plasma histidine in the chronically uraemic patients who were treated with histidine might have reflected decreased histidine intake from food taken during treatment. Renal function decreased during the treatment period in these patients, and their protein intake was reduced. The finding that plasma histidine levels decreased in the chronically uraemic patients receiving placebo supports this possibility.

Histidine is an amino-acid of particular importance for erythropoiesis. There is abundant evidence that diets deficient in histidine are associated with decreased erythropoiesis, though how histidine promotes erythropoiesis is unknown.\(^1\)\(^2\)\(^3\) It may be pertinent that histidine is an amino-acid which is particularly abundant in the haemoglobin molecule and provides the linkage for iron in the haem moiety to globin. It is not clear why the anaemia did not improve in the patients receiving histidine. Their plasma histidine levels during the baseline period were at least as great as those of normal people ingesting 40-60 g protein diets,\(^4\) and they may have had adequate body histidine pools. Hence the administration of histidine in quantities sufficient to prevent a deficiency possibly promotes erythropoiesis, but additional histidine does not further enhance red-cell production. The relation between histidine and erythropoiesis may thus be similar to that between iron or folic acid and red-cell production.

The amount of dietary histidine necessary for a maximum effect on erythropoiesis is unknown. Our patients took about 1500-1700 mg/day of histidine in their food. The quantity necessary for maximal erythropoiesis is probably not greater than this since the patients who received supplementary histidine showed no improvement in their anaemia. Our results do not exclude the possibility that supplementary histidine may promote erythropoiesis in patients with chronic uraemia or on dialysis who are poorly nourished and eating less than the 64-75 g/day of protein taken by our patients. Nevertheless, our results do suggest that the anaemia in such patients may improve as much by increasing the nutritional value of the diets as by giving supplementary histidine.

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Emergence of Group B Streptococci in Obstetric and Perinatal Infections

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Summary

A retrospective study of obstetric and perinatal illness due to group B streptococci during 1972-4 based on bacteriological referrals from Aberdeen Maternity Hospital and Special Nursery disclosed (1) a wide spectrum of maternal morbidity, particularly associated with amniotomy and a prolonged rupture-delivery interval, and (2) the emergence of the group B streptococcus as a major cause of serious neonatal infection in infants of low birth weight, often in the absence of maternal pyrexia. The group B isolates appeared to show a previously undocumented increased resistance to the aminoglycosides gentamicin and kanamycin.

A prospective study of 369 random deliveries in Aberdeen Maternity Hospital showed a group B vaginal carriage rate of 49/1000; a neonatal colonization rate of 19/1000; maternal and neonatal morbidity rates of 16 and 2/7/1000, respectively; and an overall neonatal mortality of 1/1000 live births.

Introduction

The group B streptococcus (Streptococcus agalactiae) is classically associated with bovine mastitis. Human vaginal carriage of group B strains was documented by Lancefield and Hare,\(^1\) who found a 2-3% carriage rate in the puerperium with a 20% incidence of minor maternal infective complications. With the introduction of penicillin for streptococcal infections few reports of group B streptococci appeared until Hood et al.\(^2\) and Eickhoff et al.\(^3\) in the U.S.A. showed them to be preeminent in perinatal infections. Many reports have shown the insidious nature of "early-onset" septicemic and "late-onset" meningitic forms of the infection in neonates in the U.S.A. and Europe.\(^4\)

Jones and Howell\(^5\) reported the first two cases of group B meningitis in Britain, but though official notifications have warranted epidemiological comment\(^6\) the group B streptococcus appears to be a much underrated pathogen for man. In 1974, when we were confronted with an apparently explosive increase in group B-related diseases, we attempted to determine retrospectively the obstetric and perinatal morbidity based on
data from 1972-4 and prospectively the current rates of group B carriage in pregnancy.

Methods

Retrospective.—Reports on all specimens sent from Aberdeen Maternity Hospital and Special Nursery during 1 January 1972 to 31 December 1974 were examined to establish the number of isolations of group B streptococci. The notes of all affected mothers and babies were scrutinized with particular reference to symptoms and predisposing factors.

Prospective.—High vaginal swabs were taken from a random sample of 369 women before delivery in Aberdeen Maternity Hospital over a period of 12 weeks. When possible the swab was taken before membrane rupture. All swabs were cultured aerobically and anaerobically on blood agar, gentian violet agar, and MacConkey’s agar and enriched in thioglycollate broth for 24 hours. All β-haemolytic streptococci isolated were further characterized with respect to bacitracin sensitivity and grouping by Fuller’s formamide method using antisera against groups A, B, C, D, and G. Fully standardized and controlled antibiotic sensitivity disc testing was performed using the 15 most common antimicrobial agents. Resistance was recorded only in the complete absence of an inhibition zone. All babies of affected mothers had superficial swabs taken from eyes, ears, throat, nose, and umbilicus together with blood and cerebrospinal fluid for culture when clinically warranted.

Results

Table I shows the number of isolations of group B streptococci and the maternal and neonatal morbidity during the three-year period of study. When a mother and baby both proved positive for the organism this was recorded as one isolation. The figures do not include group B streptococci isolated from urine, which are at present under study.

