HYALINE MEMBRANE DISEASE

A STUDY OF LUNG FUNCTION AND TREATMENT

by

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THESIS

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TO

DENISE, MICHAEL AND MARK

and

MY PARENTS AND TEACHERS

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CHAPTER IV

LUNG FUNCTION STUDIES IN HYALINE MEMBRANE DISEASE

ACKNOWLEDGEMENTS

In September, 1965, Dr. H. de V. Heese invited me to participate in a research project of the Department of Child Health, University of Cape Town. With the help of Professor F.J. Ford, he had established a neonatal respiratory unit and, despite ward and teaching duties, actively encouraged and directed a full research programme.

Generous grants from the Wellcome Foundation, the Cape Provincial Administration, the Hospitals' Teaching Board, University of Cape Town staff research funds and the S.A. Council for Scientific and Industrial Research, enabled all aspects of respiratory distress in newborn infants to be treated and studied in the unit. Dr. J.G.Burger, Medical Superintendent of Groote Schuur Hospital, provided access to the infants and permitted publication of results.

The unit had been established primarily to provide intensive patient care, and competent and conscientious attention was unfailingly given by Sister A. Goble and the nursing staff.

Drs. A.F. Malan and M. Klein provided much assistance in regard to the diagnosis and management of the infants.

I am particularly grateful to Dr. George Sweeney of the Department of Physiology who spent a great deal of time demonstrating the theory and mechanism of the apparatus which was to be used for the study of pulmonary function. Mr. J. van Nierop also assisted in getting the project off the ground.

Dr. Heese very kindly allowed me to be responsible for the full investigation of the infants. On some occasions, however, time did not permit me to complete each study of lung function and Miss J. Kaplan and Miss L. Symons would determine the acid base balance or the concentration of expired carbon dioxide.

The presentation of this thesis owes a great deal to the skill and care of Mrs. O.M. Cartwright who typed the manuscript. Mr. Arnaldo Netto generously provided the excellent paper and bound the copies.

To all these people I extend my sincere thanks.

INTRODUCTION

At present, both the aetiology of hyaline membrane disease and a means of preventing it remain unknown. Recent studies indicate that a significant number of infants die of respiratory failure (Warley and Gairdner, 1962) but there is no general agreement concerning the changes of pulmonary function which lead to this stage. Two approaches have been used in the treatment of respiratory decompensation. First it has been proposed that blood gas and acid base abnormalities which result from respiratory failure can be prevented by oxygen and intravenous alkali (Usher, 1963) and secondly an attempt has been made to correct abnormal lung function itself by means of artificial ventilation (Donald and Lord, 1953). These methods are directed at different aspects of the problem and their efficacy is as yet not established. The application of artificial ventilation in particular must depend on the nature of any ventilation, diffusion or perfusion defect.

This study, therefore, has been planned to investigate lung function in hyaline membrane disease and to assess the various forms of treatment, with particular reference to artificial ventilation.

The majority of distressed infants described in this work were admitted to a special neonatal unit, where ideal facilities were available both for intensive care of the babies and for investigation of pulmonary function. The first consideration was for the welfare of the infants at all stages of the disease and every attempt was made to ensure conditions optimum for normal survival. Only under these circumstances was the determination of lung function considered meaningful and justifiable.

A number of normal full-term and premature babies born in the hospital's Maternity Block acted as controls. In each case the nature and scope of the pulmonary studies to be performed was explained to the mother and her consent obtained. Certain modifications in technique were necessary in order to lessen the degree of discomfort experienced by the baby.

Standard international symbols of lung function terminology (Fed. Proc., 1950) have been used throughout the study.

Two exceptions may be noted:

TPP - used in the graphs - refers to transpulmonary pressure;

IPPR - refers to intermittent positive-pressure respiration.

CHAPTER I

MATERIAL

Diagnostic Criteria

Infants included in Study

Diagnostic Criteria

Terminology: The term Hyaline Membrane Disease has been used throughout this study in preference to that of Idiopathic Respiratory Distress Syndrome of the Newborn, or Pulmonary Syndrome of the Newborn. Disease (French des - neg., aise - ease) is defined as "A definite morbid process having a characteristic train of symptoms; it may affect the whole body or any of its parts, and its aetiology, pathology and prognosis may be known or unknown" (Dorland, 1965).

Syndrome, on the other hand, (French syn - together, dromos - a running) implies a set of signs or symptoms which occur together.

It is now clear that careful clinical, radiological and biochemical investigations can readily distinguish hyaline membrane disease from other causes of respiratory distress which might occur in the newborn period (Stahlman, 1967; Usher, 1961).

Clinical: The majority of affected infants have a preceding history of immaturity (Gairdner, 1965) which may be associated with premature delivery, either vaginally or by Caesarean section, or with maternal diabetes (Driscoll et al., 1960). They are distressed from the time of birth (Usher, 1961; James, 1959) and abnormal respiratory signs of rapid breathing, expiratory grunting and rib recession become steadily worse over the ensuing hours, in contrast to similar signs of distress in healthy premature infants, which gradually disappear over this time (Usher, 1961).

The progressive course of the disease is reflected by features of respiratory failure, namely, hypoxaemia presenting as cyanosis in room air (Prod'hom et al., 1965; Nelson et al., 1963 and Usher, 1961);

hypercapnoea (Hutchison et al., 1964) and metabolic acidosis (Usher, 1961). Finally, apnoeic spells may occur with resultant death (Usher, 1961; Avery, 1964). An important clinical sign related almost entirely to the disease is pitting oedema. This appears within 12 to 60 hours after birth and mainly involves the limbs (Usher, 1961).

The typical course starting from birth may not be observed in all infants, as many are often seen for the first time late in the disease with signs of respiratory failure. In such a situation the features distinguishing the disease from other causes of distress are obscured and further aids in the diagnosis are required.

Radiological: Donald and Steiner (1963) described the radiological appearance of early hyaline membrane disease as consisting of diffuse fine mottling of the lung fields. As the disease progressed, the mottled areas became more coarse and the bronchial tree showed up as an air bronchogram.

They felt, however, that the radiological appearance was not confirmatory in all cases, as 5 of 28 infants had diagnostic X-ray changes but lesions other than those of hyaline membrane disease were found at necropsy. These authors, however, appear to have been extremely self-critical for if these 5 'false positives', as they were termed, are considered in detail it is evident that the radiological appearance of one was equivocal, that one infant X-rayed after death was considered to have primary atelectasis, that one infant was X-rayed at 4 days of age when it was likely that resolution might already have taken place and that the fourth infant presented an X-ray picture of coarse mottling without an air bronchogram. This leaves one probable case of hyaline membrane disease diagnosed on X-ray features and not confirmed at autopsy.

Biochemical: Further assistance in the diagnosis of the disease has been obtained from a study of serum proteins. Hardie et al. (1965) indicated that the gamma globulins were deficient in hyaline membrane disease, in addition to there being abnormally low total protein and albumin. This abnormal pattern was most marked within the first 24 hours and thereafter the concentration of all fractions started to rise. A similar picture, however, has been observed in cases of Rh incompatibility, where serum gamma globulin levels fall in association with the serum antibody titres (Wiener, 1961), and one must be aware of the possibility of haemolytic disease.

Pathological: Final confirmation of the diagnosis has been obtained from autopsy studies. The lungs are uniformly dark red in colour and of liver-like consistency. Any fluid expressed from them is frothless and they sink when placed in water. Histological features reveal intense collapse of alveoli, while terminal bronchioles and alveolar ducts are distended and lined by eosinophilic hyaline material (Potter, 1961). Electron microscopy has revealed disruption of the alveolar membrane underlying the eosinophilic material (Campiche et al., 1961). Avery and Mead (1929) demonstrated that the lungs, like those of still-born infants, lacked the surface tension-lowering substance - surfactant.

These findings have formed the basis of diagnosis in the present study.

Infants included in Study

All 62 babies included in the study were premature by date, their gestational ages ranging from 28 to 38 weeks (Table 1). Their mean weight was 2.14 kg. (range 0.99 kg. to 3.29 kg.).

Thirty-six were vaginal deliveries, while the remaining 26 were born by Caesarean section. Two infants, the heaviest in the series, were born of diabetic mothers.

Males outnumbered females by two to one.

Twenty-five of the 62 babies were observed from the time of birth and presented the clinical features of grunting, rapid breathing, rib recession and cyanosis. In each case the course from delivery had been progressive over the first day. Twenty-six babies were admitted some hours after birth with similar signs and symptoms.

The remaining 11 babies were not breathing at the time of admission. Their course from birth had been described as one of progressive dyspnoea, grunting and cyanosis, culminating in apnoea. Pitting oedema, to a varying degree, was present in each baby of the series. This involved mainly the extensor surfaces of the hands and feet, also the scalp. The mean respiratory rate for the whole group was 77/min., and all infants demonstrated features of respiratory decompensation with a mean pH of 7.20, a $PaCO_2$ of 58 mm.Hg. and a base excess of -7.1 mEq./L. (Table 1). Oxygen tensions were not determined in all cases but as previously stated each infant became cyanosed when breathing room air.

Serum proteins were determined on 41 infants and gamma globulins showed a consistent depression with an overall mean value of 0.36 gm./100 ml. (normal 0.77 gm./100 ml. ± 0.14 gm./100 ml.).

TABLE 1

DATA ON 62 INFANTS WITH HYALINE MEMBRANE DISEASE

	Gestation weeks	Weight kg.	f per min.	pH	$PaCO_2$ mm.Hg.	Base Excess mEq./L	Gamma Globulin gm./100 ml.
Mean	34.9	2.14	77.1	7.20	58	-7.1	0.36
Range	28 to 38	0.99 to 3.29	0 to 119	7.00 to 7.34	43 to 107	-20 to -1	0.19 to 0.52
S.D. ±	3.3	0.48	19.7	0.04	12.6	4.4	0.10

Constant radiographic changes were observed in each case, with the demonstration of an air bronchogram and reticulo-granular lung fields.

Autopsies were performed on 10 infants who died during the acute stage of the disease. Each case illustrated the typical morbid anatomical and histological features of hyaline membrane disease.

Infants excluded from the study: One baby with hyaline membrane disease, confirmed at autopsy, was not included in this work as he had an associated oesophageal atresia. All other distressed infants, including those with congenital heart disease, hypoglycaemia, cerebral haemorrhage, aspiration pneumonia and spontaneous pneumothorax were excluded. ? included

Control group of normal infants: A series of normal full-term and premature infants acted as controls for lung function studies. All were normal vaginal deliveries and no history of maternal illness was present.

Full-Term

Thirty-three infants were included in this group. They had a mean gestational age of 40 weeks (range 39 to 41 weeks) and a mean weight of 3.22 kg. Physical maturity was determined from the characteristics of hair, ear cartilage, breast tissue and the creases of the foot. Their ages at the time of study ranged from 7 hours to 5 days.

Premature

Twenty-five infants demonstrated the features of prematurity. Their mean gestational age, calculated from maternal dates, was 36.5 weeks, while the mean weight was 2.09 kg. (range 1.70 to 2.50 kg). All had physical features of immaturity, and ages at the time of study ranged from 1 to 15 days.

CHAPTER II

PULMONARY FUNCTION STUDIES IN THE NEWBORN

Part 1 : Lung Volumes

Part 2 : Intrathoracic pressure and lung mechanics

Part 3 : Alveolar ventilation and dead space

Part 4 : Acid base balance and arterial carbon dioxide tension

Part 5 : Arterial oxygen tension

Part 6 : Lung function in normal newborn and premature infants

The selection of methods and apparatus must take into account certain peculiarities related to the newborn period, and these will be described in the various sections. Cross (1965), well aware of the problem of obtaining accurate measurements in infants, summed up the requirements for lung function studies as:

> "apparatus scaled down to size, which adds no dead space, demands no work, which is used at the right ambient temperature, which is accurate, and let it be added, which does not exist ! "

Part 1 : Lung volumes

Tidal volume, minute volume, crying vital capacity and functional residual capacity have been determined during the neonatal period, but this study is concerned with the first two only.

Apparatus dead space is of prime importance when measuring these volumes and face masks have proved unsatisfactory as they produce hyperventilation. Tooley (1961) indicated that the tidal volume increased by 30% if a 5 ml. mask was placed lightly over the face and by up to 100% if a 19 ml. mask was employed. Adequate collection of expired gas, however, could be achieved by means of a nasal coupler (Golinko and Rudolph, 1961) which made use of the fact that the newborn is an obligatory nose breather. The dead space and resistance of such a device is extremely small, but care must be taken to avoid leaks.

Body plethysmography became a popular method of determining lung volumes with the introduction of sensitive pressure transducers. A major difficulty of sealing the infant's neck outside the apparatus was overcome by Cross (1949), who devised an inflatable seal, passing along the bony structures of the mandible and occiput. In this manner the baby's face was exposed and considerable pressure could be applied without impeding flow along veins, arteries and trachea.

The method involves certain assumptions, for it is considered that the body increases in volume by precisely the same amount as the air taken in through the nose and also that the rest of the body remains incompressible (Cross, 1965). Nelson (1961), indeed, found no evidence of compression of intestinal gas and therefore did not consider this factor to be a source of error. The steady state achieved by an infant

in a body box must certainly be considered ideal as the baby can be maintained in a warm environment for prolonged periods, it can sleep peacefully and does not have to contend with added respiratory resistance. A major drawback of the procedure is the fact that simultaneous blood sampling cannot be adequately performed. To a certain extent this can be circumvented by employing reverse plethysmography, which enables the infant to breathe through wide bore tubing into a large calibrated container. The build-up of carbon dioxide concentration, however, restricts the time of recordings to one to two minutes (Avery and O'Doherty, 1962).

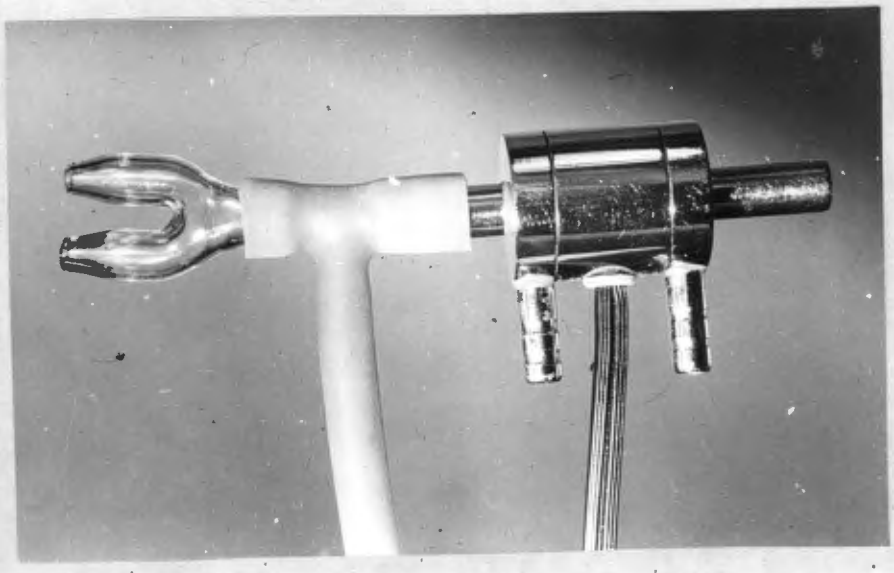
Flow rate and tidal volume have been measured by the use of pneumotachography (Kaye et al., 1949; Swyer et al., 1961). The mechanism is based on Poiseuill's Law which states that gas flow in a straight and rigid tube is proportional to the pressure fall per unit of length, provided the flow remains laminar. If turbulence develops, the instrument will erroneously record large flows. Changes in temperature, pressure and humidity and in the composition of respiratory gases, affect the various factors of Poiseuill's Law and can therefore introduce errors if they are not taken into consideration. Since volume is the integral of flow, it is possible to measure volume by determining the area under a flow curve, or by electrical integration of flow.

Equipment in present study

The apparatus for determining flow rate, tidal and minute volume, consisted essentially of a nasal piece, a pressure limb and a pneumotachograph (Fig. 1) with a total dead space of 2.2 ml. The nasal piece, made of glass, was designed to fit snugly into the infant's nostrils and was modified from the coupler described by Golinko and Rudolph (1961).

Fig. 1

Nasal piece attached to pneumotachograph



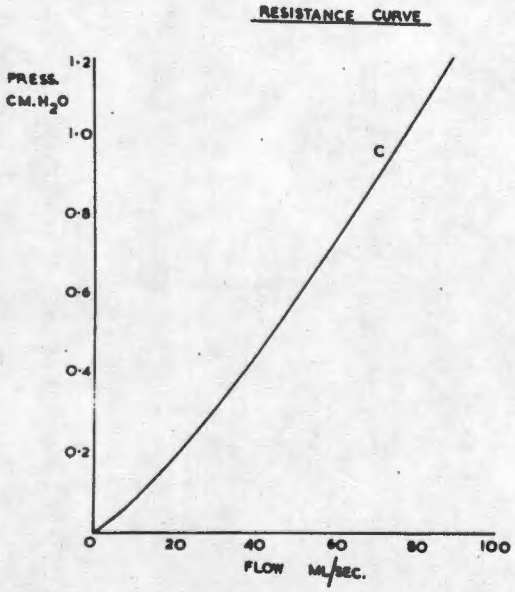


Fig. 2

Pressure-flow curve of nasal piece

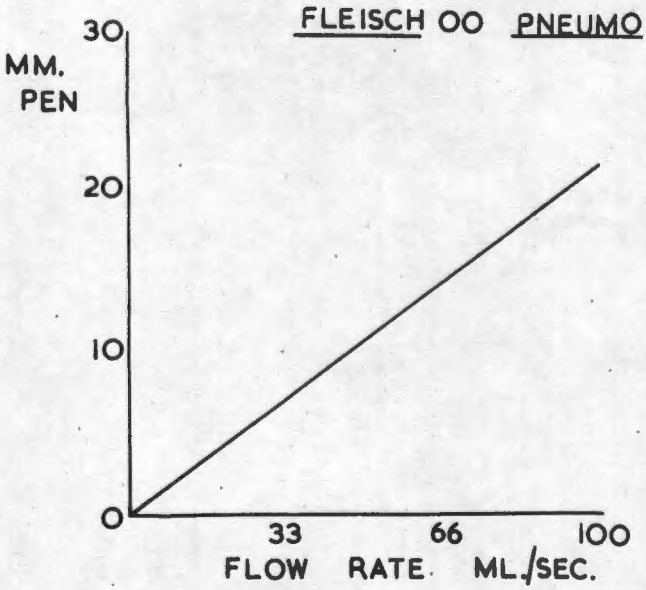


Fig. 3

Pressure-flow curve of Pneumotachograph and PM 197

The nasal limbs had an internal diameter of 2.5 mm. each, while the distal end measured 5.0 mm. in diameter. Resistance was extremely low (Fig. 2). The pressure limb connection consisted of a short rubber T-piece 6.0 mm. in internal diameter.

A Fleisch Model 00 pneumotachograph was selected for recording flow rate. It was linear up to flow rates of 100 ml./sec. (Fig. 3) and fell well within the limits of peak flows attained by the infants. Its dead space was 1.7 ml. The instrument was electrically heated to 38°C to prevent condensation of water vapour which may cause turbulence and non-linear responses. Heating, however, can also increase the temperature of passing gas. This results in an increase in gas volume of 0.34% per degree centigrade (Grenvik et al., 1966). For this reason, expired gas at body temperature and saturated with water vapour may give a larger recorded volume than inspired gas. This difference has been calculated to be 2.5% (Barrés and Gauge, 1961). The temperature of expired gas was, therefore, measured on each occasion in addition to that of the body, and the recorded volume corrected where necessary.

Pressure transducers

(a) Spontaneous breathing: Two pressure transducers were used in the study on spontaneously breathing infants. These instruments were mounted in firm plastic holders which were fixed to a table.

A Statham PM 6 was used to record transpulmonary pressure. This measurement was obtained by attaching the T-piece pressure lead which records mouth pressure or, more specifically, nasal pressure, to the dynamic pressure fitting point of the transducer, and the oesophageal pressure limb to the reference pressure point. The pressure range for

this transducer was ± 1.0 pounds/sq. inch difference and the instrument was linear over the pressure range used in the study (Fig. 4).

A Statham PM 197 transducer was used for flow rate recordings. This sensitive instrument was attached to the pneumotachograph by two rubber tubes 55 cm. long and 0.6 cm. in diameter. Pressure range was ± 0.01 P.S.I.D. The graph of linear function is shown in Fig. 3.

(b) Artificial ventilation: A Statham PM 5 transducer was used for flow rate recordings, as it was considered less likely to be damaged by transient high pump pressures. Linear function is illustrated in Fig. 5.

Opie et al. (1959) indicated the necessity of adding external dampening resistances to achieve critical dampening. If this was not done, large transient responses could be produced in the system, even when no flow occurred through a pneumotachograph.

In the present study, the shape of flow curves was dependent on the diameter of tubing connecting the transducer to the pneumotachograph, as when tubes of 2 mm. diameter were employed severe dampening of the tracings became apparent. The length of this tubing also proved to be critical, as if it was over 12 cm., further distortions of the flow curve were noted.

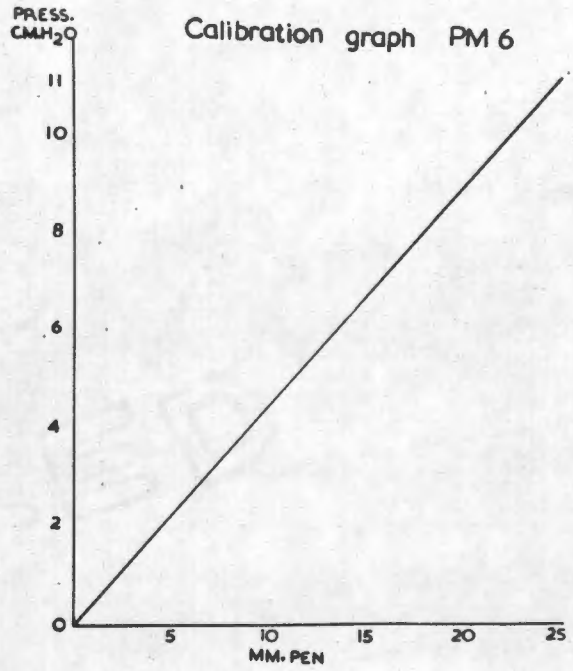
Optimum records were obtained with tubing 9 cm. in length and 0.6 cm. in diameter.

Recorder

All measurements were recorded on a Beckman Ofner Type R Dynograph. This apparatus was AC - DC coupled and consisted of six channels which were used for the following studies:

Fig. 4

PM 6 Pressure transducer: linear graph



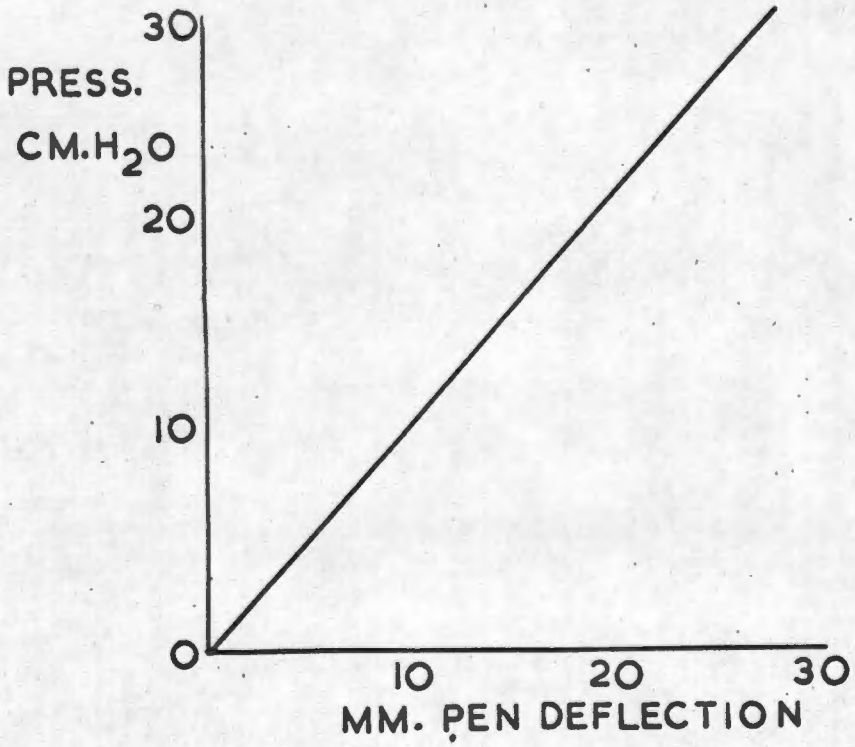


Fig. 5

PM 5 Pressure transducer: linear graph

Channel 1 : End-tidal carbon dioxide

Channel 2 : Umbilical venous pressure

Channel 3 : Electromyogram

Channel 4 : Transpulmonary pressure

Channel 5 : Flow rate

Channel 6 : Tidal volume.

Each separate record inscribed on the chart required a unit consisting of an input coupler, pre-amplifier, power amplifier and writing element. The coupler was designed to play directly into the pre-amplifier and the two were used as a single unit. Adaptation of the instrument for various records merely required an exchange of input couplers. Curvilinear records were obtained in red ink from a pen-writing system. Channel 6 was fitted with an integrating coupler (Beckman Type 9873) containing an automatic reset and two basic modes of internal reset - totalize and pulse.

Performance specifications

Sensitivity : 10 microvolts/cm. maximum to 50 volts cm. maximum

Warm-up time : Instantaneous

Frequency response: Within 10% to 150 cycles/second and 20% to beyond 200 cycles/second

Linearity : 0.5% for central 5 cm. of chart.

Calibration procedure

A standard performance was adopted before each complete study.

Determination of zero

It was essential that the pen shaft be positioned on the centre line of the axis of the printed paper to give mechanical zero. Once

the pen trace corresponded to the zero line on the chart, it was re-centred with the power amplifier. Lastly, calibration was performed with the strain gauge coupler. By disconnecting this from the Dynograph excitation source, a zero line could be recorded and any unwanted signals present in the gauge were balanced out. When the strain gauge was being used as a measuring device, calibration was done by applying a known load and adjusting the sensitivity until the pen deflected to an arbitrary level.

Flow rate

A metric X Series Rotameter was used for the calibration of the flow rate. Its specifications indicated a tube Size 10 X Duralon Flat Type A, Size 10. The rotameter outlet was attached by rubber tubing to one end of the pneumotachograph while the inlet was connected to a gas cylinder by a Draeger double reduction valve. Two gases were used, either compressed air or pure oxygen, depending on which one was being breathed by the infant. Grenvik et al. (1966) have demonstrated that if calibration is undertaken with air and measurements are performed with oxygen, the resultant error in the volume recorded will be 9%.

Before calibrations were performed, the gas was allowed to flow through the apparatus at 100 ml./sec. for 5 minutes so that temperature equilibrium could take place (Grenvik and Hedstrand, 1966). Actual flow rate was determined from a calibration chart. In spontaneously breathing infants a flow rate of 100 ml./sec. was set to give a pen deflection of 25 mm. on the dynograph. Each 1 mm. pen deflection now represented 4 ml./sec.

Volume

The volume channel (C6) integrated any voltage at the pen of flow channel (C5) and as no other variable in C5 is involved an electrical method of calibration was considered to be more accurate than one of introducing known volumes of gas. The procedure was carried out during both AC and DC coupling at six-monthly intervals.

By applying a constant electrical signal to C5, a deflection D (mm.) could be obtained.

This was maintained for a period of t seconds.

The total integral on C6 could be expressed as Q.

Therefore: Dt = volume

= Q measured XK where K is a constant of time having the dimension of seconds. This varied with the sensitivity in the main amplifier of C6.

V/cm. C6	K (sec.)
1	2.06
0.5	1.03
0.2	0.41

Measurements

Flow rate ($\dot{V}$) ml./sec. (mean of 5 measurements)

Throughout the study, inspiratory flow rate has been recorded above a zero line, while expiratory flow occurs below the same line (Fig. 6). Points of no flow can readily be determined where inspiration and expiration cut the zero line.

Peak flow rates have been measured as the vertical height of the point of maximum flow from zero times the calibration factor for the particular channel. Confidence limit ± 4.5 ml./sec.

Tidal volume (VT) ml. (mean of 5 measurements).

Tidal volume comprises both inspiratory and expiratory portions and has been measured as the vertical height between points of no flow multiplied by the time constant and the calibration factor for the flow rate channel (Fig. 6). Confidence limit ± 1.2 ml.

Minute volume ($\dot{V}$) ml. (mean of 2 measurements)

Minute volume was calculated during a period of gas collection and consists of expired volume only.

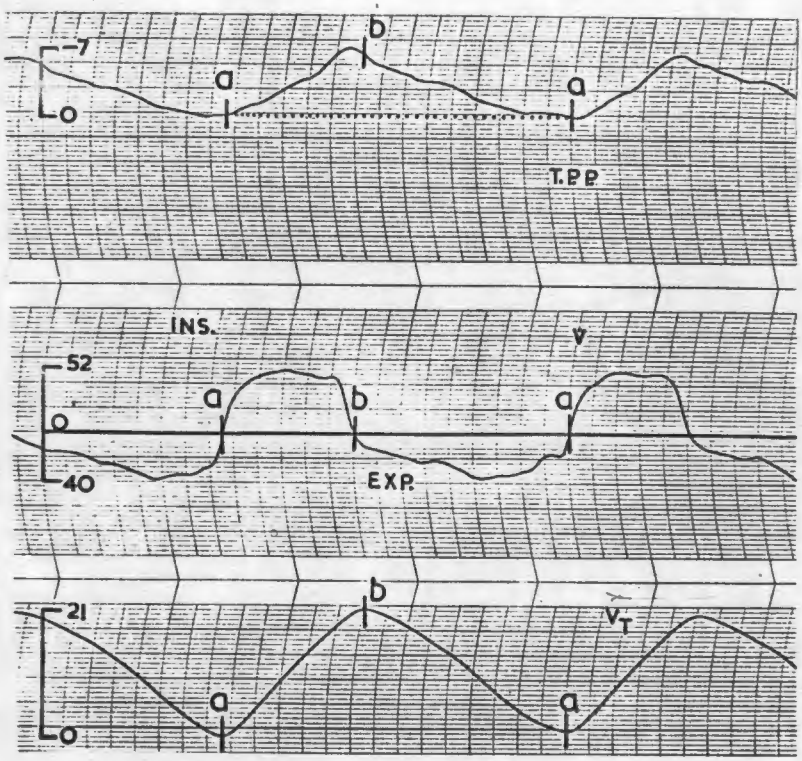
The amount of gas expired over a given period could be totalled (Fig. 7) and divided by the collection time to give expired minute volume. Confidence limit ± 72 ml./min.

Rate of breathing f per min.

The number of expiratory breaths were counted throughout a period of gas collection and divided by the total time, which ranged from 4 to 8 minutes. Confidence limit ± 3 f/min.

Fig. 6

Pressure, flow and volume curves



Spontaneous breathing
Paper speed 2.5 cm./sec.

PTP cm.H_2O

Vertical height ab - transpulmonary pressure between points of no flow

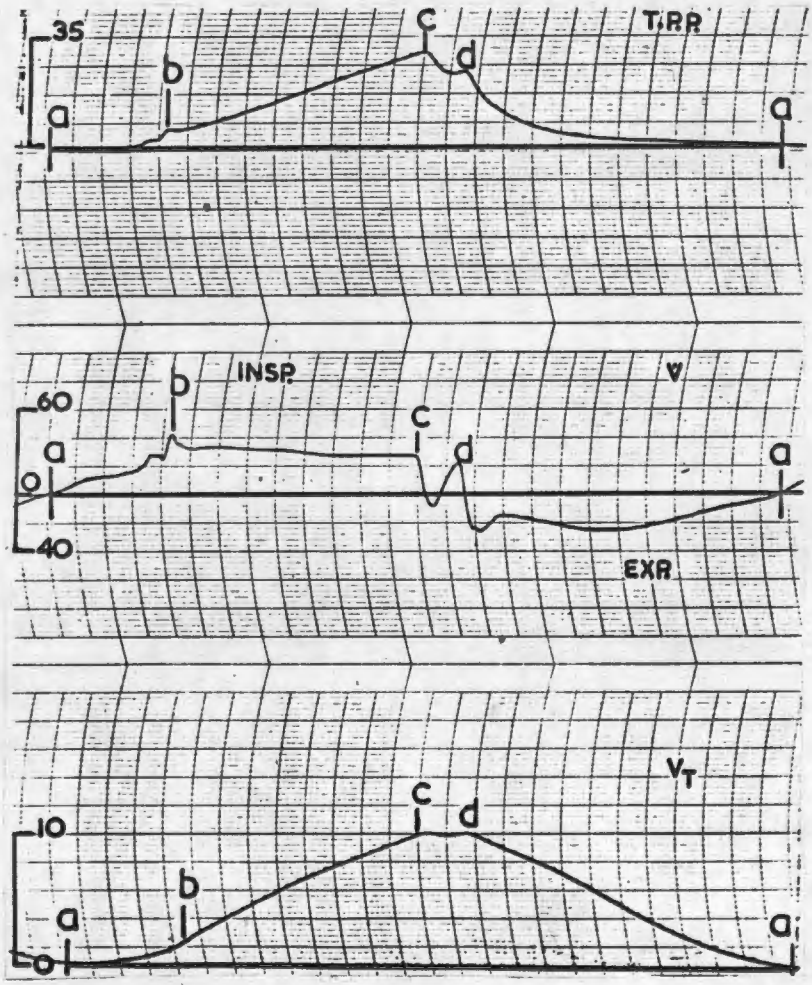
$\dot{V}$ ml/sec.

a. beginning of inspiration

b. end of inspiration

VT ml.

Vertical height ab X K - tidal volume



Intermittent positive-pressure breathing
Paper speed 5 cm./sec.

PTP cm.H_2O

Vertical height ac - transpulmonary pressure between points of no flow

$\dot{V}$ ml./sec.

a. beginning of inspiration

b. pump artefact

c. end of inspiration

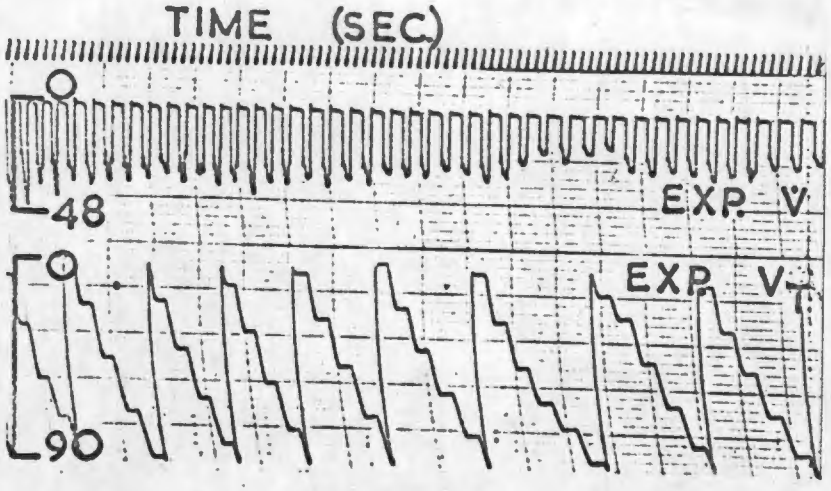
d. pump artefact

VT ml.

Vertical height ac X K - tidal volume

Fig. 7

Calculation of expired Minute Volume



$\dot{V}$: expiratory flow rate ml./sec.

