

Prospective study of serum staphylococcal antibodies in cystic fibrosis

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SUMMARY Serum IgG antibodies to teichoic acid and alpha toxin from *Staphylococcus aureus* were measured in 62 patients with cystic fibrosis by enzyme linked immunosorbent assays. The patients were followed up for 12-24 months in a prospective study. Raised titres were found exclusively in patients chronically colonised with *S aureus*. Patients colonised with both *S aureus* and *Pseudomonas aeruginosa* had significantly higher titres against teichoic acid than those carrying *S aureus* alone. Titres were significantly higher when there were clinical signs of low grade infection in the patients chronically colonised with *S aureus* alone, and in those with both *S aureus* and *P aeruginosa*. Significant reduction in titres occurred after antimicrobial treatment given either orally or intravenously in patients with normal erythrocyte sedimentation rates and white cell counts. Measurement of staphylococcal antibody titres may be valuable in monitoring pulmonary infection and antimicrobial treatment in patients with cystic fibrosis.

The major factor in determining the severity of illness and mortality in patients with cystic fibrosis is still chronic respiratory tract infection.¹ The predominant organisms isolated from sputum in these patients are *Staphylococcus aureus* and *Pseudomonas aeruginosa*.² The prognosis after colonisation with *P aeruginosa* is poor.³ Colonisation by *P aeruginosa* is usually preceded by colonisation by *S aureus* for varying lengths of time.¹ The extent of lung damage caused by *S aureus* and its role in the progression of the disease is still not clear.⁴ Different views are reflected in the treatment regimens given which range from no treatment (to protect from an overgrowth of *P aeruginosa*),⁵ long term prophylaxis,^{4, 6} or intensive treatment to eradicate the staphylococci.⁷ Eradication of the colonising organism, however, be it *S aureus* or *P aeruginosa*, is seldom more than temporary. Meanwhile the use of antibiotics controls episodes of overt infection.⁸⁻¹⁰

There is no consensus about when to prescribe antibiotics.^{4, 10} Our policy, which is to begin treatment in the initial stage of infection, is difficult in cases when the erythrocyte sedimentation rate and white cell count are normal.

New serological tests have recently shown a rapid antibody response to staphylococcal antigens, which raises the possibility of identifying patients in need

of treatment.¹¹ Enzyme linked immunosorbent assays (ELISAs), using purified staphylococcal teichoic acid and alpha toxin as antigens, have improved the sensitivity of serology in the diagnosis of septicaemia and deep staphylococcal infections.¹² We have previously used these assays in patients with cystic fibrosis and found increased titres to both antigens only in patients colonised with *S aureus*, and particularly those receiving inadequate doses of antibiotics.¹³ These observations initiated a long term prospective investigation of the changes in antibody titres associated with colonisation, early signs of active infection, and the effect of treatment with antibiotics in patients with cystic fibrosis.

Patients and methods

PATIENTS

Sixty two patients with cystic fibrosis, aged from 4 months to 32 years (mean and median 12.5 years), were studied. The diagnosis was made by the sweat test (chloride > 80 mmol/l) and typical pulmonary symptoms. All patients but one had pancreatic insufficiency. All patients were followed up monthly. The patients were classified into four groups according to the results of sputum cultures.

Group A comprised 18 patients, aged 6 to 27 years

(mean 14 years) who were chronically colonised with *S aureus*—that is, *S aureus* was repeatedly present in the sputum during the six months preceding the study. In 10 patients *Escherichia coli*, *Klebsiella* species, *Haemophilus influenzae* and *Pseudomonas maltophilia* were also occasionally found. A total of 133 samples were analysed from this group.

Group B comprised 16 patients, aged 2 to 26 years (mean 15 years) who were chronically colonised with *S aureus* but who were also either chronically colonised (13 patients) or occasionally colonised with *P aeruginosa* (three patients). One hundred and sixty two samples were analysed from these patients.

