CLINICAL STUDIES OF BREATHING DURING SLEEP AND THE SUDDEN INFANT DEATH SYNDROME

BY

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I hereby declare that except where acknowledgement is made the work contained in this thesis was executed by myself.

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NOTE OF PREVIOUS PUBLICATIONS

Some results of this and related studies have been published previously:

1. ABREU E SILVA FA, BREZINOVA V, SIMPSON H
Sleep apnoea in acute bronchiolitis
Arch Dis Child 1982; 57: 467-472

2. ABREU E SILVA FA, MACFADYEN UM, SIMPSON H
Clinical characteristics of 29 infants presenting as near-miss for SIDS
In: Sudden Infant Death Syndrome
Eds: JT Tilden, LM Roeder, A Steinschneider
Academic Press, London and New York, 1983, pp 653-667

3. MACFADYEN UM, HENDRY GM, SIMPSON H
Gastro-oesophageal reflux in near-miss sudden infant death syndrome or suspected recurrent aspiration
Arch Dis Child 1983; 58: 87-91

4. MACKAY M, ABREU E SILVA FA, MACFADYEN UM, WILLIAMS A, SIMPSON H
Home monitoring for central apnoea
Arch Dis Child 1984; 59: 136-142

5. ABREU E SILVA FA, MACFADYEN UM, WILLIAMS A, SIMPSON H
Sleep apnoea in infancy
Royal Society of Medicine 1985 (In press)

LIST OF ABBREVIATIONS

abd	Abdominal movement
Am	Abdominal movement
AS	Active sleep
C	Control
C^1	Control with previous respiratory tract infection
CA	Central apnoea
CM	Chest movement
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electroculogram
Hg	Mercury
HR	Heart rate
IS	Indeterminate or Intermediate sleep
Kg	Kilograms
mm	Millimeters
Mon	Apnoea monitor
NREM	Non rapid eye movement
NT	Nasal thermocouple
OA	Obstructive apnoea
OPCS	Office of population censuses and surveys
PB	Periodic breathing
$PtcO_2$	Transcutaneous oxygen tension
QS	Quiet sleep
REM	Rapid eye movement
RR	Respiration rate
Sec	Seconds
SIDS	Sudden Infant Death Syndrome
t	Time
Temp	Temperature

ABSTRACT

The primary aim of the research reported in this thesis was to study breathing patterns during sleep in a) apparently normal symptom-free full-term infants, b) infants admitted to hospital during and following recovery from relatively minor illnesses, and c) infants thought to be at increased risk for Sudden Infant Death Syndrome (SIDS) - siblings of previous SIDS victims, and 'near-miss' for SIDS cases, to quantify apnoea (central and obstructive) and observe its effect on heart rate and transcutaneous oxygen tension, $PtcO_2$. Secondary aims were to study gross body movements (as an indicator of arousal), and to assess whether infants at 'increased risk' for SIDS were chronically hypoxaemic during the early months of life. Polysomniographic studies lasting three to five hours during the night recorded eye movements, digastric muscle tone, electrocardiogram, electroencephalogram, airflow, chest and abdominal movements and $PtcO_2$ in 86 index cases and 11 healthy controls studied on 176 and 31 occasions respectively.

The results were as follows:

1. The 11 normal healthy infants did not have episodes of obstructive or prolonged ($\geq$ 15 seconds) central apnoea during sleep.

2. 33 'symptomatic' infants revealed:

   a) Bronchiolitis - apnoeic pauses were shorter than 15 seconds. Indices of central apnoea were increased significantly

in quiet sleep during the index illness. Prolonged ($\geqslant$ 6 seconds) obstructive apnoea was uncommon;

b) Upper Respiratory Infection - there were no prolonged pauses. Indices of central apnoea were similar, during and following recovery from infection. Brief ($\geqslant 3 < 6$ seconds) obstructive apnoea was occasionally observed;

c) Congenital Stridor - there were no prolonged pauses. Indices of central apnoea were identical to those observed in age- and sex-matched controls. Brief and prolonged obstructive apnoea was observed;

d) Pyloric Stenosis - central apnoeic pauses were sometimes prolonged. Indices of central apnoea were significantly increased in both active and quiet sleep during the index illness. Brief and prolonged obstructive apnoea were observed.

3. 24 subsequent siblings of SIDS victims showed no increase in indices of central apnoea when compared to healthy controls at comparable post-conception age. When present, brief or prolonged obstructive apnoea was associated with coincidental upper respiratory infection. Mean respiration rate was significantly decreased at 55.5 and 50 weeks post-conception age, when compared with controls. There was also a significant decrease in active sleep and an increase in quiet sleep at these ages.

4. 24 full-term 'near-miss' infants were not distinguishable from healthy controls in respect of indices of central apnoea,

respiration rate or heart rate. Brief or prolonged obstructive apnoea was observed in a minority of infants usually during active sleep, when symptoms of minor illnesses were present.

Pre-term 'near-miss' infants exhibited prolonged central apnoea, prolonged obstructive apnoea, or apparently excessive periodic breathing, when symptoms were present. Abnormalities decreased or disappeared on recovery from associated illness.

5. There was no evidence of a decrease in gross body movements in quiet sleep in the groups studied.

6. Mean $PtcO_2$ at 50 weeks post-conception age was similar in each group studied. Active and quiet sleep values were also comparable. Dips in $PtcO_2$ (>10 mmHg) were observed in 'symptom' and 'near-miss' index groups - usually in relation to prolonged central or obstructive apnoea. These dips were not observed in symptom-free infants. These results indicate that apparently 'minor' symptoms in young infants may result in abnormalities of breathing patterns which affect respiratory function during sleep. Similar abnormalities, usually of greater functional severity were observed in 'near-miss' infants exhibiting the same pattern of 'minor' illness. The relevance of these findings to possible mechanism(s) of death in SIDS is discussed.

CHAPTER 1

INTRODUCTION

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INTRODUCTION

'...and a sleep,
Full of sweet dreams, and health, and
Quiet breathing'

John Keats

Though greatly desired by parents, the situation described by Keats is not universal in infancy. Apnoea is the most common expression of instability of respiratory control during the neonatal period and may occur later in association with a wide variety of clearly defined clinical disorders - infective, metabolic, neurological, and cardio-respiratory. It is also observed in situations where a discernible disease process is less obvious.

Sudden Infant Death Syndrome (SIDS) accounts for two deaths per thousand live births in UK and has a peak occurrence between two and four months of age. The majority of SIDS victims have apparently minor symptoms within days of death. It has long been postulated that SIDS victims die an asphyxial death. Interruption of airflow between the environment and the lung would result in hypoxaemia, hypercapnia, acidaemia and tissue hypoxia followed by circulatory failure. The notion that central apnoea (cessation of airflow at nose and mouth with absent chest and abdominal movements) might initiate

this sequence stems from the observation of apnoeic episodes in infants who later became SIDS victims (Steinschneider 1972). Guilleminault et al (1975) suggested a possible relationship between obstructive sleep apnoea (cessation of airflow and continuing respiratory movements) and SIDS.

The present investigation was triggered by a clinical problem which arose following the arrival of a newly-born infant in a family in which the death of an elder sibling had been attributed to SIDS. This infant and her sibling who died had been considered by parents to have unusually long breathing pauses during sleep. In planning the investigation it was recognised that certain fundamental questions concerning SIDS might not be answerable. The question whether infants who die of SIDS are in some way 'vulnerable' from the outset (perhaps from pre-natal life) to stresses which affect the majority of infants, e.g. upper respiratory infection, in a way that infants who do not succumb to SIDS are not, is unanswered. In the 'vulnerable' infant, any such stress might initiate a sequence of events during sleep at a critical age or stage in post-natal development culminating in SIDS. The hypothesis that SIDS victims have subtle pre-existing 'defects' has led investigators to consider possible areas of vulnerability which could originate pre- or post-natally, related perhaps to immunological, nutritional, metabolic or sleep maturational factors, or to cardio-

respiratory stability. Another postulate is that all infants are potential SIDS victims, and share a 'common vulnerability' around the age of three months. The fact that only a small minority of infants dies might be related more to environmental and social factors and the influence these might have in determining the impact of natural stresses occurring at that time. Given this assumption, the environmental aspects of death and the nature and severity of stresses (infective, nutritional, etc) to which infants are subjected might seem of dominant importance to the investigator.

The present study of infants between one and six months of age concentrates on two main aspects of respiratory control: (a) the effect of relatively 'minor' illnesses on patterns of breathing in otherwise normal infants, and (b) the possible detection of 'abnormal' breathing patterns in infants thought to be at increased risk for SIDS. In siblings of SIDS such abnormalities might reveal an underlying defect in respiratory control machanisms, whereas in 'near-miss' infants it might not be possible to say whether any such abnormalities caused or resulted from 'near-miss' events. As the risk for SIDS is low in both the 'risk' groups selected for study, it seemed unlikely that all such cases would have detectable abnormalities in breathing patterns. A further uncertainty was whether the 'near-miss' infant was an appropriate human model

for the study of SIDS. It was clear, therefore, when embarking on the project that the findings might have little or no direct relation to the causation or mechanism(s) of death in SIDS. However, it was hoped to gain an insight into how infants breathe during sleep, in the presence and absence of minor symptoms, and to establish whether infants thought to be at increased risk for SIDS exhibited similar or differing patterns of breathing. The study of infants during and following recovery from minor illness would provide information on the effects of natural stresses in otherwise healthy infants; the studies in 'increased risk' infants might reveal patterns of breathing indicative of intrinsic or acquired 'vulnerability' in respiratory control.

The material in this thesis is presented in the remaining six chapters. In Chapter 2 the literature which provides the background to the present studies is reviewed, and in Chapter 3 the aims of the study and hypotheses being tested are more fully described. In Chapters 4 and 5 the index and control groups of infants are described and the methods (including their limitations) outlined. The results are presented for individual groups in Chapter 6 and an attempt has been made to synthesise the main findings. In the concluding chapter the results are discussed and placed in context in relation to the work of other investigators. The main conclusions are summarised and the implications for further research considered.

Chapter 2

Background to the studies

CHAPTER 2

BACKGROUND TO THE STUDIES

2.1 Epidemiological aspects of 'cot' death

2.1.1 Historical perspectives

Sudden death during infancy has been known since ancient times. The Bible refers to a case of 'overlaying' (I Kings 3: 19 '...and this woman's child died in the night because she overlaid it'). Since that time the unexpected death of an infant during sleep was routinely attributed to overlaying by the mother or wet nurse until the early decades of the twentieth century. In his 'Bills of Mortality for the City of London in 1632' John Graunt used 'overlaid and starved at nurse' as a cause of death category. After the 1840s death was often attributed to suffocation by an enlarged thymus (Lee 1842). In the first major report in the medical literature of sudden infant deaths in Scotland, Templeman (1892) described 258 infant deaths which had been attributed to suffocation. Overlaying was again proposed as a major cause. There was a peak occurrence of death in winter months and in lower socio-economic classes; a higher than expected proportion of illegitimate infants and a clustering at week-ends was also observed. German laws prohibiting children under the age of two from occupying the same bed as their parents reflected the prevalent belief that overlaying was an important cause

of infant death in that country also. In 'The ballad of Moll Magee' Yeats has enshrined this view in verse:

'I lay upon my baby,
Ye little childer dear,
I looked on my cold baby
When the morn grew frosty and clear.'

W. B. Yeats
(1865-1939)

Fearn (1834) was among the first to infer that unexpected infant death during sleep might be due to natural causes. In a report of two cases published in the Lancet, he described how the first has lain in bed with its mother, who discovered in the middle of the night that it was dead. The second was breast-fed, placed on its side in bed and an hour and a half later was found to be dead. From the histories and autopsy findings Fearn concluded 'I became almost entirely at a loss how to account for death in either' and '...so trifling a lesion could hardly in either instance, be supposed to be of itself sufficient to produce death...'.

During this century sudden unexpected death in infants ('cot death' or 'crib death') has become recognised as a clinical entity. Both terms are imprecise, for although most deaths occur in the cot or crib a few take place whilst the infant is being nursed in mother's arms. There is still no agreed definition of the entity (or entities) under study: 'sudden and unexpected death

in infants' (Rabson 1949), 'the sudden infant death syndrome' (Gold, Adelson and Godek 1964) and their variants have been most frequently used. The former, based on clinical criteria alone was amplified by Adelson and Kinney (1956) to indicate 'the death of a child who is thought to be in good health or whose terminal illness appeared to be so mild that the possibility of a fatal outcome was not anticipated'. The latter includes clinical and pathological criteria, defined more formally as 'the sudden death of any infant or young child which is unexpected by history and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death' (Bergman et al 1970). The requisite minimal post-mortem examination was specified to include gross examination of the thorax, abdomen, brain and larynx, histological examination of the brain, heart, lungs, liver, kidney and any other organs rendered suspect by either history or macroscopic examination; plus any ancillary studies (toxicological, chemical, special culture, virological, etc) indicated by any of the preceding.

The acronym SIDS (Sudden Infant Death Syndrome) has been applied to this definition and is strictly equivalent to 'sudden unexpected, unexplained death in infants' (Fitzgibbons et al 1969) which in turn stemmed from the earlier 'sudden apparently unexplained death during infancy' (Werne and Garrow 1953). The term 'cot death' is still widely used to refer to

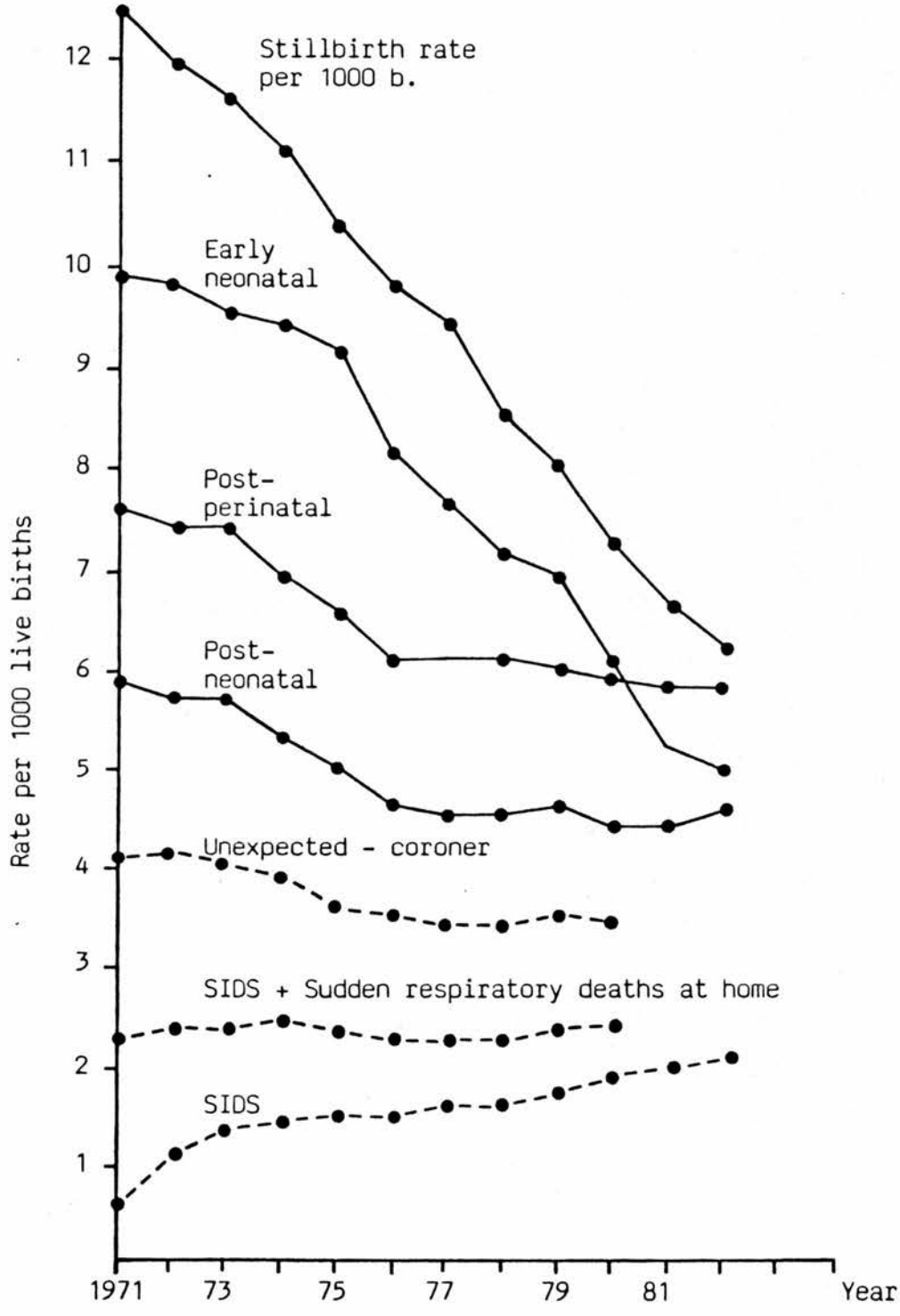
sudden unexpected death in infancy, and SIDS to unexpected and unexplained deaths. During the past twenty years the literature on this subject has become extensive. Key reviews include those by Valdes-Dapena (1967, 1980); Froggat, Lynas and Marshall (1968); Bergman, Beckwith and Ray (1970); Tildon, Roeder and Steinschneider (1983).

2.1.2 Size of Problem

This aspect has recently been reviewed by Limerick (1984a). The scale of the problem in relation to all infant deaths in England and Wales between 1971 and 1981 is illustrated in Figure 1 . During that period there was a steady decline in the perinatal mortality rate (stillbirths plus early neonatal deaths) whereas the post-perinatal mortality rate declined only minimally between 1976 and 1982. Over half of the post-perinatal deaths were unexpected infant deaths referred to the Coroner for certification. During the decade the proportion of unexpected deaths due to SIDS increased while those due to respiratory causes decreased; the combined total (SIDS plus sudden respiratory deaths at home) remained virtually unchanged.

In 1982 in England and Wales the total number of live born infants who died under one year was 6775 (OPCS 1982). Three thousand six hundred and twenty-seven died between the ages of one week and one year (post-perinatal deaths). Fifty-six per cent were unexpected infant deaths, of

Figure 1 Mortality Rates per 1000 Live Births
England & Wales 1971-81



(Limerick SR, 1983, Foundation for Study of Infant Deaths Newsletter 24, Nov. 1983. OPCS unpublished data).

which a quarter were attributed to infection - mostly respiratory, but a few intestinal, 18% to unsuspected congenital abnormalities or rare disorders and about 6% to accidents, including a few victims of non-accidental injury. The remaining 1133 deaths were registered as Sudden Infant Death Syndrome (or Cot Death) and accounted for one fifth of all infant mortality or 45% of post-neonatal infant mortality (one month to one year) in England and Wales. Thus one in 470 babies died suddenly and unexpectedly for no obvious reason at post mortem, which compares with a stillbirth rate of one in 160 births and a first week death rate of one in 200 live births.

There is considerable geographic variation in the incidence of SIDS in different parts of the world and in different parts of a particular country (Valdes-Dapena 1977; Peterson 1980). In England and Wales SIDS has been accepted as a certified cause of death since 1961 but national statistics may not reflect the true incidence of the syndrome as some cases may be coded to respiratory or other causes of death (Fedrick 1973, Naeye 1977). In areas where the subject has been under special study the impression of frequency is perhaps more accurate. Where prospective studies have been conducted or are in progress the incidence of SIDS has sometimes fallen (Valdes-Dapena 1974, Carpenter and Emery 1977, Watson 1978).

2.1.3 Epidemiological risk factors

Many of the epidemiological studies undertaken in Britain, USA, Canada, Australia and New Zealand agree on the risk factors associated with sudden infant deaths. Their relative importance and the explanations for variations observed within and between geographical areas, and the changes which occur with time have not been fully assessed. The most striking epidemiological characteristic has been the narrow age range. Seventy five per cent of deaths occur between four and twenty-five weeks of age, and less than one per cent over one year (Froggatt et al 1971). In a UK survey Limerick (1984a) confirmed that eighty per cent of sudden infant deaths occurred in babies aged between one and six months, and only 2.5 per cent in the second year of life. This age distribution with a peak incidence of forty per cent in babies between two and three months is unique to SIDS.

Infant and maternal factors

Many studies have found an excess of males, (Fedrick 1973; Working Party for Early Childhood Deaths in Newcastle 1977; Jörgensen et al 1979). In some this was no more than that among general infant deaths or could be accounted for by a slight excess of male births (Froggatt et al 1971). Fedrick (1973) observed an equal incidence in both sexes up to the age of 12 weeks, with a male preponderance thereafter. In England and Wales in 1982 60% were boys and 40% girls (OPCS 1984). The sex ratio

1.5:1 changed with age, with male vulnerability greatest at 2 months when the ratio was 1.63:1. Similar findings have been reported by Biering-Sörensen, Jörgensen and Hilden (1979) in a prospective study involving 131 sudden infant deaths in Copenhagen between 1956 and 1971 and appropriate control subjects.

Most studies show that 80% of sudden infant deaths are of normal birthweight and 85% are full-term (Valdes-Dapena 1967). Some are small for dates. Multiple birth infants are at increased risk so that one in twenty-five SIDS is one of twins. In the Copenhagen study premature babies seemed to die later than term infants but the differences were not statistically significant. The postnatal age at death was similar to that of infants who died of respiratory infection. Of maternal factors studied mothers of sudden death babies were younger, attended fewer prenatal examinations and more often delivered their babies at home than mothers of living control infants (Jörgensen et al 1979).

Maternal smoking in pregnancy is associated with an increased risk of sudden infant death (Steele and Langworth 1966). A recent American study found that 69% of SIDS' mothers smoked compared with 39% of control mothers (NICHD Collaborative Epidemiological Study 1978-1979). Maternal narcotic addiction has also been implicated

(Rajegowda et al 1978). The authors analysed data concerning infants born to mothers with histories of significant narcotic use during pregnancy and found that the occurrence of 'crib death' in infants of addicts was 20.9 per thousand live births, a 5.5-fold increase over that for all babies born in the same hospital during the 2-year period in which the prevalence was 3.8 per thousand live births ($p < 0.001$). The authors suggested that intra-uterine exposure to narcotics and subsequent effects of those drugs on the central control of respiration might be the underlying mechanism for narcotic related cases of sudden infant death. Other maternal risk factors include a short inter-pregnancy interval, urinary tract infection (Protestos et al 1973), or anaemia (Naeye et al 1976) in pregnancy.

Whether breast feeding protects infants from sudden unexpected death has been the subject of discussion for many years. Froggatt et al (1971) analysed feeding patterns in detail and could find no evidence of such protection. The more recent Copenhagen study (Biering-Sörensen et al 1979) showed that although more control infants than 'cot death' babies had been breast fed, that factor may not have conferred protection. During the study period 1956-1971 breast feeding declined while the incidence of sudden infant deaths remained unchanged. The lower frequency of breast feeding among affected

infants was thought instead to be secondary to other factors generally considered to be directly associated with sudden infant death syndrome. Valdes-Dapena (1980) refers to SIDS in five infants who had been exclusively breast fed from birth. Houstek (1970) reported 32 such cases, and Bergman et al (1972) five. Thus, breast feeding, even when it is exclusive of any supplemental feeding, does not guarantee protection against the sudden infant death syndrome. Whether partial protection occurs has not been finally established.

Environmental and social factors

Environmental and social factors are closely inter-related. There is a winter preponderance of SIDS which increases with age. Fedrick (1973) observed that while 60% of SIDS occur in the period October to March, 75% of deaths in the two to six month age group occur in this period. The deaths of very young babies are more evenly distributed throughout the year. Other series reported from UK, Australia, Denmark, France, Germany, Czechoslovakia, USA, and Japan agree that the incidence is highest during the colder months of the year (Peterson 1983).

Babies admitted to hospital postnatally appear to be at increased risk. A recent study indicates that previous hospital admissions occurred in 16% of unexpected deaths compared with 5% of control families (Stanton and Oakley 1983). The incidence is also greater in urban than

rural districts and in areas of poor housing. There is considerable unanimity about the hour of day at which deaths are believed to occur. The great majority of infants die between midnight and 6 a.m. (see Valdes-Dapena 1967). However, this contrasts with the findings of a recent UK survey of 713 sudden infant deaths (Golding et al 1985) in which as many babies died during the day as at night, including several who 'collapsed' in their mothers' arms while awake. In common with several other studies no clear distinction was made between unexpected deaths for which an explanation was found at post-mortem and deaths which were unexpected and unexplained following post-mortem examination. It may be that the times of death are different for these two groups of infant deaths. Hinton (1978) noted that many infants had not been observed by their parents for many hours before their deaths were discovered - in one such instance a young infant had not been looked at for 13 hours. Of 29 infants in the Newcastle survey 20 had also not been observed for at least 5 hours before death, and over half the deaths occurred at weekends or on Bank Holidays (Working Party for Early Childhood Deaths in Newcastle 1977). Other studies have not been consistent in correlating a particular day of the week with increasing numbers of deaths (Richards and Mackintosh 1972; Fedrick 1973).

The risk of sudden infant death is approximately similar in social classes I, II and IIIN at about 1 in 1,000 live births, but increases to 1.25 in social classes IIIM, 1.55 in class IV and 2.42 in class V (OPCS 1982). Illegitimate children are twice the risk of legitimate, and infants born to parents in the unclassified group, which can include the armed forces and the unemployed, are also at higher risk. In 1979 in England and Wales 17% of sudden infant deaths were from Class I and II, 33% in Class III, 24% in social classes IV and V, 20% among unmarried mothers, 6% among the unclassified. Thus, half occurred in social classes, I, II and III (Hansard 1982). Young maternal age and increased birth order together are more useful predictors of sudden infant death. Thus, the third child of a mother of 20 years of age is at 7 times greater risk than the first child of a 27-year-old mother (Limerick 1984). About a quarter of SIDS are first children, half are second, and the remaining quarter third or subsequent children (Limerick 1984). Babies of parents who have suffered a previous infant death are at a slightly increased risk, 1 in 160 live births compared with 1 in 470 live births in the general population (Limerick 1984). Other investigators have shown that standards of mothering are more closely related to SIDS than social class (Working Party for Early Childhood Deaths in Newcastle 1977; Watson 1978).

Symptoms prior to unexpected death in infancy

Many investigators have observed an increase in symptoms prior to death in SIDS victims (Emery and Crowley 1956; Carpenter and Shaddick 1965; Froggatt 1970; Cameron and Watson 1974). In a pathological study of 200 children who died unexpectedly Sinclair-Smith et al (1976) made important inferences concerning previous growth velocity and antecedent infection. They demonstrated costochondal junction reactions consistent with a retardation in growth velocity preceding death in over 90% of children studied. A similar proportion of children showed fatty changes in the liver which, in 5% was of a severe degree. The most striking changes were observed in children recognised to be ill prior to death. Changes in the thymus compatible with a normal reaction to infection were observed in only a little over half the child deaths. The absence of gross thymic reaction in some children with other evidence of infection suggested that an abnormal immunological reaction was taking place. The authors concluded they could not accept the popular concept that the majority of children found unexpectedly dead had previously been healthy. They suggested that, had such children been carefully monitored clinically and their growth velocity recorded, over 90% would have shown an alteration in growth rate identifiable before death. No data were given on the symptoms these children may have had prior to death so that conclusions were based on pathological

features alone and not clinico-pathological correlations. Stanton et al (1978) studied terminal symptoms in 145 children dying suddenly and unexpectedly at home, and 154 control children. 85 (59%) of the children who died had had symptoms in the last 48 hours of life compared with 40 (16%) of controls. Symptoms were classified as 'minor' or 'major'. 'Minor' symptoms were as common in controls as in index cases. However, 69 (49%) of children who died had 'major' symptoms (principally respiratory) compared with 19 (12%) of controls. Only 12 of the 69 children who died with major symptoms had been seen by doctors within 24 hours before death. The relevance of these findings to SIDS is uncertain as the authors did not report post-mortem findings. However, their findings do suggest avenues of approach to the prevention of sudden unexpected deaths.

Carpenter et al (1979) used survey data to evaluate risks of SIDS associated with minor symptoms. When two or more symptoms occurred in infants considered to be at high risk by a discriminate score there was a 1 in 50 chance of unexpected infant death occurring in the next nine days. The scoring system was based on data collected on all infants at birth and by health visitors at one month. The authors concluded that the system could identify 50% of unexpected deaths and provide a basis for prospective physiological studies. The most frequently reported symptoms were snuffles, cough,

irritability, vomiting, diarrhoea, sleepiness,skin rash, change of cry, and fever. Each was more common in index cases than controls. Overall the 97 children included in the study who died had a total of 260 symptoms in the three weeks before death and only 7 were said to have been completely symptom-free for the whole period. The 97 control children had a total of 48 symptoms in the three weeks before interview and 64 had had no symptoms in this period. This striking difference might have been partly due to preferential recall of symptoms in families where infants had died.

In an epidemiological and sociological study of unexpected death in infancy in nine areas of southern England, Watson et al (1981) studied symptoms and patterns of care. Two of her co-authors had been concerned with the study described above. However, the findings were quite different. Similar histories of illness were recorded in the three weeks prior to death for children who had died unexpectedly in infancy and for live controls in the three weeks prior to interview. Symptom analysis showed the main differences between the two groups of children was the non-specific behavioural changes manifested in the SIDS infants shortly before death. Under-estimation of the severity of symptoms by parents and medical attendants was apparent in a proportion of the cases in all areas. The use of medical services varied widely between areas with a marked tendency to use hospital

rather than general practitioner services in the inner city. It was noted that during the study period the number of sudden infant deaths in the area dropped significantly.

A significant minority of children who die unexpectedly at home have previously been admitted to hospital (Froggatt et al 1971; Fedrick 1974). Stanton and Oakley (1983) investigated patterns of illness before unexpected death at home by comparing the histories of 467 'cot' deaths and 511 controls. 71 (16%) of babies who died unexpectedly and 28 (6%) of controls had been admitted to hospital. This excess of hospital admissions in the index group was explained by acute infections, loss of consciousness, possible child abuse, and failure to thrive for non-organic reasons. The average length of admission was almost double that of controls and 31% were admitted more than once. The authors concluded that these admissions were often clues to important family problems which might have been investigated further. Whether admissions patterns were similar for explained and unexplained deaths could not be assessed as post-mortem findings in infants who died were not given.

Some investigators suspect that SIDS victims are not entirely normal from the outset. The results of the Collaborative Central Palsy Study by Naeye et al (1976) suggest that they are subtly handicapped from before birth.

Some may show features suggesting central dysfunction, particularly of the brain stem, with abnormalities of respiration, feeding, temperature regulation, and specific neurological tests in the newborn period. Others may exhibit abnormal or deficient avoidance responses to tactile stimulation of the naso-oral region (Anderson and Rosenblith 1971). Abnormalities of cry have also been observed (Stark and Nathanson 1975), as well as behavioural abnormalities, including cardiac or respiratory instability suggestive of autonomic dysfunction (Salk et al 1974; McNamara 1976). These observations have generally been made in isolated cases and are not necessarily generally applicable. Reliable methods to detect risk applicable to individual babies are not presently available.

2.1.4 Respiratory illness and SIDS - Clinical and pathological Observations

When minor symptoms precede death in SIDS victims they are often respiratory. The mechanisms underlying the possible adverse effects of those symptoms are poorly understood. Some infants in the SIDS age-range experience difficulty in breathing when the nose is 'blocked'. This clinical observation gave rise to the view that nasal obstruction might be an important cause of SIDS (Shaw 1970; 1979). The suggestion that apnoea might be relevant was made previously by Stevens (1965), and

reinforced by the observations of Steinschneider (1972) who documented episodes of apnoea in infants who later became SIDS victims. He described the case histories of five infants who presented with prolonged apnoea during sleep, sometimes severe enough to necessitate vigorous resuscitative efforts. Two died following discharge from hospital and neither showed abnormalities at necropsy. In the remaining infants, apnoeic episodes became progressively less frequent in the ensuing months. When these infants were admitted to hospital, the apnoea monitor to which they were attached alarmed more often during upper respiratory infection than at other times. Steinschneider (1975) extended these observations and confirmed an association between symptoms of nasopharyngitis and prolonged episodes of apnoea during sleep. He observed also that prolonged episodes of apnoea which had ceased to occur in symptom-free infants recurred in association with nasopharyngitis. In a subsequent study Steinschneider (1977) noted that infants with nasopharyngitis prior to death were older than those without antecedent respiratory infection. This is consistent with the findings of Naeye et al (1976) who observed that infants with histological evidence of infection were on average older than those without. Whether the lower prevalence of nasopharyngitis in younger infants reflects a decrease in susceptibility or limited opportunity of exposure to infection is uncertain. Respiratory syncytial

virus (RSV) infection, the main cause of acute bronchiolitis in infancy, also increases liability to prolonged episodes of apnoea (Bruhn et al 1977) particularly in preterm infants when they develop respiratory infection some weeks following discharge from hospital.

These observations on apnoea relate mainly to central apnoea which is defined by lack of activity of respiratory muscles and absence of chest and abdomen movements. When respiratory movements persist in the absence of airflow at the nostrils and mouth, obstructive apnoea is present. Clinically, obstructive apnoea may be a feature of choanal atresia, macroglossia or enlargement of the tonsils and adenoids. Untreated choanal atresia has a high mortality rate if surgery is not performed during the first few days of life. The affected infant presents with recurrent episodes of cyanosis and respiratory distress made worse by feeding. Survival is only possible if the infant adapts to breathing through the mouth. In a study of one such infant, Tonkin et al (1979) found that inspiration was accompanied by forward movement of the posterior pharyngeal wall and backward movement of the lower jaw resulting in obstruction to airflow at pharyngeal level. Malformation such as micrognathia or a partial cleft palate through which the tongue might prolapse when the infant sleeps in the supine position has a similar effect. Guilleminault et al (1979) described

an infant with congenital stridor in whom a sleep polygraphic record 30 hours before death (which was sudden and unexpected) showed many mixed and obstructive apnoeas leading to oxygen desaturation during sleep. Kravath et al (1980) described three children with speech disorders who developed sleep apnoea following construction of pharyngeal flaps fashioned to eliminate velopharyngeal incompetence. Obstructive episodes occurred within a few hours of surgery and one patient died several weeks later during the course of superadded respiratory infection.

An association between respiratory illnesses and SIDS is also suggested by pathological findings. Signs of naso-pharyngitis usually considered insufficient to explain death are often present at post-mortem. This does not preclude a final diagnosis of SIDS. Laryngeal necrosis has also been observed (Valdes-Dapena 1958) though the significance is uncertain. Evidence of respiratory infection has been reported by many pathologists (Werne 1942; Werne and Garrow 1947 and 1953; Coe and Hartman 1960; and Bowden and French 1951). Williams (1980) reported pathological studies of 136 cases of SIDS who died in Melbourne in the year 1976/77. SIDS was the certified cause of death. Within the group 38 had significant tracheitis as judged by the degree of lymphocytic infiltration of the mucosa both in the trachea and palate. Judgment was subjective but in

infants with a moderate to severe infiltrate the diagnosis tracheo-bronchitis was recorded as a significant finding. It was not, however, recorded as a cause of death which still remained as SIDS. Twenty-seven of the 38 deaths with tracheitis occurred in the 5-month period of the year centred in July, i.e. during the colder months of the year. Only 4 were under three months of age. The authors suggest that such deaths constitute a distinct group in whom investigations regarding the mode of death should be undertaken separately from those in infants without such lesions.

Viral respiratory infections

The seasonal variation in SIDS incidence may reflect changes in weather conditions such as barometric pressure, ambient temperature or humidity, or an increased prevalence of infection during winter epidemics of respiratory, viral illnesses. In some series about 50% of SIDS victims present symptoms such as upper respiratory infection in the week before death. At necropsy viruses such as influenza-A, respiratory syncytial virus (RSV), para-influenza viruses, rhinovirus, andadenovirus have been isolated, varying in different series from 25 to over 40% (Gold et al 1961; Brandt 1970; Ray et al 1970; Urquhart and Grist 1972, Brandt et al 1974; Nelson et al 1975; Bonsor et al 1978, Scott et al 1978. About 30-50% have evidence of mild infection pathologically (Naeye 1977). Infection occurs at a time when infants' maternal endowment of immunoglobulins are falling

exponentially - their T-cells are inexperienced and B-cells are scanty. However, an immunological defect has not been identified in SIDS. Levels of specific immunoglobulins are not suppressed. However, in one study, six of eight SIDS victims did not have evidence of secretory component in bronchial tissue, whereas all eight controls did (Ogra et al 1975). Hypersensitivity has never been discounted completely. Routine immunisations administered during the first six months do not appear to contribute to SIDS.

As a result of these clinical, pathological and virological observations, it is not surprising that a great deal of interest has centred on the physiology of breathing during sleep both in normal infants and in those considered to be at increased risk for SIDS.

2.2 Acquisition of sleep and respiratory control mechanisms

2.2.1 Sleep in Infancy

Using quantitative electro-oculogram techniques, Aserinsky and Kleitman (1953) described 'rapid jerky and binocularly symmetrical eye movements' recurring during the course of a night's sleep. Since then considerable research has been conducted on sleep and its main phases - active and quiet sleep.

Active sleep

Active or rapid eye movement (REM) sleep, also referred to as paradoxical or desynchronized sleep is that phase of sleep in which the infant presents slow rolling bilaterally synchronous eye movements appearing first as isolated movements about 3 or 4 minutes after the onset of this sleep phase. The eye movements then become more rapid and increase in frequency and amplitude. They occur in bursts lasting a few seconds at a time, and separated from other such clusters of rapid eye movements by a few minutes of active sleep during which time isolated movements may occur.

There is a significant increase in respiration and heart rates with greater variability in rate and rhythm than during quiet sleep. With bursts of eye movements respiration becomes faster and more irregular with the occasional occurrence of a pattern referred to as'disorganised breathing'. Two subsets of active sleep can be identified: tonic active sleep in which there is a low voltage high frequency EEG pattern accompanied by loss of muscle tone, regular breathing and few rapid eye movements; and phasic active sleep in which a similar EEG pattern and loss of muscle tone is associated with bursts of rapid eye movements and greater respiratory irregularity. Loss of muscle tone affects postural muscles including the intercostals; respiratory movements are then due to the action of the diaphragm during inspiration causing indrawing of the compliant rib cage resulting in 'paradoxical'

breathing (Bryan and Bryan 1978).

The eyes are closed or half-open. Periods of gross body movement occur due to the momentary recovery of muscle tone and alternate with periods during which there are no body movements apart from minor twitching, fine movements of the hands and changes in facial expression.

The term 'rapid eye movement sleep' does not adequately define active sleep. Eye movements are a phasic phenomenon and may sometimes be absent for a minute or more, during which time other characteristics of active sleep remain. Certain animals such as moles are blind with rudimentary eyes and no eye movements, but present other features which characterise active sleep.

The term 'paradoxical sleep', used synonymously with active sleep, derives from the observation that the subject appears to be in a phase of light sleep from which wakefulness seems imminent despite the loss of muscle tone (humans do in fact wake spontaneously from rapid eye movement sleep).

Quiet sleep

Quiet sleep, or non-rapid eye movement (NREM) sleep, known also as orthodox or synchronized sleep, is characterised by slower and more regular heart and respiration rates, closed eyes, absence of eye movements, and absent or infrequent gross body movements. Muscle tone persists

but is reduced compared with the wakeful state.

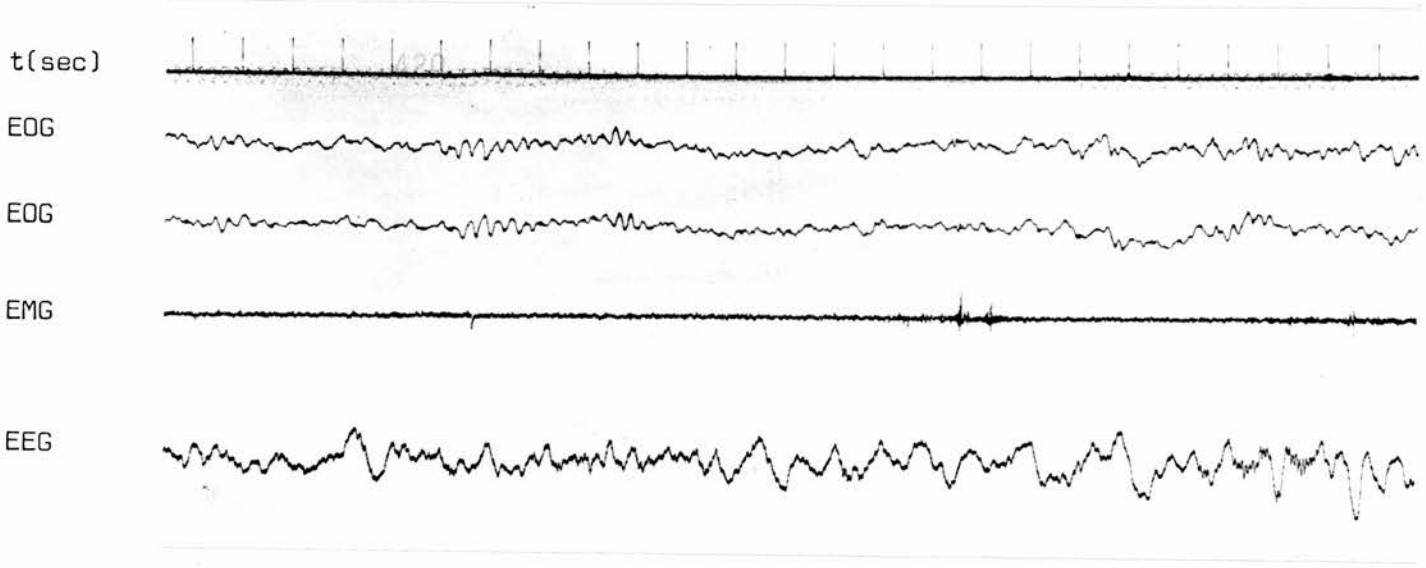
Newborn infants spend 50 to 60 per cent of their time in active sleep (Guilleminault 1978). By two years of age this has been reduced to 25 per cent, close to the 20 per cent level in adults (Anders and Weinstein 1972). There is a simultaneous and proportional increase in quiet sleep, the development of which depends on the myelinating process in the brain (Jouvet 1962). Quiet sleep is absent in decorticated mammals and in intact animals is acquired progressively during forebrain development. A period of quiet sleep initiates a night's sleep in the adult whereas in infants up to 6-12 months of age the initial sleep stage is active sleep. This may be reduced or possibly absent in infants who fall asleep after a period of excessive crying (Bernstein et al 1973).

Both active and quiet phases of sleep are longer in adults than in infants during the early months of life: in consequence, they are repeated more often in infancy during a given sleep period (Anders and Weinstein 1972).

A certain amount of sleep cannot be classified as either active or quiet. This non-classifiable sleep comprises transitional phases (which occur between active and quiet sleep) and also phases of disturbed sleep (Figs 2 and 3). According to Monod et al (1967), the amount of indeterminate sleep diminishes as maturation proceeds and sleep becomes more organised.

Figure 2

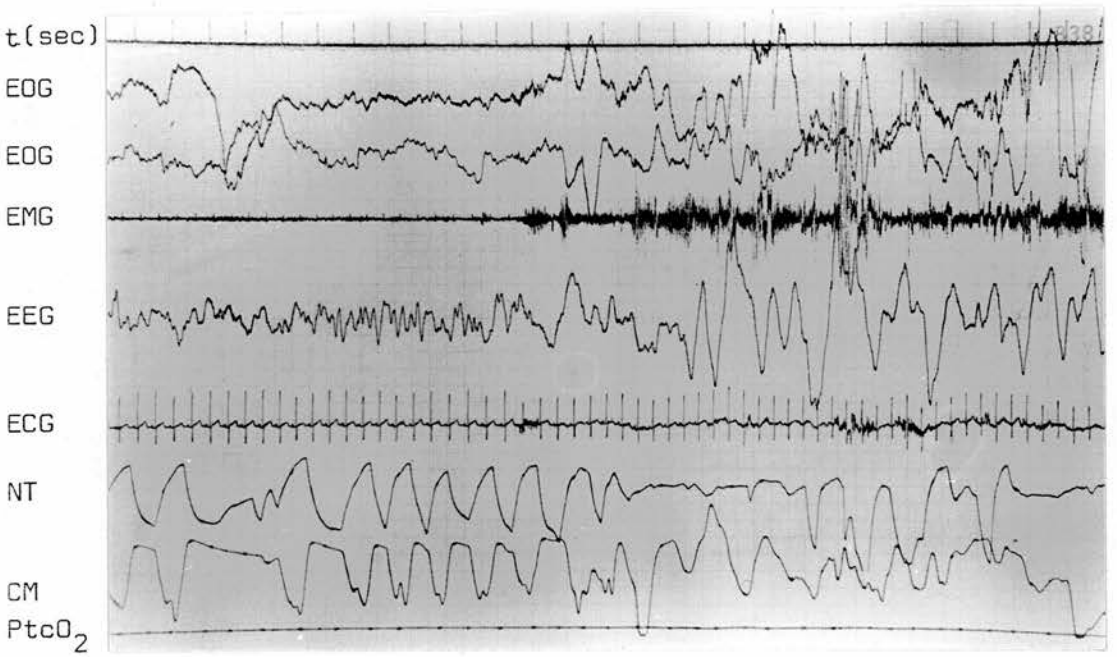
Transitional sleep. Active (AS) to quiet (QS) sleep



(Case 35 - congenital laryngeal stridor)

Figure 3

Disturbed sleep identified in all channels



Identification of sleep phase

The identification of sleep phase is made possible by the simultaneous recording and interpretation of the following variables - electro-encephalogram, electro-oculogram, electromyogram and behavioural changes.

Electro-encephalogram: the characteristic electro-encephalographic pattern of a full-term infant is present by 37 to 38 weeks post-conceptional age (Westmoreland and Stockard 1977). There is then a clear distinction between wakefulness and sleep and between sleep states, although some differentiation is possible as early as 32 weeks of post-conceptional age. Quiet sleep can be sub-divided into four stages of progressively deepening sleep. In stage I there is slowing and an increase in amplitude of the EEG pattern: in stage II sleep spindles appear (Figure 4) and occur in bursts mostly in the 12 to 13 Hz range. They become apparent at 2 to 4 months of age but rudimentary sleep spindles may be present earlier during the first weeks of life. Sleep spindles occur in continuous trains lasting 3 to 6 seconds with an amplitude between 20 to 30 uV at first increasing to 50 uV by the end of the first six months of life. They decrease in stage III and are usually absent in stage IV. The latter two stages are characteristically called 'slow wave sleep' due to high voltage delta waves and slow pattern EEG (Fig 5). Another characteristic of quiet sleep is the so-called 'trace alternant' which consists of high amplitude sharp waves (Fig 6) usually lasting 1 to 4 seconds and alternating with a low-voltage pattern of usually less than 10 seconds'

Figure 4

Sleep spindles

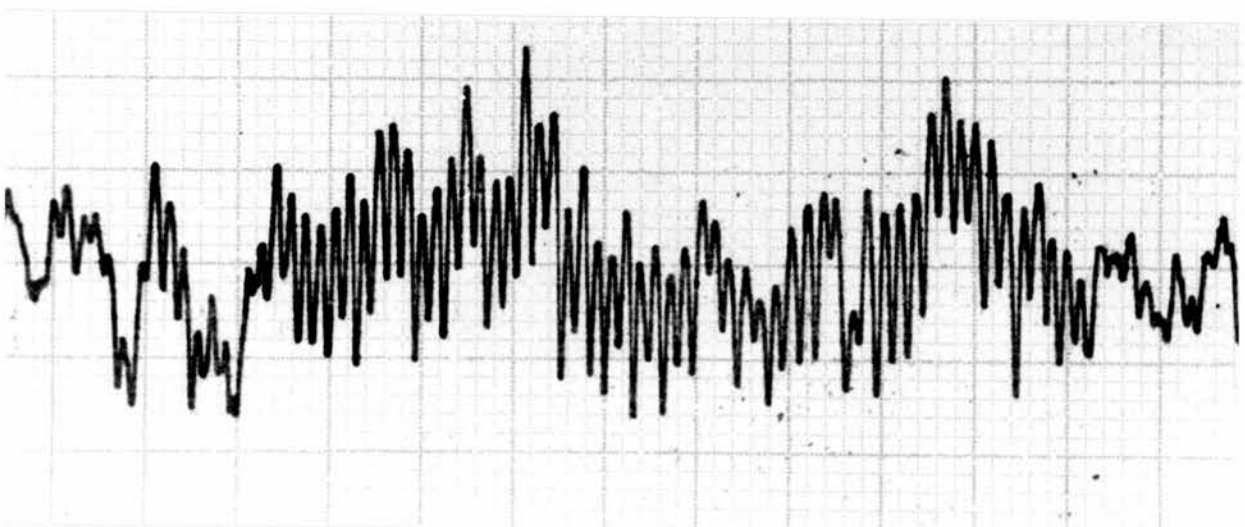


Figure 5

Quiet sleep (slow wave sleep) QS

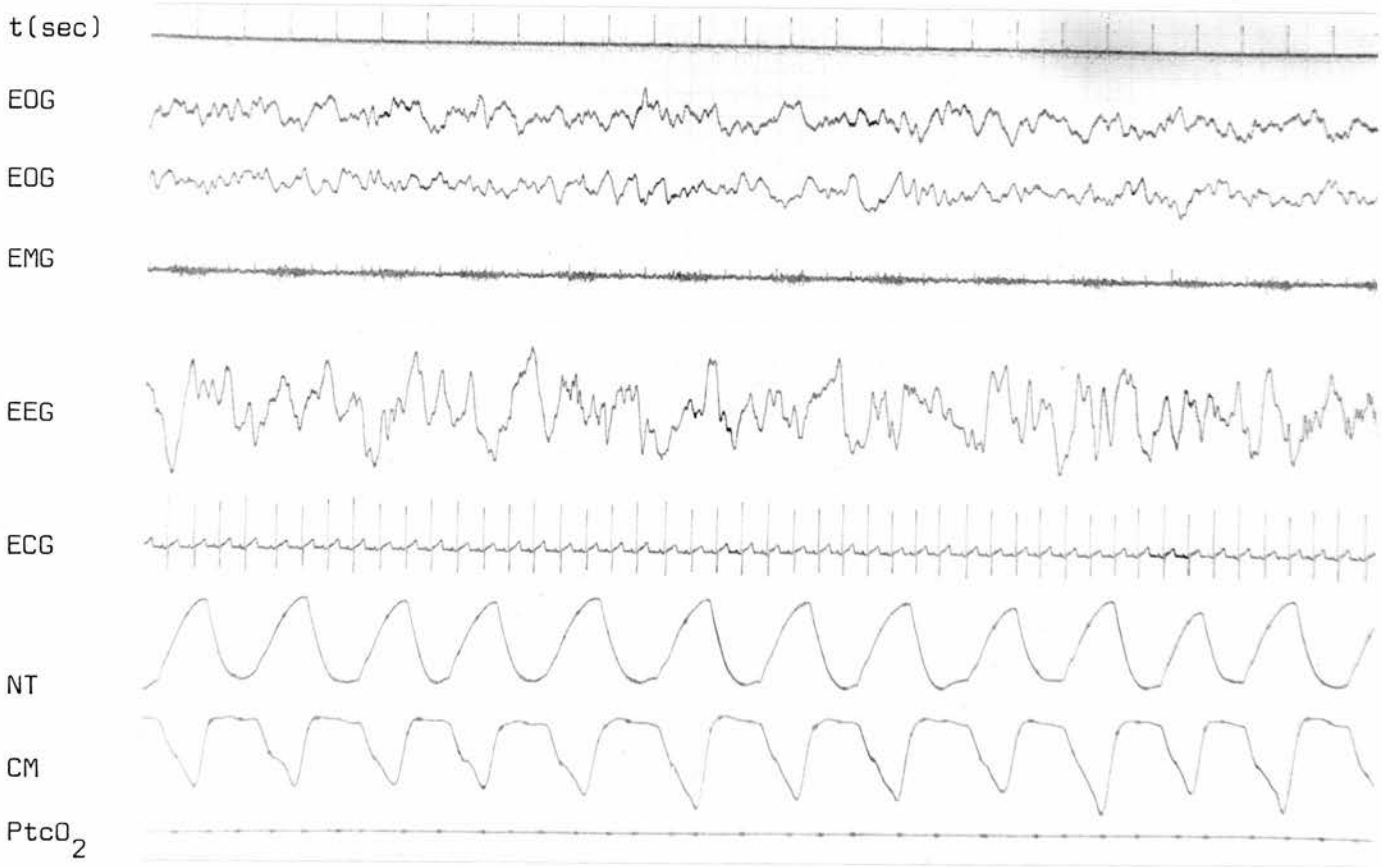
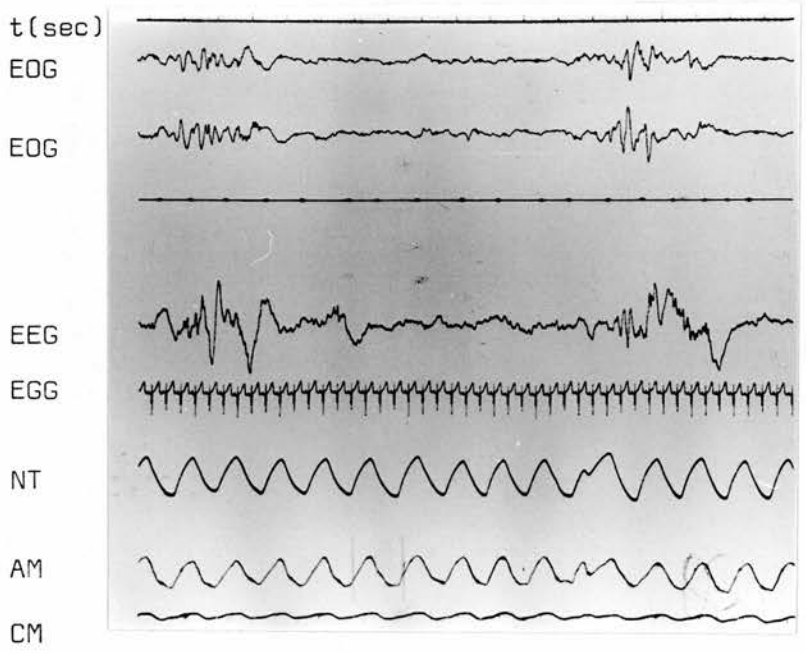


Figure 6

Trace alternant in QS



duration. This pattern disappears in the first weeks of life in mature infants and is replaced by a continuous slow wave pattern.

Active sleep is characterised by a lower voltage fast pattern (Fig 7) which may resemble Stage I of quiet sleep but is distinguished from it by other features such as rapid eye movement and the absence of muscle tone. Moreover Stage I of quiet sleep is likely to be followed by the appearance of sleep spindles or slow wave patterns without an intervening transitional sleep pattern.

Electro-oculogram: eye movements consist of bilateral, abrupt, synchronous shifts in eye position which occur either singly or in bursts some three minutes after an active sleep phase has begun. They are phasic phenomena which come and go during active sleep - there may be minutes of sleep without rapid eye movements.

Electromyogram: in quiet sleep tonic activity recorded from the digastric chin muscles shows that muscle tone is preserved (Fig 8) whereas in active sleep it is depressed (Fig 9). This is a less reliable indicator of sleep phase in the young than in the adult. Petre-Quadens (1972) has shown that the abolition of muscle tone during active sleep in mature newborn and infants under 7 months occurs in an irregular manner. Thereafter muscle activity diminishes progressively in active sleep as the infant grows older.

