THE OXYGEN CONSUMPTION IN TETANUS NEONATORUM

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CONTENTS.

CHAPTER I.

HISTORICAL BACKGROUND OF THE DISEASE AND PURPOSE OF THIS STUDY.

CHAPTER I.

HISTORICAL BACKGROUND OF THE DISEASE.

"An inhuman calamity! an unseemly sight! a spectacle painful even to the beholder ! an incurable malady! owing to the distortion, not to be recognised by the dearest friends; and hence the prayer of the spectators, which formerly would have been reckoned not pious, now becomes good, that the patient may depart from life, as being a deliverance from the pains and unseemly evils attendant on it. But neither can the physician, though present and looking on, furnish any assistance ....
With them, then, who are overpowered by this disease, he can merely sympathise".

Thus wrote Aretaeus describing tetanus (Major, 1939). The present day physician is able to do more than merely sympathise but in spite of the growth of knowledge of this now preventable disease, there remain areas of ignorance which continue to spur investigators to further study.

Clinical descriptions of the disease by the classical authors, Hippocrates and Aretaeus, bear testimony to the precision of observation characteristic of these early studies. Hippocrates observed: "The master of a large ship mashed the index finger of his right hand with the anchor. Seven days later a somewhat foul discharge appeared; then trouble with his tongue - he complained he could not speak properly. The presence of tetanus was diagnosed, his jaw became pressed together, his teeth were locked, then symptoms appeared in the neck; on the third day opisthotonus appeared with sweating" (Major 1939).

It is worth noting that Aretaeus commented on the

involvement of the respiratory system in a graphic account of this "exceedingly painful disease". He said that "there is a pain and tension of the tendons and spine, and of the muscles connected with the jaws and the cheek; for they fasten the lower jaw to the upper, so that it could not easily be separated even with levers or a wedge .... The face is ruddy and of mixed colours, the eyes almost immovable, or are rolled about with difficulty; strong feeling of suffocation; respiration bad ...." (Major 1939).

Over the centuries the theories of causation have been as colourful and varied as the forms of treatment. Tetanus was associated with injury of muscles, nerves, and "membranes"; severe cold was also quoted as a cause. Tetanus of the newborn was related to the umbilicus by Bartram in 1793. Sims (1848), however, felt that "mechanical pressure exerted on the medulla oblongata" was the cause. He reported dramatic cures by relieving this pressure. Various authors of this era ascribed the disease to "cold air", "foul air", poor ventilation and poor hygiene.

The treatment of tetanus has varied from opium, mercury, wine, warm and cold baths, venesection, ipecacuanha and digitalis to enlargement of the wound and amputation of the limb.

Nicolaier (1884), who discovered <u>Clostridium tetani</u> as the causative organism, initiated the "scientific study" of the disease.

In 1887 Rosenbach demonstrated the organisms in human lesions. Although Nicolaier (1884) had suggested the possibility of a toxin being responsible for the disease, it was Kitosato who discovered the toxin and developed the anti-toxin in 1896 (Drew 1954).

During World War I the incidence of tetanus amongst

British soldiers protected by anti-toxin (passive immunity) was lower than amongst soldiers who fought in the Peninsular War of Spain and Portugal a hundred years before (MacGregor 1815).

Although anti-tetanus serum has proved valuable in preventing the disease, the dose used for treatment has been the subject of debate for some time; indeed, the value of giving anti-tetanus serum at all in the treatment of tetanus has been questioned by some authors (Drew 1954, Johnstone 1958). Recently, however, Brown et al. (1960) and Patel et al. (1963) have shown that anti-tetanus serum is beneficial. Laurence and Webster (1963) stated that anti-tetanus serum was essential therapy for clinical tetanus and that a single dose of 50, 000 units was adequate.

Tetanus toxoid became available in 1924 following the work of Descomby (Bloomfield 1958). The efficacy of toxoid in preventing the disease was amply demonstrated during the Second World War, when the American troops inoculated with the toxoid (active immunity) were virtually free of tetanus (Long 1943). Although half a century has elapsed since the development of the toxoid, tetanus continues to plague man in some countries.

In a recent report to the World Health Organisation, Bytchenko (1966) drew attention to the high overall incidence and alarmingly high death rate of tetanus. He estimated that, in the ten-year period up to 1960, more than a million people had suffered from the disease and half of them had died.

HISTORY OF THE TREATMENT OF TETANUS IN SOUTH AFRICA.

Friedlander (1951), and Klenerman and Scragg (1955) drew attention to the high incidence of the disease in Durban. Falke (1957) from Johannesburg and Smythe (1959) from Cape Town reported on the incidence of the disease in their respective cities.

Confronted by a multiplicity of opinions about treatment, (many of which did not withstand critical analysis) Adams set up a hospital unit in Durban in 1956 to conduct properly controlled clinical trials. Initially it was decided to concentrate on the effects of drugs which controlled the manifestations of tetanus and to design trials to compare two therapeutic regimens at a time in randomised samples. The results of these trials on several forms of conservative treatment (Laurence, Berman, Scragg and Adams 1958, Adams et al. 1959) showed no evidence in favour of one form over another, as judged by death-rates. Chlopromazine was adopted as the mainstay of conservative treatment because it proved to be a convenient drug to use (Adams et al. 1966).

Following an early report on the use of curare and intermittent positive pressure respiration (I. P. P. R.) by Björnboe et al. in the treatment of tetanus (1953), Adams and his colleagues initiated a series of trials comparing I. P. P. R. with conservative treatment in 1959. The first was reported on by Wright, Sykes, Jackson, Mann and Adams (1961); Smythe (1959) had already reported using I. P. P. R. to treat neonatal tetanus in Cape Town. These studies were important in that they showed that in <u>severe</u> neonatal tetanus, I. P. P. R. initiated <u>before</u> the onset of respiratory failure, improved the chances of survival. Wright et al. (1961) in a controlled series showed that the chances of

survival were improved by 40%. These studies also emphasized the importance of respiratory failure as a cause of death.

In 1962 Jackson described the use of assisted respiration, a modified form of I. P. P. R., in the treatment of tetanus neonatorum. The earlier experiences of Adams et al. (1964) with this form of treatment seemed encouraging, but a controlled clinical trial by Thambiran (1967) showed that assisted respiration has little to commend it when compared with full I. P. P. R.

"Tracheostomy when used alone (without I. P. P. R.) seems to have many theoretical advantages in tetanus, in which respiratory problems are so common. It reduces the dead space, eliminates the danger of a fatal spasm of larynx or oropharynx, and isolates the respiratory tract from the digestive tract, thus reducing the risk of aspiration pneumonia" (Adams et al. 1966). Holloway (1967) found, however, that in neonates with severe tetanus tracheostomy alone did not confer any benefit. He concluded that I. P. P. R. is the treatment of choice for severe tetanus neonatorum as most developed respiratory failure. Furthermore, it is interesting that those infants who had been treated by I. P. P. R. as soon as the diagnosis of severe tetanus had been made, had a mortality of 36% as against a mortality of 53% for those who were treated by I. P. P. R. when respiratory failure had become manifest. Holloway's finding of a correlation between severity of disease and respiratory failure was of practical significance. Classification of severity is however complicated by the varied criteria used by different authors. The simple method employed in the Durban unit, although very useful and fairly reliable, nevertheless only provides a rough guide. The vast majority of patients diagnosed as "severe" on admission run a stormy course; those considered to be only mild or moderate cases when first seen generally continue as such. There are

exceptions: an occasional patient with severe spasms will settle on conservative treatment and have infrequent or quite mild spasms after a day or two ... Occasionally too, patients with mild tetanus ..... become inexplicably apnoeic days after admission. ..." (Adams et al. 1966).

PURPOSE OF THIS STUDY.

An objective test to grade the severity of tetanus on admission of the patient to hospital would be useful to the inexperienced practitioner in deciding which patients to refer to specialized units for I.P.P.R. and would help the experienced practitioner in deciding on the best form of treatment for patients who occupy an intermediate position in the continuous spectrum of severity of disease.

Although the method of classifying severity varies with different authors the signs which herald an ominous outcome are generally agreed upon. Cole (1940) drew attention to the interval between the appearance of the first symptom of the disease and the first spasm. He called this interval "the period of onset" and showed that a short "period of onset" was associated with a bad prognosis. Other prognostic criteria emphasized by various authors include incubation period (the interval between the injury and the appearance of the first symptoms of tetanus (Spivey et al. 1953) age of patient, fever, dysphagia, relation of respiratory rate to body temperature and the relation of body temperature to pulse rate. Adams, in a recent publication (1968) reviewed the relative significance of some of these criteria. He showed that a correlation existed between the frequency of spasms on admission and the severity of the disease (1958). Although Wright (1960) and Adams et al. (1966) found this classification more useful than the one based on incubation period or period of onset, it "still only

provides a rough guide" (Adams et al. 1966).

It is well-known that oxygen consumption of adults during steady-state muscular exercise bears a linear relationship to the severity of the exercise. If the severity and frequency of spasms is indicative of the severity of the disease, the patient's oxygen consumption should provide an objective guide to severity. The present study was undertaken to establish whether this was so; and whether the oxygen consumption determined on admission of the patient to hospital could be used to distinguish those neonates who would require I. P. P. R. from those who could be treated by conservative means, bearing in mind that:-

(1) neonates with "severe" tetanus treated by I. P. P. R. as soon as the diagnosis has been made, carried a better prognosis than those treated by I. P. P. R. following the onset of respiratory failure (Holloway 1967);

(2) neonates suffering from clinically "mild" and "moderate" forms of the disease had a mortality rate of only 3·3% and 5·8% respectively compared to mortality rate of 36·4 - 44% of clinically "severe" neonates treated by I. P. P. R. (Adams et al., 1966).

(3) I. P. P. R. carries its own hazards (Sykes 1960), which in the case of "mild" and "moderate" tetanus would outweigh the advantages to be gained from this form of treatment.

An objective assessment of severity on admission of the patient to hospital would enable one to select patients for I. P. P. R. with more precision.

The physiological and clinical implications of the study form the subject of this thesis.

CHAPTER II.

PRINCIPLES OF OXYGEN CONSUMPTION MEASUREMENT.

PRINCIPLES OF OXYGEN CONSUMPTION MEASUREMENT.

The oxygen consumption ($\dot{V}O_2$) of a subject can be measured by an open or a closed breathing circuit method.

Pettenkofer and Voit (1862) described an apparatus for the measurement of carbon dioxide production. This formed the basic design for subsequent apparatus for measuring the carbon dioxide production and oxygen consumption by the open circuit method. The method involves passing gas, usually atmospheric air, over the subject's face at a known, fixed rate, and the determination of carbon dioxide and oxygen content before and after its passage past the subject's face.

In the closed circuit method first described by Regnault and Reiset (1849), the subject is placed within a respiration chamber, forming part of a hermetically sealed system, in which the gas circulates. The carbon dioxide given off by the subject is absorbed by soda lime; the diminution in volume of the system (corrected for changes in the ambient pressure and temperature of the circulating gas) is therefore a measure of the oxygen consumed by the subject.

The open system has the advantage of ease of access to the subject; the disadvantages are those of rebreathing with attendant carbon dioxide accumulation, the inaccuracies which follow minor variations in the gas flow rate and analysis, the expense of the instruments for automatic analysis and the small but inevitable time lag in the gas analysis.

The closed system has the advantage that it is simple, accurate and gives a continuous record with virtually no time lag, thus allowing correlation to be established between events such as activity of the subject and gas exchange. Furthermore, with the closed system, provided the soda lime is changed frequently, the danger of carbon dioxide accumulation is non-existent.

THE APPARATUS USED IN THIS STUDY.

The apparatus used in this study was designed so that it would be accurate, inexpensive, simple to make and convenient to use.

Basically the closed system apparatus consisted of a sealed box (respiration chamber), surrounded by a thermostatically controlled water-bath. Carbon dioxide was absorbed by soda lime and the reduction in gas volume due to the neonate's oxygen consumption was monitored with a modified Krogh's (1922) spirometer (hereafter referred to as Krogh's Spirometer). (Figs. 1 and 2).

DESCRIPTION OF THE APPARATUS.

The respiration chamber, of 55·5 litres capacity, was constructed of 0·05 cm thick copper to allow rapid transfer of heat from the water to the gas within the chamber. The bottom of the chamber contained water to a depth of 0·5 cm. Above this, two perforated trays, one above the other and occupying the full area of the chamber, were arranged to carry 500 grams of slightly moist soda lime. Above these another perforated tray served to support the neonate (Fig. 1).

An acrylic sheet (I.C.I. "Perspex") lid was made of two layers with air trapped between them. This sandwich arrangement reduced heat loss from within the chamber. Hermetic sealing of the chamber was achieved by resting the edges of the lid in a shallow water trough surrounding the top of the copper box.

Four copper pipes projected from the side of the chamber and allowed the passage of electric cables for a fan and thermistors, polyethylene tubing for connection to a pneumograph and a spirometer (Fig. 2).

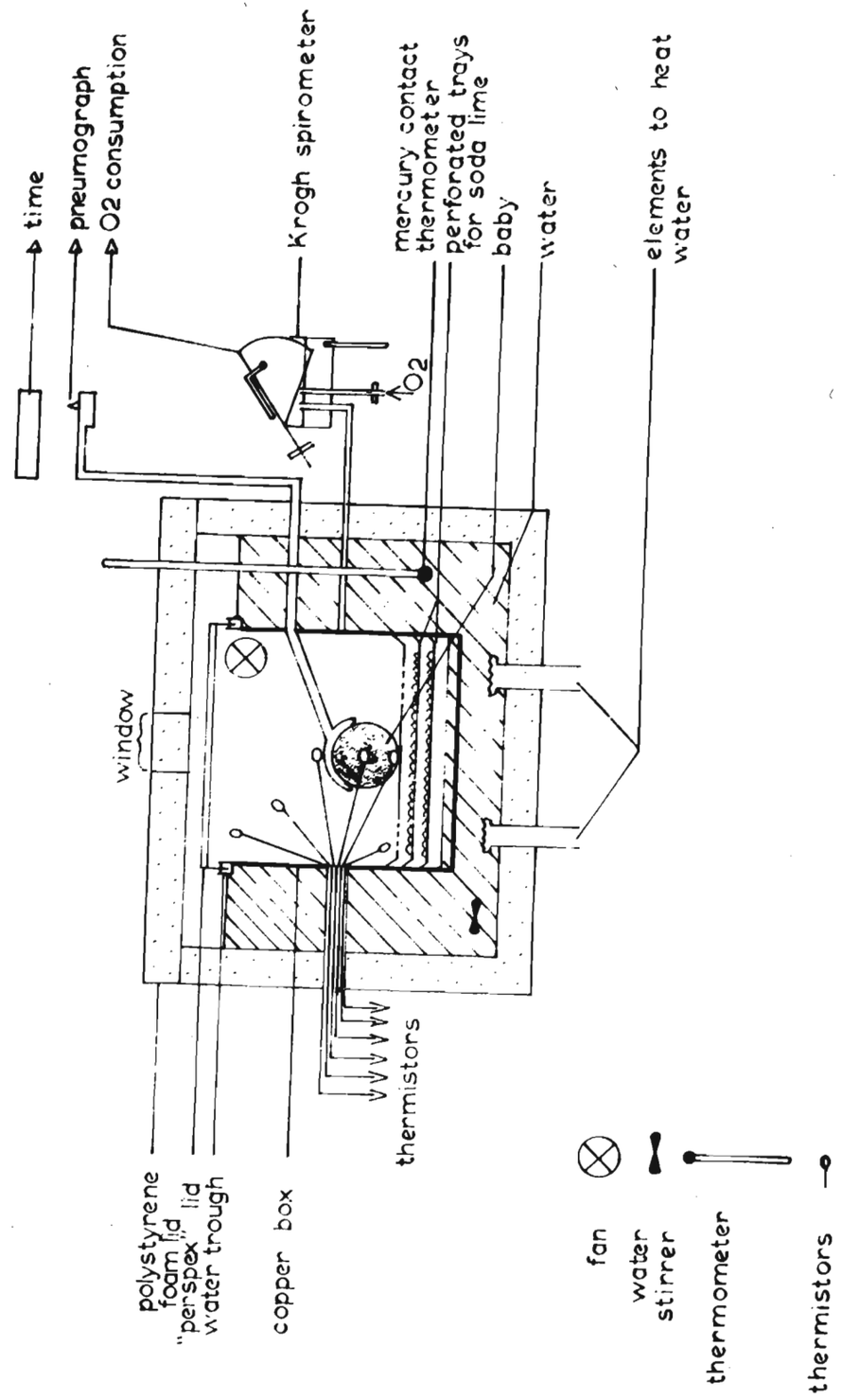


Fig.1. DIAGRAM OF THE APPARATUS

To ensure effective carbon dioxide absorption and to minimize temperature gradients, gas within the chamber was agitated by a small fan located in the chamber. During preliminary testing of the apparatus the wind velocity within the chamber, measured by the silvered Kata thermometer, did not exceed 3 cm per second.

