Acta Paediatrica Hungarica 30 (3-4), pp 351-365 (1990)

TREATMENT OF SEVERE HYALINE MEMBRANE DISEASE WITH SURFACTANT (CUROSURF)

A collaborative clinical study*

B. BÜKY, Gabriella DÉVAI, Erzsébet VÁRADY, Agnes RÓZSAVÖLGYI, I. KOVÁCH, A. KOVÁCS, Györgyi JANCSÓ, Katalin WALDINGER, A. GÖRGÉNYI, B. ZSOLNAI, B. ROBERTSON, T. CURSTEDT

Second Department of Obstetrics and Gynecology, Semmelweis Medical University, Budapest, Hungary

Received 5 September 1989

We investigated the clinical efficacy of a new surfactant product, Curosurf, isolated from porcine lungs by liquid-gel chromatography. Ten premature newborn infants (birth weight 850-1850 g), all ventilated artificially for severe hyaline membrane disease categorized radiologically as stage III-IV, received a single dose of Curosurf (200 mg/kg) via the tracheal tube. This treatment resulted in a rapid improvement of oxygenation, similar to that observed by other teams collaborating in the study and, in an astonishingly fast resolution of the radiological changes. In comparison with a control group of 8 infants, the surfactant-treated babies also had a lower incidence of acute and chronic complications.

INTRODUCTION

In recent years, exogenous surfactants have been used by several investigators for treatment or prevention /1,2,3/ of neonatal hyaline membrane disease (HMD). The surfactant material applied in these first trials was extracted from human amniotic fluid or from bovine or porcine lungs /1,4,5/.

The lungs of a baby with HMD, characteristically collapsing at end-expiration /6,7,8,14/ become stabilized through treatment with surfactant. If surfactant is administered to

* The study is carried out within the framework of an international cooperation on the basis of an agreement between the Swedish Royal Academy and the Hungarian Academy of Sciences.

Akadémiai Kiadó, Budapest

babies at risk soon after birth, the development of HMD can be prevented /2,3/. In babies with established HMD receiving surfactant, lung compliance improves, the period of artificial ventilation can be shortened and the incidence of acute and chronic complications is reduced significantly /5,9,10,11/.

At the Perinatal Intensive Center of the Second Department of Obstetrics and Gynecology, we have had the opportunity to treat babies with surfactant since 1988, within the framework of the Collaborative European Multicenter Study Group /Table I, 10/. In this paper we report our experiences from a first series of patients enrolled in a randomized trial of surfactant replacement for severe neonatal HMD.

TABLE I

Institutes taking part in assessing the effects of Curosurf

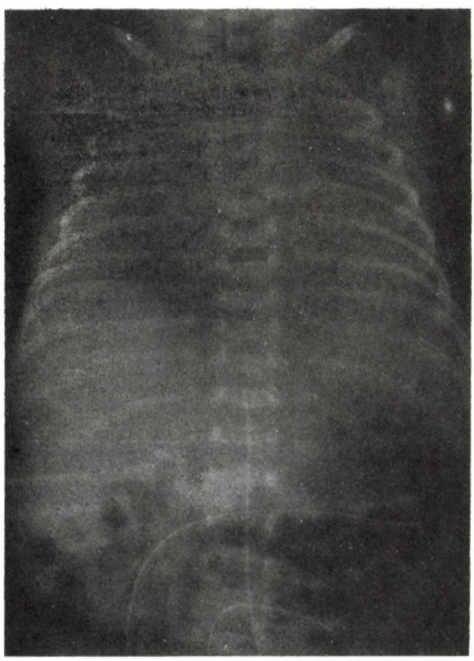
Institute	No. of treated patients	No. of control
Amsterdam, Academisch Ziekenhuis	20	18
Belfast, Royal Maternity Hospital	19	18
Groningen, University Hospital	6	3
Göttingen, Universitäts Kinderklinik	4	2
Lund, Lasarettet	9	9
Paris, Hôpital Port-Royal	5	3
Parma, Pavia, Mantua, Institutes of Neonatology	8	9
Stockholm, St. Göran's Children's Hospital	6	7
Budapest, Semmelweis University, Second Clinic of Gynaecology, Perinatal Intensive Center	10	7

Institutes of nine countries are taking part in the randomized examination of the effects of Curosurf. The Hungarian data refer to the second half of 1988 and 1989, the data of the other institutes were reported until January 19, 1988 (Pediatrics, 82, 683, 1988).