VT ml : each step represents a tidal volume: these are totalled to give minute volume

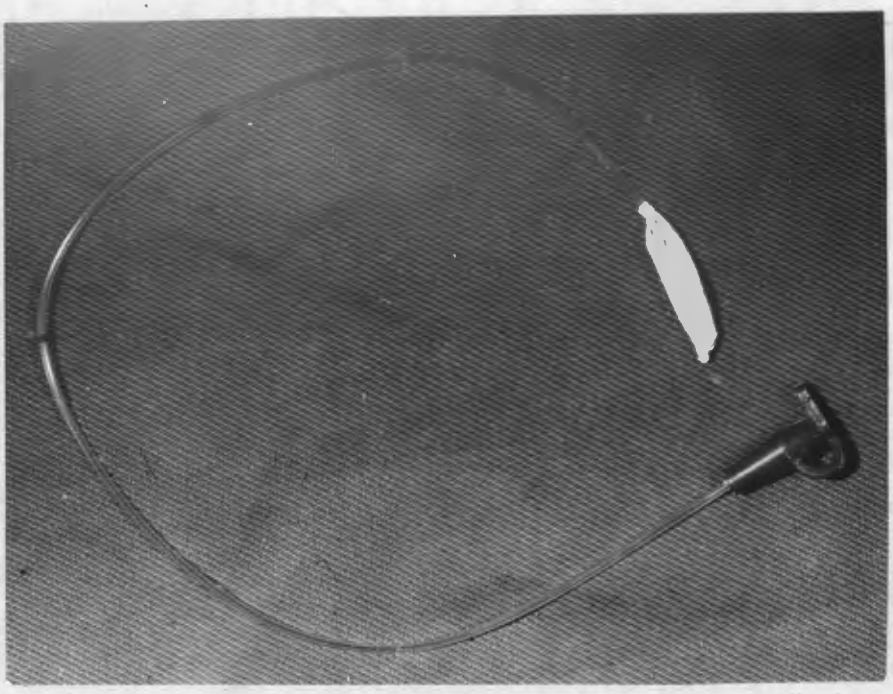


Fig. 8

Polythene catheter attached to rubber balloon

Part 2 : Intrathoracic pressure and lung mechanics

Three basic methods of determining intrathoracic pressure have been explored. They are the measurement of intrapleural pressure, peripheral venous pressure and oesophageal pressure (Fry et al., 1952). Intrapleural recordings are hazardous as they carry the risk of infection, air embolism and tension pneumothorax. The measurement of peripheral venous pressure has been found to be valueless as a method of measuring dynamic intrathoracic pressure (Fry et al., 1952) and at the present time oesophageal measurements appear the safest and most feasible method. The pressure variations in the oesophagus are of intrinsic and extrinsic origin, the latter being due to transmitted pressure from the intrathoracic cavity. This pressure has been recorded in a number of ways in both adults and infants. Methods include an air-filled system consisting of a balloon attached to a multi-perforated catheter, or a water-filled catheter only. The latter has proved the least accurate (Mead et al., 1955), being liable to block with mucus or transmit irregularities caused by motion artefact or heart beats. It is also reported to give abnormally high pressure changes if situated close to the cardiac sphincter.

The main purpose of a balloon is to prevent blockage of the recording tube, but accuracy has also been found to depend on balloon length. A long balloon lying throughout the intrathoracic portion of the oesophagus avoids interference due to localised pressure or spasm which, for instance, if present at the upper end of the oesophagus would prevent a good record still being obtained from lower down (Fry et al., 1952). A short balloon, on the other hand, reveals a wide variation in pressure changes. The most consistent recordings have been obtained in the lower third of the

oesophagus (Mead et al., 1955). Other sites are inconsistent and this fluctuation has been attributed to compression of the balloon by external structures (Mead and Whittenberger, 1953). Inconsistencies of pressure are also related to the position of the subject. This is of importance in adults but in infants there appears to be very little shift in mediastinal structures with changes in position (Cook, 1961).

An increase in the frequency of pressure changes causes both an alteration in the height of pressure recordings and a phase shift of these recordings, probably due to inertia of an air-filled recording system. In panting adults, this phase lag is in the region of 0.02 seconds while the drop in amplitude is about 25% (Fry et al., 1952). This is of direct importance in the newborn infant because of its rapid breathing, but no reported studies are available for this age group. However, a textbook figure (Avery, 1964) illustrating the comparison of intrapleural pressure with oesophageal pressure, obtained from balloon and catheter systems, shows a definite phase shift of the balloon recordings. The pressure recorded is also related to the degree of balloon distension when filled with air. In newborn studies, Krieger (1963) demonstrated that the introduction of 0.5 to 1.0 ml. of air lowered the recorded oesophageal pressure by as much as 100% and raised the end-expiratory level.

Balloon sizes used in newborn studies have varied greatly and a number are listed in Table 2.

In the present study, a balloon measuring 6 cm. in length by 2 cm. circumference was used on both full-term and premature infants (Fig. 8). This was selected on the basis of measurements made on a lateral X-ray of the chest and abdomen in 10 infants. A radio-opaque line incorporated

into the catheter facilitated easy measurement. It was evident that, depending on the weight of the baby, a catheter which was passed 10 to 13 cm. down from the lip margin would enable the balloon to lie in the thoracic portion. Cook et al. (1957) indicated that if a catheter was passed 10 to 11 cm. down the oesophagus of a newborn, the tip would lie at the junction of the mid and upper third of this organ.

TABLE 2

BALLOON SIZES USED IN NEWBORN STUDIES

Authors	Length cm.	Circumference cm.	Diameter cm.
Burnard et al., 1965	1.5 to 2.5	2.0	-
Krieger, 1963	6.0 to 10.0	-	0.5
Chu et al., 1964	5.0	-	-
Swyer et al., 1960	5.0	-	-
Present study	6.0	2.0	-

The balloon was manufactured as described by Mead et al. (1955). Briefly, the procedure consisted in dipping a glass cylinder into latex solution, slowly withdrawing it and then allowing the thin latex film coating the mould to cure by heating in an oven at 100°C for 20 minutes. The balloon was then fixed to the lower 5.5 cm. of a polythene catheter which had been perforated at approximately 12 points. Latex afforded a leak-free connection between the open end of the balloon and the catheter. The system was tested for leaks by inflating the balloon to a pressure of 3 cm.H_2O for 5 minutes. Only those balloons and catheters

which revealed no pressure drop were used for recording purposes. Balloons were approximately 0.05 mm. thick and the catheters were 1.14 mm. in internal diameter.

Static response characteristics

The balloon system was suspended from one opening of a 3-necked flask and attached to a Statham PM 5 pressure transducer. A taut, thin rubber cover was stretched over the neck of a second opening while a water manometer was connected to the third opening. The pressure in the flask was now raised to 10 cm.H_2O and the rubber diaphragm punctured, causing a sudden decompression inside the bottle to atmospheric pressure. In this manner, the response of the system to an effective square pressure change could be determined. Ten recordings gave a mean response time of 0.008 seconds, which was well within the accepted time of 0.01 seconds (Mead et al., 1955).

Frequency responses could not be determined, but the opportunity arose of studying intrapleural and oesophageal pressures simultaneously in a full-term infant who presented with a tension pneumothorax. An 8F polythene feeding catheter was inserted into the affected pleural cavity. At the same time, oesophageal pressure was recorded. Studies were performed after all the air had been removed from the pleural cavity as confirmed on X-ray.

Results

The shape and height of intra-oesophageal tracings were chiefly related to balloon size and its degree of distension with air (Table 3). Using a balloon 4 cm. in length and 2 cm. in circumference, the mean intrapleural pressure registered 9.6 cm. H_2O while the oesophageal pressure change was 8.2 cm.H_2O. Noticeable changes in pressure occurred

TABLE 3

COMPARISON OF INTRAPLEURAL AND OESOPHAGEAL PRESSURES

(a) LONG BALLOON (4 cm.)

Empty		1 cc. air added	
Intrapleural pressure cm.H_2O	Oesophageal pressure cm.H_2O	Intrapleural pressure cm.H_2O	Oesophageal pressure cm.H_2O
9.2	8.8	8.8	2.8
10.0	8.0	8.4	2.4
9.6	8.8	8.5	3.0
9.6	7.2		
9.6	8.4		
Mean 9.6	8.2	Mean 8.5	2.4

(b) SHORT BALLOON (2 cm.)

Intrapleural pressure cm.H_2O	Oesophageal pressure cm.H_2O	Intrapleural pressure cm.H_2O	Oesophageal pressure cm.H_2O
8.4	4.8	10.8	4.0
8.0	4.4	11.2	4.0
7.6	4.0	10.8	4.0
8.0	3.6	10.0	4.4
		8.8	4.0
Mean 8.0	4.2	Mean 8.0	4.2

after 1.0 ml. of air had filled the balloon: mean oesophageal pressure dropped to 2.4 cm. H_2O while intrapleural pressure was 8.5 cm. H_2O. This represented a fall of 72%.

A balloon 2 cm. in length by 2 cm. in circumference produced further inaccuracies. Mean intrapleural pressure registered 8.0 cm. H_2O and simultaneous oesophageal pressure recorded 4.2 cm. H_2O. When filled with 1.0 ml. of air, the balloon pressure dropped to 4.0 cm. H_2O, while intrapleural pressure registered 10.0 cm. H_2O.

A larger balloon system was used in the present study, but unfortunately was not compared in a similar way. Nevertheless, it is clear that the foregoing abnormalities must be considered when presenting absolute pressure values.

Pressure calibration

Transpulmonary pressure: An inclining water manometer was attached to the PM 6 transducer. A 10 cm. load was applied to give a pen deflection of 25 mm. Each 1 mm. now represented 0.4 cm. H_2O. In distressed infants higher pressures were anticipated and 20 cm. H_2O was applied to give a pen deflection of 25 mm.

Measurements

Transpulmonary pressure (PTP) cm.H_2O represented the pressure differential between the oesophagus (indirectly the pleural space) and the nose. It was measured as the total height of the pressure curve produced during a respiratory cycle (Fig. 6). Confidence limit $\pm$ 0.7 cm. H_2O.

Work of breathing (gm. cm./min.) : The work of moving only the lungs can be calculated from records of transpulmonary pressure and volume during breathing. McIlroy (Cook et al., 1957) suggested a simplified

formula of work:

$$\text{gm. cm./min} = 0.6\ \dot{P}\dot{V} \text{ where}$$

$\dot{P}$ = total pressure change in cm.H_2O during the respiratory cycle
$\dot{V}$ = minute volume in ml.

This method was compared with others commonly used and was found to have a close correlation over a wide range of compliance, resistance, respiratory rate and tidal volume (Cook et al., 1957). It was therefore employed in the present study. Confidence limit 45 gm. cm./min.

The method of measurement, however, does not take into account the work involved in moving both the lungs and the thoracic cage. This portion can be calculated only if the infant is no longer breathing spontaneously. Under these conditions the lungs, thorax and gas are moved by a body respirator which must be doing the amount of work which would have been done by the respiratory muscles (Comroe et al., 1962).

Compliance (ml./cm.H_2O) : Lung compliance, involving tissue stiffness or distensibility, is defined as the volume change per unit pressure change (Comroe et al., 1962). Ideally, transpulmonary pressure should be measured under static conditions of no air flow at a series of different end-inspiratory volumes. This, however, is not possible in the spontaneously breathing newborn infant, and pulmonary compliance has been expressed as the ratio of tidal volume to transpulmonary pressure, measured between points of no flow (Fig. 6), (Cook et al., 1957). Compliance, however, is closely related to lung volume rather than to altered tissue elasticity (Chu et al., 1964). It is, therefore, more meaningful when related to the functional residual capacity and expressed as specific compliance.

In the present study only lung compliance was determined, but for reasons related to inaccuracies in oesophageal pressure absolute values must be accepted with reserve. This applies to all reported studies. On the other hand, changes of compliance in the same infant over a number of days can be considered to be more meaningful. Confidence limit ± 0.7 ml./cm. H_2O.

Resistance : Transpulmonary pressure during flow has to overcome elastic recoil, tissue resistance and airway resistance. The frictional resistance opposing flow of air within the bronchial tree is referred to as airway resistance. This has been calculated in the newborn by the ratio of alveolar pressure to the rate of flow during either inspiration or expiration (Polgar, 1961). Air flow was interrupted by a shutter as pressure at this stage becomes uniform throughout the respiratory tract and can be measured at the mouth. Airway resistance determined in this way gave a mean value of 18 cm. H_2O/litre/second.

Calculations in other studies in infancy have included the total non-elastic pulmonary resistance, which comprises both airway and tissue resistance. By plotting a pressure-volume curve, the pressure required to overcome elastic recoil can be subtracted from the total pressure. This subtraction has also been done electrically. Although results are in the region of a mean 25 to 29 cm. H_2O/litre/second, the range has been wide, being 7 to 131 cm. H_2O/L/sec. in one series (Cook et al., 1957) and showing a standard deviation of 20 cm. H_2O/L/sec. (Krieger, 1963) in another. When flow curves were not available, certain assumptions were made as to sites of pressure measurement and linearity of flow at that particular moment. The error in estimating airway resistance, therefore,

appears to be large at the present time and for this reason this aspect of pulmonary function was not included in the present study.

Part 3 : Alveolar ventilation and dead space

The respiratory system may be divided into those parts which serve primarily as a conducting airway or dead space and those whose chief function is gas exchange, indicated by the term alveolar ventilation. A number of methods have been used to measure these compartments. The Böhr equation states that the total amount of gas in the expired tidal volume is equal to the sum of the amounts of that gas in dead space air and in alveolar air. This is related to the fraction of CO_2 in expired air, the fraction of CO_2 in alveolar air and the amount of air expired per minute, and expressed as:

$$VD = \frac{(FACO_2 - FECO_2)\,\dot{V}\,E}{FACO_2}$$

Alveolar air

In 1766 Wolloston demonstrated that only the last portion of expired air could extinguish a candle and he concluded that this portion contained more CO_2 than the air expired earlier (Bouhuys, 1964). In 1905, Haldane and Priestley introduced a method for collecting end-tidal samples by blowing expired air through a long tube and analysing the gas in the part of the tube close to the mouth. In an attempt to clarify the distinction between dead space gas and alveolar gas, Aitken and Clark-Kennedy (1928) plotted the variation in CO_2 concentration in expired air against the expired volume. Three phases could be distinguished. The first had the composition of inspired air and contained no CO_2: this represented the dead space portion. The second revealed a rapid S-shaped rise in the CO_2 concentration of expired air, indicating a mixture of dead space and alveolar gas, whilst the third phase consisted of a plateau with a

continuing slow rise of CO_2 and was considered to contain alveolar gas only.

The introduction of rapid CO2 and nitrogen analysers (Lilly, 1946) confirmed this finding and has made possible the continuous demonstration of these gas compartments. Using a nitrogen analyser, Fowler (1949) indicated that the beginning of pure alveolar gas was represented by the point at which the rising S-shaped curve met the tangent to the plateau. He further described a graphic method of dividing dead space gas from alveolar gas.

The continuing incline of the end-tidal plateau has given rise to several interpretations. It has been considered to be an artefact caused by incomplete washing out of the dead space (Armitage and Arnott, 1949), while a further opinion has been that the relatively poorly ventilated areas of the lung empty proportionally more in late expiration (Fowler, 1949). Strang (1961) has calculated both alveolar ventilation and anatomical dead space in newborn infants by means of a mass spectrometer. By plotting gas tension against expired volume, he indicated that the last 3 to 5 ml. of expired air formed a plateau distinct from that portion of the tracing corresponding to rapid wash out of dead space. This was regarded as alveolar gas. Dead space was estimated by the graphical method.

Measurement of dead space, using arterial CO_2 tension in place of alveolar CO_2 concentration, is based on the premise that the blood in each pulmonary capillary reaches complete equilibrium with alveolar gas to which it is exposed. The $PaCO_2$ then represents an average of all individual PCO_2 values. Enghoff (1938) used arterial PCO_2 to replace

alveolar PCO_2 in the Böhr equation which was then:

$$VD = \frac{(PaCO_2 - PECO_2)\ V\ E}{PaCO_2}$$

and the term 'physiological dead space' is used to denote the measurements obtained by this method.

End-tidal carbon dioxide

A Beckman Model LB 1 medical gas analyser was used to determine end-tidal CO_2 concentrations. The instrument consisted of 2 units, a pickup in which a micro-catheter sample cell was installed and an amplifier. The output was connected to an AC/DC strain gauge coupler in the recorder. A polythene tube, 5 cm. long, was attached to the pickup and the other end was inserted into the expiratory midstream of the open end of the pneumotachograph.

Specifications

Response time is 90% deflection of full scale, 0.1 seconds after the gas reaches the sample cell at 500 ml./min.

In this study, each sample of expired gas was drawn through the micro-catheter cell by means of a suction pump at a rate of 100 ml./min. The response time of the instrument was therefore determined at this rate of suction and found to be 0.13 seconds for 90% deflection of full scale.

Sensitivity: 0 to 10% on the CO_2 scale

Accuracy : From 0.3 mm.Hg. at the most sensitive scale to 0.1% CO_2 at any CO_2 concentrations between 1% and 10%.

Calibration

A stand-by switch incorporated into the amplifier allowed continuous

warming of the instrument, thus ensuring stability during recordings. Nevertheless, a calibration check was carried out each hour during any study.

Mechanical and electrical zero were set on the analyser and recorder, after which two gases of known CO_2 concentrations were introduced into the analyser. The gas CO_2 concentrations had been accurately determined beforehand by the Schölander micro technique.

The first gas, in the region of 8% concentration, was introduced from a cylinder via the same polythene tubing, and the meter was adjusted to coincide with the actual CO_2 concentration. This procedure was repeated with a second gas of approximately 4% concentration. Dry gases were used in this procedure.

The instrument is slightly non-linear and reference had to be made on each occasion to a specific calibration chart (Fig. 9). This was constructed by plotting the CO_2 concentrations of 13 gases against their resultant pen deflections on the dynograph. A range was selected to cover all anticipated concentrations of expired carbon dioxide.

Measurement and accuracy during spontaneous breathing

The formation of an expiratory plateau was accepted as representing the concentration of end-tidal CO_2 (Fig. 10 b.). The vertical height of this plateau was measured and multiplied by the calibration factor for the channel. This value was then referred to the calibration chart, and carbon dioxide tensions read from it. In order to obtain ideal records, certain precautions were necessary.

Rate of suctioning

The chosen rate of 1.6 ml./sec. fell well below the mean peak expiratory rate of 40 ml./sec. and was therefore considered to have avoided any

mixing of room air with the sample. Avery (1964) indicated that any sampling device would have to be set below 35 ml./sec. to avoid room air contamination. Rates of 10 ml. to 20 ml./min. advocated by Strang (1961) could not be achieved by the suction pump, but no advantage in this extremely low sampling rate could be envisaged. Plateaux of constant height and shape were obtained on normal infants, using a suction range of 100 to 350 ml./min. However, rates of 400 ml./min. and over produced a distorted plateau, with false low levels being registered (Fig. 10 c.).

The length of tubing from the patient to pickup was related to the delay time of recording. Using a tube 5 cm. long and 1.4 mm. in diameter, this delay averaged 0.08 seconds. Well-formed plateaux occurred, with a sudden sharp decline to zero on inspiration (Fig. 10 b.). However, if a tube 16 cm. long was used, delay time was increased to 0.3 seconds and distortion of the plateau occurred, with blunting and prolongation of the inspiratory portion. The plateau height, however, was unaffected (Fig. 10 a.).

The position of the catheter tip has been shown to be of importance by Strang (1961), who stressed the necessity for sampling gas from the mid-expiratory stream. This was found to be equally important in the present study, for if the catheter tip impinged against the infant's nostril or the side of the pneumotachograph, a distorted record was obtained (Fig. 10 d.).

The site of sampling was carefully studied. Expiratory samples obtained from both the nostril and the pneumotachograph stream revealed no significant difference in CO_2 tension, and it was therefore assumed that apparatus dead space played little importance in altering lung function of these infants whose weights ranged from 2.01 kg. to 3.70 kg. This, however, may not apply to smaller babies.

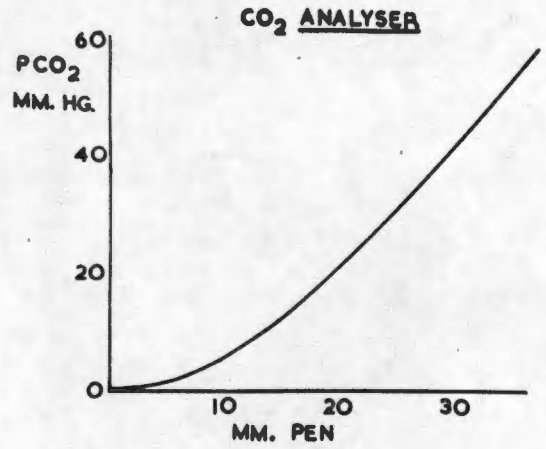


Fig. 9

Calibration chart for Beckman CO_2 analyser

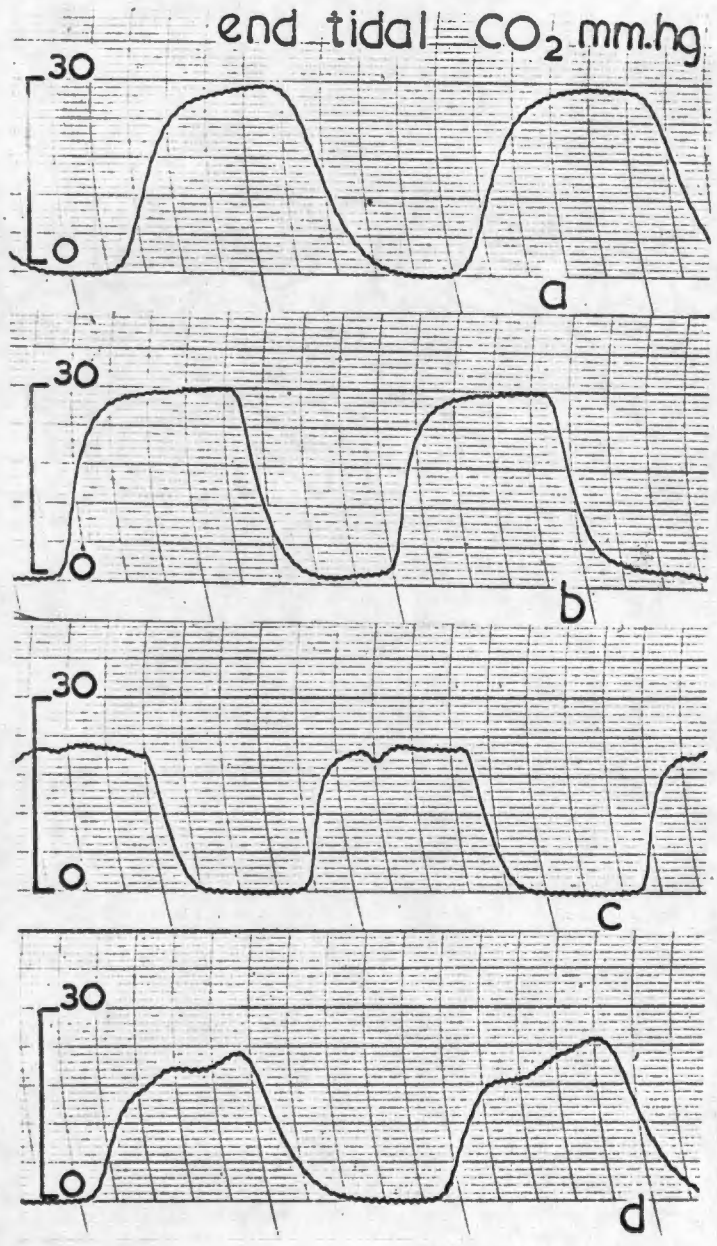


Fig. 10

Expiratory CO_2 curves - same infant

a. Rate of suction 100 ml./min.: collecting tube 16 cm. long

Plateau formation occurs, but beginning of inspiration is blunted

b. Rate of suction 100 ml./min.: collecting tube 5 cm. long

Ideal plateau formation

c. Rate of suction 400 ml./min. :

Curve distorted and flattened.

d. Collecting tube impinging on nasal mucosa

Abnormal height and shape of curve

End-tidal sampling during artificial ventilation

The catheter from the CO_2 analyser measured 10 cm. in length, and was inserted into the Y connection of the respirator tubes above the pneumotachograph. This additional length of tubing increased the delay time of the recordings and distorted the inspiratory curve as demonstrated above, although it did not alter the height of plateaux. Expiratory flow rates were more rapid during respirator therapy and it was necessary to increase the rate of suction to 400 ml./min. in order to obtain acceptable recordings.

Infants with normal lungs undergoing artificial respiration presented distorted CO_2 curves if a suctioning rate below 350 ml./min. was used.

Collection of expired gas during spontaneous breathing

Certain adjustments to basic equipment were necessary for the collection of expired gas. The glass nasal piece was attached to a small one-way breathing valve (Fig. 11). This consisted of two Teflon flap valves and had a dead space of 1.0 ml. Resistance of the valve was extremely low (Fig. 12) and no alteration of rate or expiratory breathing, characteristic of breathing against a resistance, ever occurred.

The expiratory portion of the valve was connected to one end of the pneumotachograph and this instrument in turn was attached by 4 cm. X 10 cm. rubber tubing to a 10-litre Douglas bag. The bag hung vertically during the collection and had been tested for leaks prior to use by being filled with 5 litres of air and closed off. The side arm was connected to a PM 5 pressure transducer for half an hour and during this time no alteration in pressure occurred. The bag was incapable of retaining carbon dioxide for very long. A mean CO_2 concentration of 2.2% fell by 0.1% after 10 minutes, 0.3% by 15 minutes and 1.1% by 30 minutes. It was

Fig. 11

One way valve attached to pneumotachograph and Douglas Bag

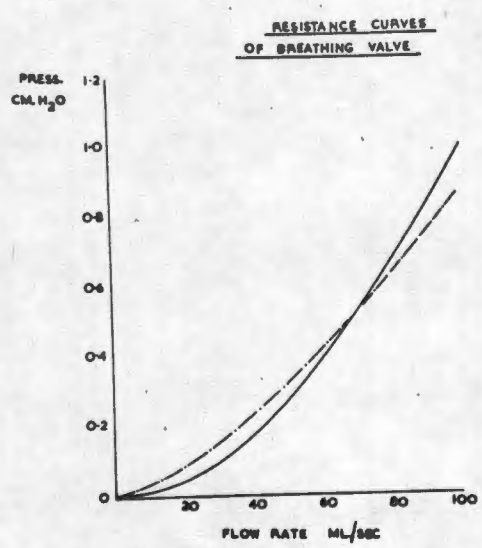


Fig. 12

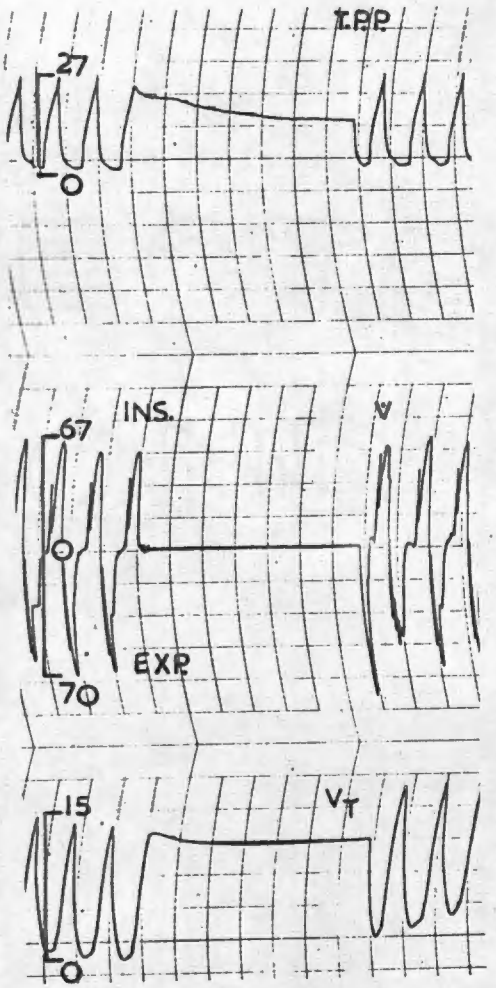
Pressure-flow graph of breathing valve

__ . __ inspiratory portion of valve

_____ expiratory portion of valve

Fig. 13

Leakage of air past endotracheal tube



PTP : cm.H_2O

$\dot{V}$: ml./sec.

VT : ml.

When endotracheal tube is clamped off at end-inspiration a fall in PTP indicates leaking of air past the tube.

therefore obvious that gas had to be drawn out of the bag immediately after the collection period. A 50 ml. all-glass syringe was used for this purpose. It was also tested for leaks and showed a mean fall in CO_2 concentration of 0.01% at the end of 10 minutes and 0.35% at the end of 30 minutes. The concentration of expired carbon dioxide was therefore determined in all cases within 5 minutes of collection.

The temperature of expired gas was determined by means of a long broad thermometer which was inserted into the bag through an airtight rubber stopper fitted into the neck.

Collection of expired gas during artificial ventilation

The gas was collected at the expiratory port of the Bird respirator. During the procedure, a large quantity of air from the respirator by-passed the lungs and for this reason a large 30-litre Douglas bag was used for the collection. The neck of the bag could be fitted tightly over the expiratory valve, thus excluding all leaks. During the gas collection leaks from around the endotracheal tube were excluded by firmly holding the tube in the mouth and clamping off the airway above the pneumotachograph at the end of an inspiration. Any leakage of air was indirectly reflected on pressure tracings (Fig. 13). The gas which by-passed the lungs was 100% oxygen and therefore considered not to alter CO_2 concentration. Collection of expired air was made over an 8 to 10 minute period. Following this, a 50 ml. sample was taken in a glass syringe for analysis. The pneumotachograph was then disconnected from the patient, the recorder set to DC and the contents of the Douglas bag slowly blown through in the reverse direction. In this manner, two volumes were obtained, the amount of expired gas originally recorded, and the amount of expired plus by-pass gas in the bag. The dilution factor of added oxygen could thus be

determined. No compression factor for gas was used as all the air which entered and left the lungs was recorded by the pneumotachograph situated close to the mouth.

Because of the numerous points at which leakage could occur, this investigation was considered to be the most likely to give false readings. The alveolar ventilation and dead space during artificial respiration must not, therefore, be accepted as reflecting absolute values, but rather as an indication of change following various procedures in each infant.

Estimation of expired carbon dioxide concentration

The concentration of expired carbon dioxide was determined by means of the Schölander micrometer gas analyser (Excelo). This instrument permits the determination of carbon dioxide, oxygen and nitrogen in 0.5 ml. samples of respiratory gases with an accuracy of 0.015 volumes per cent. Accuracy depends on maintaining constant pressure of the gas sample and constant volume and temperature of the apparatus and fluid contents.

Carbon dioxide absorber solution was kept for approximately two months under anaerobic conditions following preparation, while acid-rinsing solution was freshly prepared every third day.

Expired gas was introduced into the compensating chamber by means of a 2 mm. internal diameter glass pipette. A mercury droplet was placed in the bulb of this pipette and acted as a seal for the expired air which was pushed up past it from the 50 ml. syringe. The pipette was held almost vertical during this procedure and then placed on the capillary of the compensating chamber. A rubber tip at its end afforded perfect alignment of the delivery pipette and the capillary of the compensating chamber. The CO_2 concentration of all samples was determined in duplicate.

The Schölander confidence limit for carbon dioxide concentration

was determined on 54 paired samples of expired gas and found to be ± 0.012%.

Determination of oxygen concentration

The oxygen concentration of room air and inhaled gas was determined on a number of occasions. Triacetoxybenzene solution, stored under paraffin, was used as the absorbing agent. The investigations proved somewhat laborious when absorbing oxygen over 90% in concentration and was often discontinued once this amount had been absorbed.

Calculation of partial pressure

The Schölander apparatus determines the dry percentage of a gas, and partial pressure was calculated by the formula:

$$\frac{V}{100} (PB - PH_2O)$$

where V = volume % of gas

PB = barometric pressure (mm.Hg.)

PH_2O = water vapour pressure (mm.Hg.)

pH_2O at 37°C = 47 mm.Hg.

All gas volumes were corrected to BTPS.

Calculation of alveolar ventilation and dead space

Alveolar ventilation and dead space have been calculated in the majority of infant studies by the formulae:

Equation 1 $$\dot{V}A = \frac{\dot{V}\ CO_2\ \ BTPS\ (PB - 47)}{PaCO_2}$$

Equation 2 $$VD = \frac{\dot{V}E - \dot{V}A}{f} - \text{(apparatus dead space)}$$

Otis (1964) discussed the derivation of the first equation and indicated that it depended on two assumptions, first that CO_2 is absent from the

inspired air, and secondly, that R equals 1. The latter, however, has been shown to be nearer 0.7 to 0.8 in newborn infants (Nelson et al., 1962; Strang, 1961). Because of this, it was thought that the wide deviation between dead space derived by the graphical method of Strang (1961), and that obtained by other workers, might be eliminated by the application of the Enghoff formula:

$$VD = \frac{(PaCO_2 - PECO_2)}{PaCO_2}$$

Alveolar ventilation and dead space were therefore calculated by both formulae in the present study, but the difference proved not to be significant ($P > 0.10$). It was decided to continue using the first formula, as comparison of results with other series was more readily achieved. Confidence limit $\dot{V}A$/min. 49 ml./min.

When alveolar PCO_2 measured as end-tidal is used, the calculated dead space is considered as 'anatomical'. When arterial PCO_2 is used, the resultant dead space is 'physiological'. VD confidence limit 0.6 ml.

Part 4 : Acid base balance and arterial carbon dioxide tension

Normal infants

The pH, base excess and PCO_2 were determined on arterialized capillary blood, as these measurements compare favourably with those obtained from arterial blood (Koch and Wendel, 1967).

Distressed infants

Acid base values were obtained on arterial blood samples for the first two days of the illness and thereafter capillary blood samples were used.

Method of collecting capillary blood

The infant's heel was placed in hot water for 5 minutes and then stabbed on the medial aspect with a No. 11 Bard Parker sterile blade. The foot was replaced in water once this wound had been covered with a plastic dressing. A sample of freely flowing blood was later collected from this site during the time of expiratory gas collection. This was obtained by placing a heparinized glass capillary into a drop of blood over the site of incision, thereby excluding any contact with air. The collection was made in each case during sleep or a quiet phase, and the capillary tube was sealed at both ends with plasticine, after a wire stirrer had been introduced.

Method of collecting arterial blood

The umbilical cord was cut, leaving a stump 1.5 cm. long. The lumen of an artery was now dilated with a metal probe and a 5F polythene catheter was passed 8 cm. up the artery. This distance was selected as an X-ray in 8 infants revealed the catheter to be lying in the thoracic aorta.

The polythene tube was now filled with a heparin/saline solution (10 units heparin/ml.) and taped to the abdominal wall. Blood was collected in a 2 ml. glass syringe, the dead space of which had been filled with 0.25 ml. of heparin (1,000 units/ml.) and the syringe was then sealed with a metal stopper and placed on ice.

After 48 hours the catheter was removed and the umbilical stump tied with sterile cord.

Measurements

Base excess, pH and PCO_2 were determined by the Astrup technique (Astrup et al., 1961) within 10 minutes of the collection of blood samples.

Three measurements of pH were made at 37°C, first on the sample of collected blood to be analysed and then on samples of the same blood after they had been equilibrated with two carbon dioxide mixtures of known concentration. Gas tensions had been derived by accurate determination of this concentration in the Schölander apparatus and were in the region of 25 mm.Hg. and 56 mm.Hg.

A pH meter (Radiometer 27 GM) was attached to a pair of pH electrodes, one glass and the other caromel. The response of this electrode pair was a voltage which varied in a linear relationship with the sample pH. The electrode was standardised daily with two buffer solutions of pH 7.381 and 6.840 to bring the zero and span of the meter into agreement with the zero and sensitivity of the electrode.

Base excess PCO_2 readings were read off a curve monogram on which the pH readings had been plotted. Studies were done in duplicate.

Temperature correction (Rosenthal, 1948)

In hypothermic infants, for each 1°C below 38°C a factor of 0.015

was added to the actual pH value measured at 38°C. A similar factor was subtracted in infants with temperatures above 38°C.

Confidence limits:

pH	± 0.004
Base excess	± 0.6 mEq/L.
$PaCO_2$	± 5 mm.Hg.

Part 5 : Arterial oxygen tension

The site of sampling blood for arterial oxygen tension is extremely important in the newborn infant. Shunts at a ductal level are present for the first 15 hours of life and samples should, therefore, ideally be taken above this site. This is of equal importance in cases of hyaline membrane disease, in which large right-to-left shunts may be present. However, it is not known whether they persist during artificial ventilation.

Various sampling techniques have been described and include temporal artery puncture (Thomsen, 1964), radial artery puncture (Bucci et al., 1966), capillary blood sampling and blood obtained from the aorta (Koch and Wendel, 1967).

The discrepancy between arterialized capillary oxygen tension and that of arterial blood in normal infants is considerable (Koch and Wendel, 1967) and has been found to average 9.5 mm.Hg. with a wide range of deviation. For this reason, no attempt has been made in the present study to compare oxygen tensions obtained on capillary and arterial blood. Temporal artery sampling was found to be relatively simple in normal infants but extremely difficult in babies suffering from hyaline membrane disease, because of marked scalp oedema. Radial artery puncture also proved erratic and for these reasons arterial blood was obtained from an indwelling umbilical catheter. Although great stress is laid on arterial oxygen tension throughout this study, it must be qualified by the fact that blood was obtained below the ductus and therefore disregards the effect of any right-to-left shunting.

Arterial oxygen tension was determined by a Clark type micro-oxygen electrode (Radiometer E5046). This consisted of a combined platinum

cathode and silver/silver chloride anode, placed in an electrolytic solution behind a polypropylene membrane.

Electrode characteristics

Response time: 99% of full deflection in less than 60 seconds at 38°C.

The PO_2 meter consisted of a pH meter (Radiometer Type PHM 27) with an electronic amplifier and an indicating meter. A gas monitor (Radiometer Type PHA 927) was also used.