Calibrated thermistors (see Appendix) were used to measure the temperature of the contained gas and the neonate's rectal and skin temperatures. Gas temperatures, accurate to within 0.025° C, were measured

(1) near the perspex lid

(2) approximately half-way between (1) and (3)

(3) near the tray upon which the baby rested.

Skin temperatures were measured over the anterior abdominal wall halfway between the xiphisternum and umbilicus and over the posterior chest wall between the scapulae.

Rectal temperature was measured 10 cm from the anal margin (Karlberg 1949).

A record of the infant's chest excursion, spasms and activity was obtained from a pneumograph (Eaton et al. 1967) strapped across the neonate's chest and connected by means of polyethylene tubing to a diaphragm tambour outside the box.

The temperature-controlled water-bath was made of two galvanized steel boxes separated by 7 cm of polystyrene foam. Two 600 watt heaters, controlled by a mercury contact thermometer, kept the bath within 0.05° C of the preset temperature. The water was stirred constantly.

To reduce heat loss upwards from within the chamber a polystyrene foam lid, divided into two parts, covered the top aspect of the water bath except for a central viewing area. The

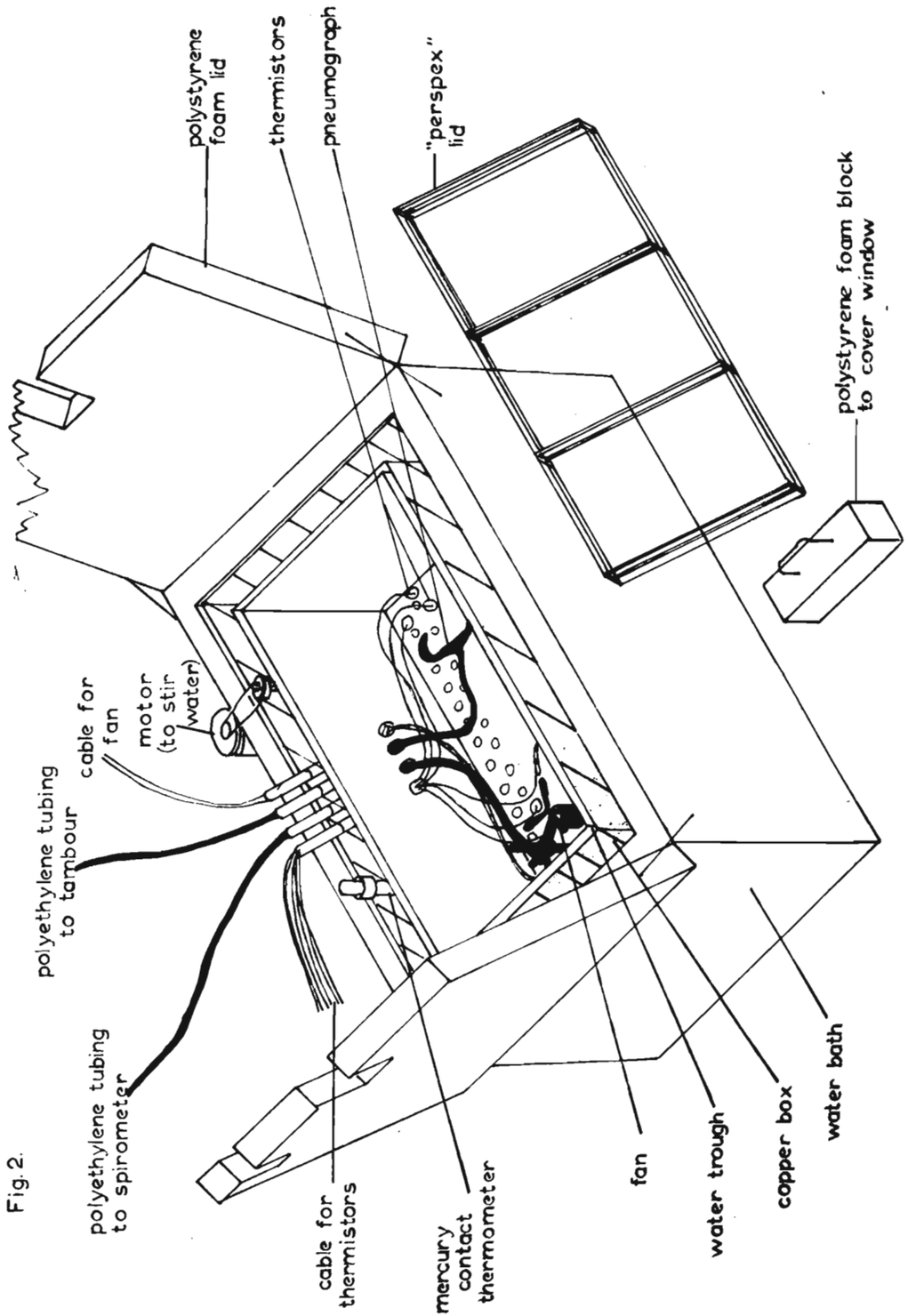


Fig. 2.

viewing area could also be covered by a polystyrene foam block (Fig. 2).

The Krogh's spirometer had a gas capacity of 1000 ml (bell). Two pipes entered the water space (well) (Fig. 3). One pipe was connected to the respiration chamber, the other to an oxygen source. One thermometer measured the spirometer water temperature and another was in contact with the oxygen under the bell. To the front end of the bell was attached a frontal ink-writing device which recorded spirometer volume changes on a kymograph. Although a weight was placed to counterbalance the bell, the spirometer excursion did not bear an exactly linear relationship to the contained gas volume; a calibration chart was prepared and consulted for volume correction when necessary (Fig. 4).

Later in the study, when it was found that the mean $\dot{V}O_2$ of neonates suffering from severe tetanus, studied over a period of 15 - 20 minutes, was approximately twice the value of that of the normal sleeping neonate, it was decided to investigate the $\dot{V}O_2$ during and between spasms. It was expected that by introducing a smaller Krogh's spirometer (60 ml capacity) in the circuit between the chamber and the larger Krogh's spirometer, one would be able to assess $\dot{V}O_2$ more accurately over a shorter period of time because of better time and volume resolution.

The smaller spirometer, over the middle third of its excursion, when counter-balanced, was found to move linearly in relation to the volume of oxygen introduced into or removed from it. Whenever a certain volume of oxygen had been removed from the smaller spirometer it was refilled from the larger one.

CALIBRATION OF THE SPIROMETERS.

The spirometers were connected to the respiration chamber as they would be during an experiment. A 50 ml glass

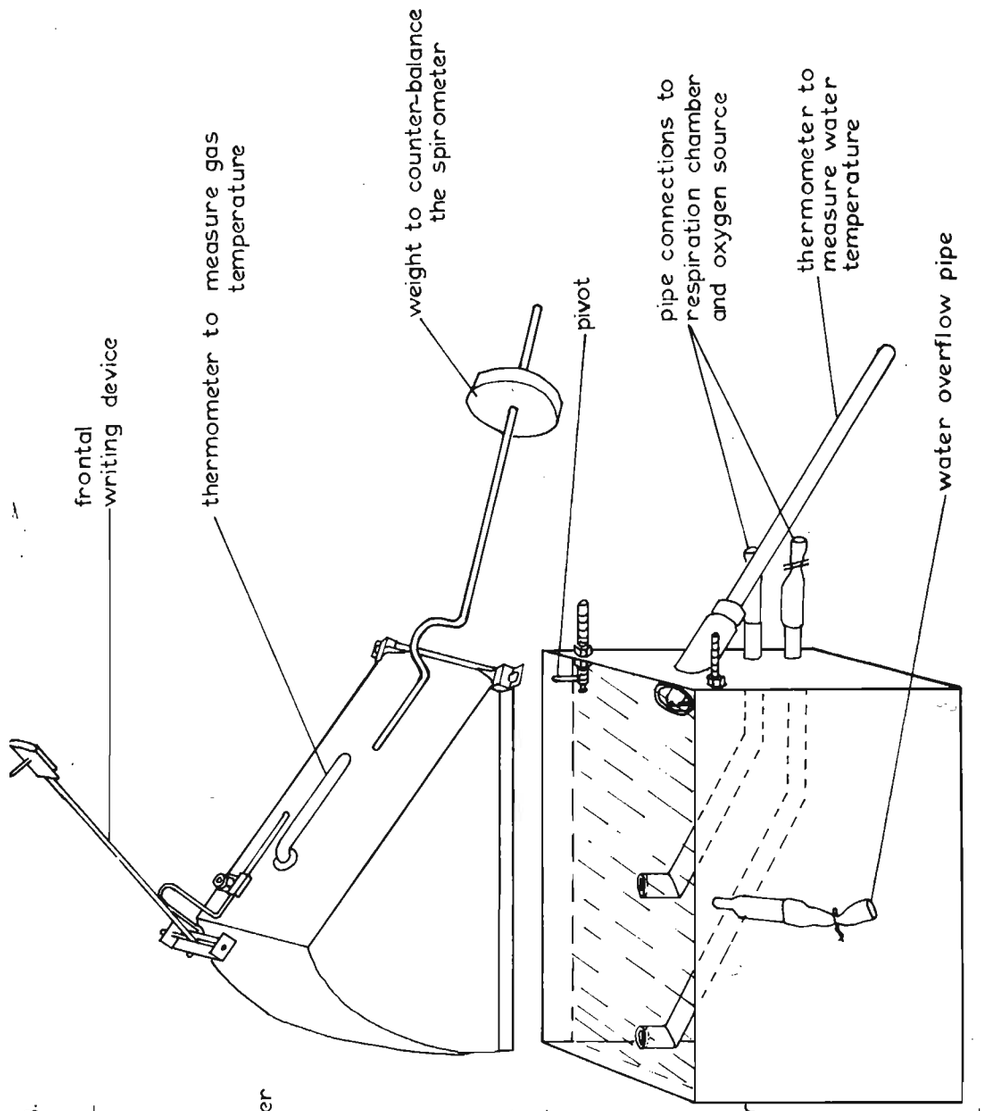


Fig.3.

syringe was connected to one of the pipes of the respiration chamber by means of polyethylene tubing. Water from the water-bath, which was kept at 33°C, was then added to the chamber in 50 ml aliquots, until 600 ml had been added during calibration of the larger spirometer (Figure 4). During calibration of the smaller spirometer, water was added in three aliquots of 5 ml each. The excursion of the larger spirometer, although not linear, was constant for fixed volumes. Water was used to calibrate the spirometer because it has a low coefficient of expansion to heat and would therefore displace its own volume of gas. If room air were used instead of water, 50 ml of gas at room temperature would expand to a new volume within the warm chamber displacing a larger volume of gas into the spirometer where again its volume would diminish due to lower spirometer temperature.

TECHNIQUE:-

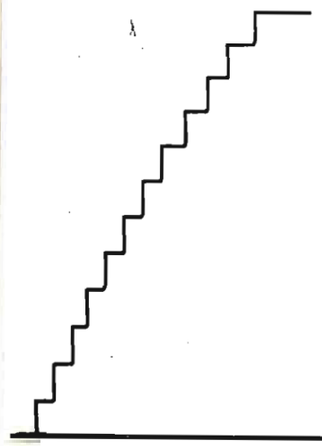
The water was kept at between 33°C and 34°C and the entire apparatus was in readiness so that the oxygen consumption of neonates arriving in the unit could be measured without delay.

The apparatus was tested for leaks by the placing of a 100 gram weight on the bell of the spirometer. A leak from the system was indicated by a fall in the level of the spirometer record.

The writing points of the pneumograph tambour and the spirometers were arranged in the same vertical line on the kymograph paper so that activity of the neonate during the study could be correlated with the oxygen removed from the spirometers. A horizontal line was drawn on the kymograph paper with the spirometer empty. Another horizontal line was drawn 52 mm above the first line, representing 600 ml of gas in the spirometer.

The naked neonate, with a pneumograph strapped across his chest and thermistors placed in the positions described earlier,

Fig.4. SPIROMETER CALIBRATION CHART



Each step in the diagram represents 50ml gas introduced into the system.

Note that the spirometer excursion is not exactly linear to the volume introduced into it. As more gas is introduced, the excursion for each successive 50ml is shorter. The spirometer travelled a verticle distance of 52mm from the zero position when 600ml had been added to the system.

was placed on a single layer napkin on the top tray in the respiration chamber. The pneumograph was connected to the polyethylene tubing leading to the tambour outside the chamber.

A paper hygrometer, calibrated against a wet and dry bulb thermometer, was placed in the chamber.

The interval between the opening and the closing of the lid was kept to a minimum. The average was ten minutes. After closure, the spirometer was filled with oxygen so that it registered a volume greater than 600 ml.

After thermal equilibrium had been established and the spirometer had fallen to the 600 ml line, a stop-watch was started, the barometric pressure read from a brass scale mercury barometer equipped with a vernier reading to 0·05 mm Hg. and corrected for changes in ambient temperature. The gas, rectal and skin temperatures were recorded. The relative humidity within the chamber was 100% throughout all the experiments. The child's activity and colour were observed through the "perspex" window. When 600 ml of oxygen had been consumed the watch was stopped, atmospheric pressure and temperatures recorded, and the spirometer disconnected. Later in the study a time-marker was used. A tight-fitting non-leaking syringe was then connected to the chamber. Having flushed out the gas in the pipe, 20 ml of gas from the chamber was withdrawn to establish the fractional concentrations of oxygen (FO_2) and carbon dioxide (FCO_2). As soon as the gas sample had been withdrawn, the chamber was opened, the thermistors detached, and the neonate removed and weighed. The chamber was washed out and cleaned with an anti-septic solution. The soda lime was renewed at the end of each experiment.