MATERIALS AND METHODS

Patients

17 patients have entered our randomized trial. These babies represent a selection of the most severely ill patients with HMD, admitted to our unit (Table II A,B). Both the surfactant-treated babies and the control patients were, as a rule, born with low Apgar scores, and the majority had a very low birth weight. The patients in both groups were in radiological stage III-IV Giedion /12,13,14/ (Fig. 1,2).



1. K.A. girl. Gestation period: 28 weeks. Birth weigh 850 g. (Patient no.4. of Table II/A). The chest X-r made during the phase of inhalation the charateristi of stage IV according to Giedion can be se (Görgényi). Received Curosurf treatment.

TABLE II/A

Data of Curosurf-treated infants and of the control group

(0-28 days)
Treated group (A)

No	Name	Sex/Gest.per. (week)	Birth weight gram	Apgar 1p/5p	RDS.Rad. stage	PDA	Complic-ation	Result
1	K.T.	M, 35	1700	1/1	IV	+	IVH	exit
2	M.V.	F, 28	1400	4/5	IV	+-	-	cured
3	S.T.	M, 27	1000	6/6	IV	+-	B.P.D. radiol.	cured
4	K.A.	F, 28	850	2/4	IV	+	-	cured
5	C.P.	M, 27	800	2/6	IV	+	PIE, IVH	HC
6	S.L.	M, 31	1830	10/10	III	-	-	cured
7	B.R.	F, 29	1200	8/8	IV	+	-	cured
8	M.C.	M, 30	1400	4/6	III-IV	-	-	cured
9	V.M.	M, 30	1500	5/7	III	+	-	cured
10	K.G.	M, 33	1850	5/9	III-IV	+	-	cured

TABLE II/B

Control group (B)

No	Name	Sex/Gest.per (week)	Birth weight gram	Apgar 1p/5p	RDS.Rad. stage	PDA	Complic-ation	Result
1	H.D.	F, 31	1800	7/8	III	+	IVH,PTX	HC
2	K.K.	M, 32	1350	6/9	III	+	-	cured
3	S.S.	F, 27	900	4/8	III	+	B.P.D.	cured
4	L.I.	M, 28	1200	4/6	IV	+	PIE,IVH	exit 3 ds
5	B.B.	F, 27	1250	3/5	III	-	-	cured
6	H.A.	M, 28	1000	3/5	IV	+	PIE,BPD	BPD
7	P.Z.	M, 28	1100	1/5	III	+	IVH	exit 3 wks

Abbreviations used:
PDA: patent ductus arteriosus
RDS: respiratory distress sydrome
IVH: intraventricular haemorrhage
PIE: pulmonary interstitial emphysema
PTX: pneumothorax
BPD: bronchopulmonary dysplasia
HC: hydrocephalus
exit: exitus
ds: days
wks: weeks

The average weight of the patients receiving Curosurf treatment (Table A) was 1350 gram, the average gestation period was 29.8 weeks.
The average weight of the patients in the control group (Table B) was 1230 gram, the average gestation period was 28.7 weeks.

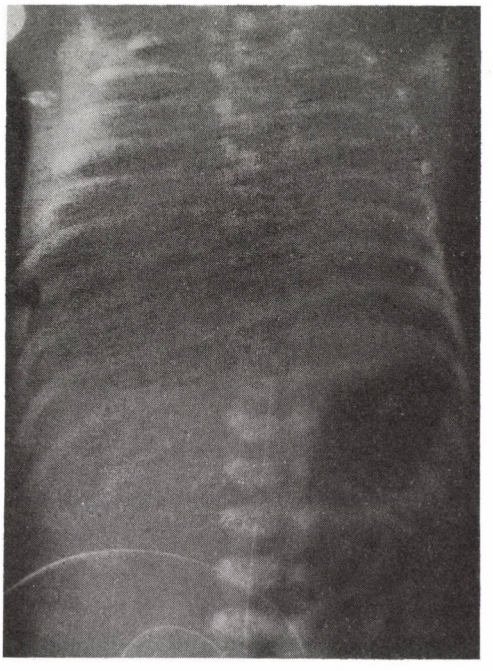


Fig. 2. L.I. boy. Gestation period: 28 weeks. Birth weight: 1200 g. (Patient No.4. of Table II/B). The chest X-ray shows the radiological signs of stage IV according to Giedion (Görgényi). Did not receive Curosurf treatment.