Figure 7

Active sleep AS; eye movements, low voltage EMG disorganised breathing

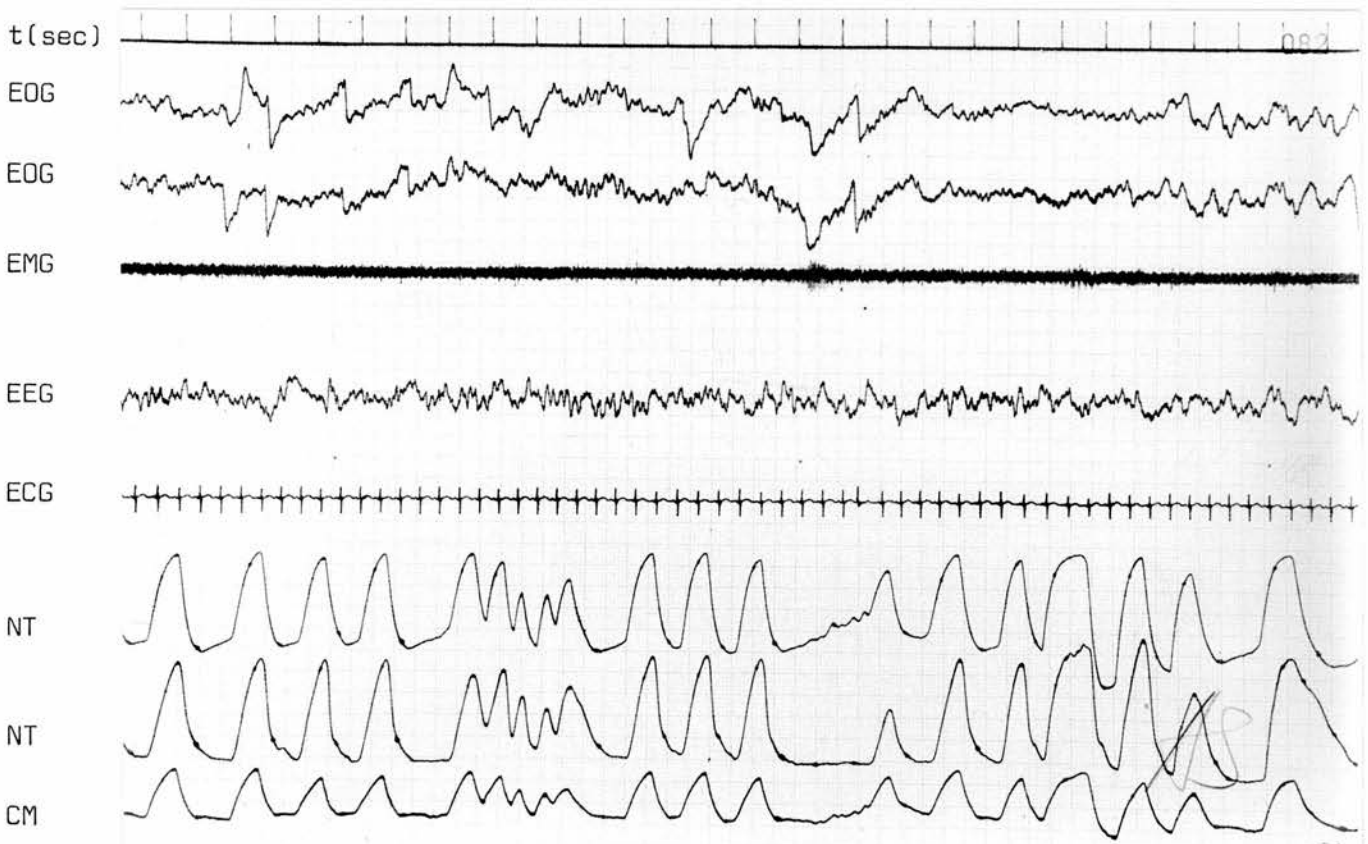


Figure 8

Electromyogram (EMG) in QS

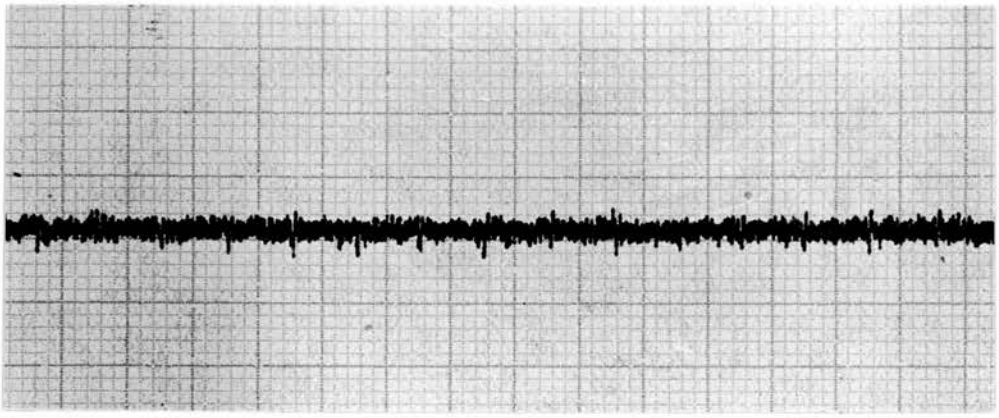
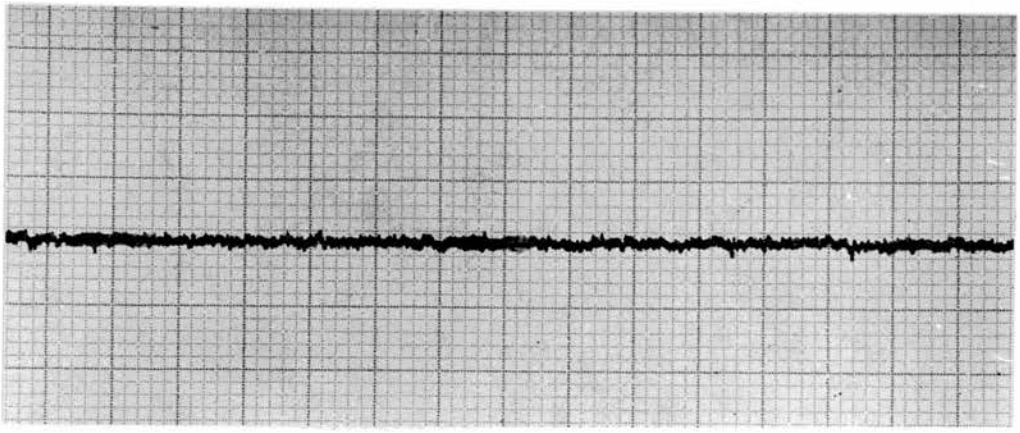


Figure 9

Electromyogram (EMG) in AS



2.2.2 Respiratory control mechanisms

The successful transition from foetal to extra-uterine environment is a remarkable accomplishment, not least in the area of respiratory control. There is, however, evidence that the infant's respiratory control system is more vulnerable than that of a mature adult despite the adaptations which occur at birth and the immediate newborn period. This may have implications in relation to liability to periodic breathing, recurrent apnoea, and the Sudden Infant Death Syndrome. A brief resumé of current knowledge is presented; Chernick (1981) and Fleming and Ponte (1983) have reviewed the regulation of breathing in the foetus and newborn infant in greater detail.

The sequence of events leading to the development of stable respiration after birth probably originates in foetal life. In mammals so far studied, including man, the foetus makes respiratory movements in late gestation. These are virtually continuous at first but become episodic and alternate with similar periods of apnoea. Just before birth they diminish and disappear. These movements are thought to occur in active sleep - they are rapid and irregular, and associated with rapid eye movements and other jerky movements of the neck and limbs, and with a low-voltage desynchronished electroencephalogram They are unaffected by afferent activity in the vagus nerve but are excited by hypercapnia and reduced by hypoxia and hypoxaemia (Dawes et al 1972 Boddy and Mantell 1972). It has been suggested that they have a rôle

in relation to the maturation of lung tissue. Available evidence suggests that the 'automatic' component of respiratory control is absent in the foetus. This includes chemical inputs mediated by the peripheral and central chemoreceptors and respiratory reflexes such as the Hering-Breuer reflex. This situation alters at birth when breathing becomes continuous in active and quiet sleep and is sensitive to chemical and other reflex inputs. Whether the 'automatic' component of respiratory control is actively inhibited or inadequately stimulated prior to birth is uncertain. The question also arises whether the respiratory controller which had never had to respond to chemical or metabolic disturbances in utero is immediately effective or whether there is a period following birth during which the controller 'acquires' the ability to respond effectively to such changes.

Central controller

The requirements for stable control of respiration include a central controller which modulates the respiratory pattern, chemoreceptor and other reflex inputs to the controller, and appropriate gain setting for the chemoreflexes. One characteristic of the newborn central nervous system, particularly that of the preterm infant, is scanty dendritic arborisation and incomplete myelination of many neurons (Schade et al 1964). The functional consequences of these observations may be profound. For a respiratory motor neurone to depolarise both spatial and temporal summations of numerous excitary post-synaptic potentials must occur.

The scanty dendritic structure affects spatial summation of potentials and the unmyelinated fibres affect the speed with which impulses are propagated making it difficult to achieve temporal summation. Thus, any presynaptic or postsynaptic inhibitory activity will have a disproportionately greater effect, and increase the vulnerability of the control system. Hathorn (1978) has described the performance of the central respiratory controller in newborn infants. Fluctuation of both tidal volume and respiratory frequency occur with a period of 8-12 seconds and are more marked in Active Sleep than in Quiet Sleep. Moreover the precise relationships between tidal volume and respiratory frequency alter considerably. In quiet sleep they are almost exactly out of phase leading to stable respiratory control whereas in active sleep phase relation is much more variable. In some infants, particularly in premature, tidal volume and respiratory frequency are in phase and increase predictably the likelihood of periodic respiration.

Chemoreflexes

Species maturity at birth probably affects chemoreceptors at that time. In the sheep carotid body chemoreceptors are inactive and insensitive before birth but are activated shortly after birth and respond to oxygen and carbon dioxide as in the adult (Biscoe and Purves 1965). In the human infant there is a biphasic response to hypoxia (Cross and Warner 1951; Sankaran et al 1979). Transient hyperpnoea is

followed by marked hypoventilation, in contrast to the adult who maintains hyperventilation in response to hypoxic stress. However, it does seem likely that the infant's chemoreceptors are active for restoration of air after breathing 15% oxygen results in a fall in ventilation for 1-2 minutes. Whether 'anoxic depression' of the medulla occurs in infants breathing low concentrations of oxygen is uncertain; foetal lambs with collicular brain sections responded to hypoxia with breathing 'which either persisted or increased in depth and regularity' (Dawes et al 1980). Similar studies have yet to be carried out in human infants with, for example, anancephaly to test whether the concept of medullary 'depression' is ill-founded.

The ventilatory response to carbon dioxide is mediated by hydrogen ion (H^+) receptors located in the medulla. The activity of the central chemoreceptors in the immediate newborn period is uncertain. The literature gives conflicting results - one might conclude that the infant is more sensitive, less sensitive, or has the same response as the adult to inhaled carbon dioxide. The CO_2 stimulus has varied in different studies and sleep state has not been defined. Some groups have found that CO_2 sensitivity increases with gestational and postnatal age (Rigatto et al 1975; Frantz et al 1976), but this has not been confirmed by others (Davi et al 1979).

Gain settings of chemoreflexes

Under basal conditions stable respiration can only be maintained if there is a precise relationship between the optimal gain settings for responses to changes in oxygen tension. Normally this relationship is such that the main chemical drive is from carbon dioxide rather than oxygen. The body stores of CO_2 are large and the respiratory response to CO_2 linear whereas body oxygen stores are relatively small and the response to the reduction in oxygen tension non-linear. When hypoxia rather than CO_2 becomes the dominant drive to ventilation asymmetry in the response to deviations from a set point results in respiratory instability (Cherniack and Longobardo 1973). Instability, manifest by periodic respiration would arise if CO_2stores were diminished, if sensitivity to CO_2 were reduced, or sensitivity to hypoxia increased. These factors probably operate in the newborn. Periodic breathing has been induced in newborn animals by bathing the ventral medullary surface in alkaline cerebrospinal fluid, and reversed by giving the animals pure oxygen to breathe (Wennergren and Wennergren 1980). It has been shown also in pre-term and full-term infants that periodic respiration can be abolished by reducing hypoxic drive (inhalation of CO_2/air mixture).

Lung and chest wall reflexes

Mechanical reflexes from the lung and chest wall also appear to play an important part in the control of respiration

in infants. The vegus has three types of receptor in the lung - the slowly adapting stretch receptors, the rapidly adapting irritant receptors, and J receptors (Widdicombe 1974). Breuer (1868) showed that sustained lung inflation inhibits respiration. Stretching of the lung is an important factor in control of respiration frequency and tidal volume. The larger the tidal volume the more the stretch receptors are stimulated and the shorter the inspiratory time. This reflex may play a significant rôle in the rapid respiratory rate of infants and in the hyperpnoea of lung diseases, and aid in the maintenance of lung volume. At high respiratory rates the infant has insufficient time to expire to his passive FRC whereas during apnoea lung volume decreases substantially during passive expiration. There is still confusion about the age at which this negative feedback control system appears and disappears. The timing mechanism is complicated by chest wall reflexes, particularly during active sleep. Deflation of the lung in many animals produces hyperventilation, a response mediated by epithelial irritant receptors. These receptors are distributed throughout the airways, and respond to direct tactile stimulation. In full-term infants, stimulation results in hyperventilation. Little is known of J receptors in the newborn lung and how reflexes associated with them vary with time.

The intercostal muscles are rich in intercostal muscle spindles that can initiate segmental and supra-segmental

reflexes. In active sleep intercostal muscle activity is low and very erratic. As a result the chest wall becomes more compliant and moves paradoxically with each contraction of the diaphragm. During the awake state or quiet sleep intercostal activity is sufficient to prevent indrawing of the ribcage if the lung is normal. The distortion of the ribcage during active sleep caused by contraction of the diaphragm can be reflexly inhibited by the intercostal phrenic inhibitory reflex (Remmers 1970) which appears to play a major rôle in the control of tidal volume and frequency during active sleep (Knill and Bryan 1976). Although its rôle in limiting chest wall distortion is beneficial initiating the reflex may result in apnoea in premature infants.

Stability of respiratory control in early infancy

Fleming and Levine (1982) have studied the development of stability of respiratory control mechanisms during the early months of life. Examination of the respiratory patterns after sighs in term infants in quiet sleep showed a pattern which changed with increasing post-natal age. In the first 24 hours after birth there was a fall in both tidal volume and frequency with a gradual return to base-line values over 25-40 seconds. Beyond two or three days sighs were commonly followed by a clear pattern of damped oscillations particularly involving tidal volume. Tidal volume and frequency oscillated with different time periods, whilst ventilation (the product of tidal

volume and frequency) oscillated with a pattern and period similar to that of tidal volume. These observations were interpreted as supporting the concept of separate control of tidal volume and frequency. The period of oscillation in tidal volume was consistent with the effect of a feedback loop with a 6-10 second lag, in turn consistent with the response time of the peripheral chemoreceptors (Hathorn 1978). Lack of such oscillations (stable sluggish response) in the first few days of life might have been due to decreased chemoreceptor activity or right-to-left shunting of blood.

Sleep state

It is clear that sleep state must be taken into account in any investigation of respiratory control mechanisms. The predominant sleep phase changes between birth and six months, during which time the total duration of quiet sleep increases significantly, particularly in the first twelve weeks (Dittrichova 1966). Coincident with these changes, stable control of breathing must be maintained. As the mechanisms responsible for this control are different in active and quiet phases of sleep any asymmetry of these developmental processes (sleep and regulation of breathing) could have adverse effects. The hazards faced by the newborn infant, particularly if born prematurely, continue throughout the early months of life until stable control of respiration is achieved. The effects of 'natural' stress, e.g. minor respiratory illness during this period

of increased vulnerability might further destabilise the system. Whether this could result in the death of any mature, apparently healthy infant (given certain conditions of sleep, respiration control and possibly added environmental factors) is not known. A defect in sleep or respiratory control mechanisms (or their maturation) predisposing to the infant's unexpected and unexplained death during the course of infection or other stresses is thought by many to be present from the outset.

Phillipson (1978) has reviewed the control of breathing during sleep. A summary of the control mechanisms is given in Table 1. It is likely that these apply in the newborn period and during the early months of life although the subdivision of quiet sleep into component phases is less readily accomplished than in the mature adult. The newborn infant spends much of its time asleep and of this 50-60% is active sleep. It is thought that in active sleep ventilation is largely driven by the behavioural 'component' of suprapontine origin whereas in quiet sleep it is driven largely by chemical and reflex inputs. This distinction is illustrated by infants with depressed chemoreflexes who maintain adequate alveolar ventilation while awake or in active sleep but who hypoventilate when in quiet sleep (Fleming et al 1980). Thus quiet sleep is acquired but during the early months of life there is increasing reliance on the metabolic or 'automatic'

TABLE 1 SUMMARY OF RESPIRATORY CONTROL MECHANISMS DURING SLEEP

	Quiet sleep (Non REM sleep)		Active sleep (REM sleep)	
	Stages 1,2	Stages 3,4	Tonic	Phasic
Dominant influence on breathing	Metabolic State	Metabolic	State Metabolic	Non-metabolic (Behavioural)
Pattern of breathing	Periodic	Regular	Regular	Irregular
Response to metabolic stimuli	Present	Present	Probably present	Decreased or absent

Terms and Abbreviations:

Non REM - non rapid eye movement
REM - rapid eye movement
Tonic/phasic - absence or presence, respectively of rapid eye and other movements
State - respiratory effort related to state of sleep per se
Metabolic/behavioural - metabolic or behavioural respiratory control system

After PHILLIPSON E A 1978

drive to ventilation. By three to four months the proportion of time spent in active and quiet sleep reverses (Parmalee et al 1967). It is therefore possible that the peak occurrence of SIDS at this age may be related to imperfect or delayed development of one or more of the factors which ensure stable ventilation under all conditions of wakefulness or sleep. Fleming and Levine (1982) have demonstrated instability of respiratory control in quiet sleep during the early months of life. Any defect in chemoreceptor function would enhance potential hazards in quiet sleep.

Active sleep is not without hazard. Inhibition of protective respiratory reflexes can occur with or without neural damage. In animal models depression of protective reflexes leading to vulnerability in active sleep has been demonstrated in a host of circumstances which increase vulnerability to asphyxia. In the dog there is absence of cough, and arousal is delayed when fluid is injected into the trachea (Sullivan et al 1978). In the sleeping newborn lamb prolonged apnoea results when laryngeal chemoreceptors are excited by fluids (Marchal et al 1982). Reduced lung volume during active sleep in the newborn depletes oxygen stores (Henderson-Smart and Read 1979) and predisposes to more rapid onset of hypoxaemia during apnoea. There is also failure to augment intercostal muscle activity during obstructed inspiration in the newborn (Henderson-Smart and Read 1978). In a study of ventilatory and waking

responses to CO_2 in sleeping dogs Phillipson et al (1977) demonstrated failure to augment ventilation and a delayed arousal during hypercapnia. Similar findings have been reported for response to hypoxia in newborn calves (Jeffery and Read 1980).

Summary

There is incomplete evidence that the system which ensures stable respiration is not fully developed at birth and that full stability may not be achieved for days or weeks afterwards. The effectiveness of the respiratory controller in modulating respiratory patterns will depend on a balance between stimulatory and inhibitory inputs - in the pre-term infant the system appears to have an inhibitory bias. Active sleep is inhibitory to intercostal muscles. This permits distortion which further inhibits inflow by the intercostal phrenic reflex. The vagal inhibitory reflex (stretch receptors) is powerful whereas facilitatory inflow (irritant receptors) appears to be weak. Of the elements which make for stable respiration, the central CO_2 mechanisms and peripheral chemoreceptors seem of paramount importance. Impairment or delay of development of these mechanisms is likely to result in instability of respiratory control which could be provoked by any additional factor which would tend to disturb ventilation, e.g. upper airways obstruction. Vulnerability would be greatest during quiet sleep. Active sleep is not without potential hazard. The depression of protective reflexes increases vulnerability to asphyxial influences, e.g. the inhalation of milk resulting from gastro-oesophageal reflux (Jeffery et al 1980).

2.3 Breathing during sleep and increased risk for SIDS

2.3.1 Apnoea and periodic breathing

In the light of clinical-pathological observations on respiratory illnesses and SIDS and the relative immaturity of respiratory control mechanisms during the early months of life, it is not surprising that cardio-respiratory function has been the subject of extensive investigation in infants thought to be at increased risk for SIDS. A great deal of conflicting data has emerged on almost every aspect of function investigated. Certain hypotheses have been difficult to test despite strong theoretical appeal, for example, the apnoea hypothesis. Test conditions such as sleep phase have often been inadequately described, and measurement techniques employed by investigators attempting to answer a common question, for example, the respiratory response to alterations in inspired oxygen and carbon dioxide concentrations, have varied both in their nature and sensitivity. It has also been sometimes difficult to obtain satisfactory control data.

It has been postulated that SIDS victims die an asphyxial death (Naeye 1966; 1974; Stevens 1965). Interruption of airflow between the environment and the lungs would result in hypoxaemia, hypercapnia, acidemia and tissue hypoxia followed by central circulatory failure. Within a certain time period the situation would be potentially reversible, either spontaneously (i.e. by arousal) or by resuscitative intervention. The

notion that prolonged central apnoea is the initiating event in this sequence stems from the work of Steinschneider (1972) who demonstrated apnoeic episodes in infants who later became SIDS victims. Studies of both healthy pre-term and term infants during the early months of life indicate that prolonged central apnoea ($\geq$ 20 seconds) is not a normal occurrence. In the 'healthy' pre-term infant respiratory pauses of shorter duration are well-recognised during sleep and persist in the first few months of life (Gabriel et al 1976). Similarly, brief episodes of central apnoea occur in term infants but do not usually exceed 15 seconds in duration (Gould et al 1977; Hoppenbrouwers et al 1977; and Stein et al 1979). Within this limit there is marked variation in the duration and frequency of respiratory pauses between different infants, and in the same infant studied at different times (Bernstein et al 1973). Such pauses are not associated with significant bradycardia (heart rate rarely falls below 80 per minute) or oxygen desaturation. They occur more frequently in active than in quiet sleep but are of similar duration in each of these sleep phases. Between birth and three months the frequency decreases considerably in active sleep but remains relatively constant in quiet sleep (Hoppenbrouwers et al 1980).

Guilleminault et al (1975) suggested a possible relationship between obstructive sleep apnoea and SIDS. Obstructive apnoea is rare in apparently healthy thriving infants. It occurs most commonly in active sleep, presumably related to the loss of muscle tone, but it may also occur in quiet

sleep. During such episodes the affected infant makes a series of regular deep inspiratory efforts against an occluded upper airway. Bradycardia and oxygen desaturation are more rapid in onset and of greater duration and severity than in central apnoea (Guilleminault et al 1975). Congenital and acquired anomalies which may cause obstructive apnoe may have been discussed (see section 2.1.4); in their absence a variet of other factors may be responsible. In a study of a group of adult patients presenting with obstructive sleep apnoea, the restoration of normal respiratory rhythm following naso-pharyngeal intubation led Remmers (1978) to conclude that neither the larynx nor lower airways were the primary factors in the genesis of this condition. In adults with obstructive or mixed central and obstructive apnoea Weitzman et al (1978) showed that upper airway narrowing occurs at the level of the tongue. The genioglossus muscle which makes up the bulk of the tongue and acts by bringing it forward has a major influence on the patency of the airway. During active sleep its tonic activity is greatly diminished or absent - only small bursts of energy are present during inspiration and some muscle units may be completely inactive for up to 90 seconds. In the supine position the effect of gravity favours prolapse of the tongue against the posterior pharyngeal walls. It seems that tonic activity of the genioglossus is necessary to maintain an airway; continuous genioglossus respiratory discharges contribute to airway patency and a decrease in resistance to airflow

(Harper and Sauerland 1978). In normal subjects the loss of genioglossus tone does not cause sleep apnoea indicating that airways obstruction does not occur in the absence of structural or functional impairment. However, a recessed mandible, a small oral cavity, or a large tongue might bring the tongue closer to the pharyngeal wall and produce critical narrowing of the airway during sleep. Further, the reduction in pharyngeal pressure produced by a sudden forceful inspiration would then have the effect of sucking the tongue and the floppy pharyngeal walls together, completing the obstruction to airflow. An analogy is made to the collapse of a straw during sucking. It will only collapse if it is soft (floppy) enough, or its internal diameter is sufficiently small and the negative pressure (suction) applied is adequate. Most of this evidence on the site of obstruction to airflow stems from observations in adults with advanced sleep disorders. Care must be taken to avoid uncritical extrapolation to young infants. The anatomy of the oro-pharynx in the infant differs in some respects from that in adults. The oral cavity is relatively smaller in relation to tongue size than in the adult and patency of the airway at pharyngeal level is potentially threatened by a very mobile tongue and soft pharyngeal tissues. With growth the mandible grows downwards and forwards, thereby increasing the width and height of the oral cavity (Tonkin 1975). The position of the uvula is high and the base

of the tongue opposite the oro-pharynx. The infant's epiglottis is at least one full vertebra higher than in the adult. In effect, there is a relatively narrow airway between the soft palate and the bony base of the skull. At rest the tongue completely fills the oral cavity and follows the contour of the soft palate - no air is visible in the oral cavity on X-ray.

In the early months of life, some infants are thought to be obligato nose-breathers at a time when the contribution of nasal resistance to total resistance to airflow is much smaller than in adults (Polgar and Kong 1965). Obstruction of the nasal air passages by secretions or an inflammatory process would increase airflow resistance and the work of breathing. Increased inspiratory effort, for example, during the course of upper respiratory infection, would result in an increase in negative pressure at pharyngeal level and favour the collapse of adjacent tissues. In a study of newborns and six-week old infants Swift and Emery (1973) found that when the nares were occluded most infants attempted to breathe immediately. In rapid eye movement (REM) sleep the proportion of slow and non-responders was 17% of 100 newborn infants tested, and 44% of 59 investigated at six weeks of age. The suggestion was made that apnoea occurs as a response to nasal obstruction. The relevance of these observations can be inferred from earlier descriptions of outcome for infants with untreated choanal atresia (Shaw, 1970, 1979; Anderson and Rosenblith 1971).

Conditions which may cause obstruction distal to the pharynx have been discussed. Guilleminault (1979) reported the death of an infant with congenital stridor in whom mixed and obstructive apnoeas leading to oxygen desaturation during sleep had been demonstrated during the preceding forty-eight hours. Sudden bronchial or bronchiolar obstruction could also occur perhaps during the course of respiratory infections, or as part of an anaphylactic response to inhaled foreign protein, such as is contained in cow's milk (Parish et al 1960a).

Periodic breathing is frequently considered to be a sign of instability of respiratory control in early infancy (see Sections 2.2.2 p46). It occurs in normal full-term infants in the early months of life and in normal adults at high altitude during sleep (Sutton et al 1979). Its significance is not clear and any relation it may have to the occurrence of prolonged central or obstructive apnoea is not fully understood.

2.3.2 Arousal responses and Chemosensitivity

Recent studies of arousal responses to an increase in inspired carbon dioxide concentrations, or a decrease in inspired oxygen concentration, are of particular interest (Hunt 1981). The investigative emphasis shifts from a consideration of why infants may stop breathing during sleep

to address the question why they may fail to re-start breathing following respiratory pauses. Evidence that over-activity of the endogenous opiate system may be related to diminished arousal responses, recurrent apnoea, and SIDS, has been reviewed by Kuich and Zimmerman (1981).

Altered chemosensitivity might also influence arousal. Interest in chemoreceptor activity has centred largely on the identification of possible defects in the structural, biochemical and functional aspects of carotid body activity. A number of structural studies of the carotid bodies in SIDS have been performed (Naeye et al 1976; Cole et al 1979; Dinsdale et al 1977; Perrin et al 1984). There appear to be no major changes in either the size or structure of the carotid bodies in SIDS victims. However, there is recent evidence that the carotid bodies of SIDS victims store much larger amounts of catecholamines than do non-SIDS carotid bodies (Perrin et al 1984). It is also known that dopamine depresses carotid body output (McQueen 1984), via a D_2 receptor (Mir et al 1982,1984). It is therefore possible that the output from the carotid bodies is reduced in potential SIDS victims, and that hypoxic sensitivity is attenuated. Evidence supporting this view is provided from observations in clinically hypoxic humans and animals. Humans living at high altitude have enlarged carotid bodies and show a blunted response to hypoxia. Animals made hypoxic for a period of three weeks develop hyperplasia of the carotid body and

an elevated level of dopamine in the carotid body; on removal from the hypoxic environment they have reduced responsiveness to carotid body stimulation. The relevance of these observations to the possible mechanism of death in SIDS is as follows: apnoea may occur during sleep from a variety of causes. This results in a rise in arterial carbon dioxide tension and a fall in oxygen tensions. Normally, the hypercapnia would stimulate both the central and peripheral chemoreceptors and lead to inspiratory activity. However, in 'at-risk' infants, the hypercapnic drive may be impaired so that hypoxia is the dominant drive to ventilation. If dopamine inhibition of the carotid bodies is added, the possibility arises that insufficient drive would be provided to the respiratory centres to arrest the apnoea. The resulting hypoxia leads to an increased secretion of dopamine from the carotid body (Al Neamy & Pallot 1983) and further depression of carotid body funtion. The interaction between chemosensitivity and endogenous opiate metabolism in the brain has yet to be fully investigated.

2.3.3 Mechanism(s) of death - pathological evidence

In recent years, evidence has accumulated that SIDS victims have subtle abnormalities such as retardation in growth velocity dating from some time before birth (Sinclair-Smith et al 1976) similar to that produced experimentally by maintaining animals in a hypoxic environment (Naeye et al 1976). This raises the question whether SIDS victims are chronically hypoxic prior to death. Clinical observations

on sleep apnoea (Stevens 1965; Steinschneider 1972; Guilleminault et al 1975) lend some support to this view and the postulate that SIDS victims die an asphyxial death.

Naeye (1973; 1974; 1976; 1977) investigated the so-called 'apnoea hypothesis' in a search for tissue markers of hypoxia - possible anatomical sequelae of apnoeic episodes severe enough to lead to chronic hypoventilation, hypoxia, and possibly death. He reported an abnormal increase in muscle in the small pulmonary arteries in 60% of SIDS victims when compared with non-hypoxic controls (Naeye 1973), and considered the increase to be the consequence of increased vasomotor activity, due to chronic hypoxaemia. Williams et al (1979) supported Naeye's findings, and also described extension of smooth muscle into arteries not usually muscularised during the first year of life. There followed reports of increased right ventricular hypertrophy (interpreted as a response to an increase in pulmonary vascular resistance) (Naeye et al 1976), abnormal retention of brown fat, persistence of hepatic erythropoeises, and proliferation of astroglial cells in the brain stem (Naeye et al 1976), phenomena known to be present in infants who are chronically hypoxaemic after birth (Brand and Bignomi 1969). Studies of carotid bodies reveal enlargement of glomic tissue in 23% and a decrease in 63% of SIDS victims (Naeye 1976). Other investigators have been unable to confirm the presence of tissue markers of hypoxia. Beckwith (1983) has reviewed the pathological

data base relating chronic hypoxaemia and SIDS, and concludes that further studies are indicated before it can be safely stated that a large proportion of SIDS victims have been chronically hypoxaemic before death.

Other investigations have shown the SIDS victims have pathological alterations in certain areas of the nervous system concerned with cardiovascular control. These alterations include increased brain-stem gliosis (Takashima et al 1978), cerebral white matter leukomalacia (Takashima et al 1978), persistance of reticular dendritic spines (Quattrochi et al 1980) and decreased numbers of small myelinated vagal fibres (Sachis et al 1981).

Nearly all of the above findings have raised questions concerning the methods and procedures used, e.g. staining techniques, and the reliability of data when there is limited information on chronological and gestational age-matched controls. Whether the lesions reported cause or result from cardio-respiratory dysfunction is not known. The pulmonary vascular changes reported have likewise evoked controversy and, indeed, have been refuted by some investigations (Kendeel and Ferris 1977).The presence of increased muscle in the walls of the small vessels provides only circumstantial evidence for chronic hypoxaemia; no direct measurements of arterial oxygen tension have been reported in such infants during life.

There is more general agreement concerning the presence of neuropathological abnormalities in the brains of many infants who die with SIDS. It seems likely that most are secondary to other problems such as chronic hypoxia or other systemic or localised insults. It is of interest that changes in the brain stem are similar to those seen in infants with congenital heart disease, and other abnormalities (Ambler et al 1981). The nature of any possible primary neurological abnormality is obscure.

Post-mortem examination findings have not led to a full understanding of the mechanisms responsible for the death of SIDS victims, and the sequence of events that leads to death is far from clear. There is no general agreement as to whether SIDS infants die of asphyxia, caused by airway obstruction (triggered by local or central abnormalities) or prolonged central apnoeas and hypoventilation or perhaps fatal arrythmias; conceivably the patho-physiology varies among SIDS deaths. This lack of certainty is illustrated by the debate on the significance of intrathoracic petechiae. They are present in approximately two-thirds of SIDS cases and were once regarded as evidence of persistent airways obstruction (Handforth 1959). This view has been challenged as they are not seen in asphyxial deaths due to acute epiglottitis or inhaled foreign body. However, they can be produced experimentally in virus-infected rats, and when hypoxia prior to cardiac arrest is associated with vigorous resuscitative efforts (Guntheroth et al 1980). The mechanism(s)

of their production are probably complex and involve both the respiratory and the cardiovascular systems (Campbell and Read 1980; Guntheroth 1982). They do not appear to be pathognomonic of any one condition and are probably multifactorial.

Beckwith (1970) and Patrick (1970) have reported independently that blood from the left ventricle of SIDS victims is largely unclotted and at a low oxygen tension. This is consistent with perfusion of tissues under hypoxic conditions when the release of fibronolysins which impair blood coagulation. These observations support the view that respiratory arrest precedes cardiac arrest and complete circulatory failure. An alternative explanation could be anaphylaxis which is considered by some investigators to be the mechanism of death in certain cases (Coombs and McLaughlin 1982). This could lead to the release of heparin from mast cells, which could explain the non-coagulation of pulmonary venous blood entering the left heart. The absence of histological markers of anaphylaxis, and the lack of data on mediators which might persist in lung tissue following death from anaphylaxis means that this hypothetical possibility remains unproven.

2.4 Infants at 'increased' risk for SIDS

It is still not possible to identify, with any degree of accuracy, the infant who will die suddenly, unexpectedly,

and inexplicably. The limitations of scoring systems, applied to the individual infant, have been mentioned previously. Two main groups of infants have been considered at increased risk for SIDS - 'near-miss' infants and siblings of previous SIDS. The degree to which risk is increased for each group is controversial and, whether any increase in risk applies equally to individual infants within either group is likewise uncertain. Other factors which increase risk for SIDS have been reviewed earlier in this chapter (section 2.1.3).

2.4.1 'Near-miss'for SIDS, siblings of SIDS

'Near-miss' infants have been considered to be at considerable risk for SIDS. The 'near-miss' infant is usually defined as one who has stopped breathing and also seemed to have almost died, suddenly and unexpectedly, but whose life is apparently saved by timely intervention by parents or attendants. Descriptions given by non-objective observers are clearly prone to error, and it is not surprising that the term 'near-miss' is generally regarded as unsatisfactory. Moreover the presentation of 'near-miss' infants is common to a variety of clinical entities including seizures, fulminant infections, hypoglycemia, gastro-oesophageal reflux, severe anaemia, cardiac arrythmia, and uncommon metabolic disorders, as well as impaired regulation of breathing. The investigative approach has been to exclude identifiable diagnoses by appropriate testing and to isolate a subgroup of infants who, for unknown reasons, have experienced an inexplicable episode of near-death. This parallels the approach to sudden infant death - SIDS

is diagnosed by exclusion of identifiable causes of death. Even the approach described does not satisfy all who are stringent about criteria for the selection of subjects for scientific observations. Some investigators demand that mouth-to-mouth resuscitation has been employed also before accepting that a particular infant has experienced a 'near-miss' for SIDS episode.Whilst recognising the importance of defining clinical entities under consideration, an arbitrarily determined narrow approach such as that described carries the risk of being unduly restrictive. Some of the results presented in this thesis question the wisdom of this approach.

Infants presenting as 'near-miss' cases have been successfully resuscitated (Valdes Dapena 1967; Bergman et al 1972, 1975). Early reports on the occurrence of subsequent unexplained death in these infants suggest a 20% to 100% mortality (Stevens 1965; Steinschneider 1972; Weitzman 1974). Kelly et al (1978) provided a home monitoring service for 84 'near-miss' infants between 1973 and 1976. The infants had been evaluated in hospital initially, and parents were instructed in the use of apnoea monitors and in cardio-pulmonary resuscitation. Four infants died at home while the monitor was being used. In three cases parents had failed to hear the monitor alarm when it first sounded and the fourth died despite attempts at resuscitation. There have been several subsequent reports of home monitoring for apnoea, or apnoea and heart rate (Ariagno et al 1981; Duffty and

Bryan 1982; Kahn and Blum 1982; and McKay et al 1984). In general, death has been uncommon, leading many to suspect that original estimates of 'risk' were unduly pessimistic. No long-term case-control studies of 'near-miss' infants who have not received treatment or monitoring in the home have yet been reported. The risk for such infants is not known. Shannon and Kelly (1982 a,b) have reviewed current knowledge of near-SIDS and SIDS. The underlying assumption is that the 'near-miss' infant is an appropriate human model for the study of SIDS.

Subsequent siblings of SIDS victims are another group thought to be a special risk for sudden death. The risk for such infants has already been discussed, and has changed little since the observations of Froggatt et al (1971) that they have a three- to four-fold greater risk of sudden death than infants in the general population.

Other groups of infants at increased risk are those born prematurely or are small for dates, infants discharged from neonatal intensive care units, and off-spring of narcotic dependent mothers, in particular methadone dependence. Reference has been made to these groups in section 2.1.3.

2.4.2 Studies in infants at increased risk

Most studies have been conducted in infants who have experienced a 'near-miss' for SIDS (aborted SIDS) episode or siblings of SIDS victims. Significant differences have been found between subsequent siblings and control infants in cardio-respiratory behaviour (Hoppenbrouwers et al 1976 and 1980). Short apnoeic pauses of 2-5 seconds occurred less frequently in subsequent siblings as compared with controls. Prolonged central apnoea $>$ 20 seconds was rare. Higher respiration rates were also observed in subsequent siblings both in active and quiet sleep. Differences were significant at one and three months in all sleep states. Thoman et al (1977) identified two infants with hyperpnoea in the first week of life, one who later died of SIDS, and one who developed unexplained apnoea. Differences have also been observed in heart rate and its variability in subsequent siblings as compared to controls (Harper et al 1978). These investigations speculated that the differences observed might reflect delayed maturation or impaired function of the autonomic nervous systems, and particularly of vagal control.

Hodgman et al (1978 and 1982) have compared cardio- respiratory variables in 'near-miss' for SIDS cases and controls carefully matched for age at recording, sex, and gestational age at

birth. The findings were more heterogeneous than those of either controls or of subsequent siblings. One fifth of the infants demonstrated abnormal findings including an increased number of central and obstructive apnoeas. Half of the infants had clinically recognised additional apnoeic episodes, usually within one week of the first episode. Clinical or polygraphic findings did not predict the recurrence of apnoea.

Guilleminault et al (1979) reported an increase in short obstructive apnoea during total sleep time at six weeks of age in 'near-miss' infants. However, Monod et al (1976) found no increase in either central or obstructive apnoea in their 'near-miss' infants. Other studies have reported a trend toward decreased apnoea and increased respiration rate (Navelet et al 1979; Haddad et al 1981).

In most control studies of infants born at term, findings are similar in 'near-miss' and normal infants. In the pre-term infant of birthweight $<$2250 gms studied after the first week of life Hodgman and Hoppenbrouwers (1983) reported prolonged central apnoea $>$ 20 seconds in 8 of 51 apparently healthy pre-term infants. In a follow-up of the six who had had two or more apnoeic episodes $>$ 20 seconds in an 8-hour period at 40, 44, and 52 weeks post-conception, clinically significant apnoea was observed in three at 40 weeks post-conception age. Two exhibited short episodes of obstructive apnoea. All had recovered by 3-6 months.

There is considerable controversy about the significance of periodic breathing, a phenomenon seldom defined by investigators reporting its prevalence in risk groups of infants. Kelly and Shannon (1979) and Kelly et al (1980) have described increased amounts of periodic breathing in siblings of SIDS and 'near-miss' infants. Hoppenbrouwers et al (1980) did not confirm this finding. Southall (1983) found that periodic breathing was not significantly increased in infants who subsequently died of SIDS.

There are conflicting data also on the ventilatory responsiveness to CO_2 in 'near-miss' infants. Shannon et al (1977) and Shannon (1980) published data demonstrating decreased ventilatory responses to CO_2. Other investigators have not confirmed a lack of CO_2 responsiveness in such infants (Ariagno et al 1980); Haddad et al 1981). Diminished hypoxic ventilatory responses have also been reported in 'near-miss' SIDS cases (Hunt et al 1981).

Studies on 'near-miss' infants have revealed impairment of the arousal response to increased CO_2 and to decreased O_2 (Hunt et al 1981). In general these infants have a high CO_2 threshold and many do not waken to the hypoxic stimulus that rouses most normal infants. Gould (1982) postulates that the maintenance of homeostasis during quiet sleep presents a major challenge to the developing infant. At two to three months of life infants' sleep time becomes prolonged and the quiet state predominates. He suggests that in SIDS

victims' ineffective arousal mechanisms compound minor defects in homeostasis and may lead to respiratory depression and death.

Several studies have been conducted on parents of SIDS victims and on parents of 'high-risk' infants to determine whether genetic factors contribute to vulnerability in these infants. These have given conflicting results, some showing diminished responsiveness to chemical stimuli, Berman et al (1981), Schiffman et al (1982) and others a normal response (Zwillich et al 1980; Kanarek et al 1981). Apart from methodological differences in assessing CO_2 responsiveness in these states, the problem is aggravated by the wide range of responsiveness that is observed in apparently normal individuals. The study of Shiffmann et al (1982) was arguably the most satisfactory methodologically, but yielded the least expected result: clear separation of 'at-risk' and control groups of parents.

2.5 Conclusions

This review of the background to the studies undertaken has concentrated on epidemiological 'risk' factors for SIDS, the maturation of control mechanisms concerned with sleep and respiration, and the evidence suggesting that the relatively precarious respiratory control of the young infant might become de-stabilised during sleep, with fatal consequences. It is not possible to judge whether SIDS victims are vulnerable from

an early stage in development as a result of genetic, pre-natal or perinatal factors acting alone or together or whether all infants are potential SIDS victims given certain adverse influences - infective, social, nutritional, etc. No attempt has been made to discuss the many hypotheses advanced to explain the mechanism(s) of death or the presumed vulnerability during life of SIDS infants; throughout, the emphasis has been on the possible relation of SIDS with breathing abnormalities during sleep. The main points which emerge are sometimes factual, for example the age of peak occurrence of SIDS, and at other times uncertain, e.g. the rôle of viruses in SIDS. They may be summarised as follows. The difficulty of defining the terms 'cot death' and 'SIDS' has made assessment of the magnitude of the problem difficult. In UK the incidence of SIDS is approximately 2 per 1000 live births.

1. The majority of SIDS deaths occur between 1 and 6 months of age, with a peak incidence between 2 and 3 months. Death is most likely during the sleeping hours. Antecedent symptoms, particularly those of respiratory tract infection, are common but the evidence that they occur more frequently in SIDS victims than in carefully matched control infants is not conclusive. Many SIDS victims are apparently well during their lives, including the days immediately preceding death.

2. Clinical and pathological observations of infants dying unexpectedly provide the basis for the present-day concept

of SIDS, i.e. the death of an infant which is both unexpected and unexplained. Little light has been shed on whether SIDS is a single entity of unknown aetiology or whether it comprises several entities, perhaps of known aetiology, whose natural endpoint is sometimes unexpected and unexplained death. The association of 'minor' respiratory infection, usually viral, with a significant proportion of SIDS deaths has been confirmed pathologically.

3. The maturation of sleep patterns is incomplete at birth - a preponderance of active sleep diminishes gradually as quiet sleep is acquired. At 2-3 months of age, sleep becomes prolonged and the quiet sleep predominates. The adult pattern is achieved by 6 months. It has been postulated that the maintenance of homeostasis by reflex mechanisms during quiet sleep represents a major challenge for the developing infant.

4. Similarly the stability of respiratory control is not fully developed at birth; it seems likely that full stability is not achieved for days or weeks afterwards. Impairment or delay in development of the central and peripheral mechanisms of control of breathing could affect stability of respiration during quiet or active stages of sleep. There is lack of agreement about the sleep stage in which vulnerability is greatest. A mis-match between sleep and respiratory control maturational processes which, presumably,

should proceed in harmony during infancy, could create conditions for respiratory instability and increase dependence on the adequacy of arousal mechanisms during the quiet phase of sleep. The latter depend on a variety of factors, including the integrity of chemoreflex mechanisms. During active sleep, protective respiratory reflexes are depressed thereby increasing vulnerability to asphyxial influences affecting either the upper or lower respiratory tract. Given the present state of knowledge, there seems no reason to suppose that SIDS victims die exclusively in one or other main sleep stage.

5. The mechanism(s) of death in SIDS are uncertain. Perhaps the balance of evidence favours asphyxia as a cause of death in most cases. Apnoea has been discussed from both clinical and pathological viewpoints. Debate on its significance is sometimes confused. Investigators have not always distinguished between apnoea as a predictor of SIDS, and apnoea as a possible mechanism of death in SIDS. There is evidence for and against the former; as a possible mechanism of death, apnoea seems no less likely than alternatives that have been suggested. It may be a mistake to conclude that because certain groups of infants with demonstrable apnoea do not succumb to SIDS, that apnoea is not a mechanism of death in SIDS. The significance of periodic breathing and its possible relation to SIDS is not known. Clinical studies of infants at 'increased' risk, and pathological studies of tissues from SIDS cases neither confirm nor refute the suggestion

that recurrent or chronic hypoxaemia severe enough to cause hypoxic 'tissue damage' is present during life.

6. 'Near-miss' for SIDS and siblings of previous SIDS cases are considered to be at 'increased' risk. The terminological difficulties surrounding 'cot death' and SIDS are paralleled in discussions of 'near-miss' infants. There is no agreed definition of the term 'near-miss' for SIDS and some of the narrow definitions that have been applied have not necessarily been conducive to increased understanding. Predictably, computation of 'risk' for this group of infants has presented difficulties. It is widely agreed that siblings of SIDS are at slightly increased risk, as are preterm infants and infants of mothers addicted to narcotics.

Almost every aspect of breathing has been studied in infants thought to be at increased risk for SIDS - breathing patterns, respiratory responses to varying concentrations of inspired carbon dioxide and oxygen, upper airway and lung reflexes, mechanical properties of the lungs, and efficacy of gas exchange. In many of the areas investigated, the results have been controversial. An outline of these studies has been presented; many were reported during the course of the investigation which is the subject of this thesis.

The current level of understanding of 'Sudden Infant Death' might well be summarised by the following:

Euthydemus: 'Then tell me, do you know anything?'

Socrates: 'Yes, I know many things but not anything of much importance.'

CHAPTER 3

AIMS

CHAPTER 3

AIMS

3.1 Problems triggering research

Despite awareness of the importance of SIDS as a cause of post-perinatal death, paediatricians have not until recently been concerned with the practical aspects of management of problems associated with it. To some extent this is not surprising as SIDS does not impinge greatly on routine clinical practice. The unexpected and inexplicable death of an infant either in or soon after discharge from hospital following treatment for a relatively mild illness is uncommon in any individual paediatrician's experience. Occasionally SIDS victims are brought directly from home to the Accident and Emergency department in a District General or Children's Hospital where the principal medical role has been confirmation of the infant's death. This is then referred to the Procurator Fiscal (Coroner in England) and the paediatric pathologist.

During the years immediately preceding this study, the provision of support for parents of infants who died of SIDS had received increasing attention in UK, first by paediatric pathologists and later by paediatricians. Downham and Limerick (1978) outlined in a thoughtful and practical way the essential components of a support system for parents, and increased medical awareness of the difficulties faced

by young bereaved parents and of the practical steps which could be taken to help them. In some centres, for example Edinburgh and Sheffield, increased involvement by paediatricians complemented the efforts of pathologists who had hitherto initiated and provided support and counselling services unaided. Such developments had been greatly encouraged by the Foundation for the Study of Infant Deaths. In Edinburgh close co-operation had been established between pathologists and clinicians in the management of SIDS by 1978. This increased paediatric commitment at the time of bereavement inevitably led parents to seek paediatric advice later regarding future pregnancies and the 'risk' to later-born children. An additional role emerged for the clinician - how best to contribute to the provision of support for parents following the birth of a subsequent sibling. It was in relation to this latter problem that a pilot study on the use of apnoea monitors in the home was initiated, and later reported as the first of its kind in UK (MacKay et al 1984).

The above description provides the background to the present study which was started in 1979 and based at the Royal Hospital for Sick Children in Edinburgh. It might have been predicted that the 'apnoea' hypothesis, based on the clinical observations of Steinschneider (1972) would have provided the stimulus for other paediatricians to study breathing patterns in infants at a much earlier date.

Although apnoea has been studied extensively in the newborn period, its occurrence and importance in older infants had not been widely investigated when the present study was commenced. Paediatricians were of course aware of 'near-miss' episodes in young infants during which breathing stopped but these were uncommon and had not been the subject of specific attention. Anecdotally, many experienced paediatricians could recall the sudden death of such an infant weeks or months following such an event. The risks to these infants were highlighted by Kelly and Shannon (1978), whose report on management of 'near-miss' coincided with the start of this study.

The immediate stimulus for the present research was provided by an unexpected clinical problem. A lady gave birth to an infant approximately one year following the death of her previous baby as a result of SIDS. She refused to be discharged with her baby from the Maternity Hospital because she feared a repetition of the previous tragedy. On questioning, she gave a clear description of her previous baby's death. He had been noted to breathe irregularly at night in the days prior to death, the normal pattern of breathing being interspersed by pauses of varying duration. On the night that baby died, the mother had lain in bed listening to his breathing. There were frequent pauses. After a particularly long pause she became alarmed and observed that he had become pale and limp. Her attempt to resuscitate him was of no avail. She had been alone with her baby at the time.

She was persuaded to take her 'new' baby home but after three weeks the infant was admitted to hospital with upper respiratory tract infection and episodes of apnoea. Periodic breathing was observed during sleep, which mother described as similar to that she had observed in her previous baby. The scene was finally set for the research which is the subject of this thesis.

Relevant literature (up to the present) has been reviewed in Chapter 2. At the start of the present study, some points seemed clear - SIDS was most common in infants under six months of age, with a peak occurrence at 2 to 3 months. The increased prevalence during sleeping hours, in the colder months of the year, and in low socio-economic class families suggested that sleep and environment were important related factors. A history of previous hospital admission for minor illness, or an upper respiratory tract infection in the 2-week period prior to death were also significant. Factors which increased the risk of SIDS included - a previous cot death in the family, low birthweight, and 'near-miss' for SIDS episodes. The latter term was applied to infants found limp, cyanosed or white, apnoeic or with extremely shallow breathing, who recovered following resuscitative intervention. Extensive investigations failed to reveal an organic cause. There was also evidence that SIDS might result from abnormalities of respiration during specific sleep states. Thoman et al (1978) had shown that respiration should be evaluated not only in

relation to states of sleep but also age and sex. After the early weeks of life, abnormalities of respiration had been noted during the course of upper respiratory infection and soon after the event in 'near-miss' for SIDS cases. These included prolonged central apnoea, multiple brief respiratory pauses, excessive amounts of periodic breathing, and mixed and obstructive sleep apnoea.

The relative contribution of respiratory and cardiac abnormalities linked to the terminal event in SIDS had also been debated (Southall et al 1977). It seemed possible that a predisposition to cardiac arrhythmia might be unmasked by hypoxia during or following apnoea. It was therefore relevant to try to identify the respiratory basis for such an event.

3.2 Aims of study

Were it possible to identify infants 'destined' to die of SIDS, the following question might be pertinent: 'Do such infants have pre-existing impairment of respiratory control manifest by abnormalities of breathing patterns during sleep in the weeks prior to death?' If the answer is yes, the following subsidiary questions arise. 'Are such abnormalities present (a) when symptoms are absent?, (b) only in the presence of symptoms, and (c) are they age-dependent?

It is not presently possible to identify infants destined to die of SIDS. Scoring systems suitable for epidemiological studies are far too insensitive to be applied to individual infants. Moreover, the precise risk to infants in 'increased' risk categories is not known. However, the same questions can be posed in relation to certain other categories of infants: (a) apparently normal, symptom-free full-term infants without previous illness or hospital admission, who do not fall into known or suspected 'increased' risk groups; (b) groups of otherwise normal infants admitted to hospital with relatively minor illnesses, studied during and following recovery from these illnesses. Such infants would not otherwise be regarded as 'at increased risk'; and (c) infants of groups thought to be at 'increased' risk - siblings of SIDS, and 'near-miss' for SIDS cases.

It would be possible to make a statement about the presence, nature, and degree of abnormality detected in infants in each category, and to define the group at greatest 'risk' with respect to these abnormalities. The effects of 'minor' symptoms on breathing patterns during sleep would also be assessable. It would prove more difficult to determine whether any abnormalities observed were age-dependent unless particular attention was paid to the timing of sequential studies of infants within each group. As has been stated above, this problem was inherently difficult and not easily overcome. Moreover, the age at which infants with symptoms

or 'near-miss' episodes presented was largely fortuitous.

The aim of the present study was to investigate the above groups of infants sequentially during the early months of life in an attempt to identify 'abnormal' patterns of breathing in (a) otherwise 'normal' infants with relatively minor symptoms, and (b) infants thought to be at increased risk for SIDS. The primary aim was to detect abnormal amounts of apnoea (central and obstructive) and to observe corresponding changes in heart rate and transcutaneous oxygen tension. A secondary aim was to assess whether infants in 'increased risk' groups suffered recurrent or chronic hypoxaemia during the early months of life.

3.3 Hypothesis being tested

It has been argued that a primary or induced abnormality of cardio-respiratory control might initiate an irreversible sequence of events during sleep and result in an infant's death. A premise fundamental to the present study was that normal, full-term, healthy infants without antecedent illness and currently symptom-free would not show abnormal breathing patterns during sleep of sufficient degree to result in bradycardia, or a potentially dangerous reduction in transcutaneous oxygen tension.

It has also been argued that the maturation of sleep and respiratory control mechanisms occurs over many months and that all infants might be relatively vulnerable between

1 and 6 months. Natural stresses might impose difficulties in control manifest by abnormalities of breathing patterns during sleep. These could affect control by increasing resistance to airflow - at the nose, pharynx, larynx, bronchi, or bronchioles. Obvious examples include upper respiratory tract infection, congenital laryngeal stridor (where an infective component is absent), and acute viral bronchiolitis. These conditions might impose further stress by affecting the mechanical properties of the lungs and/or arterial blood gas tensions. Metabolic alkalosis would provide a non-respiratory 'stress' by influencing respiratory input. For that reason, infants with pyloric stenosis who vomit recurrently and invariably develop mild to moderate metabolic alkalosis were selected for study in addition to the symptom subgroups mentioned. Given that respiratory control mechanisms are potentially vulnerable, it was anticipated that these natural stresses would produce detectable abnormalities in respiratory patterns during sleep in a significant number of apparently normal infants.

It has been argued that certain groups of infants are at increased risk. Whether this risk applies evenly to all infants within a particular 'increased' risk group or applies only to a small minority is not known. If, for example, all siblings of SIDS victims are at slightly increased risk on account of impaired cardio-respiratory control mechanisms, abnormalities of breathing patterns during sleep might be detectable perhaps in the absence

of symptoms. 'Minor' symptoms could be a major stress for this group of infants. Similar arguments can be applied to the 'near-miss' for SIDS group of infants. If all such infants are at slightly increased risk, abnormalities of breathing pattern might be detectable even in the absence of symptoms. Stresses might be uniformly hazardous. If, on the other hand, only a minority of infants in the siblings or 'near-miss' groups have impairment of respiratory control, reflected by abnormal breathing patterns during sleep, in the presence or absence of symptoms, additional stresses would have potentially profound effects only in this subgroup of cases.

The 'near-miss' infant has usually suffered a profound though non-fatal acute episode. One might expect any abnormality of breathing pattern observed to persist at least until the stresses (symptoms) provoking 'collapse' had diminished with recovery from the illnesses responsible. Persistence of abnormality beyond this time could point to a pre-existing defect or, alternatively, to one induced by the 'near-miss' episode.

CHAPTER 4

Subjects - Index and control

CHAPTER 4

Subjects - Index and control

4.1 Controls

Ten infants born at term, following uncomplicated pregnancies and deliveries, served as controls. Selection was not entirely random as only mothers living within the City of Edinburgh (and easy access to hospital), and could be contacted at home by telephone, were approached and invited to include their babies in the study. Informed consent was obtained from parents following a full explanation of the study and the nature of the investigations planned. There were six males and four females of mean gestation 40 weeks (range 29.0-46.0) who were studied between 38 and 63 weeks post-conception age. Birth and neonatal histories had been normal and all were thriving and apparently healthy during the early months of life and at the time of the study. One infant developed mild stridor during the latter part of the study period. The data obtained from this infant were incomplete. An additional healthy infant of 40 weeks gestation and birthweight 3.50 kg was therefore recruited. There were thus 11 healthy control (C) infants without antecedent history of illness at the time of inclusion who were studied on 31 occasions (Table 2). The data obtained from these previously healthy infants were utilised mainly for unmatched intergroup comparisons with data from siblings and 'near-miss' groups of patients,

Table 2

Control studies and post-conception age

Number	Post-conception age (weeks)																								
	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63
1				X					X								X									
2										X											X					
3	X						X												X							
4			X						X											X						X
5 *			X						X										X							
6		X							X											X						
7			X					X											X							
8				X					X										X							
9				X					X										X							
10				X					X										X							
11 +																										X

* excluded from analysis of obstructive apnoea, gross body movements and periodic breathing.