ESTIMATION OF OXYGEN CONSUMPTION.

Although temperature control within an extremely narrow range is theoretically possible, in practice it is impossible to prevent slight temperature fluctuations in the respiration chamber (Benedict and Talbot, 1914 and Karlberg, 1952), and these, together with the unavoidable fluctuations in the barometric pressure can account for volume changes in this system of up to 100 ml within half an hour. During "control experiments" (without the baby in the chamber - see appendix Page IV) change in volume of the system due to temperature and barometric pressure fluctuations could be predicted by the following formula:-

$$\frac{PB_1 - Pw_1}{T_1} \times V_1 = \frac{PB_2 - Pw_2}{T_2} \times V_2$$

where PB, Pw, T, and V refer respectively to ambient barometric pressure, water vapour pressure at ambient gas temperature, absolute temperature and volume of the system. The suffixes 1 and 2 refer respectively to conditions at the beginning and at the end of the experiment.

Gas temperature used in the formula was the average of the readings of the three thermistors. Although the three thermistors usually did not record the same temperatures their rises were parallel. Thus, though the carbon dioxide absorption was adequate, the fan did not agitate the gas sufficiently to eliminate temperature gradients within the chamber.

Theoretically, the Krogh's spirometer exerted a slight positive pressure on the gas contained in the chamber; however, this was so small that it could not be measured by a water manometer

connected to the chamber. For the purposes of volume corrections the gas was therefore assumed to be at ambient barometric pressure.

The change in volume of the chamber due to temperature and barometric pressure fluctuations during each experiment was converted to standard temperature and pressure dry (STPD) and added to or subtracted from the volume of oxygen removed from the spirometer (also converted to STPD) depending on whether the volume of the chamber increased or decreased. The total volume change, which represented the oxygen consumed by the subject, was then expressed as ml/min/kg body weight.

POSSIBLE SOURCES OF ERRORS AND HOW THEY WERE DIMINISHED.

1. TEMPERATURE AND BAROMETRIC PRESSURE CHANGES:-

Carpenter (1915), Lundholm (1949) and Scopes (1965), who used respiration chambers of relatively small volumes (9, 8, 10 litres respectively) were probably justified in ignoring barometric pressure and temperature fluctuations. If, however, large capacity chambers are used e. g. Benedict and Talbot (1914, 75 Litres), Karlberg (1952, 30 litres), and the present chamber (55· 5 litres), it is necessary to take into account fluctuations in both these variables. If this is not done errors of approximately 16% may occur in the oxygen consumption estimation. As indicated earlier, with this chamber, volume changes due to gas temperature and barometric pressure fluctuations were recorded with fidelity so that if volume changes did not vary with the temperature and barometric pressure changes a source of gas leak was sought and found.

The spirometer containing 600 ml oxygen and the connecting tubes containing 200 ml air were exposed to room temperature. During the course of an experiment neither the room temperature nor the spirometer gas temperature changed more than 0· 25°C. The change in volume due to temperature changes in this part of the system was negligible and therefore ignored.

2. VAPOUR PRESSURE VARIATIONS.

If water vapour pressure variations due either to alterations in temperature or relative humidity are ignored considerable errors may occur. If, for example, during an experiment at 32°C the relative humidity increased from 0% to 100%

the water vapour pressure would alter by 30 mm Hg. giving rise to an error of nearly 300% in the oxygen consumption determinations. Such errors were obviated by maintaining the gas within the chamber fully saturated with water vapour.

Changes in vapour pressure due to the temperature variations were accounted for by the formula used for volume corrections (Page 14).

3. LEAKAGE

When measuring oxygen consumption by the closed system, it is important that no gas leakage should occur. Testing for gas leakage was carried out as indicated earlier (Page 12).

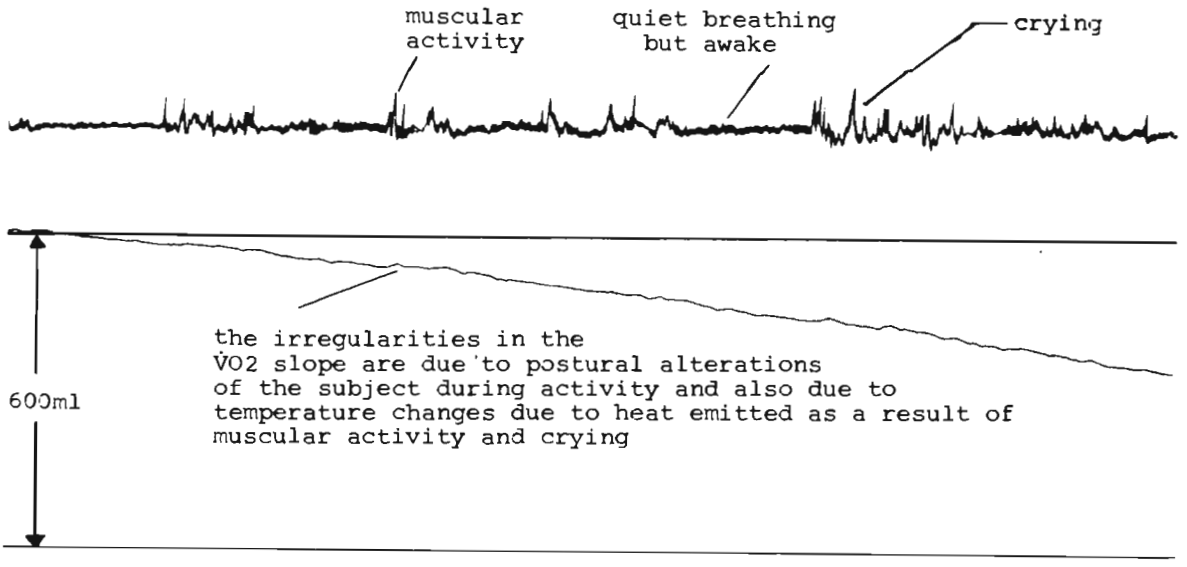
4. CARBON DIOXIDE ABSORPTION

One of the prerequisites for measuring oxygen consumption by the closed system is efficient carbon dioxide absorption; inefficient absorption of carbon dioxide will be reflected as diminished oxygen removal from the spirometer. The fan circulating the gas within the chamber allowed the soda lime to absorb carbon dioxide efficiently. In this chamber the FCO_2, measured on the Haldane gas analysis apparatus, was on an average 0·03% at the beginning of the experiment and not more than 0·06% at the end of the experiment. This would give rise to an error of nearly 3% in the oxygen consumption assessment.

5. ERRORS OF CALIBRATION.

Errors due to inaccuracies of volume assessment were obviated by frequent, regular calibration of the spirometer. Provided that the water level was maintained constant and the spirometer maintained in good mechanical condition, the calibration remained unaltered. The oxygen consumption slope was read to within 0·5 mm; as the total distance travelled by the spirometer was 52 mm (600 ml), this involved an error of

Fig.5. THE BREATHING PATTERN AND OXYGEN CONSUMPTION SLOPE OF A NEONATE EXHIBITING MUSCULAR ACTIVITY AND CRYING INTERMITTENTLY



approximately 1%.

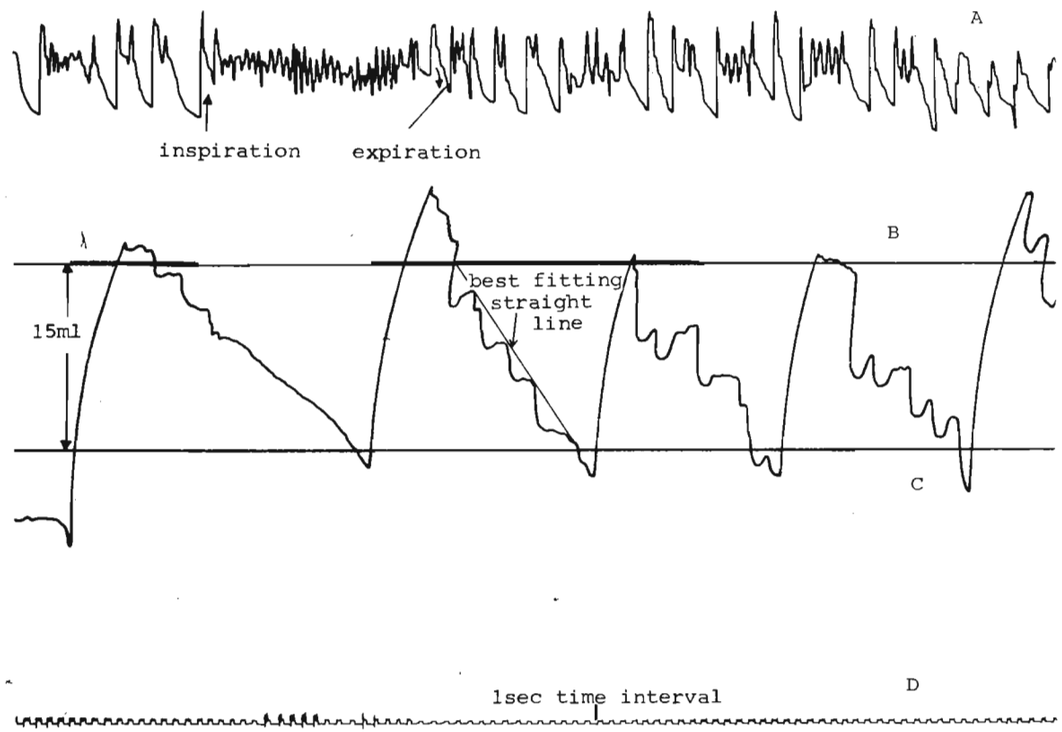
6. *MOVEMENTS OF THE CHILD*

Movements of the child with accompanying postural changes gave rise to apparent volume changes; temperature changes due to heat emitted as a result of muscular activity and crying also contributed to the changes in volume of the system. Both these factors contributed to the irregularities in the oxygen consumption slope; irregular breathing patterns resulting from movements of the child or crying and irregularities in the oxygen consumption slope are visible on the kymograph records (see Fig 5.).

In the study of normal, sleeping neonates such periods of activity were excluded. In the case of neonates with tetanus, some of whom had a spasm with each inspiratory effort, mean $\dot{V}O_2$ during spasms was assessed by drawing the best-fitting straight line, by visual inspection, through the oxygen consumption slope (fig. 6).

In summary, the errors due to temperature, barometric pressure and vapour pressure changes were corrected. The maximum combined error due to the slight carbon dioxide accumulation and calibration errors would be approximately 4%. The experimentally obtained standard deviation of the oxygen consumption is made up of two components, viz. one due to the apparatus and one due to variations in the metabolism of the tested animal (Lundholm, 1949). The standard deviation for the whole group of normal, sleeping neonates was nearly 11%. Statistically the total standard deviation (σ_t) is related to the standard deviation of the apparatus (σ_a) and the standard deviation due to variations in the metabolism (σ_m) of the

Fig.6. MEAN OXYGEN CONSUMPTION ESTIMATION DURING SEVERE, CONTINUOUS SPASMS



tested subjects by the following formula.

$$\sigma_t = \sqrt{\sigma_a^2 + \sigma_m^2}$$

Thus if σ_a *is assumed to be 4%,* σ_m *will be 10.24%. If* σ_a *is reduced to 0.4%* σ_t *will be reduced merely to 10.27% from 11%. "It is thus evident that little will be gained by reducing the errors in the recording system so long as these are small in relation to the variations in the oxygen consumption of the tested animals" (Lundholm, 1949).*

CHAPTER III.

THE OXYGEN CONSUMPTION OF NORMAL, SLEEPING NEONATES.

THE OXYGEN CONSUMPTION OF NORMAL, SLEEPING NEONATES.

MATERIAL AND METHODS:-

The $\dot{V}O_2$ of thirty-six normal African and Indian neonates born in the maternity section of King Edward VIII Hospital, Durban, was measured. The mean age of the neonates at the time of the $\dot{V}O_2$ measurement was 6·8 days. The subjects, selected at random, were examined in conjunction with a paediatric registrar or consultant and passed as normal before being accepted for the study. These dark-skinned neonates were studied for comparison with light-skinned neonates studied by other authors and also to serve as controls for comparison with neonates suffering from tetanus.

The subjects were breast-fed by the mother before being brought to the respiratory unit laboratory. Here the infants were allowed to rest for 15 - 20 minutes before the study was begun. No sedation was given. During the $\dot{V}O_2$ measurement the degree of repose was classified as follows:

1. *obviously asleep*
2. *awake but lying still*
3. *awake and moving*
4. *awake with violent movements*
5. *crying.*

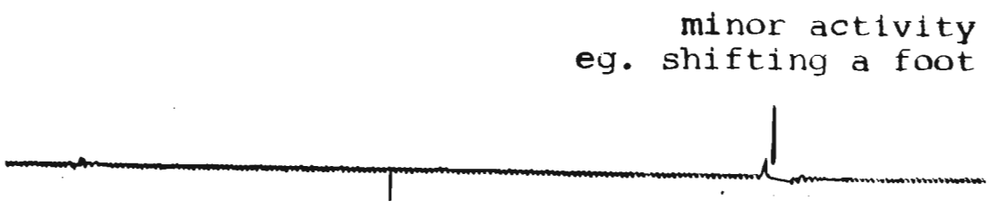
Although it was appreciated that the depth of sleep varied, (Fig. 7) no distinction between various depths of sleep was made for the oxygen consumption measurements. If the subject was obviously asleep, the minor activity which takes place during sleep was ignored (figs. 8 and 9).

The normal infants were not grouped according to gesta-

Fig.7. CHANGES IN BREATHING PATTERN DUE TO ALTERATION IN DEPTHS OF SLEEP

This alteration in breathing pattern appears more frequently towards the end of deep sleep, just before the infant is about to wake fully.

Fig.8. BREATHING PATTERN DURING MINOR ACTIVITY IN SLEEP



tion and maturity, as is done by Scopes (1965), because of the difficulty of obtaining, with any certainty, the date of the last menstrual period from the mothers of the infants. Although not strictly qualifying for the term "normal", five premature neonates (2.5 kg or less at birth) were included in the study.

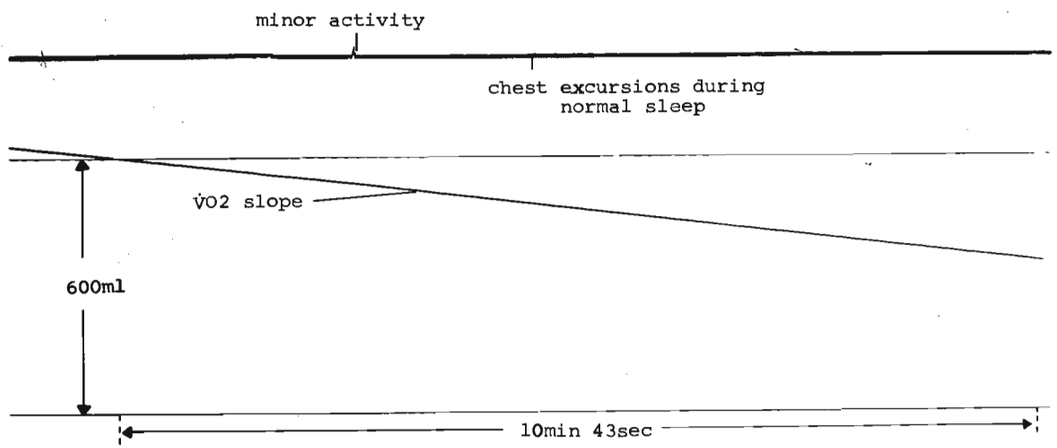
RESULTS:-

Figure 9 is part of a record representative of those obtained during $\dot{V}O_2$ measurements of normal, sleeping neonates. The upper tracing is the record of chest excursions; the two horizontal lines mark the excursion of the Krogh spirometer when 600 and 0 ml oxygen respectively were contained within it. The slope between these two lines represented the fall of the spirometer level as oxygen was removed from it.