Calibration

Zero was set using an oxygen-free solution of 0.01 M borax and crystals of sodium sulphite. This procedure was carried out once a day. Before each experiment, calibration was performed with an aqueous solution of known PO_2. As the expected PO_2 was below 200 mm.Hg. in all cases, an air equilibrated solution was used. For this purpose a sample of water was obtained from the water thermostat, as air was continually being sucked into this water by means of a built-in suction pump. Oxygen content in the laboratory air was determined in duplicate on 10 separate days, by means of the Schölander apparatus, and the mean concentration was 20.92%.

The PO_2 of the water solution was then derived from the equation:

$$PO_2 = (PB - a) \frac{O_2\%}{100}$$

where PB = Barometric pressure mm.Hg.

a = Partial pressure of water vapour at the temperature used

$O_2\%$ = Percentage by volume of oxygen in the gas mixture employed.

The blood sample was now introduced either from a capillary tube or a syringe within 5 minutes from the time of collection. Great care was taken to exclude any air bubble from the chamber. All readings were done in duplicate.

Confidence limits:

Range 0 to 120 mm.Hg. = ± 0.4 mm.Hg.
80 to 220 mm.Hg. = ± 4.1 mm.Hg.

Temperature

A skin electrode (YS1 409) was strapped to the outer aspect of a thigh and the temperature constantly monitored in each infant on a YS 1 Tele-thermometer).

Deep rectal temperature was recorded before and after any investigation by means of a rectal coupler (Ysl 401), while the temperature of gas delivered to, or expired by, an infant was obtained by means of a fine oesophageal coupler (YS1 402).

Calibration

The zero of the tele-thermometer was set each day and on one occasion this instrument was calibrated against a sensitive laboratory mercury thermometer.

No significant difference could be shown in temperatures recorded over a wide range.

Electromyogram

Electrical activity of the rectus abdominus muscles was recorded in 5 infants. This was done by inserting a fine unipolar needle electrode into the muscle mass under sterile conditions and attaching it to an E.M.G. coupler.

No calibration procedure was adopted as it was intended to demonstrate electrical activity only, rather than the degree of this activity.

Further investigations

A number of investigations, not determined by the author, have been included in order to complete the study.

Haemoglobin concentration (Department of Haematology) was estimated on a Klett-Summerson photoelectric colorimeter, using the Cyan methaemoglobin method.

Serum proteins (Department of Chemical Pathology). Paper electro-phoresis was done on 0.01 ml. of serum, and bands corresponding to the protein fractions were subsequently eluted. The optical densities of the filtered eluates were taken to be proportional to the concentration of the protein fractions.

Venous pressure (Dr. M. Klein). Umbilical and right atrial pressures were obtained by advancing a saline-filled 8F polythene catheter up the umbilical vein and using a Statham P 23 De strain gauge. Zero was set at the mid-chest level.

X-ray of chest (Department of Radiology). A postero-anterior and a lateral film of the chest was obtained on each infant, using a portable Phillips NR machine. The radiograph was taken through the incubator lid at a distance of 80 cm. from the infant (Bauman and Nadelhaft, 1958).

Postmortems (Department of Pathology). Autopsy studies were performed on 10 infants who died.

Procedure

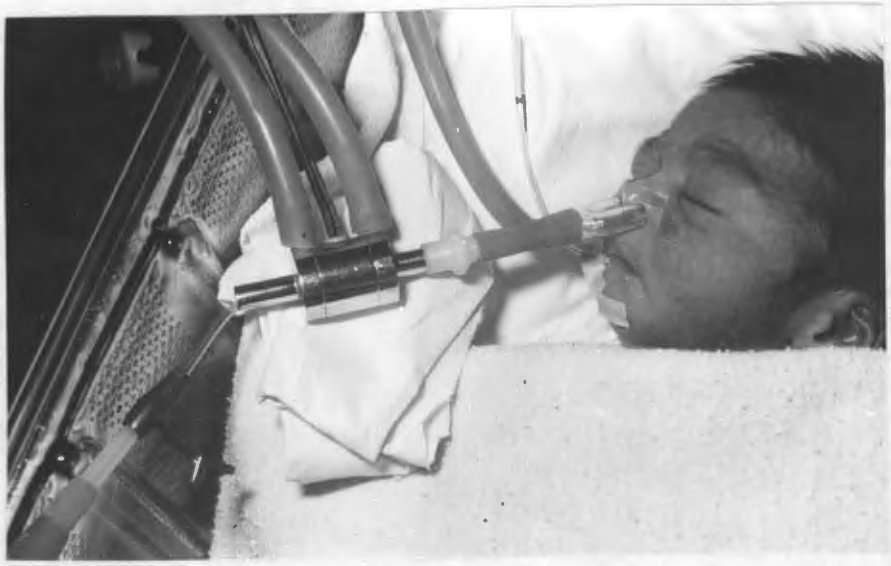
Normal infants were studied 2 hours after a feed. The full-term babies were warmly wrapped in blankets and lay supine in their cots (Fig. 14), while the majority of premature and Caesarean section infants lay undressed in incubators. The deep rectal temperature was read and following this the infant's heel was pierced, covered with a dressing and placed back in warm water. Crying infants settled down within 3 minutes.

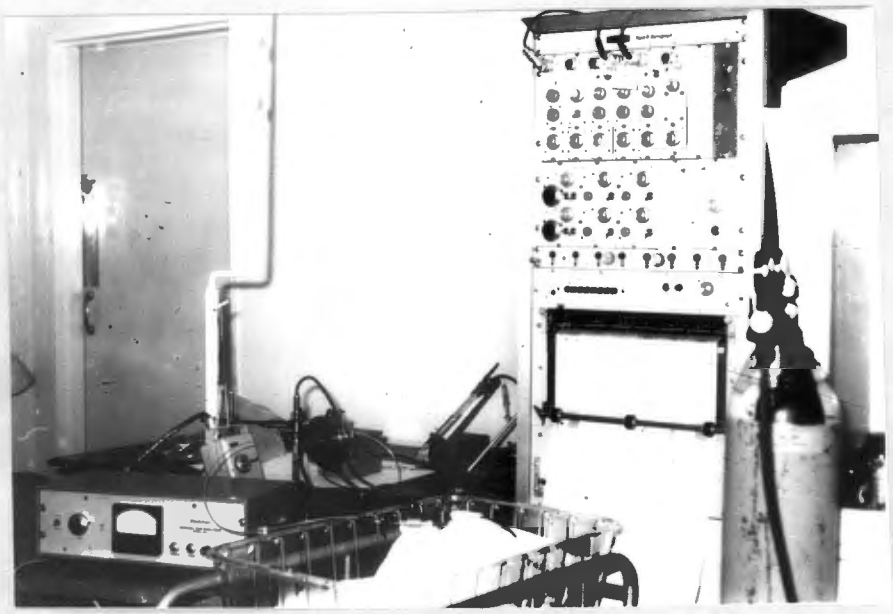
The validity of lung functions depends on maintaining a steady state, and full-term infants lying in a plethymograph have been shown to reach such a state only after 10 to 15 minutes, while premature babies require up to 20 minutes. Up to this time, a constant decline in minute volume has been observed (Boutourline-Young, 1950). Cross (1949) adopted the strictest critera for a steady state by insisting that infants remain quiescent for at least 20 minutes before readings are commenced, by investigating them only 1½ to 3½ hours after meals and by obtaining resting minute volumes over 5 to 18 consecutive minutes. During this time infants were required to sleep quietly without any limb activity, facial grimacing or sucking movements.

Criteria as rigid as these were not easily achieved in this study because of the nature of the equipment. No infant received any form of sedation and following the insertion of the nasal piece most became restless for one to two minutes but then fell asleep. The apparatus was kept in place a further 6 minutes before any measurements were made. Expired gas was collected over the next 4 to 8 minutes. Instrument leaks were eliminated by coating the glass nasal piece with a water-soluble lubricating jelly. Any escape of air was readily detected by

Fig. 14

Performance of lung function studies on a normal infant





holding the tip of the carbon dioxide analyser over the nostrils, mouth and inspiratory part of the valve and noting a deflection on the carbon dioxide record. If leaks had occurred, the expired gas was discarded and the procedure repeated.

Immediately following expired gas collection, capillary blood was obtained from the heel. If an infant cried at this stage, the sample was discarded and a further specimen taken some minutes later after the baby had fallen asleep.

The oesophageal catheter was now passed through the infant's mouth and in most cases this procedure precipitated a bout of crying or retching. Once the catheter had passed into the oesophagus it was strapped to the cheek and a further 15 to 20 minutes were allowed to elapse until the baby had returned to a basal state.

In the interval, acid base values were determined on the collected blood and the carbon dioxide tensions calculated from expired gas.

The nasal piece was now re-inserted into the nostrils and after a further 3 minutes measurements of transpulmonary pressure, flow rate and tidal volume were made. At the end of this study, the rectal temperature was again checked: in no case did it fluctuate more than $0.5^{\circ}F$ during the time of the investigation.

The procedure adopted for distressed infants was basically similar, but studies were completed as soon as possible to avoid undue interference. These infants did not resent the presence of a nasal coupler in the nostrils or the passage of the oesophageal balloon, and measurements were made 3 minutes after these procedures had been carried out.

Procedure during artificial ventilation

The study of lung functions during positive-pressure ventilation posed a number of problems mainly concerned with the adaptation of apparatus. All infants were investigated while lying on their backs in incubators. One end of the pneumotachograph was connected to the endotracheal tube while the other end was attached to the Y portion of the infant circuit tubes by means of a tightly fitting plastic connector. Because of the extremely short tubing fitted to the pneumotachograph, the PM 5 pressure transducer had to be suspended from the incubator to lie close to the infant's face. It required careful immobilisation, as any movement would cause drift from the flow base line which, in turn, would be integrated falsely as volume.

Passive ventilation was obtained on 5 infants by paralysing 2 of them with 1 mgm. of scoline given intravenously and over-ventilating the remaining 3. Scoline action lasted only 3 minutes and any investigations had to be completed in this time. The effects of over-ventilation lasted approximately 5 minutes before any spontaneous breathing efforts were again noticed.

Part 6 : Lung function studies in normal full-term and premature babies

Investigations of pulmonary function in full-term and premature infants have been carried out since 1890. Early reports dealt with the rate of breathing and tidal volume, but reasonable accuracy in these measurements was only obtained following the introduction of the body plethymograph. Refinements of apparatus and technique have broadened the scope of investigation, and all aspects of lung function determined in adults have subsequently been derived in infants.

Results

Rate of breathing

The rate of breathing differed in full-term and premature infants, being more rapid in immature babies with a mean 50 breaths a minute, while mature babies had a mean rate of 43 per minute.

Lung volumes

Mean tidal volumes reflected a similar difference for size, being 18.6 ml. in full-term babies (Table 4) and 14.1 ml. in prematures (Table 5). However, when related to weight these values were $\overline{5.7}$ ml./kg. and $\overline{6.0}$ ml./kg. respectively.

Minute volumes averaged 757 ml. (203 ml./kg.) in full-term infants and 654 ml. (312 ml./kg. in prematures).

Flow rates

Inspiration: The inspiratory time averaged 0.51 seconds in full-term infants and 0.49 seconds in prematures, while the mean peak inspiratory flow rates were $\overline{42.9}$ ml./sec. and $\overline{37.7}$ ml./sec. respectively.

TABLE 4

DATA ON 33 NORMAL FULL-TERM INFANTS

	Weight kg.	f per min.	PTP cm.H_2O	VT ml.	$\dot{V}$ ml./min.	Cl ml./cm.H_2O	Work of Breathing gm.6m/min	$\dot{V}I$ ml./sec	$\dot{V}E$ ml./sec.
Mean	3.22	41	4.8	18.7	757	4.7	2215	42.8	40.6
Range	2.55 to 4.28	28 to 58	1.7 to 6.4	12.1 to 26.8	506 to 1241	3.4 to 6.8		26 to 60	16 to 60
S.D. ±	0.55	10.1	2.1	3.3	200	2.5	987	12.6	14.2
No. of cases	31	31	23	31	31	20	23	33	33

	pH	Base Excess mEq/L	$PaCO_2$ mm.Hg.	$PACO_2$ mm.Hg.	$PECO_2$ mm.Hg.	$\dot{V}A$ ml./min.	VD ml.	VD/VT
Mean	7.35	-4.9	36	34	17.6	376	5.5	0.25
Range	7.26 to 7.44	-10 to 0	30 to 44	30 to 43	11.9 to 24.2	260 to 660	3.0 to 7.0	.16 to .46
S.D. ±	0.02	1.8	4.3	4.2	3.2	112	1.4	0.06
No. of cases	33	33	33	15	24	24	24	24

TABLE 5

DATA ON 25 PREMATURE INFANTS

	Weight kg.	f per min.	PTP $cm.H_2O$	VT ml.	$\dot{V}$ ml./min.	Cl $ml./cm.H_2O$	Work of Breathing gm.cm./min	$\dot{V}I$ ml./sec.	$\dot{V}E$ ml./sec.
Mean	2.09	50.2	4.4	14.2	654	4.0	1723	37.7	32.6
Range	1.87 to 2.46	34 to 64	2.6 to 7.2	9 to 21	400 to 870	2.2 to 5.9		24 to 72	20 to 57
S.D.±	0.60	11.6	1.5	3.1	170	1.0	580	13.2	13.1
No. of cases	24	24	20	24	24	20	20	24	24

	pH	Base Excess mEq/L	$PaCO_2$ mmHg.	$PACO_2$ mm.Hg	$PECO_2$ mmHg	$\dot{V}A$ ml./min.	VD ml.	VD/VT
Mean	7.32	-5.7	37.4	35.1	17.0	281	3.8	0.26
Range	7.23 to 7.42	-11 to -1	27 to 42	25 to 40	15.0 to 19.7	150 to 471	2.4 to 7.0	.12 to .40
S.D.±	0.08	2.9	4.6	3.0	1.7	88	1.4	0.06
No. of cases	24	24	24	7	13	13	13	13

Expiration: Expiratory flow curves, unlike those of inspiration, could clearly be divided into two types depending on the duration of expiration.

The first type (Fig. 15a) was observed in all infants and consisted of a short expiratory phase ($0.\overline{67}$ sec.) during which the peak flow rates occurred in mid- or late expiration.

The second type (Fig. 15 b) occurred in 50% of full-term babies and 25% of prematures. It was characterized by a much longer expiratory period ($1.\overline{22}$ sec.) and peak flow rates occurred early.

An infant was often noted to breathe rapidly, thereby producing the first type of expiratory curve, and then to change over to a slower rate of breathing, demonstrating the second type of expiratory curve.

Lung mechanics

Transpulmonary pressure increased to a mean negative value of 4.8 cm. H_2O in full-term babies and 4.4 cm. H_2O in prematures. The mean lung compliance in full-term infants was 4.9 cm. H_2O/ml. (Table 4), while in prematures it averaged 4.0 cm. H_2O/ml. (Table 5).

The mean work of breathing was 2169 gm. cm./min. and 1541 gm. cm./min. respectively in each group.

Acid base balance

The $\overline{pH}$ was 7.35 in full-term babies, while base excess had a mean value of -4.9 mEq/L. Respective studies in prematures revealed a mean pH of 7.32 and a base excess of -5.7 mEq/L.

Arterial and end-tidal carbon dioxide tension

End-tidal carbon dioxide tension could be derived in 15 full-term babies and in 8 premature babies who produced plateau formation on expired carbon dioxide curves. The mean alveolar carbon dioxide tension for

full-term infants was 34.0 mm.Hg. while capillary carbon dioxide tension was 36.0 mm.Hg. In prematures, alveolar carbon dioxide tension was 35.1 mm.Hg. and capillary carbon dioxide tension was 35.1 mm.Hg. No significant difference could be demonstrated between $PACO_2$ as determined from end tidal carbon dioxide concentration and $PaCO_2$ as derived from capillary blood.

It was also evident that plateau formations occurred only during intervals of prolonged expiration and were related to the second type of expiratory curve which has been described (Fig. 15b). If a rapid expiratory curve was produced (Fig. 15a), a peak CO_2 tracing, rather than a plateau, would appear. The peaks were not of the same height as plateaux and did not yield end-tidal carbon dioxide tensions comparable with those of capillary blood. In 19 full-term infants, plateau formation gave a mean PCO_2 reading of 37.8 mm.Hg., while that obtained from peaks in the same infants averaged 25.2 mm.Hg. ($P < 0.001$). These peaks were not necessarily dependent on the volume of gas expired, for no significant alteration in tidal volume occurred during peak (mean 17.5 ml.) and plateau formation (mean 17.5 ml.) in the same infant.

Alveolar ventilation and dead space

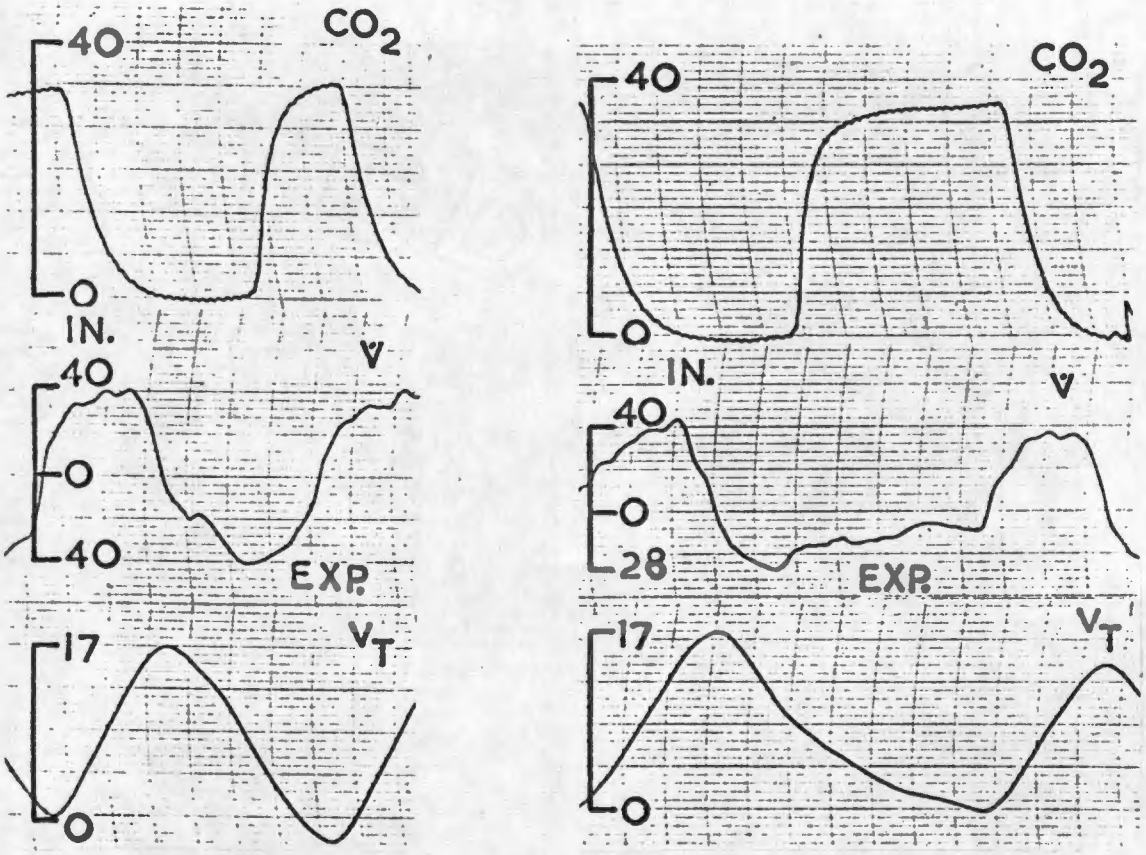
The amount of air entering the alveoli and taking part in gas exchange gave a mean value of 376 ml./min. in 20 full-term babies and 281 ml./min. in 20 premature babies. Physiological dead space averaged 5.5 ml. in the full-term group while the mean value in prematures was 3.8 ml. VD/VT ratios were $\overline{0.29}$ and $\overline{0.26}$ respectively in each group of infants.

Fig. 15

Relationship of expiratory time to shape of CO_2 curves

a. Short expiration: paper speed 5 cm./sec.

b. Prolonged expiration in same infant: paper speed 5 cm./sec.



CO_2 : mm.Hg.

$\dot{V}$: ml./sec.

VT : ml.

During a short expiratory period the CO_2 curve is peaked.

During a prolonged expiratory period the CO_2 curve forms a plateau indicating the presence of alveolar gas. $PECO_2$ can be calculated from the vertical height of this plateau.

Discussion

Breathing and volume

The rate of breathing and minute volumes have been contrasted with those of reported series (Table 6). It is evident that these investigations are dependent on maintaining a steady state throughout the study, and those authors who adopted rigid criteria for such a state obtained the lowest values for both breathing rate and minute volume. They indicated, however, that striking variations both in breathing rate and volume could occur during repeated studies on the same infant. In premature babies, breathing rates are more rapid (b, Table 6) than those of full-term babies and when Boutourline-Young et al. (1950) obtained a mean rate of 32/min., considerably lower than that of their full-term group, they concluded that the reduction in rate had been due to periodic breathing.

In the present study it is felt that added nasal irritation from apparatus accounted for the somewhat more rapid rate of breathing. In the premature group the mean rate of 50 per minute is further accounted for by the fact that all intervals of periodic breathing were excluded from measurement.

Flow

Expiratory flow curves are similar to those described by Swyer et al. (1961). The slow expiratory curve resembled their 'exponential wave', while the rapid form of expiration was similar to their 'sine wave'. These authors described a third type which they termed 'changing resistance' which they considered to be artefactual. This type was not observed in the present series but did occur in distressed, grunting infants. It does not appear, therefore, to be a form of expiration which occurs in normal infants.

TABLE 6

COMPARISON OF LUNG FUNCTION STUDIES

(a) FULL TERM INFANTS

AUTHORS	Weight kg.	f per min.	VT ml.	$\dot{V}$ ml/min.	Min./vol. kg. bodyweight	Method of study
Cross, 1949	-	28.6	-	589	171	Body plethysmography
Boutourline-Young, 1950 et al.	3.53	39	16.2	642	182	"
Deming and Hanner, 1931	-	44	19.8	851	127	"
Murphy and Thorp, 1965	3.20	43.1	16.7	721	-	"
Burnard et al., 1965	3.00	-	17.0	643	-	"
Swyer et al., 1960	3.00	36.7	20.6	730	246	Pneumotachograph
Cook et al., 1955	3.00	38	16.0	608	203	Plethysmograph
Strang, 1961	3.22	41	18.1	750	-	Spectrometer and plethysmograph
Present series	3.22	43	18.6	757	201	Pneumotachograph
(b) PREMATURE INFANTS						
Cross and Oppé, 1952	1.97	34	-	396	201	Plethysmograph
Boutourline-Young et al., 1950	1.91	32	13.3	430	225	"
Shaw and Hopkins, 1931	-	58	12.3	698	193	"
Cook et al., 1955	2.50	34	15.0	498	-	"
Present series	2.09	50	14.1	654	312	Pneumothachograph

Lung mechanics

Compliance, as well as the work of breathing, is similar to that reported in other series (Table 7).

TABLE 7

COMPARISON OF LUNG MECHANICS

Authors	Weight kg.	$P_{oes.}$ cm.H_2O	Cl ml./cm.H_2O	Work of Breathing gm. cm./min.
Cook et al., 1957.	3.00	5.0	5.2	1380
Swyer et al., 1960.	3.00	4.8	4.9	2050
McIlroy and Tomlinson, 1955.	3.10	5.0	1.8	2600
Present series	3.22	4.8	4.9	2.69

End-tidal carbon dioxide concentration

Alveolar gas yielded plateaux on expiratory carbon dioxide tracings which were similar to those obtained in adult studies. Strang (1961) estimated that a plateau was produced by the last 3 to 5 ml. of expired air in infants and that if alveolar volume were insufficient to wash out dead space, a peak rather than a plateau would be recorded. The present study illustrates another important factor which influences plateau formation, namely, the duration of expiration. It appears possible that if expired air is blown off slowly, the alveolar portion will reach a CO_2 analyser as a 'block' wave and its concentration will be recorded as a plateau. However, during rapid expiration the alveolar portion of air might mix with dead space air and not be recorded in this manner.

Nelson et al. (1962) demonstrated a close correlation between

carbon dioxide tension determined on end-tidal air and that of arterial blood (Table 8). Samples of gas had been collected in a miniature Rahn collector while capillary blood had been used in place of arterial blood. A similar correlation between $PACO_2$ and $PaCO_2$ could be shown in the present study and it is thus evident that normal full-term and premature infants, like adults, do not have any significant gradient for carbon dioxide between pulmonary capillary blood and the alveoli.

TABLE 8

COMPARISON OF LUNG FUNCTION STUDIES

Authors	Weight kg.	$PaCO_2$ mm.Hg.	$PETCO_2$ mm.Hg.	$\dot{V}A$ ml./min.	VD ml.	VD/VT
Nelson et al., 1962	2.27	35	33	309	3.3	0.25
Cook et al., 1955.	2.50	-	-	355	5.0	0.32
Strang, 1961.	3.22	-	33.2	378	9.2	0.50
Present series	3.22	36	34	376	5.5	0.29

Dead space and alveolar ventilation

Dead space measurements differ widely in reported series, even when corrected for weight. The difference can probably be attributed to the various techniques which have been used to measure this volume.

Nelson et al. (1962) and Cook et al. (1955) collected expired gas and derived physiological dead space measurements of 3.3 ml. and 5.0 ml. respectively from the Böhr equation (Table 8). A similar method was used in the present study and produced comparable values of 3.8 ml. in prematures and 5.5 ml. in full-term babies. Strang (1961), however,

used a graphical method derived from mass spectrometer tracings, and noted an anatomical dead space of 9.2 ml. in one study and 8.5 ml. in a later study. The measurement of anatomical dead space should, if anything, be smaller than that of physiological dead space. It has been indicated, however, that the response time of the mass spectrometer could result in an over-estimate of dead space by up to 5%.

VD/VT studies were similarly affected, those of Cook et al. (1955), Nelson et al. (1962) and the present study being close to the normal adult value, while Strang (1961) indicated a ratio of 0.50 (Table 8).

No difference, however, is reflected in alveolar ventilation, which is remarkably similar in all reported studies.

Summary

Measurements of lung function on 33 full-term and 25 premature infants proved to be accurate when compared with those of reported series, and will now be used as controls for studies on babies with hyaline membrane disease.

A hitherto unreported observation was the fact that alveolar gas collection depended on the nature of expiration. It is known that a sufficient volume of gas must be breathed out before the alveolar portion can be obtained (Strang, 1961) but in addition to this, expiration itself has to be slow and prolonged.

CHAPTER III

TREATMENT

Part 1 : Review of the literature in regard to treatment

Part 2 : Treatment without IPPR

Part 3 : Treatment with IPPR

Part 4 : Intracranial haemorrhage associated with hyaline membrane disease

Part 1 : Review of the literature in regard to treatment

Hyaline membrane disease is self-limiting to a certain extent, and if an infant can be kept alive over several crucial days, eventual recovery will take place. Nevertheless, there remains an almost inevitable number of deaths (Stahlman, 1964).

Many factors of prematurity have still to be explained and up to the present time treatment has varied with the current theory of pathogenesis. Control of maternal diabetes (Gellis and Hsia, 1959), and avoidance of Caesarean sections where possible, have done little to reduce the incidence or the mortality rate.

The original concept of aspirated amniotic debris being forced against the walls of alveoli and alveolar ducts (Johnston and Meyer, 1925; Dick and Pund, 1949) led Gellis et al. (1949) to propose that the stomachs of all infants delivered by Caesarean section be aspirated at the time of delivery. Such a procedure was widely carried out over the next decade but no alteration occurred in the incidence or severity of the disease.

The emphasis on membranes shifted when histological evidence of underlying epithelial injury was presented (Tregillus, 1951). However, the membranes were later shown to contain fibrin (Gitlin and Craig, 1956) and this led to the suggestion that they had been caused by a lack of fibrinolytic enzymes and could be dissolved by fibrinolysins given by nebulization (Ambrus et al., 1963). The results of this form of treatment, however, have not been convincing.

Cardiac failure

Miller (1951) suggested that deaths of many distressed infants born to diabetic mothers were related to heart failure. He further postulated

that the mechanism of cardiac failure had a bearing on the development of pulmonary membranes. This concept was taken up by Lendrum (1955) who thought that the picture of rapidly increasing dyspnoea, cyanosis, dilation of the right heart and atelectasis suggested overloading of the pulmonary circuit and failure of the left heart. The presence of a widely patent ductus arteriosus with a large left-to-right shunt in all severe cases (Rudolph et al., 1961) added further impetus to the recognition of the significance of cardiac failure and prompted the use of digitalis for the disease. Controlled trials, however, (Martin, 1963) revealed no significant difference in mortality rates between infants receiving the drug and those given a placebo. Stahlman (1964) later advised its use in selected cases only, particularly those with a pulse rate over 150 per minute. The use of adrenaline was also propounded for the treatment of cardiac failure due to shunts (Brown, 1959; Rudolph et al., 1963) but this was not widely adopted.

Alterations in blood volume then received attention. It was thought that delayed clamping of the cord would permit adequate perfusion of the pulmonary vascular bed (Moss et al., 1962), where an opposing view (Stahlman, 1964) suggested that removal of 10 to 15 ml. of blood would benefit the infant. Pulmonary hypofusion was considered to be an important characteristic of the disease (Chu et al., 1965) and it was hoped to correct this feature by the administration of acetycholine injected directly into the right atrium. Temporary improvement occurred as reflected by an increase in pulmonary blood flow, decrease in dead space and a fall in arterial carbon dioxide tension. However, no alteration in the overall mortality was demonstrated and the claims of this potentially harmful drug appear to have been exaggerated. (Moss et al., 1966).

Stowens (1965) considered that hyaline membrane disease was caused by an increased excretion of water through the lungs owing to functional immaturity of the kidney, and proposed the use of hypertonic magnesium sulphate enemas as a means of ridding the body of this extra fluid. The substance, however, is highly toxic and can be absorbed from the rectum with fatal results (Andrews et al., 1965).

The lungs themselves became the focus of attention when Avery and Mead (1959) demonstrated the lack of surfactant in pulmonary tissue extracts from infants dying of hyaline membrane disease. This unique substance has the capacity of lowering surface tension in proportion to a reduction in surface area; when it is lacking, infants must inflate their lungs against surface tension. It is not surprising that attempts were made to restore this substance and a synthetic form was administered by micro-aerosolisation to 11 infants in one trial (Robillard et al., 1964). Although 8 of the infants recovered, the results were inconclusive and the major limitation of this therapy appeared to be an inability to deliver the agent into the collapsed alveoli.

Respiratory failure

The physiological derangements of lung function in hyaline membrane disease now assumed importance, as they were found to result in respiratory failure with the appearance of hypoxaemia, hypercapnoea and metabolic acidosis.

Hypoxaemia occurred as the result of inadequate ventilation and right-to-left shunting of blood through the lungs, foramen ovale and ductus arteriosus (Stahlman, 1964), while retention of carbon dioxide also resulted from imperfect matching of blood and gas at alveolar level

(Nelson et al., 1962). The progressive fall in arterial oxygen tension was accompanied by a rise in serum lactate which contributed 20 to 90% of excess fixed acids in severe cases, giving rise to metabolic acidosis (Wang et al., 1963). Other features observed in severe cases with respiratory failure included hypoglycaemia due to depletion of glycogen stores (Shelley, 1964), azotaemia and hyperkalaemia associated with an increased breakdown of cells (Usher, 1961).

Treatment was thus directed towards the correction of respiratory failure. Warley and Gairdner (1962) proposed the use of oxygen in quantities sufficient to abolish cyanosis and maintain oxygen tension between 80 to 100 mm.Hg.,and Prod'hom et al. (1965) indicated that in severe cases such levels could only be attained by the administration of high concentrations of oxygen, up to 100%, during the acute stage of the disease.

The use of hyperbaric oxygen appeared to have no added advamtage as, although arterial oxygen tension could be raised almost immediately, it dropped precipitously during apnoeic attacks (Cochran et al., 1965) and remained low until breathing was resumed. This form of therapy could not prevent the apnoeic attacks which led ultimately to the deaths of all infants.

Metabolic acidosis had initially been treated with 5% glucose in 0.05% saline (Reardon, 1957) and further studies (Usher, 1961) indicated that hypoglycaemia, hyperkalaemia and metabolic acidosis could be corrected by the intravenous administration of sodium bicarbonate, glucose and insulin. This régime, however, merely prolonged life in the majority of infants and did not materially alter the mortality rate which remained at between 40 and 60%.

The first significant reduction in mortality rate was claimed by Usher (1963) who stressed the importance of preventing respiratory decompensation rather than correcting an already existing pulmonary failure. He indicated that the administration of oxygen, intravenous sodium bicarbonate and glucose early in the course of the disease, and as soon after birth as possible, would prevent the appearance of azotaemia and hyperkalaemia. It was necessary to maintain such therapy throughout the acute phase of the disease, as premature discontinuation of the glucose drip often led to apnoeic attacks, which were considered to be due to reactive hypoglycaemia. Hutchinson et al. (1964) favoured the use of intravenous fructose in place of glucose as it could be metabolised independently of insulin and it thereby avoided the dangers of hypoglycaemia.

By these means, the mortality rate in infants over 1500 gm. in weight was reduced by two-thirds to 17%, compared with 37% in a control group.

One criticism that may be levelled against the validity of the results is that the diagnosis of hyaline membrane disease was made solely on clinical grounds early in the disease and may have included other forms of respiratory distress; however, the author indicated his wide experience in the disease and his clinical criteria for the diagnosis must therefore be accepted.

Intensive care

It is certain that this success cannot be attributed solely to the administration of oxygen and intravenous fluids, but also to the institution of intensive patient care. Segal (1966) indicated the desirability of treating distressed infants in a well-equipped medical

centre and stressed the necessity for achieving not merely survival, but intact survival. Facilities should be as close to the delivery room as possible so that the journey for distressed infants is a short one, while laboratory aids should be available at any time for the frequent estimation of acid base and blood gas status. Distressed infants are best nursed in incubators capable of supplying warmth, humidity and varying concentrations of oxygen, while continuous monitoring of certain vital functions, particularly breathing, heart-rate and temperature, avoids the unnecessary exposure or handling of the baby. He particularly stressed the rôle of an experienced nursing supervisor who is able to detect the earliest signs of deterioration and thereby allow for the necessary adjustment in treatment before a stage of respiratory decompensation has been reached. In addition, she should be able to handle the all-important aspect of feeding and prevention of infection.

Artificial ventilation of the lungs

It is evident that the outlook is poor once features of respiratory failure appear and cannot be reversed by the foregoing therapy, and it is not surprising that some form of ventilatory assistance was proposed (Donald and Lord, 1953) in an attempt to reverse the process.

(a) Normal lungs

The concept of artificial ventilation of normal lungs is by no means of recent origin. Paracelsus, in the 16th century, described a method of inflating the lungs of asphyxiated patients with bellows. Later, the same principle was adopted by Versalius to keep animals alive while demonstrating their anatomy (Mushin and Rendell-Baker, 1953). During the 18th and 19th centuries, further methods of resuscitation were

developed in Europe and pharyngeal insufflation with a tube and bellows became well established for use on drowned patients. The development of this technique in newborn babies appeared to interest obstetricians of the time, for Chaussier in 1780 designed a simple apparatus consisting of a bag and face-mask to be used in the resuscitation of asphyxiated infants. In 1807, the development of a cannula for intubation of the larynx permitted more efficient inflation of the infants' lungs, but the method never became popular, probably owing to the practical difficulty of intubating the larynx by touch alone (Mushin and Rendell-Baker, 1953).

In 1827, however, the whole concept of intubation and artificial ventilation of the lungs suffered an incalculable setback when Leroy presented evidence of its dangers to the French Academy of Science (Mushin and Rendell-Baker, 1953). He demonstrated that by inflating the lungs with bellows it was possible to rupture the alveoli with resultant pneumothorax and thus in many cases to precipitate the death of the patient. The impact of this condemnation can only be assessed by looking at the methods and types of ventilatory assistance adopted over the next century.

Sauerbruch heralded the age of differential pressure chambers in 1904 by demonstrating that collapse of the lungs could be prevented when the chest was opened. Over the next half-century, various forms of tank respirators were devised for use in pulmonary failure.

World War II added impetus to the study of respiratory physiology. Initially, the effects of continuous positive-pressure breathing were studied. Oxygen administered under continuous pressure to airmen flying at high altitudes prevented the ill-effects of hypoxaemia but had the

disadvantage of diminishing right filling and reducing cardiac output (Barach, 1947). A further objection to this form of therapy was that an accumulation of carbon dioxide in cases of hypoventilation could not be corrected. The eventual discarding of this method and the re-introduction of intermittent positive-pressure respiration completed the cycle of history. Cournand et al. (1947) presented exhaustive studies on the various effects of this type of ventilation. They correlated cardiac output, right ventricular filling, blood pressure and minute ventilation with the form and amplitude of pressure curves and inspiratory-expiratory ratios. In this manner, criteria for the effective and safe administration of intermittent positive-pressure respiration were provided.

