Papers and Originals**STUDIES ON NEONATAL TETANUS, AND ON PULMONARY COMPLIANCE OF THE TOTALLY RELAXED INFANT**

BY

P. M. SMYTHE, M.B., Ch.B., M.R.C.P.*Department of Child Health, University of Capetown, and Red Cross War Memorial Children's Hospital, Rondebosch*

The treatment of tetanus neonatorum with total relaxation and intermittent positive-pressure respiration (I.P.P.R.) was described by Smythe and Bull (1959). More recently Wright *et al.* (1961) have shown how effective this form of therapy can be. In the present paper a further series of cases is reported. Some investigations are recounted as they seem to prove, what previously was only suspected, that the treatment of severe tetanus is basically a respiratory problem, and that there is little justification for assuming that there is a severe form of the disease in which death is inevitable from overwhelming or irreversible toxæmia. Studies on pulmonary compliance are recorded as they explain many of the early difficulties in treatment, and may contribute something to the respiratory physiology of the totally relaxed infant while using the Radcliffe respirator (Russell and Schuster, 1953) for I.P.P.R.

Subsequent to the series reported in 1959, treatment of neonatal tetanus with relaxants and I.P.P.R. proved most disappointing. Many infants after progressing satisfactorily for 48 to 72 hours, or even longer, developed a tachycardia. At this stage cyanosis was not usually present; when it did occur it was easily controlled by giving oxygen. Gradually a state of circulatory collapse developed with a slow and weak pulse and intermittent attacks of cyanosis which were prolonged when the infant was disconnected from the respirator for even short periods for suctioning. Not infrequently infection intervened to cause death; but some infants, now deeply cyanosed, lingered on with dilated fixed pupils and anuria. In the end, only the electrocardiograph could indicate if the child was alive or dead.

E.C.G. changes appeared early, before cyanosis became marked, with peaking of the P waves, ST depression, and inversion of the T waves in the

ventricular leads. Occasionally tall T waves were seen. Clockwise rotation of the heart favouring right ventricular dilatation occurred in most cases. The final change, which generally heralded death, was the appearance of a bundle-branch block (Fig. 1). In a few cases temporary improvement in the E.C.G. followed the giving of noradrenaline or intravenous alkaline solutions. Two children recovered despite showing peaked P and inverted T waves.

Necropsy Studies

Necropsy material was available in 16 cases. Bronchopneumonia was the cause of death in four infants and lung abscess in two. Six infants were found to have varying degrees of pulmonary collapse. The right ventricle or auricle was dilated in four. The brain was macroscopically normal in all but two cases. One of these showed a layer of colliquative necrosis about 3 mm. wide in the subcortical zone; the other patient, who died after seven weeks, had gross porencephaly and cerebral atrophy.

Histological examination confirmed the naked-eye pulmonary findings and also revealed gross capillary congestion. In seven cases there was a vacuolated and granular appearance of the heart muscle which was especially marked in the fibres of the chordae tendineae. One heart also showed loss of muscle-fibre nuclei with necrosis of tissue (Fig. 2). In the brain there was severe degeneration or complete loss of neurones. This was most marked in the cerebral cortex (Fig. 3), less marked in the brain-stem nuclei and cerebellar cortex, and not evident in the spinal cord where this was included.

At the time, these clinical and pathological findings were interpreted as suggesting that, apart from the infants who died of infection, the primary cause of death was circulatory collapse and that the anoxic manifestations were secondary. Undue emphasis was given to the early appearance of E.C.G. changes before any cyanosis, also to the fact that in some cases the

FIG. 1.—Typical series of E.C.G. changes evolving over a period of 30 hours to a pattern of bundle-branch block.

FIG. 2.—Histological appearance of myocardium. Some muscle fibres have a vacuolated and granular appearance, others have undergone necrosis with loss of nuclei.

circulatory collapse occurred only after many days, which seemed to make underventilation unlikely. The collapse of the lung found at necropsy was thought to be due to post-mortem resorption of air.

FIG. 3.—Histological appearance of cerebral cortex, showing severe degeneration and complete loss of neurones.

Investigations were done on the following possible causes of circulatory collapse: tetanus intoxication of the brain-stem or myocardium; I.P.P.R. raising the mean intrathoracic pressure and impeding venous return to the heart; and inadequate ventilation of the lungs.