Group C comprised 14 patients, aged 6 to 32 years (mean 17 years) who were chronically colonised with *P aeruginosa*. Cultures from five patients had also grown *S aureus* occasionally, and those from one patient grew *E coli* intermittently during the study period. One patient was chronically colonised with *E coli*. A total of 156 samples were analysed.

Group D comprised 14 patients aged 4 months to 5 years (mean 2.2 years) who were too young to collect sputum. Nasopharyngeal cultures occasionally grew *H influenzae*, *S aureus* (10 patients), and *Haemophilus parainfluenzae* but never *P aeruginosa*. Thirty three samples were analysed.

The study was originally designed to last a year but for most of the patients (44 of 62 or 71%) the study was continued for another year. Earlier samples were also available from 25 patients (40%), resulting in a follow up of 24 to 94 months.

The clinical score was recorded according to Shwachman excluding the x-ray score; thus a maximum of 75 indicated an excellent clinical condition.¹⁴ The clinical scores ranged from 30 to 75 (mean 61, median 63) at the beginning of the study. The pulmonary x-ray pictures were evaluated by a modified Norman-Chrispin score.¹⁵ The mean x-ray score was 3 (median 3, range 0–12); a value of 0 indicated a normal picture and a maximum of 16 severe disease. Forced expiratory volume in one second was measured at least once a year in patients older than 6 years and expressed as the percentage of predicted values for age.¹⁶ This averaged 67% (median 65, n = 39, range 20–111) at the first investigation of the patients during the study period.

Clinical signs and symptoms of infection such as change in the volume and appearance of the sputum, increased respiratory rate, dyspnoea, increasing abnormalities on chest auscultation, increasing cough, decreased appetite, weight loss, and

deterioration in the results of standard biochemical tests were used to indicate the necessity for antimicrobial treatment. The classification of the patients as 'infected' or 'non-infected' was based on the presence of two or more of these criteria. In most cases the clinical signs of infection were discreet and not paralleled by raised erythrocyte sedimentation rate or white cell count. Fever was seldom present.

During the two year study, 81 courses of intravenous antibiotics were given to patients in groups A–C. The effects of treatment on antibody titres were determined in blood samples taken at the start and the end of the courses, the average interval being 13 (range 9–29) days. Sixteen courses of treatment were given to six patients harbouring only *P aeruginosa*, while the remaining courses (n = 65) were given to patients chronically or occasionally colonised with *S aureus*. Chemotherapy was based on the resistance pattern of the bacteria.^{17 18} Cephalosporins either alone or in combination with an aminoglycoside accounted for 63% of the total intravenous courses and 55% of the intravenous courses given to the patients harbouring *S aureus*. The remaining intravenous courses comprised ampicillin, cloxacillin, imipenem, or a ureidopenicillin. Furthermore, some patients were frequently treated orally with flucloxacillin alone or with pivampicillin or trimethoprim and sulphamethoxazole.

Capillary or venous blood samples were taken from all patients at least once a year, giving a total of 484 samples during the study. In most cases samples were obtained before and after a period of antibiotic treatment (n = 222). Sera were frozen at –20°C until analysed. All sera from each patient were analysed at the same time.

ELISA for IgG antibody determinations to teichoic acid^{13 19} and to alpha toxin^{13 20} have been described in detail before. Briefly, cobalt irradiated polystyrene microplates (Dynatech M 129B, Plochingen, West Germany) were coated overnight with teichoic acid (2 µg/ml) or alpha toxin (5 µg/ml). Patients sera were tested in duplicate in dilutions of 1/1000 or 1/10000, incubated for one hour, and then overnight with alkaline phosphatase conjugated swine antiserum to human IgG antibodies (Orion Diagnostica, Finland). All incubation was done at room temperature (22°C). 100 µl volumes were used throughout and all washings were done three times.

The titre measured by the ELISA was defined as the absorbance value at A405 nm multiplied by the serum dilution factor—that is, 10³ or 10⁴. Known positive and negative controls (three patients and three healthy controls) were included in each test series and the results were corrected against these controls to minimise day to day variation. The

coefficients of variation were 5–10% (intra-assay) and 10–15% (interassays).