\+ excluded from analysis of apnoea variables, respiration and heart rate.

and also matched case control comparisons with those from certain subgroups of symptomatic infants. In general, infants with symptoms were studied during and following recovery from illness, and thus served as their own controls. Infants with stridor were never completely symptom-free during the early months of life and could not be studied both during illness and following recovery. Similarly, infants with recurrent vomiting were markedly alkalotic during their index illnesses, with restoration of blood acid base status at the time of follow-up studies. Minor derangement of cerebrospinal fluid acid base balance could have persisted and influenced breathing patterns by its effect on respiratory control mechanisms. For these two subgroups of infants with symptoms (stridor and recurrent vomiting) matched case control comparisons were necessary. Paired data (illness and clinical recovery) were obtained from infants with acute bronchiolitis, upper respiratory infection, and recurrent vomiting due to pyloric stenosis.

There were difficulties in recruiting an adequate number of healthy control infants. There was thus a paucity of control data for the various index/control comparisons necessary. To overcome this problem, an additional 14 apparently normal infants who had suffered, but recovered from upper respiratory infection or bronchiolitis were selected. This group (Controls C^1) comprised 7 males and 7 females of mean gestational age 39 weeks and mean

birthweight 3.09 kg who were studied between 47 and 69 weeks post-conception age.

Data from these infants were used exclusively for certain matched case/'control' comparisons to augment those obtained from control infants without antecedent illnesses.

Throughout this thesis, the utilisation of all control data is described carefully, and the limitations of the data available acknowledged. Appendices 1 and 2 give further details of controls (C and C^1) including the post-conception ages at which studies were undertaken.

4.2 'Symptom' group

This group comprised the following subgroups - acute bronchiolitis, upper respiratory tract infection, congenital laryngeal stridor and pyloric stenosis (recurrent vomiting).

4.2.1 Acute bronchiolitis

Twenty-two infants were studied during the course of acute bronchiolitis, and 16 following clinical recovery. Table 3 gives the clinical details of the 16 infants in whom both acute and follow-up studies were completed. Six of the original 22 were withdrawn, four on account of persisting symptoms, and two for non-attendance. There were 10 males

Table 3

Clinical details of infants with bronchiolitis

Number	Sex	Birth Weight (kg)	Gestation (wks)	Post-conception Age (wks)		Day of Illness (study a)	Interval between Studies (days)	Virus Isolations
				Study (a)	Study (b)			
12	F	3.20	40	47	50	8	21	RSV
13	F	3.15	40	49	53	3	29	RSV
14	F	2.73	40	49	54	10	39	RSV
15	M	4.26	42	52	56	10	28	RSV
16	M	3.13	37	47	50	8	23	RSV
17	F	3.51	39	51	56	4	26	RSV
18	M	1.56	32	45	48	8	23	RSV
19	F	3.89	42	55	59	10	26	Adeno
20	F	3.07	39	53	58	7	29	
21	M	4.32	40	54	58	6	30	
22	M	2.01	33	51	54	8	20	
23	M	2.69	41	66	69	10	21	
24	M	2.13	37	63	66	7	23	RSV
25	M	2.95	40	67	69	10	18	
26	M	3.30	40	70	73	7	22	RSV
27	M	2.33	35	69	74	3	34	

and 6 females of mean gestational age 39 weeks (range 32-42 weeks) and mean birthweight 3.01 kg (range 1.56-4.26 kg), whose mean age was 17 weeks (range 7-34 weeks) when studied initially. The diagnosis of acute bronchiolitis was made on clinical grounds. The infants were studied breathing air which, in several cases, restricted the timing of studies to a stage of illness when oxygen therapy was no longer considered necessary. The mean duration of illness from the start of coryzal symptoms was 7 days (range 3-10 days) at first studies, and the mean interval between studies was 26 days (range 18-39 days). Respiratory syncytial virus (RSV) was isolated in 9, and adenovirus in 1 of the 16 infants. Virological studies were negative in the remaining 6.

Patients were mildly to moderately affected when studied initially; most had mild recessions and occasional inspiratory crepitations or expiratory rhonchi on auscultation of the chest. At follow-up they had recovered and were clinically normal. Appendix 3 gives additional clinical details, and timing of studies.

4.2.2 Upper respiratory tract infection

Five infants were studied during, and following recovery from upper respiratory tract infection. Four had been born at term after uncomplicated pregnancies and deliveries;

the fifth was born at 29 weeks gestation following premature rupture of the membranes. There were 4 males and 1 female of mean gestation 38 weeks (range 29- 40 weeks) and birthweight 2.63 kg (range 1.29-3.46 kg) whose mean chronological and post-conception ages were 8 weeks (range 4-15 weeks) and 46 weeks (range 44-49 weeks) respectively when initial studies were carried out. The mean interval between the illness and recovery studies was 22 days (range 13-46 days).

Initially, the infants had coryzal symptoms but were not otherwise ill. At follow-up they were healthy and thriving. Mean rectal temperature was 36.9^{o}C (range 36.4-37.5^{o}C) during infection, and 36.8^{o}C (36.5-37.2^{o}C) following recovery. There were no signs of respiratory distress on either occasion and on auscultation breath sounds were vesicular without accompaniments. Immunofluorescent studies of naso-pharyngeal secretions confirmed RSV infection in one of the five infants. Table 4 summarises these clinical details. The timing of studies is given in Appendix 4.

4.2.3 Congenital laryngeal stridor

Seven infants with a history of stridor from birth or the early weeks of life were studied at a time when they were otherwise well. Table 5 gives their clinical details. There were 4 males and 3 females of mean gestation 40 weeks

Table 4

Clinical details of infants with upper respiratory tract infections (URTI)

Number	Sex	Birth Weight (kg)	Gestation (wks)	Post-conception Age (wks)		Day of Illness (study a)	Interval between Studies (days)	Virus Isolations
				Study (a)	Study (b)			
28	M	2.81	40	44	47	5	20	-
29	F	3.09	40	45	52	5	46	-
30	M	3.46	40	48	51	2	15	RSV
31	M	2.49	40	49	51	2	13	-
32	M	1.29	29	44	47	3	20	-

Table 5

Clinical details of infants with laryngeal stridor

Number	Sex	Birth weight (kg)	Gestation (wks)	Age at onset (wks)	Age studied (wks)	
					Chronological	Post-conception
33	M	2.92	40	6	7	47
34	M	2.67	40	< 1	7	47
35	M	3.82	40	1	8	48
36	F	2.91	39	4	10	49
37	F	3.23	40	6	10	50
38	F	3.51	40	5	13	53
39	M	4.14	40	< 1	15	55

(range 39-40 weeks) and mean birthweight 3.10 kg (range 2.67-4.41 kg), whose mean chronological and post-conception ages were 10 weeks (range 7-15 weeks) and 50 weeks (range 47-55 weeks) respectively when initial studies were conducted.

In each case, the diagnosis congenital laryngeal stridor ('infantile larynx') was made on the basis of history, examination, and findings at laryngoscopy. Chest X-rays were normal and visualisation of the tracheal air column and barium filled oesophagus by lateral X-rays of the neck excluded significant tracheal or oesophageal compression. There was no clinical suspicion of cardiac or neurological abnormality but one infant had mild to moderate micrognathia. As stridor persisted during the first six months of life, no studies were undertaken following clinical recovery. Appendix 5 gives details of the timing of studies, and matched controls.

4.2.4 Pyloric stenosis (recurrent vomiting)

Five infants with a history of recurrent vomiting of 4-21 days duration were studied before and after pyloromyotomy for congenital hypertropic pyloric stenosis. They had been born following uncomplicated pregnancies and deliveries. Table 6 gives their clinical details. All were male, of mean birthweight 3.27 kg (range 2.69-3.77 kg) and mean

Table 6

Clinical details on admission of infants with recurrent vomiting

Number	Sex	Birth Weight (kg)	Gestation (wks)	Post Conception Age (weeks)		Day of illness Study (a)	Interval between studies (days)
				Study (a)	Study (b)		
40	M	2.69	36	39	41	6	14
41	M	2.72	40	43	45	1	12
42	M	3.49	40	46	50	1	25
43	M	3.66	40	46	47	1	7
44	M	3.77	40	47	48	1	5

gestation 39 weeks (range 36-40 weeks) whose mean chronological post-conception ages were 5 weeks (3-7 weeks) and 44 weeks (39-47 weeks) respectively when initial studies were carried out. The mean interval between studies was 9 days (range 5-14 days) and the mean interval between surgery and follow-up studies 7 days (range 3-11 days).

Pyloric stenosis was suspected on clinical grounds in each infant at the time of admission to hospital and confirmed by palpation of a pyloric tumour during a test feed. In each infant the degree of dehydration was judged to be less than 5 per cent of body weight and intravenous administration of fluids and electrolytes were not deemed necessary to correct fluid and electrolyte imbalance. Table 7 gives serum electrolytes and blood urea concentrations, and acid-base status in individual infants when initial studies were conducted. One, Case 40, was hypokalaemic but otherwise electrolyte and blood urea values were remarkably normal. All infants showed a moderate degree of metabolic alkalosis. At follow-up clinical recovery was apparently complete. Serum electrolyte and blood urea concentration were normal and bottle feeding had been satisfactorily resumed in each case. Appendix 6 gives details of the timing of studies, and matched controls. Case 40 is also included in the 'Near-miss' index subgroup.

Table 7

Serum electrolytes, blood urea and acid-base status in infants with recurrent vomiting

Number	Serum Electrolytes			Blood Urea	Acid Base Status			
	Na mmol/l	K mmol/l	Cl mmol/l	mmol/l	pH	PCO_2 kpa	St.HCO_3 mmol/l	Base Excess mmol/l
40	138	2.4	-	5.0	7.53	7.35	40.6	+ 21.6
41	138	3.7	94	3.3	7.49	5.87	35.0	+ 11.0
42	136	3.6	86	5.6	7.49	5.70	34.0	+ 9.5
43	139	4.3	98	4.4	7.48	5.25	29.3	+ 6.6
44	138	3.4	96	3.7	7.50	5.57	30.9	+ 8.8

4.3 Siblings of previous SIDS

Twenty-four siblings of previous SIDS victims were selected for sequential studies of respiration during sleep during the early months of life. Many such infants had been included in a pilot study of home monitoring for apnoea (Mackay et al 1984), prior to their birth. The parents of infants participating in this programme had been referred from a variety of sources - family doctors, obstetricians, and paediatric colleagues, to discuss the recurrence risk for SIDS and the availability of family support following the birth of subsequent siblings. Permission was sought from parents to include subsequent babies in the present study, irrespective of whether they wished to participate in the home monitoring programme. Parents who agreed to participate were enlisted in the present study following detailed explanation of its nature and the investigations involved.

Twenty-four infants, 13 male and 11 female, of mean gestation 39 weeks (range 35-41 weeks) and birthweight 3.47 kg (range 2.35-4.33 kg) were studied on 50 occasions between 40 and 92 weeks post-conception age. All but two were symptom-free at the time of study. Cases 63 and 66 had mild upper respiratory tract infections. Table 8 indicates the post-conception age at which studies were undertaken in individual cases. Case 45 is also included in the 'Near-miss' index subgroup.

Table 8

Siblings studies and post-conception age (weeks)

Post-conception age (weeks), 38–65:

Number	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65
45						X	X		X											X								
46							X					X																
47								X											X									
48								X															X					
49									X												X							
50									X							X												
51											X				X				X									
52													X											X				
53														X														
54				X					X										X									
55			X						X										X									
56										X										X								
57									X												X							
58				X				X																				X
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61																												
62																												
63																												
64								X																				
65																	X											
66									X			X									X							
67									X																			
68					X				X					X														

Post-conception age (weeks), 66–92:

Number	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92
45																											
46																											
47																											
48																											
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61																											X
62									X																		
63				X					X																		
64																		X									
65																											
66																											
67																											
68																											

Information on siblings who died was sought. Post-mortem examination was carried out on 23 and specific causes of death excluded. Microscopic studies of necropsy material had been carried out on 17. In each case a death certificate diagnosis was 'Sudden Infant Death Syndrome'. Appendix 7 summarises post-mortem information on the previous SIDS victims.

4.4 'Near-miss' for SIDS

Twenty-nine infants were admitted to hospital following 'near-miss' (apnoeic/cyanotic) episodes during the three-year period 1979-1981. They represented approximately 1 in 1,000 infants born in the hospital catchment area during the study period. Each had experienced one or more episodes which had occurred unexpectedly and had led parents or attendants to believe that, but for their intervention, the infant would have died. By the time of arrival in hospital, usually within two hours, apparent recovery had taken place.

There were 19 males and 10 females: 7 had had a previous hospital admission, and in four families unexpected infant death had been reported previously. There were two siblings, and two half-siblings of previous SIDS victims in the group. One of the former (Case 45) is included in the siblings

subgroup of index cases. There were 12 infants who were firstborn and 9 secondborn. Ten were being breastfed and 19 were receiving artificial feed formulae at the time of admission to hospital. Table 9 gives details of gestation and birthweight, and the post-conception age at which 'near-miss' events occurred.

The events occurred between 9 p.m. and 9 a.m. in 14 cases and during the remaining hours of the day in 15. Five occurred during or within ten minutes of completion of a feed. On 8 occasions parents were in the same room as the infant when the event occurred but had not necessarily witnessed it completely. Table 10 summarises the circumstances of 'near-miss' episodes, descriptions of the appearance of the infants, and the actions taken by parents. Pallor and/or cyanosis were reported in every case; shaking or slapping was the most common action taken by parents.

Table 11 gives antecedent symptoms for the group. Nineteen infants had symptoms (predominantly respiratory) more than 48 hours prior to the 'near-miss' event, and 25 had symptoms within 48 hours. Following admission to hospital, each infant was fully investigated. The results of these investigations are presented in the Results section. Sequential polygraphic sleep studies were performed on each infant during the ensuing weeks. Tables 12 and 13 give the timing of studies

Table 9

Birth Weight, Gestation and Post-Conception Age at Time of 'Near-Miss' for SIDS Episode
n=29

Birth Weight (g)	(n)	Gestation (wks)	(n)	Post-Conception Age (wks)	(n)
1500	1	20-31	1	36-40	4
1501 - 2000	1	32-36	4	41-44	8
2001 - 2500	2	37-39	8	45-48	7
2501 - 3000	5	40-	16	49-52	3
3001 - 3500	9			53-56	3
3501 - 4000	9			57-60	2
4001 -	2			61-64	1
				65-	1

Table 10

Circumstances of 'Near-Miss' for SIDS Episodes

Season	(n)	Place	(n)	Appearance	(n)	Action	(n)
Jan-Mar	12	Home	23	Colour-pallor and/or cyanosis	29	Shaking and/or slapping	22
				Breathing-absent	17	Mouth-to-mouth breathing	3
Apr-June	6	Car	2	Shallow, gasping	4	External cardiac massage	2
				Uncertain	8	'Spontaneous' recovery	2
July-Sept	8	Pram	1	Muscle-tone limp	23		
				Stiff	2		
Oct-Dec	3	Hospital	3	Uncertain	4		

Table 11

Antecedent Symptoms (n = 29)

>48 hrs	(n)	<48 hrs	(n)
Noisy breathing	13	URTI	9
Cyanotic episodes	9	Cough	9
'Apnoea'	7	'Snuffles'	7
Choking	3	Unusual breathing	6
		Off feeds	4
Other	5	Irritability	4

Table 12 'Near-miss' full-term studies and post-conception age (weeks)

Number	Post-conception age (weeks)																																										
	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78
69																		X								X																
70									X							X																										
71																																				X						
72																X	X																									
45						X	X		X											X																					
73											X								X																						
74					X			X										X																								
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85																							X														X			
86																					X					X														X	
87							X					X											X																		
88							X													X																					
89		X					X										X																								
90																X																									
91											X	X										X																			

Table 13

'Near-miss premature' studies and post-conception age

Number	Post conception age (weeks)																							
	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61
40		X		X																				X
92	X X	X		X									X				X							
93									X		X										X			
94								X					X											
95	X X X					X							X											

in full-term and pre-term infants respectively. Appendices 9 and 10 give further details of timing and of case controls selected for matched comparisons, in full-term and pre-term 'near-miss' cases respectively.

4.5 Summary

Table 14 gives the composition of the index and control groups, the number of infants in each, and the studies undertaken. The total number of infants and studies carried out in each group has been 'corrected' to take account of the following (i) the 14 control (C^1) infants were selected from the 'symptoms' group of infants, following clinical recovery, (ii) only 16 infants in the bronchiolitis group had paired (illness and recovery) data, and (iii) two infants have been included in more than one group - one infant with pyloric stenosis (Case 40) and one sibling of SIDS (Case 45) are included in the 'near-miss' for SIDS subgroup. Two hundred and seven studies on 97 infants will be reported in this thesis. Figure 10 gives the post-conception age range for each group at which these studies were undertaken.

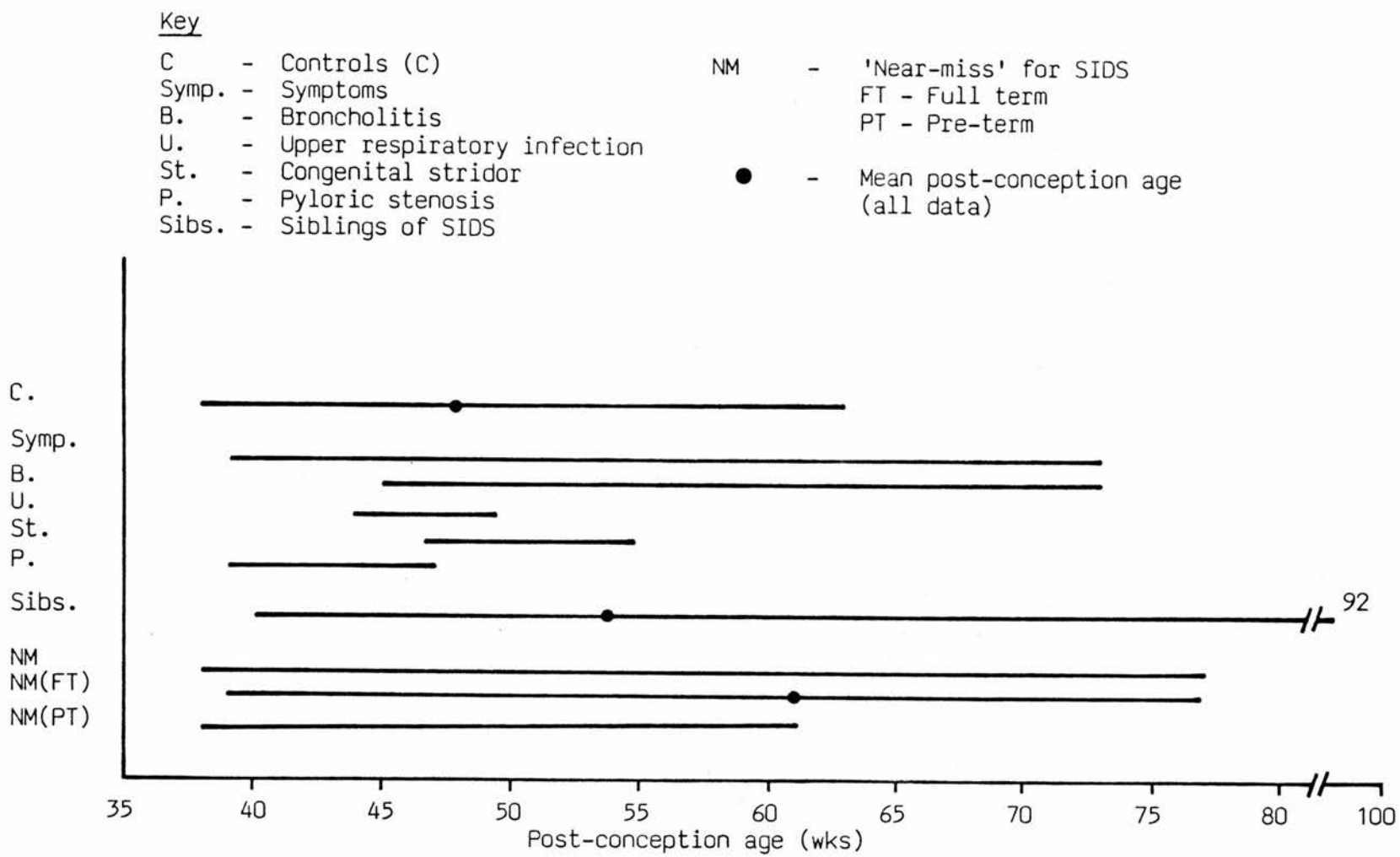
Table 14

Polygraphic Sleep Studies

Group	Infants (n)	Studies (n)
Control (C)	11	31
Control (C^1)*	14	14
Symptoms	39	69
Bronchiolitis+	22	38
Upper resp inf	5	10
Cong stridor	7	7
Pyloric stenosis	5	10
Siblings	24	50
'Near-miss' for SIDS	29	73
Full-term°	24	54
Pre-term ø	5	19
Totals	117	233
Corrected total	97	207

* Controls (C^1) included 12 infants from 'Symptoms' group - post-recovery data only
+ Paired (illness and recovery) data reported in 16 infants
o Includes one infant (Case 45) in siblings group
ø Includes one infant (Case 40) in pyloric stenosis group

Figure 10. Post-conception age range at time of sleep polygraphic studies - by graph



CHAPTER 5

METHODS

CHAPTER 5

METHODS

5.1 Plan of investigation - organisation

It was planned to study index and control subjects between the first and sixth months of life. Studies of controls and siblings were undertaken in infants who were symptom-free, with the exception of 2 siblings who were also studied during the course of upper respiratory infection. Infants in the 'symptom' subgroup of index cases were studied during and following recovery from illness with the exception of infants with stridor, all of whom remained stridulous during the period of investigation. 'Near-miss' infants were studied within 48 hours of the 'near-miss' episode and again following recovery from symptoms or illnesses coinciding with 'near-miss' events.

The study commenced with the'symptom' groups of patients. Siblings of SIDS cases were studied initially soon after birth (approximately 10 per year), and 'near-miss' cases as soon as possible after the event (approximately 10 per year). Sequential data were obtained during the subsequent weeks (symptoms cases) or months ('increased' risk groups). Control infants were the last to be studied. The research group consisted of a consultant (Dr HS), a research fellow (Dr FS) and, when available, a member of the home visiting nurse team based at the Royal Hospital for Sick Children. Later

a second research fellow (Dr UMF) and a research nurse were employed who contributed to the organisation and conduct of the study during its third year. Sleep polygraphic studies were carried out by Dr FS with the exception of studies of control (C) infants which were conducted by Dr UMF. To ensure consistency Dr FS scored sleep stages independently in this latter group. The studies were completed within a 3-year period starting in 1979.

The selection of control and index subjects has been discussed briefly in Chapter 4. The parents of normal, healthy, control children were approached on the second or third day after birth by one person (Dr UMF) and permission was sought to include these infants in the study. To ensure maximum co-operation and minimal parental inconvenience, only parents who were eager to become involved in the research after a preliminary explanation of its purpose and nature, and who lived within the City of Edinburgh (in close proximity to the Royal Hospital for Sick Children) and could be easily contacted by telephone, were enlisted. Infants in the 'symptom' groups were selected during admission to hospital, with the symptoms of the illnesses described. Parents were approached by either HS or FS and following discussion of the research and its practical implications, they were invited to participate in the study. None refused to allow their children to be included, but two infants in the bronchiolitis subgroup did not attend for follow-up studies in the weeks following discharge

from hospital. Selection of index cases was not restricted to families living within the City of Edinburgh or those having a telephone in the home. Following initial studies in hospital, the timing of follow-up investigations was arranged either at the time of discharge from hospital, or subsequently by letter. Parents were given the telephone number of a hospital secretary (DT) who referred queries concerning further appointments and arrangements for follow-up studies to HS or FS. Family doctors and health visitors were kept fully informed.

Parents of siblings of SIDS were referred from a variety of sources and were seen initially by one person (HS) either in their homes or in hospital. Family doctors, obstetricians, paediatric colleagues, pathologists or parent groups referred these parents, usually prior to the birth of subsequent siblings. At interview the following points were noted or discussed: (i) history of previous SIDS. Confirmation was sought later by contacting the paediatric pathologist involved; (ii) the expected date of delivery of the subsequent sibling, place of confinement, and the consultant obstetrician in charge; (iii) risks of recurrence of SIDS - emphasising that these were slight; (iv) the support available following the birth of a subsequent sibling, including the possible place of home monitors to detect central apnoea; (v) confirmation of whether the family could be contacted by telephone; (vi) the name and address of the family general practitioner

was obtained where this was not already known; (vii) the proposed study was mentioned and discussed at the same time or at a subsequent interview. Parents who agreed to participate were included whether or not they wished home monitoring for their babies. All parents approached agreed to participate in the study.

The action taken following interviews with parents included (i) sending a letter to the referring agency; (ii) noting the names of those who wished apnoea monitors; (iii) contacting the general practitioner by letter (whether or not he/she was the original source of referral)summarising the main points of discussion; (iv) informing Dr FS and, during the final year of the study, the research nurse, who visited the subsequent siblings in their homes on a regular basis; (v) the opening of hospital case records for each infant at the Royal Hospital for Sick Children in Edinburgh.

The action taken upon the birth of a subsequent sibling was as follows: (i) parents (usually father) notified Dr HS, who informed other members of the research group; (ii) mother and baby were visited in hospital by HS or the research nurse. For families requesting apnoea monitors, these were issued and detailed written instructions on their use given to parents; (iii) arrangements were made for follow-up home visits and sleep polygraphic studies in hospital; (iv) family doctors were contacted at the time of discharge from hospital.

Subsequent contacts with families included in the study were (i) home visits, initially by a health service nurse and later by a research nursing sister, at first weekly and later every three to four weeks; (ii) telephone calls by parents - often for advice on minor health matters or for reassurance in relation to monitor alarms; (iii) hospital visits - these were planned for sleep polygraphic studies, and at the end of the study period for developmental assessment; (iv) admissions to hospital - parents were offered immediate access to hospital staff for advice and, if necessary, admission. When brief admissions did occur, they were related mainly to parental anxiety, minor intercurrent illnesses, or 'near-miss' events.

At each hospital visit, parents were seen by a doctor (FS or HS) to discuss their baby's clinical progress and, when relevant, the results of sleep polygraphic studies.

These general organisational guidelines applied also to infants experiencing 'near-miss' events. At the time of initial admission to hospital, a detailed description of events leading up to and including presentation, the action taken by parents and the infant's response were obtained. The history also contained detailed information about the pregnancy, birth, and neonatal period, feeding, development, immunisation, and family and social background. The following information was recorded: (i) the date, day of week, and

time (24-hour clock) of the 'near-miss' event; (ii) the date and time when baby was last seen apparently well (asleep or awake); (iii) an account of the event with a description of the state of the infant, the intervention undertaken, and the response to this intervention; (iv) parental action apart from intervention, e.g. family doctor call, 999 call, etc; (v) the date and time of arrival in hospital, and the interval between the event and arrival in hospital. In addition, the examination included (vi) a report of any medical examination, e.g. by the family doctor prior to hospitalisation; and (vii) a full clinical examination on arrival in hospital. Particular attention was paid to the infant's appearance, evidence of possible trauma, growth parameters, neurological findings, and developmental status. The investigations shown on Appendix 11 were carried out. These were designed to exclude known causes of sudden collapse in infancy - convulsions, injury, sepsis, cardiac arrythmia, poisoning, aspiration, cardiorespiratory disease, metabolic abnormalities, etc. Many were readily excluded following clinical examination and appropriate investigation. Concurrently, abnormalities of physiological control were sought, including 24-hour recordings of ECG and the exclusion of reflex apnoea (e.g. that associated with gastro-oesophageal reflux). In addition, sleep recordings, the subject of this thesis, were carried out.

Following initial investigations, parents were interviewed

before their infants were discharged. The results of investigations were discussed fully and their questions were answered as far as possible. The nature, duration and practical aspects of any treatment prescribed, such as thickening of feeds in infants found to have gastro-oesophageal reflux, were also discussed. Home monitors were issued to a small number of infants in the 'near-miss' group, usually on account of prolonged central apnoea detected clinically or on sleep polygraphic recordings, or to reduce parental anxiety when reassurance alone was ineffective. At the time of discharge the organisational measures described for the follow-up siblings were also applied to this group of infants.

Summary

The conduct of the study necessitated considerable organisation. The research undertaken arose as a natural extension of a service which had been developed to provide support for parents (siblings of SIDS group) and to investigate infants presenting as 'near-miss' for SIDS. Medical and nursing personnel in both hospital and the community, contributed to both the service and research aspects of the investigation outlined. Dr FS was concerned in each area of activity in addition to his main task of conducting the sleep polygraphic studies and analysing the results. The proposed study was approved by the paediatric ethical committee of the Area Health Authority.

5.2 Monitoring Procedures

Studies were carried out after the last evening feed, usually between 11 p.m. and 4 a.m. All infants were monitored under similar conditions in a dimly-lit side room off a main medical ward especially equipped for sleep studies. The subjects were either in-patients during the course of illness, or out-patients whose admissions to hospital for sleep studies had been planned. The latter were admitted between 2 and 6 p.m. in the afternoon, and remained overnight. Mothers were encouraged to remain, especially when they were breast-feeding, and were accommodated in hospital. The baby's usual feeding schedule was followed. With mother's help, the home environment and routine were mimicked as closely as possible. The mean ambient temperature of the sleep laboratory was maintained at approximately 23^{o}C (range 22-24^{o}C). Chest and abdominal electrodes were placed in position before the last evening feed with mother or a nurse in attendance. Electrodes to record eye movements, sub-mental muscle activity, and brain electrical activity were placed when the infant was asleep. Thermocouples to monitor airflow at the nose and mouth and an electrode to measure transcutaneous oxygen tension were applied carefully during periods of quiet sleep to minimise the likelihood of disturbance. Each baby was placed, lightly clothed and unrestrained, in his/her usual sleeping position. Observations were made throughout studies and body movements or interventions were recorded on polygraphic paper.

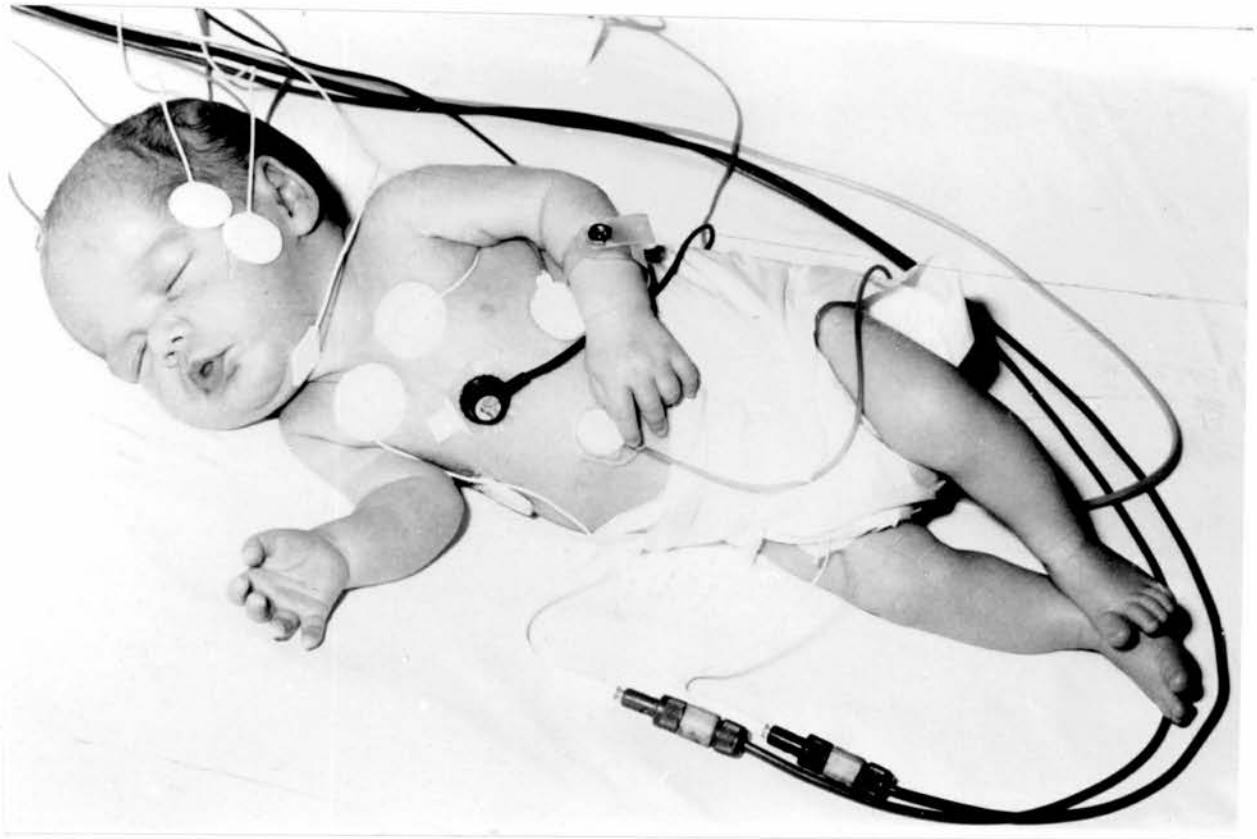
During admission to hospital, the history was obtained from the time when baby had been seen last. A routine physical examination was carried out before each recording session. Figure 11 shows an infant prepared for polygraphic studies; all the electrodes have been placed except for nasal and mouth thermocouples.

The sleep variables recorded included rapid eye movements (electro-oculogram EOG), sub-mental muscle activity (electromyogram EMG) and brain electrical activity (EEG). Cardiorespiratory variables included electrocardiogram (left shoulder-right shoulder) with a ground electrode placed on the right leg, chest and abdominal excursions, recorded by magnetometers and nasal airflow recorded independently by thermocouples placed on the upper lip. Transcutaneous oxygen tension ($PtcO_2$) was monitored by an electrode placed on the chest.

These variables were recorded on an 8-channel Mingograf 81 recorder (Elema Schonander) which incorporates a time marker channel, and was usually set to run at 10 mm per second. Four channels were dedicated to record data necessary for determining sleep state (EEG, EMG, 2EOG). The remaining 4 channels recorded cardiorespiratory variables (ECG, nasal airflow, chest and abdominal movements). Transcutaneous oxygen tension was recorded on a separate recorder;

Figure 11

Infant prepared for polygraphic studies



All electrodes placed except for nasal and mouth thermocouples

simultaneous recordings were made occasionally on the Mingograf record, an extra channel being made availabale by omitting either the chest or abdominal respiration recording. Permanent records were thus available for detailed analysis.

5.3 Apparatus

Electro-oculogram (EOG) was recorded by disposable self-adhesive electrocardiogram electrodes C-50-S, Medicotest, Denmark. A difference in electrical potential exists between the anterior and posterior parts of the eye, and the polarity of this electrical field relative to fixed recording electrodes changes as the eye moves: recordings of these potential changes constitute the EOG. Two pairs of electrodes were placed beside the outer canthuses of each eye (Figure 12) and eye movements were recorded from each diagonal pair. A minimum gain of 10 mm for 100uV was used. Figures 13-15 show respectively isolated eye movements, a burst of eye movements, and interference associated with brain electrical activity.

Electromyogram (EMG) was recorded by the same type of electrode as was used to detect eye movements (C-50-S , Medicotest, Denmark). The two electrodes were attached symmetrically beneath the chin on the area overlying the digastric muscle (Figure 16). A minimum gain of 5.0 mm for μV was used. Figures 8 and 9 show typical tracings for active

Figure 12

Placement of electro-oculogram (EOG) electrodes

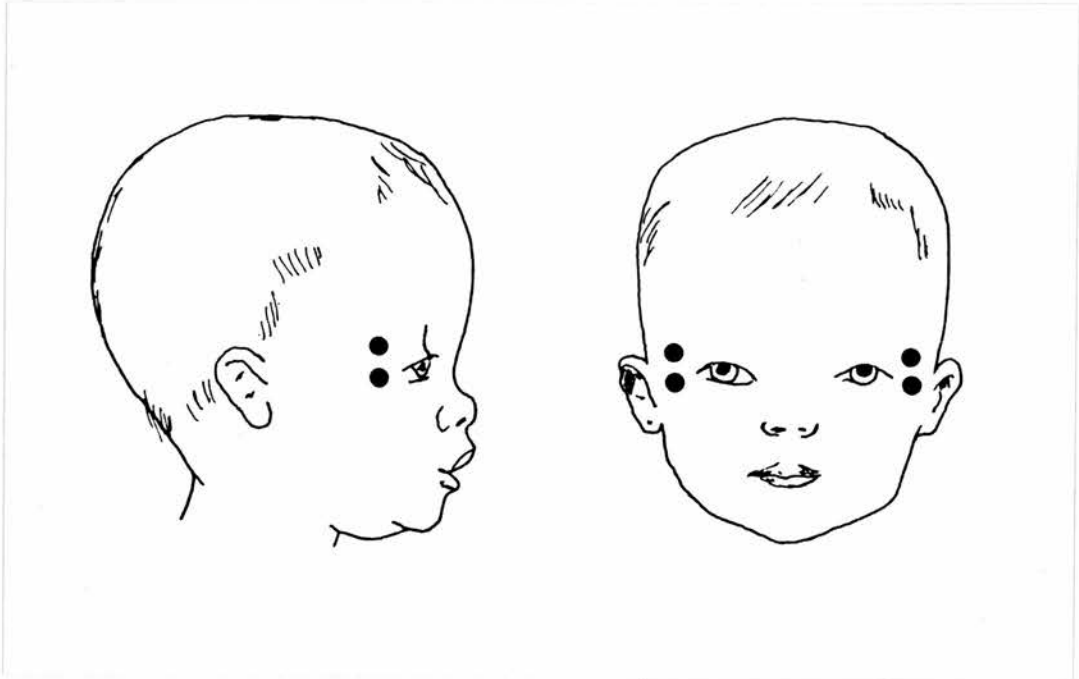


Figure 13

Isolated eye movements

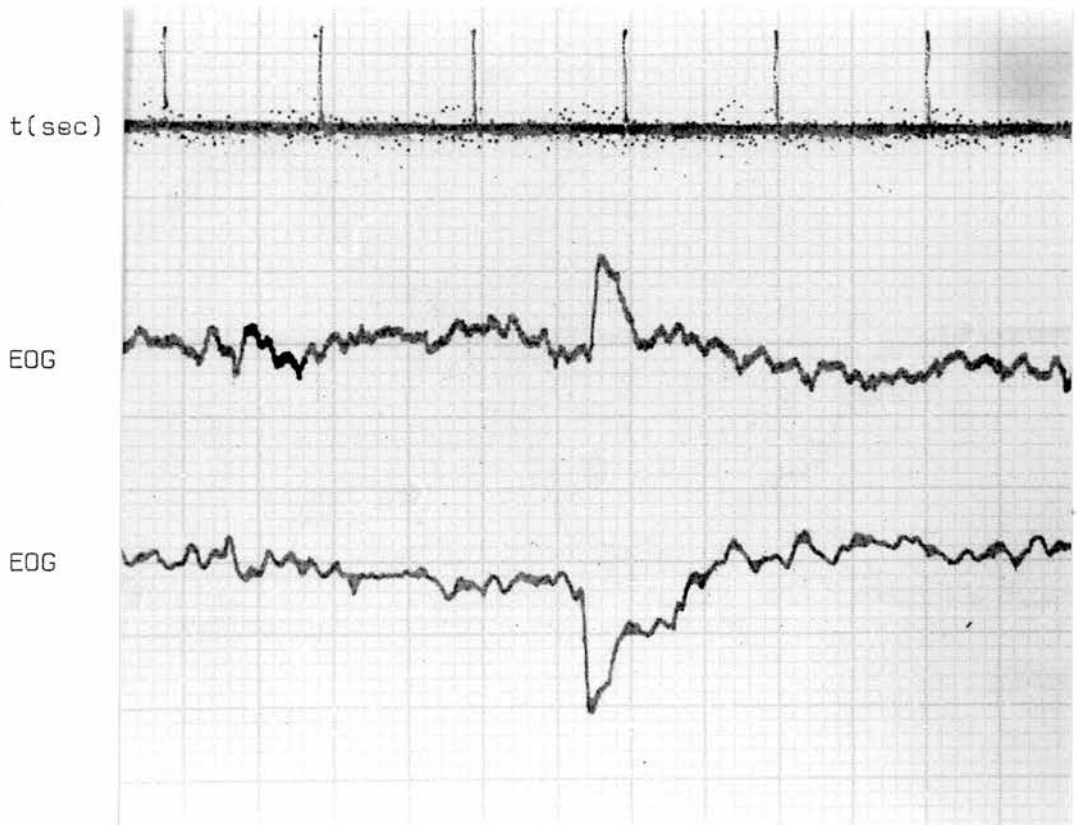
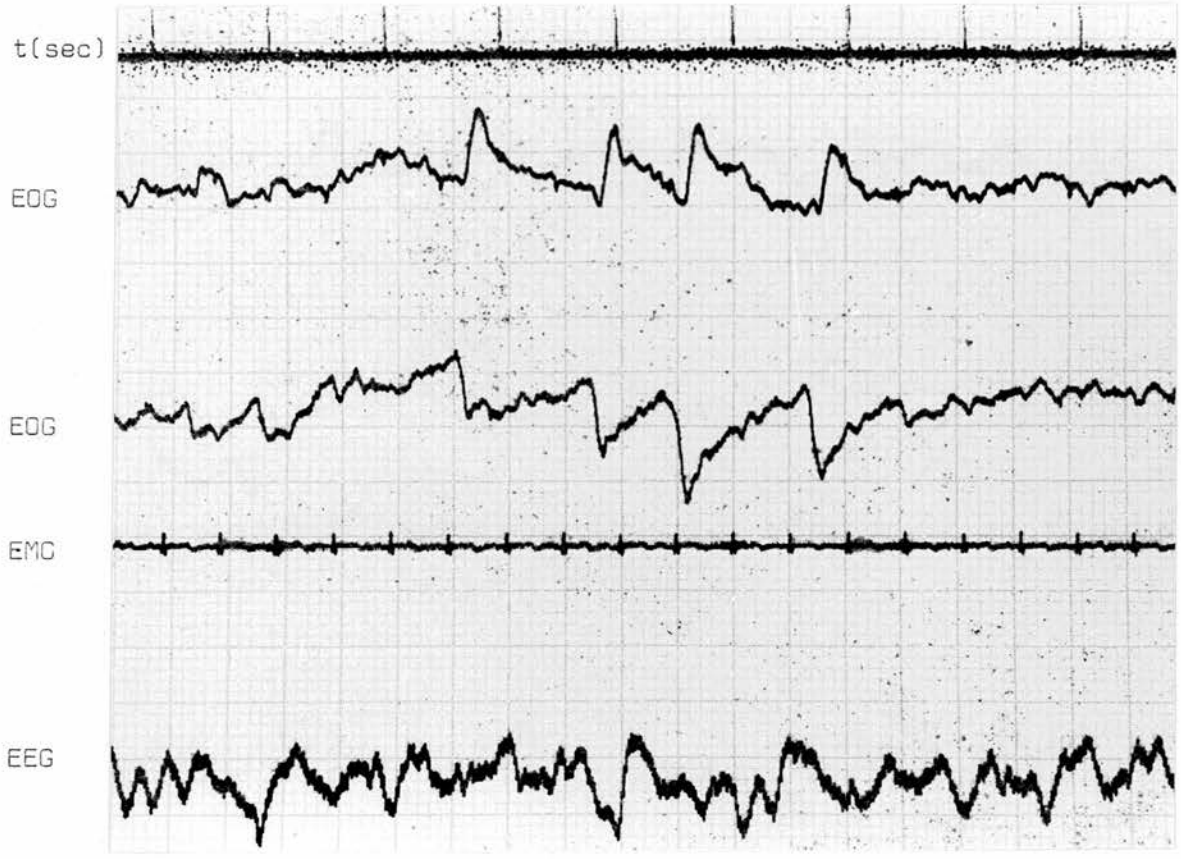


Figure 14

Burst of eye movements



(EMG is showing cardiac artifact - see Figure 17)

Figure 15

Interference on EOG channels due to brain electrical activity

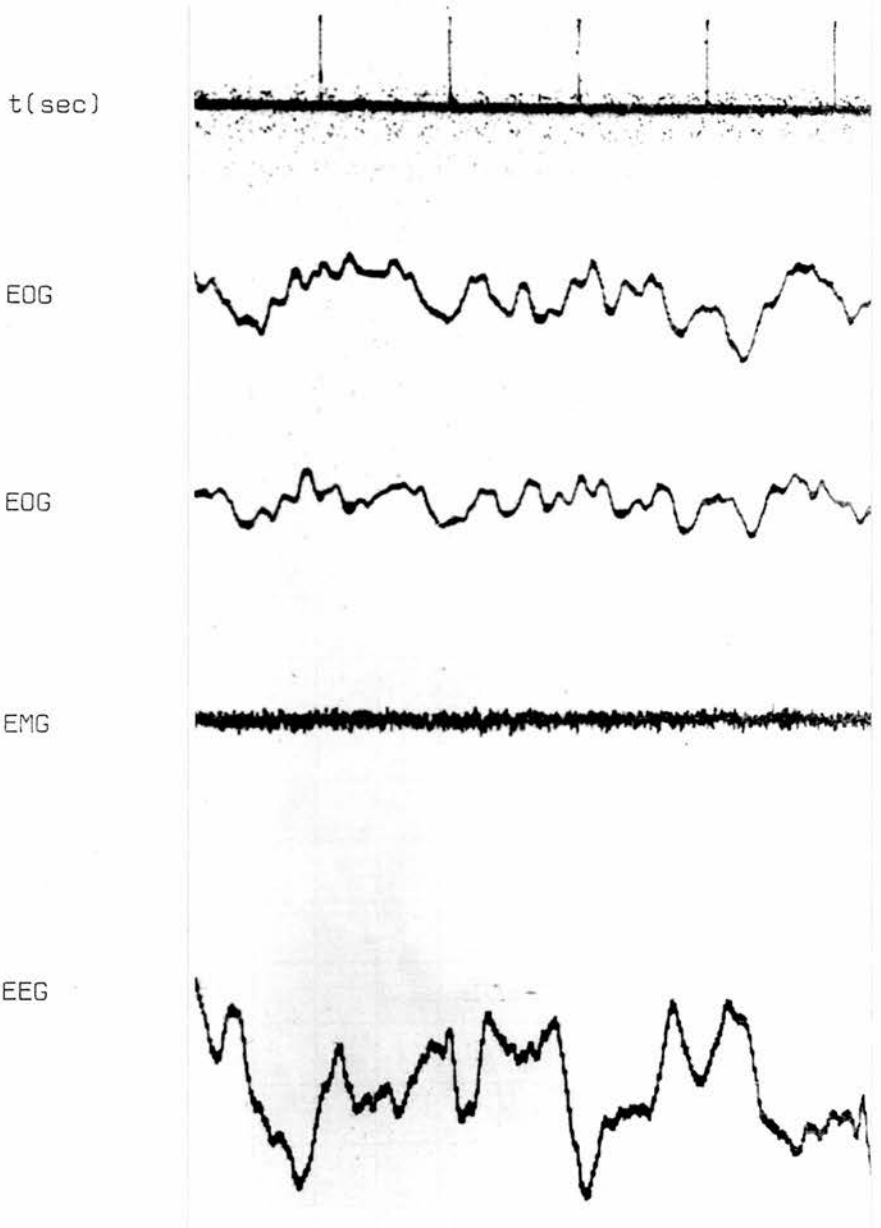
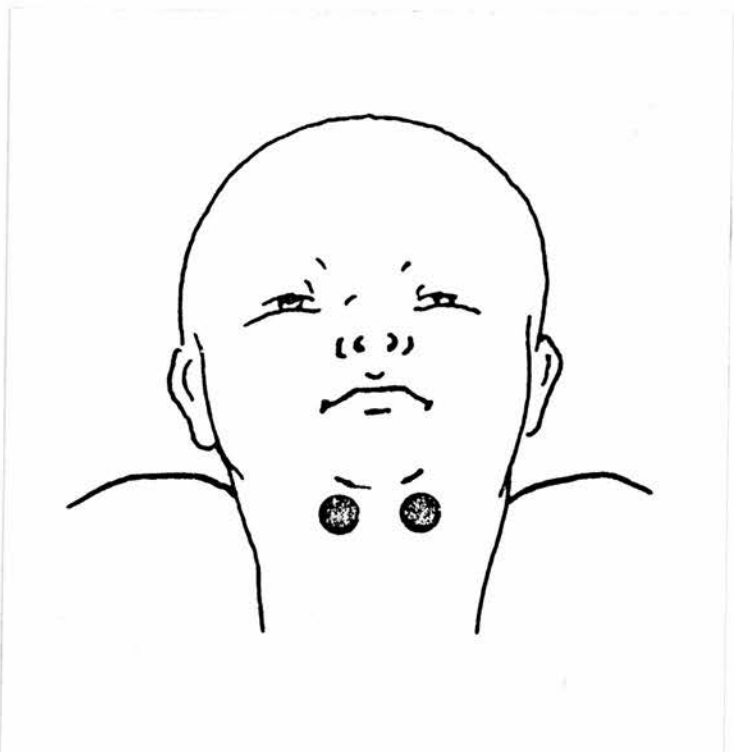


Figure 16

Placement of electromyogram (EMG) electrodes



and quiet sleep stages - the amplitude of the signal is directly proportional to the degree of muscle tone. Figure 17 demonstrates the presence of cardiac artifacts, sometimes seen in the EMG tracing. Bursts of muscle activity associated with body movements are also indicated by EMG recordings (Figure 18).

The electro-encephalogram (EEG) was recorded from 2 channels (B1/9 Silver/Silver Chloride, Specialised Laboratory Equipment, Croydon, England) placed sagitally in the frontal and parietal regions (Fz-Pz).

The electrocardiogram was recorded from electrodes (E1001 ECG Roche Electrodes, Bio Electronics) placed on the left and right sides of the chest anteriorly and on the right leg.

