infection with delayed resolution in an infant should raise the possibility of empyema; the presence of dullness to percussion makes the diagnosis likely (Glaser and Epstein, 1931). Other signs may be deceptive. Breath sounds may not be greatly altered, mediastinal shift may not be detectable, and the infant is often too ill to enable a technically adequate x-ray picture to be taken, though this may be of great help in the differentiation from collapse. Clubbing did not appear in the two cases reported here, and other authors do not stress it. In Case 2 a white blood count showed a granulocytopenia early in the disease.

Most authors agree that repeated aspiration with penicillin instillation should be tried before other treatment is contemplated (Ellis, 1951). Chaplin (1947) found that in children of all ages aspiration alone failed to cure 13 out of 21 staphylococcal empyemas, but of 4 infants under 6 months intercostal drainage was necessary only in one. In Case 1 the pus was sterile after six aspirations, and thereafter no further fluid could be obtained. Rapid sterilization of the pus with a small number of aspirations is often reported. A few cases even responded rapidly to aspiration before penicillin or sulphonamides were available (Spence, 1920). It is obvious that surgical drainage is unnecessary in these cases and is unlikely to hasten their recovery.

In pyothorax, whether air is present or not, the thoracic contents may be under pressure, and aspiration relieves the clinical condition dramatically. This was found not only at the initial needling but on later occasions, when aspiration was delayed for more than 24 hours in the belief that the fluid had resolved. Aspiration should be carried out daily, as, even though the pus may seem to be decreasing, rapid reaccumulation may be disastrous. Sterilization of the pus seems to prevent its reaccumulation; the chronic sterile collection of pus known in adults as "penicillin empyema" has not been reported in infants.

In Case 2 the staphylococcus was resistant to penicillin from the outset and, although it remained sensitive to streptomycin *in vitro*, local streptomycin failed to sterilize it. Intrapleural aureomycin was tried, but instillation of 50 mg. at a time proved too irritant. Smaller amounts did not affect the staphylococcus, probably because aureomycin is not stable in solution. No preparation of chloramphenicol for local use was available and therefore an intravenous preparation of terramycin was tried: 100 mg. intrapleurally produced no reaction, and 24 hours later only a very attenuated growth of the staphylococcus was obtained. In addition, a bacteriostatic concentration of terramycin was found in the pus after 24 hours, and there is little doubt that the sterilization of the pus and the infant's recovery were due to this antibiotic.

Few published accounts of staphylococcal pyothorax in infants mention residual effects on lung function. In Case 1 the child was apparently normal a year later. In Case 2 there was residual upper-lobe atelectasis after nine months.

The place of surgical drainage by intercostal tube is still not decided. The good immediate results obtained by this treatment suggest that it is indicated when daily aspiration and instillation of antibiotics fail to sterilize the pus within two weeks. It was probably indicated in Case 2, but it is doubtful if full expansion of the lung would thereby have been achieved.

Summary

Two cases of staphylococcal pyothorax following pneumonia in infants in the first month of life are described. Both responded to aspiration and sterilization of the pus by intrapleural antibiotics. Aetiology, diagnosis, and treatment are discussed.

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IMMUNITY OF THE NEWBORN

A STUDY OF THE TRANSFER OF ANTI-STREPTOLYSIN FROM MOTHER TO FOETUS DURING PREGNANCY

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Interest in the transfer of antibodies across the placenta has increased since the observation that cord blood may contain more antibody than that of the mother. Most of the work within recent years has been concerned with diphtherial and staphylococcal antibodies.

In order to extend the range of bacterial antibodies investigated in this way it was decided to estimate in mothers and their newborn children the blood level of antibodies to another common infecting organism. For this purpose the streptococcus was chosen because of its ubiquity, and also because there are available convenient methods of estimating anti-streptolysin. The results obtained in this investigation have amply confirmed the high antibody level previously observed in the cord blood of newborn infants.

Materials and Methods

Blood Samples.—Cord blood was obtained at delivery, and each mother was bled by venepuncture, either immediately before or soon after delivery. Samples were collected in dry tubes and allowed to clot.