Forty-four observations were made on 36 neonates. The mean $\dot{V}O_2$ of normal, sleeping neonates was 6·9 ml/min/kg. (S.D. 0·78: S.E. of mean 0·608 - see table 2, page 29 and appendix table No. 2).

The regular pattern of chest movement during sleep was disturbed when the subject awoke and cried (compare figs. 9 and 5).

Fig.9. PART OF OXYGEN CONSUMPTION RECORD OF A NORMAL, SLEEPING NEONATE



FACTORS INFLUENCING THE OXYGEN CONSUMPTION OF NORMAL, SLEEPING NEONATES

1. ENVIRONMENT:

Although earlier authors recorded the temperature of gas within the respiration chamber, it was not until 1958 that the relationships between the environmental temperature, hypoxia and oxygen consumption were demonstrated (Hill, 1958).

It has been known for a long time (Pembrey, 1898; Herrington, 1940) that within a certain range of environmental temperature (called the neutral temperature range) the metabolic rate of warm-blooded animals is minimal. At lower temperatures the animal's metabolic rate increases in order to maintain its body temperature and at higher temperatures it increases as a result of active cooling.

Cross et al.(1955) demonstrated that the $\dot{V}O_2$ of newborn infants fell when they were subjected to hypoxia. Hill (1958) working with new-born animals showed, however, that this response to diminished ambient oxygen concentration occurred only if the animals were exposed to a temperature below the neutral temperature zone. Within the neutral temperature zone, if the animal were made to breathe an atmosphere of 10% oxygen, oxygen consumption did not fall (Hill, 1959). A similar finding in the human has been reported by Oliver and Karlberg (1963), who subjected new-born infants to 15% oxygen in the inspired air.

Authors agree in broad principle that the neutral temperature range is that in which the animal consumes minimum quantities of oxygen. Opinions differ, however, on the exact range of the neutral temperature for human infants. Oliver and Karlberg (1963) have accepted 32 - 35°C as the neutral temperature range for nude

neonates; Brück et al.(1962) give 32-34°C as the acceptable range. Adamsons et al. (1964) state that the naked full-term neonate consumes minimal oxygen when the thermal gradient between body surface and environment does not exceed 1.5°C (with relative humidity 50%). Silvermann and Sinclair (1966) suggested that oxygen consumption is minimal when the temperature of the skin on the anterior portion of the abdomen in the steady state is between 36 and 37°C.

Bedford (1940) pointed out that "in two compartments the air temperature may be the same, but the humidity, air velocity and radiation intensity may differ to such an extent that the overall degree of warmth, as it affects the human body, is quite different." He therefore suggested the use of "effective" or "corrected effective temperature". Recent authors, measuring oxygen consumption have followed Bedford's suggestion and emphasised the importance of measuring and stating, in addition to temperature, the air velocity, humidity, and radiation exchanges between the subject and his environment. Despite this emphasis very few authors have, in fact, stated these factors in their publications. In this study, air temperature was between 32 and 34°C, air velocity less than 3cm/second, humidity 100%, and the two radiating surfaces (viz. the wall of the chamber and the skin of the baby) were within 3°C of each other. The effective temperature was therefore 32 - 34°C (Bedford tables). The mean $\dot{V}O_2$ of this series corresponds closely to $\dot{V}O_2$ of babies of comparable age studied at neutral temperature by other authors (Hill, 1965; Cross et al. 1966. Scopes 1965). As there is no reason to believe that this group of dark-skinned neonates behaves differently from fair-skinned normal neonates studied by other authors, there is reasonable justification for assuming that the above combination of environmental factors constituted a neutral environment for neonates in this study.

Of the five premature infants, three probably belonged to group 2 (small for dates) of Scopes (1965). They consumed more than 6ml/min/kg oxygen at the time of study on the seventh day after birth. The other two probably belonged to group 3; they consumed less than 6 ml/min/kg.

2. FEEDING

Lusk (1928), duBois (1936) and Peters and van Slyke (1946) demonstrated a 10 - 15% maximum increase in energy metabolism in adult subjects following an ordinary meal - this increase has been called "specific dynamic action of food". Levine et al. found that in infants this increase was less marked. Hill et al. (1965), more recently, found that "it made no difference to the basal metabolic rate whether the last feed had been taken half an hour or 3 hours previously".

All normal infants investigated in the present study had been breast-fed half an hour previously. This policy was adopted when it was found that those infants who were breast-fed fell asleep soon after they were introduced into the respiration chamber. A large proportion of the infants not fed before the $\dot{V}O_2$ measurement were awake and often cried vigorously following introduction into the chamber. Considering that crying can increase $\dot{V}O_2$ by as much as 100% (Brück, 1962), and the fact that $\dot{V}O_2$ may remain elevated for some time after crying has stopped, made clear the importance of the soporific effect of a pre-study breast-feed. At best the breast-feed would make no difference to the $\dot{V}O_2$ (Hill, 1965) and at worst, the error would be less than 10-15%; on the other hand, if the infant were not fed before the $\dot{V}O_2$ measurement the error could be up to 100% depending on how soon the $\dot{V}O_2$ measurement was begun after the crying had stopped.

3. SEDATIVES

In view of the fact that infants fell asleep soon after they were introduced into the respiration chamber, it was not necessary to give sedatives which might affect $\dot{V}O_2$ (Bornstein and Holm 1926; Lees 1964).

4. BODY WEIGHT

Earlier workers were preoccupied by whether the basal metabolism was more closely related to the body-weight than to the body surface area. "When the size of an individual is represented by weight alone, it is not possible to pay proper attention to the possible variations in the physical proportions of a subject. Variations in the latter exert an influence on the relationship between energy metabolism and body weight." (Karlberg 1952).

More recently, however, authors have shown that in human babies (aged between 1 week and 18 months and weighing up to 12 kg, Hill 1965 and Scopes 1966) correlation between weight and $\dot{V}O_2$ is good provided the weight range is not large.

In summary, it may be concluded that the environment was neutral in this series, and that the $\dot{V}O_2$ of dark-skinned neonates is no different from that of light-skinned neonates studied by others.

CHAPTER IV

MATERIAL, METHODS AND RESULTS OF OXYGEN CONSUMPTION MEASUREMENTS IN TETANUS NEONATORUM.

MATERIAL AND METHODS EMPLOYED IN THE STUDY OF OXYGEN CONSUMPTION IN TETANUS NEONATORUM.

A. OXYGEN CONSUMPTION MEASUREMENT:

The technique described in Chapter II was employed to measure $\dot{V}O_2$ of neonates suffering from tetanus (1) on admission, (2) following sedation, and (3) following extubation. Any one patient was not necessarily studied at all three stages.

The oxygen consumption of 37 neonates suffering from tetanus was measured soon after the neonate's arrival in the unit. This followed the clinical assessment of severity by two registrars but it was done before any sedation had been administered (admission $\dot{V}O_2$). The admission $\dot{V}O_2$ measured by the author was not available to the two registrars whose clinical assessment of severity of the disease on admission was recorded independently. The subsequent management of the neonates was in no way influenced by the $\dot{V}O_2$ values.

$\dot{V}O_2$ measurements were carried out on 29 neonates following sedation, when their muscle tone had been considerably reduced and spasms were absent or infrequent and mild. This group consisted of neonates who were treated conservatively because severity of their disease did not necessitate I. P. P. R. and "severe" neonates who could not be treated by I. P. P. R. because ventilators were not available.

The $\dot{V}O_2$ of 21 patients was measured following extubation.

B. BLOOD GAS ANALYSIS.

As an ancillary to the admission $\dot{V}O_2$ measurement, blood gas analysis were carried out in 25 neonates suffering from tetanus.

Gas tensions during spasms on "arterialized" blood, obtained by the technique of Saling (1964), were compared with "arterialized" blood gas tensions of normal neonates. Previously we have shown that no significant difference exists between arterial blood and "arterialized" blood (Desai et al., 1967). A shaven area of the scalp was cleaned with anti-septic and sprayed with ethyl-chloride until the skin developed pallor. When this was followed by a flush, a small incision was made. The freely flowing blood was then collected in heparinized capillary tubes which were held in the wound itself, care being taken to avoid air bubbles.

The pH of the "arterialized" blood was measured using a microtechnique and the carbon dioxide tension ($PaCO_2$) derived from a buffer-line obtained by equilibrating the blood with known tensions of carbon dioxide. The pH electrode was calibrated using precision buffer of pH 7.381 and 6.840 at 38°C.

The "arterialized" blood oxygen tensions (PaO_2) were measured with a Clarke electrode modified to take microspecimens (Desai et al., 1968).

The PaO_2 electrode was calibrated using water, which was equilibrated with atmospheric oxygen and a solution whose PO_2 was taken to be zero (sodium sulphite in 0·01 molar Borax). Oxygen tension of the water could be derived from the formula $PO_2 = 20·9 \times$ (Barometric pressure - 47 mm Hg).

RESULTS:

Figure 10 is representative of the records obtained during $\dot{V}O_2$ measurements of neonates suffering from severe tetanus. The upper tracing is the record of chest movements and spasms. The two horizontal lines correspond to 600 ml and 0 ml levels of the Krogh's spirometer. The slope between these two lines represents the fall in the spirometer level as the oxygen was removed from it.

Figures 6 and 11 are records obtained when the small capacity spirometer was interposed between the larger spirometer and the respiration chamber. In figure 11 A is the record of chest movements and spasms; B and C mark the 15 and 0 ml levels respectively of the smaller spirometer, the slope between B and C indicates the fall in level of the smaller spirometer as oxygen was removed from it by the patient. D is a record of 1 second time intervals. Figure 6 is the record of an infant having severe, almost continuous spasms; figure 11 is that of an infant who was having severe intermittent spasms. The pneumograph record in fig. 11 shows that at the beginning of a spasm the neonate takes a big breath. 1-1$\frac{1}{2}$ seconds later compression of the gas within the lungs, as a result of spasm of the thoracic and abdominal muscles, causes an apparent diminution in volume of the respiration chamber and the spirometer ($\dot{V}O_2$ slope). Towards the end of the spasm, as regular ventilation is being re-established, the heat generated by the intense muscular contraction is dissipated to the gas within the respiration chamber by the warmer gas exhaled by the neonate and by radiation of heat from the body surface. This heat dissipation causes expansion of gas within the respiration chamber and the spirometer. When the thermal equilibrium has been re-established, the $\dot{V}O_2$ slope becomes smooth but steeper than before the spasm indicating that $\dot{V}O_2$ has increased following the spasm.

Fig.10. RECORD OF OXYGEN CONSUMPTION MEASUREMENT DURING SEVERE SPASMS
(Large spirometer)

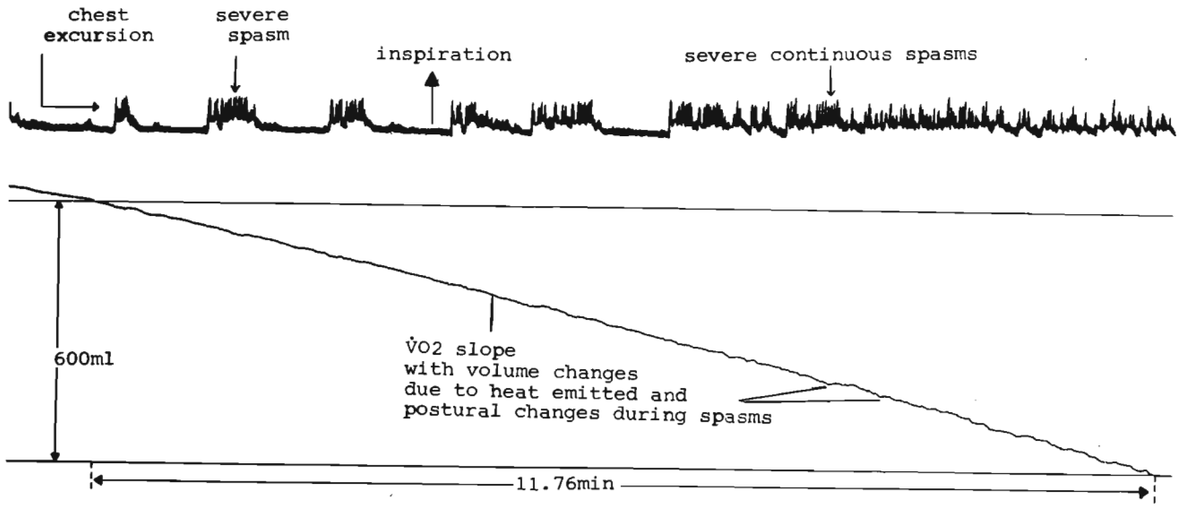


Fig.11. OXYGEN CONSUMPTION RECORD OF A NEONATE HAVING SEVERE, INTERMITTENT SPASMS

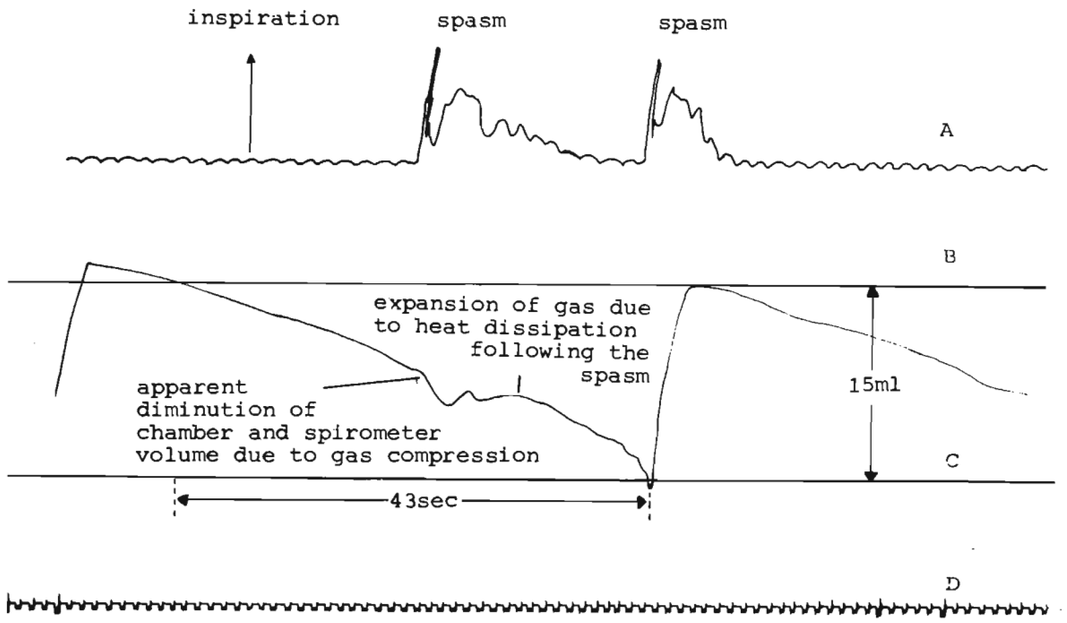


TABLE 1.