Respiratory movements were recorded using the Cambridge Respiration Monitor (Cambridge Medical Instruments, Ltd., Cambridge) which monitors breathing by means of magnetometers which detect respiratory movements of the thoracic cage or abdominal wall. The magnetometers consist of plastic encapsulated copper wire coils placed either on the chest or abdomen (Figure 19). One coil is energised by an alternating electric current. This creates an electro-magnetic field which induces a voltage in the other coil dependant on the distance between them. The signal varies as the 2 coils move together or apart as the result of

Figure 17

Electromyogram (EMG) showing cardiac artifact

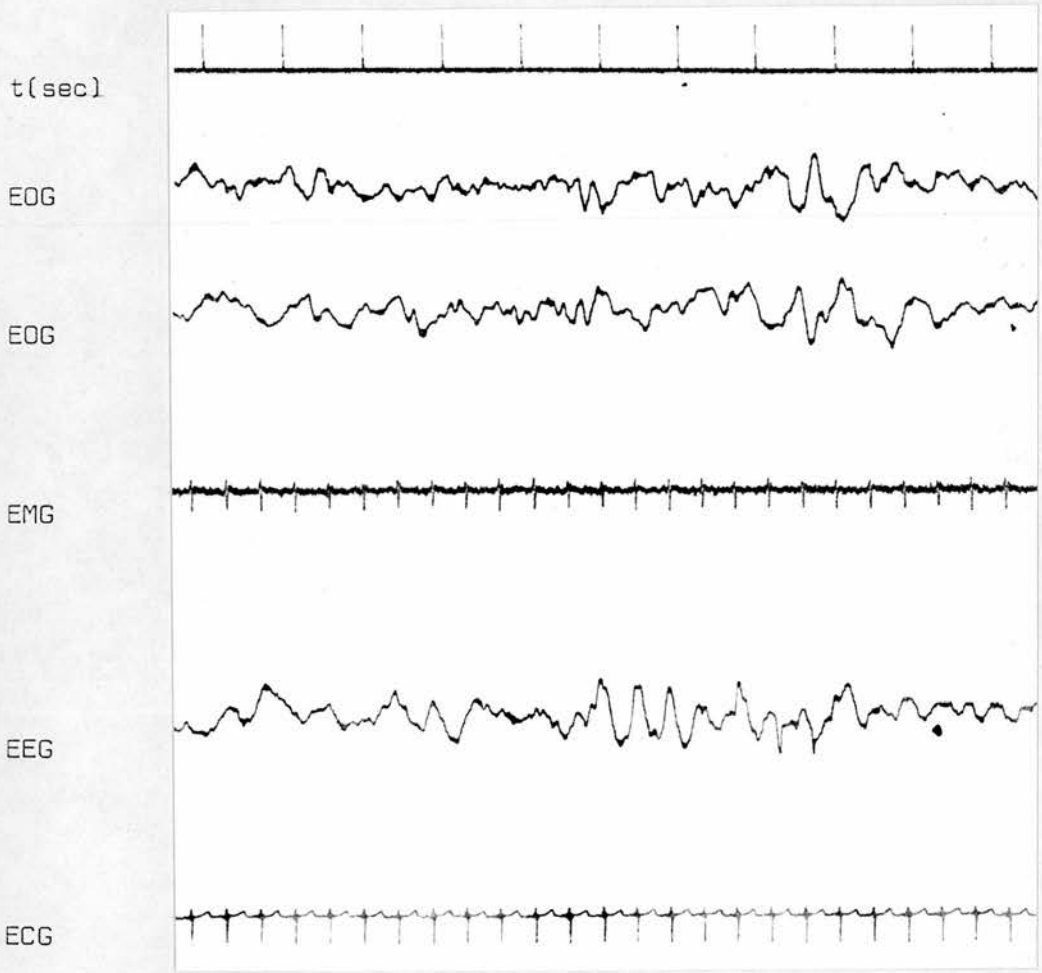


Figure 18

Burst of muscle activity associated with body movements best indicated by EMG recordings

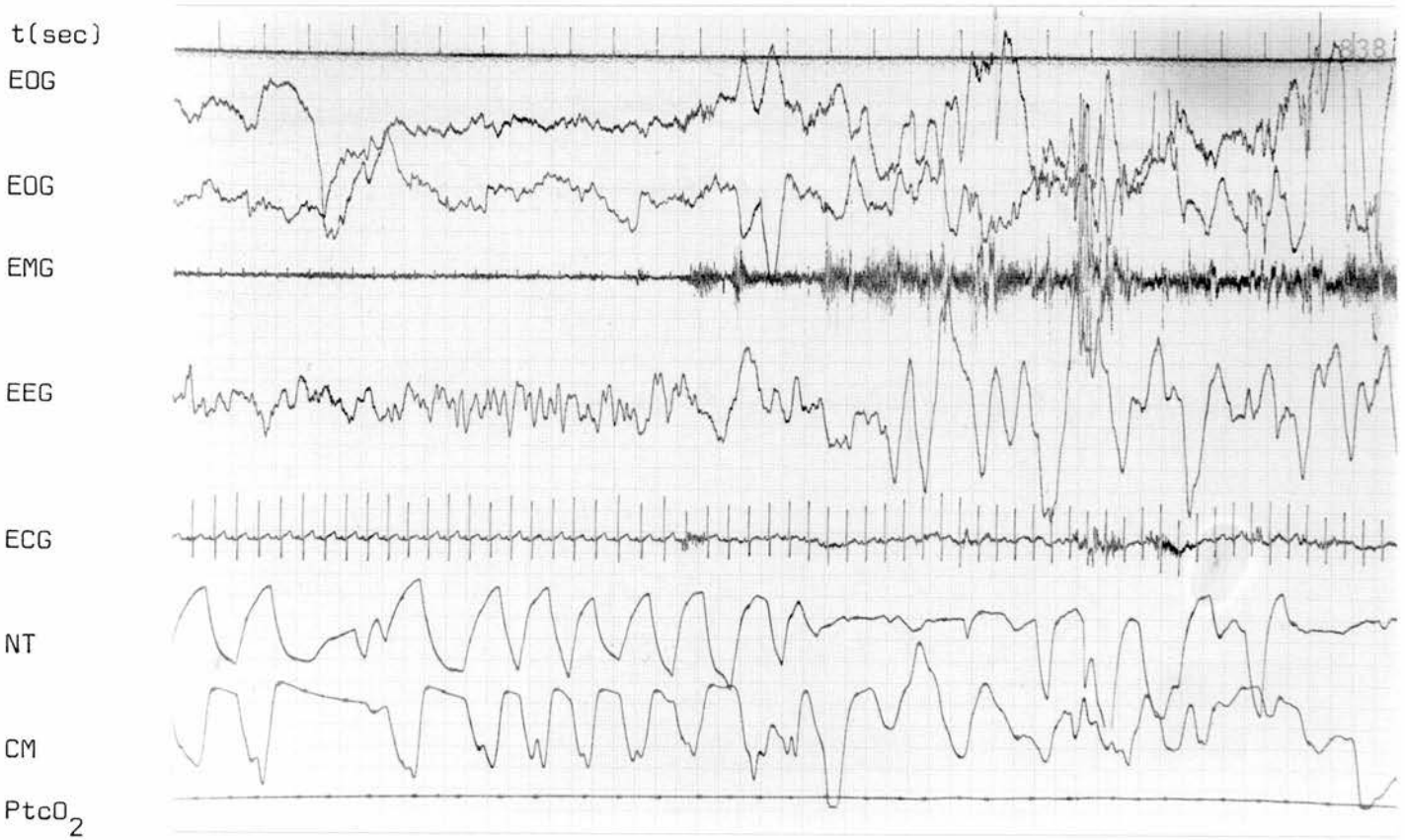
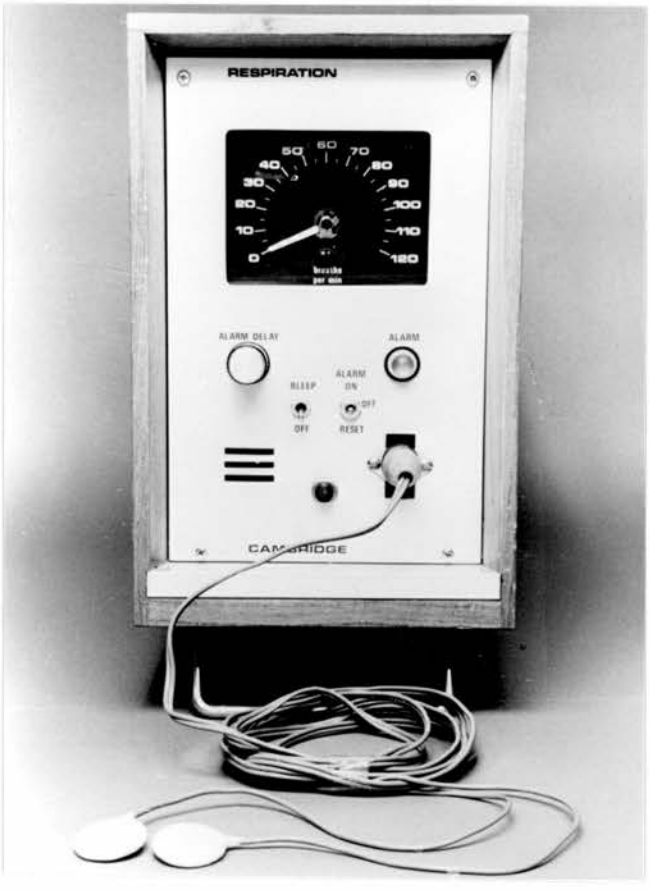


Figure 19

Respiration monitor and magnetometer



respiratory movements. Following amplification, the signal from the 'receiver' coil is rectified, smoothed, and recorded graphically as an indicator of respiration. The magnetometer coils do not make electrical contact with the patient; skin preparation or the application of electrode cream or jelly is not required. The sensors were attached using micropore tape to areas where breathing seemed to produce maximal relative sensor movement. They were placed either symmetrically at the mid-clavicular lines, at the costal margins, or anteriorly and posteriorly at a level midway between the xiphisternum and umbilicus (Figures 20 and 21). This last postiion invariably gave a good signal and was always used when the infant slept in the prone position. Care was taken to tape both sensors not further than 10 cm apart, as recommended by the manufacturers. Occasionally the respiration tracing from the thoracic cage was unsatisfactory. This could occur in active sleep when, due to loss of muscle tone in the intercostal muscles, thoracic movements were markedly diminished or virtually absent whilst abdominal movements and airflow at the nostrils and mouth continued. This is shown in Figure 22 which records chest movements and nasal airflow during sleep. Similarly there were occasions when abdominal movments were scarcely discernible even when chest movements were apparent. For the vast majority of recordings, both chest and abdominal movements were recorded simultaneously. Their presence proved a satisfactory indicator

Figure 20

Magnetometer placement on chest

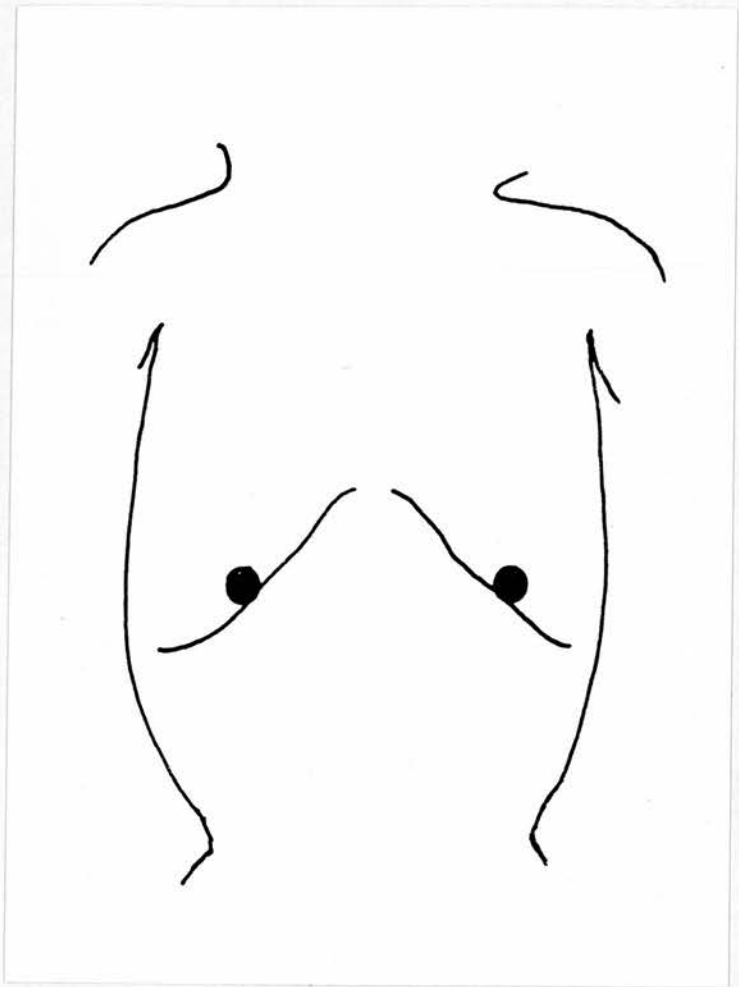


Figure 21

Magnetometer placement on abdomen

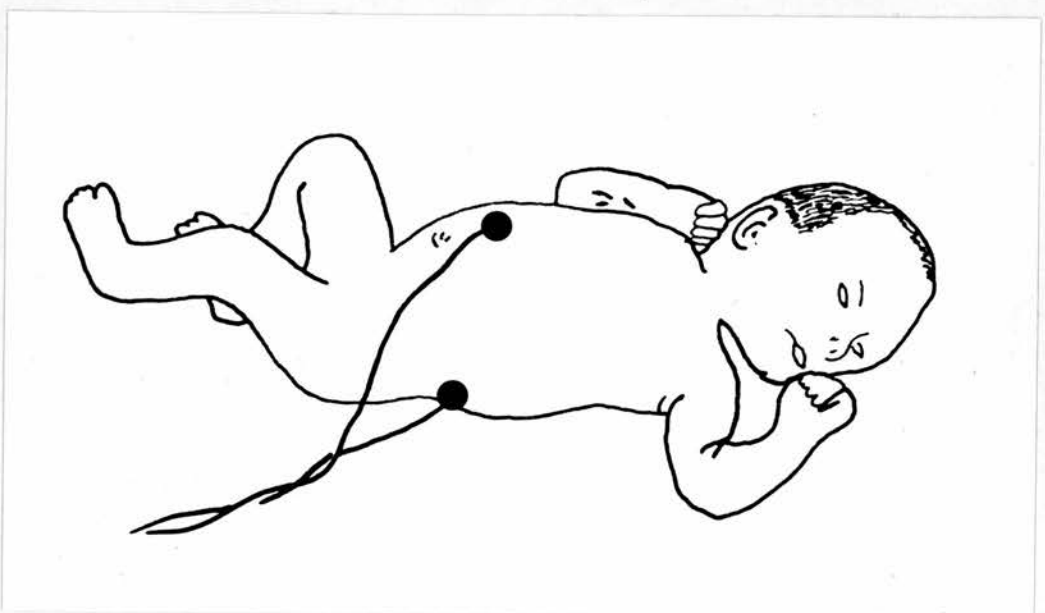
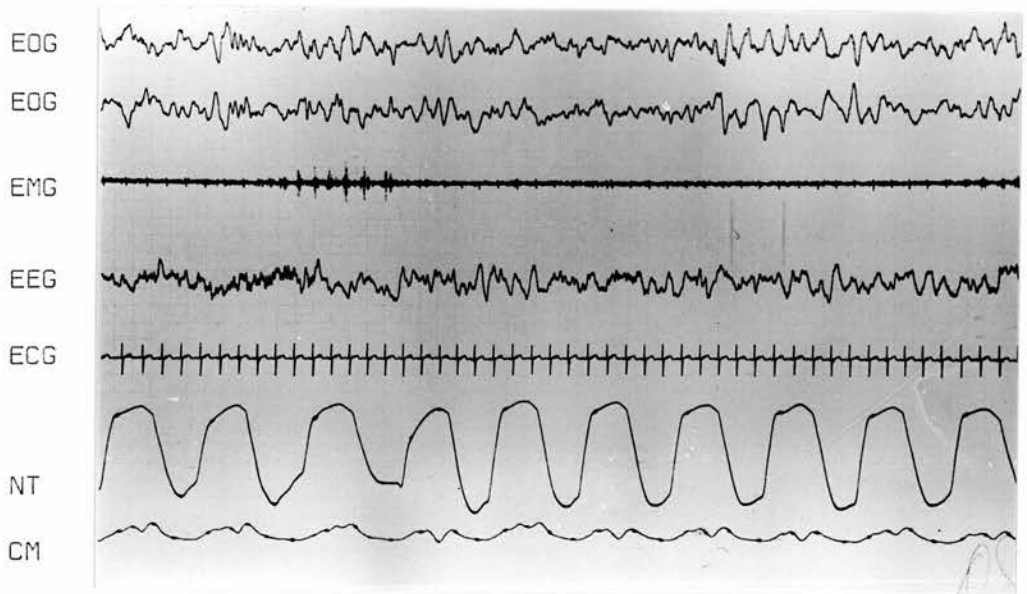


Figure 22

'Flat' thoracic respiration signal (CM) in presence of nasal airflow (NT)



of respiration in more than 200 polygraphic sleep studies in which simultaneous recordings of airflow were also available. When airflow was present, the airflow respiratory pattern was always closely mirrored by one or other magnetometer recording, and usually both.

Airflow was measured at the mouth and each nostril using three thermocouples which were joined together in a summing junction; their signals could be expressed individually or as a resultant sum. The principle underlying their use is based on the Seebeck effect, whereby thermal energy is converted into electrical energy at the junction of two dissimilar metals forming a closed circuit when exposed to different temperatures. As environmental temperature changes, a net thermal electromotive force is generated which induces a continuous electrical current proportional to the change of temperature. This electrical signal is amplified about 10,000 times and recorded as a graphic signal. Thermocouples were type Z2, poly-tetrafluoro-ethylene insulated, twin-twisted, 0.2 mm diameter wires, terminating in an exposed welded hot junction bead (Lab Facility Ltd., Hampton, Middlesex). The wires were made up of two different alloys: nickel-chromium and nickel-aluminium. The use of alloy wires ensured a fast response. The amplifier (Ancom, Cheltenham) was designed to accept a differential input with a high immunity to noise and a high gain to amplify the low input. It maintained these characteristics over a wide temperature range. The thermocouple-amplifier system was

assembled in the Electronic Laboratory, Department of Medicine, Royal Infirmary, Edinburgh (Figure 23). In use, the thermocouples were mounted in rubber foam and carefully attached to the baby's upper lip. Figure 24 shows the signal obtained. The ascending limbs of the curves represent inspiration and the descending limbs, expiration. The degree of synchrony with chest movements was satisfactory for the purpose of the present studies. Figure 25 illustrates how readily episodes of central apnoea could be observed in simultaneous thermocouple and magnetometer recordings.

Transcutaneous oxygen tension ($PtcO_2$) was measured on the skin surface by the Draeger Oximeter and Transoxode (Dragerwerk A6, Lubeck, West Germany) the application of which is based on a polarographic technique, using a modified Clark electrode (Clark 1956) (Figure 26).

In practice, the electrode was applied near the infant's nipple. A small drop of water, approximately 2 mm in diameter, was placed on the skin and the electrode fixed to a self-adhesive ring and thus insulated from the surrounding air. When the infant slept in the prone position, the electrode was placed on the back at the beginning of each study. Its temperature was set at $43^{o}C$. After placing the electrode, $PtcO_2$ dropped rapidly until vasodilation produced by heating had taken place. It then rose gradually until a steady plateau was reached after about 15 minutes. Transcutaneous

Figure 23

Nasal thermocouple system

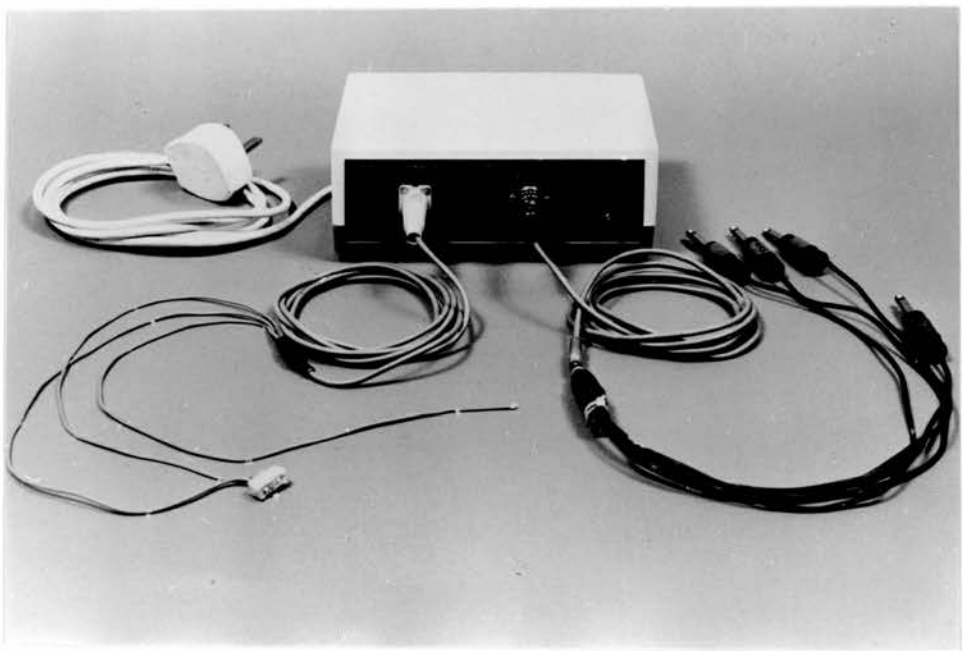


Figure 24

Wave form signal from the nasal thermocouple

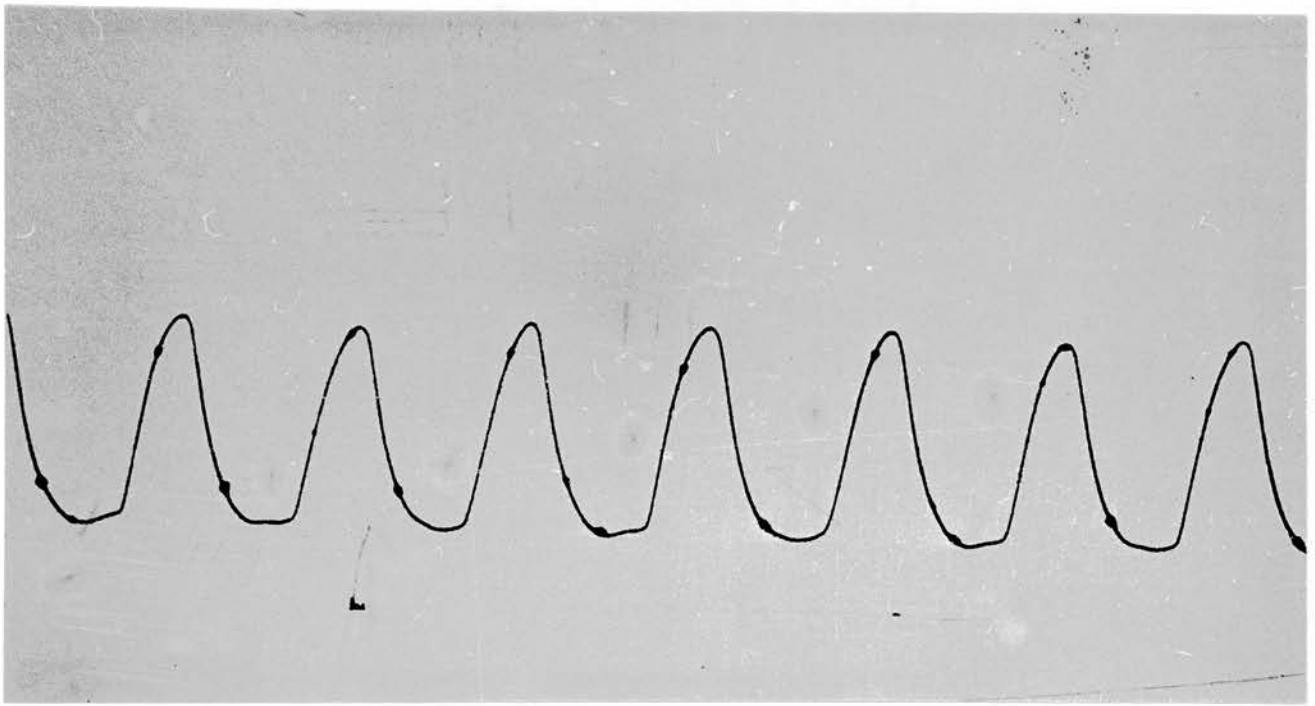


Figure 25

Central apnoea observed in simultaneous thermocouple (NT) and magnetometer (CM) recordings

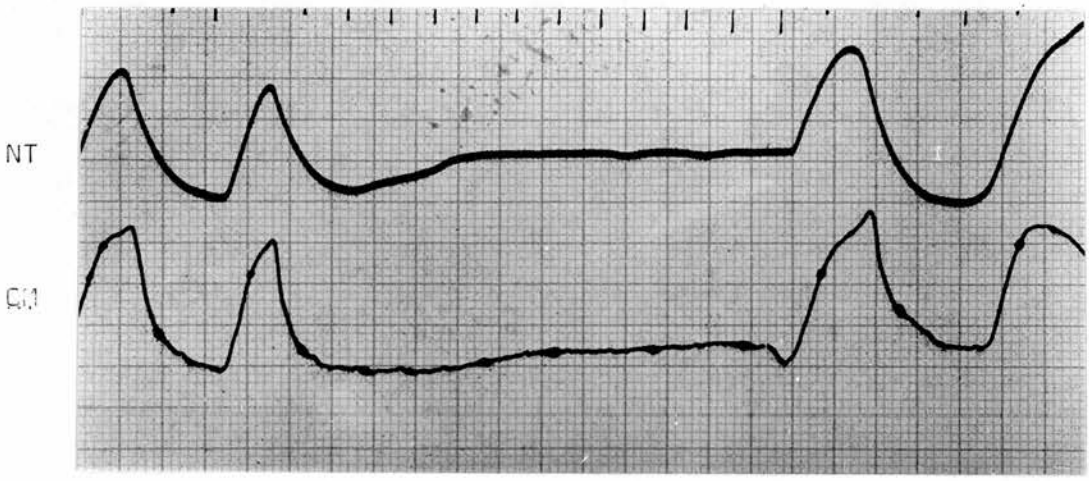
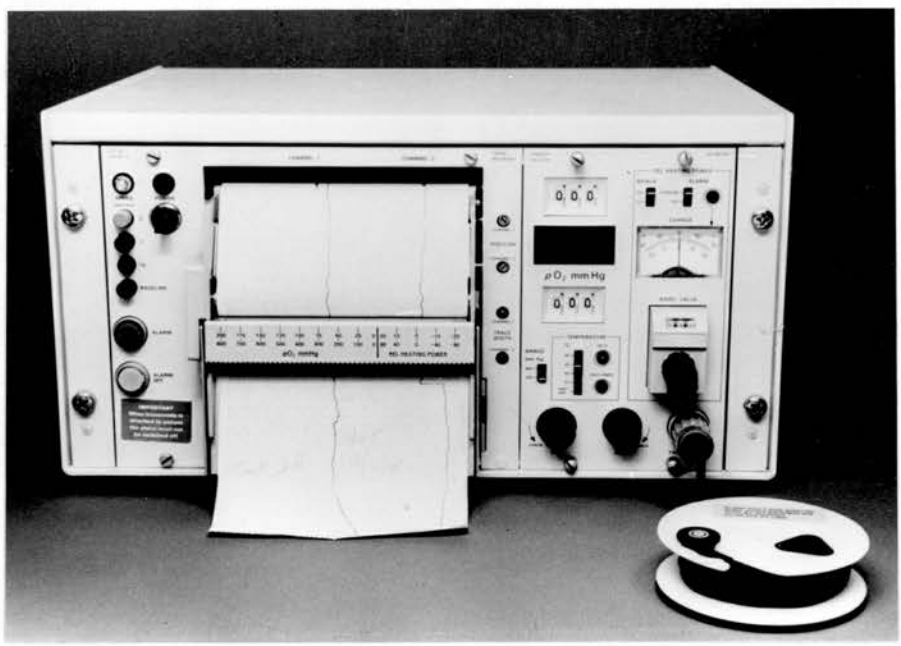


Figure 26

Oxymeter and Transoxode



oxygen tension ($PtcO_2$) values were recorded continuously on thermo-sensitive chart paper at a speed of 10 mm per minute (Figure 27) and on polygraphic records at a speed of 10 mm per second. The electrode was never attached to the same site for more than four hours at a time. On removal, the degree of drift was assessed by relating the difference between initial and final calibration values to the total time of recording. The mean drift was 1.5 mmHg per hour. The assembly of the electrode head, including membrane changing, storage, and maintenance were carried out carefully in accordance with the manufacturer's instructions.

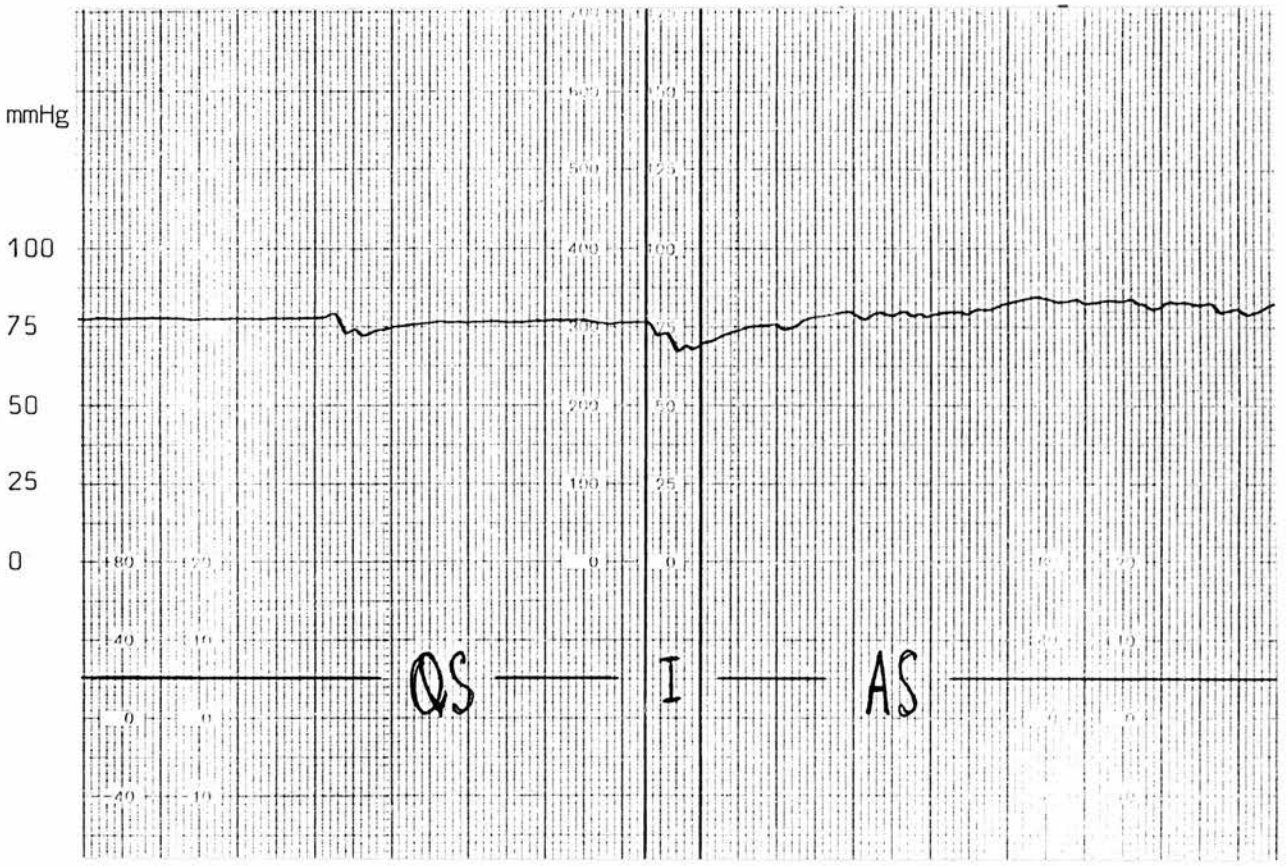
5.4 Analysis of records

Each sleep record was divided into successive 30-second periods - epochs, which were analysed visually and scored as either Awake (A), intermediate, indeterminate or Transitional sleep (IS), Quiet sleep (QS) or Active sleep (AS) by a trained observer. The scoring criteria were based on the definitions suggested by Anders et al (1971) and those of Rechtschaffen and Kales (1968). All recordings were analysed for sleep state and cardio-respiratory variables.

Table 15 describes the system adopted for analysing sleep state. It provided a relatively non-complex method of interpretation which could be learned and applied by a non-expert in sleep physiology, with little sacrifice of

Figure 27

Transcutaneous oxygen ($PtcO_2$) recording



AS Active sleep

QS Quiet sleep

IS Indeterminate sleep

1 minute

Table 15

SLEEP STATE ANALYSIS

State	EEG	EOG	EMG
Awake - A	Relatively rhythmical and containing faster elements (theta or alpha according to age). There should be no spindles, K complexes or other recognisable EEG patterns of sleep.	Blinks or other eye movements may occur.	High amplitude, sometimes with movement artefacts suggesting prolonged motor activity. During periods without much movement, at least one transitory disturbance every 30 seconds is present.
Intermediate, Indeterminate, Transitional - IS	Shows mixture of delta, theta and alpha components (according to age slower or faster waves are more prominent). May be weak signs of EEG spindling but no definite spindles or K complexes. Transitory (episodic) high voltage rhythmical slow activity is also included.	May show occasional eye movements.	Amplitude lower than during wakefulness; there may be transient increases in amplitude and movement artefact.
Quiet sleep - QS	Slower than during wakefulness, equal to or slower than in indeterminate sleep; amplitude higher than in indeterminate sleep; presence of sleep spindles or K complexes.	No rapid eye movements.	Lower than during wakefulness; equal to or lower than in indeterminate sleep. May be short interruptions by indeterminate sleep pattern (less than half the epoch) and transitory increases in EMG.
Active sleep - AS	Relatively rhythmical containing faster elements (theta or alpha according to age). No spindles or K complexes present but occasionally they might occur within an epoch; brief reversals in the pattern of I or QS.	Rapid eye movements present.	Low voltage, occasional transitory increases and general movement artefacts.

precision. For that reason, further subdivision of stages I, QS, and AS was not undertaken. Respiration, the variable under scrutiny, was not included in the assessment method outlined.

The respiration rate and heart rate were calculated for each sleep state from the beginning of the fourth minute of continuous sleep (AS and QS only). Both respiration rate and heart rate were computed over a complete minute. The number of complete respirations occurring as near as possible to 60 seconds was counted and the final rate computed as a rate per minute. Heart rate was calculated in the same way. If, during the fourth minute, the infant moved or artefact was present so that respiration rate or heart rate could not be calculated, the fifth or sixth minute was counted instead. If the AS or QS phases of sleep were equal to 8 minutes (16 epochs) or not more than 12 minutes (24 epochs) respiration rates and heart rates were calculated over the last minute as well. Final computations were the means of first and final measurements. If, however, a sleep phase exceeded 12 minutes (24 epochs), respiration and heart rate were calculated by measuring them during the fourth minute, the final minute, and the intermediate minute (between fourth and final minutes). The means of these three observations were then computed.

Central apnoea was defined as a pause in breathing during

which there was neither airflow nor respiratory movements. In the present study, episodes of central apnoea of 6 seconds or more are reported unless otherwise stated. Six seconds was chosen arbitrarily to facilitate comparison with previously reported studies. Prolonged central apnoea ($\geqslant$20 seconds) was also noted.

Obstructive apnoea was defined as an episode during which breathing movements (thoracic and/or abdominal) persisted in the absence of airflow at the nose. Episodes could be of any length and are reported as prolonged ($\geqslant$6 seconds) or brief ($\geqslant 3 < 6$ seconds) in duration. There was often a steep fall in $PtcO_2$ following obstructive apnoea. Episodes of apparent obstructive apnoea initiated by gross body movements and often without change in $PtcO_2$ were <u>not</u> recorded as obstructive apnoea. Such episodes were most common in indeterminate sleep.

The duration of both central and obstructive apnoeas was measured from the end of the last breath before cessation of airflow to the start of the next, from thermocouple tracings. Each apnoea was measured individually and the corresponding sleep state noted; the episode of longest duration was also recorded. Apnoea index was calculated for each sleep stage - AS, QS, IS, and total. It is the ratio of the total duration of apnoea (seconds) during a

sleep phase to the total duration of sleep phase (seconds) expressed as a percentage. Apnoea attack rate defined as the ratio of the number of apnoeic episodes during a sleep phase to the total duration of sleep phase (seconds) expressed as a percentage, and apnoea percent the percentage of epochs (30 second periods) during which at least 1 apnoeic pause was initiated, were also computed. The mean duration of apnoeic pauses in each sleep phase was calculated. Finally, time spent in each main sleep phase (AS and QS) was calculated as a percentage of total sleep time.

These derived indices of apnoea (apnoea index, apnoea attack rate, and apnoea percent) were based entirely on recorded episodes of central apnoea. No attempt was made to derive comparable additional information from episodes of obstructive apnoea. In general, the presence or absence of obstructive apnoea was noted in each infant and the results will be reported separately.

The duration of periodic breathing, defined as two apnoeic periods of 3 seconds or more within 20 seconds of each other (Parmalee et al 1972) was measured from the beginning of the first apnoeic episode until the end of the last. The following indices were calculated - number of periodic breathing events per 100 minutes of sleep and the total duration of periodic breathing in minutes per 100 minutes of sleep.

Gross body movement was detected both at the times of recording and also when records were subsequently analysed. Such episodes were easy to recognise, particularly from EMG recordings (See Figure 18). The number of gross body movements and their total duration in minutes, both expressed per 100 minutes of sleep time, were also computed.

Records of transcutaneous oxygen tension ($PtcO_2$) were analysed by taking the second hour of sleep, i.e. the 60th to 120th minute and identifying adjacent periods of active and quiet sleep. These were defined as sleep periods $>$ 4 minutes duration with no intervening 'awake' period, and between which any indeterminate sleep was $\leqslant$ 3 minutes duration. Measurements were made at the same point, starting at the beginning of the 5th minute: the $PtcO_2$ was noted at the end of each subsequent minute and the mean for the sleep state was computed. Thus mean, maximum and minimum values were obtained for both active and quiet sleep in the second hour of sleep. Transcutaneous oxygen tension records were also analysed for dips in oxygen exceeding 10 and 15 mmHg respectively occurring within periods of up to a minute throughout the total sleep recording. The relation of such dips to sleep state and to episodes of central or obstructive apnoea was also noted.

5.5 Statistical analysis

Continuous data from unmatched pairs was analysed using Students' unpaired or pooled t tests. The Mann-Whitney U test was applied to non-parametric data. The Chi-squared test was used for categorical data.

For matched pairs, continuous data were analysed using Stud ents' paired t test. The Wilcoxon matched pairs signed rank test was used for non-parametric data.

In the study of infants with bronchiolitis, apnoea variables, respiration rate and heart rate were compared during and following recovery from illness, and also in active and quiet sleep. Comparisons were made by analysis of variance. In the same study, the Spearman Rank correlation coefficient was used to test the relationship between the amounts of sleep state and age.

Difficulties arose in relation to certain index/control comparisons when careful matching for post-conception age was not possible. It was necessary to compare groups adjusted for age. A complex statistical analysis was required to achieve this objective. For each variable for which sequential observations were available for individual infants within a group, linear regression analyses were carried out and a pooled regression line computed for each group. Group mean values were also computed which

were adjustable for age. Group means were then compared. The analysis included analysis of covariance (with random effects for patients within groups) using programme BMDP 3V (Statistical Software 1981), to permit age-matched comparisons (apnoea variables, respiration rate and heart rate) between siblings, 'near-miss' and control groups of infants, in both active and quiet sleep. The two-tailed probability test assessed the group 'trend' for each variable with post-conception age.

The detailed analysis of sequential data on $PtcO_2$ in active and quiet sleep in healthy control, sibling, and 'near-miss' groups (full-term and pre-term) is described in the Results section. This involved analysis of mean ranges of $PtcO_2$ shown by individual infants in their first, second or third studies, linear regression analysis of active and quiet sleep data, the difference between the two values for each group of infants studied, and inter-group comparisons. The statistical package used was the GLIM 3 12(c) 1977, Royal Statistical Society, London. Curvilinear analyses were also carried out; intra- and inter-group comparisons were made for both active and quiet sleep values.

5.6 Limitations of methods

There were several potential sources of error, some of which were outside the control of the investigator.

Limitations were related to the selection of index and control cases, the number and timing of studies carried out in individual infants (in part related to parental co-operation), the adequacy of laboratory and recording facilities, the measurement precision of certain variables, e.g. $PtcO_2$, the documentation of the data recorded and its statistical analysis. The extent to which these potential sources of error influenced the accuracy and reliability of the results obtained cannot be computed directly. The following limitations of the methods described are acknowledged.

i) Patient selection - timing of studies

It was not possible to select control cases on a totally random basis. In general, parents of healthy, apparently normal infants at birth were not always willing to volunteer their infants as controls for the sequential studies outlined. Only parents who were easily approachable and fulfilled the criteria described previously were asked to participate in the study. Too few control infants were enlisted, which limited the applicability of case/control comparisons.

The same difficulties were not encountered in enlisting infants in the 'symptom' and 'increased risk' categories. Parents of symptomatic infants perceived the studies to be of value (in the investigative sense) as far as their babies were concerned; similarly, parents of 'siblings' and 'near-miss' cases were keen to co-operate and eager to know whether

abnormalities of breathing had been found in their infants.

It did not prove possible to standardise the post-conception age or chronological age at which studies were undertaken. This was potentially achievable in control and sibling groups of infants, both of whom were enrolled from birth, but the desirability of applying strict scientific criteria had to be balanced against the need to maintain parental confidence and co-operation over several months. In practice this meant that studies were often carried out at a time convenient for families. It was inevitable that the 'symptom' and 'near-miss' subgroups of infants could only be studied at the time of presentation, and this varied from infant to infant. The timing of follow-up studies was not strictly controlled in these groups. When infants were studied during and following recovery from minor illness, it was not possible to standardise either the duration of illness when initial studies were undertaken or the interval between illness and follow-up assessments. Asynchrony of timing of studies within and between control and index subgroups increased the complexity of subsequent statistical analysis of data.

A potential source of error arose from the need to admit infants to hospital for either initial or sequential studies. These were carried out during the first night following

readmission when, arguably, the infant's usual routine was most disrupted. In studies reported in adults, a minimum settling-in period of one night is usual. The extent to which the 'first night' policy adopted in the present study affected results is not known. Parents were not asked to spend two consecutive nights in hospital - such a policy would have encountered resistance and possibly withdrawal from the study. For the same reason duplicate studies in individual infants within a short period of time, to allow the reproducibility of results to be assessed, were seldom undertaken. The sequential studies reported were well spaced in individual cases, with time intervals between studies during which the values of the variables measured could have changed, thereby precluding assessment of reproducibility

The timing and duration of studies were standardised as far as possible. These were usually conducted between 11 p.m. and midnight and 3 and 4 a.m. Whether data obtained during these relatively short inter-feed three to four hour studies were representative of that which might have been obtained at other times throughout the day was not assessable. Moreover, circadian events of possible relevance to SIDS would not have been observed (Hoppenbrouwers et al 1980; Harper et al 1981). Staffing and supervision constraints meant that these ideals could not be approached in the present study. It would have proved impossible to monitor the

unrestrained infant for longer than the period described.

An additional potential source of error was the inclusion of one infant from the siblings group (Case 45) in the 'near-miss' group. The advice of a statistician was sought on this point and a positive decision was made to include this infant in the overall investigation, and not to exclude her from either of these 'risk' groups. Her presence in both subgroups of index cases would tend to minimise rather than exaggerate differences between these groups when they were compared directly. A further sibling and two half-siblings of previous SIDS victims were included in the 'near-miss' subgroups. These presented as 'near-miss' cases and were not considered for inclusion in the sibling subgroup.

ii) Laboratory and recording facilities

Ideally the environment of a sleep laboratory should be carefully controlled so that noise is minimised, and temperature and lighting are conducive to sleep. Recording apparatus is best located in a separate room from the subject being studied with adequate provision for clinical observations and the recording of events. The polygraphic recorder should be capable of recording data essential for the interpretation of sleep state, respiration, heart rate, and transcutaneous oxygen tension simultaneously. In each of these respects, laboratory arrangements were sub-optimal.

Although every attempt was made to minimise noise, its intensity varied during individual studies and between consecutive studies in the same infant. Recordings were also made in the same room as the infant, and it was not possible to record all variables simultaneously on an 8-channel recorder. In the majority of studies, transcutaneous oxygen tension was recorded separately on a recorder with a different time base from the Mingograf. This made it difficult subsequently to analyse transcutaneous oxygen tension in relation to sleep phase.

Polygraphic sleep recordings were carried out by one individual (FS), except for control cases who were studied in similar circumstances using the same recording apparatus, by a research colleague (UMF).

The respiratory variables recorded provided information on patterns of breathing which were non-quantitative. The adequacy of ventilation or changes in ventilation which might have occurred with changes in sleep state were not assessable. The adequacy of transcutaneous oxygen tension as an indicator of arterial oxygen tension could not be assessed as no direct comparisons were made between arterial oxygen tension and transcutaneous oxygen tension. The methods used have been applied in infants (Huch et al 1974), older children (Bompard et al 1979), and adults (Kleinheinz et al 1979).

Where paired comparisons have been made transcutaneous oxygen tension underestimates arterial oxygen tension. It seems likely also that abrupt changes in PaO_2 are not fully reflected by changes in $PtcO_2$. No claim is made that monitoring of transcutaneous oxygen tension gives accurate quantitative results; it was expected that trends in PaO_2 would be closely mirrored by changes in $PtcO_2$. The lag in response of transcutaneous oxygen tension (approximately 10-12 seconds) made it difficult to make precise comparisons between the timing of breathing pauses or irregularities and the associated changes in $PtcO_2$. However, the temporal sequence was usually clear - changes in respiration pattern preceded dips in oxygen tension.

Electrical noise could not be fully eliminated from the recordings. The earthing arrangements in the room set aside for sleep studies were optimised at the outset; the recorder and the transducers used were also fully tested so as to ensure patient isolation. Electrical safety precautions were checked periodically.

iii) Analysis of data

The analysis of sleep state was carried out by a neuro-physiologist (Dr VB) for'symptom' groups of infants and a high proportion of siblings and 'near-miss' cases. Dr FS was trained by her to record and interpret sleep variables,

and his findings were initially checked by her. He scored the sleep status of the remaining infants, excepting controls. The sleep status of control infants was defined initially by Dr UMF but records were rescored by Dr FS to ensure consistency in sleep staging. Thus sleep staging was carried out mainly by VB and FS.

The initial analysis and documentation of respiratory variables was done manually and proved exceedingly tedious. These analyses, carried out by Dr FS, were checked independently by members of the technical staff (Miss BO and Mrs AW). Where differences were found between observers, the original records were rescrutinised and final decisions made by Dr FS. For most measurements, for example, respiration, heart rate, duration of central or obstructive apnoea, etc, there was little disagreement between observers but no formal attempt was made to assess the degree of observer error.

The subdivision of records of transcutaneous oxygen tension in relation to sleep state was carried out by one person and computations made as described previously. The latter were checked by a laboratory technician (Mrs AW). There was seldom disagreement; mistakes occurred because of the tedium of the analyses and not their complexity.

The presentation of data for analysis was standardised

for controls and each index subgroup. Guidance on presentation for computer analysis was obtained from Dr Clayton, Department of Community Medicine, University of Leicester, and Dr Carpenter, London School of Hygiene and Tropical Medicine. Data presented for computer analysis were carefully checked by two individuals independently, thereby minimising the likelihood of error.

The statistical tests chosen have been described. These varied depending on whether comparisons were made between groups or between cases and matched controls. The tests chosen depended on the distribution of values within groups for the variables being compared. The comparisons of groups adjusted for age were subject to several sources of error. The **linearity** of sequential observations on respiratory variables in relation to post-conception age was assumed; from the data available there was no evidence to the contrary. However, it is known that changes in certain variables with age are not linear, for example, respiration rate increases in the first week or two after birth and thereafter gradually declines during the first six months (Hoppenbrouwers et al 1980). Similarly, indices of apnoea do not change in a linear fashion during active sleep; thus apnoea percent decreases rapidly at first before attaining the more stable value after the first month (Gould et al 1977). The analysis could also be distorted by the presence of outlying results for a given variable within a group. This

applied to both control and 'near-miss' groups of infants. The relative lack of control data compared with that available for the 'risk' group studied may also have weakened the statistical conclusions. Difficulties of standardising post-conception age at which studies were undertaken has been discussed. Asynchrony of timing of sequential studies within groups made it difficult to study sequential changes (within a group) in each variable.

The problem of matching for post-conception age applied also to inter-group comparisons for gross body movements. To overcome this difficulty, matched case/control comparisons were made whenever possible. Using this approach, index data were not fully utilised.

CHAPTER 6

RESULTS

CHAPTER 6

RESULTS

The results for control and index subgroups of infants are presented in two parts, (a) apnoea (central) variables, percent sleep, respiration rate and heart rate, and (b) obstructive apnoea, periodic breathing and gross body movements. Part (a) gives the results for the study as it was originally planned. Scrutiny of sleep polygraphic records for episodes of prolonged obstructive apnoea (≥ 6 seconds) was also in accord with the original aims. Part (b) is to some extent a secondary analysis to detect events which were not initially thought to be relevant. At the outset it was not planned to analyse every record for brief episodes of obstructive apnoea ($> 3 < 6$ seconds) or for gross body movements. A report by Guilleminault et al (1979) of a significant increase in the occurrence of short episodes of obstructive apnoea in 'near-miss' for SIDS infants when compared with healthy controls prompted a review of our records before the study had been completed. Similarly, a growing literature on possible defects in arousal mechanisms in infants thought to be at increased risk for SIDS (French, Morgan and Guntheroth 1972; Kosterlitz and McKnight 1980; and Guntheroth 1982) led to a fresh but retrospective analysis of all records to detect gross body movements, as an indicator of arousal.

Transcutaneous oxygen tension measurements were obtained in the majority of infants studied. Failure to do so was related either to technical difficulties or periods when the transducer was temporarily not available. The results for transcutaneous oxygen tension are not given under subgroup headings: a full account of the analysis and collation of the data available for each index subgroup is presented separately. In the final subsection of Results, illustrative cases are grouped together.

6.1 Controls

Apnoea variables, percent sleep, respiration rate and heart rate C - no previous illness

Table 16 gives the results for apnoea variables, percent sleep, respiration and heart rate in relation to sleep phase in 10 healthy infants born at term and studied on 30 occasions between 38 and 63 weeks post-conception age. The distribution of data was usually non-parametric. For each variable the mean $\pm$SE, median and range is given, corresponding to a mean post-conception age of 48 weeks. Table 17 gives, in addition, predicted mean values ($\pm$SE) for 55.5 and 50 weeks post-conception age. Corresponding values for each variable are similar at these ages, both in AS and QS. A wide range of values was observed for each measured and derived variable

Apnoea variables in relation to sleep phase
in 10 healthy control infants at mean post-conception age 48 weeks

		Observed Mean & SE	Median	Range
Apnoea Index	AS	0.73 (0.22)	0.46	0.00 - 6.13
	QS	1.12 (0.55)	0.51	0.00 - 16.23
	IS	0.56 (0.16)	0.00	0.00 - 3.51
	T	0.85 (0.32)	0.49	0.00 - 9.66
Apnoea Attack Rate	AS	0.10 (0.03)	0.07	0.00 - 0.92
	QS	0.16 (0.08)	0.07	0.00 - 2.36
	IS	0.07 (0.02)	0.00	0.00 - 0.29
	T	0.12 (0.05)	0.07	0.00 - 1.42
Episode of Longest Duration (sec)	AS	6.38 (0.62)	7.65	0.00 - 11.00
	QS	6.43 (0.69)	8.00	0.00 - 12.10
	IS	3.71 (0.76)	0.00	0.00 - 11.80
	T	7.85 (0.55)	8.45	0.00 - 12.10
Mean Duration of Apnoea (sec)	AS	5.61 (0.53)	6.80	0.00 - 8.75
	QS	5.64 (0.59)	7.21	0.00 - 8.60
	IS	3.52 (0.71)	0.00	0.00 - 9.30
	T	6.44 (0.41)	6.98	0.00 - 8.71
Apnoea per cent	AS	2.94 (0.85)	2.11	0.00 - 24.82
	QS	3.72 (1.54)	2.11	0.00 - 45.45
	IS	2.06 (0.57)	0.00	0.00 - 12.50
	T	3.09 (1.01)	1.96	0.00 - 30.17
Sleep per cent	AS	47.30 (2.19)	45.00	26.00 - 76.00
	QS	43.70 (2.28)	45.50	19.00 - 66.00
Respiration Rate	AS	36.60 (1.66)	35.50	24.00 - 55.00
	QS	33.20 (1.73)	30.50	21.00 - 52.00
Heart Rate	AS	127.60 (2.20)	127.00	105.00 - 162.00
	QS	123.50 (2.36)	121.00	96.00 - 154.00

Apnoea variables, per cent sleep, respiratory and heart rates in relation to sleep phase in 10 healthy control infants.

		Observed mean & SE	Predicted means (wks PCA) & SE	
			55.5	50
Apnoea Index	AS	0.73 (0.22)	0.73 (0.30)	0.74
	QS	1.12 (0.55)	1.10 (0.34)	1.09
	IS	0.56 (0.16)	0.47 (0.36)	0.44
	T	0.85 (0.32)	0.85 (0.25)	0.85
Apnoea attack rate	AS	0.10 (0.03)	0.10 (0.06)	0.11
	QS	0.16 (0.08)	0.15 (0.05)	0.15
	IS	0.07 (0.02)	0.06 (0.04)	0.06
	T	0.12 (0.05)	0.12 (0.04)	0.12
Episode of	AS	6.38 (0.62)	6.32 (1.00)	6.30
Longest Duration	QS	6.43 (0.69)	6.37 (0.99)	6.32
(sec)	IS	3.71 (0.76)	3.56 (0.92)	3.52
	T	7.85 (0.55)	7.80 (1.00)	7.77
Mean Duration	AS	5.61 (0.53)	5.54 (0.80)	5.52
(sec)	QS	5.64 (0.59)	5.63 (0.80)	5.61
	IS	3.52 (0.71)	3.41 (0.76)	3.38
	T	6.44 (0.41)	6.43 (0.67)	6.42
Apnoea per cent	AS	2.94 (0.85)	2.98 (1.02)	3.02
	QS	3.72 (1.54)	3.65 (1.02)	3.62
	IS	2.06 (0.57)	1.82 (1.26)	1.74
	T	3.09 (1.01)	3.08 (0.85)	3.08
Sleep per cent	AS	47.27 (2.19)	47.55 (0.25)	47.67
	QS	43.70 (2.28)	43.44 (2.38)	43.32
Respiration rate	AS	36.57 (1.66)	36.93 (2.42)	37.08
	QS	33.20 (1.73)	33.45 (1.90)	33.57
Heart rate	AS	127.63 (2.20)	128.32 (2.42)	128.57
	QS	122.47 (2.36)	123.34 (1.90)	123.65

irrespective of sleep stage. Statistical comparisons between results obtained in AS and those of QS have not been made. No infant had prolonged ($\geqslant$ 20 seconds) central apnoea.

C^1 - previous respiratory illness

Table 18 gives the results for apnoea variables, percent sleep, respiration rate and heart rate for the 14 control infants with a previous history of respiratory infection from which they had recovered clinically. The mean ($\pm$SE), median and range of values for each variable is given. Appendix 12 gives values for individual infants.

The results obtained for each variable are shown as observations for all 14 infants in Figures 28-34 which also give individual data for healthy control (C) infants. The two data sets are broadly comparable. In each there is a wide range of values for each variable during both AS and QS. The healthy control (C) data is somewhat skewed by data from two infants (Cases 3 and 4) who were entirely normal clinically. No infant had prolonged ($\geqslant$20 seconds) central apnoea.

Obstructive apnoea, periodic breathing and gross body movements C - no previous illness

The occurrence of obstructive apnoea and the prevalence of gross body movements and periodic breathing was also

Apnoea variables, per cent sleep, respiratory and heart rates (mean, median and range) in relation to sleep phase in 14 control infants with previous respiratory tract infections.