Streptolysin.—The bacterium used for the preparation of the streptolysin was a culture of Group A III *Streptococcus pyogenes* (strain No. S 84) obtained from the State Serum Institute, Copenhagen. According to Todd (1932) two streptolysins can be obtained from haemolytic streptococci of Lancefield's Group A, C, or G. One, streptolysin O, is oxygen-sensitive, and the other, streptolysin S, is oxygen-stable but heat-sensitive, and can be extracted with serum. Throughout the whole series of experiments here described a single preparation of streptolysin O was used, and this was prepared according to the method of Kalbak (1942), described in his modification of the anti-streptolysin titration technique of Todd (1932). The minimum haemolytic dose (M.H.D.) of the streptolysin was checked repeatedly, and remained constant from the beginning to the end of the series. Storage was at 4° C. under a layer of sterile liquid paraffin 1 in. (2.5 cm.) thick.

Standardization of Streptolysin.—Doubling dilutions of streptolysin were made in buffer from 1/2 to 1/256 so that

each tube contained 1 ml. To every tube were added 1 ml. of buffer and 0.5 ml. of washed rabbit cells. The last tube showing complete lysis throughout this series was 1/8. For the tests a 1/5 dilution was used, this being slightly less than 2 M.H.D.

Buffer Solution.—The buffer solution used for dilution and suspension of rabbit cells was composed of 4.8 g. NaCl, 1.45 g. KH_2PO_4 (anhydrous), and 7.6 g. $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ dissolved in one litre of distilled water.

Cell Suspension.—For each batch of tests a fresh 5% suspension in buffer of washed rabbit cells was prepared. The same rabbit was used for the whole series, in order to avoid variation in rabbit-cell fragility. The blood used was never less than 24 hours and never more than four days old; as a rule the rabbit was bled the day before a batch of tests.

Technique

Maternal and cord blood sera were diluted 1/10 with buffer after inactivation by heating in the water-bath at 56° C. for 30 minutes. Doubling dilutions were made of the diluted sera in buffer from 1/40 to 1/1,280, so that the total volume in each tube was 1 ml. Separate pipettes were reserved for each of the reagents, and special pipettes for making serial dilutions. To each tube was added 1 ml. of diluted streptolysin (0.2 ml. streptolysin + 0.8 ml. buffer), thus providing just less than 2 M.H.D. The tubes now containing 2 ml. were shaken individually to ensure complete mixing, and 0.5 ml. of the 5% rabbit cell suspension was added. The tubes were again shaken individually and then heated for 45 minutes, about half immersed in the water-bath at 37° C.

After inspection the tubes on either side of the apparent end-point were centrifuged and re-examined. The end-point was taken as the first tube which showed any naked-eye haemolysis. The degree of haemolysis was estimated with an M.R.C. grey wedge photometer, the supernatant being diluted with buffer where necessary to obtain a reading on the scale. This method proved remarkably accurate. For example, complete haemolysis of the standard volume of cells consistently gave a reading of 96 when the supernatant was diluted 1 in 4.

Inhibitory Serum Factors

Certain factors in serum may interfere with tests which use haemolysis as an indicator. The inhibitory effect of cholesterol is well known, but it is accepted that as a rule cholesterol in the cord blood is substantially below the maternal level. In consequence cholesterol was disregarded as a possible cause of the high infant levels recorded. For the same reason phospholipids were discounted.

Another substance considered was ascorbic acid, not only because it has been reported to be much higher in cord blood than in that of the mother (Mindlin, 1940), but also because of its effect on haemolysis (Traina, 1949).

Since Traina used very large amounts of ascorbic acid, it seemed extremely unlikely that inhibition due to this substance could affect our experiments. Nevertheless, experiments were made with sera to which ascorbic acid had been added. Umbilical-cord blood levels of 1.2 to 2.48 mg./100 ml. have been reported by Mindlin (1940) for plasma and by Barnes (1947) for whole blood. Consequently sera containing approximately ten times these concentrations were tested in parallel with control sera to which no ascorbic acid had been added. The results in every pair of tests were identical, and indicated that levels of ascorbic acid to be found in cord blood would not influence the experiments.

