THE PATHOGENESIS AND PREVENTION OF NEONATAL MENINGITIS AND SEPTICAEMIA

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With the decline of puerperal sepsis and of infective endocarditis and pyelonephritis in pregnant women, the problems of serious infections in obstetric practice have shifted from the pregnant or parturient woman to her unborn or infant child. The fetus and the premature newborn are physiologically disadvantaged by reason of their immaturity and are thus prey to endogenous microbes harboured in the birth canal and to exogenous microbes colonising their immediate environment after birth. Perinatal mortality is high even in Europe and the United States, and serious bacterial infections, that is, septicaemia and meningitis, are rising as a concomitant of heroic paediatric intervention in babies of low or very low birthweight, so that neonatal sepsis now contributes to a quarter or a third of deaths occurring in the perinatal period.

In terms of survival and of lack of crippling sequelae (Stewart *et al.*, 1981) the prognosis of babies born with low or very low birthweight has altered completely in the last three decades. The virtual certainty of death in 1946 (Douglas and Gear, 1977) has been replaced by an expected survival rate, in specialist centres, of 30 to 50 per cent for those born weighing less than 1000 g and of 85 per cent for those born weighing less than 1500 g (Lancet, 1980a; Starte *et al.*, 1980). Paradoxically, the improvement has led, ever increasingly, to rises in the numbers of cases of neonatal septicaemia and of meningitis, for there is agreement that the rates will be five to one hundred times higher in those of low birthweight (Klein *et al.*, 1976; Hurley and de Louvois, 1981). Neonatal meningitis is less common than septicaemia, and the data reported by Klein *et al.* (1976) suggest overall figures of 1.8 per 1000 births for septicaemia, and 0.2 per 1000 births for meningitis with rates of 13.3 and 2.6 per 1000 for those of birthweight less than 2500 g and of 74.5 and 18.6 per 1000 for those of birthweight less than 1000 g.

Both diseases have high mortality rates which, again, are inversely proportional to birthweight. Thus, Hurley and de Louvois (1981) recorded an overall mortality of 40.1 per cent for septicaemia, rising to 62.5 per cent in those born weighing less than 1000 g and to 83per cent in those in whom meningitis supervened, as it did in 6 of their 27 treated cases. All available evidence suggests that neonatal meningitis is consequent on blood stream infection; the primary site of invasion is the blood stream with spread to meninges in 25 to 30 per cent of cases. The term "sepsis neonatorum" or "neonatal sepsis" is used for both septicaemia and meningitis (Siegel and McCracken, 1981).

SEPTICAEMIA

Neonatal septicaemia is a clinical syndrome characterised by signs of systemic infection and documented by a positive blood culture in the first four weeks of

life (Gotoff and Behrman, 1970; Klein and Marcy, 1976). The difficulties of recognising the clinical stigmata of blood stream infection in the newborn have been emphasised by Davies (1977) and by Klein *et al.* (1976), for signs and symptoms are often vague and non-specific. Blood for culture should be taken from a peripheral vessel, as samples from the umbilical vein may give false positive results (Lipsitz and Cornet, 1960). Even with voluntary reporting systems (Young, 1982), it is evident that the newborn are unduly susceptible to blood stream infections, since they accounted for 3.7 per cent of all cases reported to the PHLS Communicable Disease Surveillance Centre between 1975 and 1980. Although some commentators have distinguished primary septicaemia from septicaemia secondary to congenital anomalies, surgical procedures or debility, for epidemiological reasons it is more practical to consider neonatal sepsis in terms of early and late onset disease. The cardinal distinction between the two types lies in the source of the infection which in the former is the birth canal and in the latter, the environment.

Early onset disease

Early onset disease occurs in the first week of life as a fulminant systemic illness in babies who are usually premature and of low birthweight and who have been born to women who have undergone abnormal pregnancies and deliveries. Premature and prolonged rupture of the membranes with premature labour, obstetric complications leading to operative or instrumental delivery, maternal or fetal distress, haemorrhage, maternal anaemia or intercurrent illness, and peripartum fever are all prejudicial factors. The causal bacteria of early onset sepsis are derived from the birth canal and are acquired as a result of an ascending infection in intrauterine life or during passage through the birth canal. Transplacental transmission occurs rarely, but the child may be born with a true congenital bacteraemia. The bacteria associated with early onset sepsis are usually those that are indigenous to the maternal genital tract but rarely microbes such as β-haemolytic streptococci (Lancefield group A) or *Clostridium perfringens* are isolated. These, too, may derive from an infected genital tract. The mortality rate of early onset sepsis is high, lying between 20 and 50 per cent, but it is almost certainly underestimated, for recorded rates usually take no account of stillbirths or of those who survive insufficiently long to allow clinical and microbiological investigation to proceed.