		Mean & SE	Median	Range
Apnoea Index	AS	0.38 (0.18)	0.00	0.00 - 2.33
	QS	0.23 (0.09)	0.00	0.00 - 1.03
	IS	0.50 (0.31)	0.00	0.00 - 3.84
	T	0.29 (0.11)	0.12	0.00 - 1.41
Apnoea Attack Rate	AS	0.05 (0.02)	0.00	0.00 - 0.25
	QS	0.03 (0.01)	0.01	0.00 - 0.14
	IS	0.03 (0.02)	0.00	0.00 - 0.30
	T	0.04 (0.01)	0.02	0.00 - 0.15
Episode of Longest	AS	3.47 (1.16)	0.00	0.00 - 11.50
Duration (sec)	QS	4.06 (1.21)	3.05	0.00 - 13.20
	IS	1.98 (0.87)	0.00	0.00 - 7.80
	T	6.22 (1.02)	6.70	0.00 - 13.20
Mean Duration (sec)	AS	3.15 (1.03)	0.00	0.00 - 9.33
	QS	3.71 (1.07)	3.05	0.00 - 10.47
	IS	1.97 (0.87)	0.00	0.00 - 7.80
	T	5.62 (0.85)	6.60	0.00 - 9.60
Apnoea per cent	AS	1.45 (0.63)	0.00	0.00 - 7.50
	QS	0.91 (0.35)	0.28	0.00 - 4.30
	IS	1.05 (0.65)	0.00	0.00 - 9.09
	T	1.38 (0.42)	0.57	0.00 - 4.40
Per cent sleep	AS	37.81 (2.71)	37.50	25.00 - 54.20
	QS	49.49 (2.96)	47.00	35.00 - 70.50
Respiration Rate	AS	35.16 (1.91)	35.05	21.70 - 50.70
	QS	30.86 (1.61)	30.75	22.00 - 49.10
Heart Rate	AS	119.39 (8.03)	126.45	115.00 -144.30
	QS	118.94 (3.83)	117.30	92.90 -145.50

Figure 28

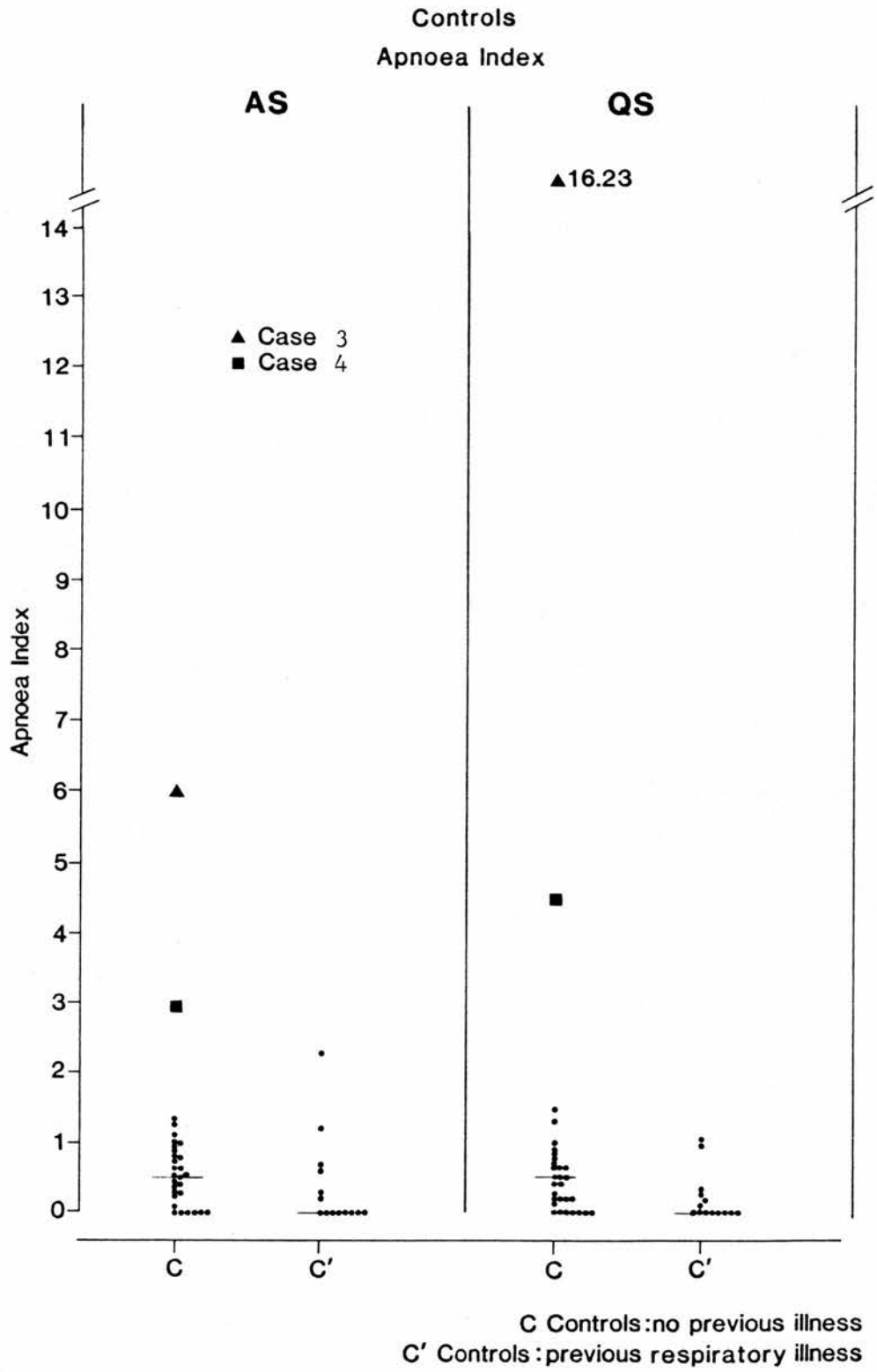

Controls
Apnoea Index
AS
QS
▲16.23
▲ Case 3
■ Case 4
Apnoea Index
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
C
C'
C
C'
C Controls: no previous illness
C' Controls: previous respiratory illness

Figure 29

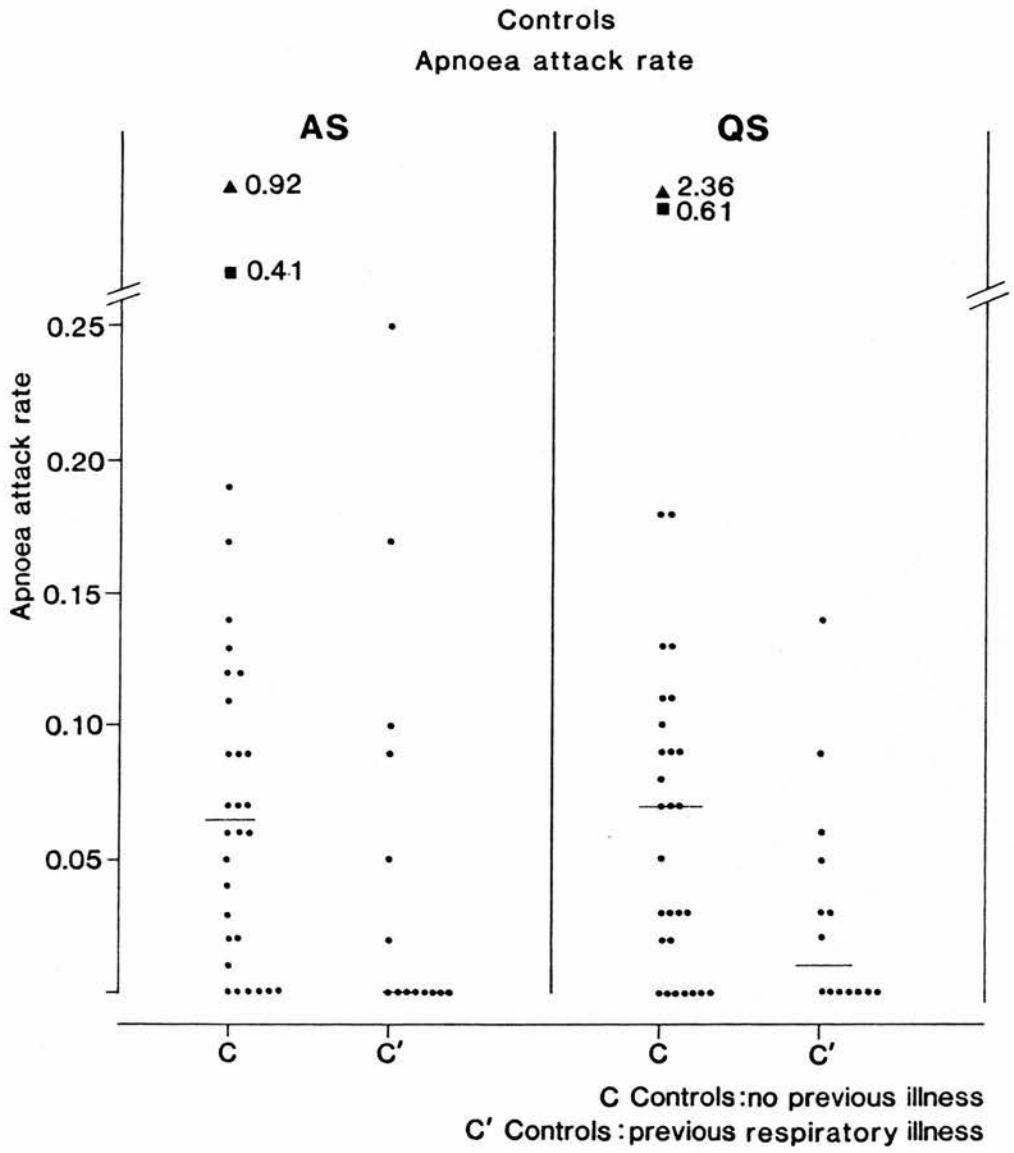

Controls
Apnoea attack rate
AS
QS
▲ 0.92
■ 0.41
▲ 2.36
■ 0.61
Apnoea attack rate
0.25
0.20
0.15
0.10
0.05
C
C′
C
C′
C Controls: no previous illness
C′ Controls: previous respiratory illness

Figure 30

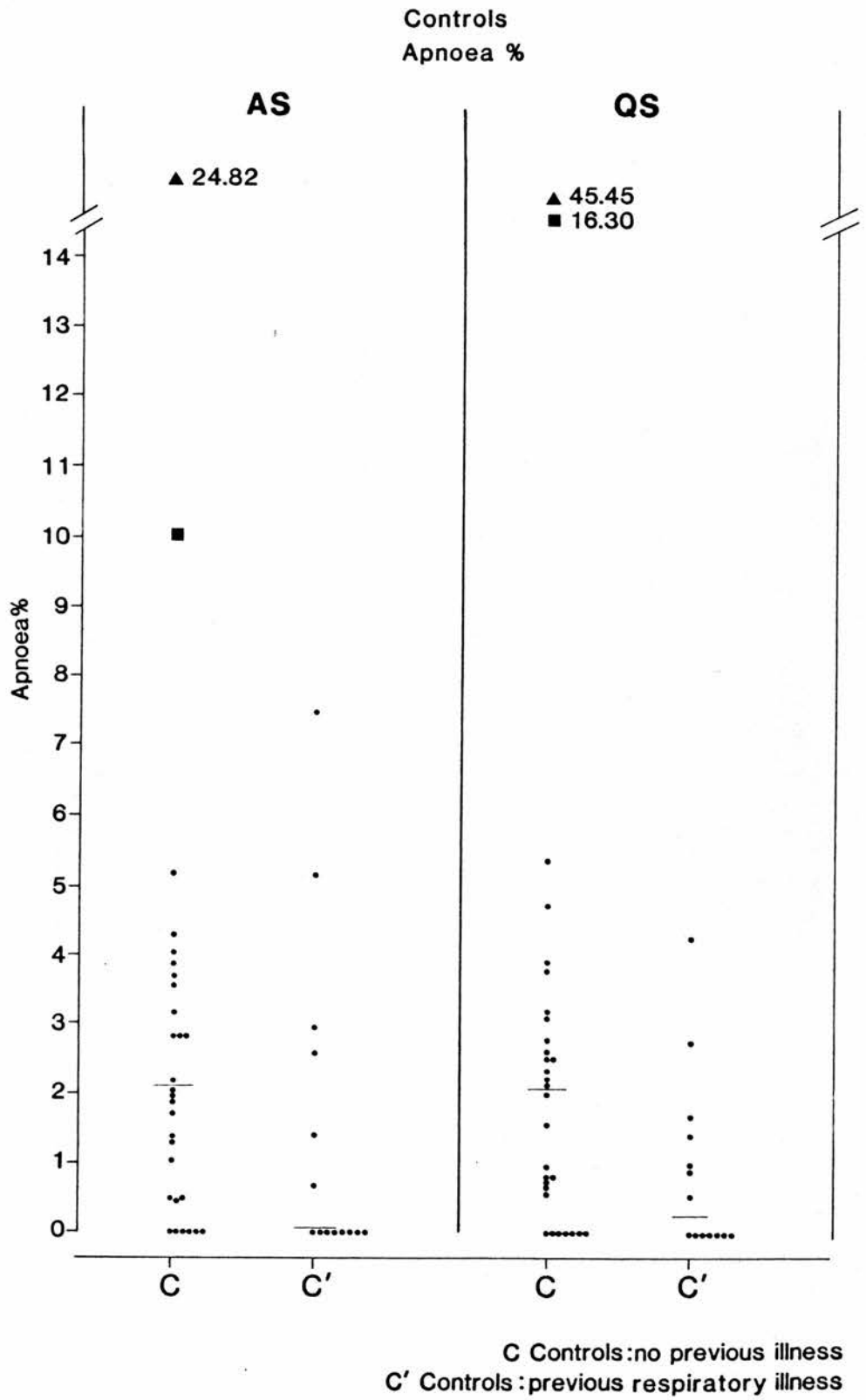

Controls
Apnoea %
AS
QS
▲ 24.82
▲ 45.45
■ 16.30
Apnoea%
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
C
C′
C
C′
C Controls:no previous illness
C′ Controls:previous respiratory illness

Figure 31

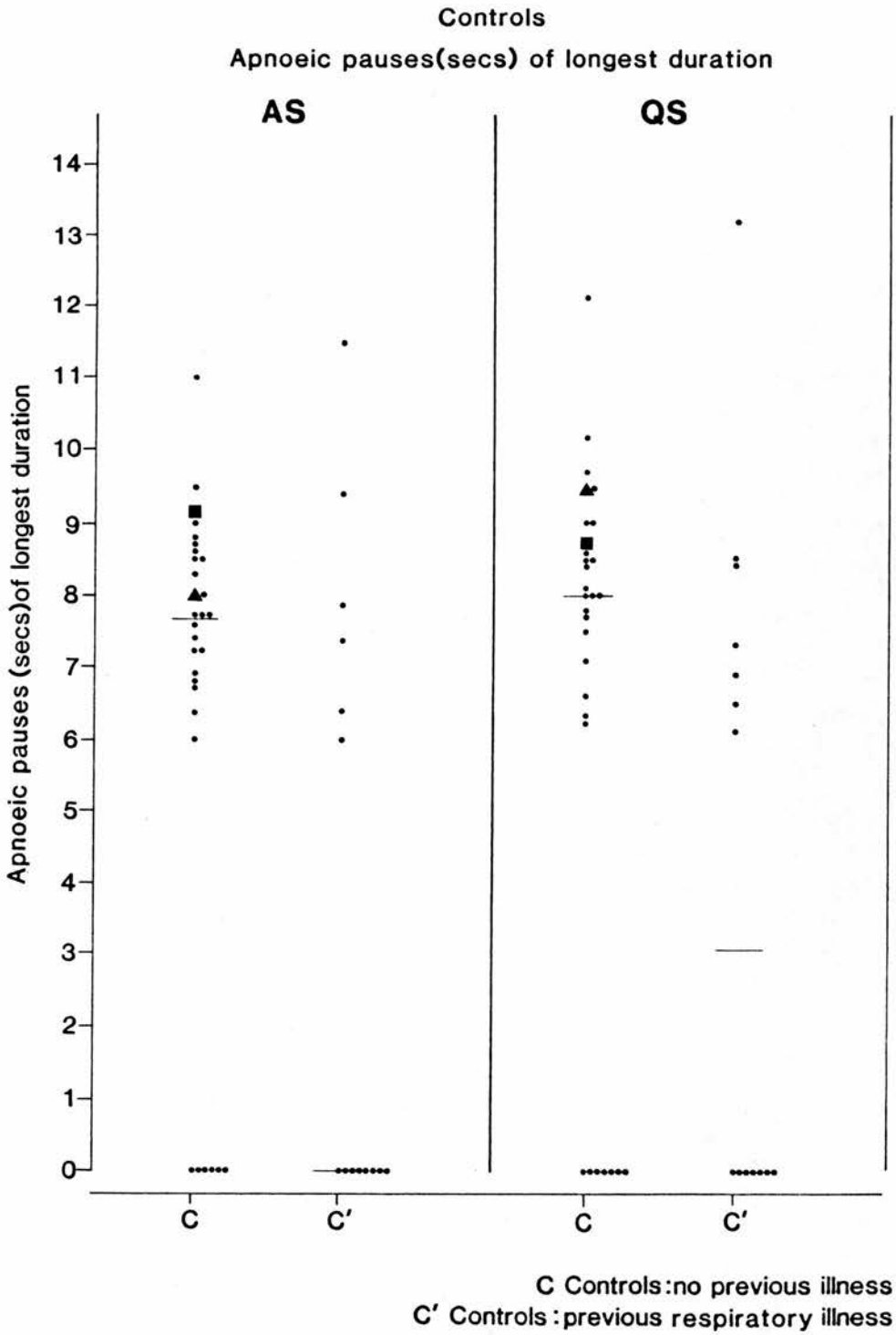

Controls
Apnoeic pauses(secs) of longest duration
AS
QS
Apnoeic pauses (secs)of longest duration
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
C
C'
C
C'
C Controls:no previous illness
C' Controls:previous respiratory illness

Figure 32

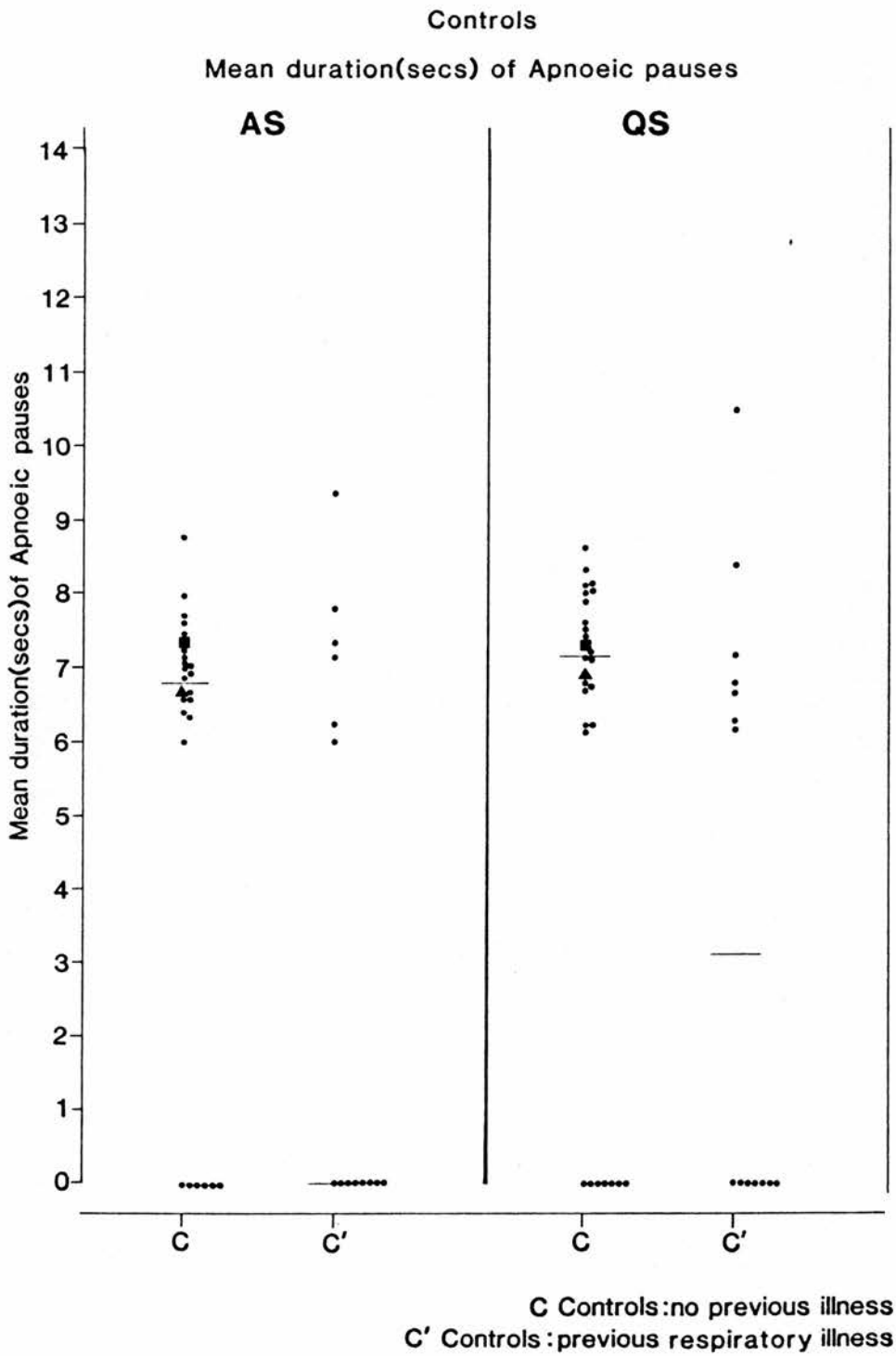

Controls
Mean duration(secs) of Apnoeic pauses
AS
QS
Mean duration(secs)of Apnoeic pauses
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
C
C'
C
C'
C Controls:no previous illness
C' Controls:previous respiratory illness

Figure 33

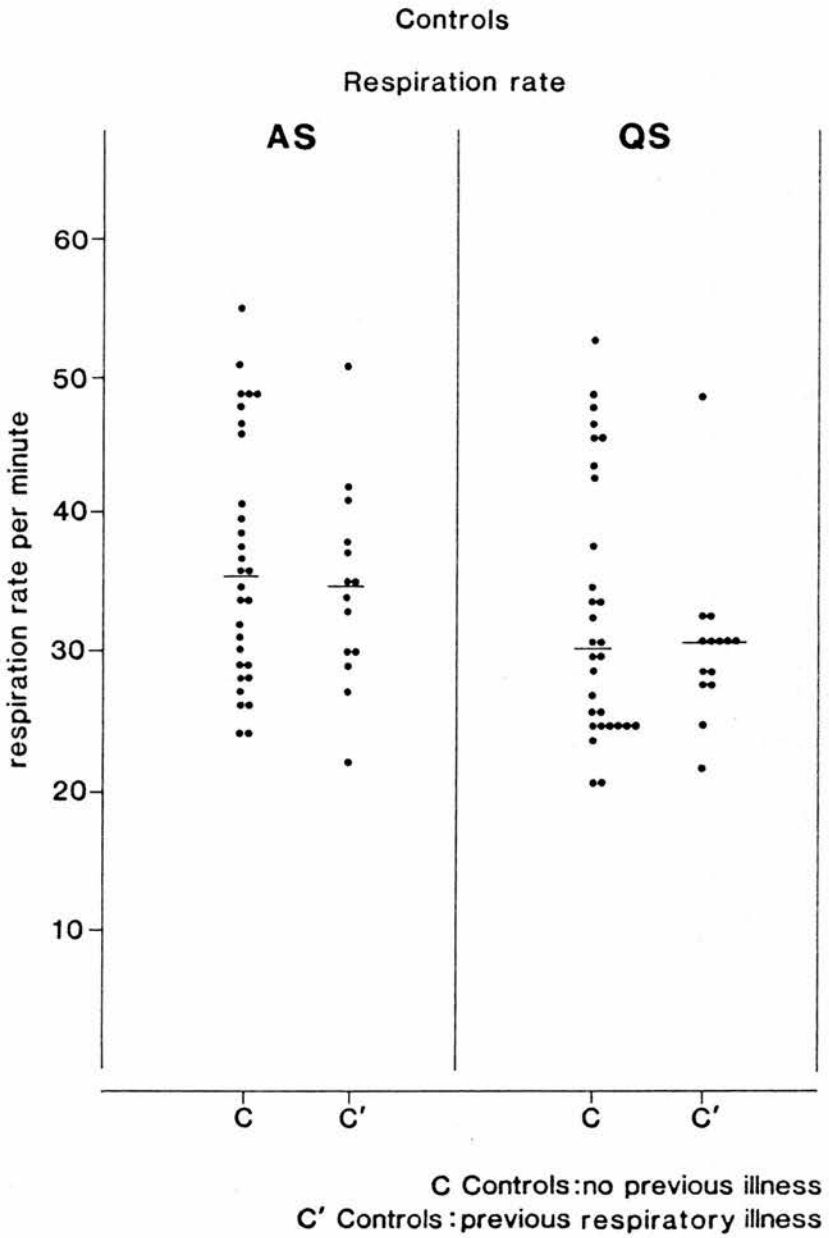
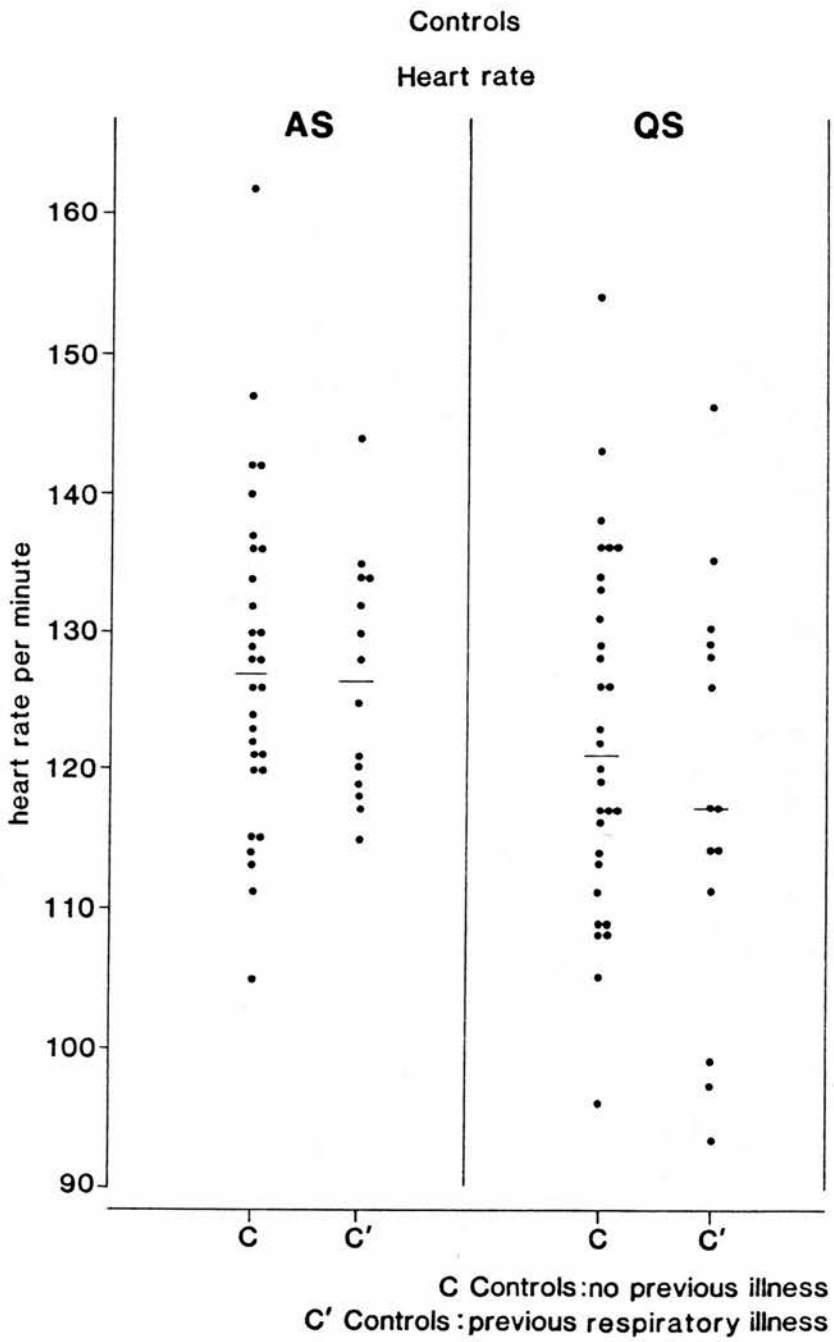

Controls
Respiration rate
AS
QS
respiration rate per minute
60
50
40
30
20
10
C
C'
C
C'
C Controls: no previous illness
C' Controls: previous respiratory illness

Figure 34


Controls
Heart rate
AS
QS
heart rate per minute
160
150
140
130
120
110
100
90
C
C'
C
C'
C Controls: no previous illness
C' Controls: previous respiratory illness

investigated in 9 of the 10 healthy controls referred to above. The tenth (Case 5 appendix 1) was excluded on account of mild stridor. An additional infant was therefore selected as a healthy control (Case 11 appendix 1). Data on 10 cases were analysed. None showed brief ($\geq 3 < 6$ seconds) or prolonged ($\geqslant 6$ seconds) episodes of obstructive apnoea. Table 19 gives the results for gross body movements and periodic breathing. Where several studies were carried out in individual cases, mean values were calculated and the group mean computed. Appendix 13 gives individual data which formed the basis of this computation. A wide range of values was obtained for each variable. Each infant had at least 5 gross body movements per 100 minutes total sleep time and all but one (Case 1 appendix 1) at least one episode of periodic breathing per 100 minutes total sleep time.

C^1 - previous respiratory illness

None of the 14 infants had brief ($\geq 3 < 6$ seconds) or prolonged ($\geqslant 6$ seconds) obstructive apnoea. In respect of gross body movements and periodic breathing (Table 20) data were comparable to those obtained in controls without antecedent illnesses. Figures 35 and 36 present observations on the number and duration per 100 minutes total sleep time of gross body movements and periodic breathing respectively in individual infants in control groups C and C^1. The findings were comparable in both groups.

Gross body movements and periodic breathing in relation to sleep phase in 10 healthy control (c) infants.

		Mean & SE	Median	Range
Body Movements	AS	4.26 (0.66)	4.70	1.40 - 6.22
Total duration	QS	0.41 (0.17)	0.20	0.00 - 1.70
min/100 min sleep	IS	40.73 (5.84)	39.77	8.33 - 66.13
	T	5.00 (0.75)	5.28	0.64 - 7.95
Body Movements	AS	21 (3.05)	20	8 - 35
Number/100 min sleep	QS	3 (1.64)	1	0 - 16
	IS	112 (11.63)	123	50 - 153
	T	18 (2.59)	19	5 - 34
Periodic Breathing	AS	2.96 (0.76)	2.51	0.00 - 6.92
Total duration	QS	0.49 (0.19)	0.23	0.00 - 1.68
min/100 min sleep	IS	2.02 (1.82)	0.00	0.00 - 18.33
	T	1.55 (0.36)	1.53	0.00 - 3.58
Periodic Breathing	AS	7 (1.62)	6	0 - 16
Number/100 min sleep	QS	1 (0.42)	1	0 - 4
	IS	2 (1.74)	0	0 - 17
	T	3 (0.75)	3	0 - 8

Gross body movements and periodic breathing in relation to sleep phase in 14 control (c') infants with previous respiratory tract infection.

		Mean & SE	Median	Range
Body Movements	AS	2.98 (0.65)	1.57	0.57 - 7.93
Total duration	QS	1.31 (0.17)	1.23	0.28 - 2.38
min/100 min sleep	IS	27.32 (2.52)	28.35	6.67 - 49.35
	T	5.30 (0.53)	5.32	0.82 - 9.01
Body Movements	AS	21 (4.14)	15	2 - 48
Number/100 min sleep	QS	11 (1.32)	10	2 - 22
	IS	107 (9.58)	99	40 -179
	T	28 (3.17)	32	5 - 46
Periodic Breathing	AS	1.52 (0.89)	0.23	0.00 - 12.50
Total duration	QS	0.14 (0.07)	0.00	0.00 - 0.75
min/100 min sleep	IS	0.05 (0.05)	0.00	0.00 - 0.77
	T	0.63 (0.30)	0.33	0.00 - 4.20
Periodic Breathing	AS	3 (1.16)	1	0 - 15
Number/100 min sleep	QS	<1 (0.23)	0	0 - 2
	IS	<1 (0.21)	0	0 - 3
	T	1 (0.38)	1	0 - 5

Figure 35

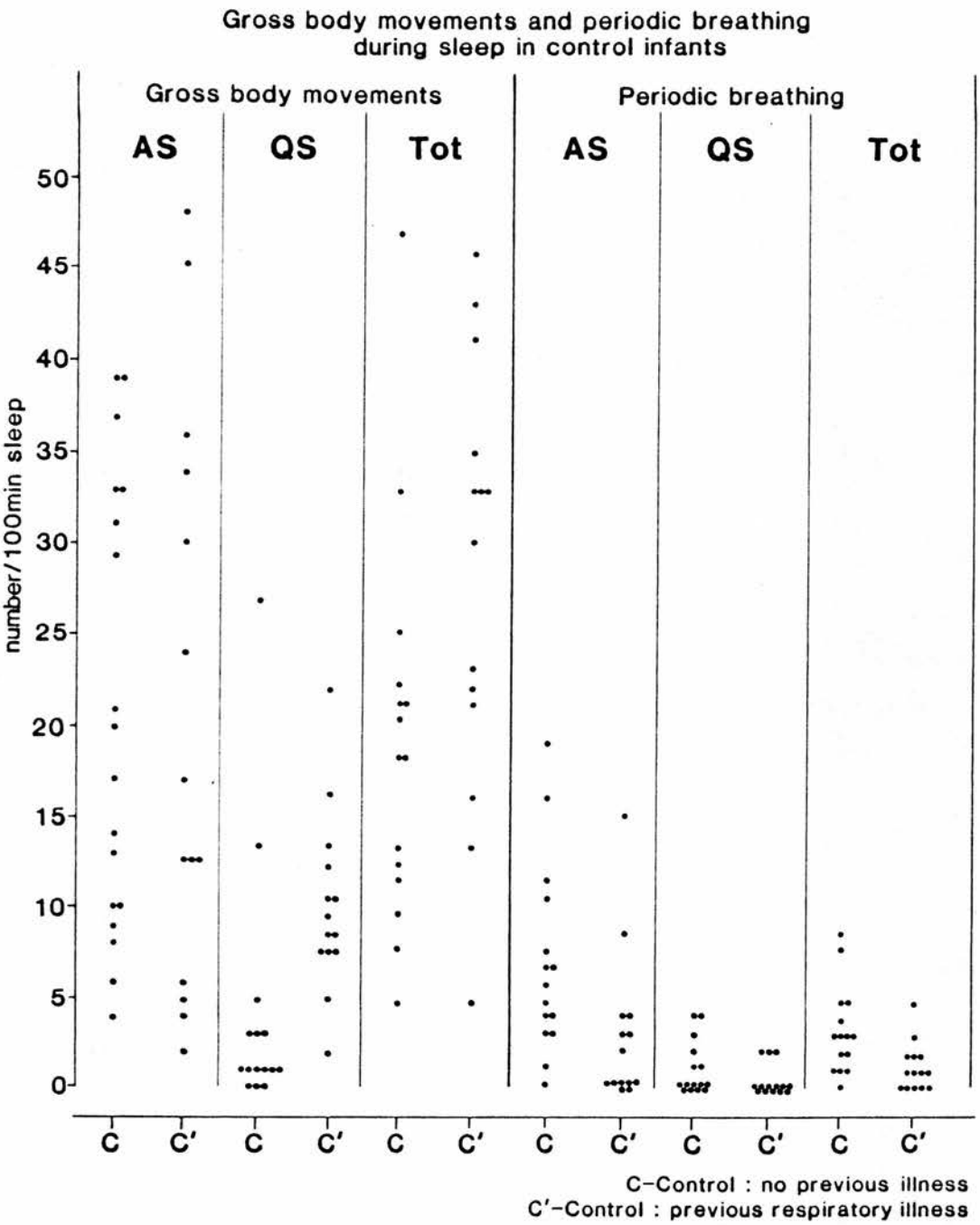
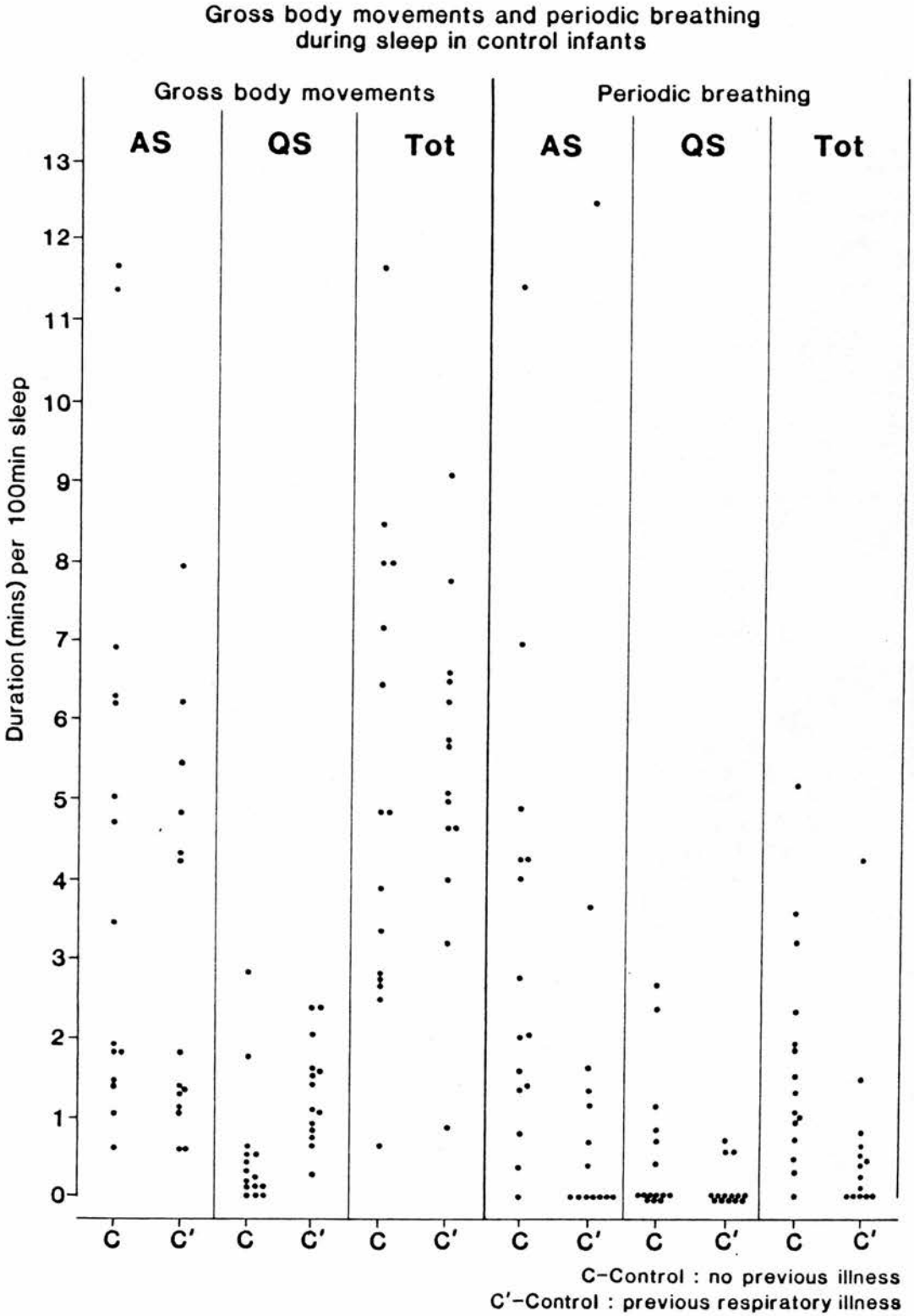

Gross body movements and periodic breathing
during sleep in control infants
Gross body movements
Periodic breathing
AS
QS
Tot
AS
QS
Tot
number/100min sleep
50
45
40
35
30
25
20
15
10
5
0
C
C'
C
C'
C
C'
C
C'
C
C'
C
C'
C-Control : no previous illness
C'-Control : previous respiratory illness

Figure 36


Gross body movements and periodic breathing during sleep in control infants
Gross body movements
Periodic breathing
AS
QS
Tot
AS
QS
Tot
Duration (mins) per 100min sleep
0
1
2
3
4
5
6
7
8
9
10
11
12
13
C
C'
C
C'
C
C'
C
C'
C
C'
C
C'
C-Control : no previous illness
C'-Control : previous respiratory illness

Appendix 14 gives the results for each infant studied.

In the light of these results, it seemed justified to utilise the data on apnoea variables, body movements and periodic breathing obtained in group C^1 infants for matched control comparisons with those of infants in the various index subgroups studied.

6.2 Symptom subgroups

Results obtained during and following recovery from illness are presented for infants with bronchiolitis, upper respiratory tract infection and pyloric stenosis. Recovery data were not available for infants with congenital laryngeal stridor.

6.2.1 Acute bronchiolitis

Apnoea variables, percent sleep, respiration rate and heart rate

Table 21 gives the results for apnoea variables, the percentage of time in active and quiet sleep, respiration and heart rates, during and following recovery from acute bronchiolitis. Apnoea index, apnoea attack rate and apnoea percent were increased in each sleep phase in bronchiolitis, the most significant increases being in quiet sleep. Comparable results were obtained for these variables when data were reanalysed for apnoeic pauses $\geq$ 2 seconds. Apnoeic pauses were invariably less than 20 seconds.

Table 21

Apnoea variables, per cent sleep, respiration and heart rates in 16 infants during and following recovery from bronchiolitis

		During (Mean & SE) n = 16	Recovery (Mean & SE) n = 16
Apnoea Index	AS	0.69 (0.18)	0.36 (0.13)
	QS	0.55 (0.14)	0.34 (0.11)**
	IS	0.99 (0.36)	0.79 (0.33)
	T	0.71 (0.13)	0.39 (0.11)*
Apnoea Attack Rate	AS	0.09 (0.02)	0.06 (0.02)
	QS	0.11 (0.03)	0.04 (0.01)***
	IS	0.14 (0.05)	0.07 (0.04)
	T	0.13 (0.04)	0.05 (0.01)*
Episode of Longest Duration (sec)	AS	6.71 (0.69)	3.85 (1.01)
	QS	7.42 (0.78)	5.28 (1.14)
	IS	3.70 (1.11)	3.29 (0.99)
	T	9.08 (0.36)	7.09 (0.84)*
Mean Duration of Apnoea (sec)	AS	6.18 (0.63)	2.30 (0.88)*
	QS	6.91 (0.51)	5.21 (0.95)
	IS	3.23 (0.95)	3.23 (0.97)
	T	7.22 (0.14)	6.21 (0.65)
Apnoea per cent	AS	2.97 (0.73)	1.58 (0.58)
	QS	2.57 (0.74)	1.28 (0.39)*
	IS	3.11 (1.23)	2.35 (1.09)
	T	2.85 (0.49)	1.82 (0.54)*
Sleep per cent	AS	35.24 (2.03)	31.18 (2.08)*
	QS	52.23 (2.01)	56.39 (3.09)
Respiration Rate	AS	33.38 (2.15)	31.20 (0.87)***
	QS	29.60 (0.87)	26.50 (0.87)***
Heart Rate	AS	113.95 (2.42)	119.60 (2.14)***
	QS	110.11 (3.12)	112.62 (2.79)***

* $p < 0.05$ ** $p < 0.02$ *** $p < 0.01$

The apnoeic episodes of longest duration were similar in active sleep and quiet sleep regardless of the stage of illness, but the mean duration of apnoeic pauses was increased in AS during the course of bronchiolitis. During bronchiolitis, 35% of total sleep time was spent in AS, compared with 31% after recovery ($P < 0.05$). Quiet sleep was increased following recovery but this did not reach statistical significance. The percentage of indeterminate sleep was similar during illness and following recovery. A significant correlation was found between the individual percentages of active sleep and the age of the infants in weeks, both in the first and second recordings ($P < 0.01$). A significant positive correlation was obtained between the individual percentages of quiet sleep and the age, both during the illness and after recovery ($P < 0.01$).

Respiration rate was significantly increased during bronchiolitis compared with recovery. It was also higher in active sleep than in quiet sleep irrespective of the stage of the illness. Similarly, heart rate was significantly increased during active sleep but was lower during bronchiolitis than after recovery.

There were 212 episodes of central apnoea $\geqslant$ 6 seconds. These started at end-expiration. The onset was spontaneous in 72 (34%), or followed a sigh in 108 (51%), or gross

body movements in 32 (15%). The percentage of apnoeic episodes initiated by a sigh or movement was 83% in QS, 34% in AS, and 68% in IS. One hundred and thirty-eight (64%)apnoeic episodes ended in a sigh and 74 (35%) with associated movements. Pre-apnoeic heart rate was significantly higher than during ($P < 0.05$) or after apnoea ($P < 0.05$). Heart rate rarely fell below 80 beats per minute, the lowest recorded being 71 per minute after an apnoea pause of 6.7 seconds. No differences were observed between heart rates compared over three successive 6-second periods which did not include apnoea pauses. Finally, there was no significant relationship between heart rate (pre, during or post apnoea) and the total duration of apnoeic pauses. Similar analyses have not been undertaken in the other symptom subgroups.

Obstructive apnoea, gross body movements and periodic breathing

Three infants had episodes of obstructive apnoea - brief ($\geq 3 < 6$ seconds) in two (Cases 13 and 17) and prolonged in two (Cases 13 and 27) with resolution on recovery, excepting Case 27. Table 22 gives the results for gross body movements and periodic breathing in 16 infants during and after bronchiolitis. A significant increase ($P<0.05$) in episodes of periodic breathing was observed during infections. This is illustrated in Figure 37. The results for body movements and periodic breathing per

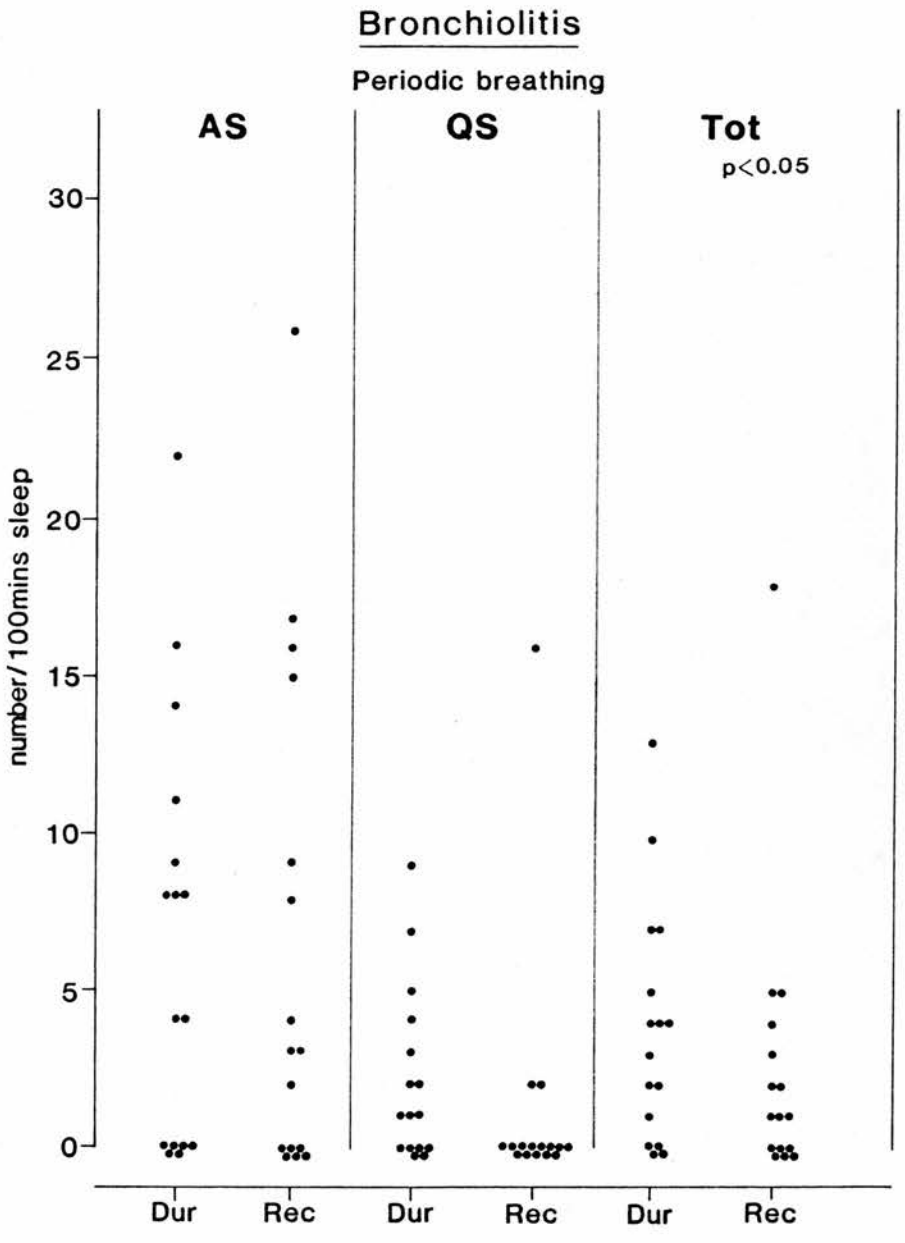
Table 22

Gross body movements and periodic breathing in relation to sleep phase in 16 infants during and after bronchiolitis.

		During Mean & SE	Recovery Mean & SE
Body Movements	AS	2.98 (0.45)	2.67 (0.44)
Total duration	QS	1.11 (0.25)	1.36 (0.19)
min/100 min sleep	IS	29.52 (2.21)	25.16 (1.43)
	T	5.29 (0.55)	5.17 (0.53)
Body Movements	AS	26 (2.50)	24 (3.22)
Number/100 min sleep	QS	9 (1.61)	10 (1.17)
	IS	140 (10.43)	119 (7.21)
	T	31 (2.23)	30 (3.51)
Periodic Breathing	AS	3.37 (1.09)	2.83 (0.96)
Total duration	QS	1.05 (0.39)	0.77 (0.69)
min/100 min sleep	IS	1.36 (0.68)	2.05 (1.59)
	T	1.84 (0.54)	1.40 (0.67)
Periodic Breathing	AS	7 (1.69)	6 (2.01)
Number/100 min sleep	QS	2 (0.69)	1 (1.00)
	IS	3 (1.75)	2 (1.59)
	T	4 (0.95)	3 (1.12) *

* $P < 0.05$

Figure 37


Bronchiolitis
Periodic breathing
AS
QS
Tot
p<0.05
number/100mins sleep
30
25
20
15
10
5
0
Dur
Rec
Dur
Rec
Dur
Rec

per 100 minutes total sleep time were also compared with data from healthy controls (C). The number of movements was increased ($P < 0.01$) in bronchiolitis. No differences were observed in the amount of periodic breathing present.

Appendix 15 gives paired data (illness and recovery) for individual cases of bronchiolitis.

6.2.2 Upper respiratory tract infection

Apnoea variables, percent sleep, respiration rate and heart rate

Table 23 gives the results for apnoea variables, percent sleep, respiration rate and heart rate in relation to sleep phase during and following recovery from upper respiratory tract infections. With the exception of respiration rate, which was slightly but significantly increased following recovery, no other significant differences were observed between corresponding variables. No infant had central apnoea $\geqslant$20 seconds.

Obstructive apnoea, periodic breathing and gross body movements

Three infants had episodes of obstructive apnoea - brief ($\geqslant 3 < 6$ seconds) in three and prolonged ($\geqslant 6$ seconds) in one, occurring during the course of infection. Table 24 gives the results for gross body movements and periodic breathing in infants studied during and following recovery

Table 23

Apnoea variables, per cent sleep, respiration and heart rates in 5 infants during and following recovery from upper respiratory tract infection

		During (Mean & SE) n = 5	Recovery (Mean & SE) n = 5
Apnoea Index	AS	0.24 (0.07)	0.69 (0.42)
	QS	1.10 (0.46)	0.67 (0.18)
	IS	0.33 (0.20)	1.11 (0.49)
	T	0.59 (0.24)	0.68 (0.23)
Apnoea Attack Rate	AS	0.04 (0.01)	0.09 (0.04)
	QS	0.14 (0.06)	0.08 (0.02)
	IS	0.06 (0.04)	0.15 (0.07)
	T	0.08 (0.03)	0.13 (0.05)
Episode of Longest Duration (sec)	AS	5.20 (1.32)	6.20 (1.83)
	QS	5.84 (2.54)	7.68 (2.16)
	IS	2.80 (1.72)	4.62 (1.89)
	T	7.22 (2.09)	7.78 (2.16)
Mean Duration of Apnoea (sec)	AS	5.09 (1.28)	5.62 (1.53)
	QS	4.95 (2.14)	5.63 (1.72)
	IS	2.67 (1.63)	4.30 (1.76)
	T	5.97 (1.62)	6.05 (1.60)
Apnoea per cent	AS	1.15 (0.36)	2.63 (1.31)
	QS	3.59 (1.58)	2.63 (0.70)
	IS	1.51 (0.93)	4.80 (2.09)
	T	2.06 (0.79)	2.61 (0.76)
Sleep per cent	AS	42.20 (6.58)	39.80 (5.89)
	QS	41.80 (5.50)	52.40 (6.95)
Respiration Rate	AS	38.25 (3.32)	36.95 (4.68)
	QS	32.04 (2.62)	34.20 (3.84)*
Heart Rate	AS	132.00 (5.74)	134.90 (5.04)
	QS	127.74 (4.79)	131.32 (5.29)

* $p < 0.05$

Gross body movements and periodic breathing in relation to sleep phase in 5 infants during and following recovery from upper respiratory infection.

		During Mean & SE	Recovery Mean & SE
Body Movements	AS	5.68 (1.99)	1.48 (0.31)
Total duration	QS	0.68 (0.34)	0.63 (0.16)
min/100 min sleep	IS	58.21 (9.28)	39.10 (10.77)
	T	12.80 (2.44)	4.01 (0.96)*
Body Movements	AS	28 (10.18)	7 (1.59)
Number/100 min sleep	QS	4 (2.13)	5 (1.88)
	IS	148 (14.87)	87 (14.11)
	T	38 (6.71)	12 (2.46)*
Periodic Breathing	AS	0.38 (0.27)	1.31 (0.89)
Total duration	QS	1.22 (0.77)	0.83 (0.28)
min/100 min sleep	IS	0.59 (0.45)	0.58 (0.58)
	T	0.75 (0.46)	1.12 (0.54)
Periodic Breathing	AS	1 (0.77)	4 (2.91)
Number/100 min sleep	QS	3 (1.84)	3 (1.02)
	IS	1 (0.73)	2 (2.20)
	T	2 (1.11)	4 (1.81)

* $P < 0.05$

from infection. The number and duration of movements expressed per 100 minutes total sleep time were significantly increased during infection; no differences were observed in the prevalence of periodic breathing. The results for movements are illustrated in Figure 38. When compared with healthy controls (C), the number ($P < 0.02$) and duration ($P < 0.02$) of movements per 100 minutes total sleep time were increased during infection.

Appendix 16 gives results for individual infants studied during and following recovery from upper respiratory tract infection.

6.2.3 Congenital laryngeal stridor

Apnoea variables, percent sleep, respiration rate and heart rate

Table 25 gives the results for apnoea variables, percent sleep, respiration rate, and heart rate in relation to sleep phase in stridulous infants and matched controls. No differences were observed between corresponding variables. The matched controls comprised infants of the same sex and post-conception age (within 3 weeks) in all but one case (- see Appendix 5). Four of these controls had no previous history of illness whereas 3 had had previous bronchiolitis from which they had recovered. Data from the latter fell within the normal limits obtained for healthy control infants without antecedent respiratory

Figure 38

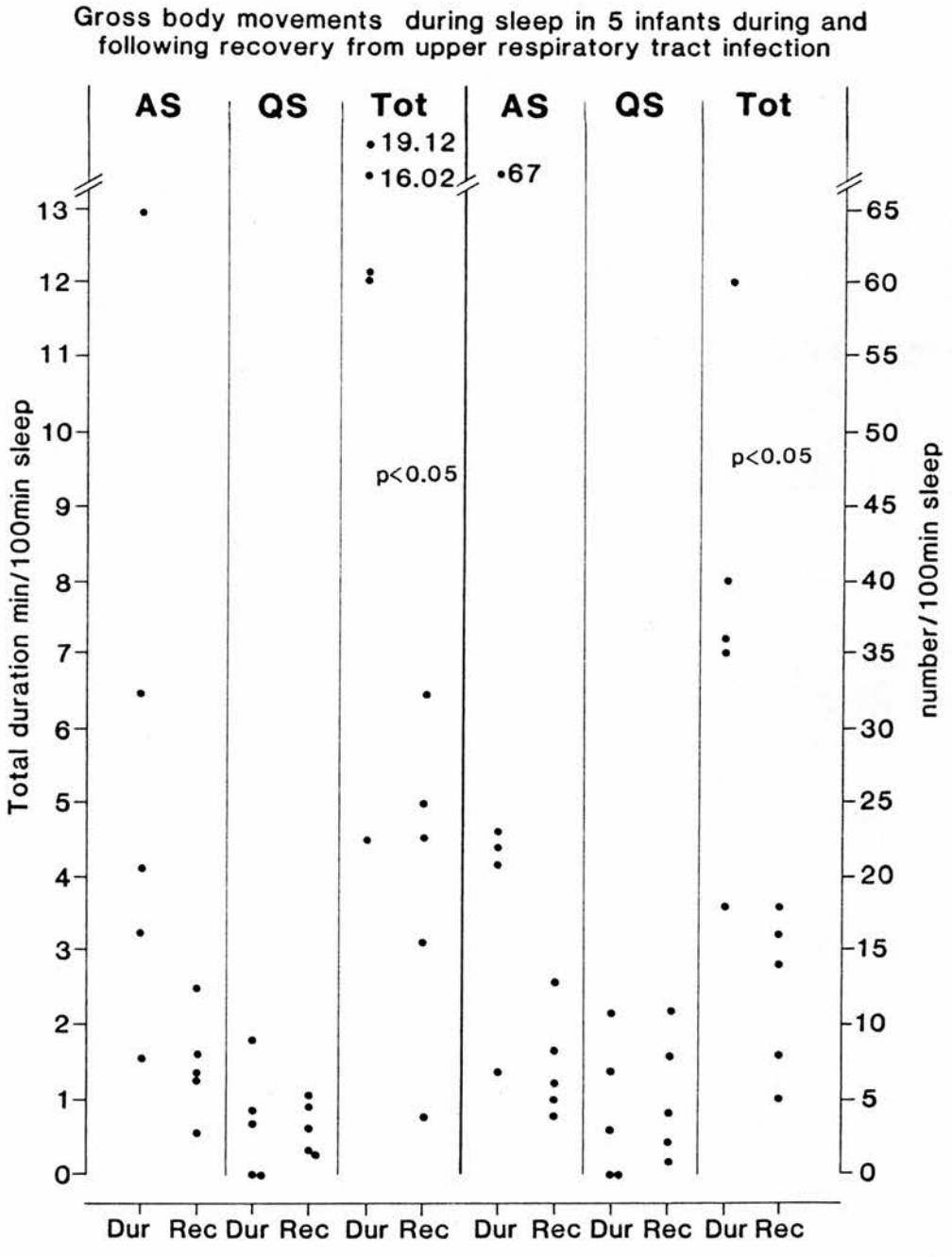

Gross body movements during sleep in 5 infants during and following recovery from upper respiratory tract infection
AS
QS
Tot
AS
QS
Tot
•19.12
•16.02
•67
p<0.05
p<0.05
Total duration min/100min sleep
number/100min sleep
0
1
2
3
4
5
6
7
8
9
10
11
12
13
0
5
10
15
20
25
30
35
40
45
50
55
60
65
Dur Rec Dur Rec Dur Rec Dur Rec Dur Rec Dur Rec

Table 25

Apnoea variables, per cent sleep, respiration and heart rates in relation to sleep phase in 7 infants with stridor and their case controls

		Index (Mean & SE) n = 7	Control (Mean & SE) n = 7
Apnoea Index	AS	0.44 (0.36)	0.29 (0.14)
	QS	0.36 (0.14)	0.38 (0.14)
	IS	1.79 (1.07)	0.26 (0.15)
	T	0.45 (0.25)	0.33 (0.10)
Apnoea Attack Rate	AS	0.06 (0.05)	0.14 (0.02)
	QS	0.05 (0.02)	0.05 (0.02)
	IS	0.25 (0.15)	0.04 (0.02)
	T	0.06 (0.03)	0.05 (0.02)
Episode of Longest Duration (sec)	AS	3.81 (1.87)	4.27 (1.55)
	QS	7.37 (1.57)	5.60 (1.52)
	IS	4.44 (1.63)	3.02 (1.44)
	T	8.71 (0.96)	7.54 (0.51)
Mean Duration of Apnoea (sec)	AS	3.15 (1.49)	3.82 (1.36)
	QS	6.52 (1.15)	5.00 (1.32)
	IS	4.14 (1.49)	3.03 (1.44)
	T	7.47 (0.29)	6.71 (0.22)
Apnoea per cent	AS	1.70 (1.36)	1.26 (0.57)
	QS	1.29 (0.50)	1.59 (0.56)
	IS	3.64 (1.63)	1.08 (0.57)
	T	1.72 (0.91)	1.88 (0.48)
Sleep per cent	AS	39.10 (4.72)	43.40 (3.80)
	QS	48.40 (4.31)	44.30 (4.20)
Respiration Rate	AS	37.00 (3.42)	39.00 (1.76)
	QS	31.40 (3.18)	34.60 (2.65)
Heart Rate	AS	128.20 (4.41)	127.20 (2.63)
	QS	120.70 (3.98)	115.50 (5.70)

infection (see Figures 28-34).

Obstructive apnoea, periodic breathing and gross body movements

Three infants had episodes of obstructive apnoea - three brief ($\geq 3 < 6$ seconds) and one prolonged (≥ 6 seconds). Table 26 gives the results for gross body movements and periodic breathing in infants with stridor and their matched case controls. No differences were observed between the groups. However, the number of body movements per 100 minutes total sleep time was increased ($P < 0.05$) and the total duration of periodic breathing per 100 minutes total sleep significantly decreased ($P < 0.05$) in stridulous infants compared with unmatched healthy controls (C) whose mean post-conception age was comparable.

Appendix 17 gives data on individual infants with congenital laryngeal stridor.

6.2.4 Pyloric stenosis (recurrent vomiting)

Apnoea variables, percent sleep, respiration rate and heart rate

Table 27 gives the results for apnoea variables, percent sleep, respiration rate and heart rate in relation to sleep state during and following recovery from pyloric stenosis, and in age- and sex-matched controls without antecedent vomiting. Appendix 6 gives further details of the matched

Table 26

Gross body movements and periodic breathing in relation to sleep phase in 7 infants with stridor and their matched case controls.