Results

Anti-streptolysin O was titrated in the sera of 46 mothers and their babies. The results of the consecutive series are presented in Table I, where the visual end-points are recorded according to titre. It was found that in 33 out of the 46 cases the cord blood level was at least twice that of the mother's blood. In one instance (Case 38) both

levels were too low to demonstrate a difference under the conditions of the test; while in the remaining 12 cases the first tube to show haemolysis was the same for both mother and child, although in most of these there was a noticeable

TABLE I.—Comparative Titrations of Anti-streptolysin O in Maternal and Cord Blood Sera

Case No.	Anti-streptolysin O Titre (Reciprocal)		Higher Level	Case No.	Anti-streptolysin O Titre (Reciprocal)		Higher Level
	M.	C.			M.	C.	
1	643	1,280	C	24	80	320	C
2	640	1,280	C	25	40	160	C
3	160	160	*	26	160	320	C
4	160	320	C	27	160	320	C
5	160	640	C	28	40	40	C
6	160	320	C	29	80	160	C
7	320	640	C	30	640	640	C
8	160	320	C	31	40	80	C
9	160	160	*	32	160	320	C
10	80	160	C	33	40	40	C
11	80	160	C	34	160	320	C
12	160	320	C	35	160	160	C
13	160	160	*	36	80	80	C
14	320	320	*	37	80	80	C
15	160	320	C	38†	<40	<40	C
16	320	640	C	39	80	160	C
17	80	160	C	40	320	640	C
18	80	160	C	41	160	640	C
19	80	160	C	42	160	320	C
20	160	160	*	43	40	80	C
21	320	320	*	44	160	320	C
22	40	80	C	45	80	160	C
23	40	80	C	46	320	1,280	C

C.—Cord. M.—Maternal.

* In 12 cases the end-point tubes gave the same titre although haemolysis was not always equal. Estimated differences in degree of haemolysis are shown in Table II.

† Both maternal and cord levels were too low to be recorded under the conditions of the test.

naked-eye difference in degree of haemolysis between the two. When this difference was estimated with the grey wedge photometer it was found that in eight cases the anti-streptolysin was higher in cord blood than in the maternal blood, in three cases the levels were approximately equal, while in only one instance was the maternal level the greater. The results of the photometer readings are shown in Table II.

TABLE II.—Estimation of Degree of Haemolysis in the Supernatant at the End-point

Case No.	Maternal		Cord		Higher Level of Anti-streptolysin
	Dilution	Photometer Reading	Dilution	Photometer Reading	
3	4 ×	84	Undil.	65	Cord
9	4 ×	78	"	63	"
13	Undil.	54	"	132	Maternal
14	"	115	"	85	No significant difference
20	4 ×	54	4 ×	84	"
21	4 ×	75	Undil.	52	Cord
28	4 ×	87	"	92	"
30	4 ×	78	"	98	"
33	4 ×	96	2 ×	43	"
35	4 ×	72	2 ×	31	"
36	Undil.	33	Undil.	35	Equal
37	4 ×	75	2 ×	43	Cord

The degree of haemolysis was used to interpolate empirical values of anti-streptolysin between the 100% differences achieved in the test proper recorded in Table I. The greater the titre of anti-streptolysin present the lower was the degree of haemolysis. Complete haemolysis of the standard dose of cells was found to give the reading 96 when tubes were diluted 1 in 4.

In the series of 46 cases it was found that the cord blood contained more anti-streptolysin than the maternal blood in 41, the levels were approximately equal in three, the maternal level was higher in one, and in one case the levels were too low for the test.

Discussion

This investigation shows that in the great majority of cases anti-streptolysin levels are much higher in cord blood than in maternal blood. This finding was not unexpected, in view of the high antibody levels in the cord blood reported with diphtheria toxin (Barr *et al.*, 1949) and with staphylococcal toxin (Murray *et al.*, 1950). It does, however, provide

another example of high antibody content of foetal blood, and in this respect confirms the previous findings. A striking feature of the results is the consistent relationship between the mother's and the infant's antibody level as well as the magnitude of the latter.

The significance of these findings, and the revised view of placental permeability to antibodies to which they lead, was discussed in a previous paper (Calman and Murray, 1951). In that paper we concluded that the simple filtration hypothesis was becoming untenable, and our present results support that opinion.

Summary

In 46 cases the anti-streptolysin O titre of the maternal and cord blood was estimated at the time of delivery. The level in the cord was at least twice that of the mother's in 33 cases; it was higher in 41 cases, about the same in three, and lower in only one. In one case both levels were too low to be measured.

