THE MEASUREMENT OF OXYGEN CONSUMPTION AND CARBON DIOXIDE PRODUCTION IN TERM AND PRETERM INFANTS BY MASS SPECTROMETRY AND METABOLIC MONITOR

THESIS FOR THE DEGREE OF MSc OF UNIVERSITY OF GLASGOW

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AIMS AND OBJECTIVES:

To investigate the effect of breast milk and formula feeds on the metabolic rate of term and preterm infants at differing post-natal ages. Using measurement of oxygen consumption (VO_2) and carbon dioxide production (VCO_2), it is possible to quantify the respiratory quotient (RQ) and the metabolic rate.

Background:- Measurement of oxygen consumption, carbon dioxide production reflects biological oxidation of substrate utilized by the body and is dependent upon uptake of oxygen. Oxygen uptake and carbon dioxide production in infants depends on many factors. For example, body temperature changes which are closely related to environmental temperature significantly affect the oxygen consumption of the infants.

In infants temperature regulation depends on the following mechanisms:-

(i) Heat production, which is a chemical process based on biological oxidation of nutrients inside the body.

(ii) Heat loss from the body.

(iii) Behavioural thermoregulation, a complex mechanism which depends on the neurodevelopment of the newborn infants.

Many researchers in the past who investigated this mechanism came to the conclusion that an appropriate environmental temperature is important to maintain a normal body temperature for the infant.

Oxygen consumption and carbon dioxide production measurement can be used to investigate the effects of changes in body temperatures due to above mechanisms.

There are other factors important in the measurement of oxygen uptake and carbon dioxide production, these include state of sleep, type of nutrition, activity state. All these factors for instance can change the rate of oxygen uptake and

carbon dioxide production.

The measurement of oxygen uptake and carbon dioxide production accurately requires an appropriate and reproducible methodology.

Method:-

We have investigated two methods to study the oxygen uptake, carbon dioxide production using the principle of indirect open method.

The first involves the Delta Track Metabolic Monitor and the second by using mass spectrometer.

INTRODUCTION:

Warm blood animals, children and adults can control their body temperature over a wide range of temperature change in their environment. Basically they achieve this by making physiological and behavioural adjustment. There are three mechanisms which are involved in this heat (temperature) regulation;

(a) Behavioural thermoregulation.

(b) Heat production as a metabolic or chemical process essentially based on the biological oxidative breakdown of nutrients inside the body.

(c) Heat elimination or loss through a number of physical body processes.

In the newborn animal behavioural thermal regulation is partly achieved by the mother contributing her heat to the newborn and by the newborn itself. An example of this behaviour is seen in the newborn seal who may seek shelter from the blizzards of the Antarctic on the lee side of his mother for a few days after birth but he quickly fills his tissue with fat and moves from his mother's side to keep cool. Another example - the newborn squirrel and hamster allow their body temperatures to swing up and down with environmental temperatures by altering their activity. The lamb has good thermal insulation and can withstand most of the world's climates on the day of birth, providing it can dry off. On the other hand one might consider that the tremendous metabolic efforts of the newborn rat or rabbit to maintain body temperatures might do more harm than good by exhausting fuel reserves. However it may be misleading to consider weight and thermal insulation alone. Both the rat and the rabbit came from large litters with specially prepared nests which provide very good thermal insulation. Thus, the true body size, zexposed surface area ratio and effective thermal insulation permit the

newborn of both species to maintain thermal control over much wider ambient temperature range than would otherwise be possible. The provision of the nest is a behavioural response of the parents, huddling together is a behavioural response of the young. Both are important in maintaining the stability of the newborn's body temperature as its own thermoregulatory responses.

Physiology of Temperature Control in the Infants:

Since the early 1960s it has been demonstrated that the newborn baby can operate successfully over a range of environmental temperatures. This is restricted when compared with that over which the adult can function. The newborn has a number of disadvantages including a relatively large surface area, poor thermal insulation and a small mass to act as a heat sink. Furthermore he has little ability to conserve heat by changing his posture and no ability to adjust his own clothing in response to thermal stress, unlike the response of the adult. His responses may be jeopardised by disease and adverse conditions such as hypoxia and drug intoxication. DAY (1943) had shown that the thriving baby, aged one or two weeks had all the responses of a homeotherm. SILVERMAN (1957 and 1958) and coworker deduced from their clinical trials that the newborn baby also had these responses. Thus a normal baby challenged by heat or cold shows typical homeothermic responses. In response to heat the baby shows vasodilatation (especially in the hands and feet) which favour increased rate of heat loss by radiation and convection. In addition sweating occurs in association with rectal temperature above 37.2°C., thus favouring increased rate of heat loss by evaporation. When challenged by cold on the other hand, the normal baby attempts to conserve body heat by cutanous vasoconstriction and to maintain body temperature by increasing heat production. To achieve all this he must

have a sensory system to appreciate temperature (an affector arc), a central control system and the means of adjusting heat production and dissipation (an effector arc).

Affector Arc:-

As in the adult, cooling the skin produces a prompt and reproducible metabolic response in the baby, showing the presence of skin receptors (Bruk, 1961). Also of interest is that the trigeminal area of the face shows a marked sensitivity to heat and cold (Mestyan, 1964). The existence of central (thalamic) cold receptors is difficult to demonstrate with precision in the human baby, although they can be inferred from the modification of response at different deep body temperature.

Central Regulating Mechanism: In adult and newborn animals, there is good evidence of a complex central regulating mechanism situated in the area of the hypothalamus. In the human infant, such an area can be inferred and can be confirmed by experiments of nature such as the studies of CROSS (1966) on an anencephalic infant. The central thermostat is not set at a fixed and unvarying temperature, it undergoes cyclic changes, falls about 0.5°C. with the onset of sleep (Day, 1941) and is affected by pyrogens, drugs and intrahypothalamic hormones as noradrenalines. Despite that, the set-point deviation can be considered a form of cold adaptation. There is no good evidence to suggest that the set-point of a newborn (around which temperature is regulated) is normally different from that seen in later life (Bruk, 1968). This control centre can of course be rendered partially or totally ineffective by various drugs and by diseases such as intracranial haemorrhage, gross cerebral malformation, trauma and severe birth asphyxia.

Effector Arc:-

Vasomotor control: From birth there is a welldeveloped ability to control skin blood flow, even in very small infants. It should be remembered that despite this ability, a baby's total thermal insulation is poor compared with that of the adult.

Increased heat production: The ability to increase heat production is a consistent phenomenon in the healthy baby, even if prematurely born (Adamson, et al., 1965) and (Scopes, et al., 1966). This heat production may be produced by shivering, with other muscular activity or non-shivering thermogenesis. The main increase in heat production occurs in babies in the absence of shivering, although at very low environmental temperature (15°C.) shivering may be observed.

From animal and human studies it can be inferred that in the human infant the thermogenic effector organ, brown fat, contributes the largest percentage of non-shivering thermogenesis. Brown fat accounts for about two to six percent of total body weight in the term human infant. Brown fat is found at the nape of the neck, between the scapulae, in the mediastinum and surrounding the kidneys and adrenals. Brown fat differs both morphologically and metabolically from the more abundant white fat. The cells are rich in mitochondria and contain numerous fat vacuoles compared with the single vacuoles in white fat. There is also an abundant blood and sympathetic nerve supply. Its metabolism is stimulated by norepinephrine released through sympathetic innervation, resulting in conversion of triglyceride by hydrolysis to free fatty acids and glycerol. The dependence of the newborn on brown fat non-shivering thermogenesis has important practical consequences because this effector mechanism may be rendered useless by hypoxia,

blockade by certain drugs and nutritional depletion.

In fasted newborn rabbits, although kept warm (35°C.), there is little utilization of brown fat. If, however, on the second day they are kept in a cool environment (30°C. to 25°C.) they show major depletion of brown fat stores. When the metabolic response fails, brown fat and white fat are both virtually depleted of lipid (Hardman, et al 1969). No evidence is available to assess how long the response to cold stress lasts in the human baby or to what extent the human infants depend on non-shivering.

Thermogenesis

Despite considerable enquiry, the precise mechanisms whereby the brown adipose tissue mitochondria release the chemical energy in fatty acids as heat are still not known. Also the mechanisms that control the growth and the thermogenic performance of the tissue in the newborn period are not understood (Hull, et al, 1969).

Evidence suggests that the thermogenic capacity of brown fat begins to decline soon after birth and that in the preterm infants it does not reach the performance level it might have achieved if intrauterine development had not been interrupted.

Sweating: Newborn term infants have six times as many functional sweat glands per unit area as adults, but the peak response of each gland is only about one third that of an adult gland (Foster, et al, 1969). One might therefore expect the baby's response to warm stress to exceed that of an adult, but in fact, the term baby only increases insensible water loss about fourfold when a warm environment has increased his rectal temperature to 37.8°C. (Hey, et al, 1968). This only represents the dissipation of his basal metabolic rate; it follows that in a heat gaining environment the risks of hyperthermia are great.

Babies born about eight weeks before term have virtually no ability to sweat and even in a baby born three weeks before term sweating is severely limited and largely confined to the head and face. Interestingly, sweat production matures relatively rapidly in preterm babies after delivery; a four week old baby born at thirty weeks gestation can therefore withstand heat stress better than a newborn baby of thirty-four weeks gestation (Rutter, et al, 1979).

Heat Loss: Heat transfer within the body or loss to the environment can be divided into two main types, (1) from within the body to the

surface of the body (internal gradient) (2) from the body surface to the environment (external gradient). A third pathway is from within the body into the cold gas stream introduced by a thoughtlessly managed respirator.

The physiological control mechanisms of the infant may alter the internal gradient (the vasomotor) to change skin blood flow. The external gradient is of a purely physical nature. Both the large surface/volume ratio of the infants (especially those below 2 kg.) in relation to the adult and the thin layer of subcutaneous fat increase the transfer in the internal gradient. The heat transfer from the surface of the body to the environment involves four mechanisms of loss (1) radiation (2) conduction (3) convection (4) evaporation of water. This heat transfer is complex and the contribution of each component depends on the temperature of the surrounding (air and walls) air speed and water vapour pressure. Because conduction depends on the thermal conductivity of the substance in contact with the body, and because infants are usually laid on a mattress of low conductivity, thermal exchange through this mechanism is usually small.

Convective exchange depends on air speed and air temperature and, with radiation, represents a major channel of heat loss, varying inversely with environmental air temperature.

Evaporative loss depends on air speed and on absolute humidity of the air (Okken, et al, 1982), (Thomson, et al, 1984), (Hammarlund, et al, 1980). This only represents a small fraction of all heat loss in a clothed baby or in a baby nursed in a regular warm-air incubator of moderate humidity. When a very immature baby with a thin skin is nursed under a radiant overhead heater in an environment of low relative humidity, it becomes a major fraction of all heat loss.

In environments warmer than the body, it represents the only means of heat dissipation. Draughts materially increase convective and evaporative losses.

Radiant heat loss depends on the presenting surface area and surface temperature of the body compared with the temperature of the receiving surface, and radiation accounts for a major proportion of all heat loss in a naked baby in an incubator (Hey, et al, 1967), (Wheldon, et al, 1982).

Respiratory Physiology:

Priestley discovered oxygen in 1772 and Lavoisier elucidated its role in respiration. The application of their discovery in human physiology lead to the understanding whereby oxygen transferred air to the cells in the body.

Since the inspired air contains 20.9% oxygen at normal barometric pressure (760 mmHg.), the partial pressure of oxygen (PO_2) in the inspired air is 149 mmHg.

The partial pressure of a gas is found by multiplying its concentration by the total pressure, for example:-

Dry air has 20.93% O_2.

Its partial pressure (PO_2) at sea level (760 mmHg.) is;

$$\frac{29.93}{100} \times 760 = 159 \text{ mmHg.}$$

When air is inhaled into the upper airways, it is warmed and moistened, since the water vapour pressure is 44 mmHg. the total dry gas pressure is only 760 - 47 = 713 mmHg.

The PO_2 of inspired air is therefore:-

$$\frac{20.93}{100} \times 713 = 149 \text{ mmHg.}$$

A liquid exposed to a gas until equilibration takes place has the same partial pressure as the gas.

In the exchanging regions of the lung alveolar level oxygen transfer starts with convective transport. When ambient air is inhaled and delivered to the alveoli in the lung, the PO_2 in the alveoli is about two thirds of that in the inspired gas. This is due to humidification in the airways which dilutes all the inspired gases, the dilution by carbon dioxide, which is delivered to alveoli by blood returning from tissues, and loss of alveolar oxygen to the blood flowing through the

lungs.

The next step in gas exchange is by diffusion through the alveolar-capillary membrane into the blood.

The arrangement of gas spaces and capillaries in the lung is an efficient one and the PO_2 of arterial blood is thus normally close to the alveolar PO_2.

The cascade continues with convective transport of oxygen via the arterial blood to tissue capillaries, where diffusion carries oxygen away from the blood through the capillary endothelium, extra cellular fluid and cell membranes to the intracellular space.

As a result of this loss to the tissue, the PO_2 in venous blood (about 40 mmHg.) is considerably lower than that in the arterial blood. However, the PO_2 in the tissues is even lower than that in the venous blood, due to the limited rate of diffusion and ongoing utilization of oxygen. In the mitochondria where the rate of oxygen consumption is greatest, PO_2 is lowest.

Oxygen is carried in the blood in two forms:-

(a) dissolved (b) in combination with haemoglobin

(a) Dissolved oxygen obeys Henry's law which states that the concentration of gas dissolved in a liquid is proportional to its partial pressure. As a result, for each mmHg. of PO_2 there is 0.003 ml.O_2/100 ml. of blood, so the normal arterial blood with PO_2 of 100 mmHg. contains 0.3 ml.O_2/100ml..

The dissolved route of transporting oxygen is inadequate because of the volume of blood passing through the lungs each minute (Q). This amount can be calculated using the Fick principle which states that the oxygen consumption per minute ($\dot{V}O_2$) is equal to the amount of oxygen taken up by the blood in the lungs per minute.

Therefore $Q = \frac{\dot{V}O2}{CaO2 - CvO2}$ where $\bar{C}VO2$ = O2 concentration entering lungs

CaO2 = O2 concentration leaving lungs

$\dot{V}O_2$ is measured by collecting the expired gas in a large spirometer and measuring its oxygen concentration. Mixed venous blood is taken via a catheter in the pulmonary artery and arterial blood by puncture of the brachial or radial artery.

Pulmonary blood flow can also be measured by the indicator dilution technique in which dye is injected into the venous circulation and its concentration in arterial blood is recorded.

The Fick and indicator dilution methods give the average flow over a number of heart cycles.

(b) Oxygen combined with haemoglobin is mainly in chemical combination. Haemoglobin consists of Haem as an iron-porphyrin compound, combined with the protein globin which consists of four Polypeptide chains. The chains are of two types; alpha and beta. Differences in their amino -

acid give rise to various types of human haemoglobin.

The commonest variety of haemoglobin is known as Haemoglobin A.

Oxygen forms an easily reversible combination with haemoglobin (Hb.) to give oxyhaemoglobin O_2 + Hb. --- Hb.O_2.

The amount of oxygen combined with Haemoglobin depends on the partial pressure of oxygen (PO_2). Each gram of haemoglobin binds 1.3 volumes % of oxygen. When air is breathed at sea level the arterial PO_2 is 97 mmHg. and haemoglobin is more than 98% saturated with oxygen. This is demonstrated in the oxygen haemoglobin dissociation curve.

It was not until the end of the eighteenth century that Priestley discovered carbon dioxide and Lavoisier described its role in respiration. A century later Miesher demonstrated its effects on the respiration.

How is carbon dioxide transferred and eliminated from the body?

Carbon dioxide is carried in blood in three forms; dissolved, as bicarbonate and in combination with proteins as carbamino compounds.

Dissolved carbon dioxide, like oxygen, obeys Henry's law. Since carbon dioxide is some twenty times more soluble than oxygen, about 10% of the gas that is delivered to the lung from the blood is in the dissolved form.

Bicarbonate is formed in blood by the following sequence:-

$$CO_2 + H_2O \underset{}{\overset{CA}{\rightleftharpoons}} H_2CO_3 \text{ --- } H^+ + HCO_3$$

The first reaction is very slow in plasma but fast within red blood cell because of the presence of the enzyme carbanic anhydrase (CA). The second reaction, ionic dissociation of carbonic acid, is fast without an enzyme. When the concentration of these ions rises within the red cell HCO_3 diffuses out but H^+ cannot easily do this because the cell membrane

is relatively impermeable to cations. So to maintain electrical neutrality, chloride ions (cl^-) diffuse into the cell from the plasma, the so-called chloride shift. The movement of chloride is in accordance with the Gibbs-Donnan equilibrium.

The H^+ ions liberated are bound to haemoglobin:-

$$H^+ = Hb.O_2 \rightleftharpoons H^+ Hb. + O_2$$

This occurs because reduced Hb. is less acid than the oxygenated form. The presence of reduced Hb. in the peripheral blood helps with the loading of carbon dioxide while the oxygenation which occurs in the pulmonary capillary assists in the unloading.

The fact that the deoxygenation of the blood increases its ability to carry carbon dioxide is known as the Haldane effect.

Carbamino compounds are formed by the combination of carbon dioxide with terminal amine group in blood proteins:-

$$Hb.\ NH_2 + CO_2 \rightleftharpoons Hb.\ NH.\ COOH$$

This reaction occurs rapidly without an enzyme and reduced Hb. can bind more carbon dioxide than oxyhaemoglobin. Once again unloading of oxygen in peripheral capillaries facilitates the loading of carbon dioxide while oxygenation has the opposite effect.

Pulmonary Function Testing in the newborn has helped clarify the many differences in respiratory function between the neonate and older subjects. It has also helped our understanding of the pathophysiology of different diseases which has contributed to the development of more effective modes of therapy. On the other hand technical difficulties including the size of the patients, their inability to cooperate and the absence of appropriate equipment, makes difficult the routine measurement of respiratory function in the neonates. These problems

have restricted the use of pulmonary function testing in neonates to research laboratories. To know the oxygen consumption you must know the lung volume because the determination of lung volume is a valuable adjunct to other volume dependent pulmonary function tests.

