Vesicoureteric reflux occurred in eight infants with bacteriuria. This was regarded as being slight in two instances and moderate in six. There seemed to be no relation between the presence of vesicoureteric reflux, raised blood urea levels, proteinuria, and symptomatic infection. All cases of moderate vesicoureteric reflux were associated with asymptomatic bacteriuria in the neonatal period. Three to four weeks were allowed to elapse after the episode of bacteriuria before the radiological studies were performed.

The screening of 1,460 consecutive infants for bacteriuria did not reveal any examples of obstructive uropathy on further investigation. Moreover, while vesicoureteric reflux was often found, it was not of the gross variety (see Table III). Recently, it has been shown that probably only this gross variety of vesicoureteric reflux is associated with progressive renal damage in a high proportion of cases (Rolleston *et al.*, 1970).

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Immunoglobulin Levels in Newborn Infants with Hepatosplenomegaly

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Summary

Serum IgM and IgA levels were measured in 97 newborn infants with and 141 without hepatosplenomegaly. All were considered normal at birth and had no apparent disease on clinical examination. Thirty per cent. of the infants with hepatosplenomegaly were found to have IgM levels of 20 mg/100 ml or greater, a level established as abnormal when compared with the control group. The number of infants with raised IgM level and the geometric mean level were significantly different ($P < 0.001$) from those in the control group. No difference, however, was found in serum IgA levels between the two groups of infants. The results suggest that intrauterine infections may sometimes be the cause of hepatosplenomegaly in newborn infants without apparent disease.

Introduction

The liver is palpable in almost all, and the spleen in some, normal newborn infants (McNicholl, 1957; Nelson, 1969). In some infants the liver is enlarged beyond normal limits and the spleen is obviously palpable. Except for the hepatosplenomegaly these infants show no other abnormalities and were considered to be normal at birth.

Hepatosplenomegaly in the normal newborn infant probably has a varied aetiology, including infection in utero. It is a common, and may be the only, clinical manifestation in intrauterine infections (Stern and Tucker, 1965; Overall and Glasgow, 1970). Intrauterine infections have been shown to be associated with raised IgM levels in infants, and the quantitation of this immuno-

globulin in cord sera has been shown to be a useful screening test for detecting mild or "silent" infections (Alford, 1971). This communication describes the results of immunoglobulin determinations in a group of newborn infants with hepatosplenomegaly and shows that this abnormality at birth, in some infants at least, may be associated with a clinically inapparent intrauterine infection.

Patients and Methods

Ninety-seven newborn infants delivered in the Kandang Kerbau Hospital in Singapore between December 1968 and March 1970 were studied. These infants were considered to be normal at birth except that they presented with an enlarged liver (≥ 3 cm below the right costal margin) and spleen (≥ 1 cm). They included both sexes in the three major ethnic groups (Chinese, Indian, and Malay) and their ages ranged from 6 hours to 3 days. One hundred and forty-one normal newborn infants who had no hepatosplenomegaly were also studied. These control infants were delivered in the same hospital from February to July 1970 and they were matched for ethnic group, sex, and age.

A complete blood count was made and radiological examination of the long bones was carried out on the infants with hepatosplenomegaly. Umbilical cord blood or blood obtained by venepuncture within three days after birth was examined for immunoglobulins IgM and IgA by a modification of Mancini's single radial immunodiffusion (Mancini *et al.*, 1965). Standard human serum and specific antisera were supplied by Hoechst Pharmaceuticals Ltd. The details of the method will be published elsewhere. The coefficients of variation for the standard serum determined from 40 estimations over a nine-month period were 6.3% for IgM and 6.2% for IgA. In this study cord sera in which IgA levels were higher than IgM levels were thought to be contaminated with maternal blood due to placental leak and were excluded from analyses. Immunoglobulin concentrations were converted to logarithms for statistical analyses.

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Results

The IgM concentrations in cord sera and sera obtained within the first six days of life in the control group of infants are presented in Table I. There was no significant increase in the geometric mean IgM level in sera taken within the first three days of life. The IgM concentrations increased significantly from the fourth day onwards. In this study the sera of infants with hepatosplenomegaly collected within three days after birth were used for comparison with cord sera in the control group.

The geometric mean for IgM concentrations in the 141 control cord sera studied is given in Table II. Ninety-seven per cent.