The material for investigation was obtained through the co-operation of the obstetricians, paediatricians, and labour ward staff of Queen Charlotte's Maternity Hospital.

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NATURAL HISTORY OF CYSTIC DISEASE OF BREAST TREATED CONSERVATIVELY

BY

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Cystic disease of the breast is a common and clearly defined clinical entity. Though it has been known since the time of Réclus that the condition is potentially multiple and bilateral, much the commonest manifestation clinically is as a solitary lump in one breast, the breasts otherwise being clinically normal. If the fluid from this solitary lump is aspirated, the affected breast, after a few hours in which the site of the aspirated cyst may be felt as a hollow, becomes normal to inspection and palpation. Cystic disease of the breast has sometimes been regarded as a potentially dangerous condition with an increased liability to the development of carcinoma. The support for this view is derived less from clinical evidence than from indirect evidence in the form of histological (Cheatle, 1934-5; Willis, 1948) and animal experimental findings (Cheatle, 1934-5).

The acceptance of the view that cystic disease of the breast is a dangerous condition naturally leads to some type of excision, often simple mastectomy. While this procedure averts the postulated danger in the affected breast, it is often at the price, from the human standpoint, of a serious mutilation of the patient's womanhood, and, from the scientific standpoint, of the destruction of the clinical evidence of the subsequent

natural course of the disease, which might have been innocent. Moreover, it is irrational to do a unilateral extirpation for a bilateral disease.

During the twenty-odd years that one of us (D. H. P.) has been in consultant practice he has consistently regarded cystic disease of the breast as essentially an innocent condition, to be treated preferably by aspiration. There has been one important exception to this conservative attitude. If there was any suspicion of intracystic growth—and this is easily determined if a few simple rules which will be mentioned later are followed—the condition was explored at operation and treated accordingly. The number of these cases was small, and in all of them the growth was present at the time that the patient first presented herself; in no case did it develop as a late complication in a simple cyst treated primarily by aspiration. It is argued later that these facts may warrant these cases with intracystic growth being placed in a separate group, not only from the point of view of practical management but also pathologically; and that in many cases the cyst may be a response to the growth rather than the growth being a complication of the cyst. Apart from evidence of growth in a cyst, the presence of any pathological solid lump in a breast which also contained a cyst was regarded as an indication for exploration and biopsy, as in a breast without a cyst.

In this paper the results of the above-defined conservative attitude to simple cystic disease of the breast are given. A detailed analysis can be made only of cases of cysts seen in private, because the much larger hospital group were treated as out-patients, and their records are buried in an unindexed mass of out-patient material. An attempt has been made to get over this difficulty to some extent by analysing in-patient hospital records of cases of carcinoma of the breast from the point of view of a previous history of cystic disease. The small number of cases of cystic disease with evidence of simultaneous intracystic growth are analysed separately.

Analysis of Results

Table I analyses all breast cases seen in private practice to show the relative frequency of cystic disease. The table almost certainly does not represent the true relative incidence

TABLE I.—*Diagnosis in 535 Consecutive Breast Cases Seen During 1931-50 (D. H. P.)*

Carcinoma of breast (including 5 cases of Paget's carcinoma) ..	260 cases
Painful breasts	102 "
Cysts of breast	76 "
Fibroadenoma	28 "
Abscess	25 "
Discharge from nipple	19 "
Miscellaneous	25 "

of breast conditions, owing to the unconscious selection imposed by private consultant practice. For example, painful breasts and fibroadenomata are probably much commoner than indicated, as also is the more recently defined entity known as periductal mastitis (Geschickter, 1943), or duct stagnation (Patey, 1949). But since carcinoma of the breast and cystic disease both present in a similar age group with the same symptom of a painless lump, the relative incidence of cases of carcinoma and cyst can probably be regarded as approximately accurate—that is, seven cases of carcinoma to two of cyst. It will be noted that no case has been diagnosed as chronic mastitis, which has been regarded as a non-existent disease (Patey, 1951), the postulated existence of which under this or any other name has befogged breast pathology and diagnosis for far too long.

In all 76 cases of cyst the diagnosis was proved—in 69 by aspiration and in 7 by operation. Operation was performed either because aspiration had failed, the cyst being