The maternal morbidity data illustrate the type of problems encountered with group B streptococci and represent the symptomatic tip of the group B "iceberg," the carriage rate being more accurately assessed in table V. The 62 women with pyrexia are further analysed in table II with respect to "high-risk" factors—namely, prolonged rupture-delivery interval and artificial rupture of membranes. Puerperal pyrexia was defined as a temperature of 37.5°C or more maintained for at least six hours.11

The cases of group B infection in neonates are classified in table I as either proved "early-onset" septicemia (7 cases) or "clinically infected" (16 cases), where the characteristic clinical picture of tachypnoea, grunting, and respiratory distress with evidence of intrapartum pneumonia was noted but blood cultures were negative, probably in many cases owing to antibiotic administration to the mother. More-detailed analysis of these cases (table III) showed certain major differences between the two groups. In the proved septicemia group all infants were of low birth weight, six were premature (less than 37 weeks of gestation), and mortality was high (four deaths). Interestingly, three of these infants were born after premature rupture of the membranes and in no case was maternal fever observed, which may well have contributed to the insidious development of group B infection with the subsequent high mortality. In contrast, most of the clinically infected infants (13) were born to mothers with evidence of fever and as a consequence were given antibiotics at an early stage with no fatalities recorded.

During 1972-4 in Aberdeen there was only one reported case of "late-onset" meningitis. This was a previously healthy 1-month-old boy, who became increasingly comatose and died despite vigorous antibiotic therapy. The pregnancy was uncomplicated and none of the high-risk factors listed in table III were present.

Antibiotic sensitivity is shown in table IV for penicillin, gentamicin, and kanamycin. The results may imply a progressive acquisition of resistance to the aminoglycosides manifest firstly towards kanamycin and then in 1973-4 towards gentamicin.

The results of the prospective study of current carriage and symptom rates are given in table V. Eighteen pregnant women (49 per 1000) were vaginal carriers of group B streptococci, six of whom developed group-B-related symptoms. Seven neonates (19 per 1000) were superficially colonized with group B acquired from the mother’s
vagina, but only one (2.7 per 1000) showed early-onset symptoms due to group B, which implies a neonatal mortality of 1 per 1000 live births.

Discussion

Though group B streptococci present a characteristic colonial morphology to the trained eye, the combination of α- or β-haemolysis on blood agar, frequent sensitivity to bacitracin (60-70%), and growth on MacConkey's agar may have resulted in the organism being erroneously labelled Str. faecalis (group D). Despite advances in techniques the characterization of the many strains of group B streptococci which fail to show β-haemolysis yet retain full virulence remains a problem for the clinical bacteriologist. This coupled with the reporting of all bacitracin-sensitive streptococci as group A without confirmatory grouping, which may occur in busy routine laboratories, may have masked the insidious emergence of the group B streptococcus. The characteristic antibiogram of group B streptococci—namely, a uniform sensitivity to most antibiotics but a pronounced resistance to gentamicin and kanamycin—has been well substantiated and was, indeed, shown by most of our strains isolated in 1974. The growing frequency of resistance apparent in table IV occurred during a period of increasing clinical usage of the aminoglycosides.

Early serotyping data from this series confirm that neonates who develop early-onset infection acquire the organisms as a result of intrapartum transmission from the maternal genital tract. The protective function in pregnancy of the glycoprotein-rich mucosa, lactobacillary flora, and acid pH, so inhibitory to exogenous group A streptococci, is not operative against the extremely acid-resistant endogenous group B organisms. Thus the risk of chorioamnionitis and its sequelae due to the ascent of vaginal bacteria into the amniotic cavity after rupture of the membranes is greatly increased. This is further compounded by the fact that amniotic fluid is an excellent culture medium for the group B streptococcus.

The maternal morbidity data for women carrying group B streptococci underline the inherent risks of amnionitis, particularly when this is coupled with a prolonged rupture-delivery interval. Premature rupture of the membranes in the presence of and perhaps even precipitated by group B streptococcal activity is clearly hazardous, particularly for the fetus, necessitating aggressive management.

Over the three-year period of study the yearly figures for neonatal coliform septicemia were 5, 7, and 4, suggesting that the phase of coliform dominance in perinatal infections may now be challenged by the group B streptococci. The incidence of so-called late-onset meningitis, at least in our experience in Aberdeen, is extremely low (one case in three years) compared with that in Houston (33 cases in three and a half years), which is apparently a "hot spot" for group B in the U.S.A. The absence of maternal pyrexia as a premonitory sign in the early-onset septicemic group emphasizes the need for increased clinical awareness of the potential pathogenicity of these organisms. Speed of diagnosis is clearly essential in late pregnancy and labour, when rapid bacteriological identification will enable rational decisions on antibiotic prophylaxis and the management of labour to be made.

Since routine vaginal swabbing of all pregnant women is probably impracticable and indeed not guaranteed to identify all susceptible cases, emphasis for controlling group-B-associated puerperal disease must be shifted to elucidating high-risk factors, some of which are highlighted here—for example, premature rupture of the membranes, amnionitis, and a prolonged rupture-delivery interval. Penicillin has proved highly efficacious in eradicating group B streptococci from the vagina, where the fetus is deemed to be at high risk, but, as Butter and de Moor and Eickhoff have indicated, the indiscriminate use of antibiotic prophylaxis is to be deprecated.

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