Estimation of Circulating Toxin

The transfer of tetanus to animals by inoculation of serum from both animal and human cases has been reported by Bolton and Fisch (1902) and by McClintock and Hutchings (1913). Francis (1924) showed experimentally that as much as 1,000 M.L.D. of toxin could be extracted from a focus of tetanus infection. It would be reasonable to suppose that toxin is continually spreading from the site of infection into the circulation, and that, even though it is rapidly taken up by the motor-nerve endings, some circulating toxin is still present at the time of onset of symptoms. Support for this concept comes from the fact that Brown *et al.* (1960) showed that antitetanic serum (A.T.S.) was of value in the treatment of tetanus. Presumably it acts by neutralizing unfixed toxin in the circulation. If this is so, a high concentration of toxin might be expected in neonates because of their small blood volumes and body weights. The demonstration of circulating toxin, and the correlation of the level of toxin with mortality, would give support to the concept of death from overwhelming intoxication.

Blood taken on admission from three infants who subsequently died of tetanus was examined for toxin at the department of bacteriology. No circulating toxin could be demonstrated by intracerebral or paravertebral intramuscular injection of serum into day-old suckling mice.

Effect of Intrathecal A.T.S.

Interest in the treatment of tetanus with intrathecal A.T.S. largely ceased with Cole and Spooner's (1935) comment that "the practice has gradually been abandoned and there has certainly been no indication that anything has been lost." Despite this, it seemed possible that intrathecal A.T.S. might help in preventing circulatory failure from brain-stem intoxication if death from central respiratory failure could be prevented by using I.P.P.R.

Five infants were given intrathecal A.T.S. in dosages ranging from 100 to 3,000 I.U. Three of them died.

At necropsy, bronchopneumonia was found in one and only atelectasis of the lungs in the others.

Effect of General Anaesthesia

Firor *et al.* (1940) found in experiments on dogs that some sedatives potentiated the effect of tetanus toxin. To exclude the possibility of general anaesthesia potentiating tetanus intoxication, infants were intubated after relaxation only with suxamethonium and manually insufflated for tracheotomy. There was no improvement in results. Six out of seven infants died.

Effect of I.P.P.R. on the Venous Return

Emphasis has been laid on the danger of a high positive inspiratory pressure transmitted to the thorax impeding venous return to the heart (Maloney *et al.*, 1953; Opie *et al.*, 1961). At the time, no respirator with a negative pressure expiratory phase was available. An alternative was to reduce to a minimum the inspiratory phase of the type "A" Radcliffe respirator. This was done by attaching a second arm to the rotating hub which released the latch supporting the bellows later in the cycle and shortened the inspiratory period.

When set so that no sooner was full inspiration attained than expiration began no difference was observed in the course of the disease.

The Dead Space

The dead space in the adapted Stott valve mechanism (Smythe and Bull, 1959) was not excessive, but there was no means of telling how efficient the valve was. The only alternative available was the Ruben valve, which was not being used for infants because of an excessive dead space of 9 ml. To correct this, a solid adaptor with a central channel of 5-mm. diameter was made which fitted into the ventilating port of the Ruben valve and reduced the dead space between the tip of the tracheotomy tube and the valve to 6 ml. (Fig. 4).

No change in the clinical picture followed the introduction of this valve system, but it proved so easy to handle and so reliable that now it is always used.

Estimations of the Efficiency of Ventilation

Attempts to measure the tidal volume of these infants while they were being artificially respired failed because both valve systems allowed an escape of air in excess of the volume respired. When attention was drawn to alveolar PCO_2 estimations as a means of estimating

FIG. 4.—Showing the way the Ruben valve was placed and supported, the metal adaptor to reduce the dead space (plastic models are now used), and the Hollinger tracheotomy tube, to which a metal T-piece has been soldered.

respiratory efficiency in neonates (Sykes, 1960a), the importance of underventilation immediately became apparent.

The following case was the turning-point in the study:

Baby P., aged 8 days, was admitted to hospital with tetanus on January 8, 1961. Early tracheotomy was followed by curarization and I.P.P.R. At an inspiratory pressure of 13 cm. H₂O and a rate of 37 cycles per minute the alveolar PCO₂ was 31 mm. Hg. At 10.30 a.m. on January 12 the infant appeared well, the alveolar PCO₂ being 38 mm. Hg. Because of a visit to another hospital, the infant was not seen again until 4.30 p.m., when she was found to be ashen grey and sweating, with dilated fixed pupils. The respiratory excursion of the chest was diminished. The systolic blood-pressure was 120 mm. Hg. The alveolar PCO₂ was 135 mm. Hg. In an attempt to correct what was then shown to be gross ventilatory insufficiency the inspiratory pressure of the respirator was raised to 19 cm. H₂O and frequent more-forceful inflations were made by hand. One hour later the pupils were small and reacted to light, the blood-pressure had fallen to 105 mm. Hg and the alveolar PCO₂ was 31 mm. Hg. By 10 p.m. the PCO₂ was 14 mm. Hg and the blood-pressure 70 mm. The inspiratory pressure was then lowered to 15 cm. H₂O. The subsequent course was uneventful and the child recovered completely.