Functional Residual Capacity (FRC) The Functional Residual Capacity includes only the volume of gas in communication with the airways and is defined as the volume of gas in the lung after a normal expiration. One method of measuring Functional Residual Capacity in newborn is the closed-system, Helium-dilution technique. In this method the infant's airway is opened by means of a stopcock at the end of expiration to a bag containing a known volume and concentration of helium, which is insoluble in blood. After thirty to sixty seconds (if the distribution of gas in the lung is normal), the helium concentration in the bag stabilizes at a lower value. This decrease in bag helium concentration is proportional to the lung volume in which the helium was diluted. The Functional Residual Capacity is calculated using the following equation:-

$$FRC = \frac{(C1 \times V1) - (C2 \times V2)}{V2}$$

Where C_1 and V_1 = the concentration and volume of helium in the bag at the beginning of rebreathing, respectively, and C_2 and V_2 are the same value after rebreathing (Berglund and Karlberg, 1956), (Krauss and Auld, 1970), (Ronchetti, et al, 1975).

Several problems can interfere with the accuracy of the measurement. If carbon dioxide and water are absorbed in the system, there will be a reduction in volume. To avoid falsely elevated helium concentration a correction factor must be used. A leak in the system such as around the face mask or endotracheal tube will interfere with the results (Fox et al, 1979).

The time required to achieve equilibrium of the helium between patient and bag depends on the relationship between the tidal volume and the dead space of the system, the respiratory rate, the initial volume of the bag and the distribution of the inspired gas.

Infants with airway disease and impaired distribution of ventilation require prolonged rebreathing to reach equilibration, so the sampled gas must be recirculated to the system to maintain the volume constant. During prolonged rebreathing, acute hypercapnia occurs and carbon dioxide output becomes smaller than oxygen consumption. This reduces the final volume of the system which alters the result.

Functional Residual Capacity can also be measured in the newborn by nitrogen washout (Nelson and Prod'hom, 1962). The infant breathes 100 percent oxygen in an open system and the expired gas is collected in a spirometer. Tha analysis of nitrogen concentration in the spirometer and in the end-tidal or alveolar gas after washout of nitrogen from the lung allows determination of Functional Residual Capacity. There is another method where inspite of collecting all the expired gas, the nitrogen washed out from the alveolar gas can also be measured by continuous analysis and integration of the nitrogen concentration in exhaled gas (Richardson and Anderson, 1982). This method has the advantage of reducing the time required to perform the test from several minutes to a few seconds and can also be used during mechanical ventilation but it is not accurate in a patient with abnormal distribution of ventilation.

This problem can be prevented by having the infants breath from a continuous flow of oxygen or oxygen and helium and measuring and integrating the nitrogen concentration after the gas passes through a

mixing chamber placed in the exhalation side of the system (Gerhardt, et al 1985). This method is easy to perform and the washout can be prolonged as much as it is necessary in infants with poor distribution of ventilation.

Functional Residual Capacity can be measured by washout of any measurable gas that is biologically inert and is nonabsorbable or nearly so.

The indicator dilution methods for determining the lung volume are basically static applications of the dynamic Fick principle which concerns itself with volume flow over units of time.

An accurate measurement of tidal volume (which is the volume of air breathed in or out during quiet respiration) is essential to the calculation of minute ventilation. Tidal volume can easily be measured but it is sensitive to an increase in dead space and flow resistance produced by the testing apparatus.

Dead space may be defined as:-

(1) Anatomical dead space.

(2) Physiological dead space.

In health the two volumes are very nearly the same. The anatomical dead space is simply the internal volume of the airways between mouth, nose and alveoli. The Physiological dead space includes this volume and two additional volumes, (i) the volume of inspired gas which ventilate the alveoli which receive no pulmonary capillary blood flow and (ii) the volume of inspired gas which ventilate the alveoli in excess of that volume which is required to arterialize the blood in their local pulmonary capillaries.

In patients with lung disease the Physiological dead space may be considerably larger because of inequality of blood flow and ventilation

within the lung.

The anatomic dead space can be measured by using Bohr equation:-

$$VD = \frac{FACO2 - FECO2 \times VT}{FACO2}$$

VD = Dead space

$FACO_2$ = alveolar fraction of CO_2

$FECO_2$ = Carbon dioxide concentration in mixed expired gas

VT = Tidal volume

Alveolar carbon dioxide can be measured by rapid CO_2 analyzer; the $FECO_2$ requires the collection of expired gas with a non-rebreathing value.

The Physiological dead space can be calculated with the same equation using arterial PCO_2:-

$$= \frac{PaCO2 - PECO2}{PaCO2} \times VT$$

By analysing the collected expired gas it is possible to determine the carbon dioxide production, oxygen consumption and alveolar ventilation using this equation:-

$$\dot{V}A = VCO_2/FACO_2 \times 100$$

Where $\dot{V}CO_2$ = CO_2 production

$FACO_2$ = percent of CO_2 in alveolar gas

$\dot{V}A$ = Alveolar ventilation

The limitations of this method are the need for a low dead space and low resistance value and the measurement of alveolar gas which is difficult in small infants due to their high respiratory rate and small tidal volume.

Plethysmography has been used to measure the tidal volume in small infants (Karlberg, et al, 1960). In this technique the infant is

placed in a box of known pressure created by a pressure transducer, and by pumping a known volume of gas in and out of the chamber. During inspiration the increase in chest volume produces an increase of pressure in the chamber which is measured by a differential pressure transducer. The chamber is affected by change in temperature and the ambient pressure. By using a Pneumatochograph (Ahlstrom, and Johnson, 1974) these changes can be minimised producing a constant pressure system. The disadvantages of Plethysmography is that these are unfortunately expensive and delicate electronic apparatus; access to the baby is difficult; adequate face seal is difficult to obtain and a closed circuit is required.

Pneumotachography has been used to measure Tidal Volume in infants connected by a face mask. The gas flow through the Pneumotachograph produces a different pressure between the two ends of a flow resistor which can be measured by using differential pressure transducer and the air flow transformed into tidal volume by an electric integrator (Grenvik, et al 1966).

The problem with the Pneumotachograph is the temperature which affects the diameter of the tube and may alter the resistance. Therefore calibration must be done using a gas of the same composition and temperature as breathed by infants. This affects gas viscosity. The use of nosepiece and face masks may alter normal respiratory pattern (Fleming, et al 1982), and cause marked increase in tidal volume and decrease in respiratory frequency as well as anxiety and discomfort to babies (Askanazi, et al 1980).

Inductive Plethysmography is a method of measuring tidal volume without physical connection by mouthpiece or noseclip which was described by Cohn et al, 1978. It has been used by Tabachruk, et al 1981

and it measures the changes in the chest and abdominal volume by detecting the respiratory changes in inductance between coils placed around the chest and abdomen. The system requires a careful calibration and is sensitive to body position and paradoxical movements of the chest wall.

Heat Balance:

In the state of energy equilibrium, heat loss balances heat production. If production exceeds loss, the body temperature rises and if heat losses exceed production, body temperature falls.

Heat production is produced by the metabolic activity of the body tissues. Metabolic rate is by definition:- the energy expenditure necessary to maintain basic physiological functions under standardized conditions. The metabolic rate is difficult to measure in a newborn who is rarely awake and quiet. As a compromise it is usual to measure the resting metabolic rate which can be described as the metabolism of an infant who is asleep, fed more than an hour before and in a neutral thermal environment. Under these conditions the heat production of the healthy term newborn is similar to that of an adult if expressed per unit weight, but it is half that of an adult when expressed per unit surface area.. So the surface area determines the heat loss. The resting metabolic rate is similar in term and preterm infants when expressed per unit weight, but considerably lower in preterm infants when expressed per unit surface area. Because of this, the newborn infant requires a much warmer environment than the adult and the preterm required a warmer environment than term infants (Hey and Katz, 1970). The resting metabolic rate rises in the immediate newborn period (Scopes and Ahmed, 1966).

In Paris in 1900 Budin was concerned about the importance of adequate environmental warmth in the care of small babies. When he clothed all his babies and covered them with light blankets he came to the conclusion that this was not enough for smaller babies. He then promoted and popularised the idea of nursing the more vulnerable babies fully clothed in specially constructed incubators. Blackfan and Yaglon

in 1933 reached the same conclusion about the environmental temperature and developed the use of an air-conditioned nursery in Boston. Hey and O'Connell in 1970 concluded that in the normal neutral thermal environment condition there is minimal oxygen consumpton when they studied heat balance in cot-nursed babies.

Energy: Just before the French Revolution Lavoisier and Laplace carried out experiments and interpreted the process of chemical combustion. They placed a guinea pig in a very small closed chamber surrounded by ice and they measured the amount of ice which melted over a ten hour period and at the same time the amount of carbon dioxide given out by the animal. They concluded that there was a relationship between heat produced by the animal and the respiratory exchange.

A hundred years after Lavoisier's death many researchers exercised their talent in designing calorimeters in which laboratory animals and men could live for many hours or even a few days while their metabolism was studied. In 1849 Reynault and Reiset in Paris carried out many experiments on small animals and planned to build a large human respiratory chamber in a hospital, but they were unable to raise funds and they dropped the project. In 1886 Pettenkofer and Voit were more fortunate and they, with help from King Maximillian II of Bavaria, had constructed at Munich a chamber in which a man could live for several days and had all his respiratory exchange measured. Rubner in Berlin, Zuntz in Switzerland and Johanson in Sweden were others who extended the work of the Munich school and so laid many of the foundations of modern nutritional science. But it was the American Atwater, a student of Voit in Munich, who carried out the experiments which established the essentials of physiological knowledge for assessment of [redacted] energy. Atwater returned to the U.S.A. from Germany in 1892 and with the help of

Rosa, an engineer, constructed a human calorimeter which could measure the heat produced by a man with an accuracy of 0.1 percent.

Forms of Energy: Biologists are interested in five forms of energy:

1. Solar 2. Chemical 3. Mechanical 4. Thermal 5. Electrical

In plants and animals many forms of energy are quantitatively interchangeable. It has been demonstrated that living creatures , like inanimate objects, can neither create nor destroy energy but can only transform it so they obey the first law of thermodynamics which states the principle of the conservation of energy. Green plants which can utilize solar energy directly differ from animals. They are able to synthesise complicated organic substances such as carbohydrates, proteins and fats from simple inorganic materials such as carbon dioxide, water, NH_3, SO_4. In this process of photosynthesis, solar energy is converted into chemical energy which is stored by the plant. Animals obtain their energy which is derived directly or indirectly from plants in chemical form. Energy taken in as food is used in the body (or by the body) to perform mechanical work and to maintain the tissues of the body and growth.

The human being acts as an engine in the conversion of chemical energy into mechanical energy with a measurable thermodynamic efficiency. Most energy is dissipated as heat, so the energy in the food is ultimately converted into heat and its dissipation maintains the temperature of the body.

The unit of energy is the Joule (J) and is the energy expended when 1 Kilogram (Kg) is moved 1 meter (M) by a force of 1 Newton (N). Formerly energy was always expressed quantitatively in units of heat, the unit used being the kilocalorie (Kcal). The thermochemical calories are based on the heat of combustion of Benzoic acid and is

4.104 J. (1 Kcal = 4.184 KJ) (The Royal Society).

Energy Content of Food (the bomb calorimeter): Foodstuff is placed in a small chamber or bomb and exposed to a high pressure of oxygen and ignited by electric current. All the organic material is burnt and the heat liberated can be measured. The bomb is placed inside a vessel of water where the temperature can be measured accurately. When foodstuff is ignited the heat produced leads to a rise of temperature in the surrounding water. There are slight differences in the heat of combustion of the nutrients in different foods.

In the animal body the tissues are able to oxidise carbohydrate and fat completely to carbon dioxide and water, but the oxidation of protein is never complete. Nitrogenous substances derived from protein such as urea, uric acid and creatinine are excreted in the urine. Many observations of the heat of combustion of urine have shown that it contains unoxidised material equivalent to 33.1 KJ/g. (7.9 Kcal/g.) of Nitrogen or 5.23 KJ/g. (1.25 Kcal/g.) of protein oxidised by the body. It is therefore necessary to subtract 5.23 KJ/g. from the heat of combustion of protein. There must therefore be a correction for the incomplete absorption of nutrients in the body.

Atwater, over fifty years ago following a large number of experiments, concluded that 92 percent of protein, 95 percent of fat and 99 percent of carbohydrate were normally absorbed. From this he produced the Atwater Factors for the available energy of the three main constituents of foodstuffs;

Carbohydrate (sugar starch)	17 KJ/g.	(4 Kcal/g.)
Protein (mixed)	17 KJ/g.	(4 Kcal/g.)
Fat	37 KJ/g.	(9 Kcal/g.)

(1 Kcal = 4.2 KJ : 1,000 Kcal = 4.2 MJ)

It is important to remember that these factors make allowance for the energy in the food lost in faeces and urine (the loss being less on an animal diet than on a vegetable diet with its greater content of cellulose). Experiments by Southgate and Durnin in Glasgow (Southgate and Durnin, 1970) on young and old persons of both sexes on diets containing varying amounts of vegetables and cereals confirmed that for most practical purposes the Atwater Factors can be used to calculate metabolisable energy.

Measurement of Energy Expenditure:

Direct Calorimetry:- Theoretically is easy, but is difficult and costly in practice. If an animal or man is put into a small chamber in which all the heat evolved can be measured, then the total energy expenditure is the sum of that heat plus any activity or work performed. This total energy expenditure (the sum of the heat produced plus the mechanical work done) is equal to the net energy from food consumed (the total chemical energy in the food minus the energy lost in the faeces and urine). So the total energy expenditure is quantitatively related to the oxygen consumption.

Indirect Calorimetry:- This is the measurement of oxygen consumption. It is based on the fact that when an organic substance is completely combusted, either in calorimeter bomb or in the human body, oxygen is consumed in amounts directly related to energy liberated as heat. Indirect calorimetry is technically a simpler procedure for the measurement of oxygen consumption than the measurement of heat. So, for example, the oxidation of glucose goes quantitatively as follows:-

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O + \text{Heat}$$

180 g. 6x22.4 litres 6x22.4 litres 6x18g. 2.78 MJ

That means for example 180 g. of glucose yields 2.78 MJ of energy or that the heat of combustion of 1 g. of glucose is 2.78/180 = 15.5 KJ (3.69 Kcal). Because 6 x 22.4 litres of oxygen has been used, 1 litre of oxygen is equivalent to 2.78/(6 x 22.4) = 20.8 KJ (4.95 Kcal). The ratio of the carbon dioxide produced (per volume) to the oxygen used is known as the Respiratory quotient (RQ). The RQ for the oxidation of glucose is 1.0 (the volume of carbon dioxide evolved is equal to the volume of oxygen used). With fatty acids derived from food the RQ of fat is about 0.7.:

$$C_{17}H_{35}COOH + 26O_2 = 18CO_2 + 18H_2O$$

$$RQ = 18/26 = 0.693$$

Fat contains very little oxygen which must consequently be provided in sufficient amounts to oxidize both the hydrogen and the carbon of the fat molecule. The oxidation of pure protein is about 0.8 (indirectly calculated). The respiratory quotient frequently gives no information about the metabolic processes in the body. On the contrary a knowledge of the metabolic processes taking place is generally necessary to interpret the RQ. In addition the RQ gives no information on the stage of intermediate metabolism. It is also known that 1 g. of urinary nitrogen arises from the metabolism of 6.25 g. of protein. If in addition to the oxygen used (O_2), the carbon dioxide produced (CO_2) and the urinary nitrogen (Un) are also measured, it is possible to calculate the amounts of carbohydrate, fat and protein metabolised. This is known as the metabolic mixture. If neither the urinary nitrogen nor the carbon dioxide output have been measured, a useful approximation of

the rate of energy expenditure (E) can be derived from measurement of the minute volume of expired air (V) and its oxygen content (O_2E) using Weir's formula - E (watts) = 3.43 V (20.9 - O_2E) (Weir, J.B. de v. 1949).

Measurement of Oxygen Consumption:

Oxygen consumption has been measured by using respiration chambers, which we are able to record over long periods of time. However, respiration chambers are expensive and difficult to manipulate, particularly in children because the subject's activities are necessarily limited. For these reasons most measurements of oxygen consumption are made by using some form of apparatus into which the subject can breath and at the same time we can measure the total volume of gas expired (the minute volume) and a sample of expired air is analysed. This involves the use of valves which separate the inspired air from expired air. It is important that gas collection does not disturb the infant during the experiment. There are closed circuit methods and open circuit methods. The latter is the indirect calirometry method for measurement of oxygen consumption and carbon dioxide production.

In adults many different types of apparatus have been used. The Benedict Roth spirometer which is a closed circuit system in which the subject breaths in oxygen from a metal cylinder and the expired air passes back through soda-lime to absorb the carbon dioxide into the same cylinder. The cylinder floats on water inside a second cylinder. As the oxygen is consumed the inner cylinder falls and the rate of fall is recorded by an ink-writer on rotating drum.

This has been used in hospitals for measuring resting basal metabolism but it is not portable. As the carbon dioxide is not measured the RQ

cannot be calculated and the heat equivalent of oxygen is assumed to be 20 KJ (4.8 Kcal). By using a Douglas bag it is possible to measure both carbon dioxide and oxygen uptake. The expired air is collected for a period of three to ten minutes and the air in the bag passed through a gas meter for analysis.

Measurement of energy expenditure during industrial work can be performed by using a Max Planck respirometer (Mulle and Franz, 1952). This apparatus facilitates the direct measurement of the volume of the expired air and simultaneously diverts a small fraction into a plastic bladder for subsequent analysis.

The Analysis of the Respiratory Gases : Oxygen and Carbon Dioxide:-

The Haldane Apparatus: A sample of inspired (or expired or alveolar) air is drawn into a calibrated burette at atmospheric pressure and the volume measured. It is then exposed to a solution of Caustic Potash (KOH) which absorbs the carbon dioxide (CO_2) content, and the residual volume is read again at atmospheric pressure. The remaining gas is exposed to chromous chloride solution, which absorbs oxygen and the final volume (nitrogen) is determined.

The Haldane apparatus is used for calibrating various types of analytical apparatus which more quickly provide the results of respiratory gas analysis. These include:-

(1) <u>The Mass Spectrometer;</u>

The mass spectrometer identifies the constitutents of a gas mixture by detection of mass/charge ratio of ions in an ionised sample of the mixture. In clinical mass spectrometer the commonest method of ionisation is by bombardment with thermionic electrons emitted from a filament.

The gas sample is introduced into the apparatus and the gas is reduced to a pressure of 10^{-6}mmHg., upon which oxygen, carbon dioxide, nitrogen and argon are ionized. These are deflected by a magnetic field; the heavier the ionic mass of the gas the longer path it takes to reach the collecting electrode (O_2 = 32, Argon = 40, CO_2 = 44 and Nz = 28). If one collector electrode is used, the path taken by the ions depends on the magnitude of the electric voltage of the collector. By varying this negative voltage between limits 25 times a second, the ions of the component gases may be sequentially collected. Electronic amplification allows a continuous recording of the change in oxygen and

carbon dioxide composition during breathing.