		At presentation Mean & SE	Matched Control Mean & SE
Body Movements	AS	3.55 (0.70)	6.95 (1.43)
Total duration	QS	1.71 (1.00)	1.23 (0.36)
min/100 min sleep	IS	51.09 (7.57)	30.25 (4.75)
	T	7.61 (1.46)	7.15 (0.65)
Body Movements	AS	23 (3.94)	29 (3.81)
Number/100 min sleep	QS	18 (9.47)	10 (3.38)
	IS	174 (49.14)	87 (13.30)
	T	34 (7.03)	29 (2.67)
Periodic Breathing	AS	0.73 (0.54)	2.18 (0.96)
Total duration	QS	0.30 (0.19)	0.61 (0.36)
min/100 min sleep	IS	0.00 (0.00)	0.00 (0.00)
	T	0.41 (0.29)	1.24 (0.58)
Periodic Breathing	AS	2 (1.56)	5 (2.10)
Number/100 min sleep	QS	1 (0.59)	1 (0.46)
	IS	0 (0.00)	0 (0.00)
	T	1 (0.77)	2 (1.07)

Table 27

Apnoea variables, per cent sleep, respiration and heart rates in relation to sleep phase in 5 infants with recurrent vomiting, and their case controls

		During (Mean & SE) n = 5	Recovery (Mean & SE) n = 5	Control (matched) (Mean & SE)
Apnoea Index	AS	7.00 (2.48)	0.99 (0.52)*	0.67 (0.43)*
	QS	8.90 (5.17)	0.91 (0.45)*	0.65 (0.27)*
	IS	9.36 (4.23)	2.57 (0.96)*	0.69 (0.44)
	T	7.56 (3.18)	1.13 (0.56)*	0.59 (0.26)*
Apnoea Attack Rate	AS	0.87 (0.29)	0.13 (0.07)*	0.08 (0.04)*
	QS	1.05 (0.62)	0.13 (0.06)*	0.08 (0.04)
	IS	1.05 (0.47)	0.31 (0.11)	0.09 (0.06)
	T	0.90 (0.37)	0.15 (0.07)*	0.07 (0.03)*
Episode of Longest Duration (sec)	AS	13.30 (1.37)	7.38 (3.15)*	6.38 (1.85)
	QS	13.02 (0.88)	7.88 (0.46)*	5.94 (2.59)*
	IS	9.14 (2.49)	8.04 (2.13)	4.18 (1.72)
	T	14.82 (0.58)	9.66 (1.03)*	7.38 (2.12)*
Mean Duration of Apnoea (sec)	AS	7.95 (0.24)	7.33 (0.32)	5.78 (1.55)
	QS	9.48 (0.91)	7.03 (0.26)*	5.02 (2.13)
	IS	6.87 (1.75)	6.65 (1.67)	4.18 (1.72)
	T	8.42 (0.18)	7.37 (0.29)	6.07 (1.61)
Apnoea per cent	AS	21.28 (6.34)	3.67 (1.83)*	2.41 (1.34)*
	QS	25.51 (14.22)	3.34 (1.42)*	2.29 (0.99)
	IS	27.36 (11.58)	8.91 (3.19)	2.86 (1.69)
	T	22.14 (8.35)	4.08 (1.64)*	2.15 (0.81)*
Sleep per cent	AS	50.20 (2.63)	46.60 (2.50)	45.60 (5.49)
	QS	38.60 (5.07)	42.00 (3.70)	44.20 (6.76)
Respiration Rate	AS	25.60 (1.11)	31.40 (2.70)	37.60 (3.00)*
	QS	22.50 (1.76)	27.20 (1.50)*	39.40 (4.12)*
Heart Rate	AS	123.40 (6.63)	129.60 (5.94)	125.10 (8.00)
	QS	115.20 (5.73)	126.50 (4.58)*	120.70 (7.23)

* $p < 0.05$

controls. One had had previous upper respiratory tract infection; the remaining 4 had had no antecedent illnesses. Apnoea index, apnoea attack rate and apnoea percent were significantly increased during illness, usually in both main phases of sleep when compared with recovery or matched control data. Similarly, the mean and longest duration of apnoea episodes were increased during illness. Two infants had central apnoea >15 seconds (Case 40 16.9 seconds AS; Case 44 15.2 seconds QS) neither had episodes >20 seconds. The proportion of time spent in each sleep phase was comparable during and following illness. Respiration rate and heart rate were significantly lower in quiet sleep during illness than following recovery; respiration rate was reduced when compared with matched controls in both active and quiet sleep.

Obstructive apnoea, periodic breathing and gross body movements

Four infants with recurrent vomiting had obstructive apnoea - two brief ($\geq 3 < 6$ seconds) and four prolonged (≥ 6 seconds) with improvement on recovery.

Table 28 gives results for gross body movements and periodic breathing before and after recovery, and also in matched control groups of infants. The increase in body movements when symptoms were present did not reach statistical significance compared with either control group, but the

Gross body movements and periodic breathing in relation to sleep phase in 5 infants during and following recovery from recurrent vomiting and their matched case controls

		During Mean & SE	Recovery Mean & SE	Matched Controls Mean & SE
Body Movements	AS	4.28 (0.83)	4.36 (0.52)	6.23 (2.32)
Total duration	QS	1.33 (0.45)	0.84 (0.32)	1.19 (0.56)
min/100 min sleep	IS	56.27 (11.34)	43.41 (3.92)	36.76 (11.57)
	T	8.56 (2.20)	7.78 (1.77)	6.80 (1.25)
Body Movements	AS	24 (5.46)	25 (2.13)	24 (7.72)
Number/100 min sleep	QS	11 (3.20)	5 (4.64)	12 (5.56)
	IS	275 (128.38)	120 (9.75)	77 (24.39)
	T	35 (10.18)	29 (5.09)	23 (4.07)
Periodic Breathing	AS	18.91 (7.43)	1.93 (1.14)	0.62 (0.50)
Total duration	QS	21.28 (12.58)	0.84 (0.83)	0.56 (0.25)
min/100 min sleep	IS	12.41 (6.14)	1.46 (1.16)	0.00 (0.00)
	T	15.65 (8.01)	1.31 (0.64)*	0.62 (0.25)
Periodic Breathing	AS	25 (7.06)	5 (2.40)	2 (1.19)
Number/100 min sleep	QS	14 (8.46)	1 (1.00)	2 (0.85)
	IS	23 (10.12)	6 (4.69)	0 (0.00)
	T	20 (7.48)	3 (1.26)*	2 (0.65)

* $p = 0.06$

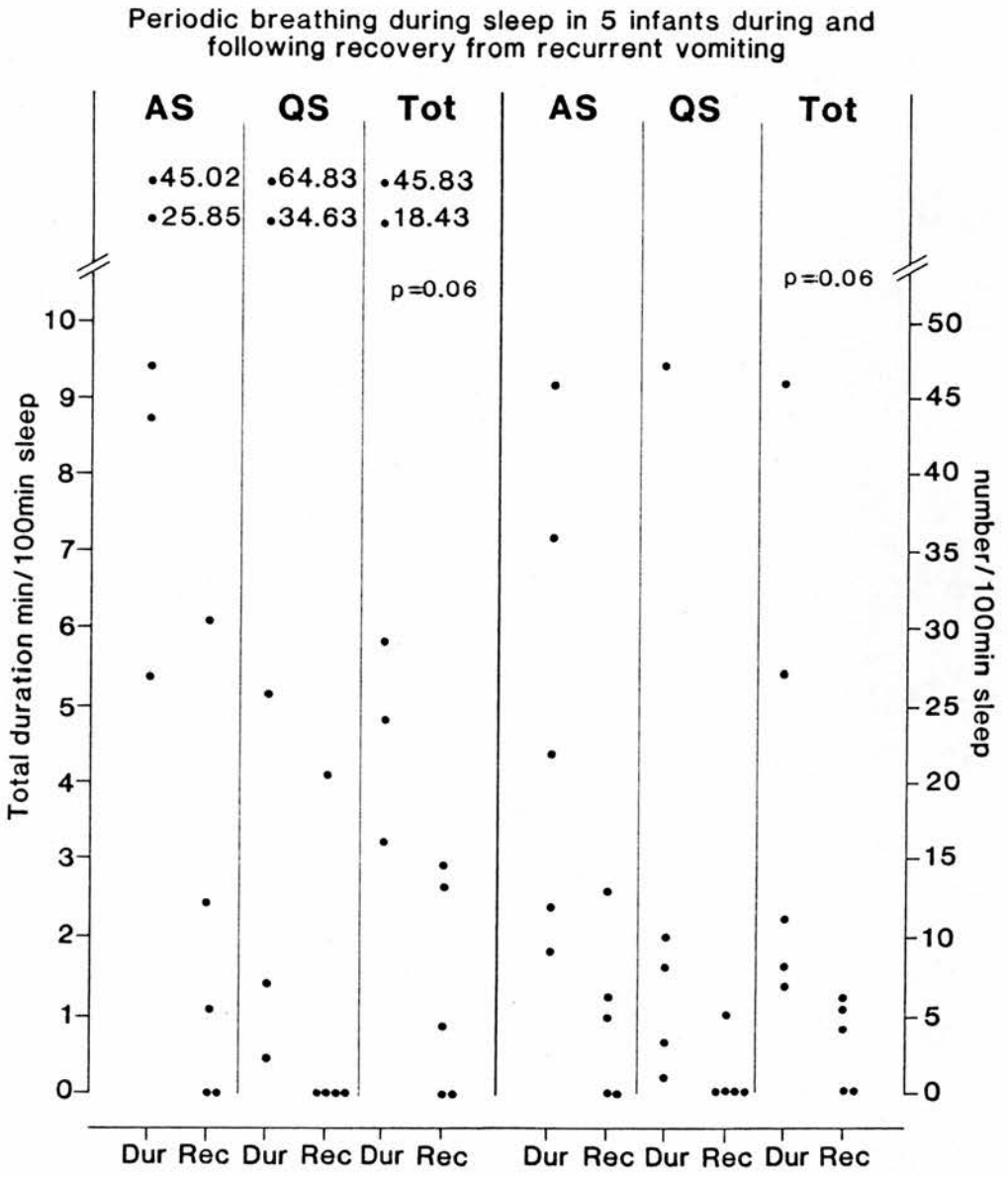
number of episodes and total duration of periodic breathing were both increased ($P = 0.06$). Failure of this increase to reach statistical significance in index/control comparisons reflects the paucity of data for paired non-parametric statistical comparisons. In Figure 39 these data are presented as observations in individual infants. However, when index data were compared with those of healthy unmatched controls (C), the amount of periodic breathing (number and duration) per 100 minutes total sleep time was significantly increased ($P < 0.05$) during illness. Appendix 18 gives the illness and recovery data in individual infants.

6.3 Siblings of SIDS victims

Apnoea variables, percent sleep, respiration rate and heart rate

Table 29 gives the results for apnoea variables, percent sleep, respiration rate and heart rate in relation to sleep phase in 24 siblings of previous SIDS victims in whom 50 studies were conducted between 40 and 92 weeks post-conception age. For each variable, the mean ($\pm$SE), median, and range are given corresponding to a mean conception age of 53.8 weeks. Table 30 gives in addition predicted mean values for 55.5 and 50 weeks post-conception age. Corresponding values for each variable are remarkably similar in both AS and QS.

Figure 39


Periodic breathing during sleep in 5 infants during and following recovery from recurrent vomiting
AS
QS
Tot
AS
QS
Tot
•45.02
•25.85
•64.83
•34.63
•45.83
•18.43
p=0.06
p=0.06
Total duration min/100min sleep
number/100min sleep
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30
35
40
45
50
Dur Rec Dur Rec Dur Rec Dur Rec Dur Rec Dur Rec

Apnoea variables, per cent sleep, respiratory and heart rates (mean, median and range) in relation to sleep phase in 24 siblings of sudden infant death syndrome victims.

		Observed Mean & SE	Median	Range
Apnoea Index	AS	0.75 (0.16)	0.38	0.00 - 6.22
	QS	0.64 (0.15)	0.30	0.00 - 4.85
	IS	0.96 (0.19)	0.21	0.00 - 4.70
	T	0.69 (0.11)	0.44	0.00 - 3.00
Apnoea Attack Rate	AS	0.13 (0.03)	0.08	0.00 - 1.34
	QS	0.09 (0.02)	0.04	0.00 - 0.68
	IS	0.13 (0.03)	0.03	0.00 - 0.76
	T	0.10 (0.02)	0.07	0.00 - 0.55
Episode of Longest	AS	5.88 (0.50)	7.30	0.00 - 10.80
Duration (sec)	QS	5.99 (0.58)	7.80	0.00 - 11.40
	IS	4.29 (0.65)	3.10	0.00 - 15.00
	T	8.02 (0.45)	8.50	0.00 - 15.00
Mean duration of	AS	5.14 (0.43)	6.59	0.00 - 9.10
Apnoea (sec)	QS	5.19 (0.49)	6.74	0.00 - 10.00
	IS	3.82 (0.56)	3.09	0.00 - 11.55
	T	6.41 (0.33)	6.92	0.00 - 9.90
Apnoea per cent	AS	2.85 (0.58)	1.33	0.00 - 22.80
	QS	2.26 (0.47)	1.10	0.00 - 14.08
	IS	3.28 (0.65)	0.00	0.00 - 15.38
	T	2.50 (0.39)	1.63	0.00 - 11.80
Sleep per cent	AS	39.56 (1.67)	38.50	17.00 - 61.00
	QS	50.98 (1.71)	51.50	30.00 - 78.00
Heart rate	AS	117.88 (3.69)	121.50	101.00 - 140.00
	QS	113.64 (3.67)	118.00	92.00 - 143.00
Respiration rate	AS	30.40 (1.64)	30.00	24.00 - 60.00
	QS	26.92 (1.37)	27.00	19.00 - 49.00

Table 30

Apnoea variables, per cent sleep, respiratory and heart rates in relation to sleep phase in 24 siblings of sudden infant death syndrome victims.

		Observed mean & SE	Predicted means (wks PCA) & SE	
			55.5	50
Apnoea Index	AS	0.75 (0.16)	0.75 (0.22)	0.76
	QS	0.64 (0.15)	0.61 (0.27)	0.61
	IS	0.96 (0.19)	0.81 (0.28)	0.78
	T	0.69 (0.11)	0.67 (0.20)	0.67
Apnoea Attack Rate	AS	0.13 (0.03)	0.13 (0.04)	0.13
	QS	0.09 (0.02)	0.08 (0.04)	0.08
	IS	0.13 (0.03)	0.11 (0.03)	0.10
	T	0.10 (0.02)	0.10 (0.03)	0.10
Episode of Longest Duration (sec)	AS	5.88 (0.50)	5.62 (0.72)	5.60
	QS	5.99 (0.58)	5.66 (0.73)	5.60
	IS	4.29 (0.65)	4.08 (0.71)	4.04
	T	8.02 (0.45)	7.69 (0.70)	7.65
Mean Duration (sec)	AS	5.14 (0.43)	4.90 (0.58)	4.88
	QS	5.19 (0.49)	5.01 (0.60)	5.00
	IS	3.82 (0.56)	3.68 (0.60)	3.64
	T	6.41 (0.33)	6.29 (0.48)	6.28
Apnoea per cent	AS	2.85 (0.58)	2.86 (0.77)	2.89
	QS	2.26 (0.47)	2.11 (0.81)	2.08
	IS	3.28 (0.65)	2.79 (0.94)	2.72
	T	2.50 (0.39)	2.40 (0.65)	2.41
Sleep per cent	AS	39.56 (1.67)	39.97 (1.82)	40.09
	QS	50.98 (1.71)	50.59 (1.93)	50.48
Heart rate	AS	117.88 (3.69)	118.41 (4.12)	118.66
	QS	113.64 (3.67)	114.22 (3.74)	114.53
Respiration Rate	AS	30.40 (1.64)	30.52 (1.81)	30.67
	QS	26.92 (1.37)	27.08 (1.44)	27.21

Table 31 compares apnoea variables, percent sleep, respiration rate and heart rate obtained in siblings with control data from 10 healthy controls (C) without antecedent respiratory illness. No differences were observed for apnoea index, apnoea attack rate, apnoea percent or the duration of apnoeic episodes.

Active sleep was significantly decreased in siblings, for mean age and matched post-conception age comparisons ($P < 0.01$). Figures 40,41 give the results for active sleep and quiet sleep respectively. A corresponding increase in quiet sleep was also observed but did not reach statistical significance. Respiration rate was significantly decreased in siblings when compared with controls for mean age and post-conception age-matched comparisons. The trends with post-conception age for each variable considered were comparable in both siblings and control groups of infants. Table 32 presents data for siblings for whom matched control data were available. No differences were observed between index cases and their matched controls during initial studies except for a significant decrease in respiration rate ($P < 0.01$) in siblings during quiet sleep. Figures 42 and 43 give respiration rates for siblings and controls, For the comparisons presented, respiration rate is lower in siblings. There is, however, marked overlap between the groups. At the time of second studies (Table 32) apnoea index, apnoea attack

Comparison of apnoea variables, per cent sleep, respiration and heart rates in siblings and controls (C)

		Observed Mean & SE	Predicted Means (wks PCA) & SE	
			55.5	50
Apnoea Index	AS (Sib	0.75 (0.16)	0.75 (0.22)	0.76
	(C	0.73 (0.22)	0.73 (0.30)	0.74
	QS (Sib	0.64 (0.15)	0.61 (0.27)	0.61
	(C	1.12 (0.55)	1.10 (0.34)	1.09
	IS (Sib	0.96 (0.19)	0.81 (0.28)	0.78
	(C	0.56 (0.16)	0.47 (0.36)	0.44
	T (Sib	0.69 (0.11)	0.67 (0.20)	0.67
	(C	0.85 (0.32)	0.85 (0.25)	0.85
Apnoea Attack Rate	AS (Sib	0.13 (0.03)	0.13 (0.04)	0.13
	(C	0.10 (0.03)	0.10 (0.06)	0.11
	QS (Sib	0.09 (0.02)	0.08 (0.04)	0.08
	(C	0.16 (0.08)	0.15 (0.05)	0.15
	IS (Sib	0.13 (0.03)	0.11 (0.03)	0.10
	(C	0.07 (0.02)	0.06 (0.04)	0.06
	T (Sib	0.10 (0.02)	0.10 (0.03)	0.10
	(C	0.12 (0.05)	0.12 (0.04)	0.12
Episode of Longest Duration (sec)	AS (Sib	5.88 (0.50)	5.62 (0.72)	5.60
	(C	6.38 (0.62)	6.32 (1.00)	6.30
	QS (Sib	5.99 (0.58)	5.66 (0.73)	5.60
	(C	6.43 (0.69)	6.37 (0.99)	6.32
	IS (Sib	4.29 (0.65)	4.08 (0.71)	4.04
	(C	3.71 (0.76)	3.56 (0.92)	3.52
	T (Sib	8.02 (0.45)	7.69 (0.70)	7.65
	(C	7.85 (0.55)	7.80 (1.00)	7.77
Mean Duration (sec)	AS (Sib	5.14 (0.43)	4.90 (0.58)	4.88
	(C	5.61 (0.53)	5.54 (0.80)	5.52
	QS (Sib	5.19 (0.49)	5.01 (0.60)	5.00
	(C	5.64 (0.59)	5.63 (0.80)	5.61
	IS (Sib	3.82 (0.56)	3.68 (0.60)	3.64
	(C	3.52 (0.71)	3.41 (0.76)	3.38
	T (Sib	6.41 (0.33)	6.29 (0.48)	6.28
	(C	6.44 (0.41)	6.43 (0.67)	6.42

Comparison of apnoea variables, per cent sleep, respiration and heart rates in siblings and controls(C)

		Observed Mean & SE	Predicted Means (wks PCA) & SE	
			55.5	50
Apnoea per cent	AS (Sib	2.85 (0.58)	2.86 (0.77)	2.89
	(C	2.94 (0.85)	2.98 (1.02)	3.02
	QS (Sib	2.26 (0.47)	2.11 (0.81)	2.08
	(C	3.72 (1.54)	3.65 (1.02)	3.62
	IS (Sib	3.28 (0.65)	2.79 (0.94)	2.72
	(C	2.06 (0.57)	1.82 (1.26)	1.74
	T (Sib	2.50 (0.39)	2.40 (0.65)	2.41
	(C	3.09 (1.01)	3.08 (0.85)	3.08
Sleep per cent	AS (Sib	39.56 (1.67)	39.97 (1.82)	40.09
	(C	47.27 (2.19)**	47.55 (0.25)	47.67
	QS (Sib	50.98 (1.71)	50.59 (1.93)	50.48
	(C	43.70 (2.28)	43.44 (2.38)	43.32
Heart Rate	AS (Sib	117.88 (3.69)	118.41 (4.12)	118.66
	(C	127.63 (2.20)	128.32 (2.42)	128.57
	QS (Sib	113.64 (3.67)	114.22 (3.74)	114.53
	(C	122.47 (2.36)	123.34 (1.90)	123.65
Respiration Rate	AS (Sib	30.40 (1.64)	30.52 (1.81)	30.67
	(C	36.57 (1.66)*	36.96 (5.60)	37.08
	QS (Sib	26.92 (1.37)	27.08 (1.44)	27.21
	(C	33.20 (1.73)**	33.45 (5.11)	33.57

* $p < 0.05$

** $p < 0.01$

Two-tailed probability test for trend of variable with post-conception age was not significant for the variables given.

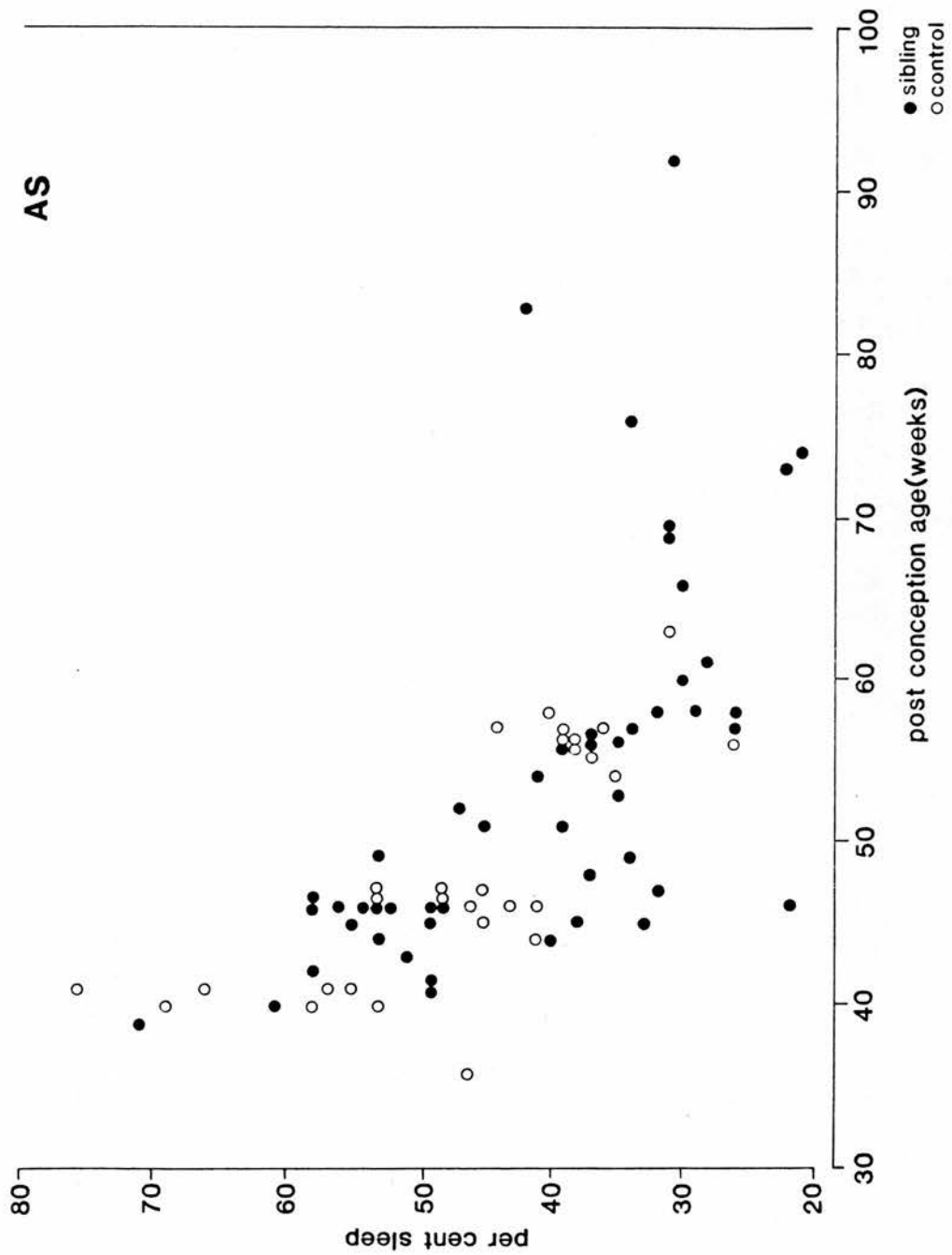

Per cent sleep in 24 siblings of SIDS and 10 control infants
AS
per cent sleep
80
70
60
50
40
30
20
30
40
50
60
70
80
90
100
post conception age(weeks)
● sibling
○ control

Figure 40

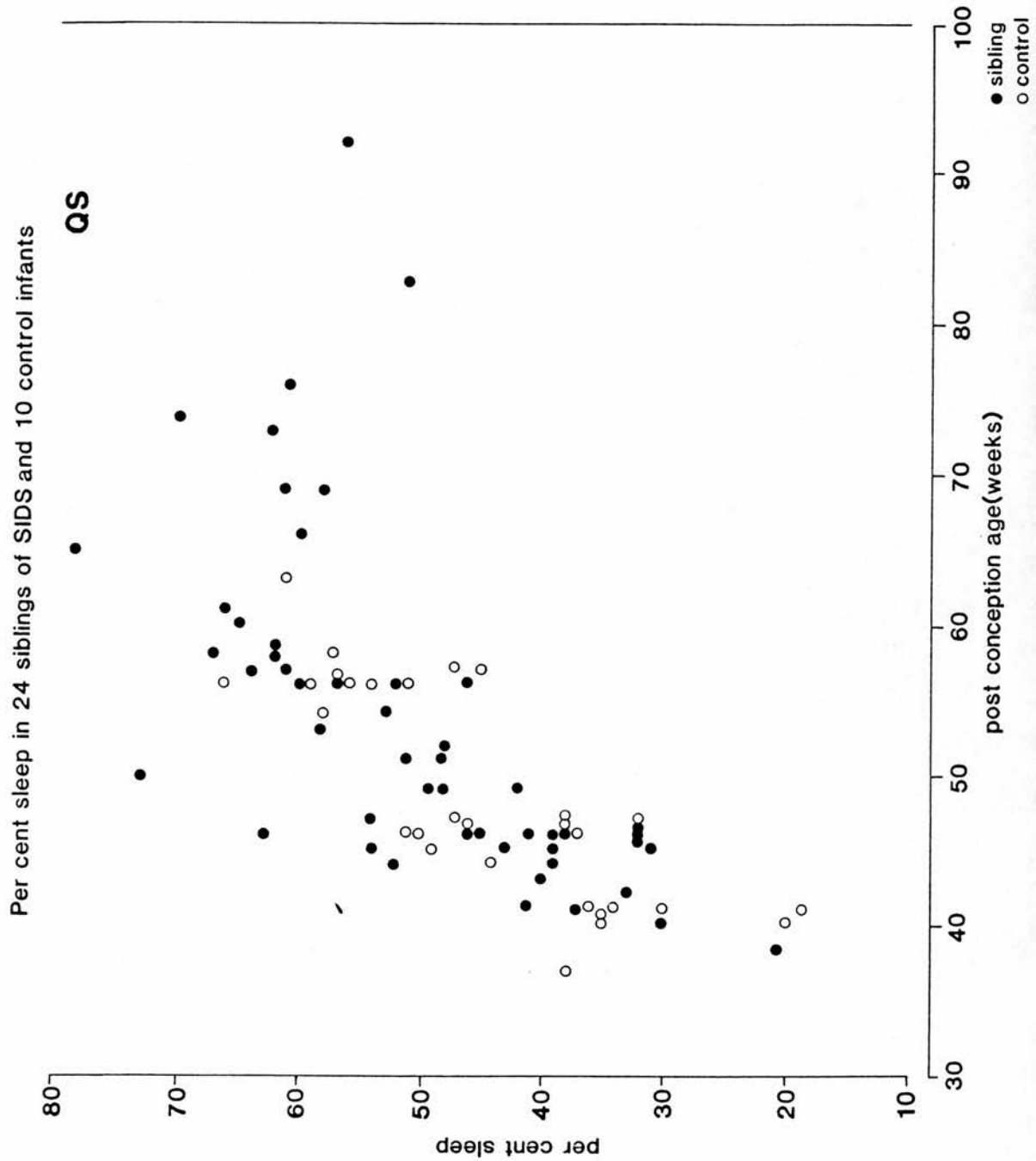

Per cent sleep in 24 siblings of SIDS and 10 control infants
QS
per cent sleep
80
70
60
50
40
30
20
10
30
40
50
60
70
80
90
100
post conception age(weeks)
● sibling
○ control

Figure 41

Table 32

Apnoea variables, per cent sleep, heart and respiratory rates in relation to sleep phase in siblings of sudden infant death syndrome victims and their case controls.

		Study 1 n = 14 (Mean & SE)	Matched Control (Mean & SE)	Study 2 n = 5 (Mean & SE)	Matched Control (Mean & SE)
Apnoea Index	AS	0.46 (0.13)	0.55 (0.18)	0.90 (0.36)	0.18*(0.11)
	QS	0.58 (0.21)	0.42 (0.13)	1.64 (0.84)	0.16 (0.08)
	IS	1.28 (0.37)	0.63 (0.30)	1.46 (0.72)	0.82 (0.68)
	T	0.59 (0.17)	0.45 (0.12)	1.32 (0.49)	0.24*(0.12)
Apnoea Attack Rate	AS	0.07 (0.02)	0.07 (0.02)	0.15 (0.04)	0.03*(0.02)
	QS	0.08 (0.03)	0.06 (0.02)	0.21 (0.10)	0.02 (0.10)
	IS	0.17 (0.05)	0.05 (0.03)	0.19 (0.09)	0.10 (0.08)
	T	0.08 (0.02)	0.06 (0.01)	0.18 (0.07)	0.03*(0.02)
Episode of Longest	AS	4.71 (1.00)	5.64 (1.05)	8.08 (0.57)	3.04*(1.88)
Duration (sec)	QS	6.05 (1.11)	5.01 (1.27)	7.10 (1.81)	4.58 (1.89)
	IS	6.00 (1.15)	3.02 (0.98)	5.10 (2.09)	3.72 (2.41)
	T	8.45 (0.51)	7.02 (0.93)	9.18 (0.34)	6.90 (1.93)
Mean Duration of	AS	4.40 (0.93)	5.06 (0.91)	7.19 (0.37)	2.77 (1.70)
Apnoea (sec)	QS	5.45 (0.97)	4.35 (1.08)	5.96 (1.50)	4.27 (1.76)
	IS	5.38 (0.98)	3.02 (0.98)	4.61 (1.88)	3.05 (1.88)
	T	7.28 (0.28)	6.09 (0.73)	7.61 (0.27)	5.69 (1.45)
Apnoea per cent	AS	2.03 (0.57)	2.09 (0.61)	4.02 (1.10)	0.80*(0.49)
	QS	2.29 (0.86)	1.58 (0.46)	5.43 (2.33)	0.68 (0.31)
	IS	5.04 (1.47)	1.57 (0.69)	5.72 (2.82)	3.01 (2.42)
	T	2.39 (0.69)	1.93 (0.42)	4.65 (1.61)	0.96*(0.46)
Sleep per cent	AS	36.64 (3.54)	41.43 (2.55)	34.60 (1.86)	36.20 (3.15)
	QS	53.71 (3.69)	46.64 (3.19)	56.60 (3.49)	56.20 (3.53)
Respiration Rate	AS	33.57 (1.76)	37.99 (1.95)	26.80 (1.00)	28.36 (1.96)
	QS	28.27 (1.61)	33.99**(1.99)	22.80 (0.55)	25.36 (1.41)
Heart Rate	AS	124.12 (2.04)	130.49 (2.50)	111.82 (2.96)	119.18 (2.17)
	QS	120.60 (2.41)	127.19 (2.77)	104.82 (3.67)	114.82 (2.00)

* $p < 0.05$ ** $p < 0.01$

Figure 42

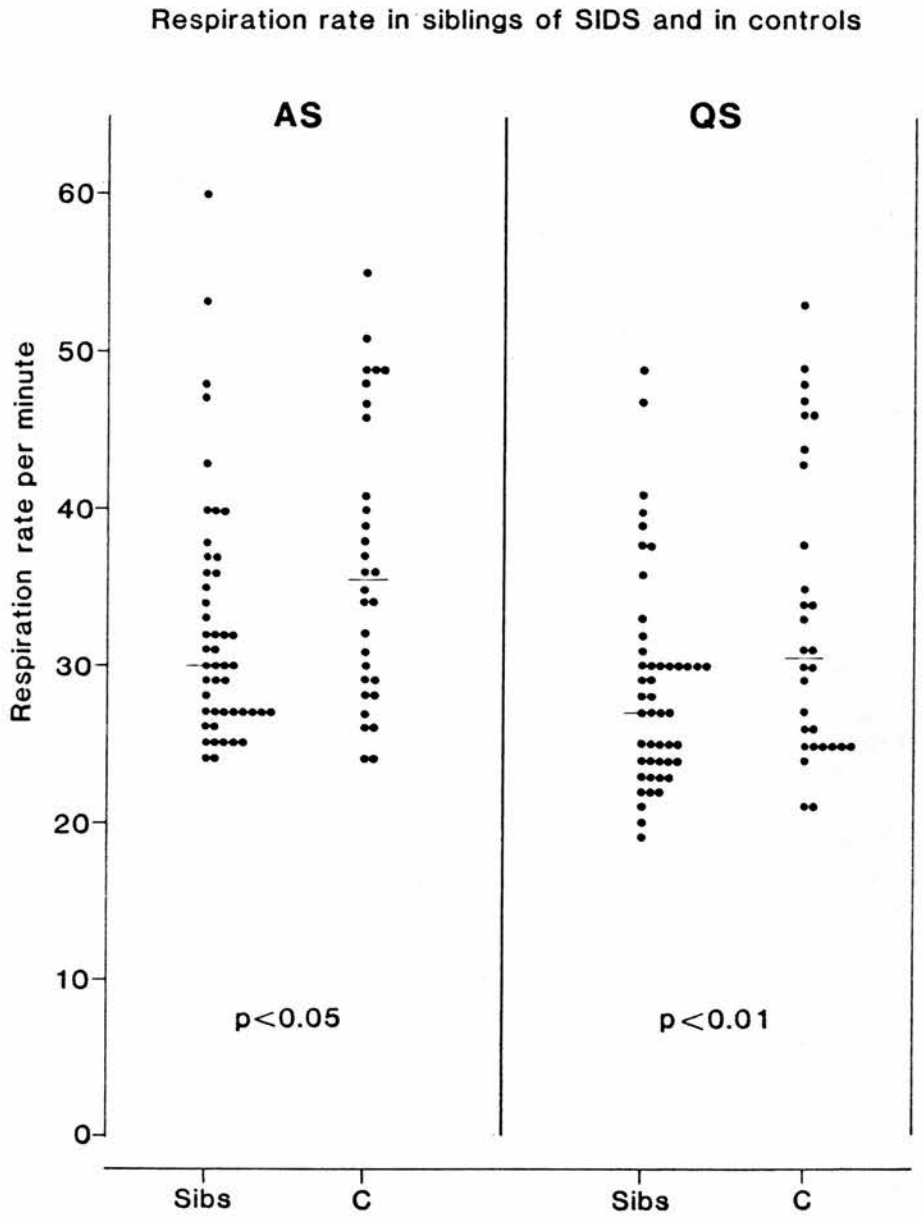
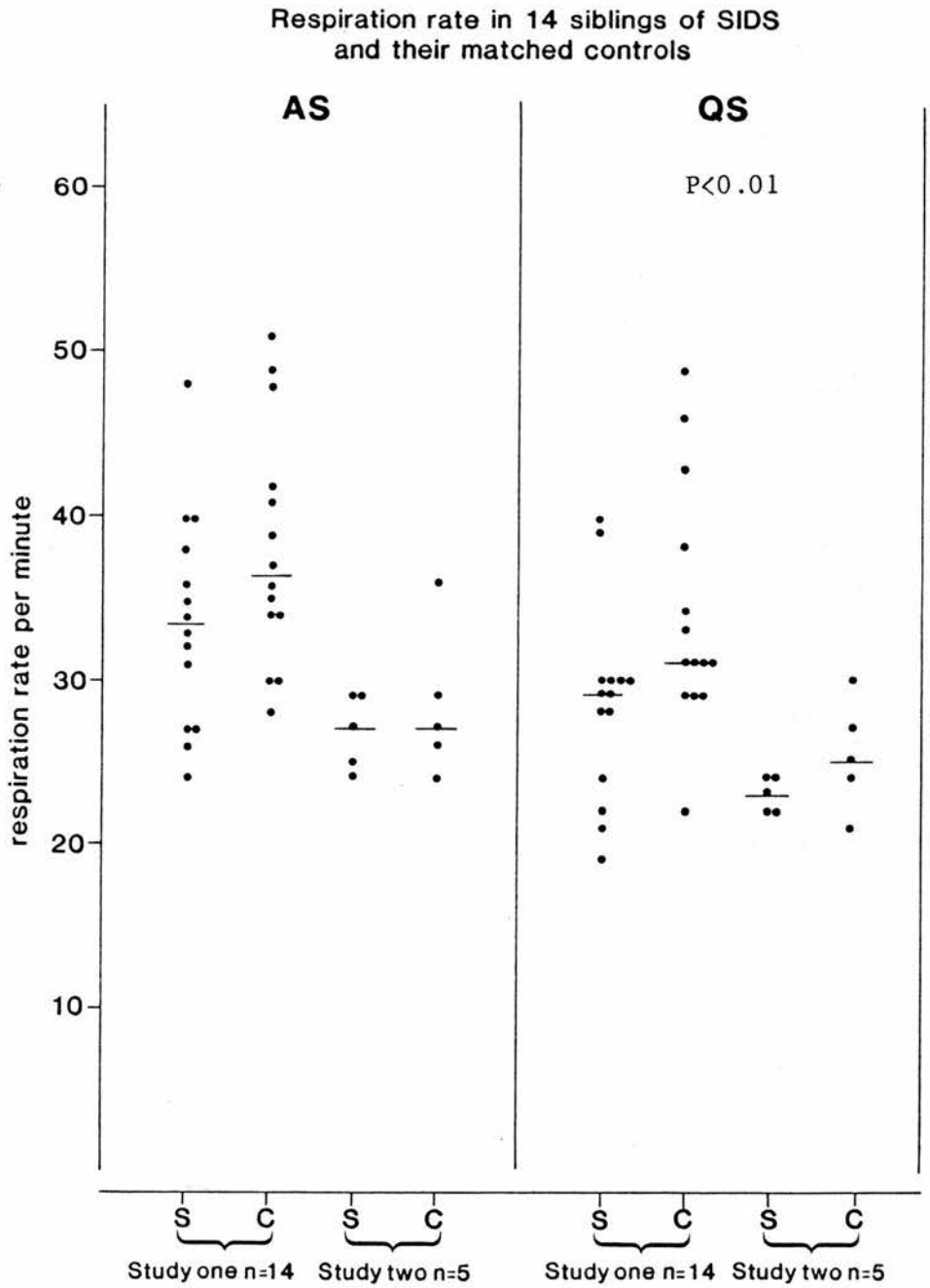

Respiration rate in siblings of SIDS and in controls
AS
QS
Respiration rate per minute
60
50
40
30
20
10
0
p<0.05
p<0.01
Sibs
C
Sibs
C

Figure 43


Respiration rate in 14 siblings of SIDS
and their matched controls
AS
QS
P<0.01
respiration rate per minute
60
50
40
30
20
10
S
C
S
C
S
C
S
C
Study one n=14
Study two n=5
Study one n=14
Study two n=5

rate and apnoea percent were significantly increased in infants during active sleep; apnoea index and apnoea percent were also increased in relation to total sleep time. Although siblings had less AS and more QS than controls at both initial and follow-up studies, these differences were not statistically significant. For initial study, 14 matched case controls were available; 8 had no previous history of illness and the remaining 6 had recovered from upper respiratory infection or bronchiolitis. Details of these controls are given in appendix 8. Although infants were carefully matched for gender and post-conception age, the age range of the infants studied varied considerably. The 5 infants in whom matched comparisons were made (Table 32) were of similar post-conception age - approximately 56 weeks.

Obstructive apnoea, periodic breathing and gross body movements

When the records of all 24 infants were examined for obstructive apnoea, 2 had episodes $\geq$ 6 seconds during active sleep (Cases 63 and 66). These, and 2 additional cases (Cases 59 and 62) also had brief episodes of obstructive apnoea ($>3<6$ seconds). Both infants with prolonged obstructive apnoea had coincidental upper respiratory infection. These were the only infants in the siblings group studied during minor illnesses.

Table 33 gives the results for gross body movements and periodic breathing in 24 infants for whom data obtained

Gross body movements and periodic breathing in relation to sleep phase in 24 siblings of sudden infant death syndrome victims

		Study 1 n=24 (Mean & SE)	Study 2 n=5 (Mean & SE)
Body Movements	AS	3.85 (0.37)	3.92 (1.42)
Total duration	QS	0.92 (0.20)	0.98 (0.32)
min/100 min sleep	IS	41.51 (3.89)	46.36 (11.76)
	T	6.04 (0.60)	6.39 (2.24)
Body Movements	AS	25 (1.97)	28 (9.87)
Number/100 min sleep	QS	8 (1.42)	11 (4.56)
	IS	130 (12.95)	128 (20.78)
	T	29 (4.24)	28 (9.65)
Periodic Breathing	AS	1.05 (0.34)	3.87 (1.24)
Total duration	QS	0.61 (0.30)	3.29 (1.79)
min/100 min sleep	IS	0.87 (0.32)	1.43 (1.01)
	T	0.82 (0.28)	3.15 (1.32)
Periodic Breathing	AS	3 (0.82)	7 (2.73)
Number/100 min sleep	QS	1 (0.58)	6 (2.56)
	IS	3 (0.93)	2 (1.47)
	T	2 (0.61)	6 (1.93)

at initial studies were analysed. The results are comparable to those obtained in healthy controls (C) without antecedent illness. Data on 5 siblings who had follow-up studies and for whom central apnoea data have been presented (Table 32) are also given. The results for body movements and periodic breathing in this subgroup are comparable to total group data. For each variable, the scatter of values is wide, in both data sets.

Table 34 summarises the results for infants for whom matched control data were available. Infants selected for matched controls have been described above in relation to findings for apnoea variables, respiration rate and heart rate. There were no significant differences between index and matched control cases either at first or subsequent studies for any of the variables computed. Appendix 19 gives the values obtained in individual infants.

6.4 'Near-miss' for SIDS

Investigation

Following admission to hospital a detailed history was obtained of each event. The investigation protocol evolved during the course of the study is given in Appendix 11. Infection, neurological, cardiac, and metabolic causes were excluded as far as possible. Detailed radiological assessment was made of the upper

Gross body movements and periodic breathing in relation to sleep phase in 13 siblings of sudden infant death syndrome victims and their case controls

		Study 1 n = 13 (Mean & SE)	Matched Control (Mean & SE)	Study 2 n = 4 (Mean & SE)	Matched Control (Mean & SE)
Body Movements	AS	4.25 (0.47)	4.19 (1.06)	2.67 (0.87)	2.44 (0.88)
Total duration	QS	1.06 (0.31)	0.92 (0.21)	0.65 (0.24)	0.21 (0.09)
min/100 min sleep	IS	46.70 (3.71)	33.01 (4.28)	42.43 (14.31)	32.49 (10.62)
	T	6.71 (0.83)	6.10 (0.77)	4.32 (1.13)	3.91 (0.89)
Body Movements	AS	24 (1.74)	21 (3.43)	20 (6.02)	16 (6.01)
Number/100 min	QS	8 (2.19)	8 (1.99)	7 (1.31)	2 (1.11)
sleep	IS	151 (18.31)	100 (10.63)	118 (23.19)	128 (25.10)
	T	26 (2.42)	25 (3.18)	19 (3.74)	16 (2.12)
Periodic Breathing	AS	1.20 (0.55)	2.72 (1.02)	3.03 (1.18)	2.15 (0.63)
Total duration	QS	0.83 (0.53)	0.47 (0.22)	1.81 (1.28)	0.11 (0.11)
min/100 min sleep	IS	0.93 (0.48)	0.06 (0.06)	1.29 (1.29)	4.58 (4.58)
	T	1.05 (0.49)	1.37 (0.40)	2.11 (1.05)	1.30 (0.41)
Periodic Breathing	AS	3 (1.64)	5 (1.65)	6 (3.20)	5 (0.95)
Number/100 min	QS	2 (1.22)	1 (0.38)	4 (2.63)	1 (0.25)
sleep	IS	3 (1.76)	1 (0.23)	2 (1.50)	4 (4.25)
	T	3 (1.08)	2 (0.69)	5 (1.85)	2 (0.48)

gastro -intestinal tract to exclude swallowing incoordination, H tracheo-oesophageal fistulae and gastro-oesophageal reflux (GOR) as possible causes of tracheo-bronchial aspiration. Radionuclide gastro-oesophagraphy (RNG) was carried out in 14 infants in addition to barium studies. The main findings have been reported by Abreu e Silva et al (1983). Chest X-rays, assessed without reference to clinical details by one experienced paediatric radiologist, showed no evidence of segmental or lobar consolidation or collapse; minimal changes, namely an increase in bronchial markings, were observed in nine infants, and an increase in pulmonary plethora, slight cardiomegaly and prominence of the left atrium noted in a further three. Virological studies were positive in 10 infants - respiratory syncytial virus (RSV) (5), rotavirus (2), polio virus (2), and parainfluenza virus (1). GOR was diagnosed in five of 25 barium studies and 7 of 14 RNG investigations. GOR was demonstrated in 10 infants. Tables 35 and 36 give the main findings on investigation for full-term and pre-term infants respectively, and details of preceding 'cyanotic', 'apnoeic' or 'choking' episodes. Swallowing incoordination was noted in two infants (Cases 73 and 84) in one of whom (Case 84) GOR was also demonstrated. No definite abnormalities were revealed on EEGs; in three infants maturational delay was reported (Cases 88, 92,94) and in two mild asymmetry (Cases 69and 83). ECG abnormalities

Table 35

Clinical Details of Full Term 'near-miss' infants and findings on investigation

Number	Sex	Post Concept. Age (wks)	Cyanosis		'Apnoea'		'Choking'		Chest X-ray on Admission	Virology	G.O. reflux		Diagnosis
			>48 hrs	<48 hrs	>48 hrs	<48 hrs	>48 hrs	<48 hrs			Ba	'Scan'	
69	M	55	-	-	-	-	-	-	Increased Bronchial Markings	RSV	-ve	-	Bronchiolitis ? cross-infection
70	M	46	-	-	-	-	-	+	"	RSV	-ve	-	URTI → Bronchiolitis
71	M	73	-	-	-	-	-	-	"	-ve	-ve	-	URTI; PEN Allergy
72	M	49	-	-	-	-	-	-	N	RSV	-ve	-ve	URTI Bronchiolitis
45	F	50	-	-	-	-	-	-	Increased Bronchial Markings	RSV	-ve	-ve	URTI
73	F	47	+	-	-	-	+	+	"	-ve	-ve	-ve	URTI; Swallowing O.A. Incoordination
74	M	45	-	-	-	-	-	-	N	-ve	-ve	-ve	URTI
75	F	48	-	-	-	-	-	-	N	p'Flu	-ve	+ve	URTI → Bronchiolitis GOR
76	M	45	-	+	-	-	-	+	N	-ve	+ve	+ve	URTI; Infantile larynx; GOR
77	F	44	+	-	-	-	+	+	Increased Bronchial Markings	-ve	-ve	+ve	URTI; GOR
78	F	51	+	-	+	-	+	-	N	Rotavirus	-ve	+ve	GOR
79	M	62	-	-	-	-	-	+	N	Mumps	-ve	+ve	GOR
80	M	47	-	+	-	-	-	-	N	-ve	-ve	+ve	GOR
81	M	53	+	-	-	-	-	+	N	-ve	-ve	+ve	GOR
82	F	42	-	-	+	-	-	+	Increased Pulmonary Plethora	-ve	-ve	+ve	GOR; Egg 'allergy'
83	M	42	+	-	+	-	-	-	N	Polio 2	+ve	-	GOR
84	M	44	+	-	-	-	+	+	Increased Heart size	-ve -ve	+ve +ve	- -	GOR; swallowing O.A.incoordination
85	M	60	-	-	-	-	-	-	N	-ve	-ve	-	-
86	F	58	-	-	+	-	-	-	N	-ve	-ve	-	-
87	F	44	-	-	-	-	-	-	N	-ve	-ve	-	-
88	M	44	-	-	-	-	-	-	N	Rotavirus	-ve	-	-
89	M	39	-	-	+	-	-	-	Increased Bronchial Markings	-ve	-ve	-ve	-
90	M	53	-	-	-	-	-	-	N	-ve	-ve	-ve	-
91	M	48	-	-	-	-	-	-	N	-ve	-ve	-	-

GOR Gastroosoesophageal reflux

URTI Upper respiratory tract infection

RSV Respiratory syncytial virus

OA Obstructive apnoea $\geq$ 6 seconds

CA Central apnoea $\geq$ 20 seconds

Table 36

Clinical Details of Pre-Term 'near-miss' infants and findings on investigation

Number	Sex	Post Conception Age (wks)	Cyanosis		'Apnoea		'Choking'		Chest X-ray on Admission	Virology	Gastro-oesophageal reflux		Diagnosis
			>48 hrs	<48 hrs	>48 hrs	<48 hrs	>48 hrs	<48 hrs			Ba	'Scan'	
40	M	39	+	-	+	-	+	-	Increased Bronchial Markings	- ve	- ve	-	URTI; CA, Pyloric stenosis
92	M	37	-	-	-	-	-	-	N	- ve	-	-	URTI, CA
93	F	43	-	+	-	+	-	-	Increased Bronchial Markings	RSV	- ve	- ve	Bronchiolitis, CA
94	M	42	+	-	+	-	+	-	N	- ve	- ve	-	Metabolic acidosis OA
95	F	36	+	-	-	-	+	-	L Atrial Prominence	- ve	+ ve	-	GOR, OA

GOR Gastrooesophageal reflux
URTI Upper respiratory tract infection

RSV Respiratory syncytial virus
OA Obstructive apnoea ≥ 6 seconds
CA Central apnoea ≥ 20 seconds

were present in two infants - mild right ventricular hypertrophy (Case 71) and probable left ventricular hypertrophy (Case 81). Neither showed evidence of cardiac disease subsequently. One infant developed stridor due to an 'infantile' larynx (Case 76) and another a slightly elevated TSH (Case 80). Serum electrolytes and blood urea, serum calcium, magnesium and urinary amino acid concentrations were within normal limits. No abnormalities of blood T4 and immunoglobulin concentrations were noted. Chromosome studies in 20 infants showed normal karyotypes.

Polygraphic sleep studies - apnoea variables, percent sleep, respiration rate and heart rate

Full term infants

Each infant was studied on at least two occasions. Table 37 gives the results for apnoea variables, respiration and heart rate in relation to sleep phase in 24 full term 'near-miss' infants in whom studies were carried out between 39 and 77 weeks post-conceptional age. For each variable the mean ($\pm$SE), median and range is given corresponding to a mean post-conception age of 54 weeks. Table 38 gives, in addition, predicted mean values for 55.5 and 50 weeks post-conception age. Corresponding values were similar for each variable, both in active sleep and quiet sleep.

Table 39 compares apnoea variables, percent sleep, respiration and heart rate with control data from 10

Apnoea variables, per cent sleep, respiratory and heart rates (mean, median and range) in relation to sleep phase in 24 'near-miss' for SIDS.

		Observed Mean & SE	Median	Range
Apnoea Index	AS	0.78 (0.03)	0.24	0.00 - 8.24
	QS	0.64 (0.04)	0.24	0.00 - 10.25
	IS	0.97 (0.05)	0.00	0.00 - 10.70
	T	0.67 (0.03)	0.32	0.00 - 8.26
Apnoea attack rate	AS	0.11 (0.01)	0.03	0.00 - 1.13
	QS	0.08 (0.01)	0.03	0.00 - 1.34
	IS	0.12 (0.00)	0.00	0.00 - 1.00
	T	0.09 (0.00)	0.04	0.00 - 1.11
Episode of Longest	AS	5.23 (0.10)	6.80	0.00 - 15.00
Duration (sec)	QS	5.54 (0.10)	6.90	0.00 - 14.30
	IS	3.44 (0.10)	0.00	0.00 - 19.30
	T	7.45 (0.10)	8.30	0.00 - 19.30
Mean duration of	AS	4.35 (0.08)	6.57	0.00 - 9.03
Apnoea (sec)	QS	4.65 (0.08)	6.45	0.00 - 12.47
	IS	2.95 (0.08)	0.00	0.00 - 10.70
	T	5.67 (0.06)	6.90	0.00 - 9.75
Apnoea per cent	AS	3.06 (0.11)	1.06	0.00 - 28.37
	QS	2.24 (0.11)	0.79	0.00 - 28.99
	IS	3.49 (0.13)	0.00	0.00 - 30.00
	T	2.50 (0.09)	1.13	0.00 - 25.94
Sleep per cent	AS	38.58 (0.26)	40.50	18.00 - 67.00
	QS	48.74 (0.27)	48.00	21.00 - 74.00
Heart rate	AS	120.49 (0.57)	124.00	108.00 - 151.00
	QS	118.28 (0.52)	119.00	99.00 - 150.00
Respiration rate	AS	33.00 (0.25)	32.00	19.00 - 71.00
	QS	29.24 (0.20)	28.00	18.00 - 59.00

Apnoea variables, per cent sleep, respiratory and heart rates in relation to sleep phase in 24 'near-miss' for SIDS.