ADMISSION $\dot{V}O_2$ (ml/min/kg) OF NEONATES WITH TETANUS, THEIR CLINICAL SEVERITY ON ADMISSION AND THE TREATMENT.

"SEVERE"		"MODERATE"		"MILD"	
$\dot{V}O_2$	TREATMENT	$\dot{V}O_2$	TREATMENT	$\dot{V}O_2$	TREATMENT.
12.9	R/	9.8	C	8.2	C
15.7	R	17.2	C+	10.1	C
15.4	R	10.5	C	7.9	C
11.0	R	15.0	C+		
10.2	C	13.5	R		
19.5	R	13.6	R		
15.5	R	10.6	C		
18.9	R	10.0	C		
14.3	R	11.8	R		
13.8	R	12.0	R		
12.0	R	12.6	R		
17.2	R	12.1	R		
14.7	R	12.7	C+		
11.1	R				
17.9	R				
16.3	R				
11.1	R/				
17.8	R/				
13.8	R				
14.7	R				
11.7	R				

R 6
4
C
3.
C+

R represents treatment by I.P.P.R.

R/ represents patients who would have been treated by I.P.P.R. had ventilators been available, and for the purposes of this analysis are regarded as having been treated by I.P.P.R.

C represents treatment by conservative methods.

C+ represents those infants who cried audibly during the $\dot{V}O_2$ determination and are excluded in all subsequent statistical analysis. (See page 41).

Figure 12 is a similar record obtained from an infant experiencing mild spasms. Note that during a mild spasm, the changes described above are less marked and the irregularities in the $\dot{V}O_2$ slope less exaggerated. However, following this type of spasm also, the $\dot{V}O_2$ slope is steeper indicating that $\dot{V}O_2$ is increased following both mild and severe types of spasms.

In table 1 are presented the mean admission $\dot{V}O_2$ values of neonates with tetanus, their clinical severity at the time of admission, and the treatment they were eventually given.

TABLE 2.

ADMISSION $\dot{V}O_2$ (ml/min/kg) OF NEONATES WITH TETANUS COMPARED WITH $\dot{V}O_2$ OF NORMAL, SLEEPING NEONATES.

	Admission $\dot{V}O_2$ of neonates with tetanus.	*$\dot{V}O_2$ of normal, sleeping neonates.*
MEAN	*13.3*	*6.9*
S.D.	*2.91*	*0.78*
RANGE	*7.9 - 19.5*	*5.1 - 8.5*
NUMBER OF OBSERVATIONS	*37*	*44*

The differences between the means are statistically different at $p < 0.001$ level.

Table 2 shows that the mean $\dot{V}O_2$ of neonates with tetanus is almost twice that of the normal, sleeping neonates (see also appendix table Nos. 2 & 3).

Fig.12. OXYGEN CONSUMPTION RECORD OF A NEONATE EXPERIENCING MILD SPASMS

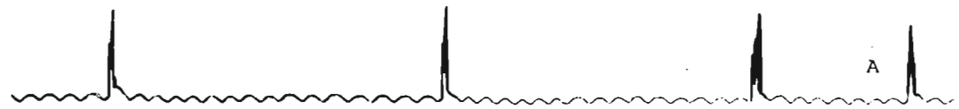


TABLE 3.

COMPARISON OF ADMISSION $\dot{V}O_2$ (ml/min/kg) OF NEONATES WITH "SEVERE" AND "MODERATE" TETANUS.

	Admission $\dot{V}O_2$ of "severe" neonates	Admission $\dot{V}O_2$ of "moderate" neonates
MEAN	14.5	11.65
S.D.	2.69	1.31
RANGE	10.2 - 19.5	9.8 - 13.6
NUMBER OF OBSERVATIONS	21	10

The differences are statistically significant at $p < 0.01$ level.

If the neonates are subdivided according to clinical severity of the disease, it is noted that the mean admission $\dot{V}O_2$ of "severe" neonates is significantly higher than the mean admission $\dot{V}O_2$ of "moderate" neonates (Table 3, Page 30). The admission $\dot{V}O_2$ values of "mild" neonates were not analysed statistically because of the small number involved and because this group generally constitutes neither a diagnostic nor a therapeutic problem. It is nevertheless interesting to note that the 3 infants with "mild" tetanus had admission $\dot{V}O_2$ values which were higher than the mean $\dot{V}O_2$ of normal, sleeping neonates.

Is it possible, on the basis of admission $\dot{V}O_2$ values, to predict which neonates with tetanus will require I. P. P. R. and which will not? The mean admission $\dot{V}O_2$ of neonates who required I. P. P. R. is significantly higher than the mean admission $\dot{V}O_2$ of neonates who were managed conservatively. This is also true of the clinically "moderate" group where the choice of treatment is often a problem (Tables 4 and 5, pages 33 & 34 respectively).

The $\dot{V}O_2$ of neonates, who had diminished muscular tone with infrequent, mild spasms or none at all during conservative treatment ranged from 4. 9 to 7. 9 ml/min/kg. The mean was 6. 4 ml/min/kg and was significantly less than the mean $\dot{V}O_2$ of normal, sleeping neonates (Table 6, page 35 and appendix table No. 4).

Twenty-one $\dot{V}O_2$ measurements were made on neonates following extubation. The $\dot{V}O_2$ ranged from 6. 6 to 11. 7 ml/min/kg. (mean 8. 4, Appendix Table No. 5). The interval between the onset of symptoms and this measurement, which was dependent on the duration of intubation, was variable. This may explain the wide scatter of the $\dot{V}O_2$ values. The increased muscular tone at the time of the $\dot{V}O_2$ measurement was variable and difficult to

quantitate clinically. This group of neonates also consumed more oxygen than the normal, sleeping neonates ($P < 0.001$).

RESULTS OF BLOOD GAS ANALYSES:-

The PaO_2, $PaCO_2$, pH and base excess values of neonates with tetanus are compared with similar figures for normal neonates in table 7, page 36. (The detailed tables appear in the appendix; tables 6 - 9). The differences in PaO_2 between the two groups are not statistically significant; those between $PaCO_2$ and base deficit are. The neonates with tetanus thus usually exhibit respiratory alkalosis and metabolic acidosis.

TABLE 4.

COMPARISON OF ADMISSION $\dot{V}O_2$ (ml/min/kg) OF NEONATES WITH TETANUS SUBSEQUENTLY TREATED CONSERVATIVELY AND BY I.P.P.R.

	Conservative treatment	I.P.P.R.
MEAN	9.7	14.3
S.D.	0.97	2.46
RANGE	7.9 - 10.6	11.0 - 19.5
NUMBER OF OBSERVATIONS	8	26

The differences are statistically significant at $p < 0.001$ level.

TABLE 5.

COMPARISON OF ADMISSION $\dot{V}O_2$ (ml/min/kg) OF NEONATES SUFFERING FROM "MODERATE" TETANUS SUBSEQUENTLY TREATED CONSERVATIVELY AND BY I. P. P. R.

CONSERVATIVE TREATMENT		I. P. P. R.	
	9. 8		13. 5
	10. 5		13. 6
	10. 6		11. 8
	10. 0		12. 0
			12. 6
			12. 1
MEAN	10. 2	MEAN	12. 6
S. D.	0. 332	S. D.	0. 72

The differences between the means are statiscally significant at $p < 0.001$ level.

TABLE 6.

COMPARISON OF $\dot{V}O_2$ OF NORMAL, SLEEPING NEONATES WITH $\dot{V}O_2$ OF SEDATED NEONATES, WHO, HAD DIMINISHED MUSCULAR TONE AND FEW MILD SPASMS OR NONE AT ALL.

	Sedated neonates	Normal, sleeping neonates.
MEAN	6. 4	6. 9
S. D.	0. 68	0. 78
RANGE	4. 9 - 7. 9	5. 1 - 8. 5
NUMBER OF OBSERVATIONS	29	44

The differences are statistically significant at $p < 0.01$ level. $t = 2.9$

TABLE 7.

COMPARISON OF PaO_2, $PaCO_2$, pH AND BASE DEFICIT OF NORMAL, RESTING NEONATES AND NEONATES WITH TETANUS.

	NORMAL RESTING NEONATES	NEONATES WITH TETANUS	STATISTICAL SIGNIFICANCE LEVELS
MEAN PaO_2 mm Hg.	76 (14)	71 (25)	P between 0.20 & 0.10
MEAN $PaCO_2$ mmHg.	34 (16)	29 (26)	$p < 0.05$
MEAN pH	7.393 (16)	7.349 (26)	P between 0.05 & 0.02
MEAN Base deficit m. eq. / Litre.	-3.2 (15)	-7.7 (25)	$P < 0.01$

The number of observations for each analysis is given in brackets.

CHAPTER V.

DISCUSSION.

A. THE VALUE OF ADMISSION $\dot{V}O_2$ MEASUREMENT IN TETANUS NEONATORUM AND ITS CLINICAL APPLICATION.

INTRODUCTION: PROBLEMS IN CLINICAL CLASSIFICATION AND SELECTION OF PATIENTS FOR TREATMENT.

On admission to the respiratory unit all neonates suffering from tetanus are seen by two registrars who assess the severity of the disease on clinical grounds before any sedation is given. Such assessment of severity is based on the following criteria:

"Mild" - muscular rigidity but no spasms.
"Moderate" - muscular rigidity with mild, infrequent spasms.
"Severe" - muscular rigidity with frequent, severe spasms.

Although it is theoretically possible, to categorise patients suffering from tetanus according to this classification, in practice the severity of the disease forms a continuous spectrum from the "mild" to very "severe" form. It is relatively easy to distinguish patients at the two extremes of the spectrum; those patients who suffer from tetanus which is neither mild nor very severe occupy an intermediate position. It is often difficult to decide clinically whether such patients are closer to the "mild" or to the "severe" end of the spectrum.

In this unit the treatment of tetanus is based on clinical assessment of the severity. The neonate suffering from "mild" tetanus is treated by conservative methods (Laurence et al., 1958, and Adams et al., 1959). Briefly, in this form of treatment chlorpromazine is used to control muscle rigidity and spasms. When necessary, phenobarbitone sodium is given in addition. All neonates with "severe" tetanus are treated in the first instance by conservative methods. If the severity and frequency of spasms are not reduced half an hour following 66 mg phenobarbitone sodium and 12.5 mg chlorpromazine given by intramuscular injection, tracheostomy is

performed and intermittent positive pressure respiration (I. P. P. R.) is started. The technique has been described in detail by Wright et al. (1961), Mann et al. (1963), and Jackson (1964). In summary, in the I. P. P. R. regimen, after intubation, tracheostomy is performed under local anaesthesia and total paralysis induced and maintained for ten days with d-tubocurarine; I. P. P. R. being supplied by mechanical ventilators. Within 24 - 48 hours after the withdrawal of d-tubocurarine, 10 days after the commencement of I. P. P. R., the muscle rigidity returns and persists for days or weeks afterwards. During this period a method of assisted ventilation is continued until the infant makes adequate spontaneous respiratory efforts. An attempt is made usually on the 21st day after the commencement of I. P. P. R. to withdraw the tracheostomy tube. If unsuccessful at the first attempt, further extubation attempts are made at weekly intervals.

The infant suffering from "moderate" tetanus is treated conservatively unless he developes one of the following criteria for I. P. P. R.:

1. severe spasms not controlled by phenobarbitone sodium and chlorpromazine,
2. central cyanosis due to laryngeal or oropharyngeal spasm,
3. apnoea.

Although it is generally true that the vast majority of patients diagnosed as "severe" on admission run a stormy course and those considered "mild" continue as such, there are exceptions. An occasional patient with severe spasms on admission, will settle on conservative treatment and occasionally too, a patient considered "mild" on admission will qualify for the "severe" category hours or days later.

Due to high admission rates and shortage of nursing staff and ventilators, occasions do arise when a neonate suffering from

"severe" tetanus cannot be treated by I. P. P. R. Such patients, although "severe", are then treated by conservative methods until a ventilator becomes available. Some of these infants lose muscle tone and become flaccid during the conservative treatment.

A. THE VALUE OF ADMISSION $\dot{V}O_2$ MEASUREMENT IN TETANUS NEONATORUM.

The accuracy of clinical assessment of severity of tetanus in the Durban unit can be gauged by the fact that of the 21 neonates classified on admission as "severe", all but one required I. P. P. R.; of the "moderate" group of 13 neonates, six required I. P. P. R. and the rest were managed satisfactorily on conservative treatment; none of the "mild" group required I. P. P. R. This pattern is typical of patients admitted to this unit and highlights the problem encountered in the "moderate" group.

The admission $\dot{V}O_2$ of neonates who required I. P. P. R. was significantly higher than the admission $\dot{V}O_2$ of neonates requiring only conservative treatment. This finding adds support to the supposition that the more frequent and more severe the spasms, the more oxygen the neonate must consume and the more severe the disease. Although this is a satisfactory generalization, is the admission $\dot{V}O_2$ of value in determining whether any specific patient should be subjected to I. P. P. R. or not? Reference to table 1 shows that none of the neonates treated conservatively had admission $\dot{V}O_2$ in excess of 11 ml/min/kg (with three exceptions to be discussed later) and none of the neonates treated by I. P. P. R. had admission $\dot{V}O_2$ less than 11 ml/min/kg. 11 ml/min/kg is thus a dividing line between those who are closer to the mild end of the spectrum and will not require I. P. P. R., and those who are closer to the severe end of the spectrum and will require I. P. P. R. At the extremes of the severity spectrum, where clinical assessment is satisfactory, $\dot{V}O_2$ contributed little; in the intermediate group it proved to be of value.

The real value of admission $\dot{V}O_2$ is that it enables one to choose at the time of admission the form of treatment the neonate should be allocated instead of having to postpone the decision for

hours or days while the neonate's degree of intoxication is clinically assessed. There were neonates in the "moderate" group who developed criteria for I. P. P. R. only hours or days following admission. All such neonates had admission $\dot{V}O_2$ in excess of 11 ml/min/kg and had this been used as the criterion, could have been treated by I. P. P. R. without delay. The early institution of I. P. P. R. in "severe" tetanus neonatorum, before the onset of respiratory failure, improves the prognosis (Holloway, 1967). Correctly classified on the basis of admission $\dot{V}O_2$ some of the "moderate" group of neonates would be saved unnecessary and relatively hazardous exposure to I. P. P. R. (mortality for "mild" and "moderate" tetanus 3. 3% and 5. 8% respectively and for "severe" tetanus treated by I. P. P. R. 36% - 44%).