Late onset disease

Late onset disease usually occurs after the first week of life, although it has been recognised on the fourth day. There are fewer prejudicial maternal peripartum events, but the babies are often afflicted by congenital malformations or illness, or other disease. The microbes responsible are usually those that are being disseminated in the infants' environment, reflecting epidemiologically the distribution of pathogens at large in a particular nursey or intensive care baby unit. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella aerogenes* are examples of such pathogens.

The mortality is lower in late onset sepsis and is of the order of 10 to 20 per cent. It is often difficult to determine the precise onset of neonatal sepsis in babies who are weakly and marasmic from birth, but the diagnosis must be considered in almost every sick newborn infant (Gotoff and Behrman, 1970).

While, in practice, it is often difficult to distinguish the type in individual babies, disease of late onset, originating as it does from microbes being disseminated in the environment of the susceptible newborn, must be regorded as essentially iatrogenic and as preventable, if rigorous standards of hygiene, antisepsis and asepsis are imposed. However, its control is growing more difficult, due to the importation of seriously ill babies, often colonised with bacteria foreign to the host centre, into special care baby units that are already overloaded and overworked with the primary care of low birthweight babies. Neonatal sepsis is itself a major reason for transfer of sick babies to special units, accounting for at least 20 per cent of all referrals. Such babies constitute an infectious hazard, for our necropsy studies (Pryse-Davies and Hurley, 1979) showed that 80 per cent of those with septicaemia harbour the microbe in the bronchial tree, whence, during life, it may contaminate the attendant's hands and clothing, adjacent fomites, or the larger environment of the Special Care Unit. Terminal septicaemia, whether treated or not, may thus contribute to late onset sepsis, and dying babies should be nursed in isolation.

The care of the newborn sick is fraught with infectious hazards because of the handling and instrumentation that is required. Certain practices increase the risks of serious sepsis, and some that are designed to minimise the spread of infection, or to treat microbial disease, may, themselves, be inimical to the well-being of the newborn. Intravenous administration of fluids and the use of cutdown in the 1940's introduced septic hazards both by the nature of the route and from the lack of suitable preparations. Drug regulation was in its infancy, and even when commercially prepared fluids became available, their quality was not impeccable as it should be today. The route itself offered the broadest access for microbes to reach the viscera, and meningitis and septicaemia often followed the giving of contaminated solutions; unhappily, the latter problem is not entirely resolved (Deeb and Natsios, 1971). Candida species grow well in hyperalimentation fluids and fungal septicaemia is a complication of parenteral hyperalimentation (Curry and Quie, 1971).

Catheters or needles are used for intravenous therapy of the newborn, intravenous alimentation often being given through a silastic central venous line into the right atrium. The risk of bacteraemia and systemic infection is least with the scalp vein needle and greatest with the indwelling venous catheter, as evidenced by the greater number of studies showing no bacteraemia with the former. Umbilical artery catheters are safer than venous catheters, but with both, serious septic complications can be reduced by prompt removal of the catheter if the patient develops signs or symptoms of infection, and bacteraemia often resolves spontaneously upon removal of the colonised foreign body. Omphalitis is a complication, with a frequency of 2.1 per cent following venous and 1.3 per cent following indwelling arterial catheterisation (Egan and Eitzman, 1971). The frequency of phlebitis, co-

TABLE 1. — *Principles underlying methods of avoidance and control of serious neonatal infections.*

Uncomplicated vaginal delivery at term
Breast feeding, or use of EBM
Quarantine or isolation facilities
Adequate number of trained personnel
Washable walls and floors
Wall-mounted monitoring and suction equipment
Aseptic care (hand washing)
Gowning policy
Scrupulous care of indwelling tubes and catheters
Adequate disposal of soiled and foul linen
Care and surveillance of baby incubators, breast pump, handbasins, etc.
Bathing kept to a minimum
Recording of data
Cleaning and disinfectant policy

lonisation of the catheter and bacteraemia increases with the length of time the catheter is left in place and all should be removed within 72 hours if possible. Application of antibiotic ointments around the site of entry extends the length of time over which the catheter may be left safely, but does not aver colonisation. *Staphylococcus aureus* tends to be replaced by *Candida species* (Barrett, 1976).