(2) The Pauling Oxygen Analyser: Measures oxygen partial pressure in a gas mixture, operating by reason of the paramagnetic properties of oxygen, the other gaseous constituents are diamagnetic. A small glass sphere filled with nitrogen is suspended by a vertically stretched silica fibre between the poles of a magnet. If the sphere moves in the magnetic field it rotates around the silica fibre.

When oxygen is passed through the space between the magnetic poles and therefore surrounds the spherule, the sphere is subjected to a magnetic force depending on the difference between its own magnetic susceptibility and that of the oxygen and rotates causing torsion of the silica fibre.

Equilibrium is reached when the magnetic rotational force is balanced by the restoring force of the twisted silica fibres. By fixing a mirror to the fibres the reflection of a light source onto a scale calibrated in units of oxygen tension permits the measurement of PO_2.

The instrument requires some few seconds to reach equilibrium and is therefore too slowly responsive for continuous measurements of oxygen partial pressure during breathing. It is however suitable for measurements of oxygen pressure in collected samples.

(3) The Paramagnetic Oxygen Analyser: All substances when placed in a magnetic field are either attracted or repelled by one pole of a magnet. Strongly magnetic substances are called ferromagnetic (iron, cobalt, nickel). Substances that are feebly attracted by a magnet are termed paramagnetic, and those that are slightly repelled by a magnet are called diamagnetic.

Very powerful magnets are required to detect paramagnetic or diamagnetic

properties.

(4) The Infrared Carbon Dioxide Analyser: Carbon dioxide absorbs radiant heat. Infrared radiation is passed from a source through a sampling chamber to a detector. When the sampling chamber is filled with a gas mixture containing carbon dioxide the radiation is lessened. The analyser can be used for continuous recording of carbon dioxide concentration in respiratory gases.

The respiratory gases have the following percentage composition as those for expired and alveolar air for a man at rest

	Inspired Air %	Expired Air %	Alveolar Air %
O_2	21	16	14
CO_2	0	4	6
N_2	79	80	80

It is noted that the percentage of nitrogen is higher in alveolar and expired air than in inspired air. This is not because nitrogen is secreted by the lungs but is due to the fact that the expired air volume is less than that inspired.

If a subject (with nose clipped) breathes through a mouth-piece fitted with inspiratory and expiratory valves, the expired air can be collected in (Douglas bag) over a known time.

The air expired is saturated with water vapour at body temperature, but cools in the bag to room temperature. Water is also condensed in the bag and the gas is finally saturated with water at room temperature.

For children and infants the minute volume is about 0.5 litre, depending on weight, and this is achieved with a high respiratory frequency 25 - 40 and tidal volume ranging from 14 ml. at 2 kg. to 20 ml. at 4 kg.. Dead space is variously reported as between a third and half of tidal volume, giving a mean alveolar ventilation of about 250 - 335 ml.

for a neonate of average size. (Nunn 1987)

The Sampling of Alveolar Air:

Haldane-Priestly method; The subject with the nose clipped makes a rapid maximal expiration down a narrow tube about three feet long and of one inch internal bore and then occludes the mouth-piece with his tongue. A sample of the air contained near the mouth-piece of the tube is withdrawn via a side tube. This, the last to be expelled from the lungs is taken to be alveolar air. This technique is difficult in children and even more difficult for infants because of the need for full cooperation.

Continuous Sampling Method:

The subject breathes through a mouth-piece fitted with inspiratory and expiratory valves.

About 10 ml. of gas is removed from the last part of each expiration via a side tube situated just beyond the expiratory valve. The alveolar air thus obtained is passed through two gas analysers, placed in parallel, which simultaneously analyse oxygen and carbon dioxide.

The apparatus dead space must be minimal. On making a normal expiration the tidal air escapes through the expiratory valve into a rubber tube. The air just beyond the valve is trapped and is ready for sampling.

Following inspiration the negative mouth-piece pressure activates a device which closes a valve relay which in turn operates and opens the sampler valve.

At the end of inspiration the mouth-piece air pressure returns to atmospheric level and the sampling valve correspondingly closes.

Indirect Methods:

To determine the effective alveolar gas pressure (that which, if present

continuously and uniformly throughout the lung in all functioning alveoli, would premit CO_2 and O_2 exchange between alveoli and blood during a series of breaths in amounts equal to the gaseous exchanges which can be actually measured by analyses of inspired and expired air). The following formula is used:-

$$\text{Effective alveolar } PO_2 = \text{inspired } PO_2 \times \frac{\%N_2 \text{ expired air}}{\%N_2 \text{ inspired air}} - \frac{\text{Arterial } PCO_2}{\text{Expired air RQ}}$$

when the expired air RQ is the ratio of:-

$$\frac{CO_2 \text{ expired per minute (ml./min./kg.)}}{O_2 \text{ used per minute (ml./min./KG)}}$$

The arterial PCO_2 is measured directly by arterial sampling.

The expired air is collected and its volume and composition is measured.

Placental Function and Substrate Supply to the Uterus and Fetus:

In late gestation, the fetus accounts for slightly more than half of total uterine oxygen consumption in the sheep, cow and horse. Comline and Silver, 1976, Meschia et al, 1980, Sparks et al, 1983, Ownes et al, 1986.

By applying the Bohr principle (the transfer of oxygen into the fetal circulation is further enhanced by the reverse transfer of carbon dioxide, the binding of oxygen to haemoglobin being increased by the increase in pH) the human fetus and placenta at term were found to consume oxygen at similar weight specific rates to those of other species (Bond et al, 1986).

The relative importance of various substrate for the gravid uterus in late gestation can be assessed from a comparison of their metabolic quotients (Battaglia, 1984).

The major substrates in most species, glucose, lactate and amino acids, appear to be utilized at least in part, if not largely, for oxidative metabolism as well as to support growth.

The placenta metabolizes oxygen and glucose at very high rates compared to the fetus and consumes the major fraction of those taken up by the gravid uterus. Another significant feature of placental metabolism is the production of lactate and its release, partly into the uterine but predominantly into the fetal circulation.

Recent studies in the sheep have revealed dramatic ontogenic changes in the weight specific rates of oxygen and glucose utilization by the fetus and placenta (Bell et al, 1986).

At mid-gestation, weight specific rates of oxygen and glucose consumption by the fetus are two and three times, respectively, those observed near term. Although at this time the fetus is growing about three times as fast in late gestation, the partition of its energy requirements between oxidative metabolism and growth remain the same.

By contrast, the placenta consumes oxygen and glucose at weight specific rates which are only a third to a fifth those near term, despite already having reached its maximal size.

At the same time, lactate is produced at only one quarter of the rate in the late gestation and is released solely into the uterine circulation.

Thus late in gestation, when the fetus and hence fetal demand for substrates is at its largest relative to the placenta, utilization of such substrate by the placenta is also at its greatest.

Although fetal consumption of oxygen and glucose declines on a weight specific basis over the latter part of gestation, the concomitant increase in fetal size means that total rates actually increase. Thus placental demand for substrates will exacerbate an already reduced

margin of safety between fetal demand for and the available supply of such substrates in the pregnancy.

Thermoregulation:

Extreme cold overpowers the biological response and body temperature drops. At the other end extreme excessive heat causes the body to gain heat more quickly than it can lose it and as a consequence hyperpyrexia follows.

Between these extremes there is a range of thermal control over which the animal maintains a near constant body temperature by regulating extra heat production by either shivering or non-shivering thermogenesis or extra heat loss by sweating.

Between these two zones there is a narrow band of temperature called thermoneutral range where the body temperature and metabolic rate remains fairly constant.

The actual ambient temperatures constituting the range of thermal control are determined by the animal size, thermal insulation and metabolic rate and their capacity to increase heat production in a cool environment and increase heat loss in hot environment.

Thermal Neutrality: The zone of thermal neutrality (Hey, 1975 a). The definition of the zone of thermal neutrality as recommended by the International Union of Physiology Sciences (IUPS) is the range of ambient temperature within which metabolic rate is at a minimum and within which temperature regulation is achieved by non-evaporative physical process.

The importance of this definitiion is that the thermoneutral range and the range over which the infant's metabolic rate is near the minimum are not the same.

Infants may increase evaporative heat loss without much increase in his

metabolic rate.

Newborn pigs prefer a thermal environment around the lower end of or just below the thermoneutral range (Mount, 1963). Adult man claims to be most comfortable around the same range (Gagge, et al 1965).

Babies are found to sleep longer when their heat production is minimal (Bruk, Parmelee and Bruk, 1962). This suggests that human infants have a similar appreciation of thermal environment as a newborn pig and adult.

Sleep itself can't be relied upon entirely as an index of comfort, for newborn animals including the human infants will continue to sleep whilst making thermoregulatory responses of either extra heat production or sweating.

The minimal metabolic rate: This is the obligatory rate of heat production which, with the infant's size and thermal insulation, determines the temperatures of the thermoneutral range.

The metabolic rate can be expressed as oxygen consumption or the rate of fuel consumption and the rate of heat production.

For the newborn the relationship between metabolic rate (resting or minimal metabolic rate) and the weight is very important and operates over a range of environmental temperatures.

The minimal or resting metabolic rate rises over the first few days of life and this increases due to establishment of independent metabolic systems, i.e. respiratory or cardiac work, excretion by liver and kidneys and above all the establishment of feeding.

The metabolic rate of many young mammals soon after birth is below that expected from the body weight/metabolic rate relationship in adults. After the postnatal rise, it is above adult ratios (Hensel, et al, 1973

,).

In premature infants the rate of rise in minimal metabolic rate over the first few days is slower than that of mature infants (Hey, 1969). Malnourished newborn infants who are light for dates who have a large brain compared to their liver size but not compared to their peers have a metabolic rate (expressed per kg. body weight) similar to normal infants. The rise in their metabolic rate after birth also occurs over the first day or so unless adequate feeding is not established (Bhakoo and Scopes,

1974).

Thermal Balance:

The factors influencing the achievement of thermal stability in the newborn are heat production and heat loss.

1. Conduction of heat:- Occurs directly through the body tissue from the internal organs to the skin surface and from the skin surface through the material in contact with the skin surfaces. There is minimal loss through the faeces and urine by this mode.
2. Convection:- The heat loss from the interior to the skin surface through the blood stream and by convection through the moving air in front of the skin surface as by the transfer of warmed inspired air to the exterior in expiration.
3. Radiation:- Transferred down a temperature gradient from the infant's skin to surrounding cooler surface. This amount of heat is the relationships between the temperature gradient of the radiating surface (the skin) and the surroundings as well as the effective surface areas.
4. Evaporation:- The evaparative heat loss occurs as insensible evaporation from the skin, evaporation of sweat and evaporation

from the mucosa of respiratory tract into expired air.

The importance of the four mechanisms of heat loss vary according to internal and external environment conditions.

The main external variables are the difference between the infant's body temperature and environment, the velocity of air from over the infant, the relative humidity of the air and exposed body surface area.

Heat exchange is dependant on whether the infant is clothed or nursed naked in an incubator.

Under thermoneutral conditions heat losses are mainly by radiation and convection.

Evaporative heat loss varies widely according to the physiological and environmental temperature, sweating and hyperventilation or any pathophysiologic condition causing hyperventilation. It is also influenced inversely by the relative humidity of the environment and directly by the velocity of air flow across the evaporating surface. Each ml. of water which evaporates from the infants will remove 560 calories of heat.

Under normal conditions in term infants the amount of evaporative heat loss is about a quarter of the resting heat production (Hey and Katz, 1969). About a quarter of this loss is by evaporation of water from the respiratory tract, the rest occuring by passive diffusion of water through the epidermis (Transepidermal Water Loss TEWL).

Evaporative heat loss is very important at delivery when the skin is wet with amniotic fluid.

Preterm infants have high evaporative heat losses whilst the insensible water loss is also high in preterm compared to term infants, especially in the most immature infants in the early neonatal period (Fanaroff et al, 1972., Wu and Hodgman, 1974 and Okken et al, 1979). This is the

result of high TEWL which is up to six times higher per unit surface area in a newborn infant of twenty-six weeks gestation than the term infant (Rutter and Hull, 1979 a).

This high transepidermal water loss occurs because the immature infant's skin has a thin, poorly keratinized stratum cornum which offers little resistance to the diffusion of water.

Nursing a naked four day old baby weighing 1.5 kg. in a single-wall incubator heated convectively by recirculating warm air entails a relatively increased heat loss by radiation to the cool walls of the incubator from the skin surface.

The internal incubator walls assume a temperature intermediate between the air temperature inside the incubator and the cooler external room temperature.

Raising the incubator air temperature to 36°C. reduces the radiative heat loss and returns total heat losses substantially to those under thermoneutral conditions. Under all conditions heat losses by conduction are minimal (less than 3 percent of total) (Hey, 1976), so in thermal equilibrium heat storage is zero and heat loss is equal to the total metabolic heat production.

The thermoneutral zone is bounded by an upper and a lower critical temperature.

The upper critical temperature is the ambient temperature above which thermoregulatory evaporative heat loss is recruited.

The lower critical temperature is the ambient temperature below which the rate of metabolic heat production of a resting thermoregulating individual increases to maintain thermal balance. Related to the neutral thermal environment, but somewhat wider, is the zone of thermal comfort (Bligh and Johnson, 1973).

The zone of minimal heat production is also defined as a range of environmental temperature over which heat production is kept at a minimum by a combination of vasodilation, postural change and increased evaporative heat loss (Hey, 1975).

The newborn infant is extremely sensitive to fluctuations of body temperature and it has been found that when deep body temperature is below 36°C. or above 37.8°C. the mortality rate increases (Yashiro et al, 1973).

This zone (36°C. - 37.8°C.) is therefore described as the optimal body temperature for survival and will usually be attained under approximately thermoneutral conditions.

The core or internal temperature represents the deep body temperature and is usually measured clinically as a colonic (greater then 5 cm. from the anus) or oesophageal temperature. The normal value in the newborn is 36.5°C. - 37.3°C.

Hey and O'Connell (1970) give a value for tissue insulation of 0.05°C./M^2/hr./Kcal. for a 2.5 kg. infant in a heat-losing environment. Because of the lower content of body fat in infants weighing less than 2 kg., tissue insulation is lower in such infants and partly explains the extreme susceptibility of the low birth weight infant to cold stress, despite an active thermoregulatory control of skin blood flow.

Thermoregulatory Responses to a Cool Environment:

As the environmental temperature falls the newborn infant makes physiological and behavioural responses in order to maintain a constant core body temperature. These responses are initiated by hypothalamic and cutaneous temperature receptors.

Since shivering does not occur in the newborn, the infant increases heat production by using non-shivering thermogenesis, which results from the

metabolic activity of a very specialised organ of heat production, brown adipose tissue (Hull, 1966). This is called "heat production by switching on his internal heat organ" (Hull, 1974), (Hull, 1976). Brown adipose tissue is composed of unilocular fat cells and it has been found in newborn infants (Aherne and Hull, 1966), lambs and calves (Alexander, 1975). Infants malnourished in utero appear to have brown adipose tissue with lower fat content.

The control of the rate of heat production is mediated via the sympathetic nervous system, which in turn influences the activity of intracellular lipases and it is possible that the rate of release of fatty acids into the cell determines the rate of oxidation.

Summit Metabolism of the Newborn:

Summit metabolism is the maximum metabolic response which the newborn infant can make. There are several factors which might determine or limit it. Firstly, the amount of brown adipose tissue present. Secondly, the response of brown adipose tissue to cold stress. Thirdly, the metabolic response might be influenced by the amount of fuel present as the stored glyceride.

To determine summit metabolism it is necessary to measure the metabolic rate at ambient temperatures close to those which precipitate hypothermia.

Hey (1966) used a closed circuit method to measure the metabolic response and Smales (1975) used open circuit method for the same goal. It is fair to conclude from their data that the metabolic rate for such infants is around 7.5 ml./kg./min. and increases to around 13.5 ml./kg./min. at an ambient temperature between 28°C. - 30°C. (NB = 7.5 ml./kg./min. oxygen consumption and 13.5 ml./kg./min. oxygen consumption).

Measurement of Heat Production:

Heat production is measured either by direct calorimetry or indirectly by measuring the rate of carbon dioxide production and oxygen utilization.

Lavoisier and Laplace used the direct method for the first time when they confined a guinea pig in a chamber containing a given weight of ice and estimated the heat production from the amount of ice melted.

Over the years although there were many modifications and technical improvements in the experimental approach, the rate of heat production has remained a difficult parameter to measure.

Direct calorimetry is technically demanding and many measurements and calculations have to be made.

Heat production can be calculated by using carbon dioxide production, oxygen uptake and by knowledge of the respiratory quotient.

Hasselback in 1904 developed a sensitive open system that measured oxygen uptake as well as carbon dioxide release on newborn infants. Modification of this system has been extensively used for studies by Pribylova et al, (1966 & 1967).

The gas flow through a mixing chamber was used, because the air volume in the chamber is relatively large and there was delay before the gases mix stabilizes. They used a headbox or face masks to reduce the air volume.

The introduction of the paramagnetic oxygen analyzer permits a fairly accurate measurement with minimal interference of the measurement, Lister et al, 1974, Smales et al, 1978.

Earlier studies are of little clinical value because the importance of environmental temperature was not fully appreciated. The face and upper airways are particularly sensitive to temperature changes and

therefore in systems using headboxes or face masks it is essential to measure the thermal conditions within these devices as well as those surrounding the infants as a whole.

Direct Calorimetry; In this method the metabolic rate is estimated from the measurement of oxygen consumption and carbon dioxide production (E. Ferrannini et al, 1988). The amount of oxygen consumed per unit of time is proportional to the energy liberated. Thus direct calorimetry really measures oxygen consumption and carbon dioxide production. On the assumption that all oxgyen is used to oxidise degradable fuels and all the carbon dioxide thereby evolved is measured, it is possible to calculate the total amount of energy produced.

Direct Versus Indirect Calorimetry; It is clear that energy production means conversion of the chemical free-energy of nutrients into the chemical energy of ATP plus loss of some energy during the oxidation process as heat. Eventually all energy will convert into heat. Any heat dissipated internally to increase body temperature or accumulated in the form of energy-rich chemical bonds is not seen by direct calorimetry.

Under conditions of unchanging temperature and energy store repletion, direct and indirect calorimetry simply looks at the two sides of the balanced equation of heat removal and heat production (Jequier, E. et al 1985).

Indirect Calorimetry: Two types - closed circuit technique
- open circuit technique

Closed Circuit Technique; In this technique the entire baby is enclosed in a chamber (Karlberg, 1952), (Hill and Rahimtulla, 1965) and (Dechert, Wesley, Schafer et al, 1985).

The baby breathes from closed gas mixture which can be pure oxygen or air-oxygen mixture.