Prolonged use of this therapy was employed by Lassen (1953) in the severe Danish polio epidemic, with a reduction in mortality from 90% to 40%, while prolonged application to newborn infants with normal lungs was instituted by Smythe and Bull (1959). This resulted in the death rate of infants with neonatal tetanus falling from 96% to 20%.

(b) Abnormal lungs

Donald (1953) established the principle of prolonged assisted ventilation in cases of hyaline membrane disease and he indicated the shortcomings of the various tank respirators which were available at the time. He designed a form of apparatus able to amplify spontaneous breaths, a respirator capable of applying up to -40 cm.H_2O pressure. However, the formidable procedure of mounting a distressed baby in it with little time to spare, precluded its use for routine therapy. Negative pressure is certainly safe (Silverman et al., 1967), but Stahlman (1964) found a combination of negative and positive pressure

to be more effective in severe cases.

A break-away from the tank tradition came with the introduction by Benson et al. (1958) of intermittent positive-pressure ventilation through a tracheostomy, while Colgan et al. (1960) instituted similar therapy through an endotracheal tube.

It is difficult to assess the efficacy of intermittent positive-pressure ventilation, as most reports are concerned with the occasional survivor. It is also not clear what criteria are to be selected for the institution of the procedure, which is potentially dangerous and therefore unlikely to be used in all cases of hyaline membrane disease.

Resuscitation of the moribund infant who may already have developed cardiac arrest is certainly not desirable: Delivoria-Papadopoulos and Swyer (1964) reported one survivor out of 19 such cases.

Reid and Tunstall (1966) proposed earlier therapy by selecting infants at the age of 3 hours on the basis of a Silverman score of 4 or more and a blood pH of less than 7.20, while in an environment of 40% oxygen. They indicated, however, that the pH had not been corrected at the time of selection, and one wonders therefore how many infants would have qualified had they received early intravenous sodium bicarbonate and higher concentrations of oxygen before the age of 3 hours. It is also unlikely that the Silverman score can be used as an index of severity (Stahlman et al., 1967). Three infants died out of a total of 9, but it is not clear whether they died in spite of, or because of, artificial ventilation, particularly as the cause of death was not mentioned. Nevertheless, the early introduction of assisted breathing may be beneficial to the immature baby below 1.99 kg., as such an infant has a

poor prognosis whatever form of therapy it may receive (Reid et al., 1967).

At the present time it seems clear that the indications for artificial ventilation lie between these extremes, and the hazards of this form of therapy must be weighed against those of the disease process.

Delivoria-Papadopoulos et al. (1965) claimed a 50% success rate if the institution of intermittent positive-pressure ventilation was related to certain features of respiratory failure, and they proposed its use if 3 of the following factors were present:

Respiratory rate per minute	Heart-rate per minute	Colour in 100% O_2	$PaCO_2$ mm.Hg	PaO_2 mm.Hg.
30	80			
		Cyanosis	80	40
120	160			

These figures provide a useful guide for the introduction of assisted ventilation, but it is essential to know if all signs are of equal importance or if one is more significant than the others. This problem of assessment has been lessened by a scoring system devised by Stahlman et al.,(1967), which provides an objective index of the severity of the disease depending on certain signs and which can reasonably predict the eventual outcome while the infant is receiving a particular form of treatment. Various factors on their own could provide rather good separation of potential survivors from potential fatalities. The inability to increase the rate of breathing in the face of severe disease is certainly considered to indicate a poor

prognosis but, on the other hand, a rapid respiratory rate in the region of 120/minute, is not necessarily a bad sign.

Arterial oxygen tension while an infant is breathing 100% oxygen is, on its own (Stahlman et al., 1967) or in conjunction with pH (Boston et al., 1966), the best determining factor of the outcome of the disease and this aspect may be more fully discussed.

Hypoxaemia

The total quantity of oxygen delivered to the tissues, rather than the arterial oxygen tension, determines whether a cell or tissue is hypoxic. Nevertheless, tissue damage has been related to arterial oxygen tension and in the adult a PaO_2 of 30 mm.Hg. is thought to be harmful, while a level below 20 mm.Hg. seems to be incapable of supporting life (Campbell, 1965). Further studies in adults with chronic emphysema (Platts et al., 1960; Baldwin et al., 1949) indicate that a level below 50 mm.Hg. has a deleterious effect.

Arterial oxygen tension in apparently normal prematures is related to weight and maturity. Infants over 2.5 kg. attain adult levels within 3 days of birth, whereas those below this weight might take up to 3 weeks to do so, and those below 1.2 kg. frequently have PaO_2 levels below 50 mm.Hg. (Thibeault et al., 1966). McDonald (1963) showed that the incidence of cerebral diplegia was extremely high in infants of low birth weight who had developed cyanotic attacks and who had received little or no oxygen. As cyanosis is only recognisable at a PaO_2 of 32 to 42 mm.Hg., it must be concluded that these levels are dangerous, and although the evidence of cerebral damage due to chronic hypoxaemia is indirect, it provides a most disturbing picture.

In infants, an impairment in metabolic response to cold has been observed at a PaO_2 of 45 mm.Hg. (Scopes and Ahmed, 1966), while in newborn calves an increase in pulmonary vascular resistance occurs with a drop in PaO_2 to below 50 mm.Hg. (Rudolph and Yuan, 1965).

There seems, therefore, to be sufficient evidence to indicate that infants with an arterial oxygen tension below 50 mm.Hg., despite breathing 100% oxygen, require some form of ventilatory assistance. It may also be noted that this PaO_2 value lies on the steep portion of the dissociation curve, on the brink of disaster, and a further fall will result in a sheer drop.

Apnoea

A severe fall in arterial oxygen tension has been noted during apnoeic spells (Miller et al., 1959) which are also associated with a slowing of the pulse rate (Avery, 1964), a rise in $PaCO_2$ and accentuation of a metabolic acidosis (Blystad, 1956a). These spells usually occur early in the disease and have been attributed to exhaustion of the infant (Cook et al., 1967), but may also result from hypoglycaemia (Usher, 1961) or immaturity of the respiratory centre. Nevertheless, they are considered to be particularly ominous signs and usually lead to death. They may be clearly distinguished from the periodic breathing pattern of prematurity, which has no alteration in pulse rate or arterial oxygen tension and does not carry the same grave implications (Blystad, 1956a).

Apnoea with cyanosis, therefore, appears to be a more severe presentation of hypoxaemia, warranting urgent correction.

Hypercapnoea

The prognostic significance of carbon dioxide retention is not clear, and Stahlman et al. (1967) found that respiratory acidosis alone,

in the presence of a normal or near normal buffer base, could be tolerated surprisingly well.

Dangerous effects of carbon dioxide retention have been reported at $PaCO_2$ levels above 100 mm.Hg. in the adult and, in the newborn infant with normal lungs, an increase in pulse rate, ECG changes and eventual circulatory collapse have occurred with $PaCO_2$ levels in excess of 100 mm.Hg. (Smythe, 1963). Hutchison et al. (1964) considered hypercapnoea to indicate an extremely poor prognosis, but their work unfortunately did not present simultaneous arterial oxygen tensions, and it is quite possible that infants die from associated hypoxaemia before the dangerous levels of $PaCO_2$ have been reached, particularly in the case of abnormal underlying lungs.

Metabolic acidosis

Lactic acid makes up most of the acids responsible for a low pH (Stahlman, 1967) but the accumulation of this acid can result from severe hypoxaemia, and metabolic acidosis in itself does not seem to indicate the necessity for ventilatory assistance.

It is considered, therefore, that severe hypoxaemia which occurs in apnoea, or hypoxaemia with PaO_2 below 50 mm.Hg., would give reasonable grounds for the use of mechanical ventilation of the lungs.

Part 2 : Treatment without IPPR

In the present study it was proposed to treat all infants on a standard régime of intensive patient care, high concentrations of oxygen and intravenous sodium bicarbonate and glucose, and if this failed to prevent or correct respiratory failure, then artificial ventilation in the form of intermittent positive-pressure respiration would be used.

Facilities

Infants suffering from hyaline membrane disease were admitted to an intensive care unit consisting of a large room which was capable of accommodating 3 babies at a time. Laboratory, storage and sterilisation facilities were available in separate rooms situated close by.

Staff

Nursing: A trained nursing sister was responsible for the day-to-day care, records and feeding of the infants, and at night she was relieved by a senior nurse who spent a two-month period in the unit, thereby avoiding frequent changes of staff.

Medical: The unit was directed by a full-time paediatrician and staffed by two research fellows who were responsible for the admission, diagnosis, investigation and treatment of all infants, thus providing a 24-hour service.

Prevention of infection

Unfortunately, the unit was attached to a general paediatric ward, and shortly after its inception a specific E coli infection was transmitted to 3 infants who subsequently died of gastroenteritis. This early tragedy led to the adoption of strict measures to prevent the possibility of further cross-infection. The entrance to the room

was separated from that to the general ward and no interchange of staff or equipment was allowed between the two wards. No infant was allowed into the unit if there was any suspicion of its harbouring an infection.

Staff wore gowns, boots and face masks and particular stress was laid on the cleaning of hands. These were washed on entering, and thereafter sprayed with an alcoholic solution of 0.5% chlorhexidine before touching an infant or items of equipment.

Each baby was provided with its own incubator, aspiration tray and catheters, suction machine, respirator, stethoscope, thermister probe, ECG cables and electrodes. These items were thoroughly washed after use with a solution of 0.5% chlorhexidine in 70% alcohol, and the incubators, suction machines and respirators were subsequently sterilized with formaldehyde gas. Before re-use, an incubator was filled with water to which 6ml of 2% acetic acid had been added to prevent the growth of pseudomonas.

Antibiotics were used only if an indwelling arterial catheter, pleural drain or endotracheal tube was in place for more than 24 hours. In such circumstances, a combination of cloxacillin and ampicillin (80 mgm./kg./day of each) was administered for a period of 5 days. These drugs were given intramuscularly for the first two days, and then orally.

Specific therapy

Transfer of infants: The staff of maternity institutions and outlying hospitals were instructed to administer sufficiently high concentrations of oxygen to avoid cyanosis in any distressed infant (Warley and Gairdner, 1962) and then to transfer the baby as soon as possible.

In the majority of cases a portable incubator was used for the journey. It was capable of providing an ideal environment of warmth and humidity but had to be specially adapted to deliver over 40% oxygen concentrations, as higher concentrations were often required to overcome cyanosis.

Admission: On admission the infant was immediately placed in a pre-warmed incubator. Oxygen was administered directly to the face by means of a cardboard carton, and in this manner concentrations of 90 to 100% could be reached (10 Schölander readings). At the same time, an intravenous drip of 100 ml. 10% glucose was commenced. This fluid was given into a scalp vein in quantities of 50 ml./kg./day.

In the early part of the study, sodium bicarbonate was administered at frequent intervals depending on acid base status. This often involved giving varying quantities directly into the drip tubing at 3-hourly intervals. The formula used for this purpose was

mEq. sodium bicarbonate = Base excess X 0.35 weight in kg.
(Hutchison et al., 1964).

In this manner the mean quantity of sodium bicarbonate required by 20 infants over the first 24-hour period amounted to 10 mEq. The largest amounts were required over the first 2 hours, as most of the infants had an initial metabolic acidosis. It was then decided to adopt a more simplified method of administration. Following the commencement of the intravenous drip, 2.5 mEq. of sodium bicarbonate was given directly into the drip tubing in all infants. A further 7.5 mEq. of sodium bicarbonate was added to the total fluid requirement for the day. If more alkali was needed it was given intravenously as a single dose. This method was applicable only during the first 24 hours of the disease, after which

sodium bicarbonate was given when required.

ECG electrodes were attached to the limbs while a thermister probe was strapped to the outer aspect of a thigh. ECG tracings were recorded continuously on an oscilloscope, skin temperature was monitored on a tele-thermometer and rate of breathing was counted visually every half-hour.

A clinical examination was performed only after treatment and monitoring had been commenced. An X-ray of the chest was then obtained. This was achieved, without moving or disturbing the infant, by a simple alteration to the incubator (Bauman and Nadelhaft, 1958).

General care: Babies were nursed from the onset in Isolette or Draeger incubators. The environmental temperature was adjusted to maintain exposed skin temperature between 36°C and 37°C, as oxygen consumption in small infants is considered to be minimal at this temperature (Silverman et al., 1966). Skin was chosen in preference to rectum for temperature recordings as the latter site is thought to reflect not only the the thermal demand of the environment but also the metabolic response of the infant (Silverman and Sinclair, 1966). Furthermore, a rectal probe was difficult to maintain in place because of the constant passage of meconium stools.

Humidity was increased only if difficulty was experienced in raising the infant's temperature. Oxygen, however, was always humidified, as the gas otherwise tended to dry the infants' lips and corneae, particularly when administered directly to the face.

Feeding: Oral feeding was commenced on the third day of the illness, for by this stage most infants were over the acute phase of respiratory

distress. Feeds were administered 3-hourly by gastric tube. Infants were started on 3 oz./kg./day of evaporated milk diluted to 1 in 3 and this was gradually increased in strength and quantity over a week, to 5 oz./kg./day.

The first two feeds, however, always consisted of 5% dextrose water, and if they were vomited up, the stomach was washed out with a 1% solution of sodium bicarbonate. This invariably prevented further bouts of vomiting. Intravenous drips were continued until oral feeding had become well established: this usually meant a further 6 to 12 hours of intravenous fluid therapy.

After the acute stage of the disease, infants were nursed as normal prematures. They were weaned from the incubators at 1.81 to 1.85 kg. in weight and kept in cots until attaining a weight of 2.26 to 2.30 kg. and receiving bottle feeds.

All were given extra iron, in the form of an iron dextran complex (Imferon), 150 mgm. intramuscularly, and vitamin D (ostelin forte), 300,000 units intramuscularly. Vitamin K1 (Konakion), 1 mgm., had been administered intramuscularly to all infants at the time of admission, or shortly after birth.

Results

Fifty-eight infants were treated in the intensive care unit. Fifty-three of these were admitted in a reasonable state, meaning that although distressed they were breathing and able to compensate for their respiratory impairment. The remaining 5 were moribund at the time of arrival. They were apnoeic, deeply cyanosed and limp, the only sign of life being an audible slow heart beat. These babies had received little or no therapy prior to admission and all required immediate resuscitation

by means of artificial ventilation. They will therefore be excluded from further discussion at this stage. All 53 infants received 100% oxygen for 24 hours, 42 infants for 48 hours and 5 infants for 72 hours. This excludes the infants who required artificial ventilation.

Complications

Apnoea: Eleven of the 53 infants developed apnoea with cyanosis, despite the measures of intensive care which had been adopted.

In 7 of these 11 cases, cessation of breathing could not be attributed to a specific cause. Blood sugar levels, determined by the Department of Chemical Pathology, were normal at this stage, and no radiological evidence of a complication could be detected.

In 4 of the 11 cases, apnoea occurred as a result of a tension pneumothorax. This was diagnosed clinically before breathing had stopped, by a bulging of the chest wall on the affected side, hyper-resonance on that side and diminished air entry. The diagnosis was confirmed radiologically in each case.

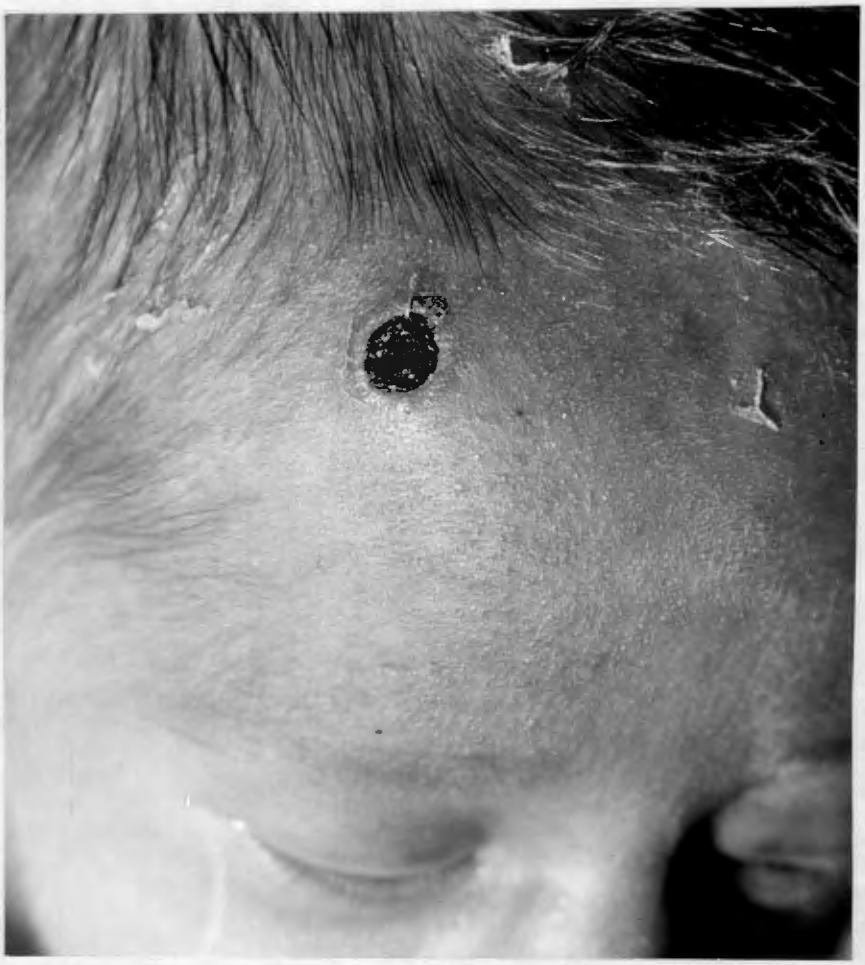
The overall incidence of pneumothorax in the series was 10%. as a further 2 infants developed this complication during spontaneous respiration. They showed no signs of deterioration, however, and recovered without additional therapy.

Hypoxaemia: Five of the 53 infants had arterial oxygen tensions below 50 mm.Hg. despite the administration of 100% oxygen. Their mean rate of breathing was 57 per minute (range 48 - 92).

Venous thrombosis: In 6 infants, superficial areas of thrombosis occurred as a result of prolonged drip therapy. These areas ulcerated in 4 cases (Fig. 16), but this complication was observed only in instances

Fig. 16

Ulceration of scalp caused by prolonged drip therapy



when 10% glucose solution had been administered into the same vein for periods longer than 36 hours. No further cases of thrombosis or ulceration were seen following a policy of changing the drip from one vein to another at 24-hour intervals.

Outcome

Thirty-four of the 53 infants recovered without any additional form of treatment and 4 died, while the remaining 15 received artificial ventilation.

Deaths

Three infants who developed apnoea were below the weight of 1.15 kg. They received no form of resuscitation and subsequently died following repeated apnoeic attacks. Postmortem findings revealed hyaline membrane disease in each case.

The fourth infant weighed 3.06 kg. and developed his first bout of apnoea at the age of 31 hours. He died within 3 minutes, before any form of resuscitation could be administered. The cause of this apnoeic spell was not established; an X-ray of the chest which was taken after death excluded a tension pneumothorax, while autopsy revealed features of hyaline membrane disease without evidence of intracranial haemorrhage. It was interesting to note in retrospect that the arterial oxygen tension had remained at 40 mm.Hg. for 12 hours before the bout of apnoea.

Follow-up

All infants were considered to have been 'at risk' during their illness and were required to attend a follow-up clinic in order to assess both their physical and developmental status. Twenty-six of the 34 survivors have so far attended and have been examined at ages ranging from 6 to 18 months. Only one infant has demonstrated any abnormality,

this being a motor weakness of the right arm. This weakness, however, cannot be attributed to the disease process or to the form of treatment administered as the infant had been asphyxiated at birth and a history was also obtained of maternal illness in the first trimester of pregnancy. No visual or hearing defects have been detected in any infant and the radiological appearance of the chest has been normal in each case.

Discussion

The régime selected for treating hyaline membrane disease proved to be both effective and safe, and broadly followed that outlined by Usher (1963) and Hutchison et al. (1964). It resulted in the complete recovery of 64% of cases without resort to additional methods of treatment.

Intensive care was essential, in that it provided for the safe administration of therapy and certainly prevented the occurrence of complications such as over-hydration, over-correction of metabolic acidosis and oxygen toxicity. Undoubtedly the greatest hazard of treatment is that associated with oxygen, for the gas can lead to damage of the retina, lungs and red blood cells. Ashton et al. (1954) and Patz (1957) indicated that damage to the retina depended on several factors, notably the stage of development of retinal vessels, their length of exposure to oxygen, and the arterial oxygen concentration. The initial effect of a high arterial oxygen concentration is that of vasoconstriction which, if it persists for more than two days, can lead to obliteration of the retinal vessels. Such a pattern has been observed in prematures with normal lungs breathing oxygen concentrations above 40%. This concentration is equivalent to an arterial oxygen tension of

between 120 and 160 mm.Hg. Every attempt was made in the present study not to exceed these levels, but it became evident that such heights were virtually impossible to achieve in the majority of infants and were exceeded by 5 infants only, at the time of admission. It was therefore considered justifiable to administer 100% oxygen initially, to all babies with hyaline membrane disease, and then to adjust the concentration according to the PaO_2 levels which were determined at frequent intervals. A factor which might conceivably alter the effect of oxygen on retinal vessels is that of carbon dioxide retention. All infants had respiratory acidosis and it is thought that the hypercapnoea could result in vasodilation, thereby affording protection to the vessels. It is interesting to note though, that carbon dioxide given to immature animals in concentrations up to 5% cannot produce vasodilation of retinal vessels (Ashton et al., 1954).

An alteration in pulmonary function has been observed in adults breathing 100% oxygen for 24 hours or more with a decrease in vital capacity (Welch et al. 1963) while in infants a decrease in lung volume and compliance has been reported (Nelson et al., 1963). Pathological changes include the formation of hyaline membranes (Bruns and Shields, 1954), vascular engorgement, capillary damage and possible deactivation of surfactant (Cedergren et al., 1959).

The majority of babies in the present study were given 100% oxygen to breathe for 48 hours. None presented any clinical, radiological or pathological evidence of lung damage due to oxygen toxicity.

Summary

Infants suffering from hyaline membrane disease were treated in an intensive care unit with oxygen, intravenous sodium bicarbonate and glucose in amounts sufficient to prevent or correct any features of respiratory failure.

This régime proved effective in 64% of cases, as 34 of the 53 infants who were breathing spontaneously at the time of admission recovered completely. No specific complications could be attributed to the therapeutic agents themselves, but they failed to prevent hypoxaemia and apnoea in the remaining 19 cases.

Four of the 19 died without any further form of treatment being applied. Three of these were below 1.15 kg. in weight and were deliberately not given further therapy, while one weighed 3.06 kg. and died during a spell of apnoea before any method of resuscitation could be introduced. The remaining 15 babies received artificial ventilation.

Part 3 : Treatment with IPPR

Certain features of respiratory failure were used as criteria for the application of artificial ventilation if they occurred or persisted despite intensive therapy.

It is evident from the discussion of the literature that apnoea, whatever the underlying cause, carries an extremely poor prognosis; and therefore any infant who developed a single episode of anoxia was given assisted ventilation. However, it also became clear that the first anoxic episode might be the infant's last, for one baby died a few minutes after developing apnoea. As this infant had a persistently low arterial oxygen tension prior to the anoxia episode, it was decided to extend artificial ventilation to all infants with arterial oxygen tensions below 50 mm.Hg., particularly as this sign carried so many potential hazards.

Initially, artificial ventilation was considered too demanding a procedure to be used in all anoxic infants, and those of very low birth weight (below 1.15 kg.) who were shown to have a poor prognosis (Usher, 1963) were excluded. However, as more experience was acquired, all low birth weight babies received assisted ventilation if the indication was present.

Intermittent positive-pressure was administered via an endotracheal tube and this section will consider both the efficacy of prolonged endotracheal intubation and the methods employed for the use of prolonged artificial ventilation.

Endotracheal intubation

Prolonged intermittent positive-pressure ventilation had, until recently, been administered via a tracheostomy (Smythe, 1963 and Mann et al., 1963). Smythe investigated the difficulties of this procedure and described two types of complication. The first was inherent in any tracheostomy, and included obstruction of the airway and the occurrence of mediastinal emphysema or pneumothorax. The second concerned the re-establishment of normal mouth breathing when an attempt is made to remove the tube. In the first group, obstruction presented a constant problem and, apart from blockage of the tube by inspissated secretions, four mechanisms of occlusion were described. These included collapse of tracheal rings weakened by ulceration, occlusion above the tracheostomy site caused by granulation tissue, buckling inwards of the upper tracheal rings by pressure from the tube, and acute angulation, with kinking of the trachea.

Infection is a constant hazard, and Aberdeen (1965) encountered this complication in a varying degree in all of the 147 infants who underwent the operation. Tracheal infection is of particular danger during positive-pressure ventilation as it is likely to be blown throughout the lungs. It is therefore obvious that the performance of a tracheostomy in the neonatal period is a major undertaking, the final outcome being related to physician experience and specialized care.

In an attempt to avoid these hazards, prolonged endotracheal intubation was introduced and its recent popularity is, no doubt, related to the non-reactive material from which tubes are made. It was expected that the technique would avoid the complications of mediastinal emphysema,

pneumothorax and sepsis (Colgan et al., 1960). The first two have not been reported, but spread of infection down the tube does occur, and in one series it was stated to be as common as in tracheostomy (Allen and Stevens, 1965) although the incidence of secondary infection was nil in infants below the age of 3 months. The tubes unfortunately are not devoid of irritating properties and the larynx is invariably found to be reddened following removal of the tube (Macdonald and Stokes, 1965). Jackson Rees et al. (1966) discussed the method in a study on 126 infants and children. Duration of intubation ranged from 2 days to 3 months. Serious laryngeal complications occurred in two cases: one had been intubated for 8 weeks and the other for 3 months. Both showed marked subglottic stenosis. One of these was a newborn, with cerebral birth injury, who subsequently required tracheostomy. They concluded that the maximum safe period for retaining a nasotracheal tube was 2 to 3 weeks.

In the absence of efficient humidification, endotracheal tubes are as liable to become blocked as are tracheotomy tubes, and it is considered that they are not as effective in the face of copious secretions as are tracheotomy tubes (Smythe, 1966).

Nasotracheal intubation has, up to now, been used in preference to the oral route (Colgan et al., 1960; Thomas et al., 1965), as immobilisation of the tube could more readily be achieved.

Methods

In the present study, prolonged endotracheal intubation was used on all infants who required assisted ventilation for respiratory failure. The oral route of insertion was chosen in preference to that of the nasal passage as it was felt that a tube could be more rapidly introduced in

this manner with the least amount of interference. A simple modification to existing equipment facilitated adequate immobilisation for prolonged periods of time (Fig. 17). A Portex tracheotomy tube (4.5 mm.) was cut close to its flange leaving a stump 0.5 cm. long. With the aid of mosquito forceps, this sleeve was stretched and pulled over a Warnes neonatal tube 12 FG. This tube has a broad portion 4 mm. in internal diameter which narrows down to 2.5 mm. The total length of tube from the flange to the narrow tip varied with the size of the baby. In order to obtain an ideal fit, the situation of the endotracheal tube was checked on a lateral X-ray of the neck in 15 infants. The distance was measured from the flange, which lay flush with the lips, to the vocal cords. The narrow portion of the tube extended below the cords and measured an additional 2.6 cm. A further 0.5 cm. was added to the overall length to accommodate respirator fittings above the flange. The measurements of tubes for premature babies determined in this manner are given in Table 9.

TABLE 9

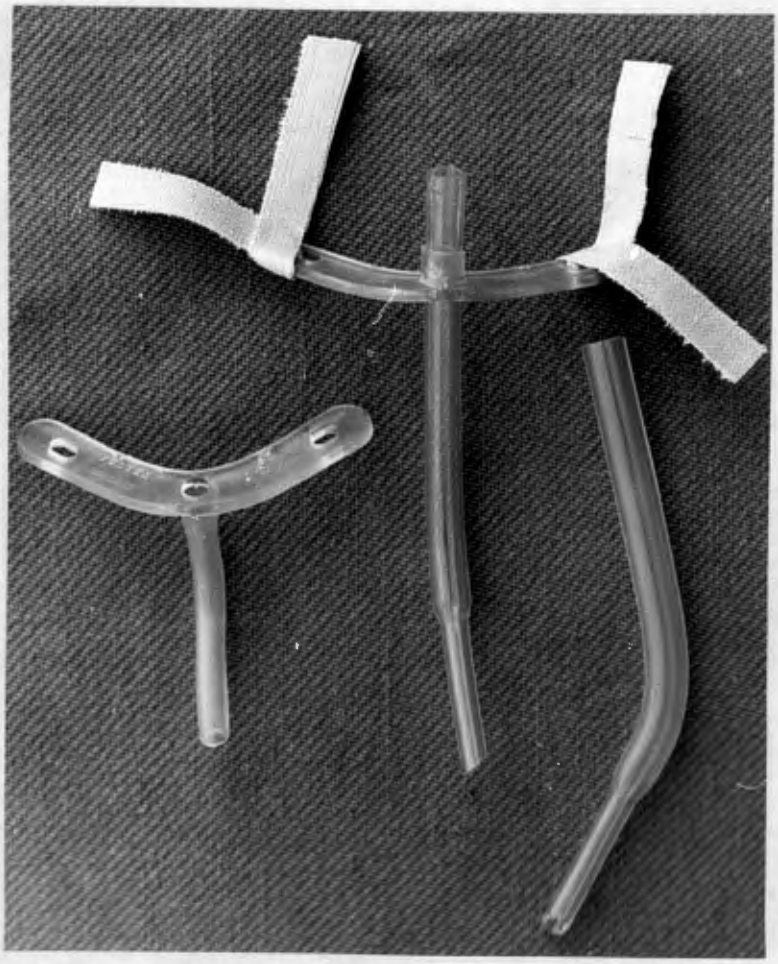
ORAL ENDOTRACHEAL TUBES IN PREMATURE INFANTS *

Weight (kg.)	Length of tube (cm.)
1.24	8.5
1.36	9.0
1.47	9.0
1.55	9.0
1.58	9.0
1.68	9.0
1.75	9.5
1.77	9.5
1.81	9.5
1.81	9.5
1.87	9.5
2.15	9.5
2.18	10.0
2.26	10.0
2.64	10.0

* In this study it was found that the above lengths were the most effective for the weights shown.

Fig. 17

Assembly of endotracheal tube



It was essential to prepare the apparatus before use. Introduction was carried out with the infant lying in an open incubator. No sedation, general or local anaesthetics were administered.

Procedure

An assistant places the baby on its back with the head and neck well extended. A straight-bladed Miller laryngoscope for prematures is inserted along the surface of the tongue, care being taken not to allow the tongue to slip to one side or the other but to remain firmly compressed in the midline. Once the blade tip has reached the angle between the tongue and the epiglottis, it is levered up. This manoeuvre elevates the epiglottis and exposes the vocal cords. A better view of the cords is obtained at this stage by asking an assistant to apply pressure on the larynx. The sterile endotracheal tube is now passed into the mouth and inserted between the cords. If these are approximated, gentle pressure is applied to the tube until it slips through. The laryngoscope is now removed and the narrow portion of the tube extends about 2 cm. below the vocal cords while its broadened shoulder rests lightly on the cords, affording an airtight fit. In this manner, any form of pressure on the tracheal wall which might lead to necrosis is avoided. Undue pressure on the cords from above is overcome by paying particular attention to the length of the tube, as described. Plaster strapping looped through the holes in the flange is fixed to the cheeks and affords adequate immobilisation. A further piece of strapping looped around the tube above the flange is fixed to the chin. In the majority of cases the infant lies quietly and no immobilisation of the head is required. The incubator lid is now closed and a 5 mm. nasal piece, inserted into the upper end of the endotracheal tube, is easily attached to the infant Q circle of a

Bird respirator (Fig. 18). The whole procedure is performed within 1½ minutes. This technique was carried out on infants who required assisted ventilation.

Management of the indwelling endotracheal tube

Humidification: Maintenance of a clear airway is the pre-requisite for respiratory support. Since the tube in fact bypasses the upper airways, inhaled air must be adequately humidified to prevent drying of the respiratory tract mucus with consequent cessation of ciliary action. This in turn results in necrosis of ciliated respiratory epithelium, retention of thick tenacious secretions and a decreased resistance of the respiratory tract to infection. The minimum requirement for humidification is that inspired gas should reach the trachea saturated with water vapour at body temperature. Two commonly used methods include heated water from a reservoir and nebulization of cold air. The latter method was employed in the present study, and suspension of water particles in a gas phase was achieved by directly compressing the inspired gas through a Venturi orifice connected to a 500 ml. water reservoir.

The effectiveness of gas re-warming was assessed by a series of temperature measurements taken at the outlet of the respirator, at the connection between the respirator tubing and the endotracheal tube, down the endotracheal tube at mouth level, and in the trachea itself beyond the endotracheal tube. A progressive increase in gas temperature was observed in all cases, the mean temperature at respirator level being 22°C while the intracheal temperature registered a mean 36.3°C.

The delivery of an inspired gas saturated with water vapour has one potential danger in that it eliminates the normal water loss

from the respiratory tract and this may lead to fluid retention by the patient. This side effect is aided by the fact that water tends to collect in the respirator tubing and may be blown into the lungs. Particular attention was therefore paid to disconnecting these tubes and draining them whenever fluid was present. The amount of absorption, if any, could not be assessed, however. Infants were usually oedematous at the start and could not be weighed while attached to the various pieces of apparatus. Nevertheless it was considered safest to use distilled water for the purpose of humidification.

Tracheo-bronchial toilet: Suctioning was carried out at half-hourly intervals. A strict aseptic technique was used on each occasion. Hands were washed and sprayed with chlorhexidine solution. A sterile 3F rubber catheter was then attached to the suction tube. This catheter was marked 11 cm. from its end. ensuring that if passed up to this mark the tip would extend beyond the endotracheal tube. To facilitate better suctioning into the trachea, the end of the catheter had been cut off at an angle leaving no sharp edges. It was also sufficiently narrow to allow for the passing of air past the narrow portion of the endotracheal tube. The incubator port was opened with the left hand which then removed the stopper of the Y connector. This hand now held the suction tubing but did not touch the catheter which was swiftly guided down the endotracheal tube into the trachea with the right hand.

In the majority of cases, the mere removal of the endotracheal stopper led to a decrease in pulse rate and the appearance of cyanosis. The suctioning procedure, therefore, was performed rapidly, not lasting for more than half a minute. The suction pressure was set at 10 cm.H_2O negative pressure, as levels below this were found to be ineffective,

particularly in the presence of thick secretions.

The nature of secretions in cases of hyaline membrane disease followed a constant pattern. Over the first 24 hours small amounts of clear mucus only, were noted. By 48 hours these had become more copious, somewhat thicker and bright yellow in colour. Microscopy and culture revealed no evidence of infection. After 48 hours and for the next 3 or 4 days, thick, brightly yellow-stained plus were obtained. These were considered to be casts from the previously damaged bronchioles and indicated resolution of the disease process. The yellow staining of the sputum is of interest in that it was noted in the absence of clinical jaundice. However, the serum was also a bright yellow at this time. It is thought that pigments other than bilirubin may account for this.

Physiotherapy was used to ensure adequate removal of plugs. This consisted of sharply squeezing the infant's lateral chest with the left hand on each expiration. Timing of this short squeeze, as described by Smythe (1963), is of paramount importance for if it does not coincide with expiration, ribs are liable to be broken. This procedure was carried out for 6 or 7 breaths with the endotracheal stopper removed and was only necessary twice a day. It proved to be extremely effective. On occasion, if secretions were difficult to dislodge, 0.5 ml. of 4% sodium bicarbonate was instilled down the tracheal tube before squeezing the chest. This solution proved more effective than sodium chloride, although it is potentially dangerous in that its alkaline medium may encourage the growth of pseudomonas, or may compromise the action of cilia which are reported to act best at a pH of 6.8 to 7.2 (nungester and Atkinson, 1944). For this reason it was not used more than twice a day unless otherwise indicated.