The criteria for admission to a Special Care Baby Unit must be strict (HMSO, 1971) because of the dangers of parent-child separation, which may lead to childhood behaviour problems, failure of bonding, poverty of later intellectual development, "non-accidental" injury, "failure-to-thrive" and maternal psychosis. These considerations generate a philosophy towards visiting which is unique and not without possible hazard: parental visiting must be encouraged ad libitum and grandparents and siblings must be urged to visit so that the family bond is strengthened. It is essential, also to regulate admission to the Unit, to avoid the twin evils of overcrowding and relative understaffing which, themselves, promote dangerous nosocomial infections. In the United Kingdom, the nurse/patient ratio for neonatal intensive care should be 5:1 for each 24 hour period, whereas that for special care (for example, care of those with jaundice, low birthweight or transient respiratory disorders) should be 1.5:1. The high nurse/patient ratio is dictated, in part, by the need for regular surveillance of invasive or adhesive devices, which may require to be relocated or replaced if serious infection is to be avoided. The principles that underly prevention of neonatal sepsis are shown in table 1.

Because of the danger of nosocomial spread with microbes such as *Pseudomonas aeruginosa*, *Klebsiella*, *Serratia* and other Gram-negative rods, and, even on occasion, of Group B streptococci, *Listeria monocytogenes* or viruses, antisepsis, asepsis and general hygiene are of paramout importance in nurseries for the newborn, or in Special or Intensive Care Baby Units. An untidy and cluttered ward or treatment area proves impossible to maintain at the high standard required, and

equipment cannot be cleaned and disinfected satisfactorily if it is permanently affixed in crowded surroundings so that it is inaccessible to the staff responsible for sanatization. These considerations apply particularly to intensive care units for the newborn sick. Amongst the welter of monitoring and resuscitative devices, often necessitated by unacceptably high rates of serious sepsis, the principles of hygiene can be neglected to the point of extinction. Sepsis rates rise inexorably and an already overcommitted staff finds itself gingerly picking a route through even more clutter, seemingly unaware that every step aids the propagation and dissemination of the very microbes that are killing their patients.

MENINGITIS

Meningitis is more frequent in the first month of life than in any other 30 day period (Smith, 1954). It is frequently undiagnosed and may not be suspected until autopsy (Bush, 1971). The lack of specific signs and symptoms have been emphasised by many, and led Overall (1970) to urge the importance of obtaining cerebrospinal fluid (CSF), blood and urine for examination and culture at the first signs of unexplained illness in an infant. He regarded the clinical indications for performing a lumbar puncture as sufficient in themselves to warrant antimicrobial therapy, in view of the high mortality rate, even of the treated condition (McDonald, 1972). Ray (1972) stressed the importance of repeated examinations of CSF in the newborn with septicaemia, since purulent meningitis is known to be a complication, even when therapy of the blood stream infection appears to be adequate. Heckmatt (1976) also commented on this.

Theoretically, lumbar or cisternal puncture may be risky in the presence of septicaemia (Petersdorf *et al.*, 1962); however, the risk must be taken.

Criteria for the diagnosis of neonatal bacterial meningitis have usually been taken to be: culture of microbes from the cerebrospinal fluid (CSF); pleocytosis of more than 20 cells per μl with a predominance of polymorphonuclear leucocytes; decreased CSF sugar of less than 40 mg per cent or less than 50 per cent of a simultaneously determined blood sugar estimation; or visualisation of bacteria in the stained smear of CSF (Overall, 1970). To these, Bush (1971) added CSF pleocytosis greater than 100 cells per μl of which more than 50 per cent were polymorphonuclear leucocytes, even in the absence of positive culture. We regard a CSF cell count of greater than 20 cells per μl as suggestive of meningitis, even in the absence of detectable micro-organisms (Mulhall *et al.*, 1982).