The carbon dioxide and water are removed from the expiratory gases and the same gas used for subsequent inspiration, oxygen is added to the circuit so the original oxygen content is maintained. Carbon dioxide production requires measurement of the flow.

Open Circuit Technique; A variety of techniques have been described for measurement of a carbon dioxide and oxygen. Many investigations have attempted by different techniques to measure CO_2 & O_2 on expired gas samples using an open circuit, flow-through procedure where only the head of the baby is enclosed in a chamber (Kappagoda, 1972), (Lister et al, 1974), (J. Evans and B.M. Holland, 1978) and (Westenskow et al, 1984). In the open circuit technique the expired gases are collected, the volume or flow of gas measured, the inspiratory and expiratory concentration of oxygen and carbon dioxide analyzed.

Oxygen consumption and carbon dioxide elimination calculated from this data by using Haldane Transformation which assumes that only oxygen and carbon dioxide are exchanged in the lungs and the rest of respiratory gases (excluding water vapour) have the same volume in both inspiratory and expiratory gases.

Accuracy; From the experience of workers in both techniques mentioned above, the open circuit technique is accurate in individuals who are not ventilated but in ventilated patients the problems are:-

(1) High pressures in respiratory circuit, PEEP, PEAK and MEAN pressure may influence the gas analyzer.

(2) High inspiratory oxygen concentration (above 60%) will increase the sensitivity of Haldane Transformation to error.

(3) Leak in the respiratory-patient circuit.

(4) Instability of the inspiratory concentration of oxygen caused by the gas mixer or pressure fluctuation in the hospital compressed gas circuit.

(5) Large flow needed to prevent the accumulation of carbon dioxide and rebreathing of carbon dioxide will lead to hyperventilation and this affects the calculation of respiratory quotient (RQ).

The closed circuit rebreathing technique based on the principle of volumetric measurement of oxygen uptake considered to be the most accurate technique for determining oxygen consumption, but there are some problems, for example:-

(1) Carbon dioxide leaks in the respiratory patient circuit (endotracheal tube, patient respirator connector and Humidifiers).

(2) Effect of temperature and humidity.

(3) Variation of breathing pattern may create slow and rapid variation in the concentration of expired gas (affecting pool of carbondioxide), this leads to increased variability of the results.

Brook et al, (1984) and E. Bell, (1986) recommended that by open circuit method the length of time needed for accuracy should be made at least six hours.

FACTORS AFFECTING OXYGEN CONSUMPTION

Environmental Temperature:-

In the thermal neutral zone the total heat loss and production are equal thus the body temperature is constant. This is affected by the ratio of surface area and body weight, the greater the surface area of the organism the higher is its heat loss. For this reason preterm infants require higher ambient temperatures than term infants (Hey and Katz, 1970).

The resting metabolic rate rises in the immediate newborn period (Hill and Rahimtulla, 1965), (Scopes and Ahmed, 1966b) and (Hey, 1969). The maximum resting metabolic rate is approximately 50 kcal. $m^{-2}.h^{-1}$ and is reached by the age of 3 - 6 months. Thereafter it remains constant through childhood into adult life (Karlberg, 1952, Lee and Iliff, 1956). Preterm infants who become cold at delivery have a greater chance of dying, particularly of hyaline membrane disease (Stanley and Alberman, 1978a, 1978b) as cold stress is associated with acidosis and hypoxia (Stephenson, 1970). Newborn infants when dressed, wrapped up, placed in a cot and nursed in a warm room are in a neutral thermal environment. Heat production is at its minimum and energy intake is therefore available for growth.

Mothers prefer to see their infants dressed rather than naked and a clothed newborn appears more contented and less restless. A naked infant is poorly insulated and heat losses are high even in a warm room. Clothing a naked infant more than doubles the insulation, and bedding further increases it, so that the resistance to heat loss of a clothed, wrapped infant is three times greater than that of a naked one (Hey, 1983).

The head is a large part of the total surface area of the newborn infant and has a higher surface temperature because of the brain's high rate of metabolism. A woollen bonnet is an effective method of increasing thermal insulation and is especially useful in low birthweight infants who have larger heads relatively and whose trunk may need to be exposed (Stothers, 1981).

The following are recommendations made for nursing healthy infants based on Hey, 1971:-

Over 2 kg. - nurse clothed, with bedding, in a room temperature of about 24°C.

1.5 - 2 kg. - nurse clothed with a bonnet and bedding in a room temperature of about 26°C.

Less than 1.5 kg. - nurse clothed with a bonnet, in an incubator temperature of about 30 - 32°C.

New Standard for Neutral Thermal Environment:-

It is generally accepted that low birthweight infants should be nursed at thermal neutral temperature - the environment in which oxygen consumption is at a minimum.

Low birthweight infants do not, however, always show an increase in oxygen consumption at temperature outside the neutral range, but react with a change in body temperature.

In 1983 Hey redefined the neutral temperature for low birthweight infants as the ambient temperature at which the core temperature of the infant at rest is between 36.7 and 37.2°C. and the core and mean skin temperatures are changing less than 0.2 and 0.3°C./hour respectively. Using this definition as a guideline, recommendations for the neutral temperature for healthy infants of 29 - 34 weeks' gestation have been made. The neutral temperature during the first week of life is

dependant on gestational age and postnatal age whereas after the first week it depends on body weight and postnatal age (Sauer et al, 1984). In a study by Wheldon and Hull in 1983, the range of thermal control and the thermoneutral range in preterm infants under 30 weeks gestation was calculated by extrapolation of data from studies on more mature infants. The range of control is less than 3°C. and the thermoneutral range is less than 0.5°C. Both are influenced by the rate of transepidermal water loss (TEWL).

The study made on six infants under 30 weeks gestation in the first week of life with the measurement of metabolic rate and effective thermal environment showed that the very preterm infants exert little thermoregulatory control and that variation in transepidermal water loss are a major factor determining the appropriate thermal environment; the metabolic heat production was calculated from the rate of oxygen consumption. Skin evaporative water loss was measured by using evaporimeter in six sites.

Heat and Water Exchange in the Newborn;

Sulyok et al in 1973 have shown in normal full term infants that the respiratory heat loss in a neutral thermal environment (32°C. and 50% relative humidity) represents 2.9% of total body heat production. In an environment of 32°C. and a low relative humidity of 20% the respiratory heat loss rose 9.5% of the total heat production. Hey and Katz in 1969 estimated that 30% of insensible water and evaporative heat loss in term infants consists of respiratory losses. O'Brien et al in 1954 showed in normal newborn infants that the average insensible water loss from the lungs was 17.4 g./kg./day in room air, and this could be reduced to 3.8 g./kg./day if air as a mist was breathed, indicating that the total evaporative loss from the respiratory tract is closely linked

to the ambient humidity as it is in the adult.

The selection and maintenance of inspired air temperature and relative humidity during mechanical ventilation can significantly affect fluid homeostasis and thermal regulation in the newborn infants with respiratory disease (Sosulski et al, 1983).

Sosulski et al in 1983 also measured the insensible water loss of intubated infants during and following extubation; they showed that respiratory insensible water loss was significantly less in the intubated infants. There was a 32% reduction in the whole body insensible water loss in the intubated infants who were receiving warm, humidified air. However they were unable to demonstrate that respiratory water loss exerts a major effect on body heat balance.

THE EFFECTS OF POSITIONING ON ENERGY EXPENDITURE AND BEHAVIOUR OF LOW BIRTHWEIGHT NEONATES:

The body positioning (supine v prone) of low birthweight infants is known to influence transcutaneous oxygen tension (Kishan, et al, 1981), (Martin, et al, 1979), arterial blood gas tensions (Wagaman, et al, 1979), (Schwartz, et al, 1975), respiratory rate (Kravitz, et al, 1958), lung mechanics and lung volumes (Hutchison, et al, 1979).

The effect of body positioning on the two fundamental physiologic variables - energy expenditure and physical activity - have been studied by Schulze et al, 1987. In summary when low birthweight infants are changed from the supine to prone position, energy expenditure decreases, time spent in quiet sleep increases and time spent awake decreases. These suggest that prone position is the position of choice for low birthweight infants.

Effect of Sleep on Oxygen Consumption:-

Studies on the effect of sleep in rapid eye movements (REM) and non-rapid eye movement (NREM) on oxygen consumption plus the effect of changes in the environmental temperature were performed by Stothers and Warner in 1978. The following results were found:

In thirty full-term infants in the first week of life, nursed in a constant volume closed circuit metabolism chamber in neutral thermal environment (31.5 - 33.5°C.) measurements were made of oxygen consumption during periods of rapid eye movements (REM) sleep and non-rapid eye movements (NREM) sleep.

The difference in oxygen consumption during rapid eye movement sleep and non-rapid eye movements was significant.

When the direction of sleep state change was taken into account, the difference in oxygen consumption between the states was much less when REM sleep was preceded by NREM than when the change was in the opposite direction. In nineteen infants in whom the change was from REM to NREM the difference in oxygen consumption was not significant. In NREM state a gradual diminution of oxygen consumption with time was consistently found. This was not the case in REM sleep.

In twelve infants studied in a cool environment (29 ± 0.5°C.) during REM sleep the oxygen consumption was higher than NREM sleep. Thus even the maximum difference found in a neutral thermal environment was significantly increased with mild thermal stress. No consistent changes in oxygen consumption with time were found in either REM or NREM sleep in twelve infants studied in a cool environment in contrast to the finding in thermal neutrality.

An observation made during the course of the study was the skin pallor frequently associated with NREM sleep. It is interesting to speculate

that this phenomenon is almost certainly due to reduced skin blood flow, provides some degree of production against heat loss in sitations involving decreased oxygen consumption with consequent diminished heat production.

Metabolic Rate and Oxygen Consumption in Newborns During Different States of Vigilance:-

Using an indirect calorimetery open circuit system 135 asymptomatic newborn infants were studied by Stabell, et al, in 1977. According to the state of wakefulness the infants showed during the testing procedure they were divided into four groups as follows:-

State of Vigilance 1 (V1) quiet sleep, State of Vigilance 2 (V2) REM sleep, State of Vigilance 3 (V3) eyes open - no movements, State of Vigilance 4 (V4) eyes open - movements.

The results showed that there are little difference in the mean values in metabolic rate and oxygen consumption in V1, V2 and V3. V4 infants however had a higher oxygen consumption and metabolic rate.

Effect of Feeding on Neonatal Oxygen Consumption:-

The first description of the effect of feeding on oxygen consumption was reported by Lavoisier in 1789. He found that in a temperature of 32°C. oxygen consumption of an adult rose about 50% above the resting value during digestion.

Biddar and Schmidt in 1877 attributed this rise to the work of digestion. This concept of increased intestinal work was challenged by Benidict and Emmes in 1912 who showed that oxygen consumption rose equally in response to either intravenous or oral amino acids. Rubner in 1902 introduced the term 'specific dyanamic action' (SDA). Early measurement of specific dynamic action in infants were made by Rubner and Heubner in 1899. Murlin et al in 1925 reported that (SDA) of

ordinary feeding within the first eight days of life was small, the largest increase being 12% after a feed of lactose. Since then a variety of workers have used different foods and in differing environment. Mestyan et al (1969) investigated the magnitude and thermoregulatory significance of the response to feeding in premature infants under carefully controlled conditions and found an increase in metabolism of 30% after feeding a milk formula in thermoneutral environment. Gentz et al (1970) studying the influence of feeding in newborn pigs, reported that in previously unfed piglets there was a significant rise in oxygen consumption after feeding; the maximum increase was 45%. Gentz et al (1976) investigated short gestation infants and those of diabetic and prediabetic mothers and reported a 10% to 30% rise in oxygen consumption.

The length of time during which the rise persisted in the series of Mestyan et al (1969) was about 240 minutes, although prefeed values were approached about 150 minutes post-prandially. In the piglets (Gentz et al, 1970), the return to mean control values was about 500 minutes in a previously fasted group. No values were given for the previously fed piglets. The oxygen consumption in infants (Gentz et al, 1976) reached a maximum at 1 to 1.5 hours and then slowly returned to prefeed values. Stother et al in 1979 studied oxygen consumption in 9 short-gestation infants before feeding and for an hour after feeding. Using a closed circuit metabolism chamber and comparing oxygen consumption by using the same system for 9 term infants for varying periods, beginning one hour from the end of the last feed; in short-gestation infants a rise was found in 15 - 45 minutes after feeding. Oxygen consumption then fell, and after 60 minutes had reached prefeed levels. The term infants showed no decrease in oxygen consumption with time after the first hour,

as would be expected if the effect of feeding on oxygen consumption extended beyond this.

The Effect of Intravenous Energy and Amino Acids in Preterm Infants:-

In a study of preterm infants 30 - 32 week appropriate for gestation age Weinstein et al in 1987 divided the infants into three groups. All the three groups received non-protein energy as dextrose. Group 1 .38 kcal./kg./day and 11.25 g./kg./day, group 2 and 3 received 64 kcal./kg./day and 18.75 g./kg./day. In addition group 3 received 1.2 g./kg./day crystalline amino acids. 36 hours after the beginning of the infusion the oxygen consumption was measured by indirect calorimetery for 5 - 6 hours. Urine was collected for urinary nonepinephrine excretion, serum thyroxine (T4) and Triiodothyroxine T3 concentration was measured. The result showed group 1 had significantly lower oxygen consumption and urinary norepinephrine excretion than the groups 2 or 3 which did not differ. T4 and T3 were not different among the three groups.

The addition of commonly used doses of amino acid to the intravenously administered alimentation solutions had no effect on any of the measured variables. Because the sympathetic nervous system is less active in infants receiving a low energy intake, resulting in lower metabolic rates and less metabolic heat production, these infants may require high environmental operational temperature than comparable infants receiving higher energy intake.

The effect of Intermittent Versus Continuous Enteral Feeding:-

To examine whether the premature infants have higher rates of energy expenditure and diet-induced thermogenesis during intermittent feeding compared with continuous feeding. Grant, et al. (1991) used an open circuit respiratory calorimetery. No response of diet induced

thermogenesis in continuous feeding was found, whereas a peak increase of 15% over baseline was observed after intermittent feeding. Overall energy expenditure during the study period was significantly greater after intermittent compared with continuous feeding. Thus there was a mean 4% difference in energy expenditure between the feeding groups.

The Effect of Birthweight and Gestational Age:-

Measurement of oxygen consumption in 19 healthy newborn infants with different birthweight and gestational age was performed to investigate the relationship between birthweight and gestational age effect on oxygen consumption by Hill and Robinson in 1968. Initial measurements of oxygen consumption were performed within 12 hours of birth and further measurements were made at intervals until the baby left hospital.

The majority of the infants (17) weighed less than 2.5 kg. at birth and were premature. Infants were divided into four groups according to birthweight and gestational age combined. At birth minimal oxygen consumption was closely correlated with birthweight in all infants and appeared to be directly proportional to it. The value for oxygen consumption per kg. was similar in all groups. Oxygen consumption was not related to gestational age per se. In the two normally grown groups oxygen consumption was roughly related to gestation because birthweight was related to gestational age. In all infants minimal oxygen consumption rose progressively with increasing age after birth, a marked increase in oxygen consumption occurred in the first week of life, despite a small decline in body weight. At age greater than two weeks a large difference appears. The full term infant's oxygen consumption was found to stay constant, roughly at 7.2 ml./kg./min. up to one year of age. By contrast premature infants continued to

increase their oxygen consumption after 2 weeks, reaching higher values around 9 ml./kg./min. by 1 - 2 months. This study suggests that calorie requirements per unit body weight are likely to be considerably greater in premature than in full term babies after the immediate neonatal period.

The Influence of Postnatal Age, Energy Intake and Weight on the Infants Metabolic Rate:-

The correlation of increasing age with metabolic rate has been studied by many workers who generally agree that oxygen consumption is lowest in the first hours after birth and increase during the immediate postnatal period.

The study of the inter-relation of postnatal age, metabolic rate, energy intake and weight-gain by Chessex et al in 1981 suggested that the increase in the metabolic rate with postnatal age is most likely due to the increasing energy intake and weight-gain and not casually related to increasing age. It appears that tissue synthesis is an energy demanding process which can only be covered by increased oxidative metabolism of the principle nutrients which induce a considerable rise in heat production. Thus the increase in metabolic rate in the early postnatal period seems to be a consequence of the energy cost of tissue synthesis.

The Influence of Relatively Large Brain Size on Raised Metabolic Rate:-

Infants who are small for gestational age have a higher metabolic rate than appropriate for gestational age infants (Bhakoo and Scopes, 1974, Brook, 1982 and Chessex, et al, 1984) and they behave like recovering malnourished infants whose metabolism has been shown to increase to higher levels than are found in normally nourished infants of the same age (Ablett, and McCance, 1971), (Ashworth, 1969) and (Brook, and

Cocks, 1973). Since the brain is the organ constributing most to total body metabolism in neonates (Kennedy, and Sokoloff, 1957), it is to be expected that the metabolic rate will be higher when the brain contributes a greater proportion of the metabolically active tissue. Because metabolism depends on the macronutrient constituents of the tissues and metabolised fuels, infants with depleted fat will have higher metabolic rate per unit weight as fat has a lower metabolic rate than protein.

This will always be a problem as there is no simple and reliable method of estimating body composition in live infants.

Brook et al (1988) studied oxygen consumption and the influence of large brain size. Brain weight was calculated from head circumference measurements and expressed as percentage of body weight and was found to be significantly higher in SGA infants than AGA ones. Metabolic rate was calculated and expressed as kcal./centimeter head circumference, kcal./g. brain weight and kcal./kg. body weight. Whereas metabolic rate expressed in kg. body weight was significantly higher in SGA infants than AGA, no difference could be detected in the values when metabolic rate was expressed as kcal/cm. head circumference or metabolic rate/g. brain weight.

The difference that exists in the metabolic rates between SGA and AGA infants can be minimised by using head circumference as a reference. Therefore the apparently high metabolic rate found in SGA infants in the neonatal period can be attributed in a major way to their relatively large brain size.

STATISTICAL METHODS

On this thesis the following stastical methods were applied:

(1) Mean, Mode, Median, Standard Deviation.

(2) Student t test modified for small number.

(3) Standard Error.

(4) Correlation Coefficient.

(5) 95% Confidence Interval.

METHODS:

We set out to evaluate two forms of indirect calorimetry in the newborn: One which was new and only available to us for a short period (Deltatrac), the other older and more complicated to operate (Mass Spectrometer).

The Deltatrac Metabolic Monitor, manufactured by Datex Instrumentarium Corp., is an indirect calorimetry device which measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2) and calculates from this the respiratory quotient ($RQ = VCO_2/VO_2$) and energy expenditure (EE). This monitor is used in the spontaneous breathing patient.