In all subsequent cases the inspiratory pressure was controlled by estimating the alveolar PCO₂ and since then attention was centred on factors likely to affect respiratory function.

Results

With the above method of controlling ventilatory pressures, 23 out of the next 25 consecutive patients with tetanus neonatorum survived the 10 to 21-day period of total relaxation and I.P.P.R. One of the infants who died might have been excluded from the series because respiratory arrest necessitating manual artificial respiration had occurred before treatment was started. The other died from the effects of a tracheal burn due to the humidifier boiling when the thermostat failed.

Three other deaths occurred after stopping I.P.P.R. while awaiting successful removal of the tracheotomy tube. Two infants died of a lung abscess. The third died suddenly and unexpectedly the first night after stopping I.P.P.R., almost certainly from respiratory arrest or the delayed release of curare. The overall mortality was 20%, and, except for the one patient who was *in extremis* before treatment was started, no deaths could be attributed to the effects of tetanus intoxication.

It still remained to explain why the early cases had done so badly. Clearly the inspiratory pressures of 10–13 cm. were too low. Nevertheless, a few infants had recovered at these pressures, many had progressed satisfactorily for a number of days before deteriorating, and others had failed to respond when inspiratory pressures were raised to much higher levels.

Pulmonary Compliance

The method of measuring static pulmonary compliance was as follows: a 50-ml. syringe was connected via a three-way tap to the upper opening of the tracheotomy tube; the respirator was then cut out during expiration by clamping the rubber tubing between the T-piece leading to the manometer and the Ruben valve; the lungs were allowed to deflate completely through the three-way tap, which was directed to the atmosphere; the tap was then turned to bring the syringe and lungs into communication; 10 ml. of air was injected and the pressure read on the manometer.

An ascending series of pressures was obtained by increasing the volume of air injected, on each occasion, by 5 ml. Readings were taken only when the infants were completely relaxed and when there was no leak past the tracheotomy tube.

Fig. 5 shows the measurements of static pulmonary compliance of different infants. The average compliance of totally relaxed infants over 5 lb. (2.27 kg.) was 2.5

FIG. 5.—Static lung compliance of 11 totally relaxed infants. The mean compliance was 2.5 ml./cm. water intratracheal pressure. The broken line represents lung compliance of one premature infant. Each of the other lines represents the average of 10 measurements made on full-term infants.

ml./cm. H₂O intratracheal pressure. The extremes were 4 and 1.7 ml./cm. H₂O. Compliance was less in the very small infants. One premature infant weighing 3 lb. 11 oz. (1.67 kg.) had a compliance of 1.5 ml./cm. H₂O.

Pulmonary compliance could vary in the same infant under different circumstances. The most important factor was the inspiratory pressure at which the infant was being ventilated. Fig. 6 shows how the compliance was reduced each time the inspiratory pressure was dropped by 2 cm. H₂O at hourly intervals. At the same time there was a rise in the alveolar PCO₂. The compliance was also found to fall with continued I.P.P.R. This was most apparent during the first few days, and called for an increase from initial inspiratory pressures of 11–15 cm. H₂O to levels of 15–18 cm. One infant, by the seventh day, required a pressure of 30 cm. H₂O before normal alveolar PCO₂ levels were maintained. Not all infants showed this fall in compliance. Three of them who were started at a pressure of 15 cm., were adequately ventilated at this pressure for the duration

FIG. 6.—Static lung compliance of three infants, measured after they had been ventilated for an hour at different inspiratory pressures. Compliance was reduced when the inspiratory pressure was lowered.

of curarization. Changes in the rate of respiration between 30 and 48 cycles per minute, after three hours, had no effect on compliance; nor did changes of the infant's posture from 15 degrees head up to 15 degrees head down.

Because of the factors affecting compliance it is necessary to add that the levels shown in Fig. 5 are the means of readings taken over 10 to 17 days, at times when the infants were fully relaxed, with normal blood-pressures and alveolar PCO_2 , and showed no clinical evidence of pulmonary collapse.