Within the "moderate" group there were three neonates who had admission $\dot{V}O_2$ in excess of 11 ml/min/kg but who did not develope criteria for I. P. P. R. These three neonates cried audibly during the $\dot{V}O_2$ measurement. Crying is known to cause increased $\dot{V}O_2$ (Brück, 1962) and the high $\dot{V}O_2$ in these neonates was due in part to the crying and was not entirely a reflection of the severity of the disease. If $\dot{V}O_2$ alone were used for assessment of severity of the disease these crying neonates would erroneously be thought to be more severe than they really were. Thus although admission $\dot{V}O_2$ is a useful guide in the "moderate" neonates its interpretation must be qualified in the presence of audible crying.

Audible crying in tetanus neonatorum is a favourable sign as indicated by the fact that in the "moderate" group none of the neonates who cried audibly required I. P. P. R.; on the other hand, none of the neonates in the "severe" group had an audible cry. Audible crying during spasms implies functional vocal cords and air passages; the absence of crying implies profound

behavioural and neuromuscular disturbance which may well involve increased airway resistance.

FACTORS CONTRIBUTING TO THE INCREASED $\dot{V}O_2$ IN TETANUS NEONATORUM.

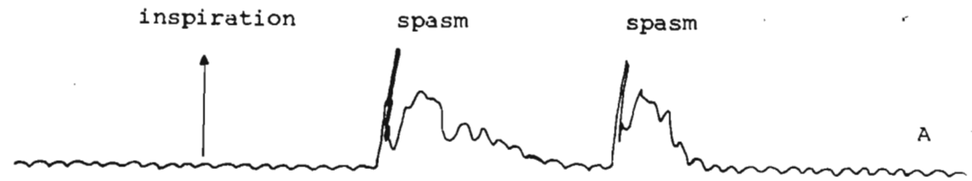
1. *MUSCULAR SPASMS:-*

During muscular exercise a healthy subject increases his tidal volume, ventilatory rate, and cardiac output to meet his extra oxygen requirements. Tetanus spasms which involve intense muscular exercise must also cause increased oxygen uptake by appropriate adjustments in cardiovascular and respiratory systems. These spasms affect all skeletal muscles, including the muscles of ventilation (Adams, 1964); rigidity of the abdomen, diaphragm, and thorax also interfere with ventilation (Kloetzel, 1964). It would appear therefore, that although tetanus spasms impose extra oxygen requirements on the organism, the simultaneous interference with the muscles of ventilation would tend to prevent the demand from being met.

In this study the mean admission $\dot{V}O_2$ of neonates with tetanus was almost twice that of the normal, sleeping neonates. How was this increased demand being met? Was it that the spasms did not interfere with ventilation sufficiently to affect oxygen uptake to any significant extent, or was it that although there was interference with ventilation during a spasm, the neonate was able in the spasm-free intervals to increase his ventilation sufficiently to meet the extra oxygen demand? Or was it that the $\dot{V}O_2$ although increased, was inadequate to meet the total requirements and the neonate remained hypoxic?

What happens to ventilation and $\dot{V}O_2$ during a spasm is best illustrated by reference to fig. 11, which is representative of a $\dot{V}O_2$ slope during severe, intermittent spasms. This record confirms the clinical observation that at the beginning of a severe spasm the neonate takes a deep inspiratory gasp; this is followed by compression of the gas within the lungs due to the increased airway resistance (possibly due to glottic or oropharyngeal spasm) and the simultaneous contraction of thoracic and abdominal musculature. The post-spasm $\dot{V}O_2$ slope is steeper than the prespasm slope, showing that $\dot{V}O_2$ following a spasm is increased. The breath holding during spasms is of variable duration and when prolonged can lead to cyanosis during the spasm. Thus either of the first two possibilities applies - the neonates can breathe during a spasm or they make up for breath holding during the inter-spasm periods. The determinations of PaO_2 (table 7, page 36 and appendix table No. 6) shows that infants with tetanus do not suffer sustained hypoxia despite increased oxygen demands and spasmodic interference with ventilation.

Fig.11. OXYGEN CONSUMPTION RECORD OF A NEONATE HAVING SEVERE, INTERMITTENT SPASMS



2. INCREASED MUSCLE TONE:-

The increased muscle tone in tetanus is manifested by generalised muscle rigidity, trismus and risus sardonicus.

Various authors have speculated on the possibility of increased muscle tone imposing extra oxygen requirements on mammals. Mott (1963) suggested that the increase in minimal oxygen consumption in the days immediately after birth may in part be due to the increased skeletal muscle tone associated with wakefulness. McCance (1959) suggested that the increased muscle tone and shivering constitute the first line of defence against a sudden fall in body temperature; he attributed the high metabolic rate following acclimatization to the increased "tone" in the skeletal muscles. Fairfield (1948) quotes Dill and Forbes (1941), Barbour et al. (1943) and Swift (1932) and agrees that "muscular rigidity and tonus are capable, in man and rats, of producing an increased metabolic rate" (Fairfield, 1948).

In the present study there were three groups of neonates who supported the hypothesis that increased muscle tone causes increased oxygen uptake.

The first group consisted of neonates suffering from "mild" tetanus and had increased muscle tone but no spasms. Although it is possible that other factors contributed to the increased $\dot{V}O_2$ in these neonates, the increased tone was the most striking clinical feature and probably caused most of the increased $\dot{V}O_2$.

The second group consisted of those neonates whose $\dot{V}O_2$ was measured during conservative treatment, when the muscular tone had been diminished considerably by chlorpromazine (Kochhar, 1961, Goodman and Gilman, 1965). The mean $\dot{V}O_2$ of

this group of neonates was significantly less than that of normal, sleeping neonates. If energy is required to maintain muscle tone, and if extra energy is required when muscle tone is increased, it is logical that less energy is expended when muscle tone is reduced.

The third group of neonates who supported this hypothesis were those, who, following I.P.P.R. and extubation, regained increased muscle tone. The $\dot{V}O_2$ of these neonates was increased to levels beyond those of normal, sleeping neonates (See appendix table No. 5).

3. TETANUS TOXIN:-

In addition to increased muscle metabolism in tetanus neonatorum, the possibility that the tetanus toxin has some unknown metabolic effects which contribute to the elevated $\dot{V}O_2$, must be considered.

The work of Müntz, which has never been published but was quoted by Pillemer and Robbins (1949), showed that the $\dot{V}O_2$ of rabbits and rats in which tetanus has been induced, rose progressively. The increase in $\dot{V}O_2$ in tetanus neonatorum found in the present study supports Müntz's finding.

Brönnimann and Stirnnemann (1955) reported that the $\dot{V}O_2$ of tissue cultures (measured in the Warburg apparatus) exposed to tetanus toxin was diminished. The tissue culture used by these authors is not specified and the fact that their methods and results have not been published in any detail makes critical appraisal of their finding impossible. However, if their observation is valid, it is necessary to explain the apparent paradox that tetanus toxin causes a decrease in $\dot{V}O_2$ in vitro; yet the whole

animal, suffering from tetanus, consumes increased quantities of oxygen.

Firor et al. (1940) suggested that tetanus toxin is altered into or liberates a different lethal agent in the animal. It is possible that this postulated lethal agent could cause an increase in $\dot{V}O_2$ whereas the toxin itself might cause a decrease. It is more likely that the tetanus toxin, though decreasing the energy metabolism of non-nervous tissue in vitro, imposes such an increased demand for oxygen by its effects on the intact neuromuscular system that the overall $\dot{V}O_2$ is increased. It is also unlikely that tetanus toxin has any action other than via the neuromuscular system in causing increased $\dot{V}O_2$. This is borne out by those sedated neonates whose muscle tone had been reduced to less than normal and who consumed less oxygen than normal, sleeping neonates. If the toxin had a stimulating effect other than via the neuromuscular system, these intoxicated but spasm-free neonates would still have consumed more oxygen than normal, sleeping neonates. It is possible that once the spasms had been eliminated, an inhibitory action of the tetanus toxin (as suggested by Brönnimann and Stirnnemann) was unmasked in these sedated neonates resulting in less than normal $\dot{V}O_2$. It seems more likely that the low $\dot{V}O_2$ was a reflection of the markedly diminished muscular tone (page 44).

If the increase in energy metabolism is brought about via the toxin's action on the nervous system, how and where is the toxin acting? It has been shown that the inhibitory post-synaptic potential produced at an inhibited motor neurone is reduced or abolished by tetanus toxin (Curtis, 1959). The resulting increased excitability of motor neurones probably accounts for the spasms and the increase of tone in tetanus (Brooks et al., 1957). It is not clear whether tetanus toxin prevents the release of a transmitter substance or becomes attached to subsynaptic inhibitory

transmitter (Brooks et al., 1957). Although it is possible that neuromuscular transmission is modified peripherally e. g. by reduction in cholinesterase activity with less destruction of acetylcholine, it is now generally accepted that "tetanus is initiated and, in its early stages at least, wholly dependent upon a central action of the toxin" (Laurence and Webster, 1963).

There is clinical evidence (Adams et al., 1966, Laurence et al. 1958, Smythe et al. 1961, Herzon et al., 1951, Garcia-Palmieri and Remirez 1957, and Montgomery 1961) which points to the toxin causing medullary depression and Baker (1942) has shown histologically that the dorsal motor nucleus of the vagus nerve is frequently selectively damaged by tetanus toxin. If the net result of the action of the tetanus toxin is stimulation of the nervous system (by whatever mechanism), how can it also be held responsible for the depression of the medullary centres? It is possible that tetanus toxin initially causes excitation and then later depression of the neuronal activity due either to initial hyperactivity or to direct secondary depressant effect of the toxin. This hypothesis is supported by the finding that reflex inhibition of the heart by vagal stimulation is first enhanced and later depressed by the toxin (Mikhailov, 1960). It is also possible that the preterminal picture of paralysis and flaccidity resulting in respiratory failure in tetanus neonatorum and in animals in whom tetanus had been induced (Brönnimann and Stirnnemann, 1956), may be a manifestation of exhaustion of energy providing mechanisms, which are drawn upon heavily during the early stimulation period.

4. BODY TEMPERATURE:-

van't Hoff (1884) observed that the velocity of chemical reaction increased with increasing temperature.

Do the warm-blooded animals and human organisms react to changes in their body temperatures in accordance with this chemical law? Mount and Rowell (1960) working with pigs, and Roberts et al. (1949) working with rats reported a linear relationship between body temperature and $\dot{V}O_2$. Fletcher and Bunker (1966) reported increases in metabolic rate of the order of 5% for each degree Fahrenheit above 99°F. du Bois (1921) came to the conclusion that in adult humans the metabolic rate increased by 13% for each degree centigrade rise in body temperature. F. H. Adams et al. (1964) working with premature infants found a close correlation between $\dot{V}O_2$ and rectal temperature, regardless of age. Scopes (1966) found a linear relationship between the $\dot{V}O_2$ and body temperature only during the first six hours of life. Adamsons et al. (1965) reported that in neonates 0 - 6 hours old the minimal $\dot{V}O_2$ was related to skin-environmental temperature gradients and not to the rectal temperature. Hill et al. (1965) working with full-term infants (0 - $10\frac{1}{2}$ days old) found that "the basal metabolic rate is very little affected by variations in body temperature of a degree or so around 37°C." Mestyan (1962) and Adamsons (1966) are in general agreement with this. If one accepts that $\dot{V}O_2$ may have been influenced by the body temperature, the increase in metabolic rate due to this factor alone cannot account for more than a maximum of 39% above the basal $\dot{V}O_2$. This estimate is reached by considering that the mean rectal temperature of the normal, sleeping neonates was almost 37°C and applying the large increment (rise in metabolic rate of 13% per degree centigrade rise in rectal temperature) of du Bois to the maximum rise in temperature (viz. 40°C)

observed in this series. This maximum possible increase in $\dot{V}O_2$ still falls far short of the almost 100% increase in $\dot{V}O_2$ noted in majority of the "severe" patients (table 1). This lends further support to the suggestion that the major factors contributing to the increased oxygen uptake in tetanus neonatorum are muscle spasms and increased muscular tone. (Pages 42 and 44).

B. BLOOD GAS ANALYSIS AND THEIR VALUE IN TETANUS NEONATORUM.

B. BLOOD GAS ANALYSES AND THEIR VALUE IN TETANUS NEONATORUM:

Although some spasms are severe enough to cause cyanosis, the mean PaO_2 of "arterialized" blood collected from tetanus neonates during spasms does not differ statistically from the mean PaO_2 of "arterialized" blood obtained from normal neonates (table 7, Page 36 - see appendix table No. 6). This finding indicates that not all spasms interfere with ventilation sufficiently to cause arterial hypoxaemia. On the contrary, the low $PaCO_2$ values indicate that these neonates are capable of, and do increase their alveolar ventilation. This low $PaCO_2$ probably corresponds to the fall in $PaCO_2$ found during heavy work by healthy, adult subjects (Holmgren and Linderholm, 1958).

If arterial oxygenation is adequate, what is the metabolic acidosis due to? (table 7, Page 36). Although not all spasms cause cyanosis and apparent oxygen lack in the tissues, the spasm which is severe enough to cause cyanosis undoubtedly causes cellular anoxia, resulting in lactic acid release. The metabolic acidosis may be a reflection of lactic acid accumulation resulting from successive episodes of anoxia (Herber, 1948) or from the normal muscular circulatory impairment found during isometric contraction in exercise. This causes some anaerobic cellular respiration and lactate is released despite normal ventilation. Although the arterial oxygenation during an average spasm is normal, it is not unlikely that the muscle cells extract more oxygen from the arterial blood during a spasm than they would do at rest. Even this extra extraction is probably not sufficient to meet the total oxygen requirements. This "relative anoxia" would also cause lactic acid release (as during exercise in a healthy subject). The neonate suffering from "severe" tetanus would be expected to suffer more episodes of cyanosis and the

degree of "relative anoxia" would also be more marked. This hypothesis is supported by the finding that all those neonates who had severe metabolic acidosis at the time of admission to the hospital, required I. P. P. R.; none of those who were managed conservatively had marked metabolic acidosis (Appendix table No. 9).(Allowing, of course, for the fact that even normal neonates have a mild metabolic acidosis).

Although a firm statement cannot be made because of the small numbers involved, it can be seen that a neonate with tetanus, who has already developed a marked metabolic acidosis at the time of admission to hospital, suffers from a severe form of the disease and will almost certainly require I. P. P. R. The absence of metabolic acidosis is, however, not necessarily a good prognostic sign.

CHAPTER VI.

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

1. The oxygen consumption of 36 normal and 37 dark-skinned neonates with tetanus was measured in a closed circuit, temperature-controlled respirometer.

2. The normal $\dot{V}O_2$ is almost 7 ml/min/kg which is the same as that for light-skinned neonates. $\dot{V}O_2$ of neonates with tetanus varies with the severity of the disease, and ranged from 7.9 to 19.5 ml/min/kg.

3. The increase in $\dot{V}O_2$ in neonates with tetanus is probably due largely to the increased muscular exercise and tone. Deep body temperature in febrile infants could contribute at a maximum only 39% of the increase over the basal $\dot{V}O_2$.

4. $\dot{V}O_2$ measurements are well correlated with the treatment allocated after clinical assessment. $\dot{V}O_2$ measurements are of assistance in determining whether to treat a "moderately" severe neonate conservatively or by I.P.P.R. Much delay in instituting the necessary therapeutic regimen could be avoided by using the "admission $\dot{V}O_2$" determination as a criterion.