The upper limit of normal values had previously been established in a healthy population of different ages.^{19, 20} As the titres showed definite variations with age the upper cut off point was set at the mean (2 SD) for different age groups, corresponding to about the 95th percentile of the normal population. Consequently, a diagnostic titre in one age group could represent a normal value in another age group. Due to the long observation period in some children, different cut off points had to be applied for samples at different times in the same patient. The ELISA titres are therefore presented as multiples of the upper limit of normal values for the relevant age group, which was set at 1. As the upper limit of normal was set at mean (2 SD) the mean titres in the healthy population ranged from 0.35 to 0.5 in the different age groups. Multiples of more than 1 were considered to be diagnostic.

The χ^2 test with Yates's correction, the Mann-Whitney U test and the Wilcoxon matched pairs signed ranks test were used to assess differences in proportions.

Results

CLINICAL MEASUREMENTS

Over the study period there was no change in the average values of clinical score, x ray score or readings of forced expiratory volume in one second, in the whole group of patients, indicating stable disease. The patients classified as 'non-infected' had a normal mean white cell count of $6.8 \times 10^9/l$ ($n = 156$, range 2.1–13.6) and normal erythrocyte sedimentation rate of 13 mm in the first hour ($n = 143$, range 1–37). Most patients showed only slight symptoms of infection when classified as 'infected'—for example, loss of appetite, increased coughing—with only a slight increase in white cell count (mean $9.7 \times 10^9/l$, $n = 126$, range 2.4–20.5), and erythrocyte sedimentation rate of 20 mm in the first hour ($n = 117$, range 2–112).

The 81 intravenous courses of antibiotics, mostly prescribed for low grade infection, resulted in clinical improvement with reduced sputum and increased body weight. A decrease in white cell count from $9.8 \times 10^9/l$ ($n = 59$, range 2.4–19.1) before treatment to $7.1 \times 10^9/l$ (range 2.1–14.1) after treatment was noted ($p < 0.001$). There was no corresponding fall in erythrocyte sedimentation rate (the mean value being 17 mm in the first hour before and 16 mm after treatment). Values for forced expiratory volume in one second showed significant improvement after antimicrobial treatment, increasing from 57% ($n = 32$, range 18–99) to 68% (range 19–110) $p < 0.001$.

ANTIBODIES TO TEICHOIC ACID

IgG antibody titres to teichoic acid were determined in 484 serum samples from the 62 patients (1–30 samples for each patient). Fig. 1 shows the distribution of titres in each group in relation to clinical signs of infection. Most patients are represented once as 'infected' and once as 'non-infected'. Diagnostic titres (above 1) were found exclusively in patients chronically colonised with *S aureus* alone or in combination with *P aeruginosa* (groups A and B compared with groups C and D, $p < 0.01$). The titres were significantly higher in the 'infected' patients compared with those in the 'non-infected' group ($p < 0.02$). One patient in group D, whose nasopharyngeal culture repeatedly yielded *S aureus*, had a slight increase in antibody titre. Three patients with dual colonisation (group B) were the only 'non-infected' patients with diagnostic titres (Fig. 1).

When analysing the results of all 484 samples, titres above the normal ranges for age were found in 29% of the sera from patients chronically colonised with *S aureus*; 17% in group A and 36% in group B (Fig. 2a). The mean titres were significantly higher in patients chronically colonised with *S aureus* (groups A and B, 0.6 and 1.5, respectively), compared with those who were not (groups C and

