This report records only the effect of gammaglobulin on maternal infection, and it is possible that the administration of gammaglobulin, though not preventing maternal rubella, may still reduce the frequency and the severity of foetal abnormalities. It is hoped to study the outcome of the pregnancies in the susceptible patients.

Summary

In six areas of England and Wales the incidence of rubella-neutralizing antibody among pregnant women exposed was found to vary from 80 to 95%.

Two different dose schedules were used and the prophylactic effect of gammaglobulin in pregnant rubella contacts was investigated. The attack rate in home contacts given 750 mg. of gammaglobulin was 26.7%. In similar contacts given an initial dose of 750 mg. followed by a further 1,500 mg. within 12 days of exposure the attack rate was 31%. In non-family contacts only one out of 69 susceptibles developed evidence of rubella infection.

It is a pleasure to record the co-operation of the many general practitioners in the areas served by the six public health laboratories; these investigations would not have been possible without their assistance. This work was supported by a research grant from the Ministry of Health to the P.H.L.S. Rubella Working Party. The members of the Working Party are: Dr. A. D. Macrae (Colindale) (chairman), Dr. D. Reid (Colindale) (secretary), Dr. C. M. P. Bradstreet (Colindale), Dr. S. K. R. Clarke (Bristol), Miss A. M.

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REFERENCES

- Beale, A. J., Christofinis, G. C., and Furminger, I. G. S. (1963). *Lancet*, 2, 640.
 Brody, J. A., Sever, J. L., and Schiff, G. M. (1965). *New Engl. J. Med.*, 272, 127.
 Brown, G. C., Maassab, H. F., Veronelli, J. A., and Francis, T. J. (1964). *Science*, 145, 943.
 Dudgeon, J. A., Butler, N. R., and Plotkin, S. A. (1964). *Brit. med. J.*, 2, 155.
 Givan, K. F., Rozee, K. R., and Rhodes, A. J. (1965). *Canad. med. Ass. J.*, 92, 126.
 Green, R. H., Balsamo, M. R., Giles, J. P., Krugman, S., and Mirick, G. S. (1964). *Trans. Ass. Amer. Physns*, 77, 118.
 Hutchinson, D. N., and Thompson, K. M. (1965). *Mth. Bull. Minist. Hlth Lab. Serv.*, 24, 385.
 Korn, R. F. (1952). *J. infect. Dis.*, 90, 183.
 Lerner, A. M., Klein, J. O., Cherry, J. D., and Finland, M. (1963). *New Engl. J. Med.*, 269, 678.
 Lundström, R. (1965). *Arch. ges. Virusforsch.*, 16, 506.
 McDonald, J. C. (1963). *Brit. med. J.*, 2, 416.
 Parkman, P. D., Buescher, E. L., and Arstein, M. S. (1962). *Proc. Soc. exp. Biol. (N.Y.)*, 111, 225.
 Schiff, G. M., Sever, J. L., and Huebner, R. J. (1963). *Science*, 142, 58.
 Sever, J. L., Nelson, K. B., and Gilkeson, M. R. (1965a). *Amer. J. Dis. Child.*, 110, 395.
 — Schiff, G. M., Bell, J. A., Kapikian, A. Z., Huebner, R. J., and Traub, R. G. (1965b). *Pediatrics*, 35, 996.
 — and Huebner, R. J. (1964). *Obstet. and Gynec.*, 23, 153.
 Stewart, G. L., Parkman, P. D., Hopps, H. E., Douglas, R. D., Hamilton, J. P., and Meyer, H. M. (1967). *New Engl. J. Med.*, 276, 554.
 Weller, T. H., and Neva, F. A. (1962). *Proc. Soc. exp. Biol. (N.Y.)*, 111, 215.

Comparison of Intragastric and Intravenous Routes of Glucose/Bicarbonate Administration in Respiratory Distress Syndrome

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After the reports of Usher (1959, 1961), who suggested that the use of glucose/sodium bicarbonate solutions had led to a significant reduction in the mortality from the respiratory distress syndrome, his form of treatment was given a preliminary trial in the neonatal ward at the Queen Elizabeth Hospital for Children during 1961 and 1962. Among 61 infants treated within 24 hours of birth with intravenous therapy according to his suggested dosage there were 18 deaths, a mortality of 29.5%. Usher emphasized the need to start the infusion early, preferably within three hours, if it was to have any demonstrable effect on the survival rate. Our experience confirmed this, for among 10 babies whose treatment was delayed for over 24 hours there were nine deaths. If these babies had been included in our preliminary trial there would have been 27 deaths out of a total of 71 babies and the mortality increased to 38%. It would, however, give a fairer estimate of the mortality if the 10 cases in which treatment had been delayed for 24 hours or more were excluded. However, even the figure of 38% is significantly lower than the average 60% mortality in most previously reported series where bicarbonate had not been administered.

