopsy are described.

**Case history**

A 3-month-old boy was admitted to the Johns Hopkins Hospital because of eyelid oedema of one day’s duration. The patient’s mother was found to have a VDRL of 32 units during her fourth month of pregnancy. She received 2-4 million units of penicillin G (benzathine and procaine in equal amounts) and her VDRL fell to 16 and 8 units on two consecutive occasions. She received no further penicillin therapy and was denied any further coitus. After an uncomplicated labour and delivery she delivered a physically normal term infant. The mother’s VDRL at the time of delivery was 16 units and the infant’s 4 units. The infant was discharged without being treated for congenital syphilis.

The infant was asymptomatic until 6 weeks of age when he developed mucopurulent rhinorrhoea and a macular papular erythematous rash over his chin, perineum, palms, and soles. These findings persisted and at 10 weeks of age he was brought to the outpatient department. The diagnosis of congenital syphilis was confirmed by a VDRL of 64 and he was
treated with 200,000 units of procaine penicillin daily for 9 days. No oedema was noted. No urinalysis was performed. 5 days after the completion of therapy, or 14 days after the initiation of therapy, his mother noted swelling of his eyelids and he was admitted.

Examination now showed that the child weighed 5.58 kg, having gained 800 g in the 14 days since initiation of penicillin therapy. There was marked oedema of the eyelids and presacral and pretibial areas. The remainder of the physical examination was within normal limits, save for the presence of the fading rash. Blood pressure 90/50 mmHg.

VDRL had fallen to 16 units, and a Reiter Treponemal complement fixation was negative. The urine was clear and yellow with a specific gravity of <1.001, pH 6, and a 4+ reaction for protein and negative reactions for sugar and acetone. Repeated urine cultures were sterile. An initial 24-hr urine protein content was 576 mg. Serum sodium, potassium, chloride, CO₂ content, calcium, phosphorius, and alkaline phosphatase determinations were all normal. Serum urea nitrogen was 11 mg/100 ml, creatinine 0.6 mg/100 ml, total protein 3.7 g/100 ml with an albumin of 1.0 g/100 ml and a globulin of 2.7 g/100 ml; cholesterol 355 mg/100 ml. The initial 24-hr creatinine clearance was 41 ml/min per 1.73 m². An intravenous pyelogram was normal as was a chest x-ray. There were areas of periosteal elevation along the shafts of the long bones in the arms and legs.

Multiple lupus preparations, antistreptolysin O titre, 24-hr urine content of heavy metals, Hb electrophoresis, serological tests for rubella, toxoplasmosis, and cyto-megalic inclusion disease, and a throat culture were all negative or within normal limits.

No specific therapy was instituted and the child fared well. Within 10 days he was oedema free and had lost 680 g, the urine was free of protein, serum albumin had risen to 2.8 g/100 ml, and cholesterol had fallen to 215 g/100 ml. At the time of discharge one week later, he was well. Physical examination, urinalysis, and serum urea nitrogen were all normal 6 months after discharge.

Renal biopsy. A percutaneous renal biopsy was performed on the 8th hospital day. The technique of fixation precluded stains for spirochaetes. The interstitium contained occasional minute foci of mononuclear round cells. The blood vessels were normal. Many of the glomeruli showed slight but definite changes (Fig.). The mesangium showed a slight increase in fibrillar, periodic acid Schiff (PAS) positive matrix as well as slight hypercellularity. Focal capillary wall thickening was apparent in haematoxylin and cosin preparations but could not be confirmed with PAS stain. Occasional eosinophils were present in glomerular capillaries. Periodic acid silver methenamine preparations did not show the spikes of membranous nephropathy.

Discussion

Significant renal disease is uncommon in congenital syphilis. The extent of clinical renal involvement in syphilis may vary from simple albuminuria to more significant disease such as the nephrotic syndrome or nephritis. Plateau et al. (1946) found clinical renal involvement in only one of 191 cases. Our patient fulfils the criteria for congenital syphilitic renal disease with evidence of syphilis in the mother, unequivocal evidence of congenital syphilis in the patient, and absence of other aetiology for his nephrotic syndrome (Scully and Yamazaki, 1949).