Changes in pulmonary compliance can explain the inconsistencies of the early results. The infants with a good compliance were the ones who recovered, while those with poor compliance died. Those who survived a number of days and then deteriorated must have been the infants in whom the compliance was initially good but in whom it fell with prolonged I.P.P.R. It only remained to explain why some infants failed to respond even when inspiratory pressures were subsequently raised to about 25 cm. H_2O . The reason for this was almost certainly the failure to clear the bronchi completely of obstructing secretions and to re-expand collapsed lung. Progressive obstruction of smaller bronchi by secretions, predisposing to collapse of the alveoli, was probably an important factor in causing a rapid decrease in lung compliance. In the case described above, after four days of effective ventilation at an inspiratory pressure of 13 cm. H_2O compliance suddenly dropped from 2 to less than 1 ml./cm. H_2O in less than six hours.

Maintenance of a Clear Airway

Signs suggesting airway obstruction were: a rise in the pulse rate, cyanosis, diminished movement and air entry of the chest, and a raised alveolar PCO_2 . Obstruction of the smaller bronchi could be located by impaired air-entry over a limited area of the chest. Radiographs were rarely taken unless for clarification of the diagnosis.

Obstruction could occur at the tracheotomy tube. The problems associated with tracheotomy in the neonate are still being investigated, but it can be stressed that the tube had to be kept clear of secretions, and that it had to lie in alignment with the lumen to avoid kinking and ulceration of the trachea. The method of overinflation and compression of the chest (Sykes, 1960b; Smythe and Bull, 1961) proved very effective in bringing secretions up from the smaller bronchi into the main bronchi and trachea, from where they could be sucked out by catheter. At times this procedure had to be prolonged before all secretions were cleared from the air passages. The presence of any residual obstruction in the bronchi could be recognized by rhonchi being felt or heard on compression of the chest. Care had to be taken that compression was not overvigorous, as ribs fractured quite easily.

Occasionally, complete obstruction and collapse of the lung did not respond to this therapy. The technique developed for these cases was to examine the trachea, using an auriscope (Fig. 7). In the curarized infant the tracheotomy tube was removed, the auriscope inserted through the tracheotomy opening into the trachea, and ventilation maintained by intermittently inserting into the speculum a tight-fitting wide-bore glass tube, capped with a piece of rubber tubing, through which oxygen was blown under pressure. Adequate ventilation was

assessed by observing the movement of the chest. Through the auriscope the trachea and orifices of the main bronchi could be seen and obstructions to the bronchi cleared with a metal sucker. Collapsed lobes of the lung were invariably re-expanded by this method.

FIG. 7.—Method of aspirating trachea and main bronchi, using an auriscope.

Treatment

The routine treatment of tetanus neonatorum with A.T.S., antibiotics, total relaxation, and I.P.P.R. has been covered by Smythe and Bull (1959), Sykes (1960b), and Wright *et al.* (1961). Only a few points require comment. The manner of placing and support of the Ruben valve is shown in Fig. 4. Care had to be taken that water or condensation did not collect in any sags in the corrugated tubing, as this stopped the valve working. Dependent sections of tubing were lifted every half-hour to drain water back into the humidifier. Occasionally the valve stuck in the inspiratory position. It was flicked back by finger until a replacement could be inserted. Mechanical failures did occur, and it was essential that some simple means of manual ventilation, such as an Ambu bag or an anaesthetic bag attached to an oxygen supply, was always readily available. Oxygen was never given routinely, so that the onset of cyanosis could give early warning that all was not well.

The respirator was run at 37 cycles a minute. The inspiratory pressure ranged from 13 to 30 cm. H_2O , the exact pressure being determined by the alveolar PCO_2 , which was kept between 25 and 35 mm. Hg. A pressure of 15 cm. proved satisfactory in the majority of cases.

Tubocurarine 10 mg. in hyalase was given intramuscularly as a relaxant. It was repeated whenever muscular twitchings developed, which was usually at intervals of 8 to 12 hours; occasionally it was required as often as every four hours. At varying intervals of 10 to 21 days after starting I.P.P.R. the infants became less dependent on tubocurarine. It was then stopped and phenobarbitone $\frac{1}{4}$ gr. (8 mg.) t.d.s. and mephensin 66 mg. hourly were given by stomach-tube to control residual hypertonicity. I.P.P.R. was continued and weaning from the respirator was carried out in the way recommended by Jackson (1961), except that, instead of leaving an escape channel for the air, the circuit was kept closed and the inspiratory pressure gradually dropped to 10 cm. H_2O over two to three days. No signs of discomfort were observed in the infants even when breathing out of phase with the respirator. In some infants this form of assisted respiration, and the allowing of increasingly long periods of spontaneous respiration, lasted up to a

week before they were finally weaned from the respirator. Undoubtedly this lessened the hazard of a sudden apnoeic episode and the effect of delayed release of curare.