Fig. 18

Immobilisation of endotracheal tube during IPPR

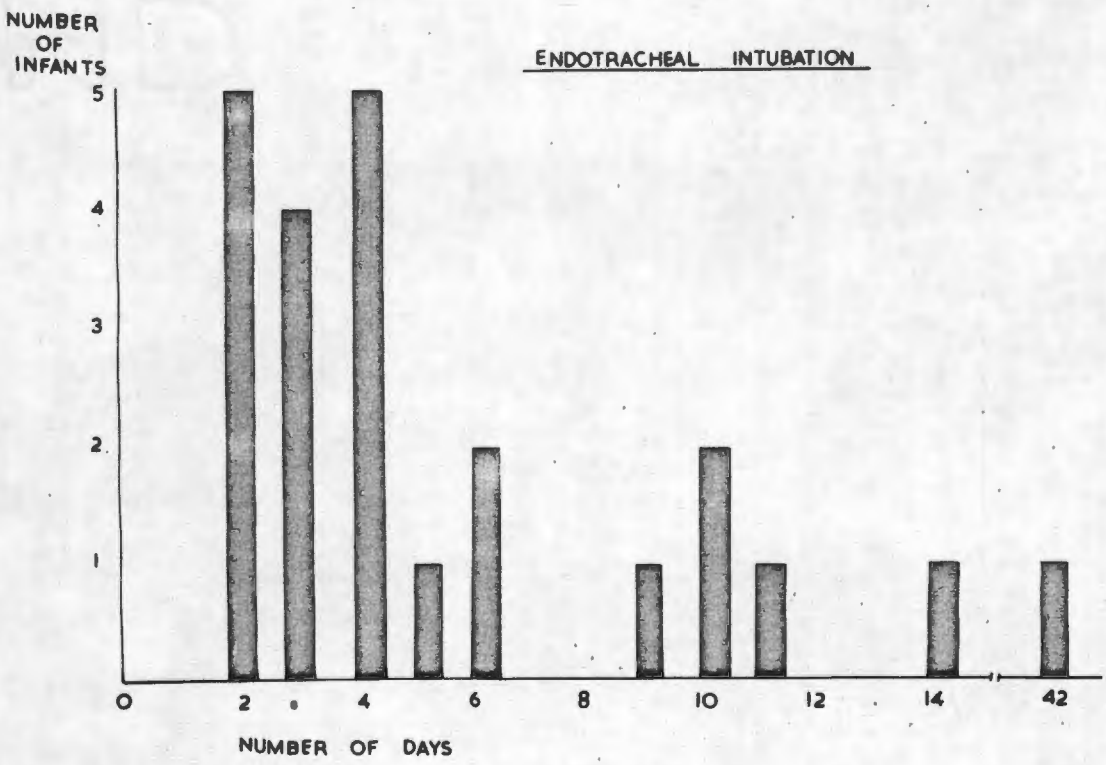


Fig. 19

Duration of intubation in 23 infants

A separate set of uncut catheters was used to aspirate the mouth and nose. The procedure was carried out only after the trachea had been suctioned.

Results

Endotracheal tubes were left in place continuously from 2 to 43 days (Fig. 19) and with adequate toilet did not require to be changed.

Complications

Obstruction caused by inspissated material accumulating at the end of the tube tip occurred in one infant. The occlusion was recognised early and corrected by suctioning after the instillation of 0.5 ml. 4% sodium bicarbonate down the tube.

Two infants succeeded in displacing the distal end of the tube into the oesophagus during episodes of vigorous coughing and struggling. Both were noted to develop abdominal distension but at this stage they were able to cope without assisted ventilation and could remain detubated.

A noticeable side effect occurring in all infants has been the presence of a hoarse voice following detubation. This has not been related in severity to the period of intubation and the larynx at this stage has appeared red and somewhat swollen. In all infants, the voice reverted to normal within 48 hours.

Infection, presumably introduced down the tube, occurred in two infants and was the direct cause of death of one infant. This baby died of a fulminating disseminated staphylococcal bronchopneumonia.

Histology

The larynx and trachea were examined in all babies who died and who had been intubated. Three died of the complications of a gastro-enteritis several months after their original illness.

Two of these had been intubated for 10 days; specimens of trachea and cords were macroscopically and microcopically normal. The third infant died at the age of 7 months. Initially, he had been intubated for 43 days without ill effects. No evidence of tracheal damage could be detected.

Method of application of intermittent positive-pressure ventilation

A mechanical ventilator forms only part of the procedure in caring for the patient with respiratory failure and the selection of one depends primarily on its being best known to the physician using it.

A Bird Mark VIII respirator was used on all infants who required assisted ventilation. It incorporated a number of excellent characteristics, being mobile, light-weight and enclosed in a transparent case which rendered the mechanism clearly visible. The infant Q circle had a dead space of only 0.28 ml. and its thin plastic tubes allowed for a certain amount of free movement of the infant's head.

The respirator is a pressure-cycled flow generator, and requires a power supply of compressed air or oxygen at 50 to 60 lb./sq.inch. Its great disadvantage lies in the fact that the amount of oxygen delivered to the patient cannot be accurately regulated if the source of power is pure oxygen. When the air-mix Venturi is used, it is claimed that a concentration of 40% oxygen can be obtained. Fairly and Britt (1964) found a wide variation in a number of respirators, oxygen levels ranging from 50% to 96%. Similar inaccuracies were observed by Stoddart (1966) and occurred in the case of both compliant and stiff lungs.

A further disadvantage was the fact that the controls, although versatile, interacted and the adjustment of one would completely upset the whole pattern of breathing. When set on patient triggering, the respirator was incapable of keeping up with breathing rates of over 80/minute, probably due to inertia of the system, and pressure did not return to zero. This was considered to be potentially dangerous as it might lead to air trapping and rupture of alveoli. The recently introduced J circuit is thought to eliminate build-up lag in the system and

is claimed to assist respiratory rates of over 100/min. with tidal volumes as low as 1 ml. (Bird pamphlet).

Method of setting

The peak inspiratory flow rate was kept as low as possible on all babies so as to simulate normal breathing, and was set at approximately 60 ml./sec.

The pressure control was then adjusted to deliver approximately 20 cm. H_2O. Patient-triggering was at its most sensitive setting to enable each inspiratory effort to be augmented. However, if the pressure could not return to zero because of an excessively rapid breathing rate, a less sensitive setting was selected, giving a slower pump rate.

The variable-leak, controlling expiratory time, was then adjusted to give an inspiratory/expiratory ratio of 1 : 1.2 and a rate of approximately 56/minute, so that if the patient failed to trigger the respirator, automatic pumping would occur at this rate.

Subsequent settings depended on the clinical, acid base and blood gas status of the infant. The initial pressure of 20 cm. H_2O was invariably too low to achieve adequate ventilation, as an infant often remained cyanosed with a low arterial oxygen tension at this setting. The pressure was then gradually increased until arterial oxygen tension had risen to normal or near-normal limits. A concentration of 100% oxygen was used throughout the period of artificial ventilation, for if any attempt was made to reduce this, a significant drop in PaO_2 occurred in all infants. The highest recorded PaO_2 while on artificial ventilation was 250 mm.Hg. during the first 24 hours, which gives an indication of the grossly abnormal lung function.

Weaning off respirator

An attempt was made each day to drop the pump pressure by 2 to 3 cm.H_2O, and subsequent pressure levels depended on the PO_2 obtained from heel blood. When the pressure could be reduced to 18 to 20 cm.H_2O the infant was given a trial off the respirator. This entailed removing the stopper to the Y connector and allowing the infant to breathe spontaneously while still receiving 100% oxygen from the respirator. If no deterioration in clinical, acid base or blood gas status occurred, the stopper was kept out, but could be replaced at any moment with the immediate resumption of artificial ventilation.

Removal of endotracheal tube

Removal of the endotracheal tube depended on several factors: first, it was considered essential that a cough reflex be present and this could be established during tracheal suctioning. A number of small infants had no cough reflex during the first few days of the illness and it was considered highly dangerous to remove the tube at this stage. Secondly, if the infant had been able to breathe spontaneously for a period of 24 hours without difficulty, the tube could safely be removed. Following this, 100% oxygen was again supplied via a cardboard carton placed directly on the face. Reduction of the oxygen concentration thereafter depended on the PaO_2, and the infants were treated in a similar manner to those who had not received artificial ventilation.

General care

Infants lay supine throughout the procedure, with the head turned to one or the other side. In the early stages of the disease, very little immobilisation was required as the babies made no attempt to resist the

type of management they received. Arm movements were restricted by fixing stockinette over the wrists and pulling the cord through the incubator ports on either side. Over the next few days most infants became more vigorous and a few larger ones required immobilisation of the head to one side or the other by means of plaster strapping, as it was feared that they would dislodge the endotracheal tube (Fig. 18).

Feeding

Oral feeding was commenced through a gastric tube on the third day as in spontaneously breathing infants. Similar amounts were given 3-hourly, but for two days the stomach was aspirated before each feed (Smythe, 1963). Because of this, vomiting or abdominal distension was most unusual and it was never necessary to resort to gastrostomy.

Results

Fifteen of the 53 spontaneously breathing infants received intermittent positive-pressure ventilation.

In 10 of the 15 cases, this was commenced following a single apnoeic attack, while in the remaining 5 cases it was administered because of a PaO_2 below 50 mm.Hg.

Artificial ventilation was commenced at a mean 22 hours of age, but the range was wide (3 to 48 hours) and it was continued from 15 hours to 42 days.

Complications

Two major complications could be related directly to artificial ventilation, namely tension pneumothorax and bronchopneumonia.

Tension pneumothorax occurred in 2 infants during the course of intermittent positive-pressure ventilation. In each case there was a sudden unexplained deterioration in the infant's condition. Pulses became

weakly palpable and cyanosis appeared. Hyper-resonance to percussion over the affected chest was a particularly striking sign, whereas bulging of the chest wall or diminished air entry was not really obvious. The diagnosis was confirmed on X-ray of the chest in each case (Fig. 20).

An 8F polythene tube was immediately inserted into the affected pleural cavity through the 2nd intercostal space in the mid-clavicular line and connected to underwater drainage.

It soon became evident, however, that this form of drainage was inadequate as more air would collect in the pleural cavity than could be blown off. This problem was overcome by attaching negative pressure suction to the underwater drain by means of a WISA pump. In each case, a pressure in excess of -30 cm. H_2O was required to empty the pleural space effectively and prevent re-accumulation of air. Drainage was maintained until no further air had been blown off for 48 hours and no radiological evidence of a pneumothorax could be detected.

This procedure had also been used on the 4 infants who required artificial ventilation because of the onset of a tension pneumothorax during spontaneous breathing.

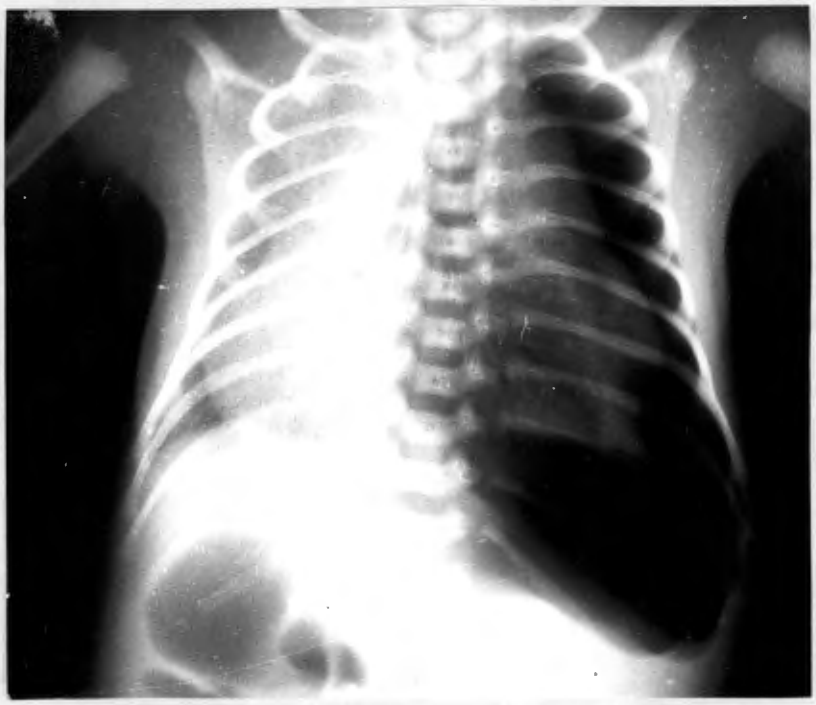
The second complication, that of infection, has already been mentioned in the section relating to endotracheal tubes. One infant developed a pseudomonas bronchopneumonia while receiving intermittent positive-pressure respiration from a borrowed ventilator. The organism was subsequently cultured from this apparatus and was thought to have been directly transmitted down the tubing into the infant's lungs.

A second baby developed a staphylococcal bronchopneumonia (Fig. 21). This baby had inadvertently not been given antibiotic cover during the period of endotracheal intubation.

Complications resulting from IPPR

Fig. 20

Tension pneumothorax



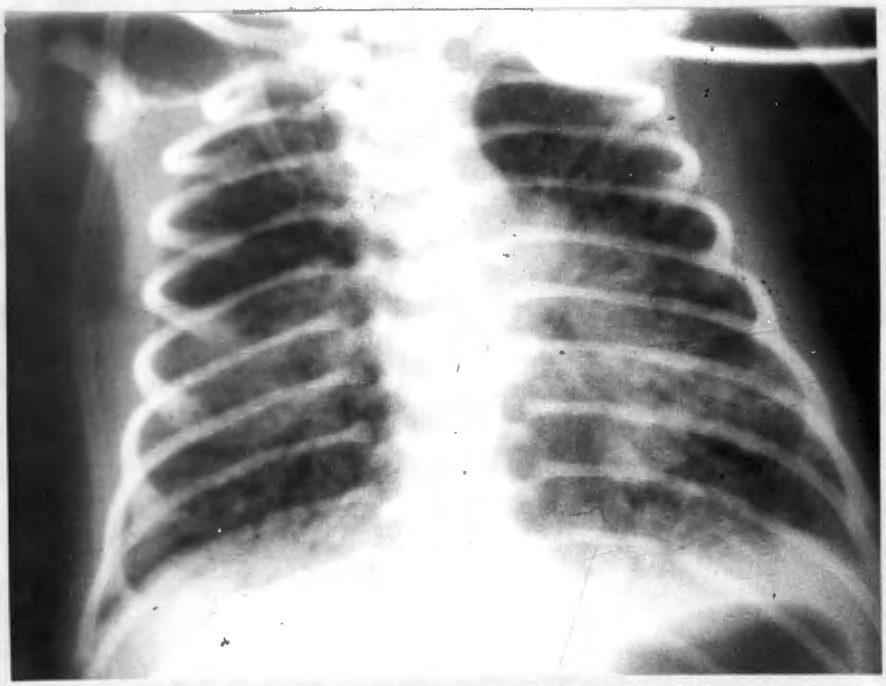


Fig. 21

Bronchopneumonia

Outcome

Three of the 15 infants died during the administration of intermittent positive-pressure ventilation.

The 2 babies who contracted pneumonia died of this complication and at post-mortem were found to have multiple lung abscesses superimposed on hyaline membrane disease. A third infant who developed a tension pneumothorax died before effective drainage could be instituted. Permission was not obtained in this case for a post-mortem examination.

Two babies who had been successfully weaned off respirator therapy contracted specific E coli gastroenteritis at the age of 2 months and subsequently died. Post-mortem findings revealed normal lungs in each case with no evidence of underlying damage or hyaline membrane disease.

One baby could only be weaned off respirator treatment at the age of 42 days. Prior to this, any attempt to discontinue intermittent positive-pressure resulted in severe distress with cyanosis. Throughout this phase, lung functions were grossly deranged with low compliance (0.31 to 0.47 ml./cm.H_2O), a raised $PaCO_2$ (75 mm.Hg. to 98 mm.Hg.) and arterial oxygen tensions in the region of 70 mm.Hg. to 80 mm.Hg., despite assisted ventilation with 100% oxygen.

The infant required 100% oxygen for a total of 62 days, and thereafter it was gradually reduced and discontinued at the age of 6 months.

By 3 months of age severe right heart enlargement was noted and there was clinical evidence of a patent ductus arteriosus: the child developed heart failure at this stage and required digitalization.

Cardiac catheterisation was performed at the age of 6 months. This revealed severe right ventricular hypertrophy and pulmonary hypertension with a pulmonary artery pressure of 80/60 mm.Hg. and

angiography indicated pruning of the pulmonary vessels towards the periphery of the lung fields.

The infant's course was one of gradual improvement. Right heart enlargement became less obvious and digitalis could be discontinued. At the age of 6 months, features of respiratory distress were still present, with rapid breathing (50 - 60/min.) and rib recession. By 7 months, lung compliance had risen to 3.8 to 4.0 ml./cm. H_2O. $PaCO_2$ had dropped to 40 - 45 mm.Hg. and breathing rate was 40 to 50 per minute. The baby then contracted a specific E coli gastroenteritis and died 2 weeks later at the age of 7½ months.

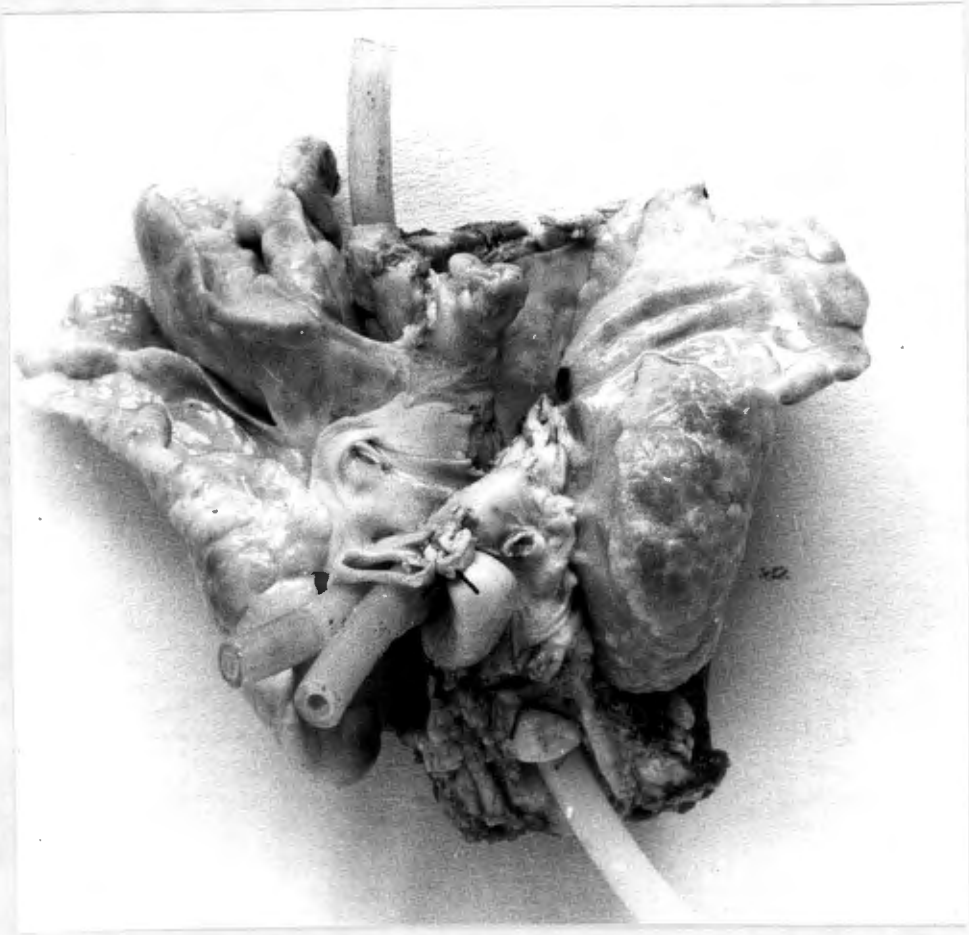
Post-mortem findings

The lungs were of normal colour, but over-distended (Fig. 22). The striking features of emphysema were confirmed on histology, which also showed numerous areas of alveolar collapse. Alveolar septi were thickened and fibrosed and muscular thickening was present in the bronchiolar walls. Bronchioles showed areas of regenerating epithelium. Both chambers of the heart were dilated and there was striking enlargement of the main pulmonary arteries with marked narrowing of the distal branches.

The remaining 9 survivors have been followed up at ages ranging from 6 to 18 months. All have developed normally for age and none has visual or hearing defects. The radiological appearance of the lung fields is normal in all cases, but one infant, now 20 months old, has developed two attacks of respiratory tract infection: on each occasion some atelectatic streaking of the right upper lobe was observed.

Fig. 22

Pulmonary dysplasia showing over-distension of lungs



Discussion

The procedure of artificial ventilation has been considered exacting enough to be carried out only in a specialised centre. This was confirmed in the present study, for an extraordinary degree of patient care was required to ensure the recovery of any one infant. Emphasis centred on intact survival and in this respect the criteria for the institution of assisted ventilation are of paramount importance. Hypoxaemia, if allowed to persist, was considered to be more harmful to the infant than artificial ventilation itself, whereas apnoea had to be corrected immediately to avoid the dangers of prolonged anoxia. It certainly would be of great assistance if apnoea could be anticipated, but in the majority of cases no premonitory signs could be detected. One infant had a persistently low arterial oxygen tension prior to cessation of breathing, but it was not considered justifiable to allow subsequent infants with low arterial oxygen tensions to remain untreated, in the hope of seeing whether they would recover, or develop apnoea. There was a constant anxiety that chronic hypoxaemia might result in the production of a mentally retarded infant, an outcome probably more tragic than death itself.

In this respect, Northway et al. (1967) reported 13 survivors on intermittent positive-pressure ventilation, but it is most disturbing to note that 6 of the 13 had evidence of probable developmental regardation. The details regarding their indications for assisted ventilation were not given, but it appears that this form of treatment was instituted in those infants who became cyanosed in 100% oxygen, who appeared moribund and who had undergone one or more spells of prolonged apnoea; presumably each infant had developed all of these features.

The side effects of intermittent positive-pressure ventilation may now be considered. Infection is doubtless preventable and could have been avoided in the two cases of pneumonia had appropriate measures been adopted early enough. The prevention of tension pneumothorax, on the other hand, poses a more difficult problem. Day et al. (1952) studied the effects of intermittent positive pressure on atelectatic lungs of puppies, and indicate that the distension of the lungs was proportional to both the applied pressure and the time during which that pressure was sustained. The longer the time interval during positive pressure, the more likely was the development of pneumothorax, and a difference as small as 0.15 to 0.20 seconds could separate a safe interval from an unsafe one. Wilson (1954) emphasized a third factor of importance, namely that of distensible lung tissue, for solid areas tend to transmit pressure to the expandable areas with resultant over-distension and rupture. It is probably fortuitous in this regard that hyaline membrane disease is a diffuse process involving both lungs more or less equally, thus diminishing the possibility of over-distension of normal areas. A fourth potential hazard is that of air trapping, with a resulting build-up pressure leading to rupture of alveoli. In the present study, the pump system as mentioned did not respond adequately to breathing rates in excess of 80 per minute and at these speeds the applied pressure remained high throughout the respiratory cycle. It was therefore necessary to adjust the pump speed to a rate that would allow mouth pressure to return to atmospheric throughout expiration.

The safe administration of intermittent positive-pressure ventilation, therefore, implied using as low a pressure as was possible for as short a time as possible to achieve adequate ventilation.

Vomiting of feeds has been considered particularly dangerous during intermittent positive-pressure ventilation and this complication has been avoided by the use of gastrostomy (Jones and Reid, 1966) which has even been proposed as an elective measure (Reid et al., 1967). Vomiting was certainly not a feature in the present study and was avoided by paying particular attention to the amount of feeds given and to aspirating the stomach before each feed. Thus gastrostomy is considered to be a somewhat unnecessary procedure.

What of the long-term effects of artificial ventilation? Studies in adults who die after prolonged intermittent positive-pressure respiration reveal characteristic pulmonary changes in many cases. The lungs are heavy and oedematous and macroscopically two phases have been observed; one consisting of congestion with alveolar oedema, the other characterised by a proliferation of fibroblasts and hyperplasia of the alveolar lining cells. These morphological changes may occur together and have been correlated with the prolonged use of ventilation in association with high concentrations of inspired oxygen (Nash et al., 1967). However, no definite cause and effect has been established as yet.

Recently, a number of cases termed bronchopulmonary dysplasia have been described in infants who have survived prolonged intermittent positive-pressure respiration (Northway et al., 1967). The process has been attributed to a combination of positive pressure, oxygen toxicity and the healing phase of severe hyaline membrane disease. In its most severe form, the condition has been characterised by progressive dyspnoea with the development of right heart failure. X-ray of the chest reveals abnormal lung fields with rounded translucent areas alternating with thinner strands of radio-density, and cardiomegaly is usually present.

Autopsy findings show emphysematous alveoli, perimural fibrosis, widespread metaplasia and an increase in macrophages, histiocytes and foam cells. Medial hypertrophy of the pulmonary vessels may also be prominent.

One such case was observed in the present series. Initially this infant appeared to be more severely affected than all others, as throughout the stage of artificial ventilation it was impossible to return $PaCO_2$ to normal limits, a feature most uncommon in the rest of the cases. One outstanding aspect of the case was the fact that although the infant required intermittent positive pressure for 42 days and 100% oxygen for 62 days to maintain adequate ventilation, his whole course was one of gradual improvement. This progress, in spite of high oxygen concentration and artificial ventilation, tends to favour the condition as being the end result of severe hyaline membrane disease.

Summary

Two features were considered to be more dangerous to an infant suffering from hyaline membrane disease than artificial ventilation itself: these were apnoea and hypoxaemia, and if either occurred intermittent positive-pressure respiration would be instituted.

Twelve of the 15 infants who received artificial ventilation recovered, giving a survival rate of 80%.

Three subsequently died of gastroenteritis, and the remaining 9 survivors appear normal in all respects.

Complications occurring during artificial ventilation included pneumonia and tension pneumothorax and one infant was left with chronic pulmonary disease, considered to be due to severe hyaline membrane disease itself rather than to positive-pressure ventilation or oxygen toxicity.

Part 4 : Intracranial haemorrhage associated with hyaline membrane disease

The infants who were apnoeic at the time of admission will now be discussed. All 5 had suffered prolonged anoxia after birth and subsequently died despite the immediate use of artificial ventilation. A similar pattern was observed in 4 infants who were treated outside the unit. Autopsy studies revealed one finding in common, that of massive intracranial haemorrhage. This complication is frequently found at autopsy in association with hyaline membrane disease. The bleeding usually occurs in the subarachnoid or intraventricular areas (Hutchison, 1964) but its cause is as yet poorly established.

In the present study attention has been directed towards defining the rôle of anoxia, in particular whether it is the cause of haemorrhage or whether it arises as a result thereof. The investigation has also been concerned with establishing whether the bleeding occurs as a chronic or an acute episode and whether intermittent positive-pressure respiration contributes in any way. Infants who suffered apnoea have been divided into two groups depending on the duration of anoxia. The course of the disease in each group will be compared.

Group I: Severe prolonged anoxia

Nine infants in all suffered prolonged anoxia. One of these, aged 7 days, had a severe anoxic episode while on the respirator, while the remaining 8 had suffered severe anoxia before admission. At least 3 apnoeic attacks associated with cyanosis and bradycardia (heart rate 20 to 60 per min.) had occurred in each of these infants: all were apnoeic and cyanosed on admission. None had received adequate resuscitation or therapy for respiratory distress prior to admission.

All but one responded immediately to endotracheal intubation and positive-pressure ventilation. Their colour became pink, tone improved and pulses became palpable. Neurological function at this stage, as assessed by their movements, Moro and sucking reflexes, appeared normal. Acid base balance, arterial carbon dioxide and oxygen tensions as well as haemoglobin levels, were all normal at this period (Table 11). Following resuscitation, however, the infants were unable to sustain spontaneous respiration without the assistance of positive-pressure ventilation.

Course

The further course of 7 infants was characterised in each case by a catastrophic collapse, developing over 15 minutes, which usually occurred on the second or third day following anoxia (Table 10). A state of shock was noted, with pallor, cyanosis of mucous membranes, mottled skin and impalpable pulses. Three babies presented abnormal neurological signs, with squinting, nystagmus and jerking movements of the limbs. In all infants there was a drop in rectal temperature from a mean 36.6°C to 33.3°C. At this stage one infant had been weaned off the respirator but the others still required assisted ventilation.

The time of collapse could not be predicted in any infant, but its appearance was associated with sudden changes in acid base balance and blood gas tensions. These values had been determined within 5 hours preceding deterioration and were repeated within 30 minutes following the onset of shock. A severe metabolic acidosis occurred during this period, with a fall in the mean pH from 7.33 to 7.00 and in base excess from -6.5 mEq/L. to -17.6 mEq/L.

TABLE 10

GROUP I - STUDIES BEFORE AND AFTER INTRACRANIAL HAEMORRHAGE IN HYALINE MEMBRANE DISEASE

Case No.	Weight (kg.)	Age (hours)		pH		$PaCO_2$ mm.Hg.		Base Excess mEq/L.		PaO_2 mmHg.		Haemoglobin gm.%		Rectal Temp. °C		Autopsy Findings Site of Intracranial haemorrhage
		a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	
1	1.53	241	246	7.40	6.99	44	42	0	-20	155	30	19	14	36.6	32.7	Intraventricular
2	3.63	50	54	7.30	7.03	43	68	-5	-12.9	88	-	21.1	18	36.3	-	Subarachnoid
3	1.70	40	45	7.30	7.01	33	33	-9	-19	115	45	16	11	36.2	32.2	Intraventricular
4	2.18	67	72	7.48	7.01	23	45	-5.1	-18	68	42	19	15	36.1	33.8	Subarachnoid
5	2.85	76	78	7.34	6.99	33	35	-7	-21	85	40	20	10	36.1	33.3	Intraventricular
6	1.70	43	49	7.21	7.19	58	50	-5	- 9	84	37	17	9.5	36.1	32.7	Intraventricular
7	1.87	74	79	7.20	7.01	34	40	-15	-19	54	30	22	17	37.2	36.1	Subarachnoid
8	1.84	49	54	7.31	7.27	32	33	-9	-11.5	145	56	15	12.5	36.2	32.7	Intraventricular
9	1.21	-	4	-	6.82	-	31	-	-22	-	52	-	12	-	32.2	Intraventricular
Mean	2.12	-	-	7.33	7.00	38	43	-6.5	-17.6	92	39	18.6	12.5	36.6	33.3	

a. Investigations within 5 hours preceding the onset of shock

b. The same investigations within 15 minutes following shock

TABLE 11

COMPARISON OF APNOEIC INFANTS DURING ARTIFICIAL VENTILATION

	Weight kg.	Gestation weeks	pH	Base Excess mEq/L.	$PaCO_2$ mm.Hg.	PaO_2 mm.Hg.	Hb. gm.%	Rectal Temp. °C	Compliance ml/cmH_2O	PM cmH_2O
GROUP I										
Mean	2.16	35.0	7.32	-5.6	37.4	99.2	18.6	36.6	0.53	33.8
S.D. ±	0.68	3.4	0.08	2.7	10.0	10.6	2.3	0.8	0.07	-
GROUP II										
Mean	2.12	35.3	7.36	-2.7	40.8	83.6	16.9	36.7	0.56	33.8
S.D. ±	0.37	2.1	0.10	2.5	8.6	23.4	1.8	0.9	0.10	-
t	1.580	1.670	0.500	1.580	0.822	1.673	1.610	0.116	0.482	-
p	> 0.80	> 0.90	> 0.50	> 0.10	> 0.50	> 0.10	> 0.10	> 0.90	> 0.60	-

GROUP I : Eight infants who presented with prolonged apnoea and cyanosis

GROUP II : Sixteen infants who developed a single episode of apnoea and cyanosis

S.D. ± : Standard Deviation

t : Deviation

p : Probability. No significant difference between the groups.

Arterial oxygen tension fell from a mean 92 mm.Hg. before the event to 39 mm.Hg. (Table 10). Artificial ventilation prevented any significant alteration in arterial carbon dioxide tension. During the stage of normality, $PaCO_2$ was 38 mm.Hg. and following the appearance of shock the mean $PaCO_2$ was 43 mm.Hg. In the infant who had been weaned off the respirator (Case No. 2, Table 10), however, the $PaCO_2$ rose to 68 mm.Hg.

The haemoglobin concentrations had been determined within 8 hours preceding collapse. They were repeated within 30 minutes after the event. In all infants a marked drop in concentration occurred. The mean value for the group before deterioration was 18.6 gm.% and this fell to 12.5 gm.% (Table 10).

Outcome

The infants died within a few hours of developing shock and at autopsy all revealed massive intracranial haemorrhage in association with hyaline membrane disease. In 4 cases bleeding was confined to the intraventricular region and in 3 cases to the subarachnoid space. No evidence of cerebral trauma could be detected and the airways were patent.

Two of the 9 infants in Group I presented in a somewhat different manner. One, (Case No. 9, Table 10), who had been moribund at the time of admission could not be revived by artificial ventilation. Haemoglobin concentration and arterial oxygen tension were low and a gross metabolic acidosis persisted despite the measures of resuscitation. The baby died in this shock-like state 2 hours after admission, at the age of 6 hours. Autopsy revealed a large intraventricular haemorrhage. The lungs had the features of hyaline membrane disease. The second infant (Case No. 1, Table 10) had been treated with high concentrations of oxygen and

intravenous alkali and glucose since shortly after birth. On the third day it developed a tension pneumothorax which was drained. Thereafter respiration was impaired and the infant remained cyanosed, with a PaO_2 of 44 mm.Hg. Artificial ventilation was therefore commenced. On the 7th day, obstruction of the endotracheal tube resulted in a prolonged bout of anoxia, lasting approximately 12 minutes. Immediate improvement followed a tube change and the baby appeared normal, but 2 days later, while still receiving assisted ventilation, a catastrophic collapse occurred with the appearance of metabolic acidosis, hypoxaemia and anaemia. The baby died some hours later and was found to have a large intraventricular haemorrhage. The lungs showed features of resolving hyaline membrane disease.

Group II : Single short episode of anoxia

Ten infants were included in this group. From the early stages of the disease all had been treated with humidified oxygen, intravenous glucose and sodium bicarbonate. Despite these measures they developed apnoea at ages ranging from 4 to 36 hours. A single apnoeic spell with cyanosis, hypotonia and marked slowing of the heart occurred in each infant. Apnoea lasted from 3 to 7 minutes before artificial ventilation was instituted. A marked improvement followed this therapy but these infants, like those in Group I, were unable to maintain adequate ventilation without the continuation of positive-pressure therapy.

Course

Their subsequent course, however, was distinctly different and no sudden collapse occurred at any stage. Two infants contracted a superimposed bronchopneumonia and their lungs became progressively more difficult to ventilate. Initially, the low PaO_2 and raised $PaCO_2$ could

be corrected by increasing the pump pressure, but over a number of days a stage was reached where correction became impossible and the babies died. No evidence of intracranial haemorrhage could be detected. The remaining 8 infants were weaned off respirator therapy and recovered, although 2 of them died subsequently of specific E coli OII gastro-enteritis at the age of 2 months. The morbid anatomical and histological appearance of the brain was normal in each case. The neurological development of the other 6 infants has subsequently been assessed at ages ranging from 5 to 18 months, and appears normal in each case.

Comparison of Groups I and II

The infants in each group were compared as to their weights and maturity (Table 11). Following the institution of positive-pressure ventilation, no features appeared which distinguished one group from the other. The clinical and biochemical aspects were similar, and there was no way of predicting when an infant would suddenly collapse and die. Lung function was grossly impaired in each group and the infants required high pump pressures to maintain the $PaCO_2$ at normal levels. Lung compliance was reduced to mean values of 0.56 and 0.53 ml./cm.H_2O in each group, while the mean peak mouth pressure was 33.8 cm.H_2O. Only 8% of this pressure was transmitted across the lungs to the veins, the mean right ventricular pressure being 2.9 cm.H_2O.

Discussion

This study contrasts two groups of infants who required artificial ventilation because of anoxia. Babies who had suffered a single short spell of apnoea could readily be resuscitated by positive-pressure ventilation and in the majority of cases recovered without complication.

On the other hand, infants who had experienced prolonged episodes of anoxia could initially be revived by artificial ventilation, but died later following the sudden onset of shock.

It is considered that prolonged or recurrent attacks of anoxia constitute the underlying factor in intracranial haemorrhage, associated with hyaline membrane disease. It may be argued that early inability to breathe is due to underlying cerebral haemorrhage which begins at or before birth. However, the phase of recovery following artificial ventilation points to a delay in the onset of bleeding. During this period the infants in the study could not be distinguished in any way from those who required assisted ventilation for a single episode of apnoea with cyanosis. It was impossible to predict at this stage which infants would develop intracranial haemorrhage.

The initial apnoea in both groups was most probably precipitated by the inability of the infants to achieve adequate ventilation. The degree of impaired lung function could be assessed from the high pump pressure required to maintain the $PaCO_2$ within normal limits and the markedly reduced lung compliance. Continued dependence on artificial ventilation was again determined by the state of the lungs, as at this stage factors which could produce cerebral depression, such as anoxia, hypercapnoea and hypoglycaemia, had been corrected.