		Observed mean & SE	Predicted means (wks PCA) & SE	
			55.5	50
Apnoea Index	AS	0.78 (0.03)	0.82 (0.22)	0.83
	QS	0.64 (0.04)	0.61 (0.28)	0.60
	IS	0.97 (0.05)	0.81 (0.28)	0.78
	T	0.67 (0.03)	0.67 (0.20)	0.67
Apnoea attack rate	AS	0.11 (0.01)	0.11 (0.04)	0.11
	QS	0.08 (0.01)	0.08 (0.04)	0.08
	IS	0.12 (0.00)	0.10 (0.03)	0.09
	T	0.09 (0.00)	0.09 (0.03)	0.09
Episode of Longest Duration (sec)	AS	5.23 (0.10)	5.03 (0.73)	5.02
	QS	5.54 (0.10)	5.38 (0.74)	5.33
	IS	3.44 (0.10)	3.17 (0.73)	3.13
	T	7.45 (0.10)	7.22 (0.71)	7.19
Mean duration (sec)	AS	4.35 (0.08)	4.17 (0.58)	4.15
	QS	4.65 (0.08)	4.63 (0.61)	4.61
	IS	2.95 (0.08)	2.76 (0.61)	2.73
	T	5.67 (0.06)	5.58 (0.49)	5.58
Apnoea per cent	AS	3.06 (0.11)	3.18 (0.78)	3.21
	QS	2.24 (0.11)	2.11 (0.83)	2.08
	IS	3.49 (0.13)	3.02 (0.96)	2.94
	T	2.50 (0.09)	2.53 (0.67)	2.53
Sleep per cent	AS	38.58 (0.26)	39.16 (1.88)	39.28
	QS	48.74 (0.27)	48.19 (1.98)	48.08
Heart rate	AS	120.49 (0.57)	121.75 (4.18)	122.00
	QS	118.28 (0.52)	120.22 (3.80)	120.52
Respiration rate	AS	33.00 (0.25)	33.61 (1.83)	33.77
	QS	29.24 (0.20)	29.66 (1.46)	29.79

Table 39

Comparison of apnoea variables, per cent sleep, respiration and heart rates in 'near-misses' and controls (C)

		Observed Mean & SE	Predicted Means (wks PCA) & SE	
			55.5	50
Apnoea Index	AS (NM	0.78 (0.03)	0.82 (0.22)	0.83
	(C	0.73 (0.22)	0.73 (0.30)	0.74
	QS (NM	0.64 (0.04)	0.61 (0.28)	0.60
	(C	1.12 (0.55)	1.10 (0.34)	1.09
	IS (NM	0.97 (0.05)	0.81 (0.28)	0.78
	(C	0.56 (0.16)	0.47 (0.36)	0.44
	T (NM	0.67 (0.03)	0.67 (0.20)	0.67
	(C	0.85 (0.32)	0.85 (0.25)	0.85
Apnoea Attack Rate	AS (NM	0.11 (0.01)	0.11 (0.04)	0.11
	(C	0.10 (0.03)	0.10 (0.06)	0.11
	QS (NM	0.08 (0.01)	0.08 (0.04)	0.08
	(C	0.16 (0.08)	0.15 (0.05)	0.15
	IS (NM	0.12 (0.00)	0.10 (0.03)	0.09
	(C	0.07 (0.02)	0.06 (0.04)	0.06
	T (NM	0.09 (0.00)	0.09 (0.03)	0.09
	(C	0.12 (0.05)	0.12 (0.04)	0.12
Episode of Longest Duration (sec)	AS (NM	5.23 (0.10)	5.03 (0.73)	5.02
	(C	6.38 (0.62)	6.32 (1.00)	6.30
	QS (NM	5.54 (0.10)	5.38 (0.74)	5.33
	(C	6.43 (0.69)	6.37 (0.99)	6.32
	IS (NM	3.44 (0.10)	3.17 (0.73)	3.13
	(C	3.71 (0.76)	3.56 (0.92)	3.52
	T (NM	7.45 (0.10)	7.22 (0.71)	7.19
	(C	7.85 (0.55)	7.80 (1.00)	7.77
Mean Duration (sec)	AS (NM	4.35 (0.08)	4.17 (0.58)	4.15
	(C	5.61 (0.53)	5.54 (0.80)	5.52
	QS (NM	4.65 (0.08)	4.63 (0.61)	4.61
	(C	5.64 (0.59)	5.63 (0.80)	5.61
	IS (NM	2.95 (0.08)	2.76 (0.61)	2.73
	(C	3.52 (0.71)	3.41 (0.76)	3.38
	T (NM	5.67 (0.06)	5.58 (0.49)	5.58
	(C	6.44 (0.41)	6.43 (0.67)	6.42

Comparison of apnoea variables, per cent sleep, respiration and heart rates in 'near-misses' and controls (C)

		Observed Mean & SE	Predicted Means (wks PCA) & SE	
			55.5	50
Apnoea per cent	AS (NM	3.06 (0.11)	3.18 (0.78)	3.21
	(C	2.94 (0.85)	2.98 (1.02)	3.02
	QS (NM	2.24 (0.11)	2.11 (0.83)	2.08
	(C	3.72 (1.54)	3.65 (1.02)	3.62
	IS (NM	3.49 (0.13)	3.02 (0.96)	2.94
	(C	2.06 (0.57)	1.82 (1.26)	1.74
	T (NM	2.50 (0.09)	2.53 (0.67)	2.53
	(C	3.09 (1.01)	3.08 (0.85)	3.08
Sleep per cent	AS (NM	38.58 (0.26)	39.16 (1.88)	39.28
	(C	47.27 (2.19)	47.55 (0.25)	47.67
	QS (NM	48.74 (0.27)	48.19 (1.98)	48.08
	(C	43.70 (2.28)	43.44 (2.38)	43.32
Heart Rate	AS (NM	120.49 (0.57)	121.75 (4.18)	122.00
	(C	127.63 (2.20)	128.32 (2.42)	128.57
	QS (NM	118.28 (0.52)	120.22 (3.80)	120.52
	(C	122.47 (2.36)	123.34 (1.90)	123.65
Respiration Rate	AS (NM	33.00 (0.25)	33.61 (1.83)	33.77
	(C	36.57 (1.66)	36.96 (5.60)	37.08
	QS (NM	29.24 (0.20)	29.66 (1.46)	29.79
	(C	33.20 (1.73)	33.45 (5.11)	33.57

(Two-tailed probability test for trend of variable with post-conception age was not significant for the variables given)

healthy controls without antecedent illnesses. No differences were observed for any of the variables compared. The trend with post-conception age for each variable considered was not significantly different between the 24 'near-miss' infants and controls.

Table 40 presents data for index cases for whom matched control data were available. No differences were observed between 10 index cases and their matched controls during initial studies or nine cases and matched controls during second studies. For initial studies 10 matched controls were available; six had no previous history of illness and the remaining four had recovered from acute bronchiolitis. At second studies six control infants had had previous respiratory tract infections. Details of these controls are given in appendix 9. Although the infants were carefully matched for gender and post-conception age the age range of infants studied varied considerably at both first and second studies.

Pre-term infants

Table 41 gives the results of initial studies on 5 pre-term 'near-miss' for SIDS infants. These are presented as observations as control data in pre-term infants were not available for comparison.

Apnoea variables, per cent sleep, heart and respiratory rates in relation to sleep phase in 'near-miss' for SIDS and their case controls

		Study 1 n = 10 (Mean & SE)	Matched Control (Mean & SE)	Study 2 n = 9 (Mean & SE)	Matched Control (Mean & SE)
Apnoea Index	AS	1.14 (0.45)	0.23 (0.08)	0.96 (0.23)	0.45 (0.16)
	QS	0.56 (0.19)	0.25 (0.14)	0.35 (0.15)	0.41 (0.12)
	IS	1.73 (0.96)	0.22 (0.10)	1.35 (1.18)	0.23 (0.29)
	T	0.84 (0.27)	0.26 (0.10)	0.61 (0.16)	0.43 (0.13)
Apnoea Attack Rate	AS	0.15 (0.06)	0.03 (0.01)	0.13 (0.03)	0.07 (0.02)
	QS	0.08 (0.03)	0.03 (0.02)	0.05 (0.02)	0.06 (0.02)
	IS	0.22 (0.12)	0.03 (0.02)	0.13 (0.11)	0.03 (0.03)
	T	0.11 (0.04)	0.03 (0.01)	0.08 (0.02)	0.06 (0.02)
Episode of Longest	AS	5.98 (1.37)	4.45 (1.22)	8.01 (1.36)	4.49 (1.46)
Duration (sec)	QS	6.91 (1.24)	3.81 (1.30)	5.13 (1.30)	5.84 (1.13)
	IS	4.57 (1.60)	2.64 (1.08)	3.79 (2.22)	0.90 (0.90)
	T	8.51 (1.10)	7.41 (0.33)	8.76 (1.69)	7.03 (0.95)
Mean Duration of	AS	5.05 (1.12)	4.13 (1.13)	6.36 (0.82)	3.89 (1.24)
Apnoea (sec)	QS	5.87 (1.01)	3.55 (1.20)	4.55 (1.14)	5.35 (1.02)
	IS	3.79 (1.27)	2.64 (1.08)	2.79 (1.44)	0.82 (0.82)
	T	6.51 (0.75)	6.86 (0.21)	6.32 (0.81)	6.19 (0.79)
Apnoea per cent	AS	4.89 (1.68)	0.99 (0.35)	3.87 (0.82)	1.76 (0.59)
	QS	2.23 (0.74)	0.95 (0.50)	1.54 (0.66)	1.72 (0.49)
	IS	6.39 (3.45)	1.01 (0.43)	3.99 (3.29)	0.62 (0.62)
	T	3.36 (1.05)	1.37 (0.44)	2.46 (0.60)	1.74 (0.48)
Sleep per cent	AS	42.20 (2.62)	43.20 (2.03)	35.11 (3.71)	33.78 (2.67)
	QS	47.00 (2.90)	43.80 (2.35)	52.00 (3.08)	58.11 (2.87)
Respiration Rate	AS	32.73 (2.77)	33.24 (2.45)	28.57 (1.65)	32.92 (1.68)
	QS	27.39 (1.73)	30.39 (1.98)	25.17 (1.00)	28.63 (1.14)
Heart Rate	AS	122.78 (3.47)	127.70 (3.57)	117.79 (2.13)	123.66 (2.70)
	QS	119.17 (4.32)	120.29 (4.28)	112.73 (2.69)	115.64 (4.49)

Cases 69, 70, 78, 85-90

Individual apnoea variables, per cent sleep, respiration and heart rates in 5 pre-term 'near-miss' infants (first study only).

Number		40	92	93	94	95
Apnoea Index	AS	16.43	7.98	0.64	0.00	5.15
	QS	28.90	24.30	0.12	0.00	3.11
	IS	19.71	5.54	0.00	0.00	9.10
	T	19.83	13.78	0.25	0.00	4.32
Apnoea Attack	AS	1.98	0.56	0.10	0.00	0.59
Rate	QS	3.44	0.97	0.02	0.00	0.40
	IS	2.16	0.56	0.00	0.00	1.03
	T	2.33	0.72	0.04	0.00	0.52
Episode of	AS	16.9	35.5	6.8	0.00	16.0
Longest Duration	QS	11.9	51.5	6.7	0.00	10.0
	IS	14.3	26.4	0.0	0.00	13.8
	T	16.9	51.5	6.8	0.00	16.0
Mean Duration	AS	8.29	14.03	6.30	0.00	8.67
(sec)	QS	8.39	25.06	6.70	0.00	7.68
	IS	9.14	9.88	0.00	0.00	8.88
	T	8.51	19.10	6.40	0.00	8.30
Apnoea per cent	AS	45.57	15.50	3.03	0.00	17.10
	QS	80.00	28.20	0.56	0.00	11.40
	IS	50.00	13.70	0.00	0.00	31.00
	T	53.85	20.00	1.18	0.00	14.80
Per cent Sleep	AS	55.0	45.0	29.0	37.0	46.0
	QS	21.0	38.0	53.0	49.0	50.0
Heart Rate	AS	133.0	152.0	124.0	131.0	151.0
	QS	130.0	150.0	121.0	131.0	149.0
Respiration Rate	AS	23.0	37.0	38.0	67.0	36.0
	QS	17.0	39.0	33.0	69.0	30.0

Obstructive apnoea, periodic breathing, gross body movements

Ten of the 29 'near-miss' infants had episodes of obstructive apnoea - brief ($\geq 3 < 6$ seconds) in seven when studied initially (Cases 40, 72, 80, 83, 84, 87, 89); and prolonged (≥ 6 seconds) in seven (Cases 40, 73, 80, 84, 87, 94, 95).

Table 42 gives the results for gross body movements and periodic breathing in relation to sleep phase in the 24 term 'near-miss' infants. Mean values are significantly higher than those obtained in healthy full-term control (C) infants (See Table 19). Appendix 20 gives data for individual 'near-miss' cases. A subgroup of 9 full-term 'near-miss' infants was compared with 9 controls matched for gestation, post-conception age and gender. This group contained 9 of the 10 infants for whom data on apnoea variables has been presented (See Table 40 Study 1). The control group comprised 5 previously healthy full-term infants from control (C) group and 4 infants who had recovered from bronchiolitis. No significant differences were observed between index and matched control data for either body movements or periodic breathing (Table 43).

When data from the same 9 index 'near-miss' cases were compared with data from unmatched control (C), the total number of movements per 100 minutes sleep was significantly increased in 'near-miss' infants ($P < 0.02$). The two groups were comparable with respect to duration

Gross body movements and periodic breathing in relation to sleep phase in 24 'near-miss' for SIDS infants

		At presentation (Mean & SE)
Body Movements	AS	3.70 (0.41)
Total duration	QS	0.94 (0.19)
min/100 min sleep	IS	39.75 (3.21)
	T	6.63 (0.69)
Body Movements	AS	25 (1.99)
Number/100 min sleep	QS	8 (1.40)
	IS	120 (10.21)
	T	27 (2.42)
Periodic Breathing	AS	3.01 (1.32)
Total duration	QS	1.50 (0.87)
min/100 min sleep	IS	0.79 (0.39)
	T	2.09 (0.98)
Periodic Breathing	AS	5 (1.84)
Number/100 min sleep	QS	2 (0.96)
	IS	2 (0.95)
	T	4 (1.23)

Gross body movements and periodic breathing in relation to sleep phase in 9 'near-miss' for SIDS infants and their matched case controls.

		At presentation Mean & SE	Matched Control Mean & SE
Body Movements	AS	3.87 (0.41)	4.18 (0.66)
Total duration	QS	1.01 (0.33)	0.88 (0.24)
min/100 min sleep	IS	43.21 (4.91)	37.46 (5.02)
	T	6.91 (1.08)	6.90 (0.73)
Body Movements	AS	29 (2.73)	25 (4.69)
Number/100 min sleep	QS	9 (2.84)	7 (1.96)
	IS	148 (17.43)	116 (10.28)
	T	32 (4.22)	30 (3.80)
Periodic Breathing	AS	3.88 (1.55)	1.97 (0.75)
Total duration	QS	0.22 (0.16)	0.21 (0.14)
min/100 min sleep	IS	1.29 (0.89)	0.00 (0.00)
	T	1.89 (0.85)	0.96 (0.38)
Periodic Breathing	AS	8 (3.01)	5 (1.74)
Number/100 min sleep	QS	1 (0.38)	1 (0.47)
	IS	3 (2.07)	0 (0.00)
	T	4 (1.65)	2 (0.85)

of movements and indices of periodic breathing.

Table 44 gives the results for gross body movements and periodic breathing in relation to sleep phase in the 5 pre-term 'near-miss' for SIDS infants at presentation. Body movements were comparable to those seen in full-term 'near-miss' cases but periodic breathing was increased in each sleep phase (See Table 42). The results for periodic breathing are skewed by one infant (Case 40) who had a greater amount of periodic breathing than any other in the series.

Appendix 21 gives values for individual infants. When compared with unmatched controls (C), pre-term infants had more body movements ($P < 0.01$), of greater duration ($P < 0.02$) than controls. Periodic breathing was comparable in pre-term 'near-misses' and unmatched controls.

6.5 Synthesis of findings

6.5.1 Apnoea variables, percent sleep, respiration rate and heart rate

Table 45 summarises the significant findings for apnoea index (the percentage of time the baby spends apnoeic), apnoea attack rate (the number of episodes of apnoea per unit time), apnoea percentage (the distribution of

Table 44

Gross body movements and periodic breathing in relation to sleep phase in 5 premature 'near-miss' for SIDS infants

		At presentation Mean & SE
Body Movements	AS	4.15 (0.57)
Total duration	QS	1.21 (0.32)
min/100 min sleep	IS	41.92 (3.20)
	T	8.28 (0.94)
Body Movements	AS	29 (4.39)
Number/100 min sleep	QS	12 (3.06)
	IS	167 (21.36)
	T	43 (8.13)
Periodic Breathing	AS	12.07 (8.40)
Total duration	QS	17.66 (12.30)
min/100 min sleep	IS	9.00 (5.72)
	T	12.68 (8.59)
Periodic Breathing	AS	15 (8.16)
Number/100 min sleep	QS	16 (8.74)
	IS	15 (8.63)
	T	15 (8.36)

Table 45

Apnoea variables, percent sleep, respiration and heart rates Summary of Index/control comparisons

Group	Number Index Cases (n)	Apnoea Index AS	QS P<	IS	T	Apnoea attack rate AS	QS P<	IS	T	Episodes longest duration AS	QS P<	IS	T	Mean duration Apnoea AS	QS P<	IS	T	Apnoea percent AS	QS P<	IS	T	% Sleep AS	QS P<	Resp rate AS	QS P<	Heart rat AS	QS P<
Bronchiolitis v Recovery	(16) 16	NS	+ 0.02	NS	+ 0.05	NS	+ 0.01	NS	+ 0.05	NS	NS	NS	+ 0.05	+ 0.05	NS	NS	NS	NS	+ 0.05	NS	+ 0.05	+ 0.05	NS	+ 0.01	+ 0.01	- 0.01	- 0.0
Pyloric Stenosis	(5)														+				+	+	+		-				-
i) Recovery	5	0.05	0.05	0.05	0.05	0.05	0.05	NS	0.05	0.05	0.05	NS	0.05	NS	0.05	NS	NS	0.05	0.05	NS	0.05	NS	NS	NS	0.05	NS	NS
ii) Matched Controls	5	0.05 +	0.05 +	NS	0.05 +	0.05 +	NS	NS	0.05 +	NS	0.05 +	NS	0.05 +	NS	NS	NS	NS	0.05 +	NS	NS	0.05 +	NS	NS	0.05 -	0.05 -	NS	NS
Siblings v	(24)																						-		-		
i) Controls (C)	24	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.01	NS	0.05	0.01	NS	NS
ii) Matched controls	14	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.01	NS	NS
iii) Matched controls	5	0.05 +	NS	NS	0.05 +	0.05 +	NS	NS	0.05 +	0.05 +	NS	NS	NS	NS	NS	NS	NS	0.05 +	NS	NS	0.05 +	NS	NS	NS	NS	NS	NS

+ increased) in index group
- decreased)

episodes of apnoea while in a given sleep stage), longest and mean duration of apnoeic pauses, percent time in each sleep state, and respiration and heart rates for the symptom, siblings, and 'near-miss' groups of index cases when compared with controls. Indices of apnoea are increased during bronchiolitis in which infection, hypoxaemia and altered lung mechanics are the principal stresses, and in pyloric stenosis in which chemoreceptor control mechanisms are affected. These increases are observed in active and quiet sleep.

In the siblings group, findings were not significantly different from controls, except for a subgroup of five infants of comparable age for whom age- and sex-matched controls were available. Indices of apnoea were increased during sleep in this subgroup. No significant differences were observed in 'near-miss' infants when compared with healthy unmatched controls (C),or in the more limited number of matched case/control comparisons which were made.

With regard to time spent in each sleep state, the most significant finding was the reduction in active sleep in siblings when compared to controls (C). The corresponding increase in quiet sleep in siblings was not statistically significant.

Respiration rate was increased during bronchiolitis,

and decreased in infants with pyloric stenosis. There was a significant reduction in respiration rate in siblings in both matched and unmatched control comparisons. Heart rate changes were unremarkable in any of the groups studied.

6.5.2 Obstructive apnoea (brief and prolonged) and prolonged central apnoea

Obstructive apnoea was observed principally in active sleep, and prolonged central apnoea in both active and quiet sleep. Table 46 summarises the results for episodes of apnoea for control (C and C^1), symptoms and 'risk' groups of infants. The results for the four subgroups of symptomatic infants have been given above - see 6.2. These are also summarised in Table 47.

Neither obstructive apnoea nor prolonged central apnoea were observed in controls. The occurrence of brief or prolonged obstructive apnoea was remarkably similar in the 'symptoms' and 'near-miss' groups in which it occurred more commonly than in siblings. Irrespective of group, the presence of obstructive apnoea usually coincided with symptoms (upper respiratory infection, bronchiolitis, stridor, recurrent vomiting), and in all but three infants (Cases 42, 59, 84) apnoea had diminished or disappeared following resolution of these symptoms. The two infants in the siblings group with prolonged obstructive apnoea

Table 46

Episodes of Apnoea

Group		Obstructive Apnoea (OA)			Central Apnoea (CA)	
		Patients (n)	Brief (>3<6 secs)	Prolonged (>6 secs)	Prolonged (>20 secs)	Prolonged (>15 secs)
Controls C	n = 11	0	0	0	0	0
C^1	n = 14	0	0	0	0	0
'Symptoms'	n = 33	13 (39)	10 (30)	8 (24)	0	2 (6)
Siblings	n = 24	4 (17)	4 (17)	2 (8)	0	1 (4)
'Near-miss'	n = 29	10 (35)	7 (24)	7 (24)	3 (10)	4 (14)

( ) = per cent

Table 47

Apnoea (obstructive and prolonged central) and sleep state

individual infants

Group	Case No	Obstructive apnoea ⩾3<6 secs	Obstructive apnoea ⩾6 secs	Sleep State	Prolonged Central Apnoea ⩾15 secs	Sleep State
Bronchiolitis	13	+	+	AS IS	0	-
	17	+	0	AS	0	-
n = 16	27	0	+	AS IS	0	-
Upper	28	+	+	AS QS	0	-
Respiratory	29	+	0	AS	0	-
Infection	30	+	0	AS	0	-
n = 5						
Congenital	33	+	0	AS IS	0	-
Stridor	35	+	+	AS IS	0	-
n = 7	36	+	0	IS	0	-
Pyloric	40	+	+	AS	+	AS
Stenosis	41	0	+	AS IS	0	-
n = 5	42	+	+	AS IS	0	-
	43	0	+	AS	0	-
	44	0	0	-	+	QS
Subsequent	51	0	0	-	+	IS
Siblings	59	+	0	IS	0	-
n = 24	62	+	0	IS QS	0	-
	63	+	+	AS IS	0	-
	66	+	+	AS QS	0	-
'Near-miss'	72	+	0	AS IS	0	-
for SIDS	73	0	+	AS IS	0	-
(full-term)	75	0	0	-	+	AS IS
n = 24	80	+	+	AS QS	0	-
	83	+	0	AS	0	-
	84	+	+	AS QS	0	-
	87	+	+	AS IS	0	-
	89	+	0	AS IS	0	-
'Near-miss'	40	+	+	AS	+	AS
for SIDS	92	0	0	-	+	AS QS IS
(pre-term)	94	0	+	AS	0	-
n = 5	95	0	+	AS IS	+	AS

had associated upper respiratory infection; on recovery, abnormalities of breathing were not detectable.

Prolonged central apnoea ($\geq$ 20 seconds) was seen only in three 'near-miss' infants born prematurely, during the course of upper respiratory infections. A further four infants had central apnoea ($\geq$15 seconds) in association with upper respiratory infection or metabolic alkalosis. One pre-term infant (Case 40) had both. Prolonged central apnoea was not observed in any infant following recovery from infection, or on restoration of normal acid-base status. Obstructive and prolonged central apnoea were not observed in 'near-miss' infants in whom investigation of the cause of the 'near-miss' episodes was entirely negative. Conversely, the summation of problems which, in isolation, might have been regarded as minor increased the likelihood of abnormal breathing patterns in individual infants, for example, Case 76.

Risk scores were computed for infants in the siblings and 'near-miss' groups using the criteria of Carpenter et al (1977). Three of the 18 siblings for whom data were available had scores exceeding 500 (high score). Three of the 24 full-term and four of the five pre-term 'near-miss' infants also had scores at birth greater than 500. One healthy control (C) infant had a high score. The proportion of full-term infants with high scores was comparable in

these groups.

All of the siblings exhibiting brief or prolonged obstructive apnoea had low scores (< 500). Only one of six full-term 'near-miss' infants with brief obstructive apnoea, and one of four with prolonged obstructive apnoea had high scores. In pre-term 'near-miss' infants obstructive apnoea was observed in two high -score and one low-score infant. Prolonged (⩾ 20 seconds) central apnoea was observed in three of four high-score pre-term infants and not in the remaining low-score infants.

6.5.3 Periodic breathing and gross body movements

The wide scatter of values in healthy control (C) infants for both the duration and number of episodes of periodic breathing per unit time in a given sleep state made it impossible to define a 'normal' range for indices of periodic breathing. Analysis of results was also made difficult by the paucity of control information available to match for gestation, sex and post-conception age. Table 48 summarises the significant results for control and index groups of infants. The number of episodes of periodic breathing per 100 minutes sleep is increased in bronchiolitis (when compared with recovery data), and pyloric stenosis (when compared with healthy controls (C)). The total duration of periodic breathing was diminished in infants with stridor compared with healthy controls (C).

Table 48

Gross Body Movements and Periodic Breathing

Summary of Index/Control Comparisons

Group	No Index cases (n)	Body movements per 100 mins total sleep time Duration (min) P<	Number P<	Periodic Breathing per 100 mins total sleep time Duration (min) P<	Number P<
Bronchiolitis	(16)				
v					
i) Recovery	16	NS	NS	NS	0.05+
ii) Controls	16	NS	0.01+	NS	NS
Upper Resp. Inf.	(5)				
v					
i) Recovery	5	0.05+	NS	NS	
ii) Controls(C)	5	0.02+	NS	NS	
Cong Stridor	(7)				
v					
i) Matched cont	7	NS	NS	NS	NS
ii) Controls(C)	7	NS	0.05+	0.05-	NS
Pyloric Stenosis	(5)				
v					
i) Recovery	5	NS	NS	NS	NS
ii) Matched cont	5	NS	NS	NS	NS
iii) Controls(C)	5	NS	NS	0.05+	0.02+
Siblings	(24)				
v					
i) Matched cont	13	NS	NS	NS	NS
ii) Controls(C)	24	NS	0.05+	NS	NS
'Near-miss(FT)	(24)				
v					
i) Matched cont	9	NS	NS	NS	NS
ii) Controls(C)	24	NS	0.05+	NS	NS
'Near-miss'(PT)	(5)				
v					
i) Controls(C)	5	0.02+	0.01+	NS	NS

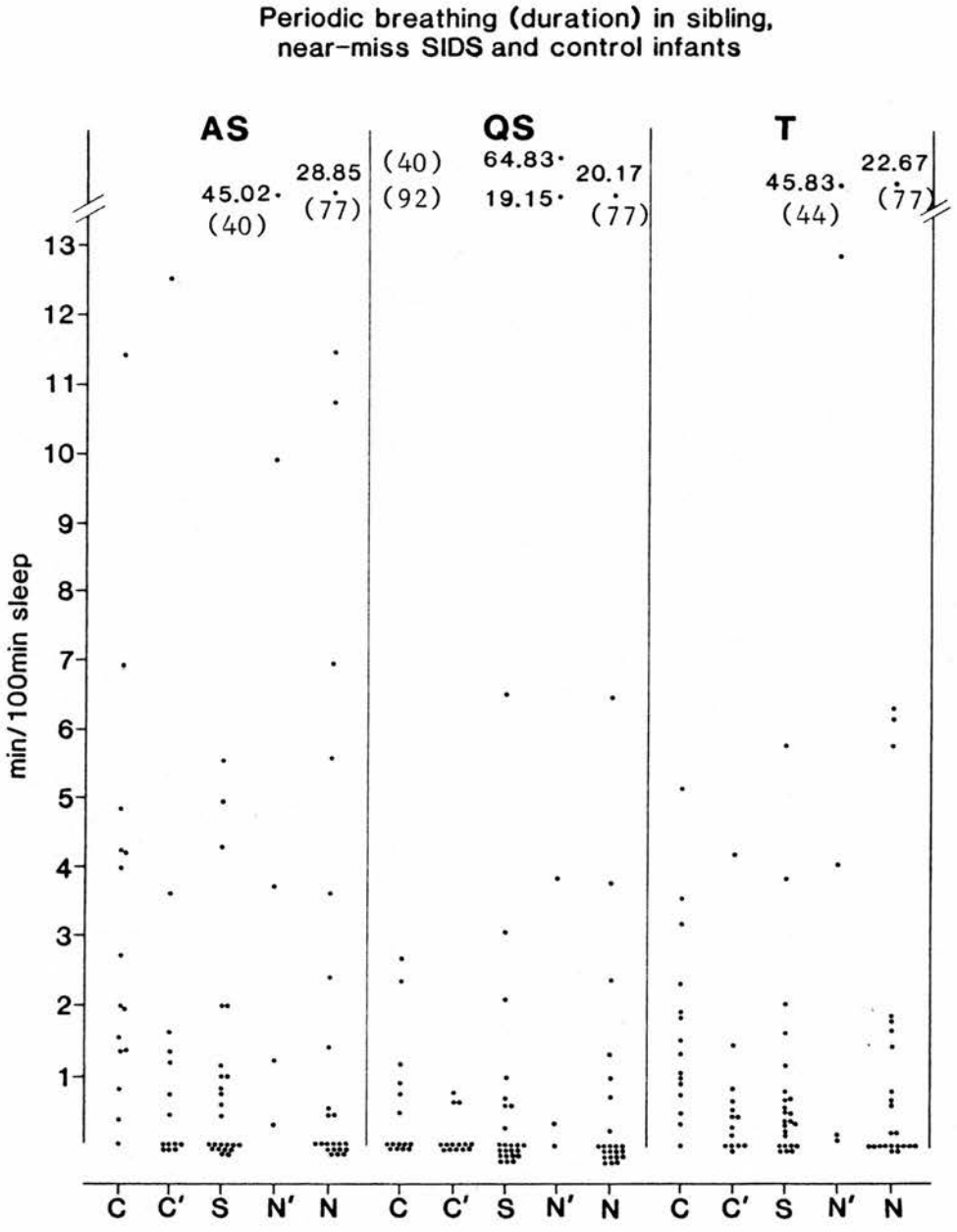
+ increased in index group

No differences were observed in stridulous infants for matched case/control comparisons. Periodic breathing was not increased in either the siblings or 'near-miss' groups. However, in the 'near-miss' group, a minority of cases had values for indices of periodic breathing outside the range observed in controls (C).

Increased body movement was most apparent in active and indeterminate sleep. Gross body movements tended to be increased during illness in 'symptom' subgroups of infants when compared with recovery or control (C) data. The most significant increases were observed during the course of upper respiratory infection. The increases in body movements in total sleep and quiet sleep in pyloric stenosis did not reach statistical significance.

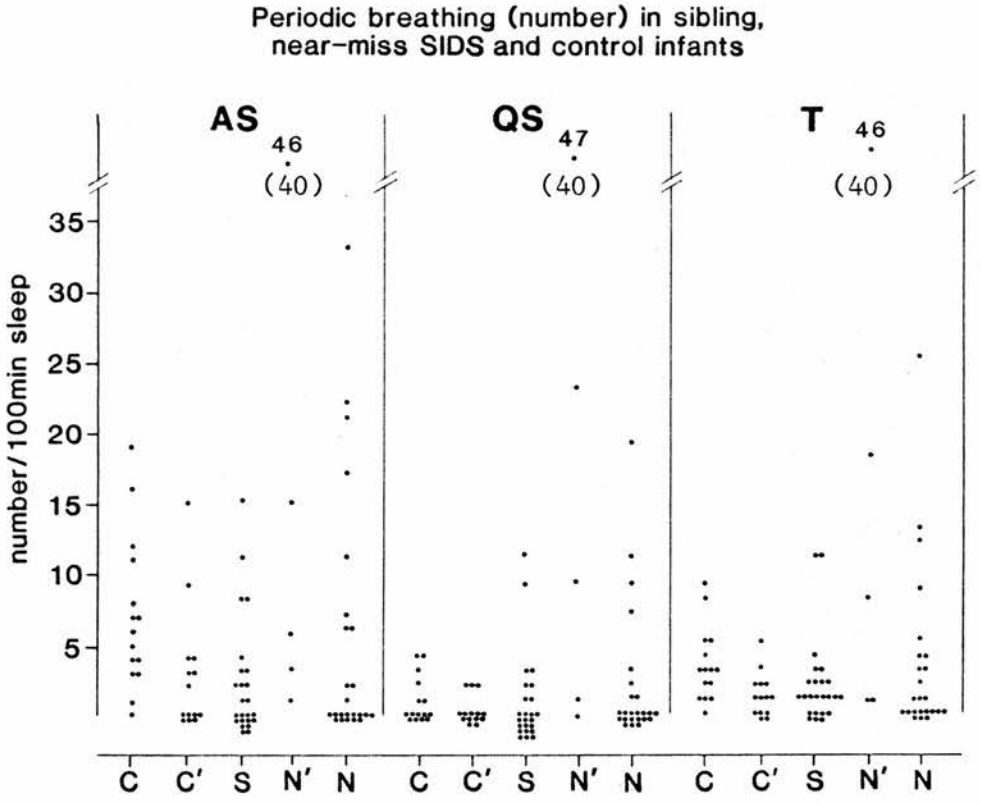
Figures 44-47 illustrate the findings for periodic breathing and gross body movements in controls (C and C^1), siblings, and 'near-miss' infants. The groups overlap considerably and within each index group a small number of observations fall outside the wide ranges shown for controls. The number of body movements per 100 minutes total sleep time is significantly increased in both full-term and pre-term 'near-miss' infants. These data do not support the view that there is either an 'excess' of periodic

Figure 44



C –Control : no previous illness
C'–Control : previous respiratory illness
S –Sibling (n=24)
N –Near-miss (full-term)
N'–Near-miss (pre-term)
( )-Case number

Figure 45



C -Control : no previous illness
C'-Control : previous respiratory illness
S -Sibling (n=24)
N -Near-miss (full-term)
N'-Near-miss (pre-term)
( )-Case number

Figure 46

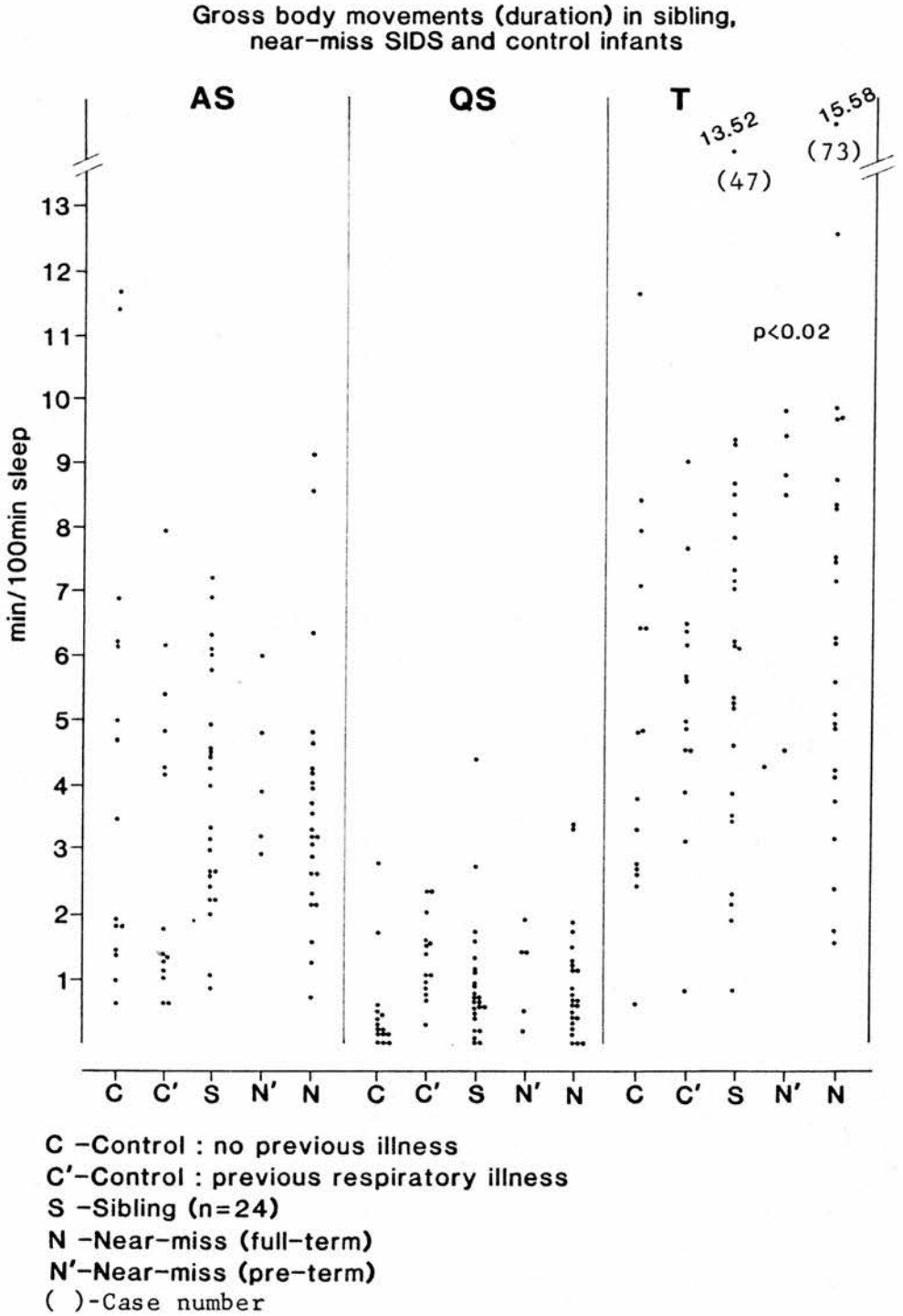
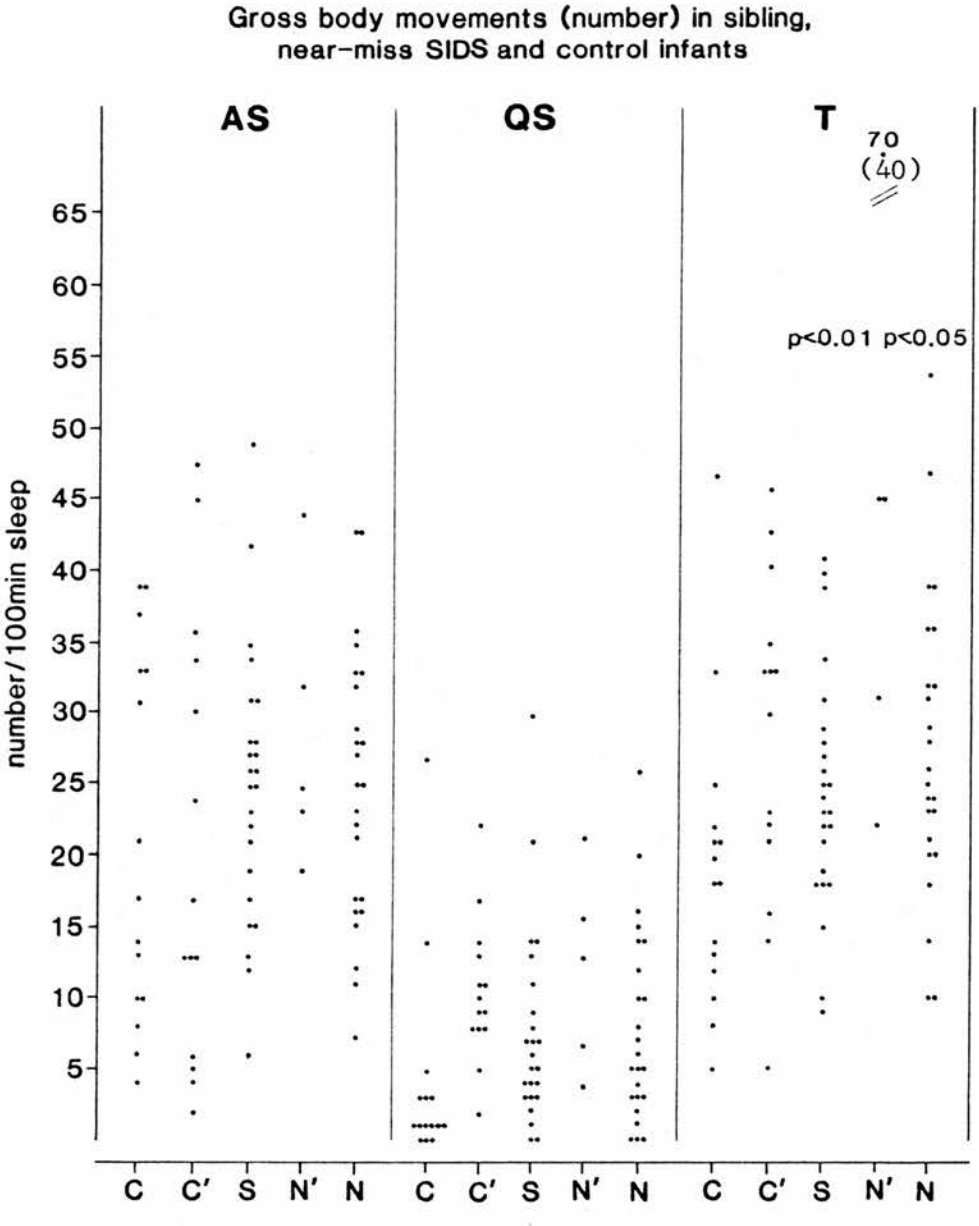

Gross body movements (duration) in sibling, near-miss SIDS and control infants
AS
QS
T
13.52
(47)
15.58
(73)
p<0.02
min/100min sleep
13
12
11
10
9
8
7
6
5
4
3
2
1
C C' S N' N C C' S N' N C C' S N' N
C -Control : no previous illness
C'-Control : previous respiratory illness
S -Sibling (n=24)
N -Near-miss (full-term)
N'-Near-miss (pre-term)
( )-Case number

Figure 47


Gross body movements (number) in sibling,
near-miss SIDS and control infants
AS
QS
T
70
(40)
p<0.01 p<0.05
number/100min sleep
65
60
55
50
45
40
35
30
25
20
15
10
5
C C' S N' N C C' S N' N C C' S N' N
C -Control : no previous illness
C'-Control : previous respiratory illness
S -Sibling (n=24)
N -Near-miss (full-term)
N'-Near-miss (pre-term)
( )-Case number

breathing, or diminution in body movements (to indicate possible defects in arousal) in the siblings or 'near-miss' groups of infants.

6.6 Transcutaneous oxygen tension ($PtcO_2$) during sleep

The maximum, minimum and mean transcutaneous oxygen tensions observed during active sleep and quiet sleep stages for individual infants, and the post-conception ages at which measurements were made were recorded and analysed. The major analysis to be presented refers to infants in Control (C), siblings and full-term 'near-miss' groups.

6.6.1 Analysis of data

Table 49 shows the mean ranges of $PtcO_2$ shown by individual infants in their first, second or third studies, i.e. the mean value of $\{PtcO_2(max - PtcO_2(min)\}$. The means are shown for both active and quiet sleep. It is apparent that the variations in $PtcO_2$ diminish as the infants get older. In the case of active sleep the reduction in the means is of the order of 40 per cent. This reduction is typical of what one might expect with percentage data as the percentages approach 100%. Variation is reduced as observations approach this limit. To overcome this problem the data set was transformed, applying the sine

Table 49

Mean range of $PtcO_2$ for active and quiet sleep recorded in first, second and third studies

Study no	No subjects		Mean age	Mean range of $PtcO_2$	
	AS	QS	(wks)	AS	QS
1	47	50	48.6	8.64	7.32
2	33	34	52.7	7.15	5.71
3	20	22	58.1	5.35	5.68

$\sqrt[-1]{P}$ transformation, where P is the observed percentage. The overall observed maximum $PtcO_2$ was 104 mmHg. It was therefore assumed that the absolute upper limit for $PtcO_2$ was 110 mmHg and the observations were regarded as percentages of 110. Applying the transformation to the data made no difference to the mean ranges. The attempt to correct the data for increasing stability was consequently abandoned. Such a correction would have made little difference to the overall analysis except when setting confidence limits for individual observations. It is possible that these would get narrower as age increases.

Analysis of means

The mean analysis focused on the mean values of $PtcO_2$ observed in each study (control, sibling, 'near-miss' groups) during active and quiet sleep, and also on the difference between $PtcO_2$ (active sleep) and $PtcO_2$ (quiet sleep). In four studies data were not available for quiet sleep, and in eight $PtcO_2$ were not measured in active sleep. The three analyses are not therefore directly related. The data were analysed with the GLIM statistical package using the standard regression model, i.e.

$$P = g + b\,(age) + error$$

where P = mean $PtcO_2$ for the study, g = a group mean, b is the regression coefficient, and the errors are assumed to be normally distributed. In a final analysis the possibility that the response was quadratically related

to age was explored - vide infra.

Linear analysis

By groups

Table 50 gives the results of linear regression analysis of active and quiet sleep data and the difference between the two values for the groups of infants studied. The following points emerge from the analyses:

i) In none of the 12 data sets was there any suggestion that the change in response with age for individual infants was different from the pooled relationship for the whole group - i.e. for the controls, siblings or 'near-miss' groups. However, the tests for homogeneity were weak because in any group there were comparatively few infants with three complete studies, but the data gave no hint of heterogeneity of slopes.

ii) In only two of the twelve data sets was there any suggestion that the mean level of response for the infants showed more than random variation about the group mean. In both cases, the 'subject variation' is only significant at the 5% level and two such significant values could easily occur by chance in 12 tests of significance. Ignoring the subject effect does not greatly inflate the standard deviation for the groups and the standard deviations are very

Table 50

Results of linear regression analysis of observations in control (C) sibling, and 'near-miss' groups for active and quiet sleep and the differences between the two $PtcO_2$ levels

Active Sleep

Group	Mean level at 50wkPCA	Slope[+]	se	S.D.	Subjects (n)	Obs (n)	Age range (wks PCA)
Control	71.94	1.236	0.254[*]	9.20	11	25	39-57
Siblings	67.06	0.222	0.158	10.61	16	30	41-79
'Near-miss'FT	72.04	0.766[o]	0.296	9.12	20	39	42-77
'Near-miss'PT	71.23	0.776	0.327	7.05	5	9	38-59
Quiet Sleep							
Control	74.50	0.709	0.302	10.81	11	23	38-63
Siblings	69.35	0.119[ø]	0.172	7.07	17	33	40-92
'Near-miss'FT	70.02	0.274	0.194	12.16	17	42	39-77
'Near-miss'PT	70.14	0.967	0.248	5.54	5	10	38-61
Active Sleep - Quiet Sleep							
Control	-1.91	0.464	0.144	5.15	11	22	38-63
Siblings	-2.44	0.182	0.086	5.75	16	30	40-92
'Near-miss'FT	0.489	-0.029	0.665	3.38	20	39	39-77
'Near-miss'PT	0.520	-0.156	0.324	6.81	5	8	39-61

* $P < 0.001$

FT Full-term

PT Pre-term

\+ Significantly different between groups in active sleep $P < 0.01$.

o Refers to pooled within subject computation, as subjects vary. Ignoring subjects the slope is 0.291 and SD 11.75

ø Pooled within subject computations. Ignoring subjects SD becomes 10.23.

similar in all groups.

The variation in subject means tends to reduce the regression on age for the group as a whole. For this reason the average within subject slope is shown on Table 49 when the subjects may vary.

iii) The differences between observed and fitted values in these analyses were checked (i.e. predicted by the regression relationship). In no case was any extreme value found, e.g. greater than 2.5 SD and such as might be considered for exclusion.

Comparison of groups

Table 50 shows the estimated mean level of response at 50 weeks post-conception age for each group of infants. The group means are not significantly different for $PtcO_2$ in active sleep, quiet sleep, or for the difference in $PtcO_2$ levels.

The rate of increase of $PtcO_2$ with age in active sleep varies statistically between the groups $P.01 > P > 0.001$. For controls, the rate of increase is 1.24 mmHg per week SE 0.254 which is highly significant. The rate of increase for 'near-miss' pre-term infants is just significant ($P < 0.05$). For the sibling and 'near-miss' full-term groups of infants the rate of increase is comparatively

small and if differences among the 'near-miss' infants are ignored, not statistically significant.

For controls the rate of increase of $PtcO_2$ in quiet sleep is much less than in active sleep - 0.71 mmHg per week SE 0.302. The rate for 'near-miss' pre-term infants is greater and that for siblings and 'near-miss' term infants smaller than this. Overall the rates of increase do not differ significantly between the groups in quiet sleep.

If all active and quiet sleep data related to the same studies, then the intercepts and slopes shown in the third section of Table 50 for AS-QS would correspond to the differences of the corresponding AS and QS shown above, e.g. for controls the slope for AS-QS would be 1.24-0.71 = 0.53 instead of 0.46 as shown. The regression slopes would also have to be calculated either as overall for each group or pooled within subjects if the figures are to correspond, e.g. for 'near-miss' 0.29-0.27 = 0.02 should correspond to -0.029 as shown.

The standard error of the estimates takes account of the pairing of the data in different studies and is consequently not related to the standard deviations and standard errors given in the upper part of Table 50.

Because there are marked differences between the groups in the rate of increase in $PtcO_2$ for active sleep but rather smaller differences for quiet sleep it is not surprising to find that the rate of change in AS-QS is different in different groups. For controls and siblings $PtcO_2$ in active sleep rises faster with age than in quiet sleep so that the former is expected to overtake the latter at around 60 weeks post-conception age. For both 'near-miss' groups $PtcO_2$ tensions are essentially similar in both sleep states and the differences between the two are comparatively small.

Curvilinear analysis

Inspection of the age range of the observations on each group of infants shows that for controls the data relate to ages 39-57 weeks with one exception - 63 weeks. In other groups the ages range up to 63 weeks and many of the studies relate to older infants. It may be that $PtcO_2$ levels approach a standard level asymptotically. If this were so then the rate of increase in $PtcO_2$ response would be faster in a younger (control) group than in a group including infants with a wider age span. To explain this possibility a quadratic response curve was fitted with a maximum at age 75 weeks. The maximum was chosen at this age because it seemed a reasonable choice and this would vary from studies on infants older

than this - when the quadratic would predict a falling $PtcO_2$.

Active sleep

Applying this model in active sleep there was no evidence of any group differences.

The data are described by

$PtcO_2 = 77.5 - 0.0167 (age - 75)^2$ (A)

with SD = 10.55 and se of the regression coeff 0.0035

This equation gives:

Post-conception age in weeks:

40	45	50	55	60	65	70	75

Predicted $PtcO_2$ (Active sleep):

57.2	62.6	67.1	70.9	73.7	75.8	77.0	77.5

If a regression line is fitted to each group of infants the pooled within group residual SD is 10.42, which is very little less than results from fitting the overall quadratic curve.

Quiet sleep

Analysis shows that the simple relationship

$PtcO_2$ (quiet sleep) = 70.7 + 0.2527 (age - 50)

SD: 11.12 and se of regression coeff. 0.101

adequately describes the data. Differences between the groups are not statistically significant.

However, the relationship

$PtcO_2$ (quiet) = 76.6 - 0.00853 (age - 75) (B)

has SD 10.94 se of regression coeff 0.00270 fits slightly better, and this provides an exactly comparable model to equation A. Estimated values are

Age:

40 45 50 55 60 65 70 75

Predicted $PtcO_2$ (Quiet sleep):

66.2 69.0 71.3 73.2 74.7 75.8 76.4 76.4

Curve A predicts values at 50 weeks rather lower than reported in Table 50. Curve B on the other hand predicts a value close to those shown in Table 50 for quiet sleep. The two curves cross at 65 weeks. When the differences between $PtcO_2$ found in active and quiet sleep are analysed in this way it appears that differences between the groups cannot be fully accounted for and that the rate of change of $PtcO_2$ (active) - $PtcO_2$ (quiet) is different in different groups: $P < 0.01$.

6.6.2 Trends in Control and Index subgroups

The analyses outlined above (6.6) were carried out for control (C), siblings, and 'near-miss' groups of infants. Figures 48 and 49 give longitudinal data for controls (C) presented as quadratic response curves for active sleep and quiet sleep respectively. Values for individual infants in the control (C) group, which formed the basis of the computations, are also given, together with available

Figure 48

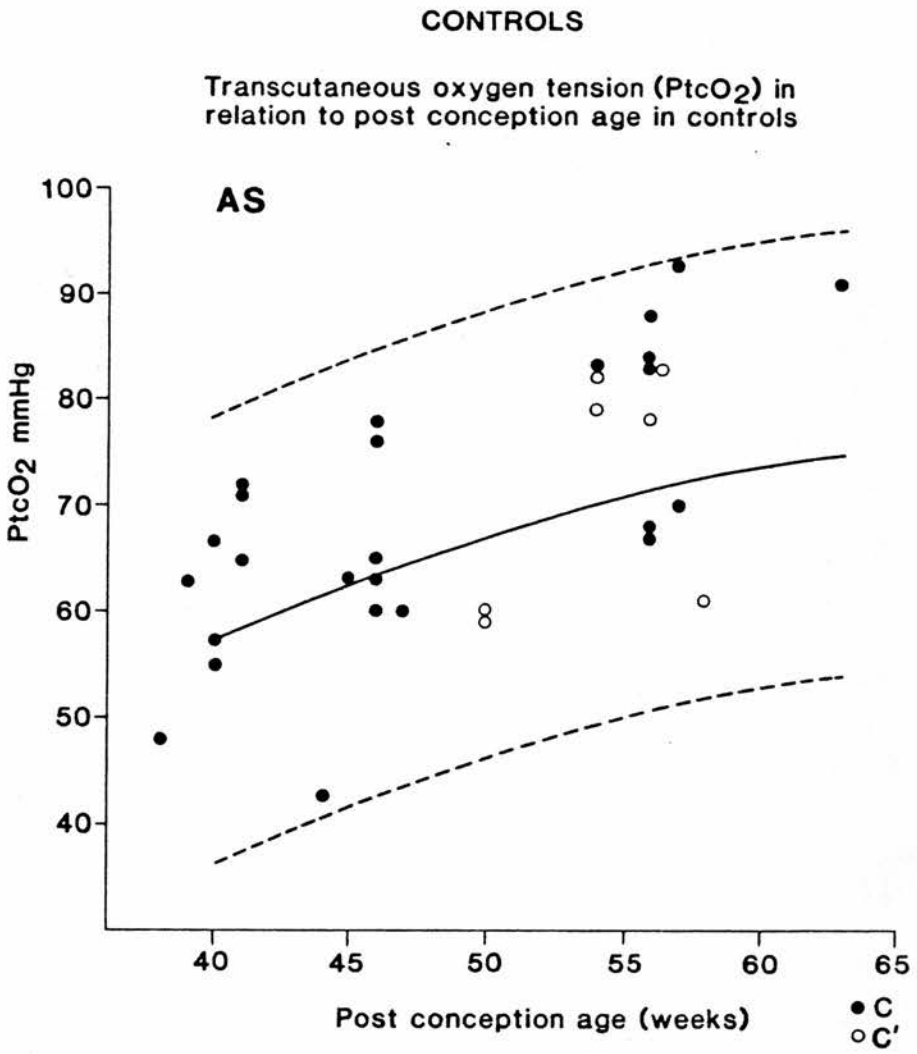
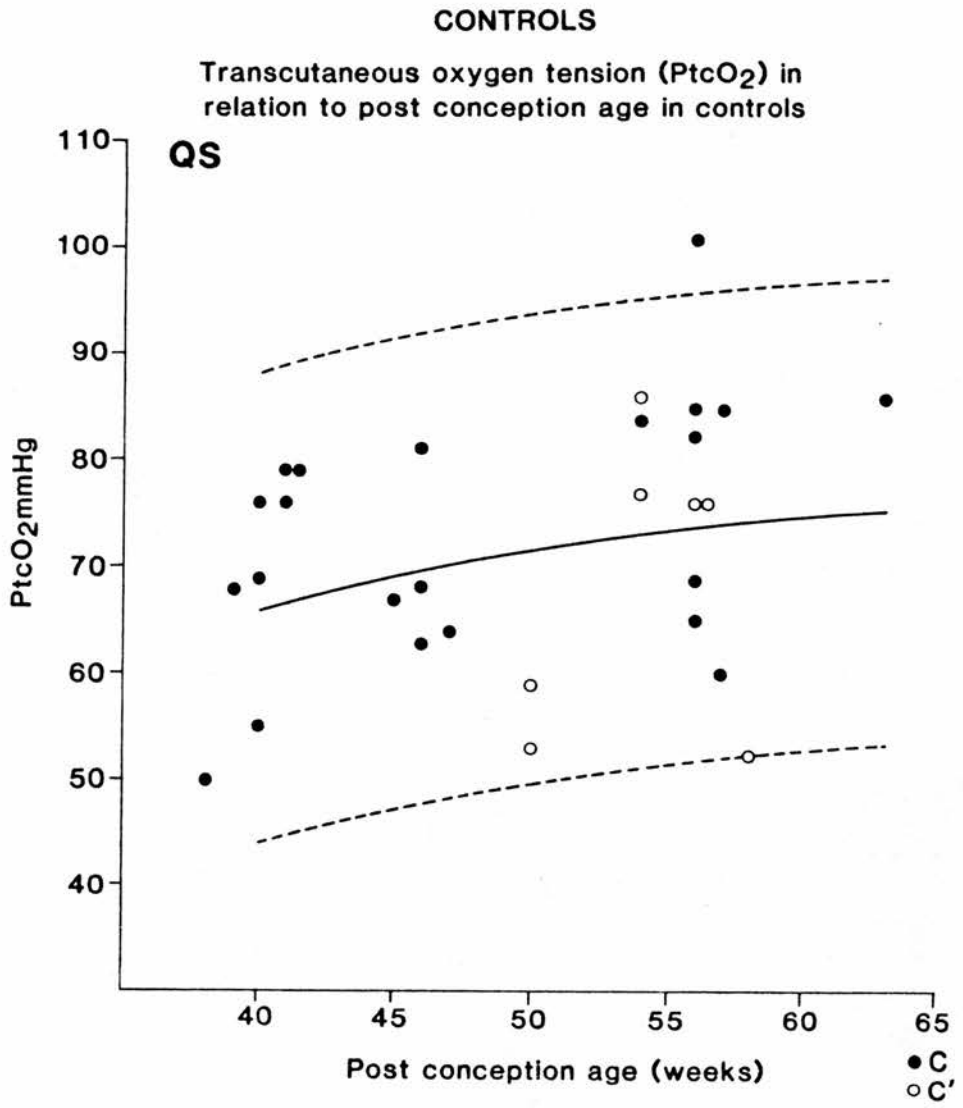

CONTROLS
Transcutaneous oxygen tension ($PtcO_2$) in relation to post conception age in controls
AS
100
90
80
70
60
50
40
$PtcO_2$ mmHg
40
45
50
55
60
65
Post conception age (weeks)
C
C'

Figure 49


CONTROLS
Transcutaneous oxygen tension ($PtcO_2$) in relation to post conception age in controls
QS
110
100
90
80
70
60
50
40
PtcO2mmHg
40
45
50
55
60
65
Post conception age (weeks)
C
C'

data from infants in the control (C^1) group. The latter fell within the control (C) group range of values.