Unfortunately, in this hospital there were not enough controls to provide statistical proof that the treatment was of value,

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though there had been 32 babies who had received oxygen and increased humidity but no bicarbonate, and among these there were 17 deaths, a mortality of 53%. The results are given in Table I, alongside some results reported from Glasgow (Hutchison *et al.*, 1962).

TABLE I.—Comparison of the Mortality Rates from R.D.S. With and Without Treatment With Intravenous Glucose/Sodium Bicarbonate Infusion in Two Centres

Source	Q.E.H.C. (1961-2). Glucose/NaHCO ₃ by I.V. Infusion				Glasgow (1962). Glucose and NaHCO ₃ by "Titra- tion"				Glasgow. O ₂ and Humidified Air			
	I All Cases		II Omitting Cases Treated After 24 Hours		No.		%		1960		1961	
	No.	%	No.	%								
Deaths ..	27*	38	18	29.5	11	41	25	66	38	21	64	36
Survivals ..	44	62	43	70.5	16	59	48	34	25	31	36	64
Total ..	71		61		27		73		59			

* Nine of these deaths occurred among 10 cases that did not start therapy until 24 hours or more had elapsed, thus causing the mortality to be increased by nearly 10% more than need be.

Differences between percentage mortality rates in the two Glasgow series (results for 1960 and 1961 combined) $P < 0.02$ (this is "significant").

The Glasgow figures are quoted from Hutchison *et al.* (1962).

Though lacking strict statistical proof, the results of our preliminary trial engendered a firm conviction that prompt treatment directed against a metabolic acidosis by means of infusions of glucose and sodium bicarbonate could reduce the mortality of the respiratory distress syndrome. With experience the team concerned in the management of these cases became skilled in setting up scalp-vein infusions. In spite of this, difficulties were often encountered which entailed too much handling of very ill infants. Once an intravenous infusion containing glucose has been started there is the risk of "hypoglycaemic shock" if the drip should stop. To avoid this the needle must be reinserted into another vein within an hour, often into an already oedematous scalp. For these reasons it did not seem feasible to use this treatment in the maternity units unless a simpler method of infusion could be used. Because of the dangers of phlebotrombosis it was thought inadvisable to use the umbilical vein.

It was decided, therefore, to carry out a trial in which alternate infants were given the solution intravenously and intragastrically.

Material and Method

Babies were referred from maternity units in affiliated hospitals, mostly within a few hours of delivery, on developing clinical signs of respiratory distress (R.D.S.). They were transported in portable incubators in oxygen (about 25% concentration at the nostril) without increased humidity and before any treatment was initiated. If on arrival they were thought to conform clinically to hyaline membrane disease (H.M.D.) they were allocated alternately to one of two ways of glucose/sodium bicarbonate administration, the one parenterally through a scalp-vein needle (I.V.), the other by gavage (I.G.). Otherwise management was identical for both groups, by the same staff.

The babies were nursed in humidified incubators, and oxygen was administered in a concentration which was thought by the ward sister to be sufficient to control their cyanosis. The usual percentage ranged between 40 and 60% at the nostril. The dosage of sodium bicarbonate in 10% dextrose solution (65 ml./kg./day) was regulated according to serial pH estimations of heel capillary blood (Usher, 1961). The solution was given as a slow continuous drip through a polyvinyl stomach tube. Insulin was never used. Antibiotics (penicillin 150,000 units and streptomycin 50 mg. b.d.) and on many occasions a synthetic pressor amine, mephentermine sulphate (1.25 mg. two-hourly when the patient was severely distressed), were administered. Severity of respiratory distress was judged clinically by the respiratory rate, the degree of cyanosis, and the Silverman retraction score (Silverman and Andersen, 1956). With the last, those scoring up to 5 were regarded as mild, 5-7 as moderate, and 8-10 as severe cases. The chest was radiographed on the first morning after admission. A radiograph showing an air bronchogram, a diffuse reticulogranular pattern, or both, was regarded as positive for hyaline membrane disease.