MICROBIAL AETIOLOGY

The microbial aetiology of neonatal septicaemia and meningitis is similar. Most accounts including the first systematic study of septicaemia by Silverman and Homan (1949) attest the pre-eminence of *Escherichia coli* and other Gram-negative rods as causative bacteria. Before their account, *Str. haemolyticus* (Lancefield, group A streptococci) often consequent on puerperal sepsis, seems to have caused the majority of reported cases. Davies ((1971) discussed the source and pathoge-

TABLE 2. — *Neonatal septicaemia confirmed or demonstrated at necropsy: rates per 1000 births, QCMH 1972-76.*

	No. of cases	Rate
All microbes	46	2,59
Gram-negative rods	36	2.03
Gram-positive cocci	9	0.50
Escherichia coli	19	1.07
Pseudomonas aeruginosa	7	0.39
Klebsiella aerogenes	6	0.34
Other gram-negative rods	4	0.23
Group B streptococci	5	0.28
Other streptococci	2	0.11
Staphylococci	2	0.11
Listeria monocytogenes	1	0.06
Total	46	2.59

nesis of bacterial infection in the newborn fully, chronicling the changing pattern of sepsis and alluding to the falling incidence of staphylococcal disease and the prominence of the Gram-negative rods as causes of serious infection. Many studies in the 1960's, from North America, had emphasised the increasing frequency of Gram-negative rod sepsis (Gluck *et al.*, 1966; McCracken and Shinefield, 1966). The Group B streptococcus is an important cause (Patterson and Hafeez, 1976; Parker, 1979), recognised by Siegel and McCracken (1981) as the predominant pathogen in most North American nurseries and accounting with *Escherichia coli* for 60 per cent of all cases. The relative incidence of the causal microbes varies in different parts of the world; *Listeria monocytogenes* is common in Spain, while Gram-negative rods, especially *Salmonella species* are most frequently implicated in Latin America (Siegel and McCracken, 1981). Recent reports from the United Kingdom (Hurley and de Louvois, 1981; George, 1982) show similar ratios of 7:1 and 10:1 for Gram-negative rods, principally *Escherichia coli* and Group B streptococci respectively. In the former series (27 cases), the ratio in the inborn population was 7:1 and in those referred from other units it was 8:1; the only other causes were *Listeria monocytogenes* in one case and *Staphylococcus aureus* in another, the latter being an intrauterine infection resulting in stillbirth. In George's series (24 cases) *Staphylococcus aureus* and *S. albus* each caused six cases and *Candida albicans* caused one. The staphylococcal infections were consequent on surgery, or on infected cannulae or ventriculo-atrial shunts. Of six cases of meningitis complicating septicaemia (Hurley and de Louvois, 1981). *E. coli* caused three, *Pseudomonas aeruginosa* two and *L. monocytogenes* one. Only the last patient survived. Table 2 shows the distribution of microbes in fatal cases of septicaemia at Queen Charlotte's Maternity Hospital over a four year period. Amongst the rare causes of neonatal and early infantile sepsis are *Pasteurella multocida* (Bhave *et al.*, 1977), *Flavobacterium meningosepticum* (Hazuka *et al.*, 1977), *Haemophilus influenzae*

(Bale and Watkins, 1978) and *Vibrio fetus* (now Campylobacter) (Eden, 1966). *Neisseria meningitis* (Oakley and Stanton, 1979) is a rare cause (Overall, 1970) although it does occur in early infancy. Candida septicaemia is well known and three recent cases are described by Tettenborn *et al.* (1982). A good account of the aetiology and experience of bacterial meningitis in children under one year is given by Lin and Lanier (1973). Epidemics of neonatal sepsis have been associated with *Citrobacter koseri* (Gross *et al.*, 1973; Gwynn and George, 1973), *Achromobacter* (Foley *et al.*, 1961) and *Listeria monocytogenes* (Le Souëf and Walter, 1981).