5. The dividing line separating candidates for conservative treatment or I.P.P.R. is 11 ml/min/kg. Allowance has to be made for neonates who cry during the determination as this elevates the metabolic rate.

6. PaO_2 measured on "arterialized" blood during spasms is not significantly different from that of normal neonates. $PaCO_2$ is less than normal.

Normal oxygenation is maintained despite the impairment of ventilation by spasmic contractions. If metabolic acidosis is marked on admission of the neonate to the hospital the chances are that he will need I. P. P. R.

APPENDIX

THERMISTORS - PROBLEMS IN DESIGN AND CALIBRATION.

Introduction:- The thermistor is a device whose electrical resistance alters measurably with its temperature.
This relationship is given by

$$R = A\ e^{B/T}$$

A, B are constants depending on the method of construction and nature of material used in the manufacture of the thermistors.
R is resistance in Ohms.
T is the absolute temperature.
e is the base of the natural logarithm. (e= 2. 7183).

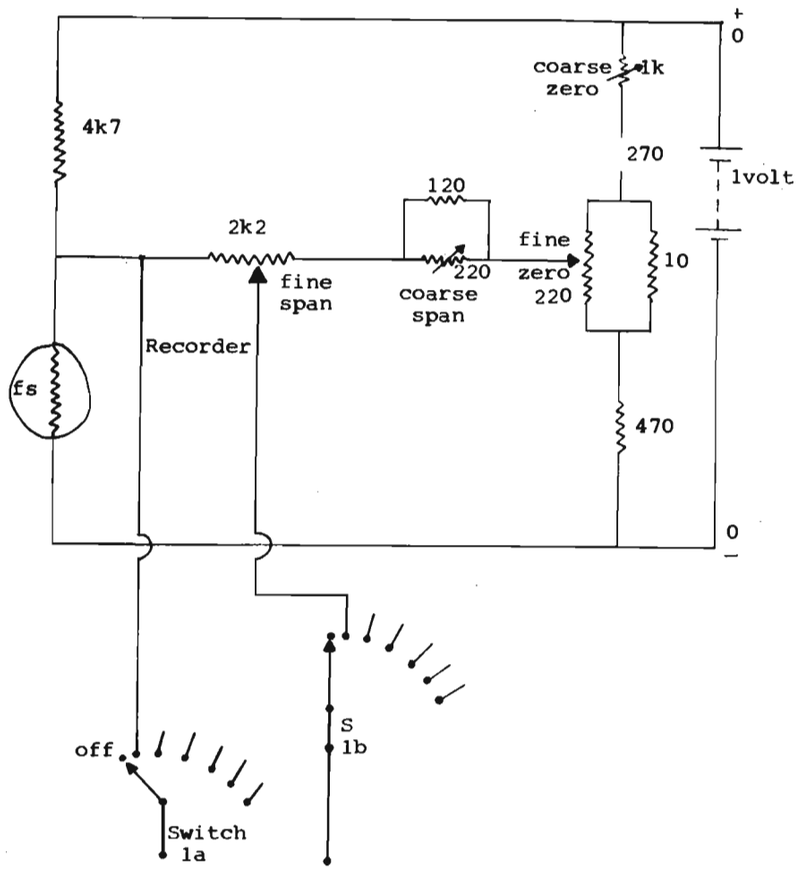
Though two thermistors may exhibit the same resistance at one temperature, their resistance will not necessarily be the same at another temperature.

USE OF THERMISTORS IN THIS STUDY:-

In this study three thermistors were required to measure temperature of the gas within the chamber, two to measure the baby's skin temperature, and one to measure the baby's rectal temperature. The locally available commercial units had a recording device attached to each thermistor; they were very expensive and did not satisfy the degree of accuracy required.
A switching circuit was designed so that the six thermistors' outputs could be recorded on a single channel direct writing recorder. (Circuit diagram).

Initially glass probe thermistors (type Fs-2, Stantel) were used to measure all temperatures. They were calibrated against a mercury thermometer in the water-bath (in which the water was circulated and the preset temperature did not vary

THE THERMISTOR CIRCUIT DIAGRAM



by more than 0·05°C.). The mercury thermometer whose degree of resolution was 0·01°C, read from 0°C to 50°C. When these thermistors were used for measuring gas temperatures and checked against the same mercury thermometer the temperatures recorded by the two measuring devices did not agree.

It was suspected that the heat dissipated by the glass thermistors differed in gas and water. This suspicion was borne out by the fact that over the same temperature ranges the voltage difference across the thermistor was different when used in gas and in water. The subsequent use of contact thermistors (type M 52-Stantel) did not exhibit the same phenomenon. Although calibrated in water the glass thermistor (type Fs - 2) did not present the above problem when used for measuring rectal temperature. Thus contact thermistors were later employed to measure all temperatures except rectal.

In this study gas temperatures were read to an accuracy of 0·025°C; the skin temperature to 0·1°C and the rectal temperature to 0·125°C.

The temperature of the thermistor element may rise considerably if the current passing through it is high. On the other hand, if very low voltage is used to reduce this self-heating effect, the sensitivity is decreased. For the purposes of this study, the ideal voltage was found, after trial and error, to be 1 volt.

A "drift" of up to 2°C within 48 hours was found during the early stages of the use of these thermistors. It was noted later that if the power supply was not switched off this "drift" did not occur.

APPENDIX TABLE NUMBER 1.

VOLUME CHANGES IN THE APPARATUS DUE TO BAROMETRIC PRESSURE AND TEMPERATURE FLUCTUATIONS - (ml).

Calculated volume changes	Volume changes recorded by the apparatus.
+8	+5
-8	-11
-6	-5
+14	+11
+13	+16
0	0
+35	+38
-8	-5
-26	-27
-7	-5
0	0
-14	-16
+4	+5
-11	-11
-11	-11
-16	-11
+8	+11
+74	+77
+32	+33
+33	+33
+25	+22
+16	+16

VOLUME CHANGES DUE TO AMBIENT BAROMETRIC PRESSURE AND GAS TEMPERATURE FLUCTUATIONS

To assess the volume changes in the apparatus due to changes in the barometric pressure and temperature of the gas within the respiration chamber, control experiments without the subject in the chamber were carried out.

The apparatus was connected as it would be during a $\dot{V}O_2$ measurement and tested for leaks; no subject was put into the chamber. The barometric pressure, gas temperatures and the time were recorded.

The expected volume changes calculated on the basis of the formula

$$\frac{PB_1 - Pw_1}{T1} \times V_1 = \frac{PB_2 - Pw_2}{T2} \times V_2$$

are presented with actual volume changes recorded by the apparatus during one such control experiment. (Appendix table No. 1).

APPENDIX TABLE NO. 2

Hospital No., race, sex, age, weight, and $\dot{V}O_2$ of normal, neonates in this study.

Hospital No.	Initials	Race	Sex	Age (days)	Weight (kg.)	$\dot{V}O_2$ (ml/min/kg.).
27389	P. N.	A	M	7	3. 35	7. 7
25749	E. M.	A	F	6	2. 56	6. 9
28432	G. K.	A	M	7	2. 70	7. 0
29531	T. G.	A	F	7	2. 87	7. 6
28954	T. P.	A	F	8	3. 18	6. 5
27064	N. K.	A	M	4	3. 52	5. 6
5186	H. H.	A	F	8	2. 45	5. 1+
27954	E. M.	A	F	8	3. 30	7. 0
25715	A. M.	A	F	6	2. 84	6. 2 6. 9
27983	D. D.	A	F	6	3. 50	8. 5
27038	M. B.	A	M	7	3. 01	6. 4 6. 2 6. 4
25261	A. M.	A	M	13	3. 41	6. 3
29194	M. N.	A	F	12	3. 18	8. 0
7190	P. S.	I	F	6	3. 61	6. 1
28228	N. M.	A	F	10	3. 18	7. 5
6878	P. N.	I	F	7	3. 13	6. 9 6. 8
26865	E. S.	A	F	6	3. 52	5. 9
27507	V. N.	A	F	4	3. 30	6. 2
26872	N. S.	A	F	9	2. 30	7. 2+ 7. 5
28077	A. G.	A	F	6	3. 21	6. 4
5978	H. A.	I	F	7	2. 45	5. 3+
33733	R. M.	A	F	9	3. 27	6. 7

APPENDIX TABLE NO. 2 - CONTINUED

7149	P. S.	I	F	6	2. 61	6. 9
80	F. M.	A	F	5	3. 41	7. 5
34	M. Z.	I	M	5	2. 64	7. 0
26410	A. N.	A	M	6	3. 55	6. 3 6. 0
6669	M. N.	I	M	7	3. 52	7. 0 7. 6
26000	K. T.	A	M	8	2. 84	7. 5
25549	D. M.	A	M	6	3. 60	8. 0
25632	F. M.	A	M	4	3. 43	7. 3 6. 3
6975	G. N.	I	M	5	3. 01	5. 9
26187	D. N.	A	M	5	2. 50	7. 6+
30605	O. N.	A	F	11	3. 04	8. 2
8038	L. H.	I	F	4	3. 27	7. 5
28545	B. M.	A	M	6	2. 30	8. 1+
29350	T. N.	A	M	6	3. 47	7. 0
			MEAN	6. 8	3. 08	6. 9

+ indicates neonates whose birth weight was 2. 5 kg. or less.

Brackets indicate those neonates on whom more than one $\dot{V}O_2$ measurement was carried out.

I represents Indians

A represents Africans

APPENDIX TABLE NO. 3.

Hospital No., race, sex, age, weight and admission $\dot{V}O_2$ of neonates with tetanus.

Hospital	Initials	Race	Sex	Age (days)	Weight (kg.)	Admission $\dot{V}O_2$ (ml/min/kg.)
4815	P. N.	A	F	5	3. 07	12. 9
1753	K. H.	A	F	5	2. 90	15. 7
1750	A. Z.	A	M	8	2. 93	15. 4
1748	M. Z.	A	F	14	2. 95	9. 8
1747	M. G.	I	M	6	2. 95	11. 0
1744	Z. M.	A	M	7	2. 98	10. 2
1743	W. D.	A	F	7	3. 07	8. 2
1742	M. M.	A	M	10	2. 50	17. 2
1741	P. S.	A	M	10	2. 81	10. 5
1739	G. M.	A	M	14	2. 90	15. 0
1738	M. T.	A	F	8	3. 24	19. 5
1727	N. B.	A	F	7	3. 01	15. 5
1722	T. F.	A	F	3	2. 79	18. 9
1718	Z. H.	A	M	8	3. 32	14. 3
1704	B. H.	A	M	8	3. 64	13. 8
1700	V. K.	A	M	5	2. 47	12. 0
1697	P. K.	A	M	8	3. 18	13. 5
1696	T. S.	A	F	6	2. 75	17. 2
1691	M. N.	A	M	5	2. 87	14. 7
1689	N. S.	A	M	5	3. 00	11. 1
1687	M. B.	A	F	7	2. 56	17. 9
1808	S. D.	A	F	10	3. 18	13. 6
1809	P. M.	A	M	6	3. 04	10. 6
1811	N. K.	A	F	7	3. 07	16. 3
1813	S. S.	A	M	5	3. 77	11. 1
1814	B. J.	A	M	5	2. 90	17. 8
25502	D. N.	A	F	7	2. 50	10. 0
1819	N. C.	A	F	8	2. 81	11. 8
1826	T. M.	A	M	7	3. 20	12. 0

APPENDIX TABLE NO. 3 - CONTINUED

1827	S. Z.	A	F	6	3. 21	12. 6
1832	C. G.	A	M	7	3. 24	10. 1
1835	P. M.	I	F	8	1. 97	13. 8
1836	B. M.	A	M	12	4. 04	7. 9
1841	H. V.	A	M	7	3. 69	12. 1
1846	Z. N.	A	F	8	2. 93	12. 7
1848	N. N.	A	F	5	1. 49	14. 7
1847	P. M.	A	F	6	2. 64	11. 7
			MEAN	7. 3	2. 96	13. 3

APPENDIX TABLE NO. 4

Hospital No., race, sex, age, weight, and $\dot{V}O_2$ of neonates who, during conservative treatment, had few, mild spasms or no spasms at all.

Hospital No.	Initials	Race	Sex	Age (days)	Weight (kg.)	$\dot{V}O_2$ (ml/min/kg.)
4815	P. N.	A	F	5	3.47	6.7
1753	K. H.	A	F	5	2.88	6.7
1750	A. Z.	A	M	8	2.93	6.4
1744	M. Z.	A	M	7	2.98	6.8
1743	W. D.	A	M	7	3.01	6.3
1742	M. M.	A	M	10	2.73	5.3
1741	P. S.	A	M	10	2.90	6.9
1739	G. M.	A	M	14	2.90	7.9
1736	D. N.	A	F	7	4.15	6.3
1745	C. M.	A	F	15	2.81	6.9
1726	B. M.	A	M	8	3.55	6.1
1719	N. Z.	A	F	9	2.40	6.8
1717	B. N.	A	M	8	2.61	5.0
1711	N. K.	A	F	13	3.07	6.5
1708	T. M.	A	F	7	3.01	6.1
1707	N. M.	A	M	7	2.45	6.1
1700	V. K.	A	M	5	2.47	6.1
1697	P. K.	A	M	6	3.27	6.9
1691	M. N.	A	M	5	2.87	6.9
1687	M. B.	A	F	7	2.80	6.2
1686	P. D.	A	M	5	3.40	4.7
1681	Z. N.	A	M.	8	2.40	6.7
1680	T. D.	A	M	10	3.40	6.6
1808	S. D.	A	F	10	3.18	6.3
1809	P. M.	A	M	6	3.24	6.6
1811	N. K.	A	F	6	3.10	6.2
25507	D. N.	A	F	7	2.50	7.2

APPENDIX TABLE NO. 4 - CONTINUED

1819	N. C.	A	F	8	2. 81	6. 3
1832	C. G.	A	M	7	3. 60	4. 9
			MEAN	7. 9	3. 00	6. 4

APPENDIX TABLE NO. 5.

$\dot{V}O_2$ OF NEONATES TREATED BY I. P. P. R. AND STUDIED FOLLOWING EXTUBATION (ml/min/kg. S. T. P. D.)

	8.5
	11.5
	7.8
	8.2
	7.7
	7.3
	8.6
	8.3
	8.3
	8.6
	8.7
	7.5
	6.9
	6.6
	8.2
	7.0
	7.8
	10.6
	9.6
	11.7
	7.3
MEAN	8.4

There is a statiscally significant difference ($p < 0.01$) between the mean $\dot{V}O_2$ of this group of neonates and the mean $\dot{V}O_2$ of normal, sleeping neonates.

APPENDIX TABLE NO. 6

OXYGEN TENSIONS OF "ARTERIALIZED" BLOOD FROM NORMAL AND TETANUS NEONATES (mm. Hg.)

	NORMAL	TETANUS
	73	57
	75	72
	76	72
	73	37
	70	88
	90	79
	71	80
	75	65
	82	82
	77	81
	78	74
	73	65
	77	77
	75	63
Mean	76	70
		68
		65
		76
		81
		70
		72
		81
		78
		51
		76
Mean		71

APPENDIX TABLE NO. 7

CARBON DIOXIDE TENSIONS OF "ARTERIALIZED" BLOOD FROM NORMAL AND TETANUS PATIENTS (mm. Hg.)