Flow Measurement:

Dilution Principle;

The air dilution method used in Deltratrac is a modification of the flow-through canopy principle commonly used for spontaneous breathing system meaasurement of gas exchange. Measurements are performed with a modification of the flow-through canopy system, since masks and mouthpieces may induce changes in breathing pattern and may cause anxiety and discomfort which may lead to error in results. Hyperventilation is especially common with masks and mouthpieces. When this modification system is used the total flow of gas needed in order to avoid carbon dioxide accumulation within the system depends on the surface area of the infant and in our patient was 6 l./min.. - the flow rate required modification of the system and made it possible only to measure a healthy infant.

Oxgen Measurement:

Since oxygen is a gas which has a large paramagnetic susceptibility compared to other common respiratory gases, the oxygen in this system is

measured using paramagnetic analysers. This system is modification of Pauling's Principle (Pauling, J. Amer. Chem. Soc. 68 : 795, 1946) where oxygen causes a mechanical displacement of a dumb-bell suspended in a non-uniform magnetic field. The design of the differential O_2 sensor OM-101 in this system started from the same principle using a measuring cell with chopped field.

Carbon Dioxide Measurement:

Carbon dioxide is measured in the Deltatrac with a Datex infra red sensor of type CX-104. The commonly constant flow we used is 6 l./min. The flow constant is defined by the requirement that the energy expenditure has to be calculated with formulas where the gas volumes are in STPD (standard temperature and pressure - 760 mm/Hg.), dry gas.

Canopy Measurement:

Canopy Constriction: The Deltatrac canopy was designed to decrease the inspiratory carbon dioxide level by decreasing the canopy volume and partly by improving its internal aerodynamic properties to flush out the carbon dioxide produced by the patient more effectively. The Canopy has a basic geometry of half ellipsoid (see fig.) and it is manufactured of a 1 mm. thick transparent PVC plastic.

It is provided with adapters for tubing and with a wide edge of soft plastic cloth to make the construction airtight under the head and around the neck of the patient.

Measurement Principle:

The measurement of carbon dioxide production and oxygen consumption are calculated from gas concentration differences measured to the Deltatrac between up and down stream flows. There are two tube connections, one over the dome and the other at the air flow hose inlet. CO_2 is measured at both sites to the Deltatrac.

Elimination of Humidity Effects:

In the Deltatrac a Datex watertrap is used to collect the water condensed in the external sampling tube in a bottle situated on the front panel of the device. Thus the water condensed into the tubing is removed before it can enter the sensor and the partial pressure of the water vapour is maintained during all measurement and calibration phases to obtain correct results for dry gas concentration.

Calibration:

The gas sensor has to be calibrated at least daily to ensure accurate results with calibration gases. Calibration of the constant flow generator can be made indirectly with a carbon dioxide injection.

Gas Calibration:

The carbon dioxide and oxygen can be calibrated with a gas mixture or with separate gas to provide the accuracy of the final results.

Software of the Deltratrac:

The designs of the software to ensure ease-of-use in routine measurement, the video screen is used effectively and provides you with trends of results.

Patient Data Input:

Weight, height, age and sex of patient can be entered to calculate O_2 consumption and body surface area.

Alarms:

In the mode malfunction of the flow generator or loosening of tubing (canopy tubing) which may lead for instance to an accumulation of carbon dioxide inside the canopy, the alarm will sound to warn the user.

Display Options:

Deltratrac displays the results in numerical and graphics from both on the video screen and on paper printed by a printer.

The Deltratrac Metabolic Monitor displays the following parameters:-

oxygen consumption (VO_2)

carbon dioxide production (VCO_2)

Respiratory quotient (RQ)

Energy expenditure (EE)

Tidal volume (VT) in respiratory mode

Minute ventilation (VE) in respiratory mode

Inspired oxygen fraction (FiO_2) in respiratory mode.

Deltatrac Metabolic Monitor Datex Study:

The oxygen consumption and carbon dioxide production and respiratory quotient (RQ) can be calculated from the constant airflow and the down stream gas. This flow is a fixed factory set.

Inspired oxygen concentration is always assumed to be room air 20.9% (FiO_2). The temperature: Deltatrac measures the temperature of the expired gas after the flow generator.

Pressure: The ambient pressure is measured after switching on and during each calibration procedure.

Water Vapour:

No humidity correction needed because the constant flow generation is calibrated with known injection of dry gas. Therefore oxygen consumption and carbon dioxide production are normally expressed under standard condition of (STPD) Standard temperature pressure and dry.

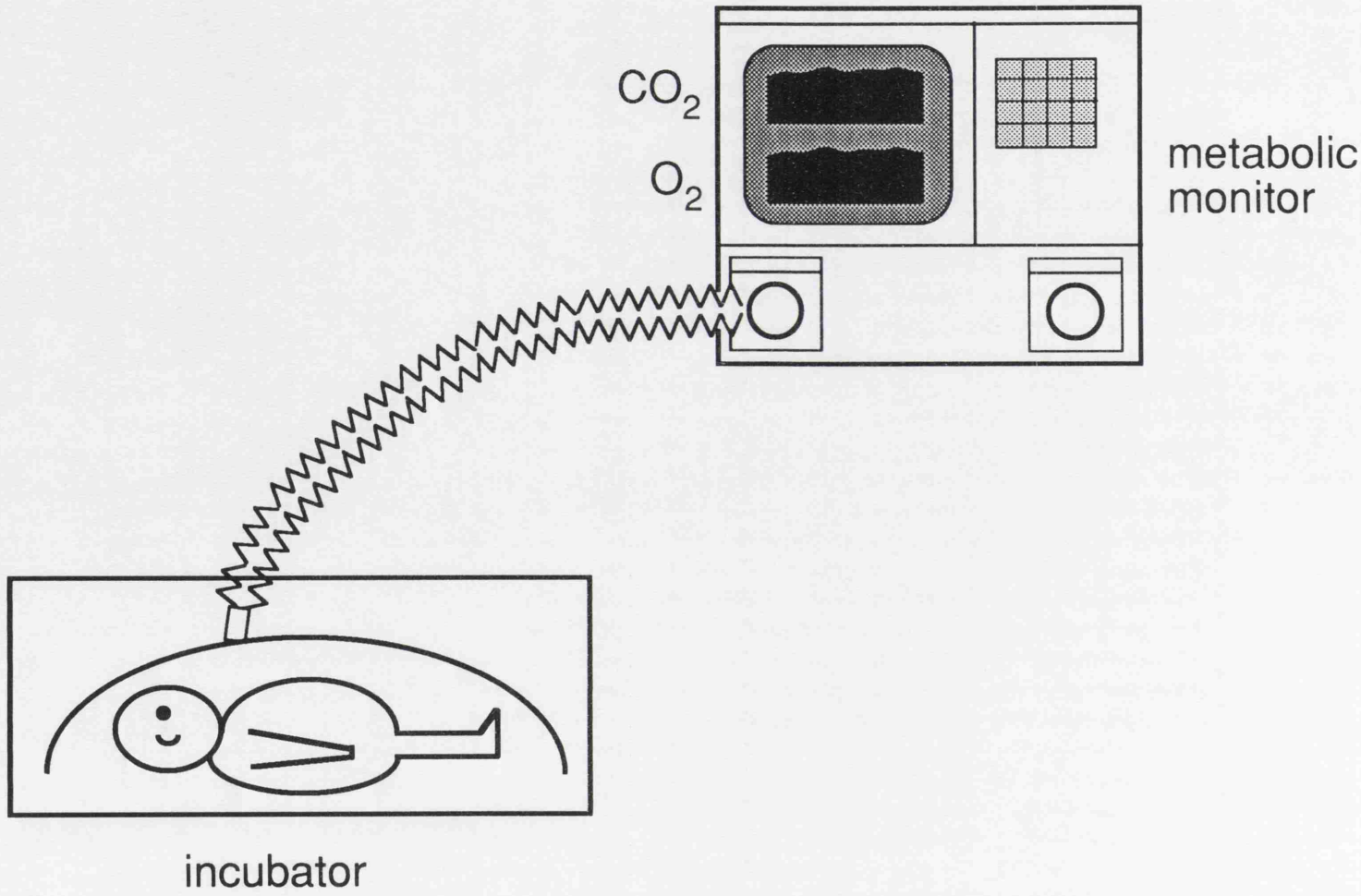


FIGURE I

USE OF METABOLIC MONITOR FOR MEASUREMENT OF OXYGEN UPTAKE, CARBON DIOXIDE PRODUCTION IN INFANTS

Patients:

Fifteen breast fed babies were investigated in our Study. The clinical characteristics of the infants are shown in Tabel I.

TABLE I (a)

Clinical Characteristics of Breastfed - Deltatrac investigated infants

No.	Sex	Gest. Age	Weight (kg.)	Length (cm.)	Age at Study	Surface Area M^2
1.	F	Term	2.56	50	5	0.16
2.	F	"	2.92	53	3	0.20
3.	F	"	2.70	50	4	0.19
4.	M	"	3.52	54	4	0.25
5.	M	"	3.40	50	4	0.19
6.	M	"	4.20	54	3	o.23
7.	F	"	3.20	50	4	0.19
8.	M	"	3.76	51	4	0.22
9.	F	"	3.36	52	4	0.22
10.	F	"	3.30	55	5	0.23
11.	F	"	3.10	50	4	0.22
12.	F	"	3.45	50	3	0.22
13.	F	"	3.60	50	5	0.22
14.	F	"	3.90	48	3	0.21
15	M	"	3.36	50	4	0.19

Weight in kilograms, sex, length (in cms.), age at the Study (postnatal age in days), body surface area (m^2) and gestational age.

TABLE I (b)
Mean and Range of Clinical Characteristic

	MEAN	RANGE
Weight (kg.)	3.55	2.5 - 4.2
Length (cm.)	51.00	48 - 55
Age at Study (days)	4.2	3 - 6
Body Surface (M^2)	0.02	0.19 - 0.22

The M : F ratio was 1 : 2

Method: Indirect Calorimeter;

Whilst in the range of thermoneutrality recommended by Hey, the environmental and room temperature were recorded automatically by the Deltratrac sensor. The infants were placed in an open cot and the infant's head covered by a transparent plastic hood through which air was drawn at a precisely measured rate. The exhaust air was passed through the Deltatrac dual channel paramagnetic oxygen analyser and the infra red carbon dioxide analyser. From the differences in oxygen and carbon dioxide concentration between room air entering and leaving the hood, the infant's oxygen consumption (STPD), carbon dioxide (STPD) and respiratory quotient were determined.

The oxygen and carbon dioxide analysers were calibrated at the start of each study automatically. The infants activity was continuously monitored and infants oxygen consumption and carbon dioxide production measured whilst infants were in the sleep state of rapid eye movement (REM). Any active or crying infants were removed from the study. All oxygen consumption and carbon dioxide data was expressed in ml./kg./min.. The respiratory quotient was calculated from this.

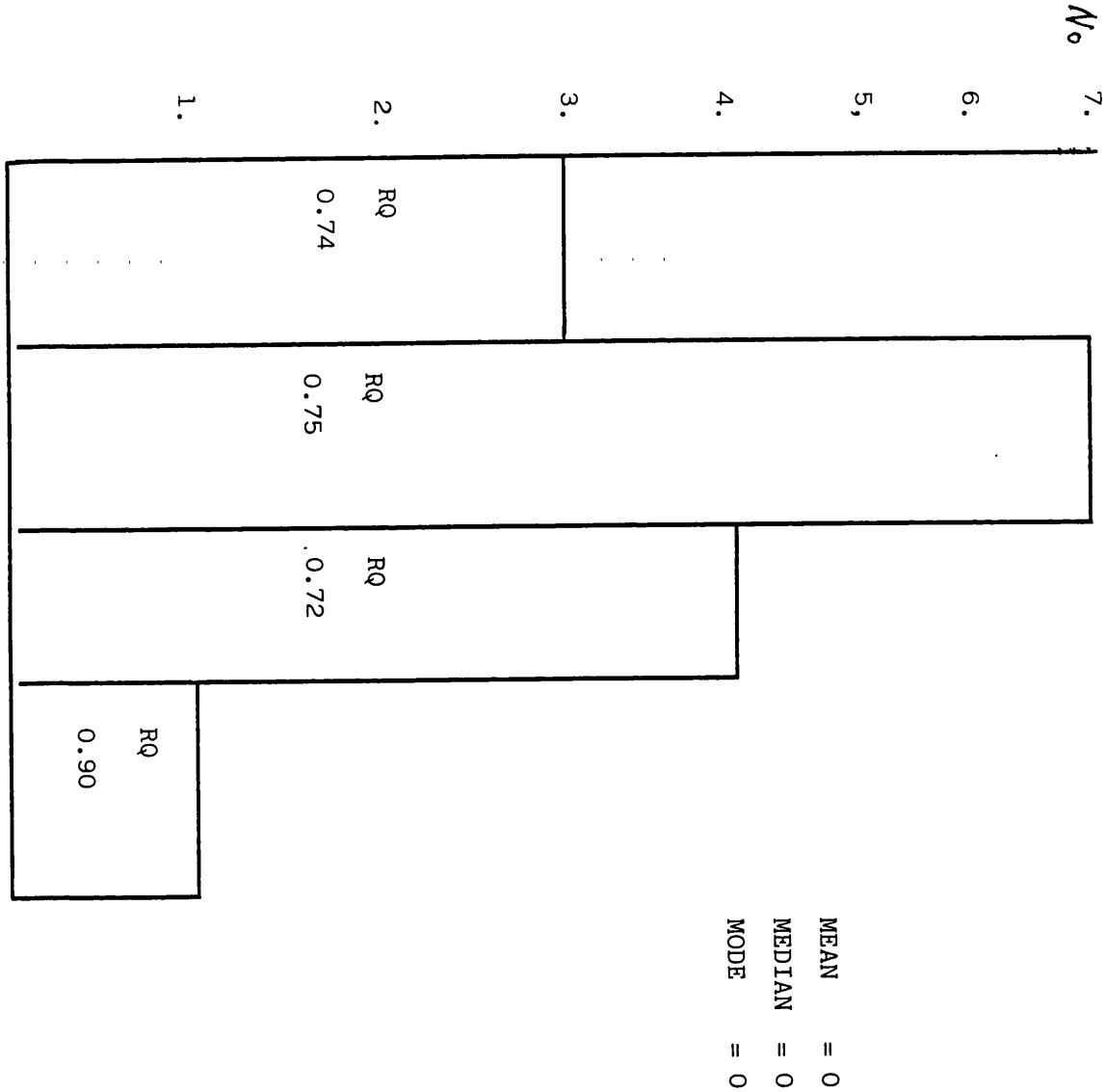
Duration of Study: The duration of the study takes thirty to fifty-five minutes.

TABLE I (c)
(Result)

No.	Atmospheric Pressure mmHg.	Oxygen Consumption ml./min.	CO2 Production ml./min	Respiratory Quotient	Basal Metabolic Rate Kcal
1.	766	6.6	5.46	0.827	770
2.	745	5.14	3.08	0.60	780
3.	736	3.70	2.96	0.80	360
4.	755	11.0	7.3	0.66	400
5.	741	3.2	2.05	0.64	360
6.	755	5.0	4.5	0.90	790
7.	749	6.9	4.8	0.695	780
8.	756	7.18	4.8	0.67	380
9.	760	5.95	4.76	0.80	790
10.	752	7.5	5.7	0.76	800
11.	753	6.7	5.48	0.82	790
12.	753	6.6	5.5	0.83	790
13.	753	5.8	4.4	0.76	370
14.	753	5.1	4.1	0.80	780
15.	763	6.3	4.5	0.71	360

VO_2, VCO_2, RQ and BMR in Term infant using Deltatrac.

FIGURE II



THE RELATIONSHIPS BETWEEN RQ AND WEIGHT OF INFANTS STUDIED BY DELTATRAC

RESULT:

Oxygen consumption and carbon dioxide production was measured in fifteen term, breast feeding infants using the indirect calorimetery open circuit method (the Delta Trac Metabolic Monitor). Results shown in Table I (c) indicate that oxygen consumption ranged from minimum 3.2 ml./kg./min. to a maximum of 11 ml./kg./min. for the fifteen infants investigated, with an oxygen consumption mean of 6.2 ml./kg./min., standard error mean of + 0.468. The carbon dioxide production ranged from 2 ml./kg./min. to a maximum of 7 ml./kg./min. with a mean of 4.6 ml./kg./min. and standard error mean of + 0.329.

For the weight range 2.5 - 3 kg. the mean RQ is 0.74, for the weight range 3 - 3.5 kg. the mean RQ is 0.75, the weight range from 3.5 - 4 kg. the mean RQ is 0.72 and weight of 4 kg. RQ is 0.90 (see Figure 2).

The respiratory quotient for the whole study group produced a mean of 0.75, mode of 0.80.

Discussion:

In comparison with the work of others (Scopes et al, 1974, Forsyth et al, 1991) our results are at the lower end of the standard range for oxygen consumption and carbon dioxide production, i.e.

6 - 8 ml./kg./min, 4 - 6 ml./kg./min. respectively. The correlation of oxygen consumption to carbon dioxide production is 0.926 which is acceptable.

In the Deltatrac using a modification of flow-through canopy principle for sponteneous breathing patients the oxygen consumption and carbon dioxide production can be calculated from the constant air flow which may be a source of variation in the oxygen consumption.

As a consequence of this variation may lead to a small respiratory quotient. The length of the study is short, the longer the more

accurate the study, but at least three hours is needed which sometimes becomes difficult to obtain because of awaking the infants and they have to be kept in REM sleep.

Because of fixed flow rate of Deltatrac it might be less suitable for infants with low tidal volume.

The Deltatrac system is a non-invasive technique, easy to operate. The last but not least, the Deltatrac metabolic monitor which we have been using in our study was on loan from the company for a limited time and did not allow us to confirm that the monitor can be used in the future as a metabolic monitor for infants.