Feeds were given by stomach-tube. After an initial trial period of 48 hours with glucose-water, half-strength milk feeds were given. This was increased to full-strength as soon as the bowels had acted. The stomach was aspirated before each feed as an excess residue indicated the onset of ileus. When this occurred, milk feeds were stopped, but glucose-water was still given by stomach-tube and the stomach aspirated at three-hourly intervals until the ileus cleared. Usually this was in two to four days. Intravenous fluids were not given. Considerable quantities of saliva were aspirated from the pharynx. Measured over 24 hours, the volume in one infant was 60 ml. with a potassium content of 1 mEq. The addition of 0.25 g. of potassium chloride to the daily fluid intake seemed to lessen the incidence of ileus.

Infants were nursed on their backs for the entire period of artificial ventilation. This avoided displacement of the tracheotomy tube, which may occur if the infant is turned from side to side. No pressure effects resulted except on the head, which had to be turned every half-hour to avoid sores and flattening of the occiput.

The highest praise must be given to the coloured nurses. Without their excellent nursing, and devoted care of the infants, these results could not have been achieved. It is essential that nursing-staff be trained to recognize and deal with emergencies.

Discussion

Wright *et al.* (1950) have shown in their animal experiments that tetanus toxin can reach and spread within the brain-stem. Clinical experience also supports the concept of brain-stem intoxication. In some of the early cases in this series treated with tracheotomy and sedation alone breathing invariably became shallow or irregular, or stopped, if I.P.P.R. was not applied. The apnoeic episodes which occasionally occur in the neonate after stopping I.P.P.R. may also be a late manifestation of intoxication of the respiratory centre in the brain-stem. Circulatory collapse has also been attributed to brain-stem intoxication, although Alhady *et al.* (1960) favour a direct intoxication of the myocardium. They cite the E.C.G. and morbid histological changes found in the heart as evidence of an inevitably fatal tetanus toxin myocardiopathy. Baker (1943) described histological changes in the brain-stem indicating a specific selective effect of tetanus toxin on the motor nucleus of the fifth cranial nerve and the dorsal nucleus of the vagus. The changes in some of the cells were said to be irreversible. Montgomery (1961) in a detailed clinical and pathological study, although failing to confirm Baker's findings except in two neonates, concluded that intoxication of the vital centres which stopped short of structural damage appeared invariably to be the cause of death in severe tetanus, and commented that this has perhaps always been more apparent in neonatal disease.

Similar if not identical clinical, electrocardiographic, and pathological manifestations of irreversible tetanus intoxication of the brain-stem and myocardium could be identified in the early cases of this series. Investigations, such as they were, based on this concept of fatal tetanus, failed to improve results. Yet as soon as

ventilation was adequately controlled deaths from these manifestations of intoxication ceased. It is difficult to avoid the conclusion that death in severe tetanus is the result of asphyxia as well as intoxication, and that, provided efficient ventilation is maintained, the intoxication is reversible.

There is no reason to suppose that what applies to infants does not also apply to older children and adults. Montgomery (1961) has pointed out that tetanus may vary in its severity in different part of the world, and that there are pitfalls in the study of mortality figures. Neonatal tetanus, however, is universally regarded as a severe form of the disease, and the mortality previous to this study of 96% in 50 consecutive infants in Cape Town is higher than most recorded large series.

Sykes's (1960a) application of the rebreathing method of estimating alveolar PCO_2 to infants proved an accurate and easy means of controlling ventilation. More than anything else this helped in the successful treatment of these infants. Errors may occur if there is collapse of the lung, or if the tracheotomy tube enters one of the main bronchi, but these sources of error could be diagnosed on clinical grounds.

Although no direct measurements were made, the minute-volume could be roughly calculated from the tidal volume, estimated from the compliance studies, multiplied by the number of respirations per minute. This gave a minute volume of between 1,100 and 1,800 ml., a figure in excess of 400–980 ml., which is the normal range for spontaneously breathing infants (Cook *et al.*, 1955). Flow resistance may account for part of this difference. It is also probable that the infants were overventilated, although no ill effects resulted from the alveolar PCO_2 being kept as low as 25 mm. Hg.