Criteria for entry

The protocol criteria for the administration of the artificial surfactant we applied, Curosurf, were, in addition to the need for artificial ventilation, the following: the possibility of obvious severe intraventricular hemorrhage and fetal sepsis had to be excluded before treatment, the age of the patient had to be between two and fifteen hours of life, the weight of the newborn had to be between 800 and 2000 grams and major congenital anomalies were also reasons for exclusions. (Protocol for randomized clinical trial of surfactant replacement 1988).

Procedure

Laboratory tests were carried out according to a strict protocol. Randomization was carried out by means of sealed envelopes. Before that, radiological examination of the chest was performed on two occasions, blood gas levels were checked regularly, and, whenever possible, an ultrasound scan of the brain was obtained to rule out the presence of a grade III-IV

cerebral hemorrhage. In addition, transcutaneous oxygen parameters were continuously recorded (Hellige PO2 monitor and Ohmeda Pulse Oximeter). All data were stored in a mini-computer.

Upon entry, the babies were ventilated with a Bourns baby respirator or a BP 2001 respirator set at a tidal volume of 5-7 ml, a maximum peak inspiratory pressure of 30 cm H_2O and a positive end-expiratory pressure of 4-6 cm H_2O. In the case of one patient suffering from acute pulmonary complications, we shifted from conventional to high frequency ventilation.

Treatment with Surfactant

The surfactant used in the present trial (Curosurf) was isolated from minced porcine lungs by a combination of washing, centrifugation, chloroform-ethanol extraction and liquid-gel chromatography. It contained approximately 99 % polar lipids, mainly phospholipids and 1 % hydrophobic proteins (SP-B and SP-C) (Table III). The final material was suspended in sterile normal saline at a lipid concentration of 80 mg/ml.

TABLE III

Composition of phospholipids in the batch of porcine surfactant (T. Curstedt and B. Robertson)

Phospholipids	%
Phosphatidylcholine	76,3
Phosphatidylethanolamine	6,4
Phosphatidylserine	3.2
Phosphatidylinositol	4.4
Phosphatidylglycerol	4.2
Lysophosphatidylcholine	0.7
Sphingomyelin	4.8

Patients randomized to the treatment group were disconnected from the ventilator and surfactant was instilled into each mean bronchus by means of a feeding tube (Ch 5.39) as previously described /10/. The total amount instilled was 2.5 ml/kg body weight, or 200 mg surfactant lipids/kg. After each instillation, the baby was ventilated manually for 1 minute with an Ambu balloon using a maximum insufflation pressure of 30 cm H_2O and a positive end-expiratory pressure of 5-6 cm H_2O. During this maneuver, the respiratory frequency and FiO_2 usually corresponded to the original ventilator setting.

One patient (No. 8 in Table I), not responding to the first treatment at the age of 4 h, received a second dose of surfactant (200 mg/kg) 4 h later. All other patients in the treatment group received only a single dose of surfactant.

Treatment of the control group

The control babies were not disconnected from the ventilator; in other respects, their treatment coincided with that of the surfactant-treated group.

Further management common to treated and control groups

After the instillation or control maneuvers, the babies were re-connected to the respirator system. The setting of the ventilator was modified in line with the clinical response. Weaning from the ventilator was initiated when

- a tidal volume of 5-7 ml could be maintained with an insufflation pressure < 20 cm H_2O;
- normal levels of PaO_2 (65-80 kPa) and oxygen saturation of 90 % with a FiO_2 <0.4; and
- there was no radiological evidence of alveolar collapse during ventilation without positive end-expiratory pressure.

RESULTS

Of the patients treated with Curosurf, we lost only one at the age of one day due to the consequences of fetal hypoxia and a superimposed cerebral hemorrhage. In the other patients, pulmonary interstitial emphysema was noted on one occasion. There was no case of pneumothorax or other forms of intrathoracic pneumatosis. One of the survivors developed transient radiological evidence of bronchopulmonary dysplasia at the age of 14-17 days. A total of 7 treated patients survived the neonatal period without evidence of pulmonary or cerebral complications.