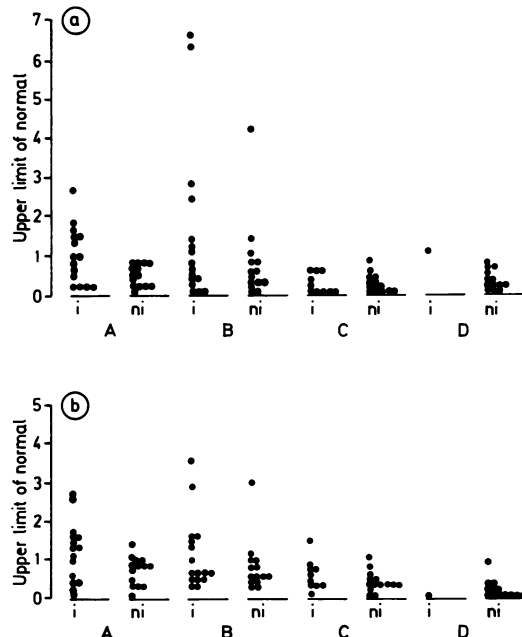


Fig. 1a and b Serum titres of IgG antibodies to staphylococcal teichoic acid (1a) and α toxin (1b) in groups A, B, C, D; i = infected; ni = not infected

D, 0.3 and 0.4, respectively, $p < 0.001$). The difference in mean titres between groups A and B was also significant ($p < 0.001$).

The frequency with which diagnostic titres were found varied with clinical signs of infection, 7% in group A and 29% in group B when the patients were 'non-infected'—and rising at the time of symptomatic infection to 38% ($p < 0.001$) and 47% ($p < 0.02$), respectively. The titres were also significantly higher in 'infected' patients in group A and B, 1.0 and 2.1, compared with those who were 'non-infected', 0.5 and 1.2 ($p < 0.001$ and $p < 0.01$, respectively).

ANTIBODIES TO ALPHA TOXIN

The serum samples were also analysed by ELISA

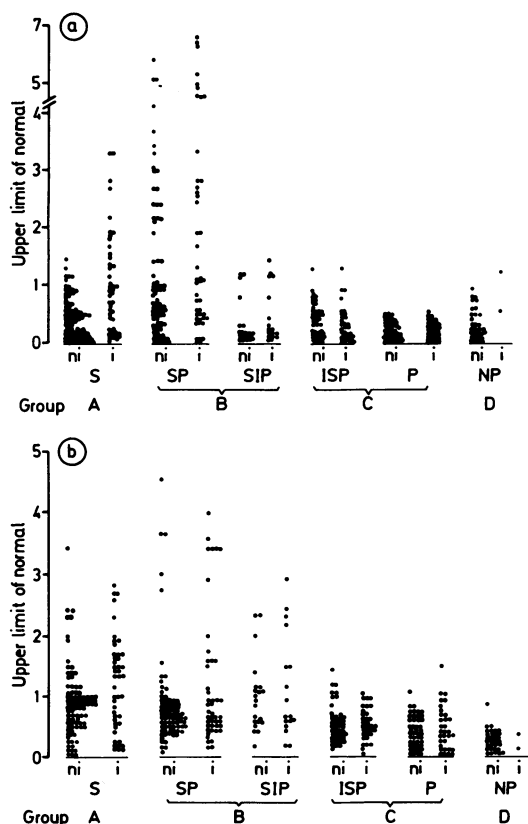


Fig. 2a and b Serum titres of IgG antibodies to staphylococcal teichoic acid (2a) and α -toxin (2b) S = chronic *S aureus*; SP = chronic *S aureus* and *P aeruginosa*; SIP = chronic *S aureus* and occasional *P aeruginosa*; ISP = occasional *S aureus* and chronic *P aeruginosa*; P = chronic *P aeruginosa*; NP = nasopharyngeal culture.

for IgG antibodies to alpha toxin. Fig 1b shows the distribution of titres in the different patient groups. Again, pathological titres were almost exclusively found in patients chronically colonised with *S aureus* with or without *P aeruginosa* ($p < 0.001$ when groups A and B were compared with groups C and D). 'Infected' patients had a significantly larger number of diagnostic titres than those not clinically infected (48% v 14%, $p < 0.02$).

Raised antibody titres were found in 29% of all the samples of patients chronically harbouring *S aureus*, 35% of samples in group A and 27% in group B (Fig 2b). Significantly higher mean titres were found in patients chronically colonised with *S aureus*, groups A and B (1.0 and 1.0, respectively) compared with groups C and D (0.5 and 0.2, $p < 0.001$, respectively). 'Infected' patients in groups A and B showed higher mean titres, 1.2 and 1.2, than those clinically 'non-infected' (0.9 and 0.9, $p < 0.02$, respectively).