	NORMAL	TETANUS
	36	25
	35	27
	34	15
	34	27
	45	32
	35	41
	32	26
	34	29
	37	36
	32	25
	32	31
	34	27
	22	33
	35	36
	37	36
	34	37
		36
Mean	34	38
		35
		23
		28
		22
		30
		25
		15
		41
		MEAN 29

APPENDIX TABLE NO. 8

THE pH VALUES OF "ARTERIALIZED" BLOOD FROM NORMAL AND TETANUS NEONATES.

NORMAL	TETANUS
7.360	7.333
7.398	7.420
7.388	7.145
7.380	7.400
7.345	7.380
7.354	7.250
7.380	7.440
7.450	7.425
7.400	7.310
7.390	7.425
7.410	7.315
7.433	7.430
7.465	7.350
7.362	7.375
7.380	7.320
7.393	7.365
	7.350
Mean 7.393	7.310
	7.365
	7.350
	7.330
	7.310
	7.320
	7.408
	7.450
	7.190
Mean	7.349

APPENDIX TABLE NO. 9

THE BASE DEFICIT VALUES OF NORMAL AND TETANUS NEONATES (M. Eq. / Litre).

In the case of Tetanus Neonates R represents I. P. P. R.
C represents Conservative treatment.

	NORMAL	TETANUS	
	-4. 5	-11. 0	R
	-2. 5	-4. 2	C
	-3. 8	-24. 0	R
	-4. 3	-5. 7	R
	-1. 4	-10. 5	R
	-5. 6	-3. 0	R
	-5. 0	-3. 2	R
	-1. 0	-8. 0	R
	-5. 0	-4. 2	R
	-3. 3	-9. 3	R
	-0. 8	-3. 8	C
	-4. 2	-6. 0	R
	-4. 8	-3. 0	R
	-2. 8	-8. 0	R
	+0. 3	-3. 6	C
		-5. 0	R
MEAN	-3. 2	-7. 0	R
		-4. 5	R
		-8. 2	R
		-9. 0	R
		-13. 5	R
		-8. 8	R
		-7. 0	R
		-7. 0	R
		-14. 1	R
	MEAN	-7. 7	

Environmental gas temperatures in respiration chamber during $\dot{V}O_2$ measurements of normal neonates. (degrees centigrade.)

Beginning of expt.	*End of expt.*
33. 15	33. 20
33. 625	33. 675
33. 175	33. 30
33. 30	33. 30
33. 675	33. 70
33. 30	33. 35
33. 20	33. 55
33. 275	33. 35
33. 575	33. 625
33. 175	33. 525
33. 225	33, 55
33. 875	33. 925
33. 75	33. 825
33. 825	33. 875
33. 10	33. 375
33. 20	33. 50
33. 10	33. 325
33. 175	33. 475
32. 975	33. 175
33. 225	33. 25
33. 70	33. 775
32. 75	33. 15
33. 425	33. 65
33. 425	33. 80
33. 20	33. 25
33. 625	33. 675
33. 325	33. 425
32. 975	33. 35
33. 35	33. 575
32. 825	32. 925
32. 875	32. 90
33. 625	33. 90
33. 05	33. 40
33. 40	33. 475
33. 225	33. 60
33. 325	33. 65
33. 325	33. 65
33. 65	33. 675
32. 87	33. 125
33. 025	33. 75
33. 025	33. 475
33. 025	33. 025
33. 925	33. 25
33. 275	33. 325

Skin temperatures on anterior abdominal wall during $\dot{V}O_2$ measurement of normal neonates (degrees centigrade).

Beginning of expt.	*End of expt.*
35. 2	35. 2
37. 0	37. 2
35. 1	34. 5
36. 0	36. 0
36. 0	36. 1
36. 0	36. 1
35. 1	34. 6
36. 0	35. 9
36. 7	36. 8
36. 1	36. 5
36. 2	36. 4
37. 2	37. 4
36. 8	36. 8
36. 8	37. 5
34. 4	34. 7
35. 4	35. 7
35. 7	35. 9
36. 0	36. 1
36. 2	36. 3
36. 4	36. 5
36. 6	36. 7
35. 6	35. 8
37. 0	37. 1
37. 0	37. 1
35. 9	36. 1
37. 0	37. 1
35. 9	35. 7
36. 6	36. 7
36. 0	36. 1
35. 6	35. 4
38. 1	38. 1
37. 7	38. 0
36. 0	35. 9
36. 1	36. 2
36. 8	36. 9
36. 5	36. 0
36. 0	36. 7
36. 8	36. 8
35. 9	36. 1
36. 7	36. 7
36. 6	36. 8
35. 9	35. 7
36. 0	36. 1
35. 9	36. 0

Skin temperature on posterior chest wall during $\dot{V}O_2$ measurement of normal neonates (degrees centigrade).

Beginning of expt.	*End of expt.*
35. 7	35. 8
36. 3	36. 3
35. 4	35. 6
35. 4	35. 4
36. 1	36. 1
35. 9	35. 9
35. 6	35. 0
35. 4	35. 2
35. 7	36. 1
35. 2	35. 6
35. 8	36. 2
36. 1	36. 3
36. 4	36. 4
36. 3	36. 2
35. 3	35. 4
35. 5	35. 4
35. 4	35. 6
36. 4	36. 3
35. 9	36. 1
36. 1	36. 2
36. 0	35. 8
35. 5	35. 6
36. 0	36. 1
36. 0	36. 1
35. 9	35. 9
36. 2	36. 2
35. 7	35. 5
36. 2	36. 5
36. 0	36. 2
35. 7	35. 7
37. 3	37. 4
36. 9	37. 3
35. 6	35. 9
35. 9	35. 9
35. 5	35. 7
37. 0	35. 8
35. 5	35. 8
36. 1	36. 1
35. 8	35. 9
35. 8	36. 2
37. 0	37. 1
35. 8	35. 5
36. 1	36. 2
35. 9	35. 8

Rectal temperatures during $\dot{V}O_2$ measurements of normal neonates (degrees centigrade).

Beginning of expt.	*End of expt.*
36. 750	36. 750
36. 875	37. 000
36. 250	36. 375
36. 750	36. 750
37. 125	37. 125
36. 750	36. 750
35. 250	35. 600
36. 375	36. 375
36. 875	37. 125
36. 250	36. 625
36. 500	36. 750
37. 500	37. 500
37. 125	37. 125
37. 125	37. 125
36. 875	36. 875
36. 750	37. 000
37. 125	37. 125
37. 000	37. 250
37. 250	37. 375
36. 625	36. 750
36. 500	36. 500
36. 750	36. 750
36. 750	36. 750
36. 750	36. 750
36. 875	36. 875
36. 750	36. 750
37. 875	37. 750
37. 000	37. 000
36. 375	36. 375
36. 750	36. 750
36. 750	36. 750
37. 000	37. 000
37. 000	37. 000
36. 625	36. 875
36. 500	36. 500
36. 875	36. 875
36. 625	36. 625
36. 875	37. 500
37. 500	37. 500
37. 500	37. 500
36. 750	36. 875
37. 000	37. 000
36. 750	36. 750
36. 875	36. 875

Environmental gas temperatures in respiration chamber during admission $\dot{V}O_2$ measurement of neonates suffering from tetanus. (degrees centigrade).

Beginning of expt.		*End of expt.*	
32. 95	33. 05	33. 025	33. 15
32. 425	33. 05	32. 625	33. 10
32. 15	33. 80	32. 25	34. 00
32. 525	32. 975	32. 55	33. 00
32. 525	33. 25	32. 60	33. 425
32. 85	32. 925	32. 95	33. 025
32. 95	33. 10	33. 10	33. 10
33. 25		33. 25	
33. 45		33. 55	
33. 65		33. 75	
33. 725		33. 80	
33. 50		33. 75	
33. 30		33. 475	
33. 35		33. 525	
33. 625		33. 75	
33. 525		33. 825	
33. 25		33. 35	
33. 600		33. 75	
33. 65		33. 775	
33. 50		33. 65	
33. 45		33. 575	
33. 30		33. 30	
33. 15		33. 275	
33. 30		33. 30	
32. 60		32. 60	
33. 175		33. 225	
33. 175		33. 225	
33. 40		33. 60	
33. 40		33. 50	
33. 475		33. 625	

Skin temperatures on anterior abdominal wall during admission $\dot{V}O_2$ measurement of neonates suffering from tetanus (degrees centigrade).

Beginning of expt.	*End of expt.*
38. 00	38. 30
37. 10	37. 30
36. 30	36. 40
36. 50	36. 40
36. 90	36. 70
35. 50	35. 80
36. 20	36. 30
37. 60	37. 80
37. 30	37. 30
37. 30	37. 60
39. 50	39. 60
40. 40	40. 60
37. 50	38. 00
36. 70	36. 70
38. 00	38. 30
37. 60	38. 00
36. 80	37. 00
38. 70	38. 60
37. 50	37. 70
37. 10	36. 60
37. 60	37. 70
38. 10	38. 10
36. 50	36. 50
36. 80	36. 80
34. 30	34. 30
37. 60	37. 60
37. 60	37. 60
36. 50	37. 10
37. 20	37. 30
36. 20	36. 60
36. 20	35. 80
35. 50	35. 50
35. 40	35. 40
35. 50	35. 50
33. 60	34. 00
33. 50	33. 50
34. 60	34. 80

Skin temperatures on posterior chest wall during admission $\dot{V}O_2$ measurement of neonates suffering from tetanus (degree centigrade)

Beginning of expt.	*End of expt.*
36. 7	36. 8
36. 8	36. 8
35. 2	35. 3
35. 7	35. 7
34. 4	34. 3
35. 3	35. 5
35. 7	35. 7
37. 0	37. 4
36. 4	36. 4
37. 2	37. 5
36. 8	37. 2
39. 9	40. 2
37. 1	37. 5
36. 2	36. 2
37. 1	37. 4
36. 8	37. 1
37. 0	37. 0
37. 5	37. 3
37. 3	37. 7
36. 4	36. 6
38. 2	38. 3
37. 4	37. 4
36. 2	36. 2
35. 6	35. 6
33. 1	33. 1
37. 0	37. 0
37. 0	37. 0
36. 5	37. 1
37. 1	37. 2
36. 1	36. 5
36. 2	35. 8
34. 9	34. 9
35. 5	35. 5
36. 6	36. 6
36. 2	36. 6
35. 2	35. 1
36. 3	36. 0

Rectal temperatures during admission $\dot{V}O_2$ measurement of neonates suffering from tetanus (degree centigrade).

Beginning of expt.	*End of expt.*
38. 750	38. 875
38. 125	38. 375
37. 250	37. 375
37. 500	37. 500
38. 500	38. 125
37. 000	37. 125
37. 500	37. 500
38. 500	38. 750
37. 500	37. 500
38. 375	39. 000
40. 000	40. 000
40. 000	40. 000
37. 875	38. 500
37. 625	37. 875
37. 750	38. 000
38. 000	38. 250
38. 000	38. 250
38. 750	38. 750
38. 125	38. 250
37. 875	38. 000
39. 750	39. 875
38. 875	38. 875
38. 250	38. 250
37. 750	37. 750
35. 875	35. 875
37. 250	37. 250
37. 375	37. 500
37. 500	37. 500
38. 250	38. 375
37. 375	37. 750
37. 375	37. 375
37. 500	37. 500
37. 375	37. 375
37. 750	37. 750
37. 750	37. 875
36. 875	37. 000
37. 000	37. 000

ENVIRONMENTAL GAS TEMPERATURE IN RESPIRATION CHAMBER DURING $\dot{V}O_2$ MEASUREMENT OF SEDATED NEONATES SUFFERING FROM TETANUS. (degrees centigrade).

Beginning of expt.	*End of expt.*
32. 70	32. 85
32. 30	32. 40
32. 325	32. 40
32. 70	32. 80
32. 85	33. 025
32. 85	32. 925
33. 525	33. 525
33. 15	33. 35
33. 30	33. 40
32. 90	32. 95
33. 175	33. 575
33. 25	33. 375
32. 85	32. 975
33. 325	33. 35
33. 20	33. 25
32. 725	33. 15
33. 25	33. 50
33. 45	33. 50
33. 50	33. 525
33. 175	33. 30
33. 075	33. 25
33. 15	33. 35
32. 95	33. 05
33. 475	33. 475
32. 80	32. 80
32. 975	32. 975
32. 875	32. 875
33. 025	33. 30
32. 70	32. 825

Skin temperature on anterior abdominal wall during $\dot{V}O_2$ measurement of sedated neonates suffering from tetanus. (degrees centigrade).

Beginning of expt.	*End of expt.*
38. 3	38. 1
35. 6	35. 8
35. 1	35. 2
35. 0	35. 1
35. 8	35. 9
35. 3	35. 2
36. 2	35. 9
35. 5	35. 6
36. 0	36. 0
36. 5	36. 2
36. 5	36. 7
36. 0	36. 0
33. 8	34. 2
35. 7	35. 8
35. 6	35. 7
34. 7	34. 9
34. 2	35. 1
35. 6	36. 1
37. 2	36. 9
35. 6	35. 7
33. 5	34. 3
34. 4	34. 8
35. 6	35. 7
36. 2	36. 2
34. 3	34. 3
35. 1	35. 1
34. 7	34. 7
33. 8	34. 2
34. 0	34. 4

Skin temperature on posterior chest wall during $\dot{V}O_2$ measurement of sedated neonates suffering from tetanus. (degrees centigrade).

Beginning of expt.	*End of expt.*
37. 4	37. 2
34. 7	34. 9
34. 6	34. 6
34. 3	34. 4
35. 1	35. 1
35. 0	34. 8
33. 9	33. 9
35. 2	35. 4
35. 5	35. 5
35. 6	35. 2
36. 3	36. 5
35. 5	35. 6
33. 7	34. 1
35. 6	35. 7
35. 8	35. 8
34. 7	34. 8
33. 8	34. 6
35. 6	35. 8
36. 9	36. 1
35. 5	35. 5
33. 8	34. 3
33. 6	33. 9
35. 5	35. 5
35. 5	35. 5
34. 6	34. 6
35. 0	35. 0
34. 1	34. 1
34. 1	34. 1
35. 5	35. 5

Rectal temperatures during $\dot{V}O_2$ measurement of sedated neonates suffering from tetanus. (degrees centigrade).

Beginning of expt.	*End of Expt.*
39. 375	39. 000
36. 125	36. 375
35. 800	35. 875
35. 875	35. 875
37. 000	36. 875
36. 500	36. 250
36. 250	36. 250
36. 875	37. 000
36. 625	36. 625
36. 625	37. 000
37. 000	37. 250
36. 625	36. 750
35. 250	35. 375
35. 000	35. 250
36. 750	36. 750
35. 250	35. 375
35. 000	35. 250
36. 750	36. 750
37. 500	37. 250
36. 375	36. 750
35. 000	35. 250
35. 250	35. 375
36. 900	36. 875
38. 250	38. 250
36. 250	36. 250
35. 500	35. 500
34. 750	35. 250
36. 750	36. 875
36. 900	36. 875

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