MASS SPECTROMETER

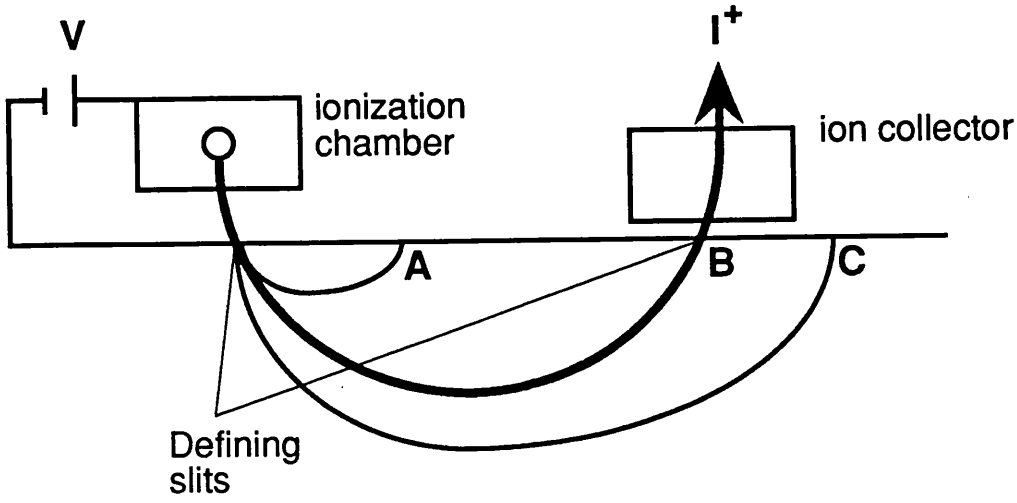
The earliest practical mass spectrometer was described by Dempster as long ago as 1918. It is interesting that many instruments in common use today follow closely his design.

The principle of Dempster's magnetic deflection instrument like all mass spectrometers operates in a vacuum system so that the influence of molecular collisions is negligible or very small.

The action starts in the ionization chamber, where positive ions are produced from gases molecules. These ions are all accelerated through the same potential difference, thus all gaining the same energy before being projected into a magnetic field as a slight convergent beam. They move in a homogenous magnetic field following circular trajectories like an object moving in air in a circular path (see Figure I).

FIGURE III

The Dempster type of mass spectrometer



The beam of ions is constrained or enforced to paths having small radii, the heavier ions following longer trajectories, the lightest ions being refocused at A and the heavy ions at C.

The ions refocusing at B pass through defining aperture and are collected in a metal box (Faraday Cage). The passage of the ions to the box creates an ion current I+, proportional to the ion beam intensity. If the field strength is increased the radius of each heavy ion is reduced and they are successively passed through the aperture and are collected. These instruments are very expensive to produce because of the magnetic materials so further developments have led naturally to the sector field instrument where the working principle is the same as the Dempster instrument. Molecules of the sample gas are ionized by electron bombardment within the ionization chamber, accelerated through a potential difference and projected in a slightly divergent beam into the electric field.

Multi-gas Monitor MS2 (MASS Spectrometer):

The multi-gas monitor can be divided into four systems:-

1. Vaccuum system
2. Inlet system
3. Analytical system
4. Protection system

1. **Vacuum system;**

The vacuum system provides the very low pressure which is essential for the operation of all spectrometers, the main component is the oil vapour diffusion pump which provides a pressure typically less than 10^{-9} atmospheres in the analytical chamber. The oil diffusion requires a second mechanical pump for back-up and time to heat up the oil to vaporise it. The thermo-electric cooling needle of the Peltier Baffle

condenses any oil vapour which may escape from the diffusion pump, preventing contamination of the analytical chamber. If an accidental break in the vacuum is produced the oil will burn onto the inside of the mass spectrometer.

The problems of vapour diffusion pump is that pumping speed stability can suffer from term fluctuations due to pump boiling in the boiler. This can affect the speed in two ways. First by formulation of oil droplets which are thrown up and emitted from the jets and secondly, particularly in the case of lighter gases, variation in the boiler pressure associated with intermittent boiling, may lead to contaminant in the inner mass spectrometer (the analyzer) with droplets of oil. This consequently leads to drift in the calibration baseline and to inaccurate measurement.

2. **Inlet system;**

This is normally made of fine bore plastic capillary tubes heated to approximately 80°C. to prevent water vapour condensation and blockage. The gas sample of 20 - 40 ml./min. is drawn in by sample rotary pump. They lead to a sample chamber. This sample chamber is connected to the ionisation chamber of the mass spectrometer via porous ceramic (metrosil) with long delivery inlets. Gas flow takes time to move the concentration boundaries in gas sample down the inlet and this is dependent on the consumption rate of gas into the inlet, speed of response of the machine, selection of material for the inlet and the length and bore of tubing used. Most of the problems is the lag introduced by the transit time down the inlet.

Transit time:- is the time for ion source pressure to change from 0 - 90% of its final value following a step change in sample composition. This parameter is important because it affects the time resolution

of the analyzer.

3. **The Analyser (Mass Filter);**

The most common mass filter used in respiratory mass spectrometer is the quadrupol. The quadrupol consists of four metal rods approximately 20 cm. long. The rods are arranged so that opposite pairs are electrically coupled and between the two pairs a combination of radio frequency voltage and steady voltage is applied. The filter uses the resonant properties of ions inside the electrical field created, for a particular set of voltage. Only ions of one mass charge ratio will pass the rods and produce a current at the collector proportional to the partial pressure of the molecules of that mass in the sample gas.
Any other ions are deflected onto the quadrupol rods, because the ionization efficiencies of different masses are different. The instrument must be calibrated to give accurate comparisons of partial pressure for different gases.
The analyser stability reduces at high resolving power. This means the stability of ion current is a strong function of mass scale stability and has a great influence on the accuracy of analytic measurement and all the sensitivity of the machine.

4. **Protection system;**

The multigas mass spectrometer has an automatic protection system which operates in the case of component failure, a leak or a power failure as well as providing the semi-automatic pump down and shut down sequence.

Calibration Procedure:

ADC/Personal Computer (Atari) was used to output the mass spectrometer (multiplexer) to convert the voltages to signals and thus a digital display. This connection with a personal computer makes it easier for observation of the measurement of oxygen consumption and carbon dioxide

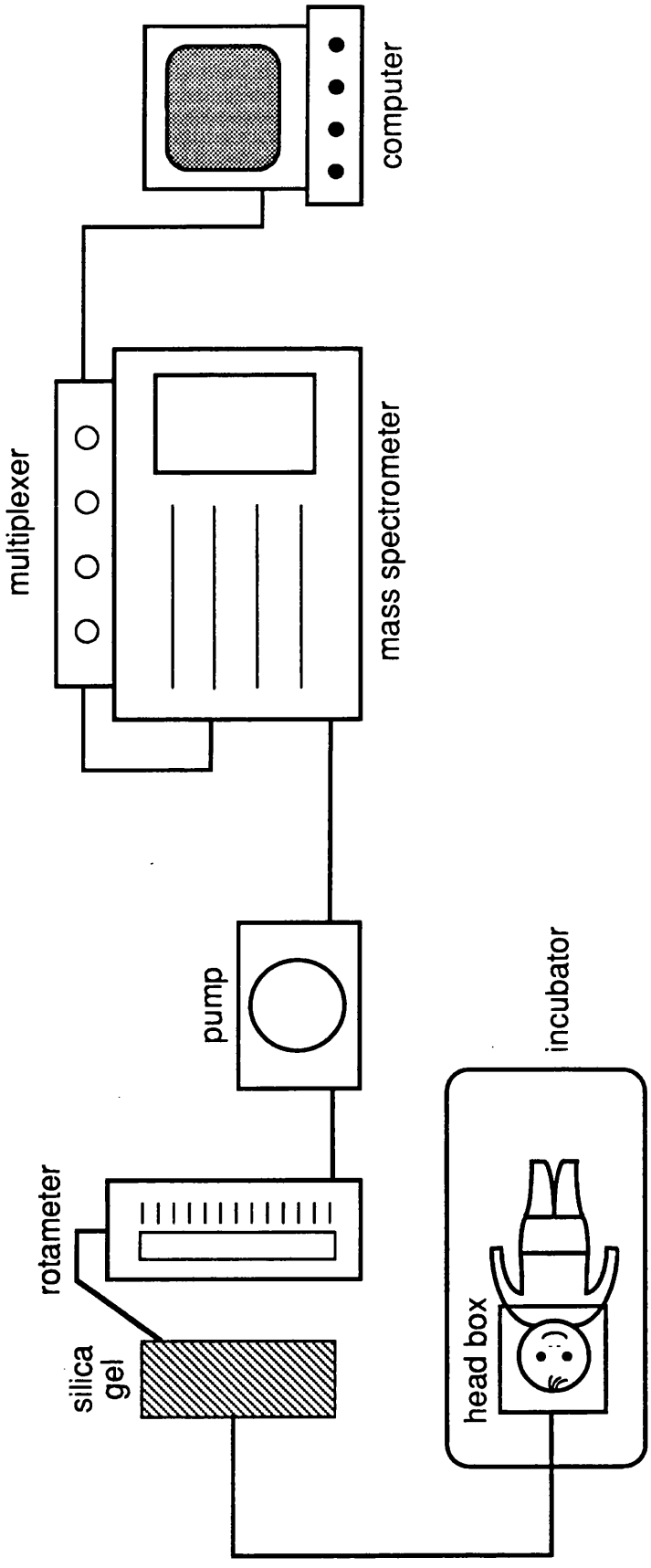


FIGURE IV

USE OF MASS SPECTROMETER FOR MEASUREMENT OF OXYGEN UPTAKE, CARBON DIOXIDE PRODUCTION IN INFANTS

production easier. Calibration with gas cylinder 3% CO_2, 3% Argon, 40% oxygen balance of Nitrogen.

The calibration procedure is as follows:-

1. Correct the multiplexer with 4 channels connected to personal computer.
2. Select channels 1, 2 for oxygen and channels 3, 4 for carbon dioxide.
3. For channels 1 and 2, adjust gain switch to lower value.
4. Expose mass spectrometer probe to gas mixture from the cylinder (standard gas), adjust for zero output both channels.
5. Remove probe mixture and place in gas stream.
6. Adjust channels 3, 4 for zero output.
7. Feed gas stream with 3% carbon dioxide and adjust channels 3 for an output of 240 bits and set channels 4 to 4 - 5 signals.
8. Replace gas stream with atmospheric air and adjust 1 and 2 channels for an output of 220 bits.
9. Use zero output to reduce to 110 bits, use gain "pot" to increase output to 220 bits once both channels 1, 2 are 220 bits.
   Don't touch gain "pot" but use zero "pot" to achieve 220 bits.
10. Observe plotted values and use very small changes in sensitivity pot to alter direction of drift.

Method:-

The mass spectrometer when not in measuring mode remains in the standby mode. Prior to measurement calibration is performed.

An infant who has been fed within the hour and is asleep, quiet and breathing air, is placed in an incubator (incubator S & W Airshields Vickers Neocare Air Controlled Incubator Model 141 MK2), under normal

environmental temperature recommended elsewhere.

A headbox (there is a thermometer in headbox to monitor the temperature) is placed over the infant's head and a sampling tube is placed in the headbox connected to the Rotameter (110 Rotameter GEC - Elliot Process Instrument Ltd.) to regulate and measure the flow rate. This is recorded as ml./min.. The flow rate is adjusted according to surface area of the infant (body weight x 1.34 = flow rate). From the Rotameter the gases pass over silica gel to dry and then to the mass spectrometer for analysis. In addition to the mass spectrometer vacuum we employed additional vacuum (DIA Pump Airshields USA) to increase the gas flow through the headbox.

Once the gases have been analysed they are displayed on computer (Atari).

The multiplexer control box connected to MS2 mass spectrometer contains four channels which displays simultaneously each channel, which is updated every 20 milliseconds. Each channel has an independent mass selection control, variable, switched calibration control and zero offset control. All four channels are affected by a response time control and each has same response time. The response time is nominally 0.03 seconds, but when monitoring small concentrations of gas it may be necessary to increase the response time to obtain a reduced noise level.

The sensitivity control effects all four gas channels once the calibration has been made for each gas mode in use.

This control can be used as a simple means of correcting for any drift.

There is a high sensitivity switch which increases the filament electron emission current by a factor of approximately 5; so the single noise ratio will be ten times better.

Reactions:-

The reaction of oxygen and molecules containing oxygen at active surfaces in vacuum is a source of error in mass spectrometer. Oxygen reactions occur at the heated surface of ion-source filament. The rate of oxygen reaction at a heated filament is a function of a filament surface temperature and the oxygen partial pressure. The principle reaction products are oxides of the filament surface. As in all respiratory mass spectrometers, ionisation is achieved by electron bombardment from thermionic filaments mounted outside a positively charged cage. The electrons collide with the gas molecules heating positively charged ions which are extracted by an electrical field. Not only does the bombardment cause singly charged ions to be heated, but many gases break down chemically. Carbon dioxide, when bombarded with ions, produces not only CO_2+ ions but CO^+ and O^+ ions. A particular substance will break down in characteristic fashion, determined by its atomic structure, the ratio of the ions produced being described as "cracking pattern". Such coincidences are termed cracking pattern overlaps. The result is that at the secondary electron multiplier, ion current may be due to a mixture of ions. In calculating the measured concentration, these cracking patterns have to be corrected. Obtaining concentration values from the machine requires considerable calculation and calibration of the machine is complicated by the strong need to ensure that all the gases present are calibrated in quick succession.

CONCLUSION:

The error of measurement of VO_2 and VCO_2 with this mass spectrometer is 5% for oxygen and 3.3% for carbon dioxide. Using this method of gas exchange breath by breath (open circuit) as a comparison, the error of

measurement is 3% for oxygen and 3% for the carbon dioxide.

In every day use the speed with which inexperienced staff can use a mass spectrometer will be crucial and time consuming and it seems this mass spectrometer is not appropriate for the measurement of simple metabolic function on Intensive Care Units unless simplicity of intervention in the patient's breathing system is of paramount importance.

The Mass Spectrometer which we attempted to use behaved erratically despite many attempts to modify its performance.

The present generation of mass spectrometers may be used easily by using automatic calibration procedure, by controlling the mass spectrometer via an in-built microprocessor system and computerised to detect even small leaks of gases around the ventilated babies.

Correction of Measurement:

The correction for PO_2 = 20.9/100

$$VO_2 = \frac{x}{220} \times 20.9$$

where = 20.9% the percentage of O_2 in dry air

x = the amount of O_2

220 = the correction by the micro-computer from voltage to signals.

The correction for PCO_2

$$VCO_2 = \frac{x}{240} \times 3$$

where = 3% CO_2 is used for calibration of the mass spectrometer

x = the amount of CO_2

240 = the correction by microcumputer from voltage to signals.

All measurements of VO_2 and VCO_2 were calculated accurately by using reduction of saturated gas volumes to body temperatures STPD charts from the biochemistry department and the atmospheric pressure mmHg obtained from the biochemistry department every specific time when the experiment is in process.

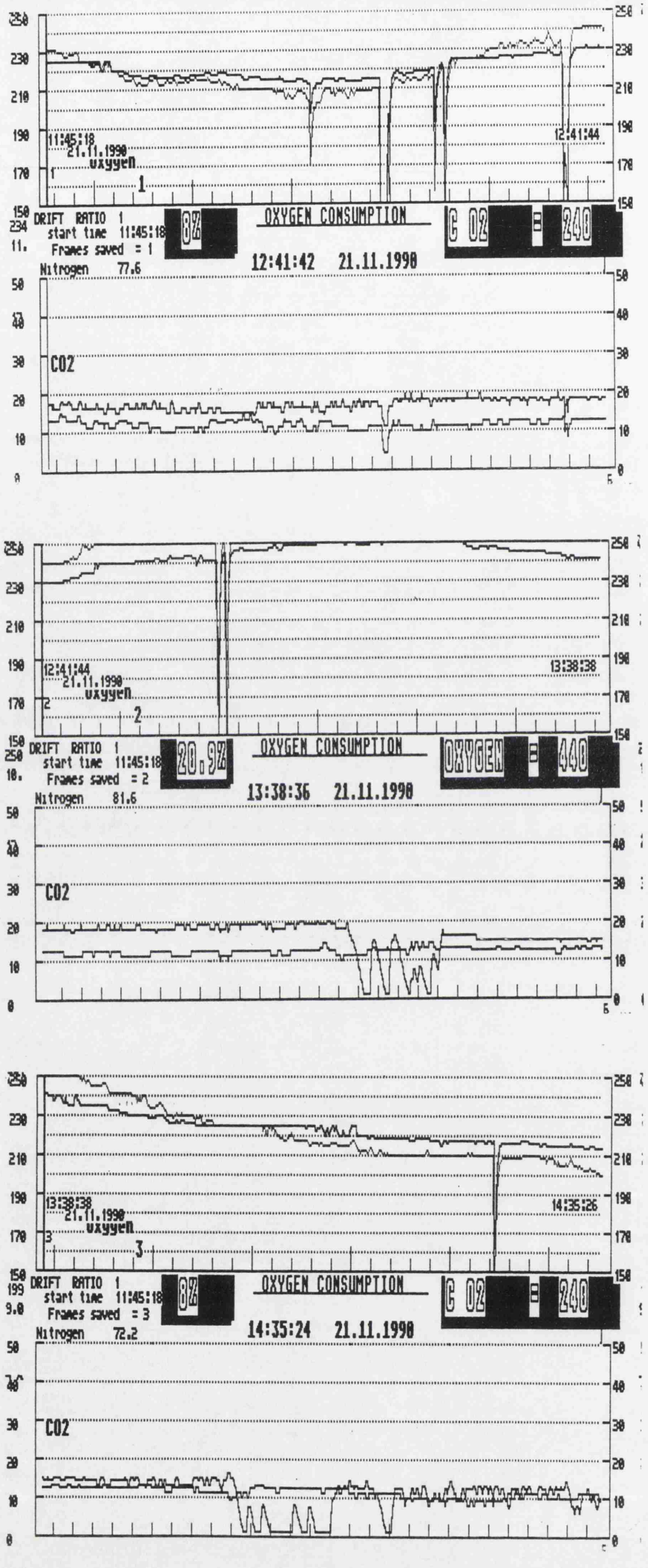
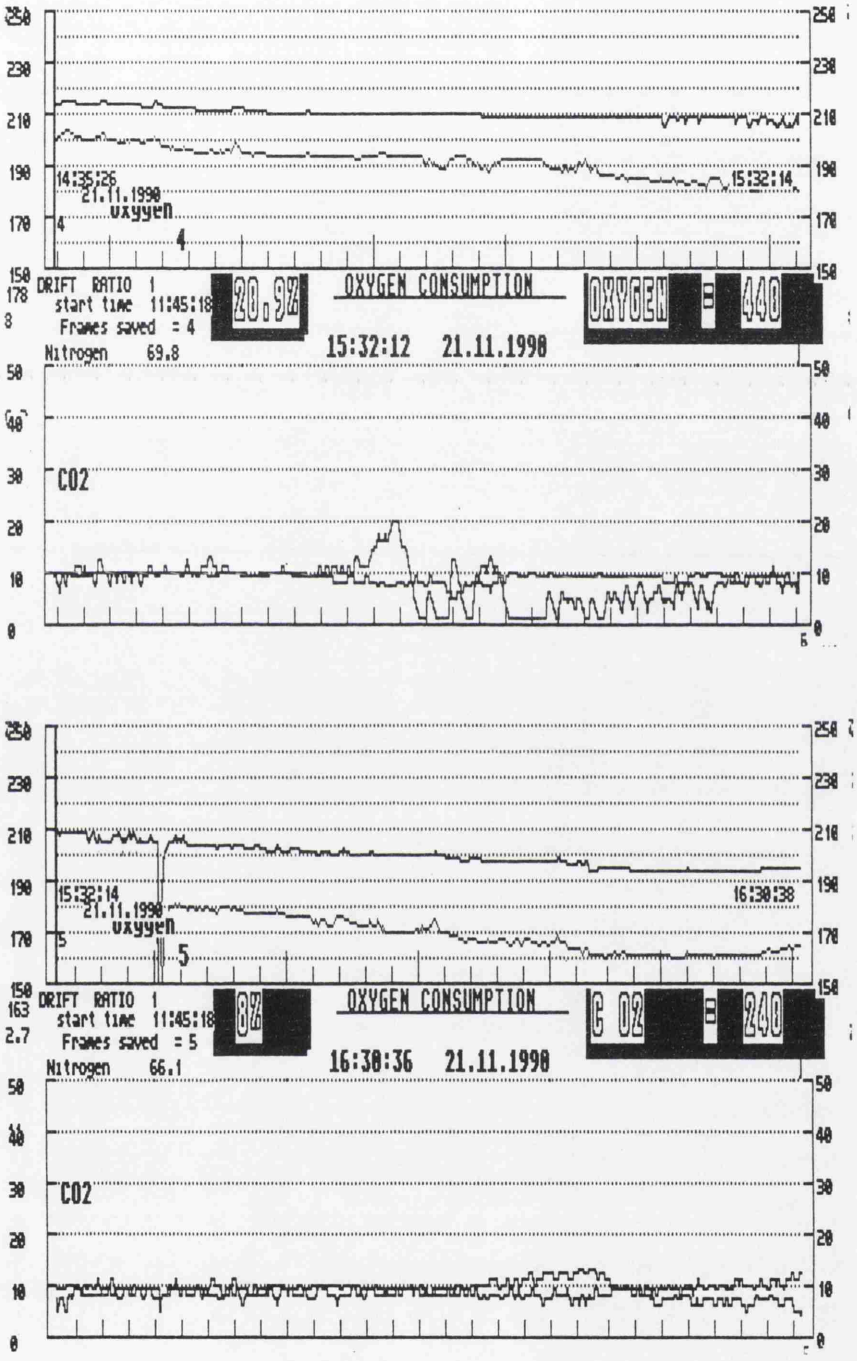