Diagnostic titres (> 1) were found in 26% of samples from 'non-infected' patients in group A, the number rising to 53% when 'infected' ($p < 0.01$). The corresponding figures for group B were 21% and 35%, respectively ($p < 0.05$). One patient (two samples) had slightly increased serum titres to alpha toxin despite the absence of *S aureus* from his sputum (group C). This patient had been chronically colonised with *S aureus* for many years before sampling, the last positive sputum culture being one year before the study.

Diagnostic titres (> 1) to both teichoic acid and alpha toxin were found in 11 patients (32%), a total of 9% of the samples. Three patients had diagnostic titres only to teichoic acid, and another eight patients exclusively to alpha toxin. Twelve (35%) of the 34 patients who were chronically colonised with *S aureus* never showed diagnostic titres to either teichoic acid or alpha toxin, some not even during a seven year observation period.

ASSOCIATION BETWEEN ANTIBODY TITRES AND ANTIMICROBIAL TREATMENT

Increases in antibody titres usually related to clinical infection while decreases occurred after antimicrobial treatment. Figs. 3 and 4 show two examples of typical patterns of antibody responses to both teichoic acid and alpha toxin in association with both oral and intravenous antibiotic treatment.

In the six patients harbouring only *P aeruginosa* the serum titres against staphylococcal antigens were within normal ranges and were not significantly influenced by the 16 courses of antibiotics. The remaining 65 courses given to patients colonised with *S aureus* resulted in significant decreases in titres to both teichoic acid ($p < 0.01$) and alpha

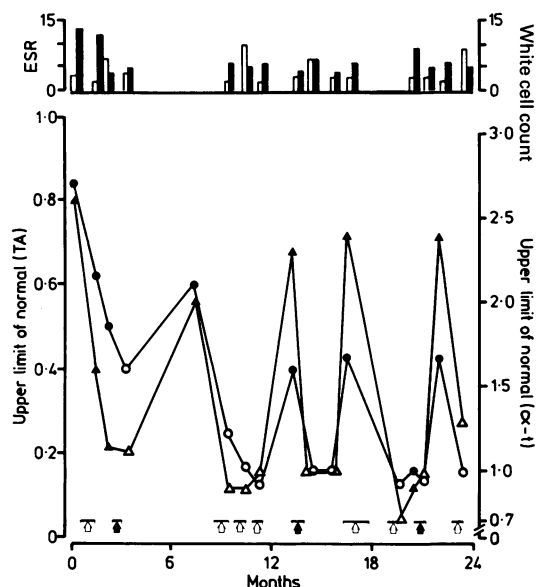


Fig. 3 Serum antibody titres to teichoic acid, TA (○) and α toxin, α t (Δ) and antibiotic treatment in boy aged 12 with *S aureus* and *P maltophilia*. Open arrows—oral treatment; closed arrows—intravenous treatment; solid bars—white cell count; open bars—ESR.

toxin ($p < 0.001$). This was true for the 36 of 65 (55%) treatments with cephalosporins alone or in combination with aminoglycosides ($p < 0.01$ and $p < 0.001$, respectively). The remaining 29 courses of cloxacillin (eight of 29), piperacillin (six of 29), ureidopenicillin (eight of 29), and other agents (seven of 29) also resulted in decreased titres ($p < 0.05$ for both antigens, $n = 29$). Twelve of the 22 patients with increased serum titres in groups A and B showed a return to normal titres after antimicrobial treatment. In another nine patients the titres decreased—seven to just above normal. The effect of oral antibiotic treatment on titres could only be evaluated in 28 instances. Significant decreases of titres to both teichoic acid and alpha toxin were also seen on this regimen ($p < 0.05$).