Results

Table II shows the scope of the trial. Of 120 patients who were provisionally given the diagnosis of hyaline membrane disease and started on the alternate treatments 21 were excluded, either because there was no confirmatory biochemical and radiological evidence of the disease and subsequent progress showed nothing more than minimal intercostal recession, or because an alternative diagnosis became obvious later. In retrospect it was apparent that sufficient care had not been taken to obviate bias in the selection of treatment for babies who happened to arrive on the ward simultaneously. Though these included four sets of twins, it was reluctantly decided that

they should be excluded from the trial. Babies who were more than 24 hours old on arrival were also excluded, because the preliminary trial had shown that treatment did not influence the survival rate in this group (see Table I). Finally, it was necessary to exclude all those babies for whom the treatment had subsequently been changed for one reason or another.

TABLE II.—Scope of Trial and Reasons for Exclusion of 73 Cases Referred Initially With Signs of Respiratory Distress

Period of trial: May 1964–November 1965 (excluding June and July 1965 owing to temporary change of staff)					16 months
No. of cases referred as R.D.S.	..	..	..	..	152
Excluded:					
(1) Not H.M.D. on initial clinical examination	..	..	..	..	32
(2) Not H.M.D. on retrospective analysis	15*	6†	21		
Symptoms insufficient for diagnosis of H.M.D.	..	8	3		
Pneumonia	..	4	1		
Urethral valve: severe metabolic acidosis	..	1	—		
Neonatal hypoglycaemia	..	—	1		
Congenital heart disease	..	1	—		
Cerebral irritation	..	1	1‡		
3) Clinically H.M.D. but omitted for following reasons	..	..	..	20	
Twins (4 × 2)	..	..	8		
Arrived simultaneously (2 × 2)	..	..	4		
Change of treatment I.G. to I.V.	..	..	5		
Over 24 hours old on admission	..	..	3		
No. of cases remaining in the trial	..	..	..	..	79

* Intragastric. † Intravenous. ‡ Died with intraventricular haemorrhage.

Of the remaining 79 cases 36 were in the "intragastric group" and 43 in the "intravenous group," with 8 and 17 deaths respectively (Table III). Of the 20 cases which finally came to necropsy 18 showed typical hyaline membranes, a reflection of the accuracy of the initial diagnosis.

TABLE III.—Comparison of Mortality Rates of Two Groups of Alternate Intragastric and Intravenous Administration of Glucose and Sodium Bicarbonate Mixture, and Time When Milk Feeds Begun in Survivors

	Total No.	Deaths	Time When Milk Feeds Begun
Intragastric	36	8 (22.2%)	67.9 (26–140) hours
Intravenous	43	17 (39.5%)	64.9 (22–115) "

Difference between mortality rates = 17.3%. S.E. of difference = 10.5 : 2 (S.E.) = 21. On χ^2 analysis, $P = 0.10$.

It was hoped that by alternate allocation the two groups would match. However, it will be seen that, though the mean values in many instances are comparable (Table IV), the distribution of some important criteria is not (see Chart). Even allowing for this the difference between the mortality rates is not statistically significant ($P = 0.10$).

TABLE IV.—Analysis of Clinical and Biochemical Data of 79 Subjects Included in Trial and the Necropsy Findings in 20 Cases

	Whole Group		Deaths	
	I.G.	I.V.	I.G.	I.V.
Number	36	43	8	17
Birth weight (g.) mean ..	2,000	1,988	1,623	1,786
Gestation (weeks) mean ..	34.2	33.7	33.2	33.1
Sex { Male	22	35	4	13
Female	14	8	4	4
Delivery { Vaginal	26	36	7	15
Caesarean	10	7	1	2
pH (heel capillary blood) mean ..	7.15	7.14	7.04	7.09
PCO ₂ (heel capillary blood) (mm. Hg) mean ..	72.6	66.2	99.3	76
Severity on admission { Mild	14	12	1	3
Moderate	14	21	5	11
Severe	8	10	2	3
Chest x-ray { Positive	14	12	2	5
Negative	7	3	—	—
Not done	15	28	6	12
Treatment: Age started (hours) mean ..	7.7	7.6	10.6	9
Age at death (hours) mean ..	..	..	30.4	33.5
Necropsy: Number ..	..	..	6	14
Hyaline membrane ..	..	..	5	13
Pneumonia	..	..	1	2
Pulmonary haemorrhage ..	..	..	—	2
Atelectasis	..	..	6	12
Intraventricular haemorrhage ..	..	..	1	6
			(female)	(1 female)

Discussion

The results of this trial are capable of different interpretations. If one is sceptical of the value of this type of treatment it could be argued that it has done nothing to help these infants, and the difference between the survival rates in the two groups is entirely due to chance. Indeed, it could be suggested that infusing relatively large amounts of fluid and sodium bicarbonate into distressed premature babies is even positively