Intracranial bleeding occurs as a catastrophic event, rather than as a slow leak. This assertion is supported by the fact that the collapsed state observed in the infants was of sudden onset and had the features of acute blood loss, with anaemia, cyanosis and impalpable pulses. The haemoglobin concentration, which up to this stage had been normal, dropped precipitously. Both metabolic acidosis (Simone, 1965)

and a decreased oxygen transport capacity of the blood (Cournand, 1963) are known to occur in hypovolaemic states due to haemorrhage. Stahlman et al. (1967) described intracranial haemorrhage occurring in 13 of 26 cases who died of hyaline membrane disease. Her impression was that the complication presented as a catastrophic event late in the course of the disease.

The factors responsible for the delay in bleeding are unknown. It is conceivable that tissue becomes necrotic and ruptures at a later stage. The interval between anoxia and haemorrhage was usually 2 days, but in one infant bleeding was present at 4 hours of age, and factors other than tissue necrosis may have precipitated intracranial haemorrhage in this case. The rôle of contributory factors such as hypoprothrombinaemia and hypofibrinogenaemia were not assessed in this study, but no infant revealed clinical evidence of a haemorrhagic tendency.

The investigation does not support the view (Tizard, 1964, Strang and Macleish, 1961) that hypercapnoea plays an important rôle in the causation of cerebral haemorrhage. The complication occurred in the presence of a normal or near-normal $PaCO_2$. Presumably hypercapnoea was present only early in the disease, during the period of ventilatory failure.

All infants died while receiving positive-pressure ventilation; it therefore remains to consider this form of therapy as a causative factor. No radiological evidence of a pneumothorax was present at the time of collapse. Despite high pump pressures which were delivered to the lungs, very little of this pressure was transmitted to the veins, because of the abnormal solid pulmonary tissue. It thus appears improbable that

intermittent positive pressure influences the onset of intracranial bleeding, particularly as infants who did not experience prolonged anoxia recovered without this complication.

Summary

Prolonged anoxia is considered to be the major factor responsible in the aetiology of intracerebral haemorrhage associated with hyaline membrane disease. Bleeding is confined to the intraventricular and subarachnoid regions and occurs as a catastrophic event, usually two to three days following the anoxic episode. This pattern was observed in 9 infants who required artificial ventilation for repeated apnoeic attacks. These babies would probably have died of respiratory failure had they not received positive-pressure ventilation. This form of therapy, rather than causing the complication, permitted the study of its course.

A short spell of anoxia, on the other hand, does not carry the same ominous implication and may be treated by means of artificial ventilation without fear of intracranial haemorrhage occurring during the course of the disease.

CHAPTER IV

LUNG FUNCTION STUDIES IN HYALINE MEMBRANE DISEASE

Part 1 : Spontaneous breathing

Part 2 : The significance of grunting

Part 3 : Intermittent positive-pressure respiration

Part 1 : Spontaneous breathing

The pathological findings in hyaline membrane disease reveal gross structural changes of the lungs and it would, therefore, be surprising if the severity of the disease process were not reflected in an alteration of lung function during life. Reports, however, indicate a difference of opinion concerning the various aspects of pulmonary function.

An increase in the rate of breathing has consistently been observed. This formed the basis for the division of respiratory distress after birth into groups depending on the rate of breathing (Miller and Smull, 1957). Those with normal rates had significantly higher tidal volumes than those in whom the rate of breathing was increased. This method of classification unfortunately did not distinguish the various forms of respiratory distress, and these findings of reduced tidal volume may not be related specifically to hyaline membrane disease. Strang (1963) indicated the possibility of low tidal volumes occurring in the disease, but did not present actual measurements. On the other hand, a series of studies (Karlberg et al., 1954, Nelson et al., 1962 and Prod'hom et al., 1965) reported normal or slightly reduced tidal volumes. In this situation the minute volume, as expected, was raised. Crying vital capacity is known to be diminished (Sutherland and Ratcliff, 1961, Drorbaugh et al., 1957), while functional residual capacity is also reported to be decreased (Berglund et al., 1956).

Alveolar ventilation was found to be reduced in two studies (Nelson et al., 1962, Prod'hom et al., 1965), but normal in a third (Karlberg et al., 1954). In all, however, the dead space to tidal volume

ratio was increased.

Intrapleural pressure, as reflected by oesophageal pressure recordings, is invariably raised, and wide ranges of -10 mm.Hg. to -25 mm.Hg. have been recorded (Stahlman, 1964). This results from a marked reduction of dynamic compliance (Drorbaugh et al., 1963, Cook et al., 1957), which also increases the work of breathing (Karlberg et al., 1954). Resistance is considered not to be appreciably altered (Cook et al., 1957).

Ventilation/perfusion defects are constantly found. A significant arterial to alveolar gradient for carbon dioxide was thought to reflect poor perfusion of well-ventilated portions of lung (Nelson et al., 1962) and a similar gradient for oxygen indicated right-to-left shunting of blood at either intrapulmonary, ductal or foramen ovale levels. This right-to-left shunting has been demonstrated by an inadequate response to the hyperoxia test (Strang and MacLeish, 1961, Warley and Gairdner, 1962 and Prod'hom et al., 1965), and also by means of dye dilution curves (Stahlman, 1964). Arterial oxygen tension is invariably low when compared with normal infants (Warley and Gairdner, 1962).

Acid base abnormalities are commonly present, most infants having a respiratory acidosis with raised arterial carbon dioxide tensions (Hutchison et al., 1964, Usher, 1961, Blystad, 1956b), yet others have normal $PaCO_2$ (Karlberg et al., 1954).

Stahlman (1960), using carbon monoxide, demonstrated a diminished diffusion capacity for the gas in 4 infants with hyaline membrane disease, while two less severely affected babies presented normal results. This abnormal diffusion, however, was not accepted by Nelson et al. (1963) in another study.

It is thus evident that most lung functions are altered in the disease. The degree of change, however, is probably related to the severity of the condition in any particular infant and to the stage at which the investigations are determined. This is of particular importance in that the disease process in many cases is self-limiting and tends to revert to normal within the first week, in spontaneously breathing babies. In the present study, pulmonary functions were determined in 11 infants at various stages of the disease. Investigations were performed at the time of admission which in all cases was within 24 hours of life. All infants at this stage were distressed with rapid breathing, grunting, a Silverman score of over 8 and cyanosis in room air. Studies were repeated on the 3rd day, and again on the 7th day.

Results (Table 12)

The breathing rate in all infants was increased to a mean 76.8/min. By the third day, this was down to $\overline{61}$.9/min. and had further decreased to $\overline{50}$/min. by the seventh day (Fig. 23).

Tidal volume also reflected a constant pattern (Fig. 23). It was markedly diminished on the first day, with a mean of 8.4 ml. This rose to $\overline{10}$.1 ml. by the third day and at the end of a week was up to $\overline{13}$.7 ml., which means an increase of 60%.

Minute volume changes were not so striking. The mean first day volume was 572 ml.; on the third day it was $\overline{560}$ ml. and by the seventh day it was $\overline{640}$ ml.

Transpulmonary pressure averaged -12 cm.H_2O to +3.9 cm.H_2O on the first day. This was associated with expiratory grunting which had disappeared by the third day. By this time, the mean transpulmonary

TABLE 12

LUNG FUNCTION IN 11 SPONTANEOUSLY BREATHING INFANTS DURING THE COURSE OF THE DISEASE

	Weight kg.	f per min.	VT ml.	Cl ml/cm.H_2O	$\dot{V}$ ml/min.	Work of Breathing gm.cm/min.	pH	Base excess mEq/L.	$PaCO_2$ mm.Hg	$PECO_2$ mm.Hg.	PaO_2 * mm.Hg	$\dot{V}A$ ml/min	VD ml.	$VD_{/VT}$
Day 1. 11 cases														
Mean	2.24	76	8.4	0.9	572	6963	7.28	-5.3	51.9	10.3	73.7	110	4.4	0.50
S.D. ±	0.59	20	1.9	0.3	167	-	0.04	3.8	8.1	2.7	14.4	33	1.6	0.12
Day 3. 11 cases														
Mean		61	10.1	2.0	560	2049	7.33	-3.3	40.4	13.6	87 **	191	3.5	0.35
S.D. ±		9.0	1.9	0.9	134	-	0.11	2.2	2.8	2.2	25	57	0.8	0.03
Day 7. 7 cases														
Mean		50	13.7	3.2	640	2074	7.33	-4.4	37.8	16.4	78 ***	280	4.4	0.32
S.D. ±		4.7	2.5	0.8	62	-		3.6	3.4	1.5	14.4	52	1.4	0.08

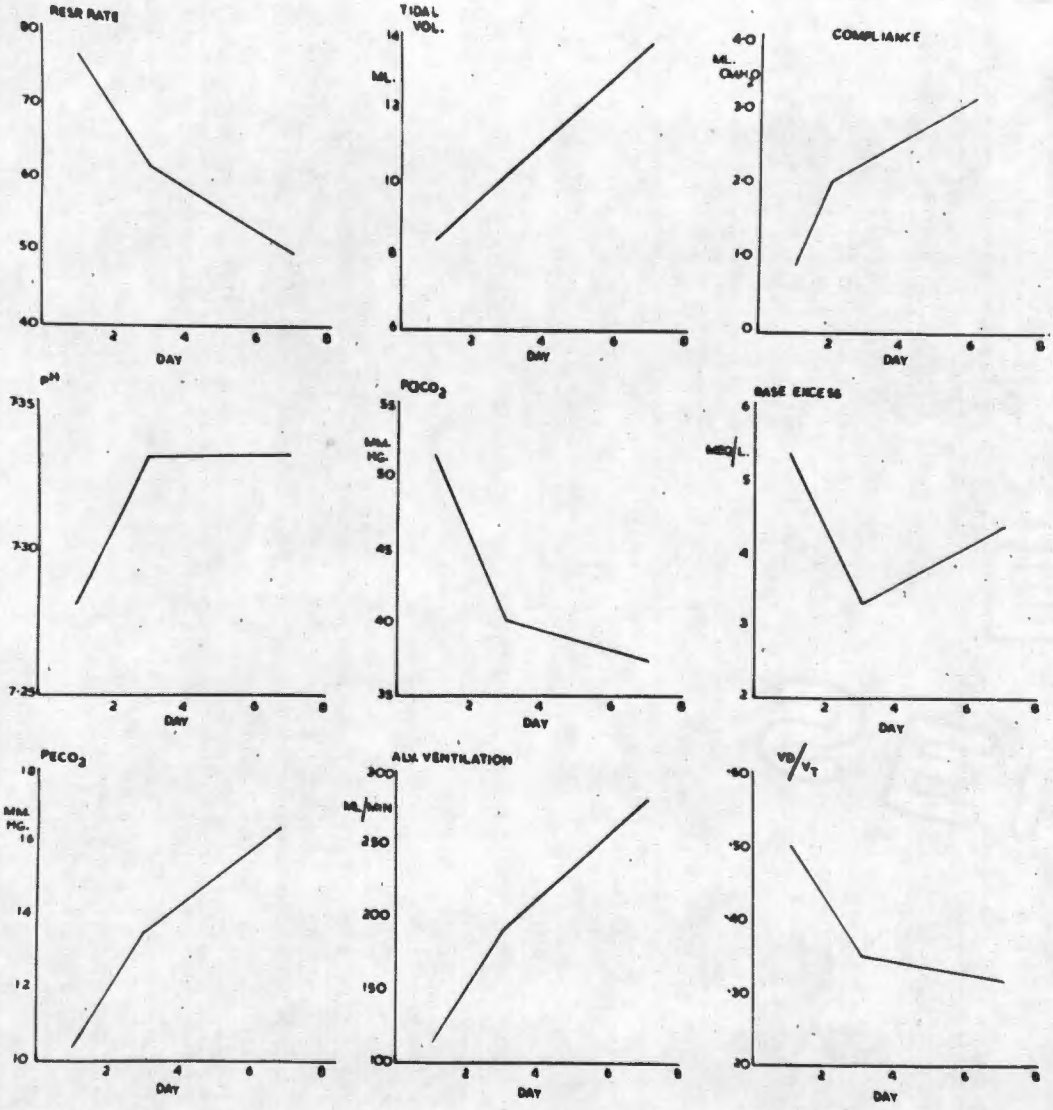
* Breathing 100% oxygen

** Breathing varying concentrations of oxygen

*** Breathing room air

Fig. 23

Graphs of lung function in hyaline membrane disease



Mean results obtained on the first, third and seventh days of the illness.

pressure had dropped to -6.3 cm. H_2O and at the end of the week it was -5.4 cm. H_2O. Compliance increased from a mean 0.9 ml./cm.H_2O on the first day to 2.0 ml./cm.H_2O on the third day, up to 3.2 ml./cm.H_2O on the seventh day. Work of breathing which was initially 6963 gm. cm.H_2O/min. showed a steady decline to 2049 on the third day and 2073 on the seventh day.

Alveolar ventilation was reduced on the first day (Fig. 23), averaging 110.2 ml./min. By the third day it had risen to $\overline{191}$.9 ml./min. and on the seventh day it was $\overline{280}$ ml./min. and reflected a rise of 40%.

Physiological dead space did not alter appreciably, with values of $\bar{4}$.4 ml. on the first day, $\bar{3}$.5 ml. on the third day and $\bar{4}$.4 ml. on the seventh day. The VD/VT ration, however, showed a progressive improvement with readings of 0.$\overline{50}$, 0.$\overline{35}$ and 0.$\overline{32}$ respectively (Fig. 23).

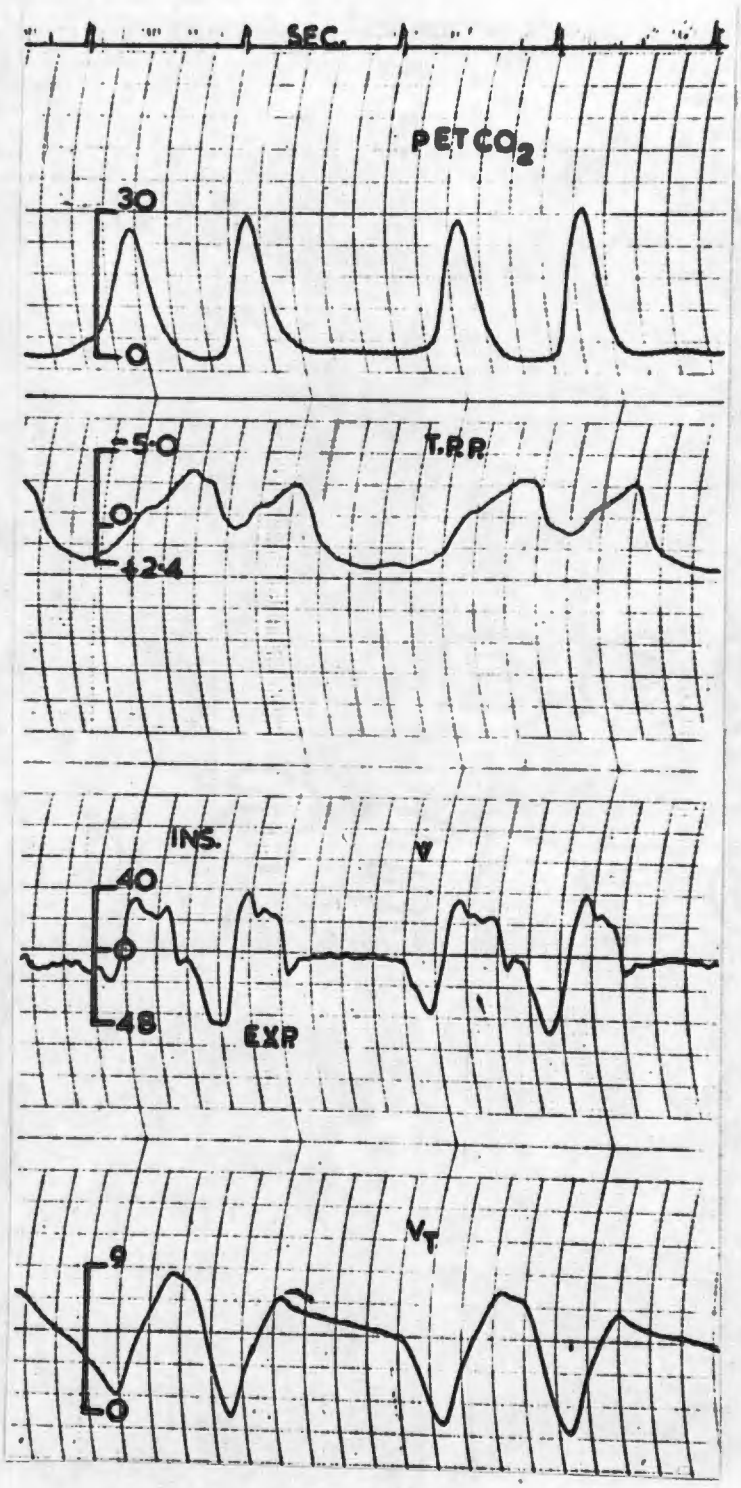
Acid base values showed an initial respiratory acidosis with a mean PCO_2 of 51.9 mm.Hg., pH of $\bar{7}$.28 and base excess of -$\bar{5}$.3. By the seventh day this had altered to a PCO_2 of $\overline{37}$.8, a pH of $\bar{7}$.33 and a base excess of -$\bar{4}$.4.

Initial PO_2 estimations which were determined after the infants had breathed high concentrations of oxygen for at least 30 minutes, ranged from 50 mm.Hg. to 105 mm.Hg. with a mean of 73.7 mm.Hg. Follow-up PO_2 values, however, were determined in the presence of varying concentrations of environmental oxygen and, therefore, cannot be used as an assessment of lung function. In addition, the site of blood sampling was altered.

End-tidal sampling of expired air did not yield plateau formation during the state of acute distress in any infant (Fig. 24). A series

Fig. 24

Characteristic peaked CO_2 curves in hyaline membrane disease



Paper speed 2.5 cm./sec.

PCO_2 : mm.Hg.

PTP : cm.H_2O

V : ml./sec.

VT : ml.

No plateaux occur on CO_2 curves during grunting and in quiet phases of breathing in distressed infants.

of peaks only were observed on expiration. It was, therefore, impossible to obtain true alveolar gas in distressed infants with hyaline membrane disease, and no values for $PACO_2$ could be determined.

Discussion

The changes in lung function throughout the course of the disease were remarkably constant for each infant. The babies could be considered to be severely affected in view of their rapid respiratory rates, raised $PaCO_2$ and low PaO_2 despite administration of high environmental oxygen. Nevertheless, all returned to normal within a week. It should be stressed that none of these infants required artificial ventilation to correct respiratory failure and they did not demonstrate persisting features of abnormal lung function which may occur either as a result of a more severe form of the disease or as a complication of therapy. All had a Silverman score of over 8, but this bore no relationship to the final outcome of the disease, and is in agreement with the view of Stahlman et al. (1967) that the degree of retraction is not of prognostic significance.

Tidal volumes were strikingly diminished during the acute phase and this is thought to reflect the severity of the disease. Although tidal volume is directly proportional to body weight (Cook et al., 1957) in the newborn period, this relationship was not applied because of the considerable oedema present in the early stages.

Karlberg et al. (1954) reported VT to be within normal limits in a series of 13 cases but complete investigations, including pH, $PaCO_2$ and alveolar ventilation, were presented in 3 cases only. As arterial carbon dioxide tensions were not raised, it is conceivable that the infants were easily able to compensate by increasing their breathing rates. They were

probably mildly affected and thus had normal tidal volumes. Nelson et al. (1962) presented a more severely distressed group in whom tidal volumes were reported as normal. The majority of infants, however, were born of diabetic mothers. The group therefore included a number of heavy babies who would normally be considered to have a larger VT than lighter premature infants of the same gestational age. Of 15 cases, 10 were studied within the first 24 hours during the stage of acute distress. Five of these had respiratory distress, not specifically related to hyaline membrane disease as seen on X-ray of the chest. A further 2 cases may be considered as mildly affected in view of normal arterial carbon dioxide tensions. This leaves 2 infants with severe distress who are comparable to those in the present study. One of the infants at the age of 5 hours had a VT of 10.6 ml. which rose to 16.6 ml. at 21 hours. The other had a VT of 7.0 ml. at 4 hours. No follow-up was obtained. These 2 infants nevertheless illustrate a significant reduction in tidal volume.

Prod'hom et al. (1965) divided distressed infants into groups on the basis of the hyperoxia test. The overall tidal volumes were considered to be normal within the first 24 hours of the disease. However, on studying their Group I, which had all the features of severe hyaline membrane disease, it is evident that 5 of a total of 7 infants had tidal volumes below the expected value.

Alveolar ventilation was initially diminished in the present study. This is not surprising, particularly in view of the raised $PaCO_2$, and is in agreement with reported series (Nelson et al., 1962, Prod'hom et al., 1965). Cases described by Karlberg et al. (1954) had normal $PaCO_2$ and alveolar ventilation but, as previously suggested, must have suffered the mild form of the disease.

Nelson et al. (1962), using a modified Rahn end-tidal sampler to collect alveolar gas, found a large arterial-alveolar gradient with a mean of 13.9 mm.Hg. for carbon dioxide tension. This figure, however, is thought to be inaccurate for it appears unlikely that true alveolar gas can be collected in the disease. When continuous records of end-tidal CO_2 concentration are obtained, no plateaux are seen. These are an essential requirement for alveolar gas and the low peaks which do appear must indicate a mixture of dead space and alveolar gas. Similar peaks were demonstrated by Strang (1963), who considered the tidal volume to be too small to wash out dead space.

Summary

Pulmonary functions were studied in 11 infants with severe hyaline membrane disease. During the acute phase, within the first 24 hours, all infants demonstrated inadequate ventilation with a decrease in tidal volume and alveolar ventilation despite an increase in the rate of breathing and a raised transpulmonary pressure. This inadequacy, primarily due to the decreased lung compliance caused by collapsed alveoli, was also shown in blood gas readings, as $PaCO_2$ was raised above normal while PaO_2 was markedly reduced despite breathing 100% oxygen. By the third day a definite improvement had been observed in all aspects of lung function, and by the seventh day measurements had reached the normal limits for premature babies.

Part 2 : The significance of grunting

Expiratory grunting is a characteristic feature of hyaline membrane disease, but this striking sign has received scant attention in the literature. Grunting is usually not observed in the first half-hour following delivery and is often more severe in small babies (Usher, 1961), tending to disappear following adequate oxygenation of the infant (Stahlman, 1964). It is associated with a raised positive intrathoracic pressure, believed to be caused by partial closure of the glottis during the latter half of expiration (Gairdner, 1964).

In the present study it was observed that grunting could be prevented by endotracheal intubation. During this period, however, the infants' condition deteriorated and cyanosis became prominent despite the administration of high concentrations of oxygen. Improvement in the babies' colour occurred if the tube was removed and grunting again commenced. In the same infants, prolonged bouts of crying improved their colour. The question arose whether the colour change associated with crying reflected an increase in arterial oxygen tension and whether grunting, which in certain respects resembled crying, would improve oxygenation of the distressed infant. This part of the study was planned to assess the physiological importance of grunting and to elucidate its mechanism.

Investigations

Lung function studies and abdominal muscle activity were determined on a number of distressed babies:

During the phase of grunting	- 22 infants
During 2 minutes of continuous crying	- 8 infants
20 minutes following endotracheal intubation; and	
10 minutes after the removal of the endotracheal tube	- 5 infants

TABLE 13

LUNG FUNCTIONS IN 22 GRUNTING INFANTS WITH RESPIRATORY DISTRESS

Mean Values ± Standard Deviations

Weight	PTP	VT	Peak inspiratory flow rate	Mid-expiratory flow rate	Peak end-expiratory flow rate	Inspiratory time	Expiratory time	Inspiratory /expiratory ratio	pH	PCO_2	Base Excess
kg.	$mm.H_2O$	ml.	ml/sec.	ml/sec.	ml/sec.	sec.	sec.	ratio		mm.Hg.	mEq/L
2.19	+12.0 +3.4	9.2	52.1	3.9	48.3	.30	.90	1 : 3	7.23	54.6	-6.9
±0.20	± 5.7 ±1.8	±1.6	±10.7	±2.2	±17.4	±.09	±.32		±0.36	±14.0	±3.3

Results (Table 13)

Grunting: Flow rate, transpulmonary pressure and tidal volume records differ significantly from those of normal babies (Fig. 25a).

Inspiration is rapid (mean 0.30 seconds) during which time the peak flow rate is a mean 52.1 ml./sec. and tidal volume averages 9.2 ml., while transpulmonary pressure rises to a mean -12 cm.H_2O.

Expiration: On the other hand, expiration is unduly prolonged to a mean 0.90 seconds. Initially, only a small amount of air escapes from the lungs (mean 5.2 ml.) at an average speed of 3.9 ml./sec. Oesophageal pressure is deflected to a mean +3.4 cm.H_2O while mouth pressure remains at zero (Fig. 25b). Grunting is audible during this period only and strong electrical activity of the abdominal muscles is recorded (Fig. 26).

In late expiration the air remaining in the lungs is rapidly expelled (mean 48.3 ml./sec.), grunting ceases and oesophageal pressure returns to zero (Fig. 25).

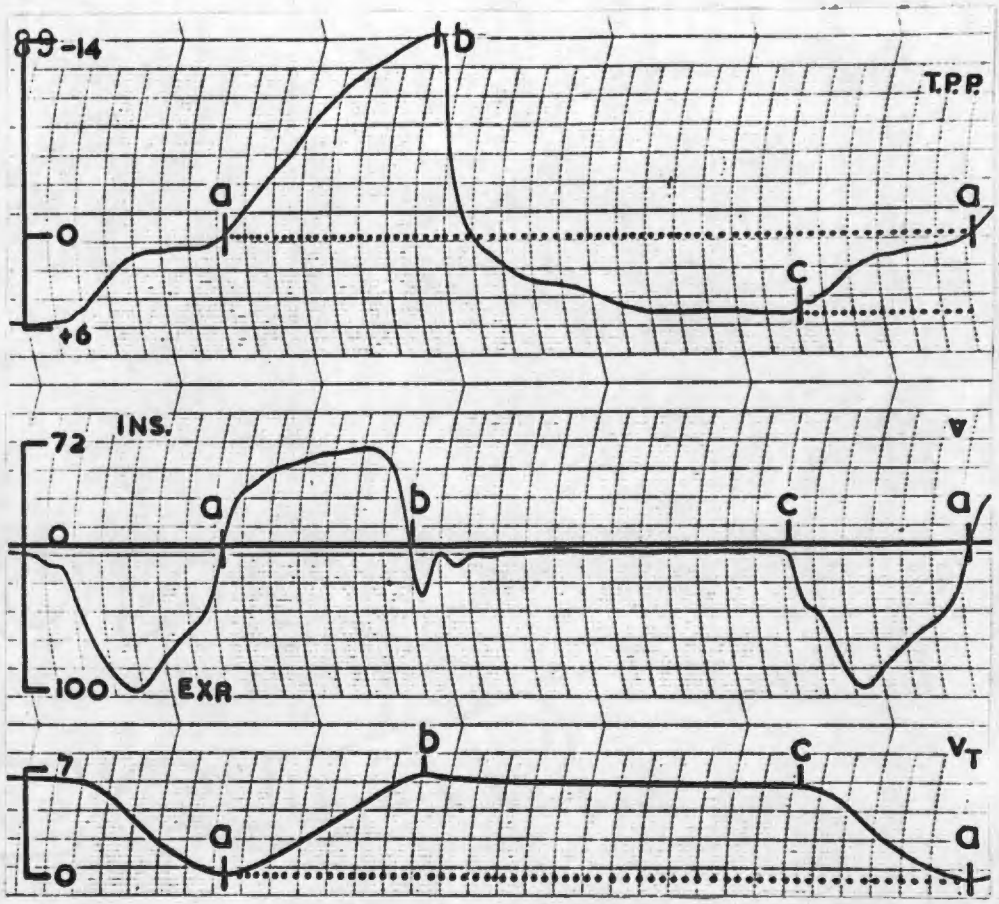
Grunting is not always continuous, and during quiet breathing no positive oesophageal pressure or muscle activity is registered (Fig. 27).

Crying: Changes in oesophageal pressure during crying are somewhat similar to those noted during grunting (Fig. 28) in that the pressure reaches a mean -17.7 cm.H_2O during inspiration while positive pressure averaging 6.0 cm.H_2O occurs during expiration. Abdominal muscular activity is present during the whole of expiration.

Flow rate and tidal volume records cannot be interpreted during crying because of leaks which occur through the mouth.

Fig. 25a

Grunting



Pressure, flow and volume curves
Paper speed 12.5 cm./sec.

PTP cm.H_2O

Vertical height ab - total negative transpulmonary pressure during inspiration

b - c pressure forced over zero to a positive value during expiration

c - a positive pressure returns to zero in step-like fashion

$\dot{V}$ ml./sec.

a - b inspiration

b - c phase of grunting: slow flow of air out of lungs

c - a grunting ceases: rapid expiratory flow of air

VT ml

Vertical height ab X K = tidal volume

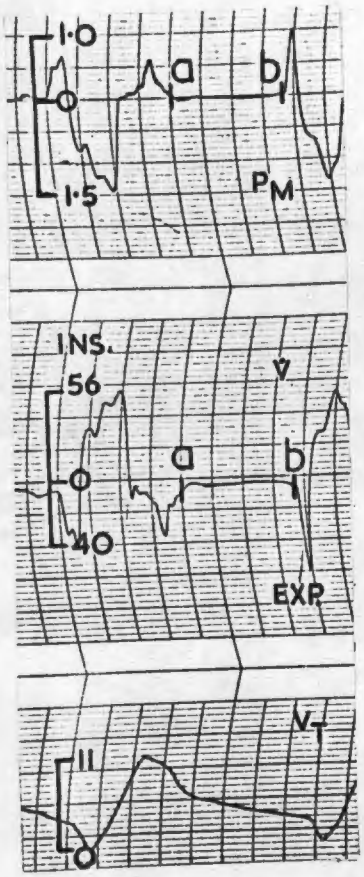
b - c retention of air in lungs

c - a sudden release of air from lungs.

Fig. 25b.

Mouth pressure during grunting

PM : cm.H_2O
$\dot{V}$: ml./sec.
VT : ml.

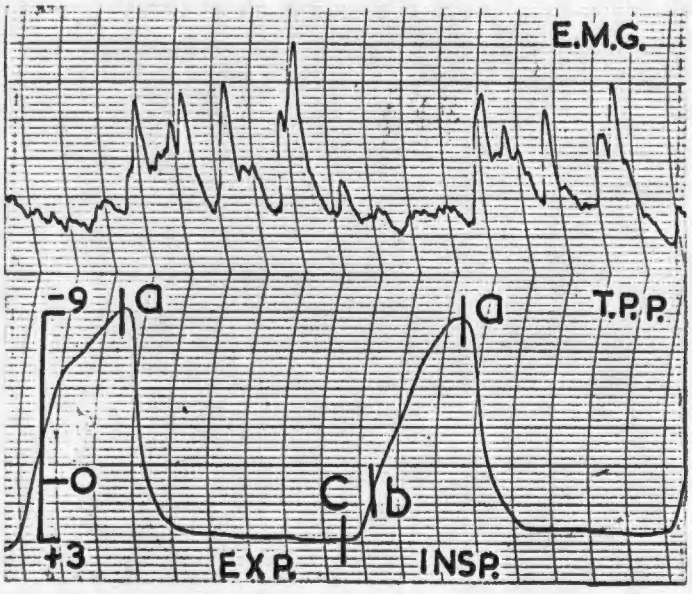


During the phase of grunting a - b, pressure remains at zero and only oesophageal pressure changes are recorded

Fig. 26

Electromyogram of rectus abdominis during grunting.

EMG : Electromyograph
PTP : cm.H_2O



Electrical activity is observed during the phase of grunting and positive intrathoracic pressure a - c.

No electrical activity occurs during rapid expiration c - b, or inspiration b - a.

Fig. 27

Periodicity of grunting

PTP : cm.H_2O

$\dot{V}$: ml./sec.

During rapid breathing PTP returns to zero and air is rapidly expelled, while during grunting air is expelled slowly and a positive PTP is produced.

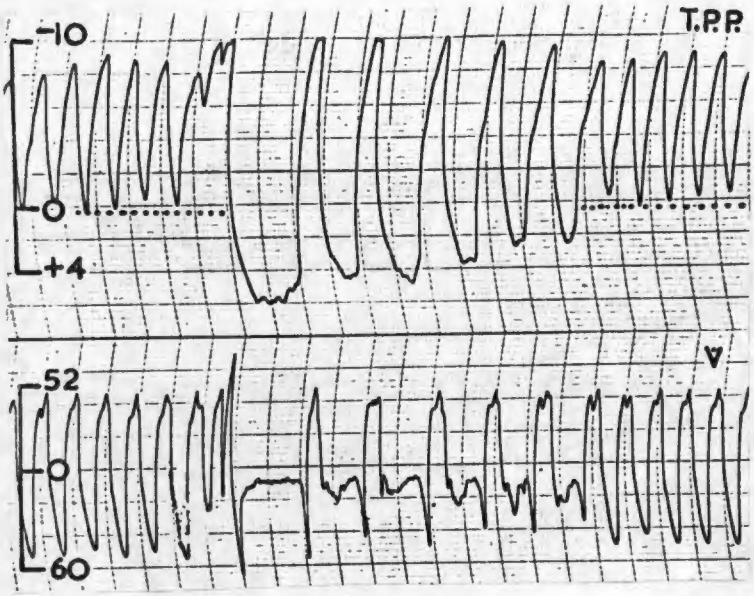


Fig. 28

Oesophageal pressure during crying

P_{oes} : cm.H_2O

Inspiration is associated with a large negative intrapleural pressure while expiration is prolonged and forced and associated with a positive intrathoracic pressure.

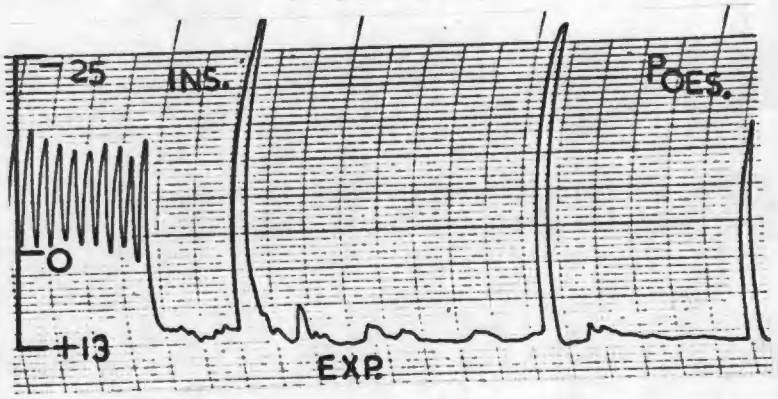


Fig. 29

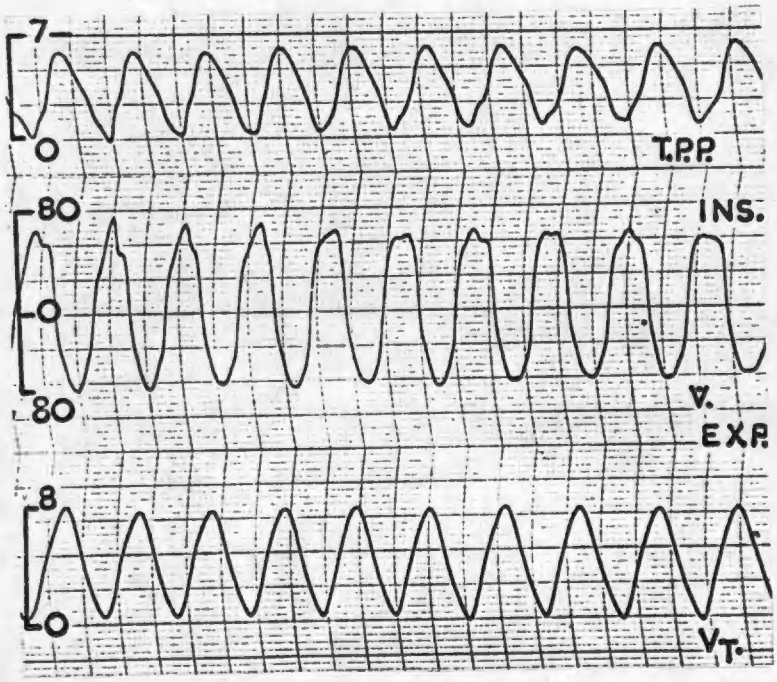
Pressure, flow and volume curves during intubation

PTP : cm.H_2O

$\dot{V}$: ml./sec.

VT : ml.

During intubation, grunting cannot occur. Breathing is rapid and no retention of air occurs.



Endotracheal intubation: A dramatic change is noted in the expiratory pattern during intubation (Fig. 29). Expiration becomes rapid (mean 0.35 sec.), no positive pressures are recorded and there is a cessation of abdominal muscle activity. Tidal volumes are maintained at the same level (mean 9.0 ml.) as during grunting, but gradually diminish over 20 to 30 minutes.