The mean pulmonary compliance of 2.5 ml./cm. H_2O found in these totally relaxed infants is half the mean of 5 ml./cm. H_2O found in spontaneously breathing infants (Cook *et al.*, 1957). A similar difference has been reported in adults, and is thought to be due to an inability, during spontaneous breathing, to relax completely the muscles of respiration (Nims *et al.*, 1955). Richards and Bachman (1961) found no significant difference between the compliance of the lung in the spontaneously breathing infant and the compliance of the lung and chest wall in the totally relaxed infant. Differences in technique may account for these divergent findings. Their measurements were all made over a short period of five minutes, using much higher pressures of up to 34 cm. H_2O to inflate the lungs, and after full inflation had been maintained for a period of 10 seconds.

Theoretically their estimations may be more accurate, but the method employed in this series approaches more closely the conditions under which I.P.P.R. is carried out. There is, however, an unwillingness to accept their explanation of why compliance was the same in the spontaneously breathing and the totally relaxed infant. This was that the thorax of the infant plays little part in lung compliance because it is cylindrical in shape, with ribs horizontally placed and almost all respiratory movement is diaphragmatic. On the contrary, free movement of the chest wall was observed in many infants on I.P.P.R.; in fact, it was a good sign that ventilation was adequate, and the impression was that compliance was better in the infants with free movement than in those with limited movement of the chest.

Emphasis has been laid on the relation between inflationary pressures and lung compliance. This is best

explained on a mechanism suggested by Bernstein (1957) to account for compliance of the rabbit's lung being reduced after prolonged I.P.P.R. He attributed this to collapse of the alveoli, and postulated that elastic expansion of the lung varies with the total number of patent alveoli, compliance increasing as more patent alveoli are recruited. In the rabbit's lung he found that the critical pressure at which collapsed alveoli could be reopened was 10–15 cm. H_2O . This corresponds with the 15 cm. H_2O which was the lowest pressure that could be maintained unchanged throughout in some infants while on I.P.P.R.

The exact pressure at which infants are respired appears to be of considerable importance. When in doubt, it is safer to err on the side of pressures being high in order to maintain compliance. Clinical manifestations of respiratory alkalosis from overventilation were not seen, but then the alveolar PCO_2 was not allowed to fall too low. The very much higher insufflation pressures recorded by Swennson (1962a) do suggest that the upper limit of safety may be wide. The minimum effective pressure may be quite critical. Because of the associated reduction in compliance a marked fall in the tidal volume could occur with a reduction of only 2 cm. H_2O in the inflationary pressure. In one infant (Fig. 6) the tidal volume at an inspiratory pressure of 15 cm. H_2O was 35 ml. Had the compliance remained constant, reduction of the inspiratory pressure to 13 cm. H_2O would have lowered the tidal volume to 30 ml., but because of the fall in compliance it in fact fell to 25 ml.

The maintenance of adequate alveolar ventilation was of much greater importance than the level of the mean intrathoracic pressure or the shape of the pressure curve of the respirator. The type "A" Radcliffe respirator, which proved perfectly satisfactory, has no negative-pressure expiratory phase, is generally considered to be inefficient, and is now obsolete. This emphasis on respiratory rather than circulatory factors resulted in the inspiratory pressure being raised in circulatory collapse in order to improve ventilation, whereas in the past the tendency had been to lower the pressure to improve venous return to the heart. It also raises the question whether the risk of a negative-pressure phase during expiration, causing bronchiolar collapse and trapping, may not outweigh the advantages of a low mean intrathoracic pressure increasing venous return to the heart.

An interesting phenomenon was the indifference of these infants, while breathing spontaneously out of phase with the respirator, to I.P.P.R. continuing at quite high inspiratory pressures. Recently a premature infant weighing 4 lb. (1.8 kg.) with pneumonia and obstructive bronchiolitis, who had stopped breathing, recovered after being treated with I.P.P.R. and no relaxants for five days. During this period there was no distress despite breathing out of phase with the respirator. This seems to emphasize, at least in infants, the value of positive-pressure respiration maintaining the patency of the airway and alveoli even at the expense of a rise in the mean intrathoracic pressure.

A wider application of tracheotomy and I.P.P.R. to neonatal respiratory problems seems inevitable, particularly as premature infants were ventilated without undue difficulty. Some of the early problems encountered at the time when infants were being underventilated were in many ways similar to those of hyaline membrane disease (Usher, 1961). There was an emphasis on the

circulatory and E.C.G. changes: a start had been made on correcting these with intravenous alkali solutions, but this was abandoned, as soon afterwards it became unnecessary when efficient ventilation was achieved. As has also been found in hyaline membrane disease, cyanosis was not a marked feature in the early stages of underventilation. This tended to draw attention away from the subtle and cumulative ill effects of minor degrees of underventilation and the need to investigate every means of maintaining effective ventilation. A few investigations along similar lines have been carried out on infants with hyaline membrane disease. Measurements in three infants gave a lung compliance of 1 ml./cm. H_2O or less. Similar reduced levels have been reported by Cook *et al.* (1957). Clearly, very high pressures are required to inflate the lungs when I.P.P.R. is used to treat this disease.