In the control group, on the other hand, 5 babies developed various combinations of pneumothorax, pulmonary interstitial emphysema (Fig. 3) and cerebral hemorrhage. Two patients died before the age of 28 days. Bronchopulmonary dysplasia developed in two patients. Only two control babies survived the neonatal period without evidence of air leaks or chronic lung disease. (Table II, A, B).

The radiological changes were surprisingly fast in the Curosurf-treated groups. As we indicated in the introduction, we deviated from the other centers taking part in the cooperation with respect to patient selection only in one significant aspect. We began the Curosurf treatment of patients

in stage III-IV according to Giedion. According to the original prescriptions of the protocol, the appearance of any stage of HMD and the age of the patient between two and fifteen hours of life are sufficient criteria /10,13/. The age of the patients treated by us - although always exceeding two hours of life - never reached the sixth hour of life at the time of the administration of Curosurf (on average: 4 hours 32 minutes).

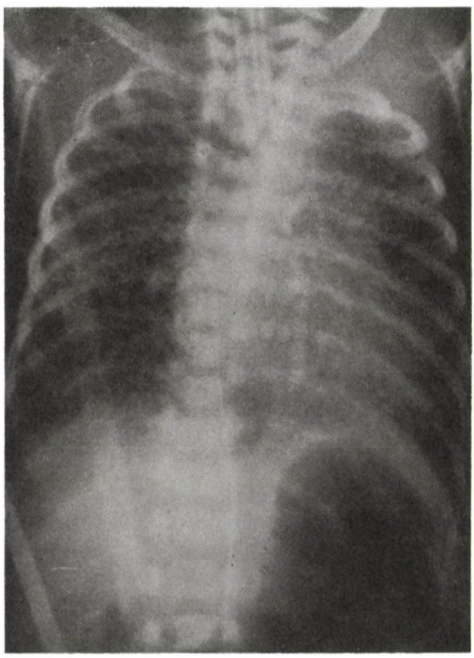


Fig. 3. L.I. boy. Gestation period: 28 weeks. Birth weight: 1200 g. (Patient 4 of Table II/B). In the sixth hour of artificial ventilation pulmonary interstitial emphysema occurred, which became visible in the entire lung after 24 hours.

Upon the administration of the surfactant, with the fast improvement of compliance and as an effect of the distending pressure, the alveolar space expanded fast. A change of such dramatic rate was inconceivable earlier, without the administration of the surfactant (Fig. 5, 6).

Patent ductus arteriosus was a frequent complication in both groups.

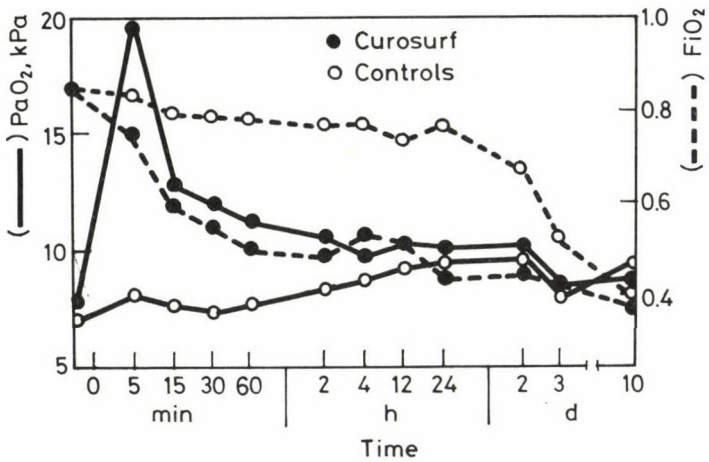


Fig 4. Ratio of arterial oxygen tension and FiO_2. The continuous lines indicate the changes in the oxygen values. Curosurf was administered in 10 cases, 7 patients did not receive treatment. FiO_2 was set at the possible minimum level. The curves showing the values are nearly identical with the average of the data of the other teams taking part in the cooperation. (Pediatrics 32, 688, 1988)
On the time scale, minute „0" indicates the time of the administration of Curosurf.

DISCUSSION

The combined data from the present study and the large European Multicenter Trial /10/ reveal a decreased mortality in the group of severely affected, low birth-weight infants treated with surfactant. Babies receiving surfactant also had a lower incidence of pulmonary interstitial emphysema and pneumothorax /9,10,15/.