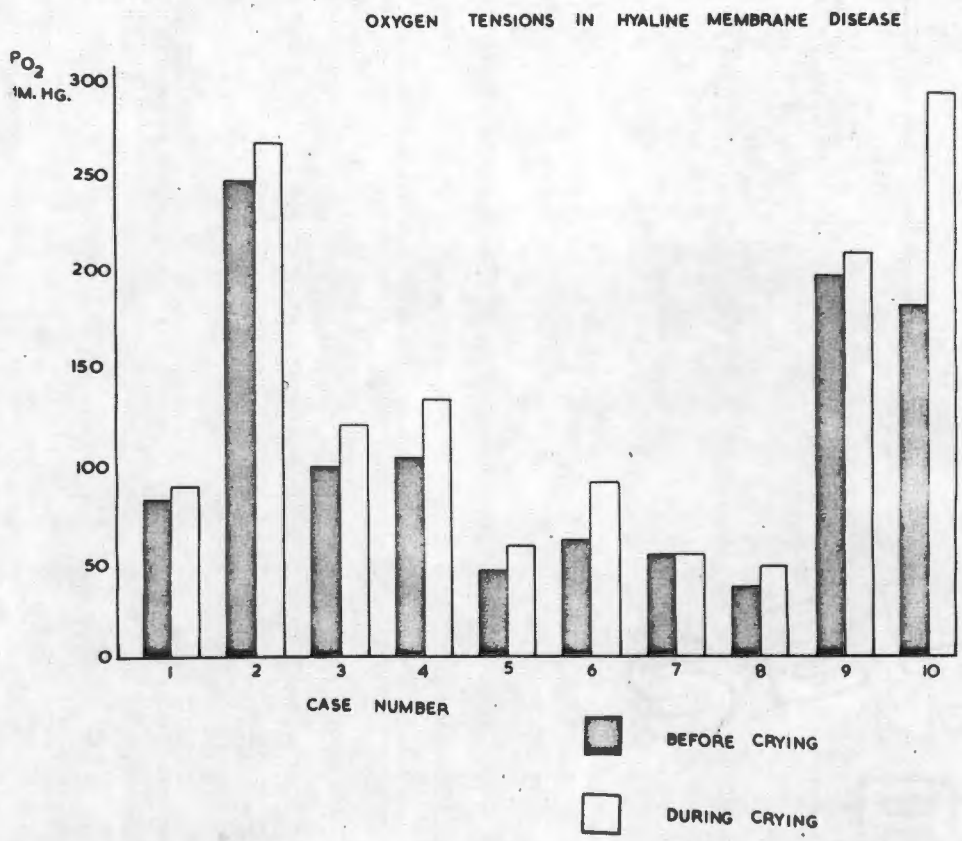
Arterial oxygen tension: All infants were breathing 100% oxygen during the study and their arterial oxygen tensions ranged from 36 mm.Hg. to 250 mm.Hg. (Table 14). When they were stimulated to cry there was a significant increase in PaO_2 in all but one infant (Fig. 30). It should be mentioned that this child was severely affected and could not grunt or cry effectively. Once the infants were intubated (Fig. 31) a significant fall in PaO_2 occurred in each case after a period of 20 minutes (Table 14). This situation was reversed following extubation, as 20 minutes later a significant rise in PaO_2 had occurred in each infant (Table 14).

TABLE 14

OXYGEN TENSIONS IN HYALINE MEMBRANE DISEASE

Case No.	Before crying mm.Hg.	During crying mm.Hg.	Difference mm.Hg.	Before Intubation mm.Hg.	During Intubation mm.Hg.	Difference mm.Hg.	After Intubation mm.Hg.	Difference mm.Hg.
1	84	90	6	81	70	11	84	14
2	250	270	20	255	157	98	255	98
3	100	121	21					
4	106	135	29					
5	46	59	13					
6	62	92	30					
7	53	53	0	56	41	15	49	8
8	36	48	12	36	15	21	34	13
9	200	212	12					
10	185	296	111					
11	-	-	-	42	20	22	44	24
Significance x^2			$p < .001$			$p < .001$		$p < .001$

Fig. 30


OXYGEN TENSIONS IN HYALINE MEMBRANE DISEASE
P_{O_2} MM. HG.
300
250
200
150
100
50
0
1
2
3
4
5
6
7
8
9
10
CASE NUMBER
BEFORE CRYING
DURING CRYING

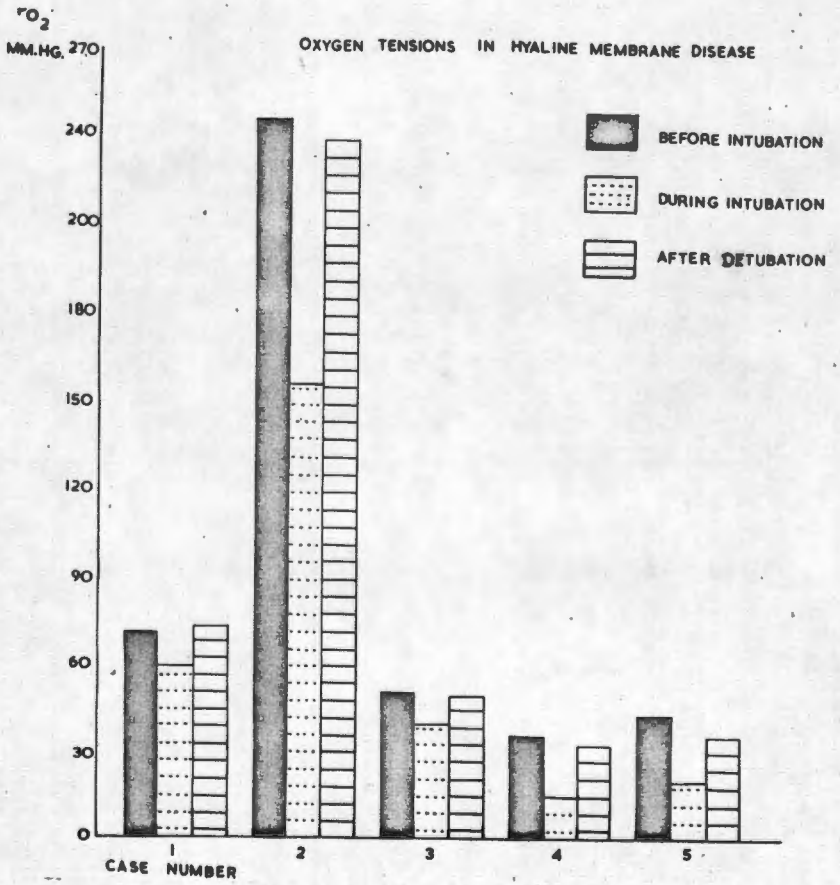

P_{O_2}
MM.HG.
270
240
200
180
150
120
90
60
30
0
OXYGEN TENSIONS IN HYALINE MEMBRANE DISEASE
BEFORE INTUBATION
DURING INTUBATION
AFTER DETUBATION
1
2
3
4
5
CASE NUMBER

Fig. 31

Discussion

Grunting is similar to a Valsalva manoeuvre, for by contracting the abdominal muscles these infants are able to raise their intrathoracic pressure to positive levels during expiration. They appear to do this by forcing air against a partially closed glottis, as during periods of intubation grunting cannot occur and no positive intrathoracic pressure can be produced. The significant positive intrathoracic pressure can best be demonstrated when grunting is periodic (Fig. 27) and does not represent an artefact due to a shift in the base line.

Criticism may be expressed against the significance of arterial oxygen tension changes during intubation. It is well known that any handling of these infants in their precarious condition may precipitate respiratory failure. It may also be argued that they must now breathe against an added resistance which may prove critical. However, there was no associated slowing of respiratory rate characteristic of breathing against an obstruction; nor was any flattening of the expiratory flow rate curve observed.

The manner in which grunting can prevent a fall in arterial oxygen tension is of considerable interest. Air is held in the lungs during the major portion of expiration and this probably improves alveolar ventilation by keeping the alveoli patent. These would otherwise tend to collapse during expiration because of the absence of surfactant.

In certain respects crying resembles grunting so that it too is a Valsalva manoeuvre and is able to raise arterial oxygen tension. This mechanism may result from improved ventilation, diffusion or the reversal

of a shunt. Prec. and Cassals (1952) investigated oxygen saturation in normal crying infants and noted that 64% of those over 4 days of age frequently demonstrated a rise in oxygen saturation, considered to be due to improved ventilation as it is certainly evident that tidal and minute volumes are increased during crying (Deming and Hanner, 1932). In young babies, however, oxygen saturation fell in 59% of cases during crying. The infants in the present series are not strictly comparable as all had grossly abnormal lungs.

Arterial oxygen tension is known to be particularly high when expiratory pressure is raised, presumably due to a rise in alveolar oxygen tension (Purves, 1966) and the diffusing capacity of carbon monoxide is increased following a Valsalva manoeuvre (Daly and Roe, 1962).

It is therefore conceivable that all these factors may play a part in raising arterial oxygen tension during both grunting and crying.

Summary

Grunting was studied in 22 distressed infants and demonstrated to consist of a series of modified Valsalva manoeuvres, as during expiration intrathoracic pressure is increased by closing the glottis and contracting the abdominal muscles. This procedure presumably helps to keep alveoli patent, thereby improving ventilation and raising arterial oxygen tension. This improvement, however, may also be caused by an increase in diffusion of oxygen following the Valsalva manoeuvre. Grunting affords a protective mechanism, for if it is interrupted there is a precipitous fall in arterial oxygen tension.

Part 3 : Intermittent positive-pressure respiration

".....much valuable research effort in the neonatal field over the past two decades has necessarily come into the category of 'proceedings not of direct benefit to the individual.' When the clinician and the researcher are different individuals the issue is clear: the doctor is in charge of the patient and will lean on his medical ethic to decide what is and is not allowable. But one individual may have the ultimate responsibility in both spheres. What then? In the last resort there can be no substitute for the conscience of the individual. "

Editorial, Arch. Dis. Childh., 42, 109, 1967.

Artificial ventilation can dramatically improve the clinical acid base and blood gas status of infants with hyaline membrane disease. The manner in which this is done has never been clearly demonstrated and the successful use of intermittent positive pressure has been based on an empirical selection of pump pressures, speeds and flow rates.

Donald and Lord (1953) maintained that augmented breathing would benefit an infant to a greater extent than any other form of ventilatory assistance, but this view was not generally accepted as infants were later curarised during intermittent positive-pressure ventilation for fear that it would harm them to breathe against the respirator. Thus it is also doubtful whether augmented breathing is more effective than passive ventilation.

Most reports concerning the effects of intermittent positive pressure on pulmonary function in diseased lungs are confined to studies on emphysematous adults. Torres et al. (1960) showed an overall improvement in ventilation as a result of an increase in tidal volume and an improved distribution of air to the lungs. Jameson et al. (1959) demonstrated a direct relationship between the increase in minute volume and the resulting changes in blood gas data, as ventilation had to be increased 25% before the $PaCO_2$ fell and 35% before the oxygen saturation rose.

A series of investigations were therefore planned in order to elucidate the mechanism of intermittent positive-pressure ventilation in the treatment of hyaline membrane disease.

Investigations

Spontaneous breathing to IPPR

The alteration in lung function from spontaneous breathing to intermittent positive-pressure breathing was assessed in 8 infants. Studies were performed 2 to 6 hours before IPPR and then repeated 1 hour after the introduction of IPPR. Gas was not collected from the spontaneously breathing infants as they were considered to be too ill at the time.

Effects of IPPR on lung function

An effective form of artificial ventilation had been established in 12 infants by adjusting pump pressure and speed until the blood gas tensions had reached normal limits. In all cases this involved the use of rather high pump pressure and speed and the effects of this combination on lung function, together with several other combinations, will be established.

Three major groups will be considered:

High Pressure	High Speed
Low Pressure	High Speed
High Pressure	Low Speed

Once studies had been completed using the initial combination of high pressure and high speed, the pump pressure was then reduced approximately 30% while the speed of cycling remained unaltered. Lung functions were determined after an interval of 30 minutes and then the pump pressure was returned to its original level. Fifteen minutes later the speed of cycling was reduced by approximately 40% while the pressure was kept constant. Lung functions were again studied after an interval of 30 minutes.

Augmented vs. Passive ventilation

The efficacy of augmented breathing was compared with that of passive ventilation in 5 infants. Lung function studies, excluding gas collection, were performed within 2 minutes of passive ventilation because of its short duration.

Results

Spontaneous breathing to IPPR (Table 15) : Intermittent positive-pressure respiration led to a significant increase in tidal volume from a mean 8.2 ml. during spontaneous breathing to $\overline{20.0}$ ml., and there was a corresponding increase in minute volume from $\overline{631}$ ml. to $\overline{1132}$ ml. (Fig. 32).

This improvement in ventilation was reflected in the acid base and blood gas status, which after one hour had returned to normal on IPPR therapy. pH rose from a mean 7.18 to $\overline{7.34}$ while $PaCO_2$ fell from a

TABLE 15

ALTERATION OF LUNG FUNCTION FROM SPONTANEOUS BREATHING TO INTERMITTENT POSITIVE PRESSURE VENTILATION

	f 1 min.	PTP cm.H_2O	VT ml.	$\dot{V}$ ml./min.	Cl ml./cmH_2O	pH	Base Excess mEq/L	$PaCO_2$ mm.Hg.	PaO_2 mm.Hg.
SPONTANEOUS BREATHING									
Mean	79	-5.8	8.2	631	1.8	7.18	-7.6	66	38.1
S.D. ±	18	4.1	1.4	139	0.9	0.14	5.5	14.3	11.7
AUGMENTED BREATHING ON IPPR									
Mean	54	35	20.0	1132	0.8	7.36	-5.0	33	102
t	-	-	5.619	3.412	3.00	2.244	1.08	4.78	3.333
p	-	-	< 0.001	< 0.01	< 0.01	< 0.05	> 0.30	< 0.001	< 0.01
			*	*	*	*		*	*

* = Highly significant difference

mean 66 mm.Hg. to $\overline{33}$ mm.Hg. A significant increase occurred in PaO_2 from $\overline{38.3}$ mm.Hg. during spontaneous breathing to $\overline{102}$ mm.Hg. while on IPPR (Fig. 32).

This overall improvement in ventilation occurred despite a striking decrease in lung compliance from a mean 1.8 ml./cm. H_2O to 0.8 ml./cm.H_2O.

Inspiratory and expiratory flow rates were not appreciably altered and the inspiratory to expiratory time ratio was maintained at 1 : 1.4 during IPPR.

End-tidal carbon dioxide concentration could not be determined during either spontaneous or augmented breathing, as no true plateau formation occurred on the expiratory CO_2 tracings (Fig. 33).

Effects of varying pump pressure and speed during IPPR (Table 16)

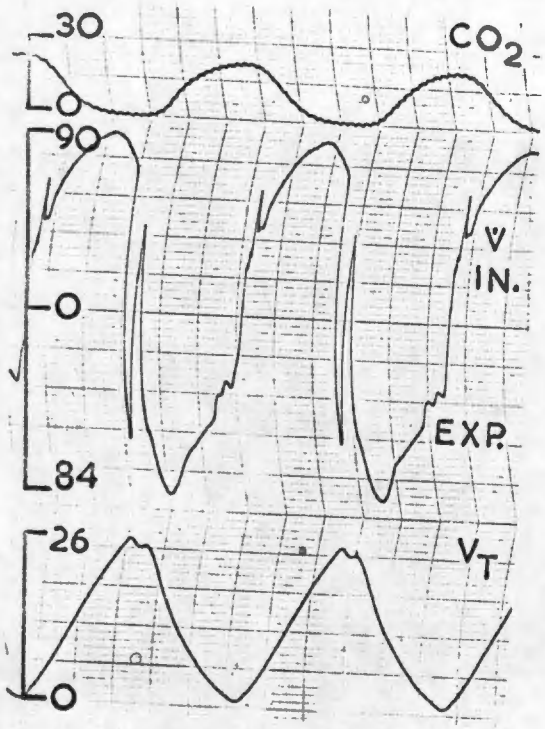
Decrease in pump pressure: A decrease in the mouth pressure from a mean 35 cm.H_2O to 26 cm. H_2O led to a significant deterioration in ventilation (Fig. 31).

Tidal volume fell from a mean 20.0 ml. to $\overline{13}$.0 ml. Minute volume was reduced from $\overline{1132}$ ml. to 189 ml., and the alveolar ventilation decreased from a mean 371 ml/min. to $\overline{92}$ ml./min. The VD/VT ratio increased from $0.\overline{51}$ to $0.\overline{74}$. No striking changes were noted in acid base balance. $PaCO_2$ increased from a mean 33 mm.Hg. to $\overline{48}$ mm.Hg., while a most significant fall occurred in PaO_2 from $\overline{102}$ mm.Hg. to $\overline{47.8}$ mm.Hg.

Decrease in pump speed: Pump speed was reduced from a mean 54 cycles per minute to $\overline{32}$ cycles per minute, while the pressure remained constant at $\overline{43}$ cm. H_2O. This procedure resulted in diminished

Fig. 33

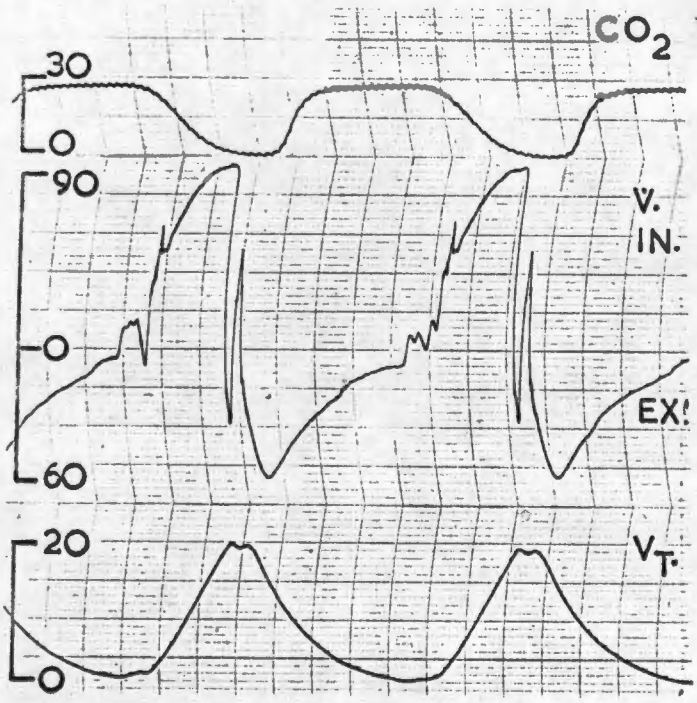
Expiratory carbon dioxide tension during IPPR



Short expiration - passive ventilation
Paper speed 5 cm./sec.

CO_2 : mm.Hg.
$\dot{V}$: ml./sec.
VT : ml.

During a short expiratory period no plateau can be produced on CO_2 curve



Prolonged expiration. Passive ventilation on same infant.
Paper speed 5 cm./sec.

During a prolonged expiratory phase plateau formation occurs on CO_2 curve, indicating the presence of alveolar gas.

TABLE 16

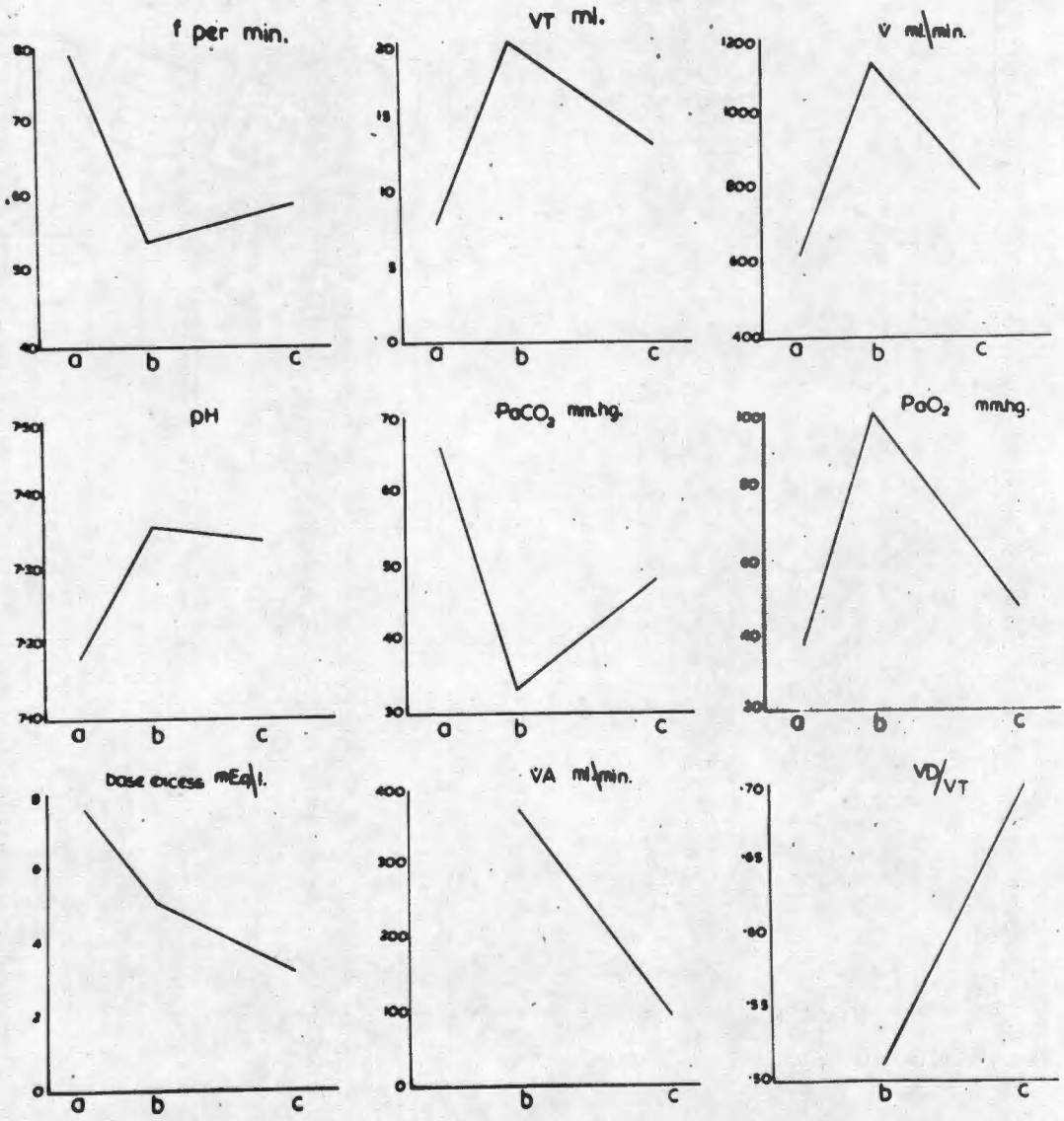
EFFECTS OF INTERMITTENT POSITIVE PRESSURE ON LUNG FUNCTION

	f cycles/min.	PTP cm.H_2O	VT ml.	$\dot{V}$ ml/min.	Cl ml/cm.H_2O	pH	Base Excess mEq/L	$PaCO_2$ mm.Hg	PaO_2 mm.Hg	$\dot{V}A$ ml/min.	VD ml.	VD/VT
HIGH PRESSURE HIGH SPEED												
Mean	54	35	20.0	1132	0.8	7.36	-5.0	33.0	102	371	10.8	0.51
S.D. ±	18	11	5.9	76	0.4	0.14	5.0	15.1	58	252	6.1	0.27
LOW PRESSURE HIGH SPEED												
Mean	59	26.3	13.0	789	0.6	7.34	-3.2	48.1	47.8	92	9.3	0.74
S.D. ±	9	6.8	3.7	274	0.2	0.06	5.6	25.7	21.7	41	3.8	0.16
t	1.157	.659	3.333	4.180	.250	.456	.782	1.623	2.258	3.128	.365	2.300
p	> .20	> .40	< .001 *	< .001 *	> .80	> .60	> .40	> .10	< .02 *	< .001 *	> .70	< .02 *
HIGH PRESSURE LOW SPEED												
Mean	32	43	13.7	464	0.5	7.32	-3.8	50	49	98	9.3	0.75
S.D. ±	4	4.6	1.0	22	0.1	0.14	3.0	18	12	33	3.4	0.10
t	6.27	1.538	2.333	7.40	1.619	0.370	1.20	1.90	2.304	2.275	0.129	2.183
p	< 0.001 *	> 0.20	< 0.05 *	< 0.001 *	> 0.10	> 0.80	> 0.70	> 0.10	< 0.05 *	< 0.05 *	> 0.90	< 0.05 *

* Difference highly significant

Fig. 32

Graphs of Lung Function



a. During spontaneous breathing

b. During IPPR:

High pump pressure and rapid rate of cycling

c. During IPPR:

Low pump pressure and rapid rate of cycling

ventilation. Tidal volume was high during an augmented breath, but between such periods the weak breathing efforts of the infant yielded small volumes (Fig. 34). The overall mean tidal volume was 13.7 ml. Minute volume decreased to a mean 464 ml., while alveolar ventilation declined to $\overline{98}$ ml./min. and VD/VT ratio rose to $0.\overline{75}$.

Acid base balance was again slightly affected, but $PaCO_2$ rose to $\overline{50}$ mm.Hg. while PaO_2 dropped precipitously to $\overline{49}$ mm.Hg.

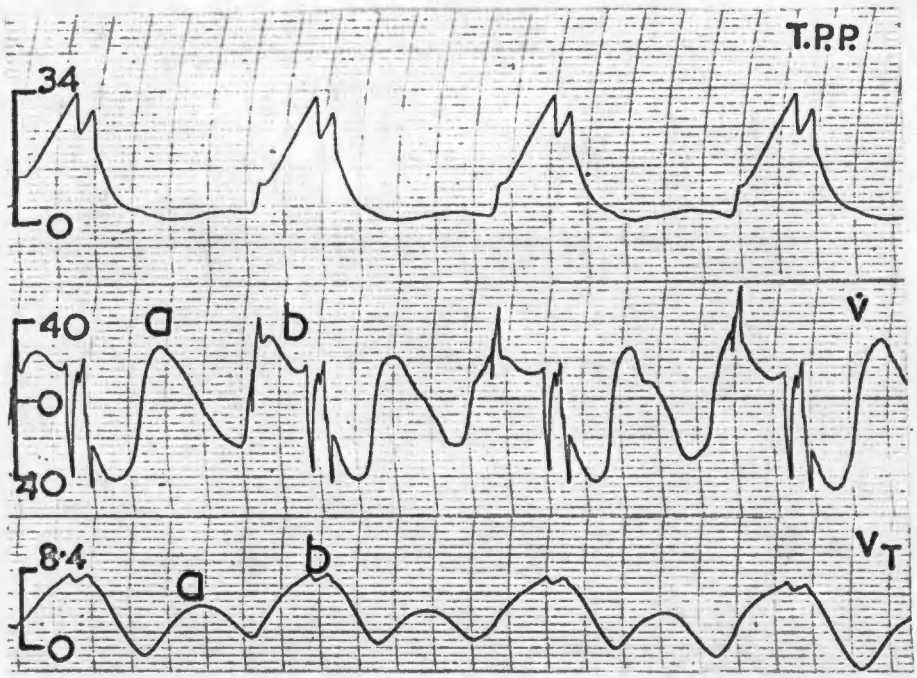
Augmented vs. Passive ventilation (Table 17):

The most striking feature during passive ventilation was a drop in arterial oxygen tension which occurred in each infant within 2 minutes following paralysis. This fall in PaO_2 averaged 38% and was not related to any change in tidal volume, mouth pressure or pump speed. The expiratory rate of flow was prolonged (Fig. 33) and plateaux were recorded on the tracings of expiratory CO_2. These were accepted as being representative of end-tidal carbon dioxide concentration.

The mean $PACO_2$ determined on 4 infants was 16 mm.Hg., while $PaCO_2$ measured on the same infants was 32 mm.Hg. giving an a - A gradient for PCO_2 of 16 mm.Hg.

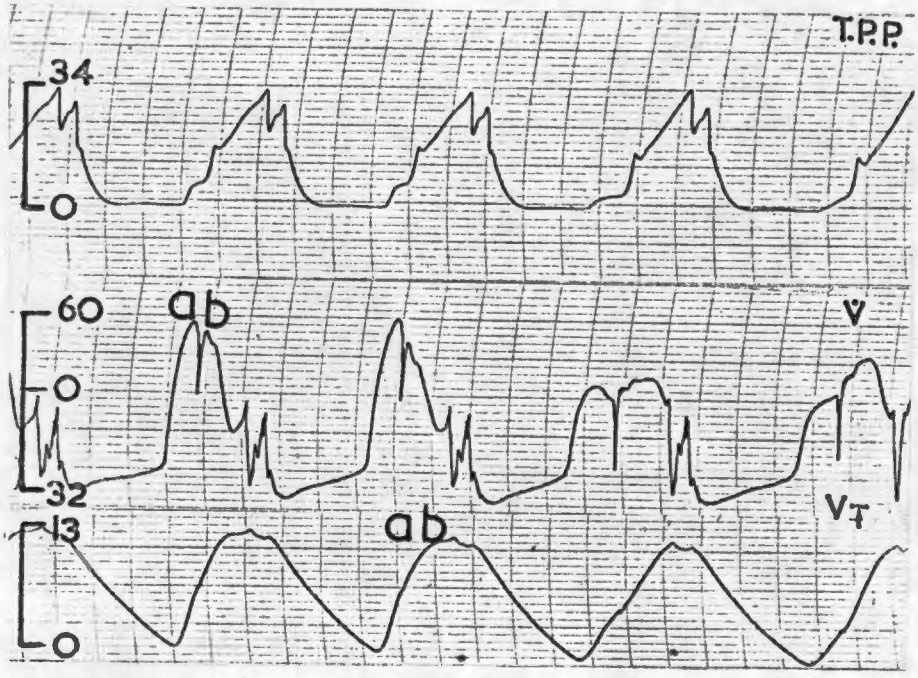
Fig. 34

Tidal volume changes during augmented breathing



a. spontaneous breath
b. pump-induced breath

If pump cycling is slow, a. and b. do not synchronise and small tidal volumes are produced.



When the infant is allowed to trigger the respirator a. and b. occur together and a larger augmented tidal volume is produced.

TABLE 17

AUGMENTED VS. PASSIVE VENTILATION

Number	VT ml		PTP $cm.H_2O$		PaO_2 mm.Hg.		% Fall
	a	b	a	b	a	b	in PaO_2
6	18.0	18.4	42	41	81	71	12%
1	14.3	15.1	40	41	61	38	40%
3	18.4	17.9	44	43	72	42	41%
* 7	21.0	21.8	34	32	102	50	50%
* 15	15.9	17.6	20	23	82	41	50%

* Given 1 mgm. Scoline intravenously

a. Augmented breathing

b. Passive ventilation

Discussion

Intermittent positive-pressure ventilation has been shown to reverse the features of respiratory failure by an overall improvement in ventilation. Correction of blood gas abnormalities was achieved in each case by the production of a normal alveolar ventilation.

This, however, necessitated a 50% increase in the original minute volume. Tidal volume varied with the pressure delivered by the respirator, and in order to attain a satisfactory minute volume, the augmented tidal volume had to be introduced a mean 54 times a minute. The pressure required to augment tidal volume could be critical for any one child, for if it is decreased there is a precipitous fall in PaO_2 to dangerous levels of hypoxaemia. It is conceivable that the high mean pump pressure of 35 cm. H_2O may be necessary to expand collapsed alveoli, but a large amount of ventilation is wasted as can be observed from the physiological dead space of 10 ml. and the VD/VT ratio of 0.51.

An increase in dead space is known to occur during IPPR in adults and has been attributed to a mal-distribution of air to the alveoli, which becomes particularly marked if the inspiratory time is reduced to 0.5 seconds or less (Watson, 1962). It is also likely that a large amount of inspired air fills the dilated bronchi during each respiration.

Improvement in ventilation occurred despite a striking fall in lung compliance. This decrease in distensibility during prolonged intermittent positive-pressure respiration is well recognised (Opie et al., 1961, Smythe, 1963), and has been attributed to the collapse of alveoli, so that a new ratio of volume change to pressure change now measures the expansion

of alveoli which remain open (Bernstein, 1957). This factor, however, cannot be considered to be applicable in the present study, as the change in compliance occurred within an hour of commencing IPPR and it is most unlikely that lung tissue could have become less distensible in so short a time. It is more likely that the changes in compliance were due to maldistribution of air to the alveoli and could have been better explained by the measurement of specific compliance.

Therapy did not improve the underlying disease process in any way, and correction of blood gas abnormalities was achieved in the face of severe physiological abnormalities. The inability of PaO_2 to reach a higher mean level than 105 mm.Hg. despite ventilation with 100% oxygen must reflect persisting right-to-left shunts, while the arterial to alveolar gradient for $PaCO_2$ probably indicates poor perfusion of well-ventilated alveoli.

Augmented breathing is certainly more effective than passive ventilation. From the purely mechanical point of view it does not seem to matter whether an infant breathes in or out of phase with the respirator so long as he breathes, for as soon as respiratory muscles are paralysed, there is a significant fall in PaO_2. This cannot be attributed to an alteration in ventilation and probably depends on the adverse effects of artificial ventilation on the cardiovascular system.

Intermittent positive pressure has been compared with a series of Valsalva manoeuvres, and during inspiration the intrathoracic pressure rises, right ventricular filling is delayed, right stroke volume is decreased and right ventricular output falls. Peripheral venous pressure rises because of a decrease in central venous pressure and in venous return. Total thoracic blood volume is decreased and, as a result, left

ventricular filling and output rise for a few beats, but they decrease if inspiration is prolonged (Motley et al., 1948). In adults, these effects of IPPR are minimized during the stage of paralysis if normal circulatory control is present and if the mean mouth pressure is kept as low as possible (Spalding and crampton Smith, 1963).

It is likely that similar abnormalities may occur in paralysed infants with abnormal lungs, as Klein (1967) has demonstrated a significant rise in the right atrial diastolic pressure during IPPR. This pressure decreases as soon as spontaneous breathing recommences. The fall in PaO_2 may occur as a result of a decreased right ventricular output, and whereas it may not prove significant in an infant with normal lungs, it would be fatal in one with abnormal lungs.

Summary

Lung functions have been studied in 12 infants who received intermittent positive-pressure ventilation. This form of therapy was able to reverse all features of respiratory failure by providing a normal alveolar ventilation. This necessitated a 50% increase in minute volume which in turn depended on a significant increase in tidal volume, achieved only by high pump pressures (mean 35 cm.H_2O) and a rapid rate of breathing (mean 54 pump cycles/min.). Other combinations of pump pressure and speed were studied but these could not provide adequate ventilation. The importance of using assisted as opposed to passive breathing was also illustrated, for the latter tended to drop PaO_2 by its adverse effects on the cardiovascular system.

SUMMARY

This study concerns the treatment and pulmonary function of 62 infants suffering from hyaline membrane disease. All babies were immature and presented characteristic clinical, radiological and biochemical features of the disease.

Fifty-eight of the 62 infants were admitted to a neonatal intensive care unit. Fifty-three of these were breathing at the time of admission and were treated with high concentrations of oxygen and intravenous glucose and sodium bicarbonate. This therapy, which is known to prevent respiratory failure if started early (Usher, 1963), was continued throughout the stage of acute distress and led to complete recovery in 34 of the 53 infants. Its safety was illustrated by the fact that no evidence of lung disease, retrolental fibroplasia or mental retardation could be detected in any infant who was later examined at a follow-up clinic.

Pulmonary function studies were carried out on 11 of the 34 infants during the course of their disease. The apparatus and methods used for these investigations were considered to be both safe and accurate and had yielded results on normal infants which were comparable with those of other series.

The 11 infants selected for these studies were severely distressed during the first day of their illness. Their lungs were extremely stiff as shown by low compliance measurements and they were unable to produce normal tidal volumes, despite a threefold increase in intrapleural pressure. Even a significant increase in their rate of breathing failed to provide minute volumes which could adequately ventilate the alveoli. As a result, arterial carbon dioxide tension was raised while arterial oxygen tension was reduced. During treatment, however, the carbon dioxide

retention was prevented from reaching dangerous heights and arterial oxygen tension could be maintained at relatively safe levels by the 100% oxygen which the infants breathed, and by grunting.

The latter procedure resembled a Valsalva manoeuvre in that abdominal muscles contracted during expiration while the glottis remained partially closed, thereby raising intrathoracic pressure. This in turn was thought to force air into alveoli which otherwise would have collapsed during expiration owing to the lack of surfactant. If grunting was prevented by endotracheal intubation, there was a resultant decrease in PaO_2 which could be corrected if grunting was again allowed to take place. This protective mechanism is further illustrated by the fact that grunting tends to disappear once an infant is adequately oxygenated (Stahlman, 1964). The severe sternal recession and increased work of breathing, which were originally present, did not in any way reflect a poor prognosis, and by the third day all aspects of lung function had improved, while by the end of a week they had returned to within normal limits.