During the entire study period only one patient's serum titres did not decrease towards normal after antibiotic treatment. The antiteichoic acid titres fluctuated between 4 and 7 and anti alpha toxin titres between 3 and 5, despite frequent oral and intravenous courses of antibiotics. He was one of our most seriously ill patients, although his clinical score during the study period was 48–35–50, his forced expiratory volume in one second 42–43%, and his body weight -1.5 SD. At the age of 11 he was colonised with both *S aureus* (phage type 94/96)

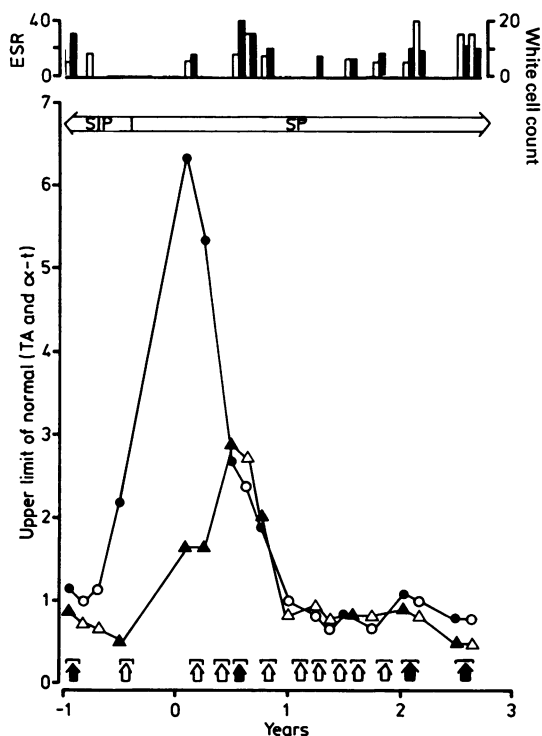


Fig. 4 Serum antibody titres to teichoic acid (○) and α toxin (Δ) in relation to change in colonisation, infection and antibiotic treatment in a boy of 3. Open arrows—oral treatment; closed arrows—intravenous treatment; solid bars—white cell count; open bars—ESR.

and *P aeruginosa*. This consistently increased antibody pattern was not seen in other patients with dual colonisation or in patients with the same phage type of staphylococci.

Discussion

The upper limit of normal values established in the healthy population^{19 20} probably reflects antibody responses on repeated contact with, or transient colonisation of, *S aureus* in the general population. This is shown by the 20-fold increase in mean titres to teichoic acid between the age of 6 months and young adulthood, necessitating the use of age correlated normal values. The additional colonisation of *S aureus* in the lungs of patients with cystic fibrosis does not seem to result in higher basic values. Diagnostic titres of serum antibodies to teichoic acid or alpha toxin, or both, were found only in patients who were chronically colonised with *S aureus*. Of these patients, 65% showed occasional diagnostic serum titres during the two years. The incidence of increased titres was significantly higher

in 'infected' patients, 44% v 17% in 'non-infected' ($p < 0.01$). Interestingly, 86% of the patients with increased titres (> 1), showed a decrease compared with those found in healthy controls of the same age groups after antimicrobial treatment.

Diagnostic titres were seen almost exclusively during periods of infection. In patients with endocarditis and septicaemia due to staphylococcal infection the sensitivity of the ELISA assays was 80–90%. The corresponding value was not established for other serious infections (such as pneumonia) but we would expect them to give rise to a similar antibody response. The very high titres seen in some of our 'infected' patients, similar to those seen in staphylococcal endocarditis,^{19–21} support this hypothesis. The observation that only 65% of our patients with chronic *S aureus* colonisation had diagnostic titres could reflect differences in the aggressiveness of the infections. Our patients were often treated as soon as signs of infection developed, and this could have hindered the antibody response. For this reason our results might not be applicable to other centres with different policies of treatment. Furthermore, the reference methods used to evaluate the sensitivity of the ELISA are different for different infections. In patients who did not have cystic fibrosis the diagnosis was verified by blood cultures, whereas in patients with cystic fibrosis the diagnosis of 'infection' was based on clinical changes, which might not be due to exacerbations of the *S aureus* infection.^{19–22} Of the 12 patients who were chronically colonised with *S aureus* and who had normal titres, only three were chronically colonised with *S aureus* alone.