The therapeutic effect of Curosurf could be documented immediately after the administration of the surfactant material /10,13,17/ and was as fast in our patients as in those treated by other teams taking part in collaborative trial (Fig. 4) /10/. In all but one of our cases, FiO_2 had to be reduced within minutes of treatment to counterbalance the rapidly rising PaO_2.

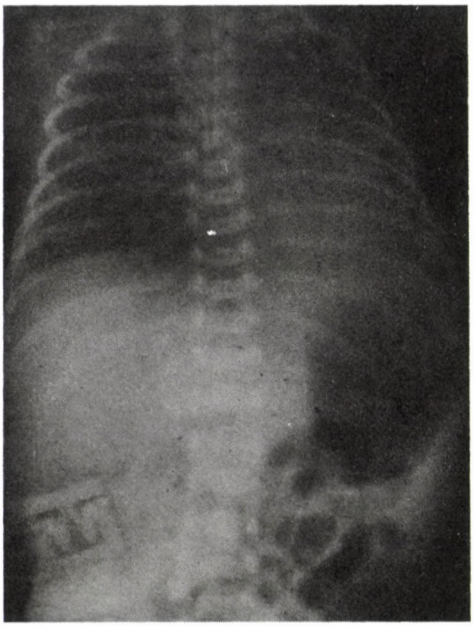


Fig. 5. S.T. boy. Gestation period: 27 weeks. Birth weight: 1000 g. (Patient No.3. of Table II/A). Picture indicative of radiological stage IV of the hyaline membrane disease. Received Curosurf treatment.

The large fluctuations of the arterial oxygen tension during the first few minutes after surfactant treatment were not associated with corresponding changes in oxygen saturation. The relative stability of the latter parameter may be related to the well-documented high quantity of circulating fetal hemoglobin in low birth-weight infants /18/. The fetal hemoglobin has a strong propensity to bind oxygen, which, under the present clinical circumstances, would tend to counterbalance the rapid changes of PaO_2. Variations in the PaO_2/FiO_2 ratio after the treatment with surfactant probably reflect the degree of shunting through a patent ductus arteriosus to a large extent, in turn due to fluctuations in the pulmonary vascular resistance.

The radiological improvement was fast. As indicated above, we deviated from the original protocol for patient selection

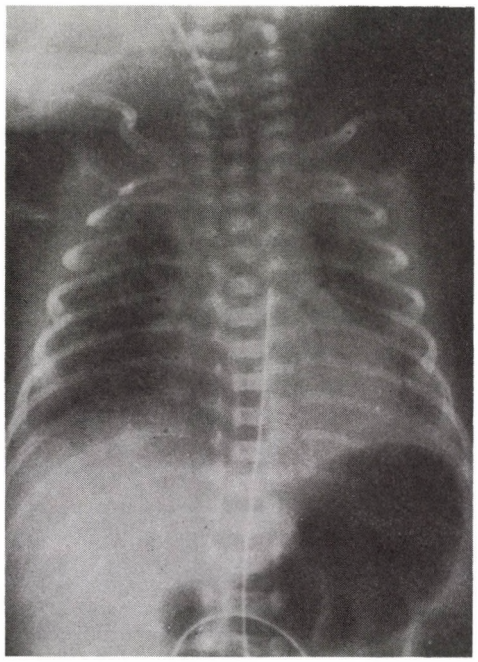


Fig. 6. S.T. (Patient No. 3. of Table II/A). The X-ray made 24 hours after the administration of Curosurf shows that the lungs are pneumatized, the air bronchogram and the reticulogranular pattern disappeared. (Görgényi)

/10/ in one important aspect: babies were enrolled if they fulfilled the radiological criteria for HMD, stage III-IV /12,13/, irrespective of their FiO_2 requirements. In fact, the chest films indicated total alveolar collapse in most of our cases. Also, all our patients in the treatment group received surfactant before the age of 6 h.

The relative ease with which the lungs expanded after the administration of surfactant suggests that, at this comparatively early stage, the terminal airways were not yet obstructed by cell debris as might occur later on during the development of the disease. Many terminal airspaces of the babies treated with Curosurf in our series were probably simply collapsed and could, therefore, quickly become aerated once the basic deficiency of surfactant material in the alveolar lining was corrected.