TABLE I—IgM Concentrations (mg/100 ml) in Cord Sera and Sera Obtained Within the First 6 Days of Life in Control Infants

Specimen	No. Tested	Geometric Mean	± 2 Standard Deviations
Cord	108	9.7	5.0-19.0
Day 2	16	9.4	4.6-19.0
Day 3	17	9.4	4.5-19.5
Day 4	20	11.7	5.6-24.4
Day 5	15	14.4	6.4-32.8
Day 6	12	17.4	6.8-44.1

TABLE II—Levels of Serum IgM in Control Infants and in Infants with Hepatosplenomegaly

Range (mg/100 ml)	Number of Sera	
	Control Infants	Infants with Hepatosplenomegaly
0- < 5	0	1
5- < 10	81	30
10- < 15	45	31
15- < 20	11	6
20- < 25	4	15
25- < 30	0	4
30- < 35	0	4
35- < 40	0	0
40- < 50	0	2
50- < 60	0	1
60- < 80	0	3
> 100	0	3
Total	141	97
No. with ≥ 20 mg/100 ml	4*	29*
Geometric mean (mg/100 ml)	9.6†	13.9†
± 2 S.D. (mg/100 ml)	4.9-18.9	3.3-58.3

*The difference is highly significant ($P < 0.001$) by the χ^2 test.

†The difference is highly significant ($P < 0.001$) by the t test.

of the control cord sera had levels of IgM less than 20 mg/100 ml. In the present study IgM levels of 20 mg/100 ml or greater were therefore considered to be abnormally raised. In the control group 4 out of 141 (3%) had raised IgM levels, whereas in the infants with hepatosplenomegaly 29 out of 97 (30%) had raised IgM levels. The difference between the numbers with raised IgM levels in the two groups of infants is highly significant ($P < 0.001$) when analysed by the χ^2 test. In the infants with hepatosplenomegaly the geometric mean level for IgM was 13.9 mg/100 ml with ± 2 S.D. of 3.3 to 58.3 mg/100 ml. When the t test is applied the difference in the mean levels of the two groups of infants is found to be highly significant ($P < 0.001$).

A total of 138 cord sera from the control group of infants were examined for IgA levels. Only 49 (35%) of them had detectable levels of IgA, with the values ranging from 2.9 to 15.1 mg/100 ml (Table III). The geometric mean IgA concentration in this group was 4.7 mg/100 ml with ± 2 S.D. of 2.0 to 7.4 mg/100 ml. The IgA concentrations found in the infants with hepatosplenomegaly were very similar to those of the control

group. Of 93 infants with hepatosplenomegaly tested, 31 (33%) showed detectable levels of IgA, ranging from 3.4 to 17.0 mg/100 ml. The geometric mean level was 5.0 mg/100ml with ± 2 S.D. of 3.0 to 8.0 mg/100 ml.

Discussion

Many intrauterine infections may be inapparent at birth (Eichenwald, 1960; Miller *et al.*, 1967; Alford, 1971). The measurement of IgM and IgA in newborn sera has been shown to be a useful screening procedure in the detection of such infections (Stiehm *et al.*, 1966; Alford *et al.*, 1967; Alford, 1971). In the IgM screening method 20 mg/100 ml or greater in newborn sera has been considered abnormal by many investigators (Alford, 1971). This value for raised IgM was also used in the present study, since the upper limit of normal for cord IgM in our series was 18.9 mg/100 ml.

The association of raised IgM levels with hepatosplenomegaly in an appreciable proportion (30%) of newborn infants with this abnormality is of interest. Intrauterine infections are a well-known cause of hepatosplenomegaly (Stern and Tucker, 1965; Overall and Glasgow, 1970) and the present finding seems to suggest such a relationship. However, hepatosplenomegaly in many infants was probably due to other causes, as shown by the failure to demonstrate raised IgM levels in most of these infants.

No difference was found in IgA concentrations in the two groups of newborn infants. In contrast to many reports (Alford, 1971), we found that a high proportion (35%) of normal cord sera contained IgA with levels ranging from 2.9 to 15.1 mg/100 ml and a mean level of 4.7 mg/100 ml. The mean IgA level in our series is somewhat higher than the level (3.35 mg/100 ml) reported for newborns in Taiwan (Yang *et al.*, 1970).

Further studies are in progress to identify the specific agents that caused the raised IgM levels in newborn infants with hepatosplenomegaly. Among the known pathogens that cause intrauterine infections are rubella virus, cytomegalovirus, herpes simplex virus, *Treponema pallidum*, and *Toxoplasma gondii*.

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TABLE III—Levels of Serum IgA (mg/100 ml) in Control Infants and in Infants with Hepatosplenomegaly

	No. Tested	No. and % with IgA	Geometric Mean	± 2 S.D.	Range
Control infants	138	49 (35%)	4.7	2.0-7.4	2.9-15.1
Infants with hepatosplenomegaly ..	93	31 (33%)	5.0	3.0-8.0	3.4-17.0