FIGURE V

EXPERIMENT Ia MASS SPECTROMETER



CONTINUATION OF EXPERIMENT Ia

CONSTANT MEASUREMENT OF ATMOSPHERIC GASES OVER 5 HOURS

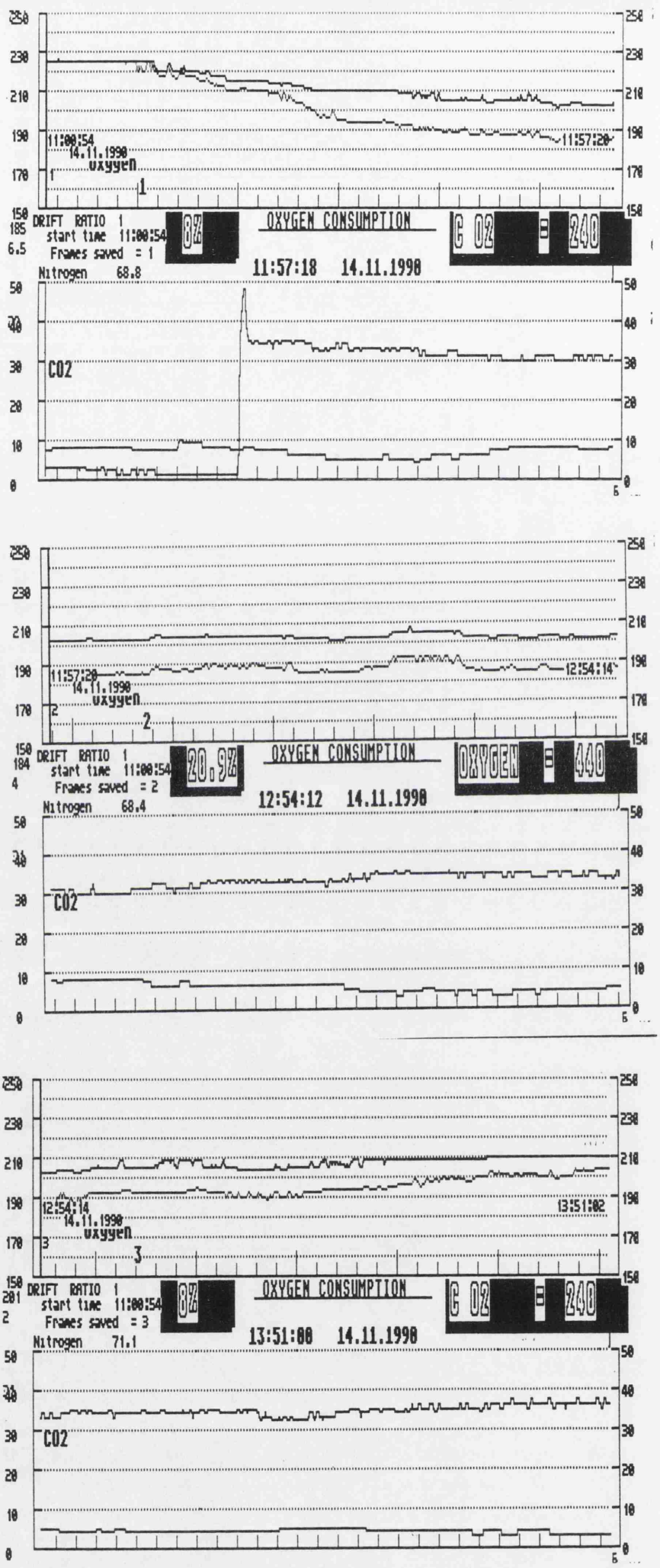
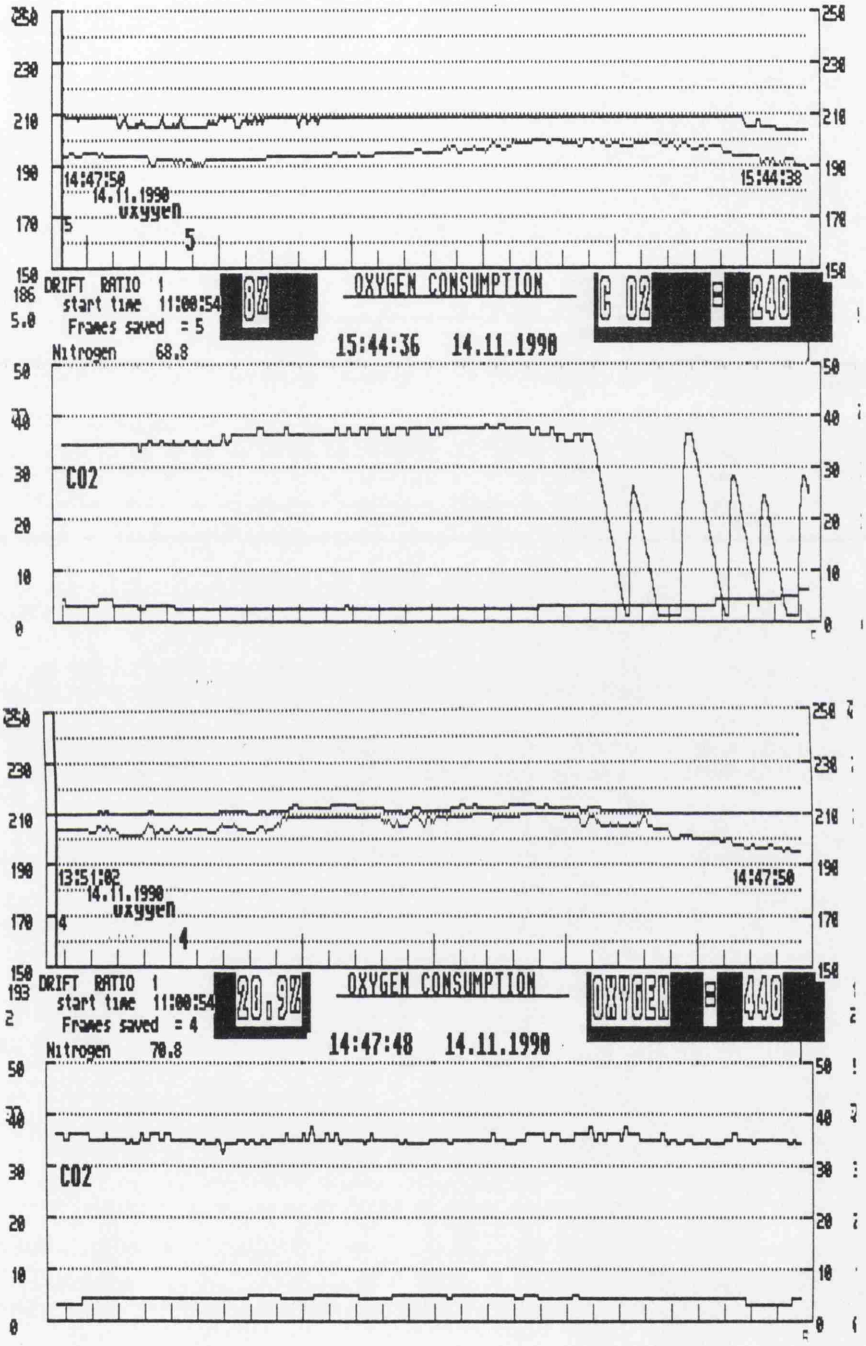


FIGURE V1

EXPERIMENT Ib MASS SPECTROMETER



CONTINUATION OF EXPERIMENT Ib

CONSTANT MEASUREMENT OF ATMOSPHERIC GASES OVER 5 HOURS

MASS SPECTROMETER EXPERIMENT I

To evaluate M2 Mass spectrometer's capacity to measure oxygen consumption and carbon dioxide production we performed two separate experiments in which we observed the mass spectrometer after calibration (see calibration procedure).

Experiment Ia/Ib;

Attempted to evaluate the function of the mass spectrometer in a steady state and with alterations in flow rate.

In the first expirement (Ia) the flow rate was 4 l./min. constant and atmospheric gases were measured for five hours through two tubes connected to a three-way tap. It was possible every hour to change the flow rate from one tube to the other to observe how the mass spectrometer altered when there is interference with flow rate.

In the second experiment (1b)at a constant flow rate of 4 l./min., atmospheric gases were measured for five hours after calibration without change in the flow rate or any other interference.

Result: The mass spectrometer shows drifting in both experiments in carbon dioxide and oxygen by about 5 - 10% in over an hour.

MASS SPECTROMETER EXPERIMENT II

Calibration and use without a baby;

Term infants were chosen randomly from the postnatal ward of the Queen Mother's Hospital. Preterm infants were chosen randomly from the Special Care Unit of the Queen Mother's Hospital. Written consent and information sheets were given to the parents and more explanation provided if needed.

The sleep state of the infants were assessed by visual inspection after

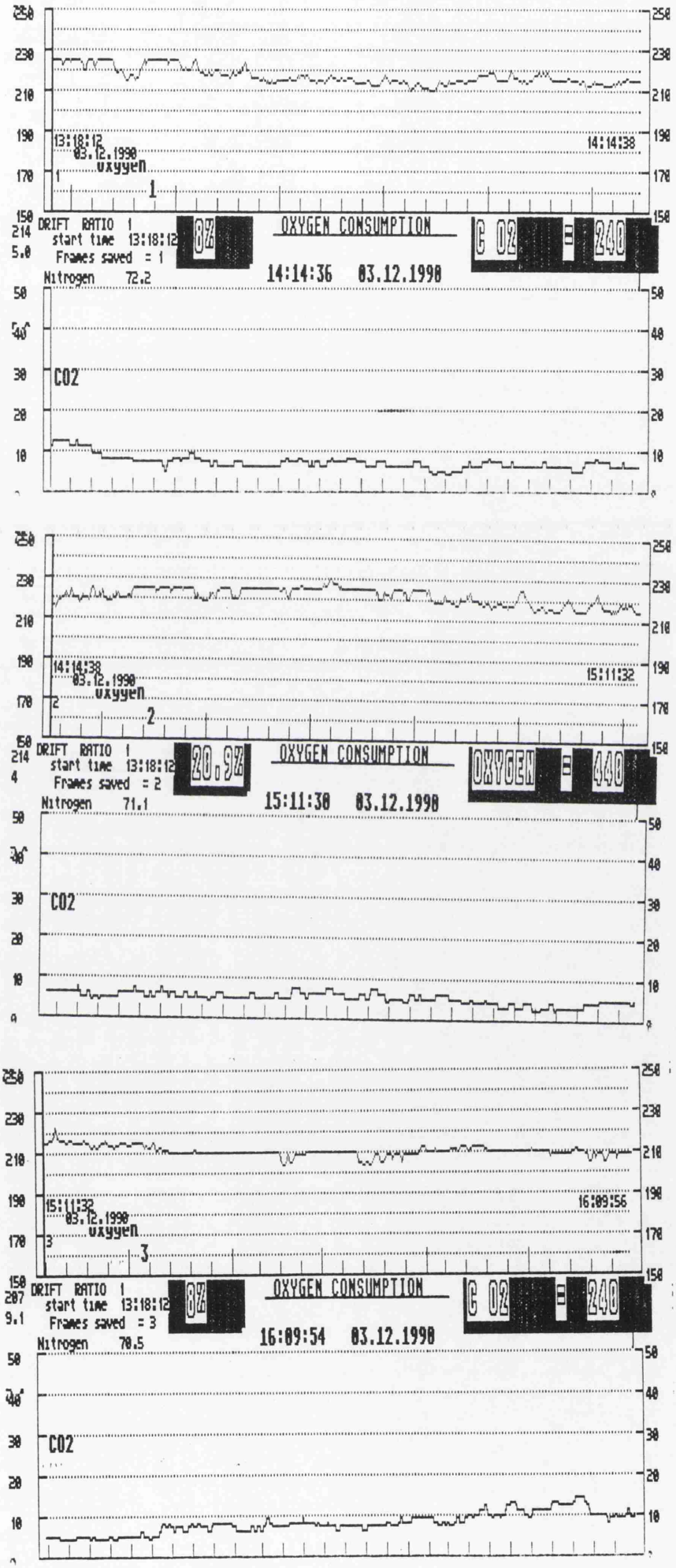


FIGURE VII

EXPERIMENT II MASS SPECTROMETER

the infants were placed in an incubator at thermal neutral temperature, quiet and in REM sleep at least one hour after feeding by the mother, in the case of term infants, or fed by nursing staff in the Unit in the case of preterm, then they were investigated.

In view of difficulties with drifting we attempted to observe if this drift pattern could be prevented by prolonged running of equipment. Much time was spent attempting to eliminate drift which appeared inherent in the equipment used. Before each use the mass spectrometer was allowed to run with the circuit complete and uninterrupted without an infant in the system. Despite these measures, drift remained a major problem as noted below.

Oxygen: The mass spectrometer was left after calibration for three hours without interfering - the results were as follows;

In the first one and a half hours the drifting start about 5% in the first half hour to reach the maximum of 10%. Then drifting goes back to 5% to reach maximum of 10% by the end of an hour.

Carbon dioxide: The mass spectrometer was drifting during the three hours from 5% from the base line.

MASS SPECTROMETER EXPERIMENT III

In this experiment we attempted to analyse VO_2/VCO_2 in two groups of term infants fed by different means using a fixed flow rate.
Oxygen consumption and carbon dioxide production were measured in two groups of term newborn infants. Following calibration of the mass spectrometer, each group of 10 infants were studied.
Group I was breast fed, Group II formula milk fed (Ostermilk).
In this experiment a fixed flow rate of 6 L./min. through the mass spectrometer was used. We use the infant's surface area in calculating VO_2/VCO_2.
The result of each group is summarised in Tables II and III.
Group I composed of nine boys and one girl, whose weight range was 2.58 - 4 kg., mean weight 3.24 kg..
The mean oxygen uptake was 17.6 ml./kg./min., range (8.8 - 25.5 ml./kg./min.). The mean carbon dioxide production had a mean of 5.41 ml./kg./min. and range 1.7 - 12.8 ml./kg./min..
The RQ mean was 0.33 with a range (0.14 - 0.54), S.D for VO_2 = 0.2557, S.D. for VCO_2 = 0.1868 and S.D. for RQ = 0.1577.
In the Group II (artificial feed) there were seven boys and three girls, weight range 2.60 - 4.29 kg., mean of 3.58 kg..
The mean oxygen consumption was 11.28 ml./kg./min., range 3.2 - 14.6 ml./kg./min., and carbon dioxide production mean was 5.78 ml./kg./min., range 2.4 - 14 ml./kg./min..
The RQ showed a mean of 0.47 with range 0.25 - 0.73,
SD of VO_2 = 0.382, S.D. of VCO_2 = 0.2177 and S.D. of the RQ = 0.1605.
The standard deviation of oxygen consumption (SD) for breast milk infants group was 4.75, the mean of standard error for the same group was 1.5, compared to the formula milk group the mean of standard

deviation was 5.33 and the mean of standard error was 1.7. The 95% confidence interval 1.6, 11.1.. The difference between the mean of the group shows the P = 0.012 which is insignificant.

The standard deviation of carbon dioxide production (SD) for breast milk group was 3.47, the mean of standard error 1.1 for the group compared to the group of formula milk the SD was 3.15 and the mean of SE was 0.99. The 95% confidence interval - 2.3, 3.96 shows P + 0.58 which is significant.

The SD for RQ for the breast milk was 0.158 and mean of SE 0.050 compared to formula milk SD was 0.147 and SE was 0.046.

The 95% confidence interval - 0.282, 0.006 and the P + 0.059 which is insignificant.

Comment: In neither experiment was the oxygen consumption able to be measured within the normal range for term infants. Indeed, it was in some infants up to twice their maximum levels measured by the Deltatrac and the calculated range was unacceptable for further study. Similarly the measured CO_2 production range was very wide but less so than the test for O_2 consumption. Our mean value was just within the normal range. The result of oxygen consumption in both groups are high. Possible reasons include;

1. Fixed flow rate - other workers have shown the importance of standardising flow rate to surface area.
2. Drifting of the mass spectrometer which was inherent in the system and difficult to overcome.
3. Infants state of arousal which we minimised by standardising their feed time in relation to measurements and excluding infants who were not compliant from the study.