WEIGHT (g.)	INITIAL pH OF HEEL CAPILLARY BLOOD
>2500	ΔΔΔΔ ●○○○○○○
2251-2500	ΔΔΔΔΔΔΔΔ ○○○○○○
2001-2250	ΔΔΔΔΔΔΔΔ ○○○○○○
1751-2000	ΔΔΔΔΔΔ ●○○○○○
1501-1750	ΔΔΔΔΔΔΔΔ ●●●●
<1500	ΔΔΔΔΔΔ ●●●●○○○○

Distribution of birth weight and initial pH in the two groups.

harmful, but less so when the intragastric route is used, because of poor absorption from the alimentary tract, and hence the lower mortality in this group. Neither of these explanations is really acceptable. It is reasonable to expect that careful correction of a metabolic acidosis will benefit a sick infant as it does when acidosis results from other causes such as severe gastroenteritis.

The published results of several trials have all shown an appreciable reduction in the mortality from the respiratory distress syndrome when intravenous infusions of glucose/sodium bicarbonate have been administered (Usher, 1959, 1961, 1963; Hutchison *et al.*, 1962), and the preliminary trial of intravenous therapy in this hospital showed a definite improvement over other forms of therapy which had been used previously. Thus there is no good evidence that these infusions are harmful. The evidence of positive benefit is not quite so convincing, because it is to be expected that intensive care in special units will by itself result in an improved survival rate, but many people have been convinced of this by Usher's (1963) controlled trial.

If it is assumed that the infusion of glucose/sodium bicarbonate solutions is beneficial the results of the present trial show that it is just as effective when given by the intragastric route. In all the cases given intragastric therapy there was biochemical evidence that the bicarbonate was well absorbed and was able to correct the pH just as effectively as the intravenous bicarbonate (Table V). Though the mortality in the intravenous group is much greater than in the intragastric group, statistical analysis shows that this difference could have occurred by chance. However, it is remarkable that the intragastric group seems to fare better in consideration of nearly all

criteria, and it may be that the greater degree of handling necessary for intravenous therapy is an important factor.

Absorption from the neonatal gut is facilitated by the presence of a well-developed mucosa, though its rate in the first few hours is uncertain. There has been evidence of good absorption of sodium bicarbonate from the gut of babies in this trial, not only from the satisfactory correction of an existing meta-

TABLE V.—Comparison of Biochemical Changes Produced by Intragastric and Intravenous Therapy

	Baby V. Intravenous		Baby T. Intragastric	
	1	2	1	2
pH	7.12	7.39	7.04	7.31
Pco ₂	72.2	57	106	85
Base excess	-14.2	+6.3	-17.7	+9.7
Buffer base	41.1	55.8	38.9	59.0
Standard bicarbonate	15.1	29.3	13.6	31.7
Actual bicarbonate	23.8	33.0	28	41.0
Total CO ₂	26.0	35.0	31	43.6

In each case, column 1 represents initial findings. Column 2 represents the findings after less than 24 hours' sodium bicarbonate therapy.

bolic acidosis, but also from the considerable rise in the total bicarbonate in several cases.

Administration of these infusions by the gastric route has obvious merits, and now that it has been shown that the results are as good as those obtained by intravenous therapy, if not better, it can be firmly recommended as the route of first choice. Rarely, resort has to be made to the intravenous route because of vomiting.

Summary

A clinical trial was carried out to compare the relative values of the intravenous and the intragastric routes for infusion of solutions of glucose and sodium bicarbonate in the management of babies with the respiratory distress syndrome. Somewhat surprisingly those babies who received their infusions intragastrically had a lower mortality rate. Though the difference between the mortality rates was not statistically significant, there is reason to believe that the intragastric route of administration should be preferred.

We are indebted to Sister B. S. Beech, who was in charge of the unit throughout the period of trial and played a helpful and active part in the management of the babies, and to Dr. S. H. Ng, who carried out a great deal of work involved in the preliminary trial. We are also grateful to Dr. R. H. Dobbs and Dr. A. D. M. Jackson for allowing us to include patients under their care, to Dr. B. Levin for the biochemical investigations, and Dr. N. E. France for the morbid anatomy and histology.

REFERENCES

Hutchison, J. H., *et al.* (1962). *Lancet*, 2, 465.
Silverman, W. A., and Andersen, D. H. (1956). *Pediatrics*, 17, 1.
Usher, R. (1959). *Ibid.*, 24, 562.
— (1961). *Pediat. Clin. N. Amer.*, 8, 525.
— (1963). *Pediatrics*, 32, 966.

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