It would be most important to know whether compliance varies with the inspiratory pressure and how much it can be increased by applying very high inspiratory pressures. Measurements made in one infant (Fig. 8) suggest that some improvement in compliance can be achieved, and that earlier application of I.P.P.R. might prevent lung compliance falling to critical levels. Unfortunately, cardiac arrest necessitating intracardiac adrenaline and extracorporeal resuscitation had occurred before I.P.P.R. was started and the infant survived only another 17 hours. But, apart from the increase in compliance, the definite

FIG. 8.—Static compliance of lung of an infant with hyaline membrane disease. Compliance can be seen to improve as the inspiratory pressure was raised from 15 to 28 cm. H_2O over a period of 17 hours.

improvement in the excursion of the chest that was observed, and the fact that at necropsy portions of the lung were found to float, suggest that ventilation was materially assisted. Warley and Gairdner (1962) have emphasized the work imposed on the respiratory muscles in the respiratory distress syndrome and the need for lightening the load. I.P.P.R. and total muscle relaxation seems the logical approach. Total muscle relaxation, by reducing metabolic demands, might determine the outcome when critical levels of pulmonary insufficiency have been reached.

Swennson (1962b) has shown how assisted respiration can give relief to children over critical periods of respiratory insufficiency. Very severe cases of pneumonia might also derive considerable benefit. Secretions obstructing the airway could be aspirated. Surface-tension effects, where swelling of the bronchial mucous membrane is obstructing the air passages and increasing

flow resistance, could be reduced. Assistance could be given to muscles labouring to ventilate lungs reduced in compliance by consolidation and collapse. Improved ventilation may even help to overcome infection. This was common in the underventilated infant and much less frequent once adequate ventilation was ensured. When it did occur, survival appeared to be prolonged beyond what might have been expected from the gross post-mortem findings.

Summary

A series of infants with tetanus neonatorum were treated with relaxants and I.P.P.R., with disappointing results. In fatal cases the clinical, electrocardiographic, and pathological changes closely resembled those previously ascribed to overwhelming tetanus intoxication. No improvement followed investigations and treatment based on concepts of tetanus intoxication of the brain-stem or myocardium, nor from lowering the mean intrathoracic pressure to improve venous return to the heart. Only when ventilation was controlled by measuring the alveolar PCO_2 and the emphasis changed to respiratory efficiency did deaths from tetanus intoxication virtually cease. The conclusion is that tetanus intoxication is reversible provided that adequate ventilation is maintained.

Two factors were of importance in ensuring efficient ventilation of the totally relaxed infant while on I.P.P.R. They were the changes in pulmonary compliance and the maintenance of a clear airway.

Estimated under optimum conditions, the mean static compliance of totally relaxed infants of over 5 lb. (2.27 kg.) was 2.5 ml./cm. H_2O intratracheal pressure. In the same infant the pulmonary compliance was found to vary directly with the inspiratory pressure. This made the determination of the minimum effective inspiratory pressure quite critical. Compliance tended to fall with prolonged I.P.P.R. but not in all cases. It was unaffected by changes in the rate of ventilation and the posture of the infant.

The airway was kept clear by placing the tracheotomy tube in alignment with the lumen of the trachea, by aspirating bronchial secretions brought up into the trachea by hyperventilation and compression of the lungs, and, when this failed, by direct aspiration using an auroscope to visualize the main bronchi.

At present, total muscle relaxation and I.P.P.R. is the best method of treating tetanus neonatorum. With quite simple equipment the mortality in a consecutive series of 25 cases was 20%.

The wider application of I.P.P.R. to infants in respiratory distress and the relevance of the studies, in particular those on compliance, to the treatment of hyaline membrane disease are discussed.

I wish to thank the registrars for all their help, particularly Dr. W. Wittmann for his help during the early difficult period; the E.N.T. surgeons, particularly Dr. P. Maytham and Dr. J. Marais, and the anaesthetists for the tracheotomies; Dr. D. McKenzie for the pathological investigations; Dr. J. A. H. Campbell for histological examination of the brain; Professor A. Kipps for the toxin assays; Dr. A. Swanepoel for help with the E.C.G.s; the Provincial Administration for the equipment and modifications; the matron for her help and co-operation with the nursing arrangements; Dr. J. F. W. Mostert, medical superintendent of the Red Cross War Memorial Hospital, for help and permission to publish; Professor F. J. Ford for facilities; Mrs. O. M. Cartwright for the typing; and Miss C. Freese-mann for the graphs.