The incidence of raised serum titres in our patients harbouring *S aureus* was similar to that in earlier studies using precipitating antibodies.⁷ Precipitating antibodies were, however, not affected by treatment. The ELISA showed higher specificity, as precipitating antibodies were also reported in patients without *S aureus* in sputum cultures.

An unexpected finding was the significantly higher antibody titres to teichoic acid in patients with dual colonisation of *S aureus* and *P aeruginosa* compared with those harbouring only *S aureus*. As all our titres were expressed as multiples of the upper limit of normal for appropriate ages the higher titres could not be explained by age. Patients in groups A and B also had similar clinical scores (61 and 58), lung function, and forced expiratory volume in one second being 76% and 65%, respectively. *S aureus* in dual colonisation with *P aeruginosa* might therefore have an impact on the deterioration reported in patients, when *P aeruginosa* colonisation is established.^{1–3} This might have important clinical implications as in our

experience the colonising pattern seldom shifts abruptly from *S aureus* to *P aeruginosa*. Both pathogens coexist for a variable length of time, and this has to be taken into account when choosing the antibiotics.

The serum titres returned to normal in nearly 90% of the patients after antimicrobial treatment. Thus the present data suggest that measurement of antibodies to teichoic acid and alpha toxin may be useful in the treatment of infections in patients with cystic fibrosis who are colonised with *S aureus*, especially if they have low grade infections with normal haematological findings.

We thank Ms E Andersson, Ms E Norström and Ms I Olsson for technical assistance and Dr A-S Malmberg for bacteriological examination. This work was supported by grants from the Swedish Association against Heart and Chest Disease, the Swedish National Association for Cystic Fibrosis, and the Karolinska Institutet.

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Received 27 April 1987

Thirty years ago

Cyanotic attacks in newborn infants

R S Illingworth (Sheffield)—Arch Dis Child 1957;**32**:328–32

Paediatrics has been greatly enriched through the years by Professor Ronald Illingworth's careful clinical studies of the development and behaviour of infants and children, normal and abnormal. In this paper of 30 years ago he recorded his observations of cyanotic attacks in 170 newborn infants. Sixty per cent were premature. The attacks began in the first 24 hours in 40% and in the first three days in 70%. In 40% there was only a single attack, while 32% had two to four attacks and 28% five or more attacks. In the mothers of the affected babies there was a significantly high incidence of toxæmia, hypertension, and antepartum haemorrhage. Asphyxia neonatorum of some severity had been recorded in 24% of the babies. Twitching or convulsions developed in 27 babies, but in only four of these was there twitching at the time of a cyanotic attack. The mortality in this series was 48%. Mortality was 70% in premature babies compared with 15% in those born at full term. This corresponded with figures of 10.9% and 0.7%, respectively, in all other premature and term babies in the hospital. Fifty eight per cent of the babies who had one to four cyanotic attacks recovered compared with 32% of those who had five or more attacks. Of the 27 infants with twitching or convulsions, 19 died. The principal necropsy finding was severe atelectasis with or without hyaline membrane disease. The second commonest finding was gross cerebral haemorrhage (site not specified). Pronounced cerebral oedema was also noted.

Illingworth discussed the difficulty in determining the cause of cyanotic attacks in the newborn. He concluded that while some were due to respiratory obstruction from mucus, meconium, or vomitus, many were due to apnoea without respiratory obstruction. The reasons for the apnoea could not be determined, but he noted a contemporary American observation that apnoea was mostly confined to babies in whom there had been a notable rise in respiratory rate after the first hour.

Comment. It is easy to forget that in 1957 we knew very little about the pathophysiology of the respiratory distress syndrome or of the microanatomy and pathogenesis of intracranial bleeding and the effects on the cerebral blood vessels of sudden alterations in blood gas tensions. The highly sophisticated diagnostic and therapeutic techniques that are routine in the intensive neonatal care units of today had still to be developed.

J H HUTCHISON