Table II

BREAST FEEDING INFANTS

Sex/Weight	Type of Feeding	VO_2 ml./min./kg.	VCO_2 ml./min./kg.	STPD	RQ
Boy/3.25 kg.	Breast	16.44	7.93	0.9067	0.43
Boy/3.45 kg.	"	21.8	12.8	0.8819	0.51
Boy/3.70 kg.	"	15.4	3.04	0.8973	0.17
Boy/4.00 kg.	"	16.0	5.43	0.9020	0.30
Boy/3.46 kg.	"	15.9	8.2	0.8937	0.46
Boy/2.94 kg.	"	14.5	1.7	0.8560	0.10
Boy/2.58 kg.	"	22.0	9.8	0.8931	0.40
Boy/2.68 kg.	"	8.8	5.2	0.8949	0.54
Boy/3.66 kg.	"	19.9	3.3	0.8878	0.14
Girl/2.72 kg.	"	25.5	8.7	0.9067	0.30

The Wt. (kg.) VO_2, VCO_2 and RQ of term breastfed infants.

Mean Results

The Mean Wt. (Kg.)	The Mean O_2 Consumption ml./min./kg.	The Mean CO_2 Production ml./min./kg.	The Mean RQ
3.24 kg.	17.6 ml./kg./min.	5.41 ml./kg./min.	0.33

Table III

FORMULA FEEDING INFANTS

Sex/Weight	Type of Feeding	VO_2 ml./min./kg.	VCO_2 ml./kg./min	STPD	RQ
Girl/3.75 kg.	Formula	9.4	3.9	0.8890	0.37
Boy/3.70 kg.	"	8.9	4.5	0.8819	0.45
Boy/3.45 kg.	"	7.2	4.3	0.8949	0.54
Boy/4.00 kg.	"	3.2	2.4	0.7574	0.59
Boy/4.00 kg.	"	20.8	14.0	0.8925	0.60
Boy/3.56 kg.	"	11.8	5.0	0.8913	0.38
Boy/3.43 kg.	"	9.6	5.9	0.8795	0.50
Girl/4.29 kg.	"	18.6	5.4	0.8795	0.25
Boy/2.60 kg.	"	14.6	5.3	0.8961	0.32
Girl/3.06 kg.	"	8.7	7.1	0.9067	0.73

Mean Result

Mean Wt. (Kg.)	Mean O_2 Consumption ml./min./kg.	Mean CO_2 Production ml./min./kg.	Mean RQ
3.58 kg.	11.28 ml./kg./min.	5.78 ml./kg./min.	0.47

The Wt. (kg.) VO_2, VCO_2 and RQ of term formula fed infants

MASS SPECTROMETER EXPERIMENT IV

Similar to Experiment III but with allowances made for surface area effects on flow rate.

In this experiment firstly we used term infants as a control for comparison to the next experiment for preterm infants and secondly tried to evaluate the mass spectrometer efficiency as a tool for measuring oxygen consumption and carbon dioxide production. Thirdly, we performed these experiments trying to get rid of the drifting behaviour of the mass spectrometer.

Oxygen uptake and carbon dioxide production were measured in newborn infants using mass spectrometer.

Calibration were performed.

Five term infants were evaluated by using surface area×1.34 for calculation of the flow rate.

The infants being fed breast milk, postnatal age range 3 - 7 days mean of 4.4 days, weight range 3.27 - 3.80 kg. mean was 3.5 kg., the duration of experiment was about one hour (range 1 - 1½ hours).

The oxygen consumption ranged from 11 - 14.8 ml./kg./min. with mean of 12.32 ml./kg./min.. The carbon dioxide production range was 5.7 - 9.6 ml./kg./min. and mean of 6.56 ml./kg./min.. The RQ was mean of 0.62. and range of 0.39 - 0.80.

Mass Spectrometer IV

Age	Wt. Kg.	Flow	Oxygen Rate/l.	Carbon Dioxide Consump	RQ Production
Term 4 days	3.27 kg.	4	11 ml./kg./ min.	7.5 ml./kg./ min.	0.68
Term 4 days	3.80 kg.	5	12 ml./kg./ min.	8.8 ml./kg./ min.	0.73
Term 7 days	3.42 kg.	5	12 ml./kg./ min.	9.6 ml./kg./ min.	0.80
Term 3 days	3.50 kg.	5	14.8 ml./kg./ min.	5.7 ml./kg./ min.	0.39
Term 4 days	3.45 kg.	5	12.4 ml./kg./ min.	6.2 ml./kg./ min.	0.50

Age, wt. (kg.), flow rate, VO_2, VCO_2 of term breastfed infants

Comment: In this experiment we are trying to avoid the drifting of the mass spectrometer by changing the flow rate according to the weight of the infants but again it is a difficult task and the results of oxygen consumption are very high compared to the standard for the oxygen consumption which were measured before in other previous studies.
We think drifting of the mass spectrometer which was inherent in the system is difficult to overcome.

MASS SPECTROMETER V

In this study a group of infants were investigated under a different technical procedure to avoid the drifting problems of mass spectrometer. The infants were placed in the incubator with a headbox covering only their head. Gases from the headbox was extracted using a DIA pump directly to the mass spectrometer at standard flow rate. This was used in an attempt to reduce the drift noted in the mass spectrometer.
In this group, six breast feeding, term infants were studied and one bottle fed infant. The first two infants were studied continuously with constant suction of gas from the headbox. The remainder were studied in different conditions; atmospheric gas was introduced into the system at intervals during the study to allow analysis of the atmospheric gases and comparison with those produced in the headbox by the infants. The gas flow were all adjusted for infants surface area.

The results were as follows in the table;

Table

No.	Age	Wt./kg.	Flow rate	Oxygen Consumption	Carbon Dioxide Production	RQ
1.	Term 4 days	2.62 kg.	4 l./min.	7.2 ml./kg./ min.	5.9 ml./kg./ min.	0.82
2.	Term 3 days	3.69 kg.	5 l./min.	4.6 ml./kg./ min.	3.6 ml./kg./ min.	0.78
3.	Term 5 days	3.04 kg.	4 l./min.	6.5 ml./kg./ min.	3.6 ml./kg./ min.	0.55
4.	Term 5 days	3.60 kg.	5 l./min.	4.4 ml./kg./ min.	3.6 ml./kg./ min.	0.82
5.	Term 5 days	2.88 kg.	4 l./min.	7.8 ml./kg./ min.	4.3 ml./kg./ min.	0.55
6.	Term 5 days	3.64 kg.	5 l./min.	6.5 ml./kg./ min.	3.6 ml./kg./ min.	0.55
7.	Term 5 days	3.54 kg.	5 l./min.	6.7 ml./kg./ min.	7.5 ml./kg./ min.	1.10

Age, wt. (kg.), flow rate, VO_2 and VCO_2 and RQ of term infants

Infants 6 and 7 were studied in a continuous two-hour period with constant suction of gas from the headbox. The remainder were studied in a similar fashion but, at intervals during their study, atmospheric gas was introduced into the system to allow analysis of gases.

Result: Seven term infants weight range 2.62 - 3.69 kg., mean weight was 3.28 kg. were investigated. Six infants were breast.

Postnatal age range 3 - 5 days, mean 4.4 days.

Flow rate range 4 - 5 L./min., mean was 4.57 l./min.

The oxygen consumption ranged from 4.4 - 7.8 ml./kg./min., with mean 6.2 ml./kg./min.. The carbon dioxide production range was 3.6 - 7.5 ml./kg./min. and the mean was 4.58 ml./kg./min..

The RQ ranged from 0.55 - 1.1, the mean was 0.73.

Only one infant had oxygen consumption of 6.7 ml./kg./min. and carbon dioxide production 7.5 ml./kg./min. and RQ was 1.1 which almost met the normal range for oxygen consumption, carbon dioxide production and the RQ. The rest of the infants' results were substantially different for oxygen consumption and carbon dioxide production and RQ, from standard values which are 6 - 8, 4 - 6 and 1 respectively.

MASS SPECTROMETER EXPERIMENT VI

The aim of this study was to evaluate the effectiveness of the mass spectrometer in measuring VO_2/VCO_2 in preterm infants and to adapt the drifting behaviour of the mass spectrometer.

The incubator was set to provide a thermal neutral environment using the criteria developed by Hey et al, 1975. Following calibration of the mass spectrometer, the infants were placed in an incubator one hour after feeding. The infant was covered with a light sheet and recordings were taken with the infant in REM sleep. Recordings were made over a 45 - 60 minute period. We studied thirteen infants with written consent from parents. The gestational age, weight and age at experiment, type of feeding are shown in Table I and II.

TABLE I

PRETERM (Breast Feeding)

GA/Age wks/days	Weight	VO_2	VCO_2	RQ
33/13	2.00 kg.	7.2	4.4	0.61
30/25	1.68 kg.	7.8	5.4	0.69
32/17	1.75 kg.	7.7	4.9	0.64
34/12	2.16 kg.	9.0	4.4	0.48
34/12	1.82 kg.	14.0	6.5	0.46
33/23	1.83 kg.	8.5	4.8	0.56
33/23	2.23 kg.	6.5	4.98	0.77

Gestational age - postnatal age, wt. (kg.), VO_2. VCO_2 and RQ of breastfed preterm infants.

TABLE II

PRETERM (Formula Feeding)

GA/Age	Weight	VO_2	VCO_2	RQ
34/13	1.71 kg.	6.3	4.7	0.74
34/13	2.04 kg.	7.0	5.6	0.80
38/40	2.27 kg.	5.0	4.5	0.90
31/13	1.32 kg.	8.6	4.6	0.53
32/14	1.68 kg.	4.2	3.4	0.80
31/5	2.24 kg.	5.9	6.2	1.05

Gestational age - postnatal age, wt. (kg.), VO_2, VCO_2, RQ in formula-fed preterm infants.

RESULTS:

Breast fed infants:- N = 7.

The gestational age ranged from 30 - 34 weeks with a mean of 32.7 weeks. The weight ranged from 1.68 - 2.23 kg. with a mean of 1.92 kg.. The postnatal age of the infants ranged from 12 - 25 days with a mean of 17.9 days. The oxygen consumption ranged from 6.5 - 14 ml./kg./min. with a mean of 8.7 ml./kg./min.. For carbon dioxide production the range was 4.4 - 6.5 ml./kg./min. with a mean of 5 ml./kg./min.. The RQ range was 0.46 - 0.77 with a mean of 0.60.

Formula fed infants:- N = 6.

The gestational age ranged from 30 - 34 weeks with a mean of 32 weeks. The weight ranged from 1.32 - 2.27 kg., with a mean of 1.8 kg.. Postnatal age at the experiment ranged from 5 - 40 days with a mean of 16.3 days (postnatal age). The oxygen consumption ranged from 4.2 - 7 ml./kg./min., with a mean of 6.2 ml./kg./min.. Carbon dioxide production ranged from 3.4 - 6.2 ml./kg./min.. with a mean of 4.8 ml./kg./min., and the RQ range 0.53 - 1.05, mean RQ was 0.80.

The standard deviation of VO_2 (SD) for the preterm infants being fed breast milk was 2.49, the mean SE (standard error) was 0.94.

The SD of VO_2 for the preterm infants fed a formula milk was 0.63, SE was 0.63, the probability P = 0.051 which is insignificant.

The mean of SD of VCO_2 for the preterm infants fed breast milk was 0.726 and mean SE of 0.27 compared to preterm infants being fed formula milk, the SD was 0.969 and mean of SE was 0.40 and P = 0.66 which is significant.

The SD of RQ for preterm infants being fed breast milk 0.111 and mean SE 0.042 compared to SD of RQ for the preterm infants 0.173 and mean of SE 0.070 and P = 0.39 which is insignificant.

Comment: For breast feeding infants the mean oxygen consumption was 8.7 ml./kg./min., which is the upper limit of the standard oxygen consumption for term infants whilst the carbon dioxide production mean of 5 ml./kg./min. which is within the normal range for term infants. The RQ calculated is very low compared to normal data, largely because of the measured O_2 consumption. One infant of 34 weeks gestational age and weight 1.82 kg. had VO_2 of 14 ml./kg./min. and VCO_2 of 6.5 ml./kg./min., and RQ of 0.46. This abnormally high VO_2 result was almost certainly due to mass spectrometer drifting from the base line. The VO_2 drifting was 2.5% in thirty minutes whilst the VCO_2 drift was 5% in the same time.

For the formula infants the mean VO_2 was 6.2 ml./kg./min., which is the lower end of the normal range for term infants, whilst the mean VCO_2 of 4.8 ml./kg./min. is also at the lower limit. The mean RQ of 0.80 is considered to be within the range of normal.

One infant fed Ostermilk with Duocal supplement at a gestational age of 31 weeks and postnatal age of five days. weight 2.24 kg., had an oxygen consumption of 5.9 ml./kg./min., and VCO_2 of 6.2., the RQ was 1.05 which is close to an acceptable normal RQ.

We assume that the higher energy content of the mixture (CHO and fat) is responsible for the near normal RQ.

(The content of Duocal/Ostermilk, Breast milk - see Appendix I and II)

Discussion: Oxygen consumption in term infants rises between birth and 7 - 10 days of age, without any important change in body weight. From about 1 week up to 1 year the basal oxygen consumption remains at about 7 ml./kg./min. which is equivalent to 48 Kcal./kg./24 hours.

The value of minimal oxygen consumption for preterm infants at birth does not appear to be dependent on gestational age, but is directly proportional to birth weight. Beyond the age of two weeks a large difference appears between the full term infants VO_2 which remains constant at about 7.2 ml./kg./min. up to one year of age and that of preterm infants whose VO_2 continues to rise to higher values of around 9 ml./kg./min. by 1 - 2 months. This suggests that calorie requirements per unit body weight are likely to be considerably greater in preterm than in full term infants after the immediate neonatal period.

Our studies were confounded by problems in the mass spectrometer itself. Firstly the drifting behaviour of the mass spectrometer proved technically very difficult to avoid. This drifting appears inherent in this mass spectrometer and various efforts to prevent it were unable to effect the stability of the process, i.e. experiment II and III. Furthermore when the infant's weight was less than 1,500 gms. the mass spectrometer stability was even more rarely to be maintained. Drifting from 5% to 10% was observed and may reflect the low flow rate used to accommodate the infants surface area and the mass spectrometer appeared extremely sensitive to the effect of the low flow rate as seen in experiment III and IV.

Secondly, and not surprisingly, the type of infant feeding has a great influence on the infants oxygen consumption. This is especially so in preterm infants because of their higher caloric requirement per kilo

than those of full term infants.

The third main problem relates to the infants themselves. Throughout an experiment we attempted to create a quiet, stable environment, and, whilst the infant was in REM sleep, to record any relevance to oxygen consumption as shown in the studies of U. Stasell, et al in 1977. Unfortunately the mass spectrometer generates substantial noise which was found in some infants to cause disturbances such that recording either became erratic and had to be abandoned.

Our experience with this mass spectrometer technique led us to believe that the achievement of a stable environment for the infants was at best erratic. When we were able to standardise the environmental conditions with some confidence, the inadequacies of the mass spectrometer were never fully correctable.

The new generation of mass spectrometers are much less likely to be beset by such difficulties and hence almost certainly will prove more appropriate tools for neonatal research.

APPENDIX I

NUTRITIONAL COMPARISON OF BABY MILKS - COMPOSITION PER 100 ML. OF RECONSTITUTED FEED

		Mature Breast Milk (Average Values)	Prem. Farley's Ostermilk
ENERGY	Kcal	70	68
	kj	293	284
Protein	g	13	1.45
Taurine	mg	6.0	5.0
Casein: Whey Ratio		40.60	40.60
Fat	g	4.2	3.82
Source			Veg Oils
Linoleic Acid	mg	285	433
Carbohydrate	g	7.4	6.96
Lactose		7.0	6.96
Maltodextrin			
Amylose			
MINERALS			
Sodium	mg	15	19
Potassium	mg	60	57
Chloride	mg	43	45
Calcium	mg	35	35
Phosphorus	mg	15	29
Ca. P Ratio		2.3:1	1.2:1
Magnesium	mg	2.8	5.2
Iron	mg	0.076	0.65
TRACE ELEMENTS			
Copper	ug	39	42
Manganese	ug	NA	3.4
Zinc	mg	0.30	0.34
Iodine	ug	7.0	4.5
Potential Renal Solute Load	mOsmol/l	86	94
VITAMINS			
A Retinol	ug	60	100
B1 Thiamin	ug	16	42
B2 Riboflavin	ug	31	55
Niacin	mg	0.23	0.69
B6 Pyridoxine	ug	5.9	35
B12 Cyanocobalamin	ug	0.01	0.14
Folic Acid	ug	5.2	3.4
Pantothenic acid	mg	0.26	0.23
Biotin	ug	0.76	1.0
C Ascorbic acid	mg	3.8	6.9
D3 Cholecalciferol	ug	0.01	1.0
E d- -tocopherol	mg	0.35	0.48
K Phytomenadione	ug	NA	2.7

NA = Data not available

APPENDIX II

DUOCAL:

Ingredients: Maltodextrin, Refined Vegetable Oils (Maize, Coconut), Fractionated Coconut Oil, Emulsifiers (E471, E472(e)).

Typical Composition	**(per 100g)**
Lactose g	0
Moisture	max. 5.0%

Fatty Acids	**(g per 100g Fatty Acids)**
Caprylic (Cb)	27.9
Capric (C10)	6.7
Lauric (C12)	15.0
Myristic (C14)	5.6
Palmitic (C16)	8.1
Stearic (C18)	2.1
Oleic (C18:1)	11.7
Linoleic (C18:2)	22.5
Linolenic (C18:3)	0.4

Fat present is in the form of
35% MCT and 65% LCT

Minerals	
Sodium mg (mmol)	$\leqslant$ 5 ($\leqslant$ 0.2)
Potassium mg (mmol)	$\leqslant$ 5 ($\leqslant$ 0.1)
Chloride mg (mmol)	$\leqslant$ 20 ($\leqslant$ 0.6)
Calcium mg (mmol)	$\leqslant$ 5 ($\leqslant$ 0.12)
Phosphorus mg (mmol)	$\leqslant$ 5 ($\leqslant$ 0.16)

Osmolalities for alternative dilutions;

Dilution	**Volume of Water (ml)**	**SUPER SOLUBLE DUOCAL POWDER (g)**	**Kcal/ml**	**Osmolality (mosm/kg)**
1:4	150	37.5	1.0	196
1:3	150	50	1.2	310
1:2	150	75	1.7	525

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