Despite intensive care and therapy, 4 of the 53 infants died. Three were below 1.15 kg. in weight and developed apnoeic attacks, while one heavier infant stopped breathing and died before any form of resuscitation could be applied. This infant during the course of the disease demonstrated a persistently low PaO_2 which may have heralded the apnoea.

A review of the literature now indicated the importance of hypoxaemia as a prognostic sign in respiratory failure. Its presence, in the face of a high environmental oxygen concentration, outweighed the dangers of hypercapnoea and metabolic acidosis and subsequently formed the basis for assisted ventilation. The initial therapeutic régime was considered to have failed should an infant's PaO_2 fall to below 50 mm.Hg. or should the

infant develop a single apnoeic spell.

Thus the remaining 15 of the 53 infants received intermittent positive-pressure respiration, 11 because of apnoea and 4 because of a persistently low PaO_2. These babies were intubated through the mouth, using a plastic endotracheal tube, and were ventilated by a Bird Mark 8 respirator. The duration of intubation lasted from 1 to 42 days and no serious complications could be attributed to the indwelling endotracheal tubes which were considered to have played an important part in the successful management of these infants.

All features of respiratory failure, namely hypoxaemia, hyperapnoea and metabolic acidosis, were rapidly corrected by IPPR. This therapy could achieve normal alveolar ventilation in the presence of severe ventilation - perfusion imbalance, but it necessitated a 50% increase in the minute volume. This in turn depended on an increase in the tidal volume which could only be produced by high pump pressures (mean 35 cm.H_2O) and on a high rate of breathing (mean 54 pump cycles/min.).

Passive ventilation was not as effective as augmented breathing, probably due to its adverse effects on the cardiovascular system which resulted in a precipitous drop in PaO_2. Intermittent positive-pressure respiration had been used, on the consideration that it acted purely as a ventilatory aid which could not improve the underlying disease process, and that its dangers to the infant were outweighed by those of hypoxaemia. Two complications could be directly attributed to this form of therapy: a tension pneumothorax developed in 2 infants (one died), while superimposed bronchopneumonia occurred in a further 2 infants who later died. Thus 12 of the 15 infants were successfully weaned off respirator therapy.

Three of these subsequently died of gastroenteritis, and postmortem studies revealed normal lungs in two, while the third infant had evidence of chronic lung disease with areas of emphysema, collapse and fibrosis. These changes could not be attributed solely to IPPR and were considered to have been caused by a combination of severe underlying disease and therapy.

The 9 surviving infants have been examined at a follow-up clinic and appear to be normal in all respects.

It has been concluded that artificial ventilation plays an important but strictly limited rôle in the treatment of hyaline membrane disease. When used for specific features of respiratory failure and in association with routine early therapy, it led to the survival of 87% of all affected infants.

Up to this point, the summary has dealt with 53 of the 58 infants who were treated in an intensive care unit, and will now consider the remaining 5 babies. These had suffered repeated and prolonged bouts of anoxia since birth and were apnoeic at the time of admission. Nevertheless they improved dramatically on intermittent positive-pressure respiration and could not be distinguished in any way from infants who had received assisted ventilation because of a short spell of hypoxaemia. Their further course, however, was distinctly different, as on the second or third day all developed sudden shock, with the features of acute blood loss. They became pale and cyanosed, their haemoglobin level dropped and they developed severe metabolic acidosis. All died despite adequate ventilation, and at autopsy were found to have massive intracranial haemorrhage. A similar course and outcome were observed in 4 more infants who had suffered

repeated bouts of apnoea and who were not treated in the unit. It has thus been concluded that anoxia is the direct cause of intracranial haemorrhage in hyaline membrane disease and the complication occurs as a catastrophic bleed if an infant is kept alive sufficiently long.

This study has indicated the importance of maintaining arterial oxygen tension within normal limits if intact survival of distressed infants is to be achieved.

A recommendation is made for the use of a simple and safe means of continuously monitoring arterial oxygen tension, as present methods are strictly limited in their application. It may be of value to reconsider the introduction of a sensitive oximeter which could be adapted to fit on the lip of an infant and continuously record the concentration of oxygen in arterial blood.

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APPENDIX

Statistical Methods

Tables I - XX

Figures I and II

STATISTICAL METHODS

The arithmetic mean (mean) and the mean quadrantic deviation (standard deviation) were determined on all collective samples.

The significance of the difference of two means was calculated by dividing the difference of the means $(x - \bar{x})$ by the standard deviation of the difference of the means. In all cases the standard deviation of the difference of the means was calculated for small samples.

Confidence limits were expressed at the 95% level and determined for small samples as the mean ($\bar{x}$) $\pm$ significance (t) X standard error $\frac{\hat{\sigma}}{\sqrt{n}}$

The Chi-square test (x^2 distribution) was used to determine the significance of the difference in oxygen tensions before and after intubation and during crying, in the same infants.

TABLES I - XX

FIGURES I, II.

TABLE I

LUNG FUNCTION STUDIES ON 24 NORMAL PREMATURE INFANTS

No.	Age days	Wt. kg.	f /min.	PTP cm.H_2O	VT ml.	$\dot{V}$ ml./min.	Cl ml./cm.H_2O	Work of breathing gm. cm./min.	Peak Insp. flow ml./sec.	Peak Expir. flow ml/sec.	pH	$PaCO_2$ mm.Hg.	$PACO_2$ mm.Hg	Base Excess mEq./L	$PECO_2$ mm.Hg.	$\dot{V}A$ ml./min.	VD ml.	VD/VT
1	2	2.21	50	3.2	13.0	600	4.3	1152	52	57	7.36	34		-5.0				
2	21	2.01	48	7.2	15.5	724	2.3	3127	40	32	7.42	33		-2.0				
3	7	2.06	53	5.6	11.4	498	2.2	1673	32	25	7.33	42		-3.3				
4	15	2.49	51	6.0	15.1	765	2.5	2754	40	44	7.34	41		-3.0				
5	14	1.87	49	3.5	8.4	411	2.3	863	24	24	7.28	38		-8.0				
6	1	2.15	64	2.4	9.6	614	4.5	884	32	20	7.36	33	31	-6.0				
7	10	2.09	57	2.6	18.1	800	6.9	1248	40	48	7.25	43		-8.0				
8	11	2.52	48	4.5	12.3	576	3.0	1555	32	27	7.29	37	35	-8.0				
9	1	2.41	34		13.4	455			32	8	7.33	38	35	-5.0				
10	16	2.09	62	3.8	17.6	1054	4.9	2403	24	16	7.35	45	39	-1.0				
11	1	2.12	59	3.0	15.1	885	5.0	1593	24	20	7.37	35	32	-4.0				
12	16	2.26	54	3.8	12.6	584	5.9	1331	40	44	7.35	38	37	-4.0	18.5	150	4.0	.25
13	2	1.95	42		21.0	768			44	36	7.23	40		-9.1	16.9	307	5.5	.27
14	1	1.98	49		10.4	644			25	22	7.29	46		-4.1	15.2	214	4.2	.40
15	15	2.06	50	6.0	14.2	672	4.3	2419	36	44	7.33	34		-7.0	14.1	275	3.2	.23
16	20	1.94	50	4.0	17.6	873	4.6	2095	56	48	7.24	33		-11.0	17.7	471	4.2	.24
17	3	1.87	52	4.8	17.4	648	3.7	1866	36	40	7.32	33		-7.1	15.8	311	3.3	.21
18	7	2.46	65	6.0	14.2	756	3.0	2721	48	40	7.37	37		-3.5	19.7	437	3.4	.26
19	5	1.87	47	3.6	10.1	420	3.3	907	52	32	7.28	40	40	-6.5	20.3	212	2.4	.24
20	17	2.32	60		18.4	793			72	48	7.33	36		-6.2	17.2	330	4.0	.21
21	1	2.04	34	2.6	12.6	409	5.0	638	28	16	7.39	35		-3.0	19.3	202	2.9	.23
22	6	1.70	56	3.8	10.9	452	3.2	1030	32	28	7.38	27		-7.8	16.1	266	1.1	.12
23	3	1.92	50	5.6	15.8	591	5.7	1985	28	32	7.20	37		-12.5	15.8	248	5.1	.30
24	19	1.98	47	5.6	14.2	665	3.3	2234	40	32	7.40	42		0	14.3	232	7.0	.40

TABLE II

LUNG FUNCTION STUDIES ON 33 NORMAL FULL-TERM INFANTS

No.	Age	Wt.	f	PTP	VT	$\dot{V}$	Cl	Work of Breathing	Peak Insp. flow	Peak Expir. flow	pH	$PaCO_2$	$PACO_2$	Base Excess	$PECO_2$	$\dot{V}A$	VD	VD/VT
	Days	kg.	per Min.	cm. H_2O	ml.	ml/ min.	ml/ cmH_2O	gm./ cm/min.	ml./ sec.	ml/ sec.		mm.Hg.	mm.Hg	mEq/L.	mm.Hg.	ml/ min.	ml.	
1	3	3.00	56	2.8	18.1	992	7.2	1666	44	52	7.29	39	37	-7.5				
2	5	3.45	45	3.6	14.7	641	4.6	2465	36	44	7.26	37		-9.5				
3	5	2.78	42	3.8	17.6	752	6.8	1710	32	48	7.28	42		-7.0				
4	3	2.69	47	3.8	16.8	750	4.5	1714	44	32	7.28	39	36	-4.0				
5	4	4.28	50	1.7	13.4	605	8.8	616	32	32	7.35	36	33	-5.0				
6	5	2.72	50	8.8	23.4	977	3.2	5158	30	49	7.37	47	47	-1.0				
7	5 hrs	2.89	52	5.4	20.1	994	3.8	3220	56	48	7.42	30		-4.5				
8	6 hrs	3.06	40	3.3	12.1	492	4.5		44	68	7.35	40		-3.5				
9	5	2.58	47	4.0	17.6	1241			48	52	7.34	35	32	-3.0	11.9	459	5.0	.29
10	7 hrs	3.55	28	4.0	23.5	722			48	48	7.32	41	38	-4.9	20.8	379	5.2	.23
11	2	2.89	48	2.1	17.6	1004	8.0	1264	44	36	7.34	35	32	-5.1	14.1	451	6.5	.37
12	2	2.92	28	2.6	17.5	506	6.6	789	28	14	7.36	32	30	-6.5	17.3	307	4.0	.23
13	1	3.55	50		23.5	700			56	80	7.39	33		-4.2	11.5	245	4.0	.20
14	1	3.14	30	6.0	17.7	504	3.4	1814	40	32	7.39	35	32	-3.0	24.6	352	3.0	.17
15	3 hrs	3.25	46		17.6	665			60	40	7.39	32	32	-4.3	15.2	312	5.6	.31
16	1	3.32	50		16.8	708			36	28	7.35	39		-4.0	18.9	339	5.3	.30
17	1	3.34	31	7.2	24.6	485	4.1	2095	32	40	7.32	36		-5.7	19.5	261	5.2	.22
18	1	4.25	37		23.5	825			60	44	7.33	30		-9.5	18.6	511	6.4	.27
19	1	2.78	49		14.2	945			40	32	7.31	44		-4.0	12.6	268	7.0	.46

continued/

TABLE II (continued)

LUNG FUNCTION STUDIES ON 33 NORMAL FULL-TERM INFANTS

No.	Age	Wt.	f	PTP	VT	$\dot{V}$	Cl	Work of Breathing	Peak Insp. flow	Peak Expir. flow	pH	$PaCO_2$	$PACO_2$	Base Excess	$PECO_2$	$\dot{V}A$	VD	VD/VT
	Days	kg.	per min	cm. H_2O	ml.	ml/ min.	ml/ cmH_2O	gm. cm/min	ml./ sec.	ml./ sec.		mm.Hg.	mm.Hg.	mEq/L.	mm.Hg.	ml./ min.	ml.	
20	1	3.50	38		20.1	755			64	36	7.30	43			16.8	316	6.0	.30
21	1	2.55	40		21.0	628			44	36	7.32	32		-4.0	16.6	376	4.7	.30
22	1	3.30	38		19.3	935			40	28	7.41	33	31	-3.0	14.9	420	8.0	.40
23	13	2.94	43	6.0	20.0	907	4.5	3265	24	40	7.40	32		-4.2	17.6	499	6.7	.30
24	1	3.06	37	5.9	19.3	700	3.8	2478	40	28	7.39	37		-1.5	17.8	335	6.8	.30
25	2	3.06	49	4.7	23.0	1165	5.1	3285	32	36	7.36	34	31	-5.6	18.9	605	8.0	.34
26	6 hrs.	3.06	39	6.2	12.1	471			44	68	7.35	40		-3.5				
27	1	3.17	34	5.8	16.8	732		2547	36	24	7.40	35	33	-2.1	20.3	424	7.0	.40
28	6 hrs.	3.46	33	6.4	18.8	500	4.6	1920	40	32	7.34	36		-6.0	19.2	265	5.0	.27
29	5 hrs.	3.30	59	6.0	15.9	586	4.2	2109	44	68	7.30	36		-7.5	13.1	211	4.3	.29
30	1	4.20	35	5.5	26.8	882	6.7	2910	80	60	7.40	28		-6.0	21.1	661	4.3	.16
31	6 hrs.	3.70	30	4.4	18.4	554	4.4	1462	36	16	7.32	36	36	-6.7	22.0	337	5.2	.28
32	1	3.57	28	5.6	16.8	452	4.0	1518	36	24	7.32	30	30	-10.0	16.8	253	5.1	.30
33	1	2.83	33	6.4	16.8	655	3.1	2515	44	24	7.44	32		-1.0	22.2	440	4.5	.25

TABLE III

DATA ON 22 GRUNTING INFANTS WITH HYALINE MEMBRANE DISEASE

Case No.	Weight	Gestation	Age	VT	Transpulmonary pressure cm.H_2O		Peak Insp. flow	Mid-Expir. flow	Peak end-expir. flow	Insp. time	Expir. time	pH	PCO_2	Base Excess
	kg.	weeks	hours	ml.	+	-	ml/sec	ml/sec	ml/sec	sec.	sec.		mm.Hg.	mEq/L
1	2.35	35	13	12.4	2.8	10.0	56	8	40	.32	1.5	7.29	57	-1.0
2	1.93	37	4	8.4	3.2	8.0	40	4	28	.30	0.8	7.27	45	-6.0
3	1.98	36	4	10.2	3.0	10.0	34	2	33	.30	1.0	7.07	64	-11.0
4	2.90	36	6	13.9	2.4	13.2	72	4	60	.32	0.9	7.22	58	-4.8
5	2.80	37	5	10.5	1.0	7.0	60	4	40	.32	0.8	7.15	46	-11.0
6	2.06	34	9	8.4	2.0	12.5	60	4	60	.52	1.1	7.21	46	-9.5
7	1.61	35	4	6.7	2.0	8.0	40	4	32	.24	1.2	7.26	59	-3.0
8	1.58	35	5	6.0	3.0	7.0	36	8	24	.40	0.6	7.23	50	-6.5
9	3.06	36	4	9.7	1.5	12.5	68	2	24	.36	1.2	7.29	52	-4.0
10	1.92	37	7	10.9	2.2	8.6	56	8	60	.20	0.6	7.23	44	-9.5
11	1.49	33	8	7.4	3.2	14.0	64	8	48	.20	0.6	7.27	85	-2.0
12	2.72	38	12	8.8	8.0	22.0	56	2	68	.24	0.6	7.33	43	-3.0
13	2.83	38	6	8.0	4.0	15.0	68	4	80	.48	0.6	7.20	68	-8.0
14	1.67	35	4	8.0	4.4	8.8	60	2	52	.28	1.3	7.27	52	-8.0
15	3.34	38	6	11.6	6.0	21.0	48	4	60	.32	0.6	7.25	42	-8.0
16	1.87	34	16	9.1	4.0	10.0	48	1	40	.36	1.5	7.40	40	0
17	2.63	38	15	8.8	8.0	23.0	44	4	60	.36	0.9	7.31	55	-13.0
18	1.81	36	5	7.5	3.2	11.6	40	4	88	.24	1.2	7.31	53	-2.0
19	1.41	32	10	8.4	2.4	13.0	40	4	25	.28	0.7	7.21	58	-7.0
20	1.87	34	16	7.1	3.2	12.8	48	2	40	.24	0.9	7.23	54	-7.1
21	2.72	38	13	9.2	2.0	7.4	56	2	52	.32	0.9	7.23	49	-5.5
22	1.82	36	6	10.0	4.0	10.8	48	4	56	.32	1.1	7.20	75	-7.5

TABLE IV

LUNG FUNCTIONS ON 11 SPONTANEOUSLY BREATHING INFANTS DURING THE COURSE OF THE DISEASE

DAY 1

No.	Wt. kg.	Age hrs.	f /min.	VT ml.	Cl ml/cmH_2O	$\dot{V}$ ml/min.	pH	Base Excess mEq/L.	$PaCO_2$ mm.Hg.	PaO_2 mm.Hg.	$PECO_2$ mm.Hg.	$\dot{V}A$ ml/min.	VD ml.	VD/VT
1	2.63	15	78	8.8	0.5	585	7.31	-13	55	55	8.9	93	4.3	0.55
2	2.83	6	119	8.0	0.6	862	7.20	- 8.0	68	67	11.9	146	5.2	0.62
3	1.67	4	70	8.0	1.0	462	7.27	- 8.0	52	71	12.9	115	3.0	0.41
4	3.34	6	90	11.6	0.6	716	7.25	- 8.0	42	76	9.3	158	4.2	0.31
5	1.61	4	65	6.7	1.4	476	7.26	- 3.0	59	73	10.3	80	4.0	0.60
6	1.58	5	63	6.0	1.4	382	7.23	- 6.5	50	77	8.0	61	3.1	0.50
7	2.72	12	105	8.8	0.7	831	7.33	- 3.0	43	105	10.8	157	4.4	0.50
8	1.81	5	69	7.5	1.0	413	7.31	- 2.1	53	84	8.4	66	3.5	0.40
9	2.35	13	50	12.4	1.2	588	7.29	- 1.1	57	78	11.8	117	9.0	0.70
10	1.87	16	59	7.0	0.7	405	7.40	0	40	50	10.9	108	3.2	0.43
11	2.66	14	106	5.8	0.9	522	7.38	- 7.0	46	88	7.3	83	2.1	0.36
	DAY 3													
1			59	10.1	1.5	554	7.35	- 6.0	38	78	16.1	232	3.4	0.33
2			69	12.0	2.3	748	7.24	- 3.0	40	70	15.8	301	4.5	0.37
3			70	11.6	2.3	710	7.30	- 5.0	42	80	15.0	236	4.0	0.32
4			53	11.7	2.4	575	7.28	- 7.0	41	78	15.2	212	4.8	0.40
5			66	7.8	1.3	400	7.35	- 1.0	43	70	13.2	140	2.1	0.30
6			62	8.8	1.5	420	7.38	- 1.0	40	145	10.3	109	3.0	0.37
7			80	9.6	1.1	700	7.33	- 2.0	45	120	10.3	159	4.0	0.41
8			52	9.2	2.1	416	7.40	- 3.0	34	100	13.6	166	2.2	0.24
9			49	13.4	4.5	672	7.32	- 5.0	41	78	15.5	256	4.0	0.30
10			59	7.0	1.1	405	7.42	0	40	55	10.9	108	3.0	0.43
11			76	8.2	1.7	650	7.35	- 1.0	47	77	10.8	149	4.3	0.52

For Day 7, see next page

DAY 7

TABLE IV (continued)

No.	f /min.	VT ml.	Cl ml/cmH_2O	$\dot{V}$ ml/min.	pH	Base Excess mEq/L.	$PaCO_2$ mm.Hg.	PaO_2 mm.Hg.	$PECO_2$ mm.Hg.	$\dot{V}A$ ml/min.	VD ml.	VD/VT
1	44	15.4	3.7	601	7.32	- 6.0	39	78	16.4	252	5.1	0.33
5	52	10.1	3.3	571	7.26	- 6.0	42	80	13.5	188	5.0	0.45
6	51	10.5	2.1	599	7.38	+ 1.0	39	70	18.1	275	3.3	0.31
7	48	13.4	2.2	623	7.42	- 1.0	35	95	16.8	300	3.0	0.26
9	40	18.4	4.6	720	7.35	- 5.0	36	80	17.8	349	6.8	0.36
10	52	14.2	3.1	727	7.35	- 4.0	34	92	15.8	317	3.3	0.24
11	49	12.1	4.2	581	7.30	- 7.0	37	-	18.9	296	3.8	0.31

TABLE V

LUNG FUNCTION ON SPONTANEOUSLY BREATHING INFANTS BEFORE IPPR

No.	Gestation	Wt.	f	PTP	VT	$\dot{V}$	Cl	$\dot{V}I$	$\dot{V}E$	pH	$PaCO_2$	PaO_2	Base Excess	$\dot{V}A$	VD	VD/VT
	weeks	kg.	/min.	cmH_2O	ml.	ml/min.	ml/cmH_2O	ml/sec.	ml/sec.		mm.Hg.	mm.Hg.	mEq/L.	ml/min.	ml.	
1	36	2.04	62	$\frac{-11}{+2}$	9.0	621	1.1	37	48	7.09	64	14	-11			
2	38	2.15	78	- 4	0.2	716	1.9	32	48	7.24	52	47	- 2			
3	37	2.26	68	-15	7.9	524	0.5	60	60	7.20	84	32	- 2			
4	32	1.53	102	$\frac{-4}{+3}$	8.4	799	2.1	40	25	7.32	42	53	-4.5			
13	38	2.72	90	$\frac{-8}{+2}$	9.6	831	1.3	56	52	7.20	75	36	-7.5	83	6.3	0.65
10	33	2.60	66	-2	6.3	410	1.1	44	44	7.20	68	42	-9			
14	37	2.26	64	$\frac{-11}{+4}$	9.2	502	0.8	48	56	7.21	80	48	-5	60	5.0	0.55
7	37	1.84	106	- 4	6.3	647	1.6	54	36	7.00	65	35	-20			
9	32	1.19	42	- 6	7.0	312	2.8	42	40	7.50	38	-	+ 6			

TABLE VI

EFFECTS OF INTERMITTENT POSITIVE PRESSURE ON LUNG FUNCTION: PUMP PRESSURE AND SPEED KEPT CONSTANT

No.	Gestation Wks.	Weight kg.	PTP $cm.H_2O$	VT ml.	$\dot{V}$ ml./min.	Cl $ml./cm.H_2O$	pH	Base Excess mEq/L	$PaCO_2$ mm.Hg.	PaO_2 mm.Hg.	$\dot{V}A$ ml./min.	VD ml.	VD/VT	$\dot{V}I$ ml./sec.	$\dot{V}E$ ml./sec.	Pump speed cycles/min.	Unsp./Exp. Time ratio
1	36	2.04	40	13.6	830	0.4	7.38	-1	39	80	203	5.1	0.40	72	60	60	1 : 1.1
2	36	2.15	30	17.6	1199	0.8	7.24	-1	41	60	120	18.0	0.81	48	48	60	1 : 1.2
3	37	2.26	38	20.2	961	0.9	7.27	-4	67		183	13.8	0.68	76	80	48	1 : 2.0
4	32	1.53	42	12.6	690	0.4	7.32	-7	36	87	396	3.2	0.27	32	44	54	1 : 1.5
5	38	2.18	44	18.4	1120	0.5	7.54	-1	18	72	840	3.6	0.21	36	40	62	1 : 1.6
6	35	1.98	42	18.0	1700	0.5	7.41	-6	27	111	272	18.0	0.88	48	48	70	1 : 1.1
7	37	1.84	16	16.8	874	1.0	7.27	-4	32		227	8.7	0.51	30	30	55	1 : 1.1
8	28	0.99	28	20.8	1017	0.8	7.25	-16	16	121	650	4.4	0.23	60	72	49	1 : 1.7
9	32	1.19	18	21.8	854	1.5	7.59	+4	17	250	461	6.3	0.28	60	64	42	1 : 1.8
10	33	2.60	46	26.0	1300	0.6	7.33	-5	54	55	143	18.0	0.69	96	72	53	1 : 1.2
11	32	1.64	52	21.8	1360	0.4	7.35	-10	30	45	151	19.0	0.87	56	90	56	1 : 1.2
12	33	1.70	24	34.0	1733	1.9	7.38	-11	20	117	814	12.0	0.35	44	40	46	1 : 1.8

TABLE VII

EFFECTS OF INTERMITTENT POSITIVE PRESSURE ON LUNG FUNCTION:

PUMP PRESSURE REDUCED. SPEED UNALTERED

No.	PTP $cm.H_2O$	VT ml.	$\dot{V}$ ml./min.	Cl $ml/cm.H_2O$	pH	Base Excess mEq/L.	$PaCO_2$ mm.Hg.	PaO_2 mm.Hg.	$\dot{V}A$ ml./min.	VD ml.	VD/VT	Pump speed cycles/min.
1	28	9.6	499	0.4	7.30	- 2	48	41	74	6.0	0.60	58
2	20	13.2	891	0.7	7.40	+ 4	37	43	53	12.0	0.90	54
3	26	14.2	658	0.7	7.24	+ 5	97	-	85	10.0	0.73	47
4	28	10.4	680	0.4	7.36	- 5	43	54	50	8.0	0.89	54
5	28	11.7	755	0.5	7.38	0	44	59	98	8.6	0.72	64
6	26	12.0	886	0.5	7.36	- 6	33	84	186	8.0	0.66	70
8	17	6.2	323	0.4	7.23	-16	27	23	71	2.6	0.41	54
10	38	17.8	1295	0.5	7.47	+10	98	33	77	14.0	0.79	79
11	36	15.3	1165	0.5	7.36	-10	30	20	140	15.0	0.97	64
12	16	19.7	738	0.4	7.30	-12	24	62	-	-	-	46

TABLE VIII

EFFECTS OF INTERMITTENT POSITIVE PRESSURE ON LUNG FUNCTION:

PUMP SPEED DECREASED. PRESSURE UNALTERED

No.	PTP $cm.H_2O$	VT ml.	$\dot{V}$ ml./min.	Cl $ml/cm.H_2O$	pH	Base Excess mEq/L.	$PaCO_2$ mm.Hg.	PaO_2 mm.Hg.	$\dot{V}A$ ml./min.	VD ml.	VD/VT	Pump speed cycles/min.
1	42	12.4	440	0.5	7.36	-4	45	47	107	10	0.80	30
4	42	13.9	485	0.4	7.35	-3	41	60	43	11	0.90	34
3	38	15.4	462	0.6	7.22	-2	86	-	97	10	0.65	30
11	52	12.7	431	0.4	7.31	-9	32	29	147	8.6	0.70	33
5	44	14.1	501	0.5	7.38	-1	46	60	96	9.9	0.70	34

TABLE IX

COMPARISON OF $PaCO_2$ AND $PACO_2$ DURING PASSIVE VENTILATION

	$PaCO_2$ mm.Hg.	$PACO_2$ mm.Hg.
	39	20
	41	25
	18	8
	30	11
MEAN	32	16

$t = 2.461$

$p = < 0.05$

Significant difference between the two readings.

MEAN a - A gradient for PCO_2

= 16 mm.Hg.

TABLE X

STUDIES ON INFANTS WHO RECEIVED IPPR BECAUSE OF APNOEA AND WHO DID NOT DEVELOP INTRACRANIAL HAEMORRHAGE

Weight kg.	Gestation weeks	pH	$PaCO_2$ mm.Hg.	Base Excess mEq/L.	PaO_2 mm.Hg.	Haemoglobin gm.%	Temperature °C	Cl ml/cm.H_2O	PTP cm.H_2O
2.15	36	7.32	42	-4.5	135	17	36.1	0.7	32
1.98	36	7.33	33	-8.0	58	18	36.3	0.5	38
1.87	34	7.43	43	0	52	19	36.9	0.4	40
2.26	36	7.32	35	-8.0	77		36.9	0.6	42
2.26	37	7.27	64	-4.1	83	17	37.0	0.4	48
2.18	37	7.38	44	0	72		37.1	0.5	29
1.98	35	7.34	33	-6.2		17.5	36.9	0.5	33
1.58	32	7.39	32	-3.6	85	16.5	36.4	0.6	34
2.66	36	7.40	42	+2.0	85	18.9	37.0	0.3	32
2.49	37	7.47	33	+2.0	57	13.1	37.1	0.7	33
2.69	37	7.41	32	-3.5	122	17.7	36.8	0.5	31
2.72	38	7.36	44	-4.1	75		36.8	0.5	29

TABLE XI

CALIBRATION OF FLEISCH 00 PNEUMOTACHOGRAPH AND PM 197 TRANSDUCER

Rotameter Reading cm.	$\dot{V}$ L/min.	Pen Deflection cm.
0.90	1.7	7.2
1.65	2.0	8.4
2.30	2.3	9.2
3.18	2.6	10.3
4.10	3.1	12.0
5.30	3.6	14.0
6.60	4.2	16.4
7.90	4.8	18.9
9.18	5.3	21.4
10.18	5.7	23.2
11.15	6.3	25.6
11.91	6.7	27.2
9.98	5.7	23.0
8.20	4.8	19.1
6.00	3.8	15.0
3.90	2.9	11.2
1.84	2.1	8.0
0.00	0.0	0.0

TABLE XII

CALIBRATION OF TRANSDUCERS

PM 5		PM 6	
Pressure cm.H_2O	Pen Deflection mm.	Pressure cm.H_2O	Pen Deflection mm.
2.0	2.0	0.3	0.4
3.8	3.6	2.4	5.0
7.0	6.8	4.0	8.5
9.5	9.0	5.2	11.5
12.5	12.5	6.2	13.0
15.0	14.8	7.6	16.5
17.3	17.0	8.6	20.0
19.7	19.2	11.0	25.0
23.0	22.6		
26.0	25.6		
32.0	30.0		
41.0	41.0		

TABLE XIII

STATIC RESPONSE TIME OF BALLOON SYSTEM

(seconds)

	0.010
	0.008
	0.007
	0.007
	0.009
	0.008
	0.009
	0.009
	0.009
	0.008
MEAN :	0.008

TABLE XIV

RESPONSE TIME OF BECKMAN CO_2 ANALYSER TO A SAMPLING RATE OF 100 ML/MIN

90% DEFLECTION
Seconds
0.10
0.15
0.12
0.13
0.13
0.13
0.14
0.13

TABLE XV

CALIBRATION GRAPH FOR BECKMAN CO_2 ANALYSER

Pen Deflection mm.	PCO_2 mm.Hg.
2.5	2.6
5.0	5.1
7.0	8.0
9.5	13.1
11.0	16.0
14.0	23.2
16.0	27.8
17.5	31.6
20.0	38.3
22.0	44.0
23.4	48.0
26.1	56.5
28.0	62.0

TABLE XVI

END TIDAL CO_2 TENSION SAMPLED AT NOSE AND PNEUMOTACHOGRAPH

Weight kg.	Nasal $PACO_2$ mm.Hg.	Pneumotachograph $PACO_2$ mm.Hg.
2.01	33.1	33.1
2.12	35.0	35.3
3.55	38.8	38.8
2.69	38.8	39.1
3.17	34.0	35.1
3.70	36.0	36.0
2.32	41.1	40.8
2.89	32.6	32.7
2.72	47.4	47.4

t 0.2402

$p > 0.80$

TABLE XVII

RESISTANCE OF ONE WAY BREATHING VALVE

Inspiratory portion		Expiratory portion	
Flow ml/sec.	Pressure cm.H_2O	Flow ml/sec.	Pressure cm.H_2O
8	0.02	16	0.10
14	0.07	32	0.28
18	0.09	44	0.40
24	0.10	52	0.50
32	0.15	68	0.63
36	0.20	84	0.80
44	0.25	92	0.90
52	0.30	100	0.99
64	0.45		
76	0.60		
88	0.70		
98	0.85		

TABLE XVIII

RESISTANCE DOUGLAS BAG AND TUBING

Flow ml/sec.	Pressure cm. H_2O
20	0.21
32	0.42
36	0.50
44	0.61
52	0.70
56	0.80
60	0.90
68	1.10
76	1.15
80	1.25
88	1.40
92	1.48
96	1.49
100	1.50

TABLE XIX

CALIBRATION OF YS1 TELETHERMOMETER AGAINST MERCURY THERMOMETER

YS1 Temperature °C	Mercury Temperature °C
41.9	42.2
35.7	35.8
32.2	32.3
29.1	29.2
26.8	26.7
23.6	23.3
20.1	20.4

t 0282

$p > 0.90$

TABLE XX

NORMAL INFANTS:

COMPARISON OF CO_2 TENSION OF ARTERIAL BLOOD WITH CO_2 TENSION DERIVED FROM EXPIRATORY CO_2 PEAKS

	$PaCO_2$	PCO_2 (Peak)
	27	20
	33	19
	33	26
	34	25
	38	34
	38	33
	45	34
	35	19
	46	24
	34	15
	33	15
	42	30
	31	13
	38	21
	39	30
	43	35
	37	34
	40	34
	39	18
Mean	37.8	25.2

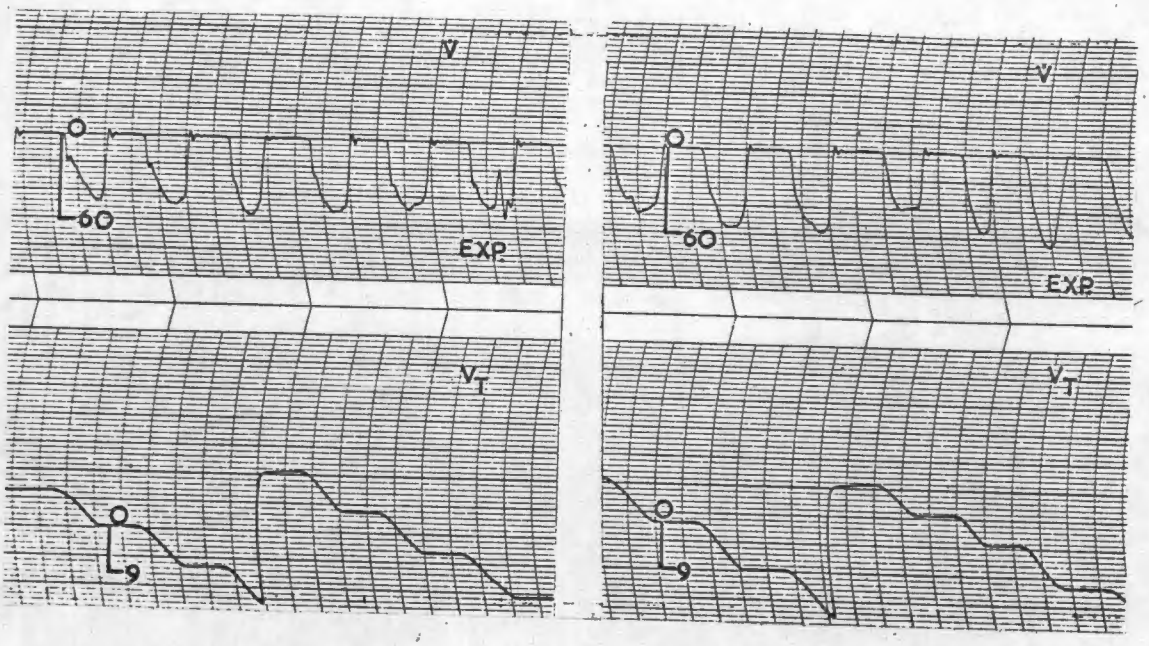
t 19.36

p $<$ 0.001

Highly significant difference

FIG. I

Comparison of one way breathing valves



a. Valve used in present study b. Aimer ball-valve

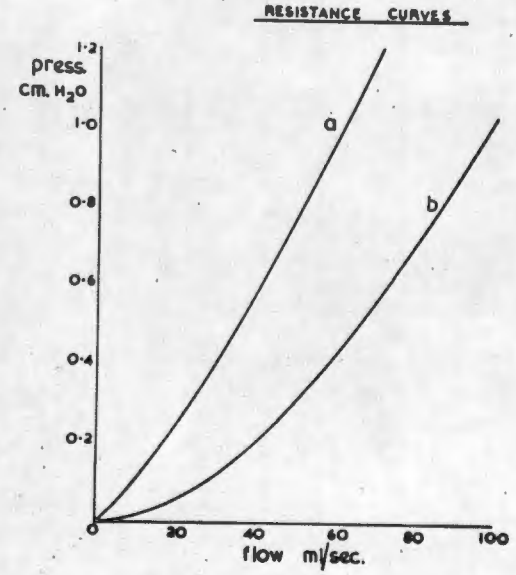
$\dot{V}$: expiratory flow rate ml./sec.

VT : ml.

The graph illustrates that no leaks occur during inspiration. If they did, flow would be recorded above zero line and a slope would occur on each step of tidal volume.

FIG. II

Pressure-flow curves



a. Endotracheal tube.

b. Douglas Bag and fittings