PROGNOSIS AND CONTRIBUTION TO PERINATAL MORTALITY

The prognosis of neonatal sepsis may vary with the aetiological agent as well as with the type. It is poor, indeed, in the case of coliform meningitis, Heckmatt (1976) reported only 14 survivors in 36 cases in Glasgow hospitals between the years 1970 and 1974, while Overall (1970) recorded 10 deaths in 13 cases of meningitis caused by Gram-negative rods, but only 5 deaths in 12 others, caused by diverse bacteria. The less favourable prognosis with Gram-negative rod sepsis accords with our own experience (Hurley and de Louvois, 1981). Although reported mortality rates for neonatal Group B stretpococcal disease vary widely (Patterson and Hafeez, 1976) from none to 100 per cent, on balance the prognosis for comparable birthweight groups seems better than that of sepsis associated with Gram-negative rods. Mulhall *et al.* (1982) studying 70 neonates and infants with clinical evidence of meningitis showed that the mortality rate following infections with Gram-negative organisms was significantly lower ($\chi^2 = 3.9$; $p < 0.05$) than that associated with Gram-negative organisms. Mortality in the latter group showed no improvement over that recorded by Heckmatt (1976).

Whether acquired by the fetus in utero or by the infant at birth or in early postnatal life, neonatal sepsis is an important cause of perinatal mortality. Pryse-Davies and Hurley (1979) combined morbid anatomical, histological and microbiological investigations in a ten-year study of 835 necropsies performed on 130 aborted fetuses of more than 500 g, 371 stillborn fetuses, 307 neonates dying in the first week and 27 neonates dying later in the first month of life, obtaining specimens for microbiological examination from 96.2 per cent of necropsies. Body storage and postmortem delay did not affect the microbiological findings. Although infection was recorded as a primary cause of death in 32 instances (3.8%) other than in listeriosis and the two cases of intrauterine infection, septicaemia or neonatal sepsis did not figure as a primary cause of death, and in all cases in which blood stream infection was demonstrated (21.1 per cent), death was ascribed to other or deformity. Blood stream infection, through very frequent in this necropsy series, was therefore regarded as a secondary event, often terminal, contributing to death in the course of other disease processes. Widely disseminated infection with some histological evidence of the same pathogen from the heart blood, cerebrospinal fluid and bronchi occurred in 4.4 per cent of 340 necropsies.

Thus, in the newborn there is a tendency of the approximate order of one in five for the meninges to become involved in the course of blood stream infection,

an observation borne out in clinical practice. Infection of the bronchial tree with the same microbe as that present in the blood stream occurs in over 80 per cent of cases of blood stream infection.

Fatal viral infection with viraemia or viral meningoencephalitis is rare in the nemborn period and life-threatening disease is overwhelmingly of bacterial origin. Only five cases including varicella-zoster, herpesvirus hominis and coxackievirus B have come to necropsy in our hospital in a 17-year period, that is, in 58,160 births. Disseminated candidosis is also rare, six cases having encountered over the same period.

TREATMENT

The treatment of neonatal sepsis is clearly unsatisfactory, as witnessed both by high mortality and morbidity rates and by the number of babies who develop meningitis while on apparently adequate schedules of therapy for septicaemia. Potentially and actually toxic drugs (gentamicin; chloramphenical) are widely used and must in some instances contribute to mortality and morbidity (Mulhall *et al.*, 1983). Extensive trials of more recently introduced antibiotics are being undertaken in many centres, including our own, though it is hard to assess comparative efficacy when drugs must be used on suspicion of serious sepsis. Amongst the agents tried in our Unit have been mecillinam (de Louvois *et al.*, 1981) cefuroxime (de Louvois *et al.*, 1982), moxalactam (de Louvois *et al.*, 1984), cefotaxime (de Louvois *et al.*, 1972), ceftriaxone and ceftazidime.

Details of treatment with these and other drugs cannot be discussed here (see Mulhall; de Louvois, this volume). Nelson (1981) deals with paediatric antimicrobial therapy in a very useful handbook while McCracken and Nelson (1977) deal with antimicrobial therapy in the newborn. Lorber (1977) addressed himself to the treatment of neonatal meningitis. A schedule for provisional initial treatment of serious infection in neonates is tabulated in Drug and Therapeutics Bulletin (1981), together with guidance on antibacterial chemotherapy in other infections in the newborn. Some pitfalls in the general management of neonatal meningitis are outlined by Johnsen (1975). The place of intrathecal therapy is discussed in a Lancet leader (1976) and by Yeung (1976), while McCracken (1977) comments on intraventricular treatment of neonatal meningitis. Whatever the schedule of therapy, it is important that potentially toxic drugs such as gentamicin and chloramphenicol should be assayed by the laboratory.

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