REFERENCES

- Alhady, S. M. A., Bowler, D. P., Reid, H. A., and Scott, L. T. (1960). *Brit. med. J.*, **1**, 540.
 Baker, A. B. (1943). *Amer. J. Path.*, **19**, 709.
 Bernstein, L. (1957). *J. Physiol. (Lond.)*, **138**, 473.
 Bolton, B. M., and Fisch, C. (1902). *Trans. Ass. Amer. Physns.*, **17**, 462.
 Brown, A., Mohamed, S. D., Montgomery, R. D., Armitage, P., and Laurence, D. R. (1960). *Lancet*, **2**, 227.
 Cole, L., and Spooner, E. T. C. (1935). *Quart. J. Med.*, **4**, 295.
 Cook, C. D., Cherry, R. B., O'Brien, D., Karilberg, P., and Smith, C. A. (1955). *J. clin. Invest.*, **34**, 975.
 — Sutherland, J. M., Segal, S., Cherry, R. B., Mead, J., McIlroy, M. B., and Smith, C. A. (1957). *Ibid.*, **36**, 440.
 Firor, W. M., Lamont, A., and Shumacker, H. B. (1940). *Ann. Surg.*, **111**, 246.
 Francis, E. (1924). *Bull. U.S. hyg. Lab.*, No. 95.
 Jackson, B. G. (1961). Quoted by Wright *et al.* (1961).
 McClintock, T. C., and Hutchings, W. H. (1913). *J. infect. Dis.*, **13**, 309.
 Maloney, J. V., Elam, J. O., Handford, S. W., Balla, G. A., Eastwood, D. W., Barnes, E. S., and Ten Pas, R. H. (1953). *J. Amer. med. Ass.*, **152**, 212.
 Montgomery, R. D. (1961). *W. Indian med. J.*, **10**, 84.
 Nims, R. G., Conner, E. H., and Comroe, J. H., jun. (1955). *J. clin. Invest.*, **34**, 744.
 Opie, L. H., Spalding, J. M. K., and Smith, A. C. (1961). *Lancet*, **1**, 911.
 Richards, C. C., and Bachman, L. (1961). *J. clin. Invest.*, **40**, 273.
 Russell, W. R., and Schuster, E. (1953). *Lancet*, **2**, 707.
 Smythe, P. M., and Bull, A. (1959). *Brit. med. J.*, **2**, 107.
 — (1961). *Ibid.*, **2**, 732.
 Swennson, S. A. (1962a). *Arch. Dis. Childh.*, **37**, 156.
 — (1962b). *Ibid.*, **37**, 149.
 Sykes, M. K. (1960a). *Brit. J. Anaesth.*, **32**, 256.
 — (1960b). *Anaesthesia*, **15**, 401.
 Usher, R. (1961). *Ciba Foundation Symposium on Somatic Stability in the Newly Born*, edited by G. E. W. Wolstenholme and M. O'Connor, p. 92. Churchill, London.
 Warley, M. A., and Gairdner, D. (1962). *Arch. Dis. Childh.*, **37**, 455.
 Wright, E. A., Morgan, R. S., and Wright, G. P. (1950). *J. Path. Bact.*, **62**, 569.
 Wright, R., Sykes, M. K., Jackson, B. G., Mann, N. M., and Adams, E. B. (1961). *Lancet*, **2**, 678.

DIET AND PLASMA CHOLESTEROL IN 99 BANK MEN

BY

J. N. MORRIS, D.Sc., F.R.C.P.

JEAN W. MARR

J. A. HEADY, Ph.D.

Social Medicine Research Unit of the Medical Research Council, London Hospital

G. L. MILLS,* Ph.D.

Courtauld Institute of Biochemistry, Middlesex Hospital, London

AND

T. R. E. PILKINGTON,* M.D., M.R.C.P.

Medical Unit, St. George's Hospital, London

To-day's main hypothesis on ischaemic heart disease relates the saturated-fat content of the diet through blood-cholesterol level to the production of the disease. Much information is available about *populations* in terms of these variables. In particular, it has been established that peoples at an early stage of social and economic development, and low consumption of saturated fat, have low mean cholesterol levels and suffer little ischaemic heart disease. In Western countries, where ischaemic heart disease is "epidemic," the mean intake of saturated fat and cholesterol levels are both high. There are, however, wide *individual* differences

*Work supported by the Medical Research Council.