Unfortunately no urinalysis had been done before the initiation of penicillin therapy, so that one cannot say whether or not there may have been albuminuria without clinical oedema. Nevertheless, it was not until 14 days after the initiation of penicillin therapy that the patient developed the clinical signs associated with the nephrotic syndrome. In previously reported cases of the nephrotic syndrome due to congenital syphilis, the nephrotic syndrome was present before treatment with penicillin and resolved with the penicillin therapy for syphilis. This case serves to show that the clinical manifestation of the nephrotic syndrome

FIG.—Representative glomerulus showing slight prominence of mesangium consequent to increase in matrix and hypercellularity, and suggestive focal thickening of capillary walls. (Haematoxylin and eosin. × 954.)
syndrome may develop well after the treatment of syphilis has been initiated.

Scott and Clark (1946) reported what they believed to be a possible renal Herxheimer reaction in an adult with an acquired syphilis. Their patient had a febrile reaction after the initiation of penicillin therapy and then developed the nephrotic syndrome 14 days later. Our patient had no known initial manifestations of the Herxheimer reaction. One can only speculate as to whether Scott and Clark’s case and our case may indeed represent renal Herxheimer reaction.

The pathogenesis of the nephrotic syndrome in syphilis is obscure. However, the morphological studies of others may afford a clue. Electron dense deposits in the area of the glomerular basement membrane have been described in adults with syphilis and the nephrotic syndrome (Falls et al., 1965). Braunstein et al. (1970) have identified these as complement-fixing \( \gamma \)-G2 heavy chains and \( \lambda \)-light chains. Churg (1968) has also identified electron dense deposits in the glomerular capillary wall of an infant with syphilis and the nephrotic syndrome. Pollner (1966), utilizing light microscopy, reported glomerular basement membrane thickening in a similar case. Thus the nephrotic syndrome in congenital syphilis appears to be associated with what are ordinarily considered ‘immune deposits’ in the region of the glomerular basement membrane: these apparently regress with clinical improvement (Falls et al., 1965).

Summary

A 3-month-old infant with congenital syphilis developed the nephrotic syndrome 14 days after having been adequately treated with penicillin. This case is believed to be the first reported instance of nephrotic syndrome occurring in congenital syphilis after treatment with an adequate dose of penicillin.

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Severe cutaneous reactions to phenytoin

Since the first reports of the effectiveness of phenytoin in the treatment of epilepsy (Merrit and Putnam, 1938), it has established itself as the drug of choice in many of the forms of epilepsy. The many side effects reported are usually attributed to blood levels in excess of 20 \( \mu \text{g/ml} \) (Kutt and McDowell, 1968). Signs such as gingival hypertrophy and skin rashes are not usually related to phenytoin blood levels but indicate a sensitivity to the drug.

The purpose of this paper is to describe a child who developed a fatal skin reaction to the drug when only therapeutic blood levels of the drug were reached, and another case where a severe sensitivity reaction was associated with toxic blood levels of the drug.

Case reports

Case 1. A 10-year-old boy was admitted with a history of six generalized seizures within 1 year. There was no previous history of illness in himself or his family. He had received no anticonvulsant therapy. Physical examination was normal. EEG indicated an active epileptogenic focus in the right midtemporal region, involving the cortex. He was given phenytoin 200 mg daily. He had no further convulsions, but 10 days after starting phenytoin he developed a morbilliform rash. Blood phenytoin level on this day was 18.3 \( \mu \text{g/ml} \). Phenytoin was stopped. By the next day the rash had extended and became more intense. Bullous formation occurred and he became ill and toxic. Rupture of the bullae and leak of serous fluid occurred. Intravenous fluids, antihistamines, and analgesics were given. Dermatological opinion confirmed a diagnosis of Stevens-Johnson syndrome, the rash being confluent, sheets of skin desquamating, and the oral mucosa, by now, being affected.
Nephrotic syndrome in congenital syphilis.

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