CONCLUSION

The results of our study and those of the previously published European Multicenter Trial /10/ indicate that, in babies with severe HMD, treatment with Curosurf improves gas exchange, reduces the incidence of air-leak problems and increases the survival rate. There is also a rapid improvement of the radiological findings, especially in babies who (as in the present series) are treated before the sixth hour of life. Further investigations are required to explore the hemodynamic effects of surfactant replacement in immature babies, especially as regards shunting through a patent ductus arteriosus, and to identify possible hazards of the high oxygen tension levels usually seen immediately after surfactant administration (unless FiO_2 is quickly reduced). Analyses for circulating antibodies to surfactant-associated proteins in Curosurf-treated patients and morphological studies of lung tissue from non-survivors are in progress, and will be reported at a later date.

REFERENCES

1. Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T: Artificial surfactant therapy in hyaline membrane disease. Lancet I. 55, 1980

2. Shapiro DL, Notter RH, Morin FC. et al: Double-blind randomized trial of calf lung surfactant extract at birth to very premature infants for prevention of respiratory distress syndrome. Pediatrics 76: 415, 1981

3. Enhorning G, Shennan A, Passmayer F, Dunn M, Chen P, Milligan J: Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant: a randomized clinical trial. Pediatrics, 76: 145, 1985

4. Shapiro DL: The development of surfactant replacement therapy and the various types of replacement surfactant. Sem. Perinatol. 12: 174, 1988

5. Merritt TA, Hallman M, Bloom Berry Ch, Benirschke K, Sahn D, Key T: Prophylactic treatment of very premature infants with human surfactant. N Eng J Med 315: 785, 1986

6. Avery ME, Mead J: Surface properties in relation to atelectasis and hyaline membrane disease. Am J Dis Child 97: 517, 1959

7. Speidel BD, Dunn PM: Effect of continuous positive airway pressure on breathing pattern in infants with respiratory distress syndrome. Lancet 1, 302, 1975

8. Büky B, Görgényi A: Idiopathic respiratory distress syndrome: acoustic, laryngoscopic and radiological investigation. Acta Paed Hung 17: 219, 1976

9. Kendig JW, Notter RH, Cox Ch, Aschner JL, Benn S, Bernstein MR, Hendricks-Munoz K, Maniscalco WM: Surfactant replacement at birth: final analysis of a clinical trial and comparisons with similar trials. Pediatrics 82: 756, 1988

10. Collaborative European Multicenter Study Group: Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial. Pediatrics 82, 683, 1988

11. Dunn MS, Shennan AT, Hoskins FM, Lennox K, Enhorning G: Two-year follow-up of infants in a randomized trial of surfactant replacement therapy for prevention of neonatal respiratory distress syndrome. Pediatrics 82: 543, 1988

12. Giedion A, Haeflinger H, Dangel P: Acute pulmonary X-ray changes in hyaline membrane disease treated with artificial ventilation and positive end expiratory pressure. Pediatr Radiol 1: 145, 1973

13. Hjalmarson O: Epidemiology and classification of acute neonatal respiratory disorders. Acta Pediatr Scand 70, 773, 1981

14. Görgényi A: Kandidátusi értekezés (Ph. D. Thesis), 1979

15. Halman M, Merritt TA, Jarvenpaa AL et al: Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. J Pediatr 106: 963, 1985

16. Gitlin JD, Soll RF, Parad RB, Horbar JD, Feldman HA, Lucey JF, Taeusch HW: Randomized controlled trial of exogenous surfactant for the treatment of hyaline membrane disease. Pediatrics 79: 31, 1987

17. Dévai G, Rózsavölgyi A, Kovách I, Kovács A et al: Poster. Művi surfactant (Curosurf) alkalmazásával nyert tapasztalataink IRDS-ben (Experiences of applying artificial surfactant- Curosurf - in IRDS). Scientific Session of the Hungarian Perinatological Section, 1989

18. Bókay J, Idei M, Gróf J, Büky B et al: The role of degradation of foetal haemoglobin in the energy supply of very low body weight pre-term babies. Acta Physiol Acad Sci Hung 60, 37, 1982

19. Robertson B, Curstedt T, Johannson et al: Structural and functional characterization of porcine surfactant isolated by liquid-gel chromatography. 1989 (in press)

20. Curstedt T, Jörnwall H, Robertson B et al: Two hydrophobic low molecular mass protein fractions of pulmonary surfactant: characterizaton and biophysical activity. Eur J Biochem 168: 255, 1987

B. BÜKY, MD

H-1083 Budapest
Üllői út 78/a
Hungary