Figures 50 and 51 give the values obtained for siblings of SIDS for active sleep and quiet sleep respectively. The siblings data extend well beyond the post-conception age for which control (C) computations have been made. Where the age-spans of the control and siblings groups coincide, $PtcO_2$ in siblings falls within the range of values obtained for controls (C).

Figures 52-55 give the values obtained in both active and quiet sleep for full-term and pre-term 'near-miss' infants. The data for full-term 'near-miss' cases also extends beyond the control (C) age range. Where the age-ranges overlap, data from all but 2 'near-miss' infants fall within the predicted control (C) range. These infants (Cases 70 and 90) had upper respiratory tract infection at presentation; one developed acute bronchiolitis in the following 48 hours (Case 70). The lowest values were obtained in quiet sleep. Initial and subsequent data on $PtcO_2$ in 'near-miss' cases lie close to mean control (C) values both in active and quiet sleep.

Figures 56 and 57 give $PtcO_2$ values obtained in active and quiet sleep in bronchiolitis during and following recovery. For both sleep phases $PtcO_2$ is lower during

Figure 50

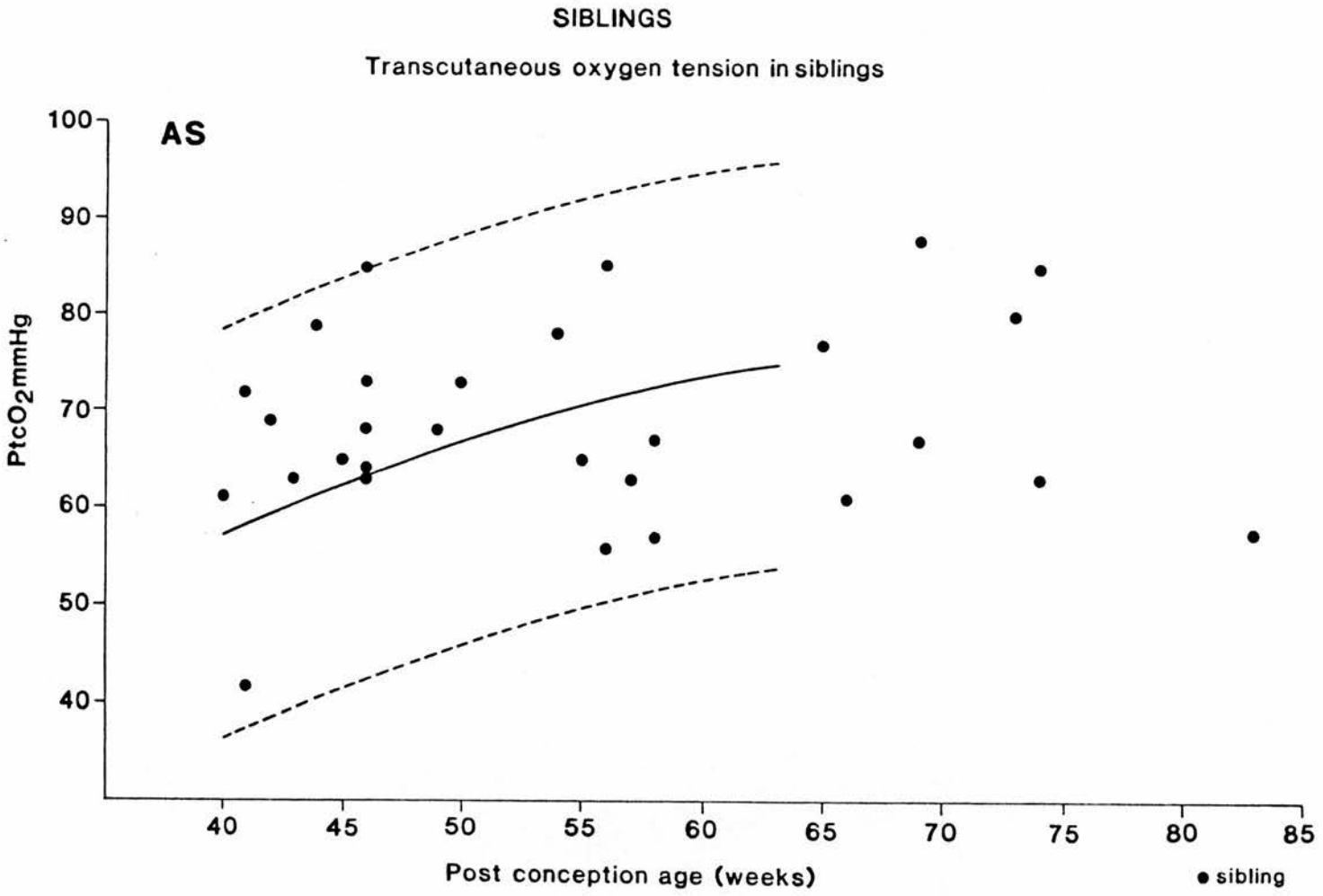

SIBLINGS
Transcutaneous oxygen tension in siblings
AS
100
90
80
70
60
50
40
PtcO2mmHg
40
45
50
55
60
65
70
75
80
85
Post conception age (weeks)
● sibling

Figure 51


SIBLINGS
Transcutaneous oxygen tension in siblings
QS
100
90
80
70
60
50
40
PtcO2 mmHg
40
45
50
55
60
65
70
75
80
85
Post conception age (weeks)
● sibling

Figure 52

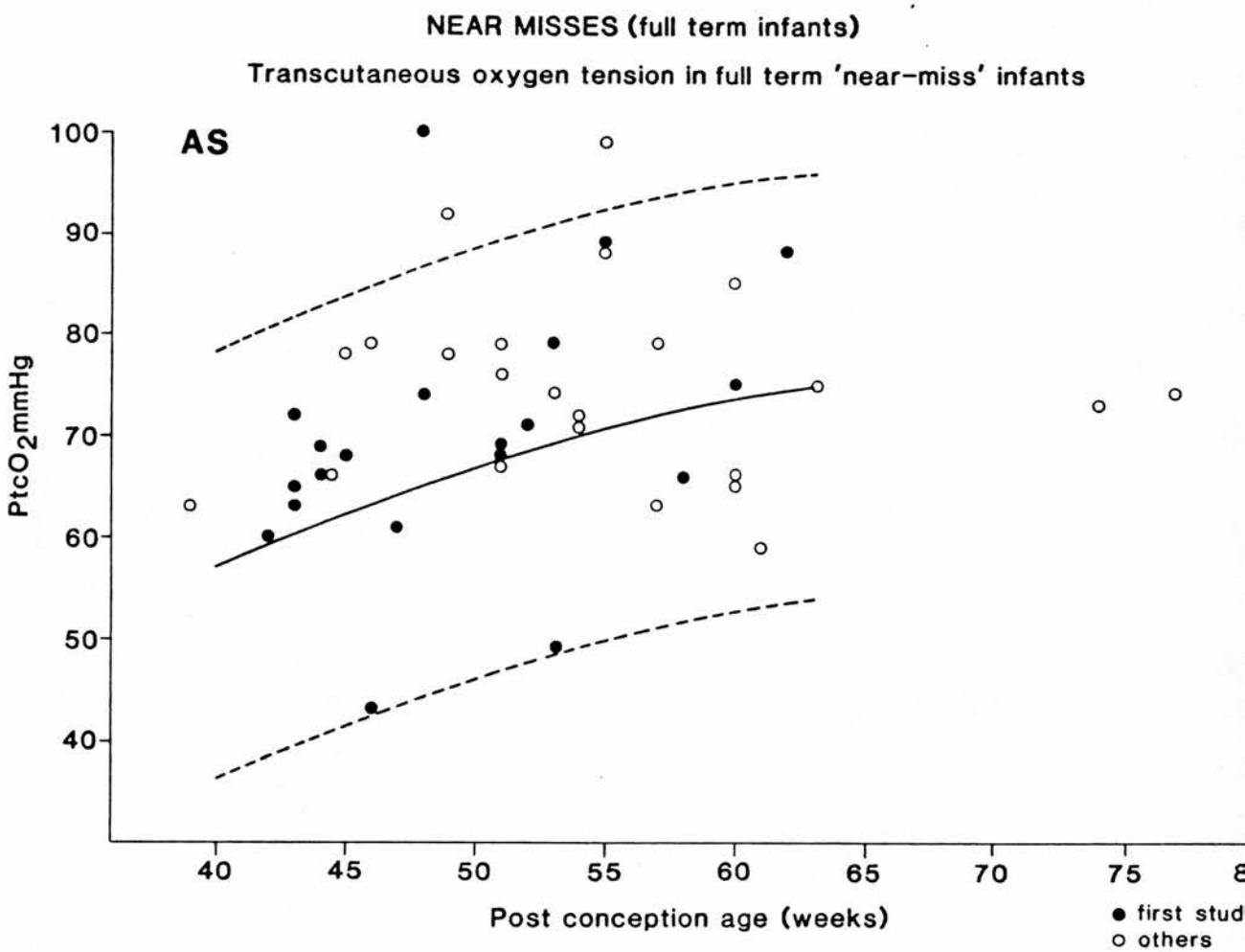
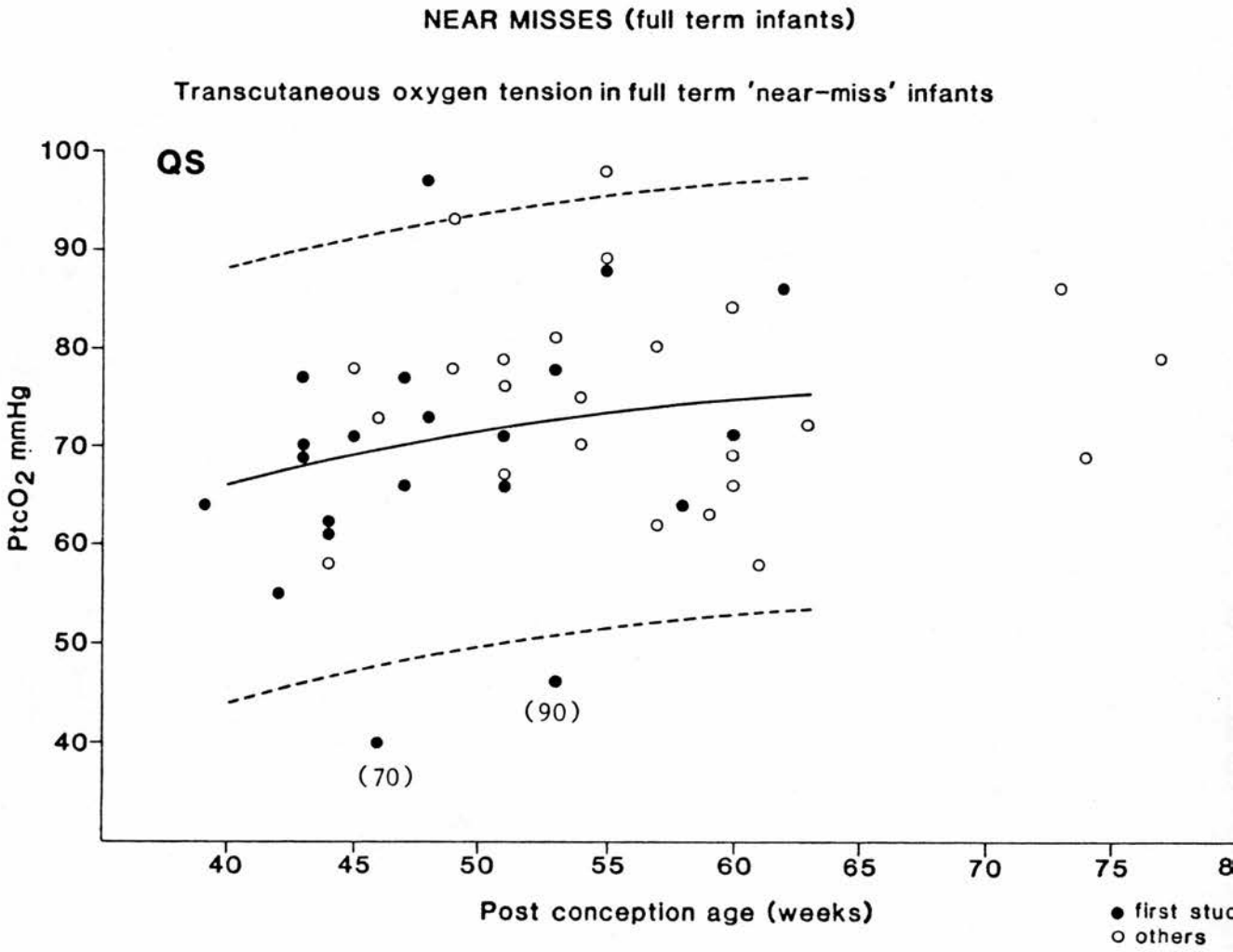

NEAR MISSES (full term infants)
Transcutaneous oxygen tension in full term 'near-miss' infants
AS
100
90
80
70
60
50
40
PtcO2mmHg
40
45
50
55
60
65
70
75
Post conception age (weeks)
● first stud
○ others

Figure 53



( ) Case number

Figure 54

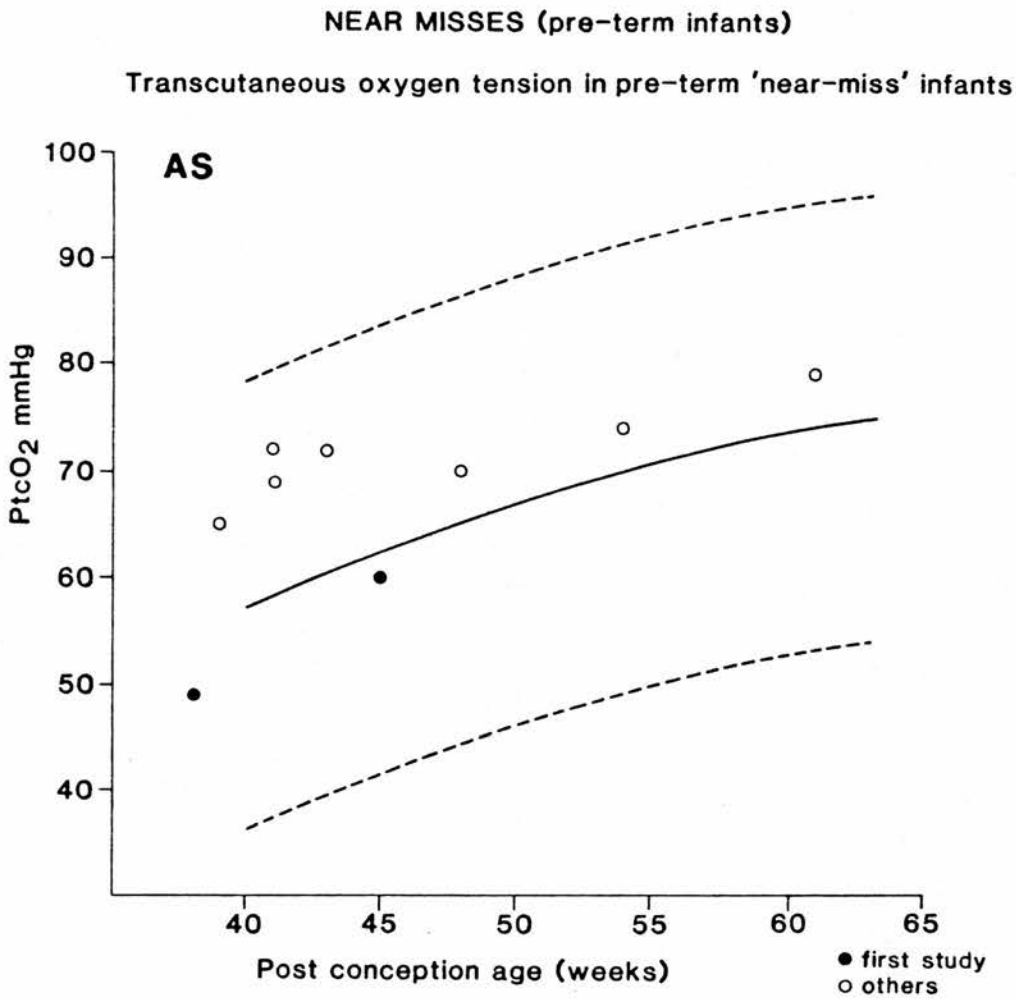

NEAR MISSES (pre-term infants)
Transcutaneous oxygen tension in pre-term 'near-miss' infants
AS
100
90
80
70
60
50
40
PtcO2 mmHg
40
45
50
55
60
65
Post conception age (weeks)
● first study
○ others

Figure 55

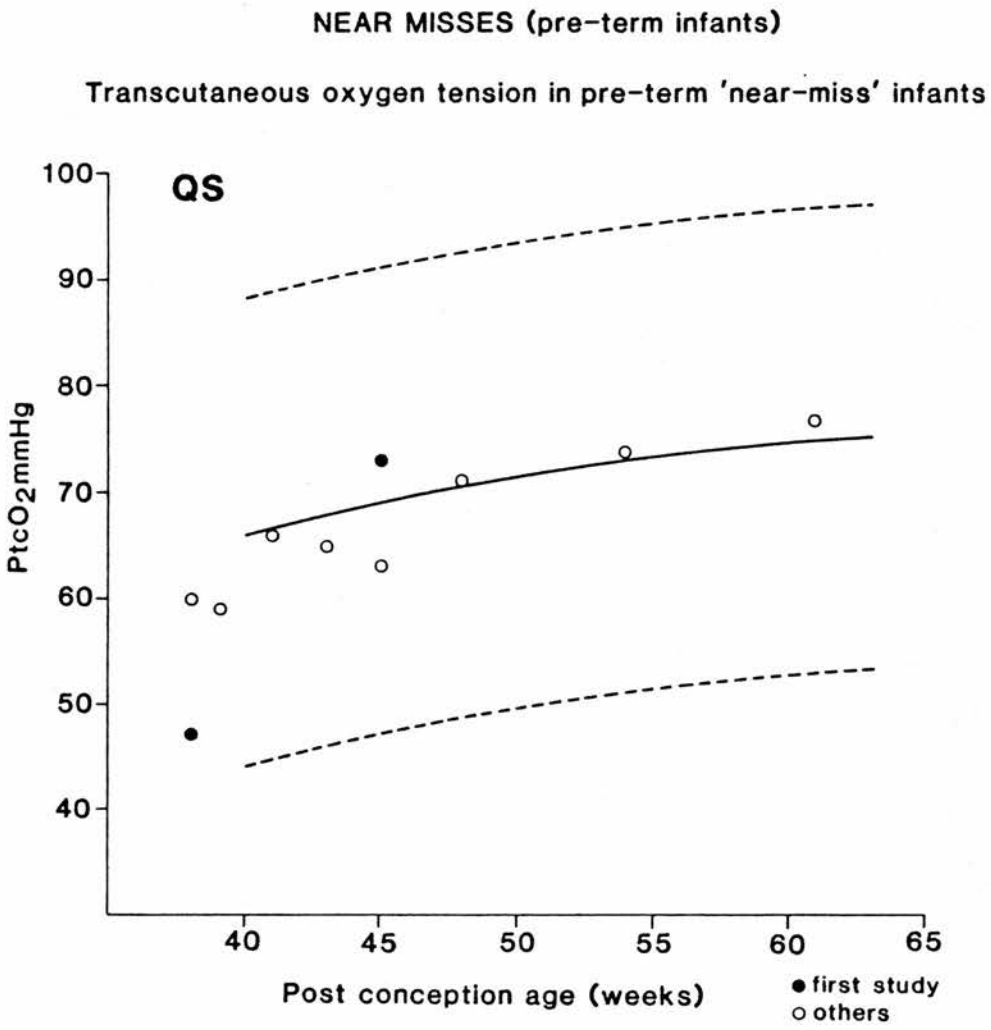

NEAR MISSES (pre-term infants)
Transcutaneous oxygen tension in pre-term 'near-miss' infants
QS
100
90
80
70
60
50
40
PtcO2mmHg
40
45
50
55
60
65
Post conception age (weeks)
● first study
○ others

Figure 56

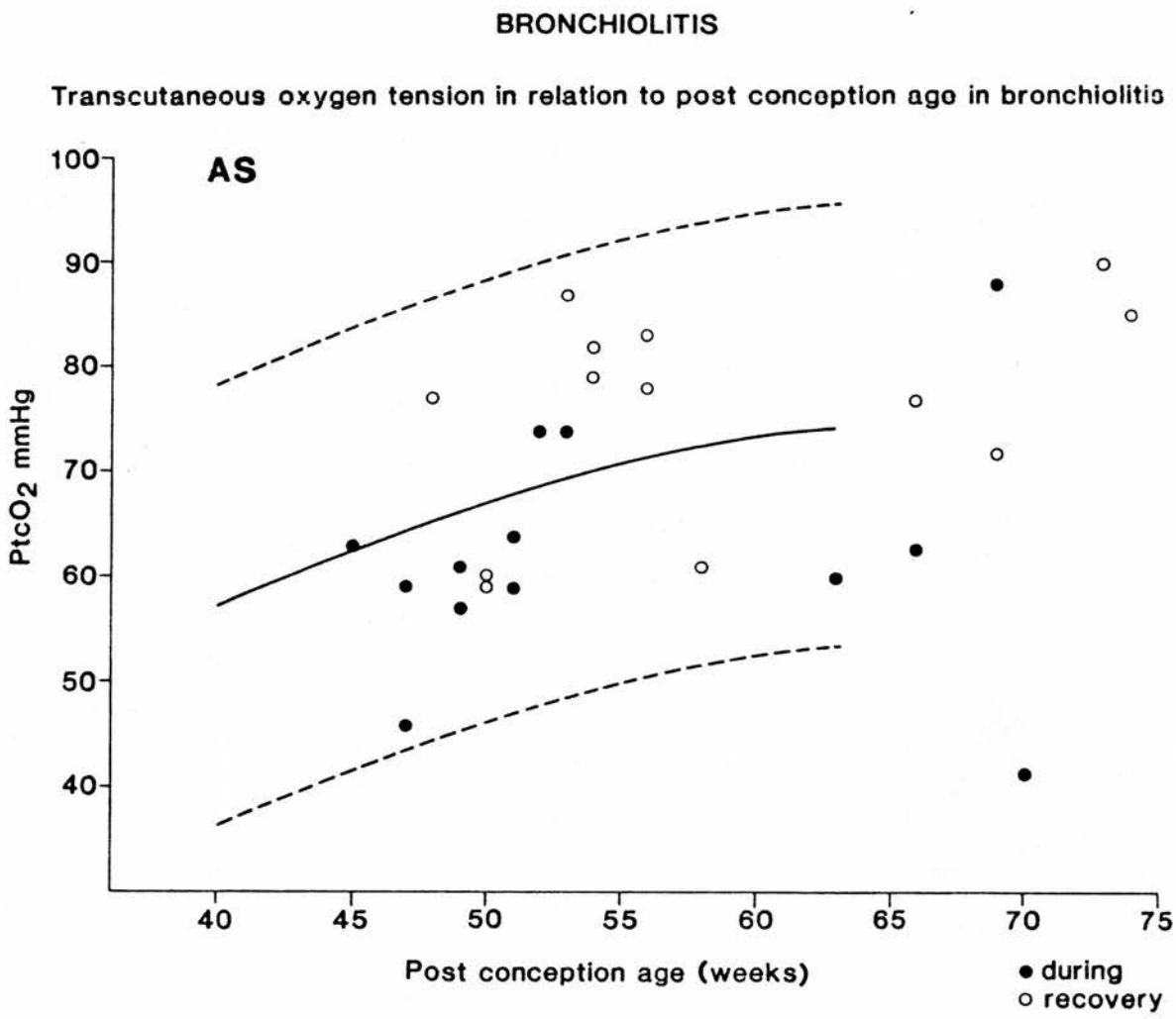
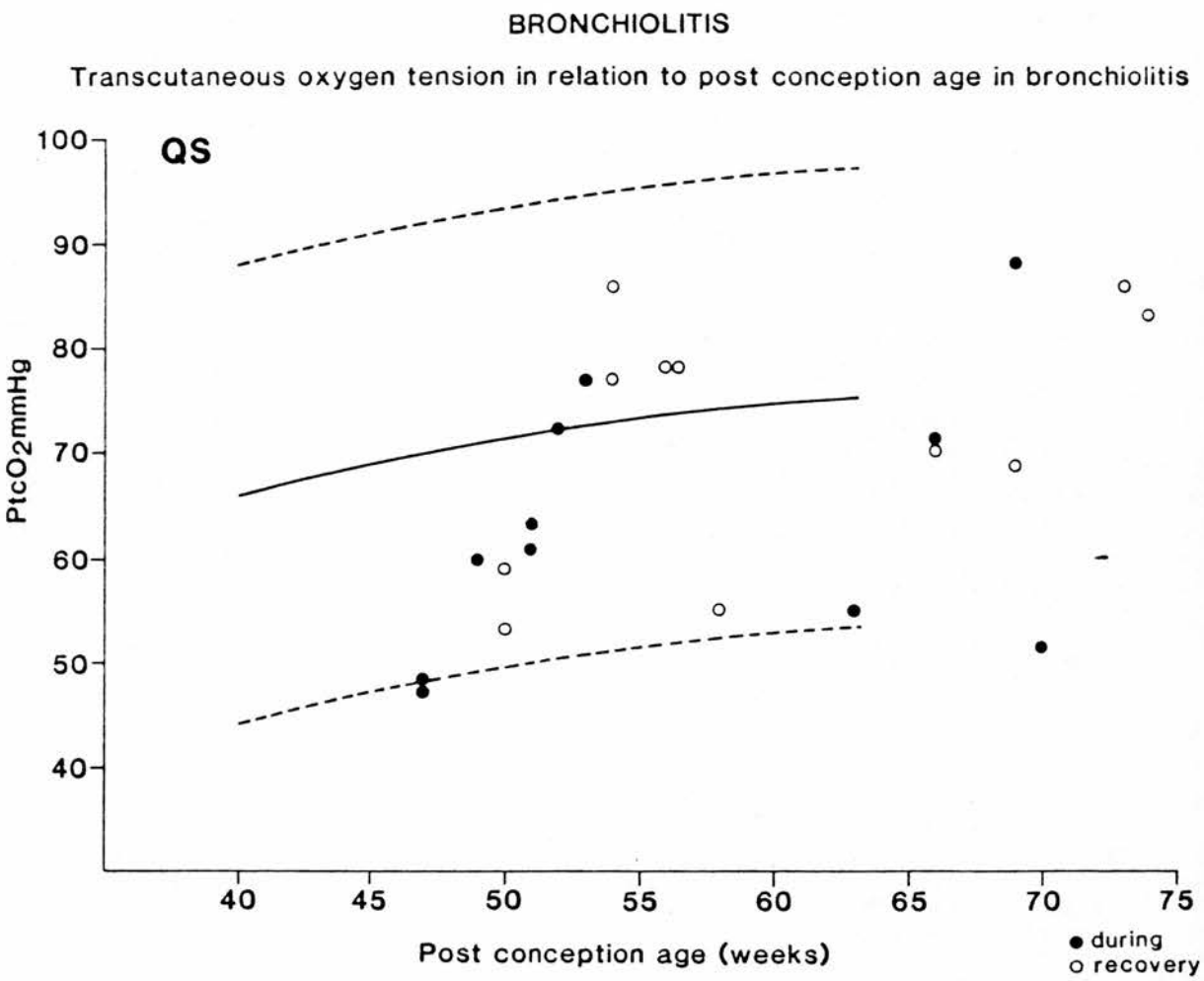

BRONCHIOLITIS
Transcutaneous oxygen tension in relation to post conception age in bronchiolitis
AS
100
90
80
70
60
50
40
PtcO2 mmHg
40
45
50
55
60
65
70
75
Post conception age (weeks)
● during
○ recovery

Figure 57


BRONCHIOLITIS
Transcutaneous oxygen tension in relation to post conception age in bronchiolitis
QS
100
90
80
70
60
50
40
PtcO2mmHg
40
45
50
55
60
65
70
75
Post conception age (weeks)
● during
○ recovery

infection. Table 51 summarises the results obtained for $PtcO_2$ during infection and following recovery in active and quiet sleep. Mean $PtcO_2$ in active sleep was 61.5 ± 10.6 mmHg and 77.9 ± 8.9 mmHg after recovery from bronchiolitis ($P < 0.001$). $PtcO_2$ was also significantly reduced in quiet sleep during bronchiolitis ($P < 0.001$). No differences were observed between mean $PtcO_2$ in active and quiet sleep phases when paired comparisons were made during infection and following recovery.

Figures 58 and 59 give the results for the remaining 'symptom' subgroups for both active and quiet sleep in relation to corresponding control (C) data. Although the data set for each symptom subgroup of infants is incomplete, the values obtained tend to cluster around mean control (C) values for both active and quiet sleep; none of the infants with upper respiratory infection, stridor, or pyloric stenosis was hypoxaemic either during or following recovery from illness.

6.6.3 Dips in transcutaneous oxygen tension

Individual records of transcutaneous oxygen tension were scrutinised for dips in oxygen tension. These usually started abruptly but could last up to a minute. Table 52 gives the results for dips in $PtcO_2$ exceeding 10 and 15 mmHg respectively. One control infant, with striking

Table 51

Transcutaneous Oxygen Tension $PtcO_2$

in Bronchiolitis

	During	Recovery	
Active Sleep (AS)	61.5 ± 10.6	77.9 ± 8.9	$p < 0.001$
Quiet Sleep (QS)	60.3 ± 11.2	77.6 ± 9.9	$p < 0.001$

Figure 58

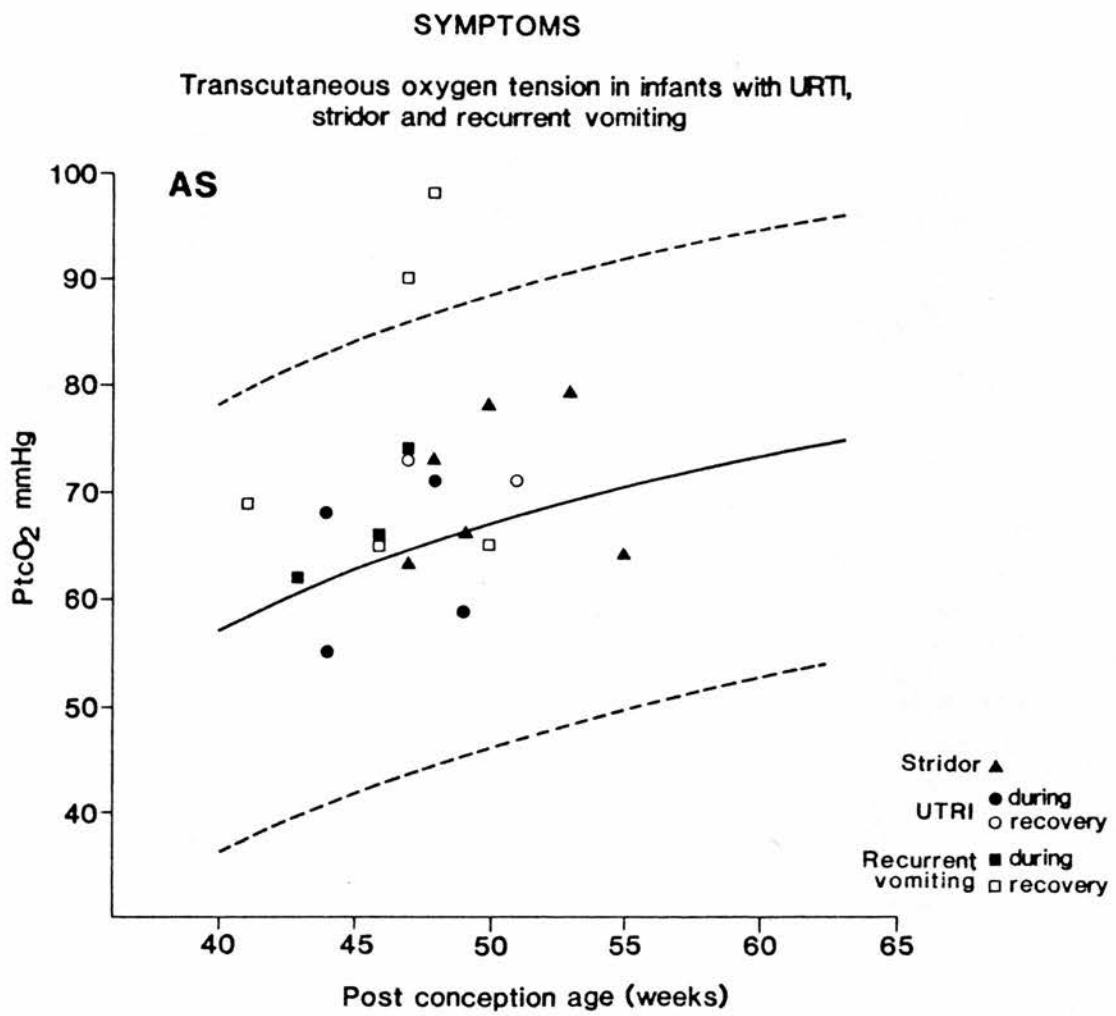

SYMPTOMS
Transcutaneous oxygen tension in infants with URTI, stridor and recurrent vomiting
AS
100
90
80
70
60
50
40
PtcO2 mmHg
40
45
50
55
60
65
Post conception age (weeks)
Stridor ▲
URTI ● during
○ recovery
Recurrent vomiting ■ during
□ recovery

Figure 59

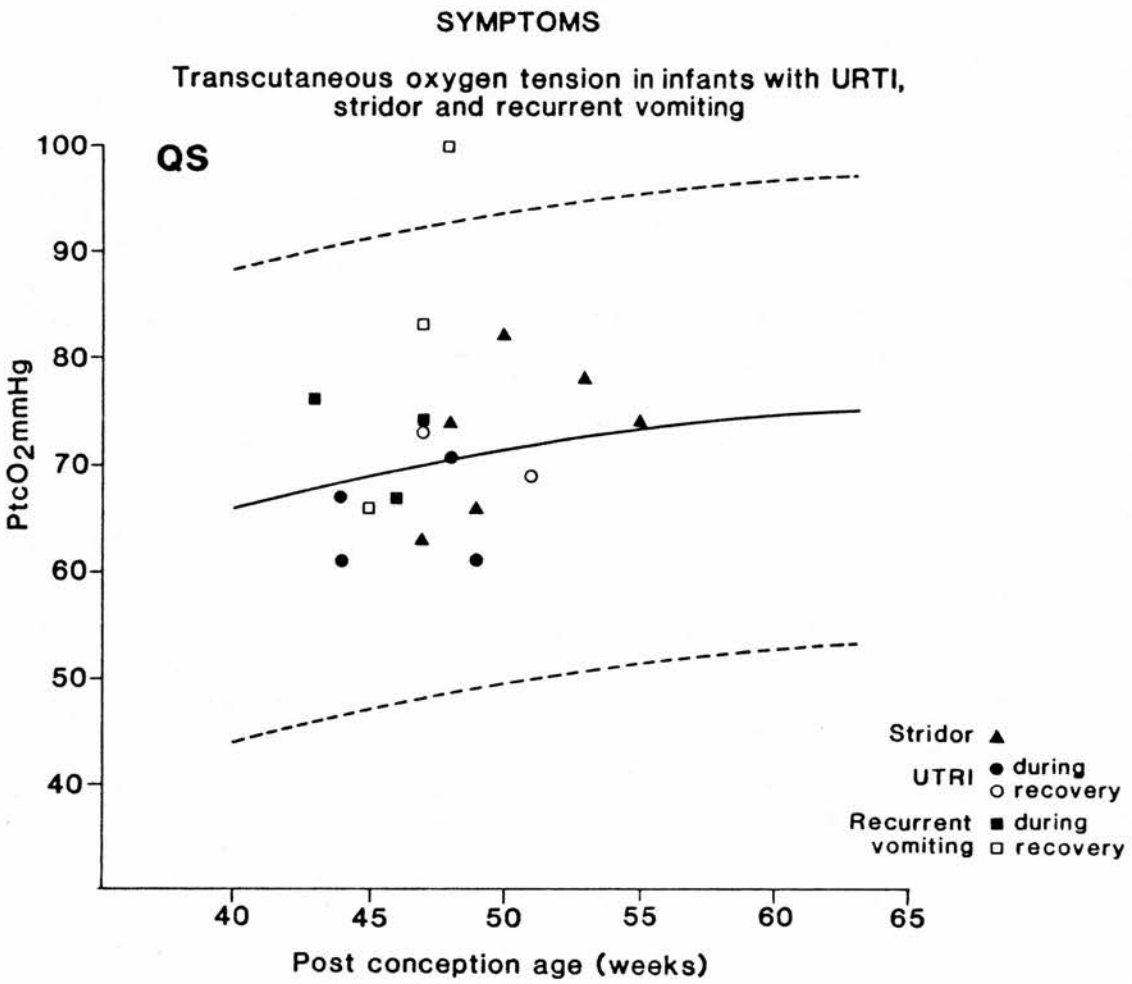

SYMPTOMS
Transcutaneous oxygen tension in infants with URTI, stridor and recurrent vomiting
QS
100
90
80
70
60
50
40
PtcO2mmHg
40
45
50
55
60
65
Post conception age (weeks)
Stridor ▲
UTRI ● during
○ recovery
Recurrent vomiting ■ during
□ recovery

Table 52

Dips in $PtcO_2$

Group	Infants	Number Obs	Dips in $PtcO_2$ >10mmHg	>15mmHg
Control	11	25	1(9)	0
'Symptom'	29	48	10(34)	5(17)
Siblings	18	34	8(44)	2*(11)
'Near-miss'	27	60	10(10)	5(19)

( ) percent

* During course of upper respiratory infection

periodic breathing, had occasional dips in $PtcO_2$ exceeding 10 mmHg (Case 7, dip of 12 mmHg). Dips in oxygen tension were observed in infants within each index subgroup, particularly the symptoms and 'near-miss' subgroups where the proportions of infants affected were comparable. However, the most striking decreases in oxygen tension occurred in a small number of 'near-miss' infants, associated with prolonged central or obstructive apnoea, for example Cases 84 and 92.

Dips in oxygen tension occurred in association with obstructive apnoea, central apnoea, periodic breathing or body movements. Obstructive apnoea was seen principally in active sleep; and gross body movements predominantly in active and indeterminate sleep. Dips in $PtcO_2$ were most prominent during illness in symptoms groups and were uncommon following clinical recovery; in 'near-miss' infants, dips in $PtcO_2$ during sleep were most apparent within 1-2 days following initial presentation, and were <u>not</u> observed in infants in whom extensive investigations of the 'near-miss' episode were negative. In one infant, dips in $PtcO_2$ associated with obstructive apnoea were confirmed repeatedly during the early months of life, with spontaneous resolution by six months of age (Case 84).

6.7 Illustrative cases

These have been chosen to illustrate patterns of breathing abnormality in the groups studied. These were observed most frequently in the 'symptoms' and 'near-miss' for SIDS infants than in other groups, the most striking abnormalities being seen in a minority of 'near-miss' for SIDS infants. In such cases, the concurrent changes in transcutaneous oxygen tension were often profound.

Cases are also presented to illustrate important aspects of the history, examination, or investigation, sometimes in the absence of demonstrable breathing abnormality. Others may show ususual features or unexpected findings in sleep polygraphic studies.

Case 13 (AH) - Acute Bronchiolitis

A two-month old female infant born at 40 weeks gestation, of birthweight 3.15 kg presented with a 4-day history of coryzal symptoms followed by cough, irritability, and refusal of feeds. She had been exclusively breast-fed. On the day before admission to hospital, cough had increased and parents noted that baby was breathing rapidly and noisily. Clinical examination revealed a clear nasal discharge and moderate intercostal and subcostal indrawing. Respiration and heart rates were increased for age, the chest was distended, and on auscultation breath sounds were harsh, vesicular, with prolonged expiration and accompanied by medium-pitched

rhonchi throughout both lung fields. A diagnosis of acute bronchiolitis was made.

Polygraphic sleep studies in the acute stage of illness revealed several episodes of prolonged (>6 seconds) obstructive apnoea. In one such episode (Figure 60) there is cessation of nasal airflow and continuing movements of the chest, during active sleep. $PtcO_2$ falls from 74 to 59 mmHg. There is associated slowing of the heart. Apnoea ends spontaneously by coughing, followed by a regular low-amplitude pattern of breathing.

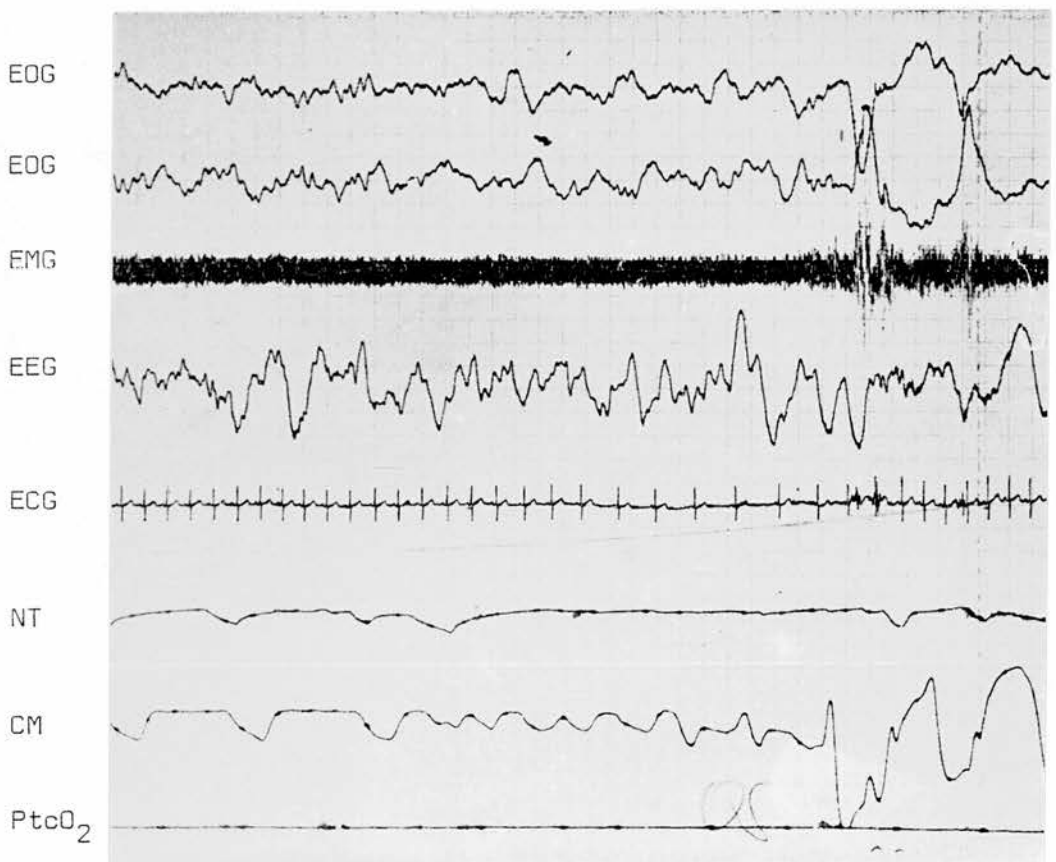
She recovered spontaneously from each episode of obstructive apnoea and $PtcO_2$ never fell below 55 mmHg. Following clinical recovery from bronchiolitis, repeat monitoring showed that these abnormalities had disappeared. In this infant obstructive apnoea always occurred in active sleep; in others it was occasionally observed in quiet sleep also.

Case 28 (SB) - Upper respiratory infection

A one-month old male infant born at 40 weeks gestation and birthweight 2.81 kg was admitted to hospital with a 2-day history of a 'runny' nose, cough and mild fever. Apart from a clear nasal discharge which made breathing somewhat 'snuffly' in character, clinical examination was normal.

Figure 60

Obstructive apnoea in QS during bronchiolitis



There is cessation of airflow (NT) and continuing movement of chest (CM). There is associated slowing of the heart rate. $PtcO_2$ falls from 74 to 59mmHg. Apnoea ends spontaneously by coughing.

Polygraphic sleep studies showed several short episodes of obstructive apnoea between 3 and 6 seconds in duration. These episodes were not associated with fall in heart rate or decrease in $PtcO_2$. Figure 61 shows a 3-4 second episode of obstructive apnoea occurring in active sleep without significant change in heart rate or simultaneously recorded $PtcO_2$.

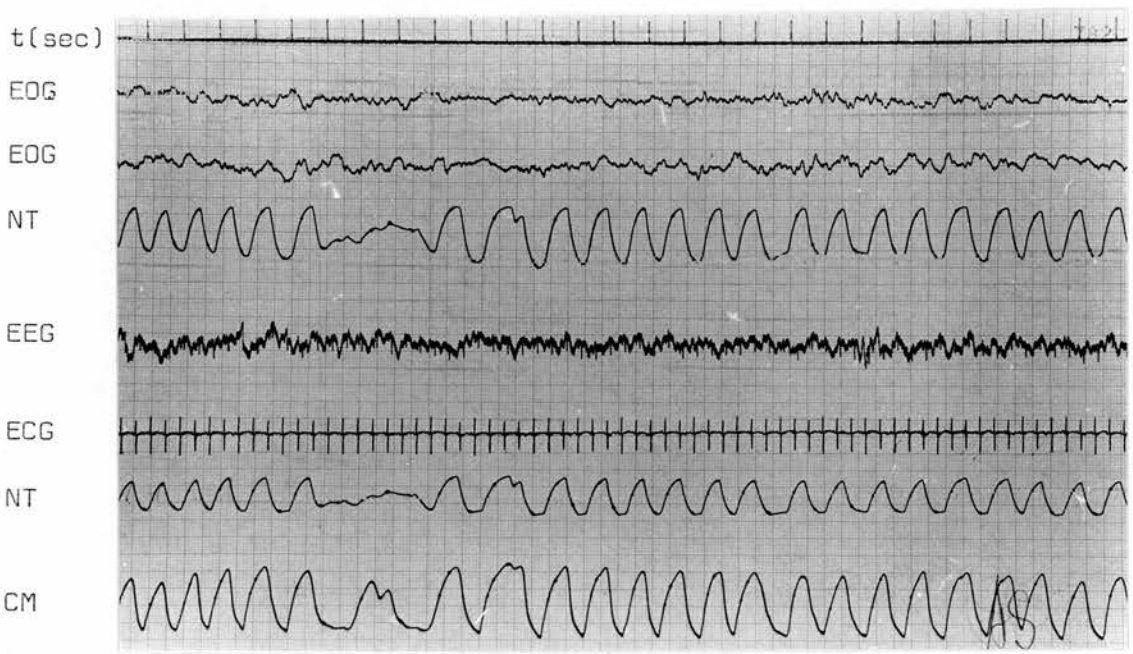
Repeat monitoring following recovery from upper respiratory tract infection showed no abnormalities.

Case 35 (JM) - Congenital stridor

An 8-week-old male infant born at 40 weeks gestation and birthweight 3.8 kg was referred for investigation of noisy breathing from the early weeks of life. When seen initially, he had obvious stridor. Laryngoscopy revealed a floppy epiglottis which was sucked over the larynx with each inspiration. Polygraphic sleep studies showed episodes of obstructive apnoea similar to that illustrated in Figure 62. This occurred in active sleep and lasted 4.5 seconds during which time heart rate remained virtually unaltered and transcutaneous oxygen tension fell approximately 7 mmHg over the subsequent 15 seconds. Figure 63 shows an episode of central apnoea in QS of 11 seconds duration, apparently triggered by movement, during the same recording. There is an associated fall in heart rate and decrease in oxygen tension during the subsequent

Figure 61

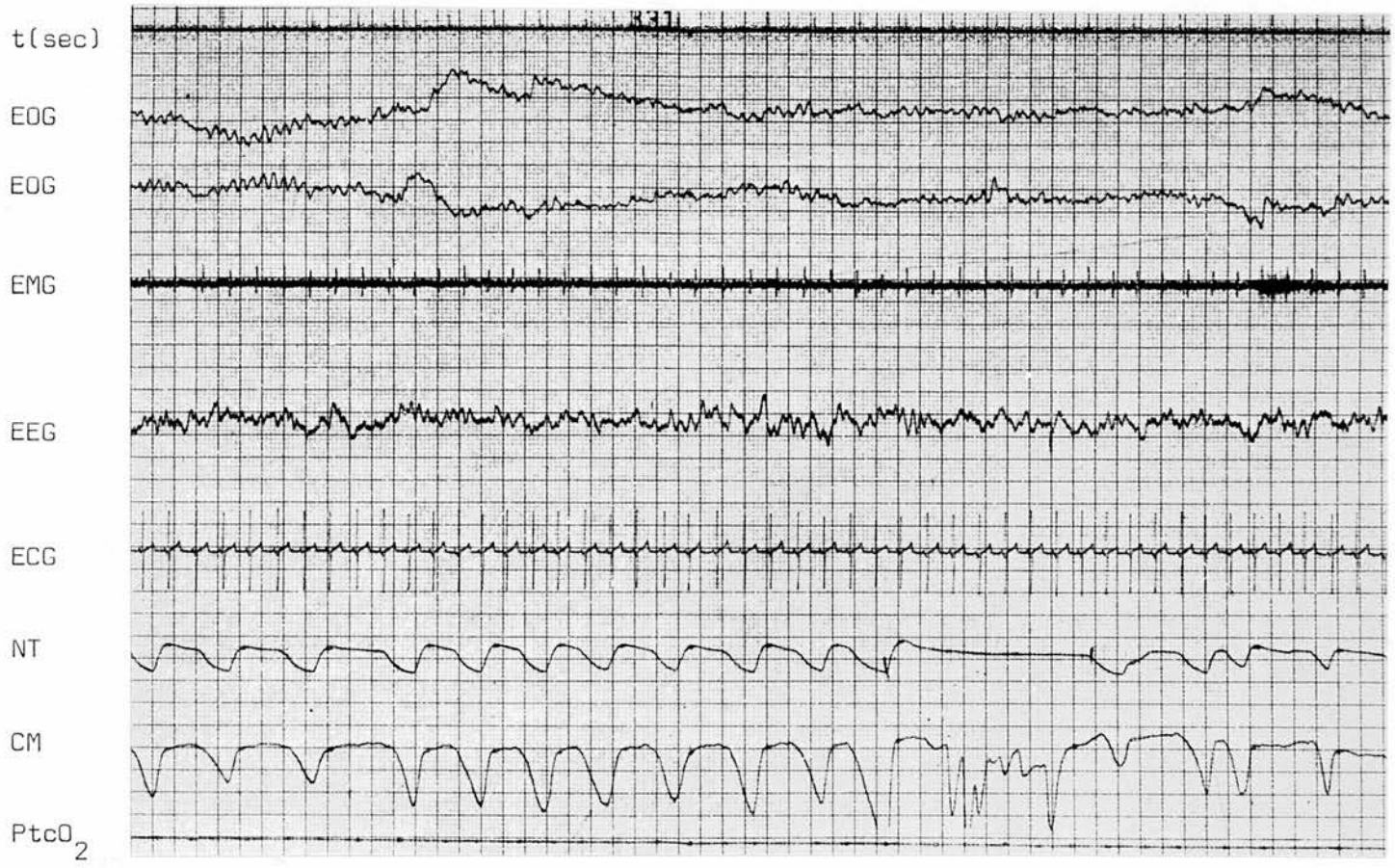
Brief obstructive apnoea in AS during upper respiratory infection



Heart rate and $PtcO_2$ did not change

Figure 62

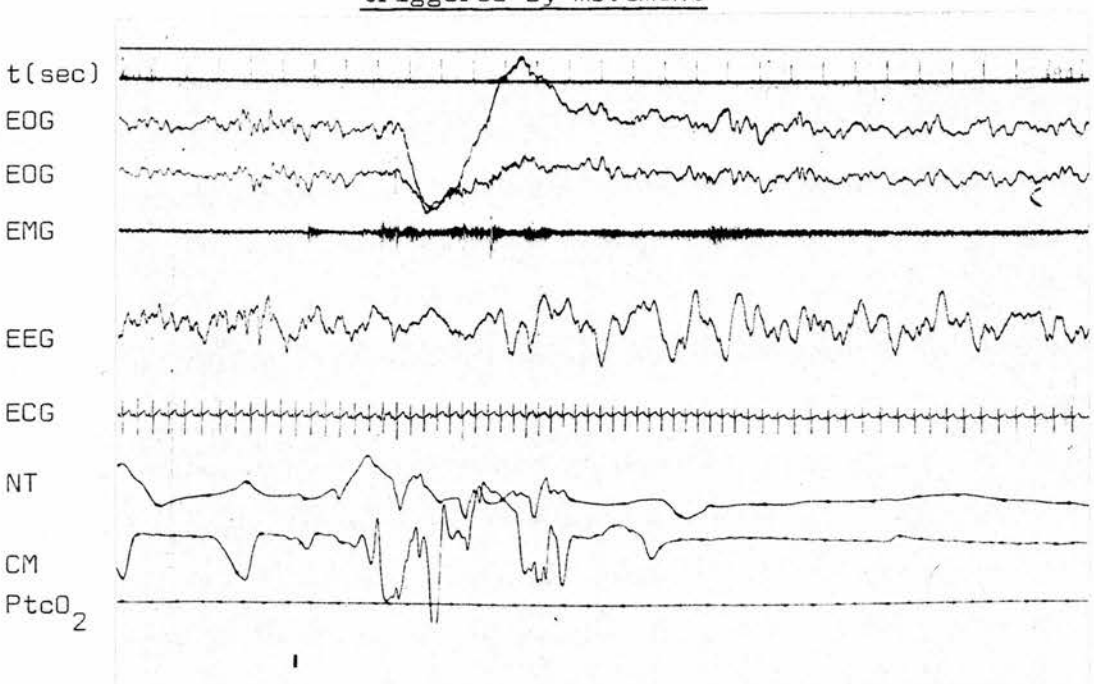
Brief obstructive apnoea in AS - congenital laryngeal stridor



No significant change in heart rate; peak fall in $PtcO_2$ of 7 mmHg (not shown)

Figure 63

Central apnoea in QS apparently triggered by movement



There is gradual slowing of heart rate and decrease in $PtcO_2$ during subsequent 20 seconds.

Normal breathing pattern was resumed after 12 seconds (not shown).

20 seconds. In the same infant, the smooth transition from active to quiet sleep is beautifully illustrated in Figure 2. This infant remained stridulous for most of the first year of his life.

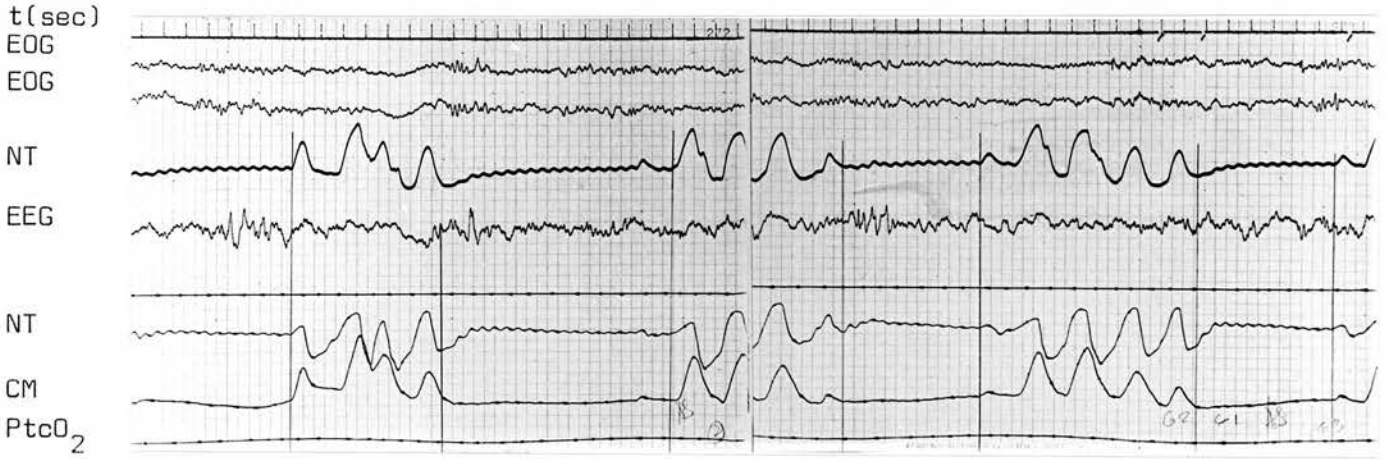
Case 41 (ST) - Pyloric stenosis

A 3-week-old male infant born at 40 weeks gestation and birthweight 2.72 kg was admitted with a 4-day history of vomiting which started gradually and progressed in frequency and amount. He had been breast-fed from birth. On the day of admission he had several projectile vomits consisting of milk and mucous, sometimes during feeds and invariably after them. On clinical examination he was mildly dehydrated and lethargic. His breathing was slow, shallow and irregular. At test feeding there was visible peristalsis over the upper abdomen and a pyloric tumour was palpable. Pyloric stenosis was confirmed at operation.

Polygraphic sleep studies confirmed a periodic pattern of breathing. This is illustrated in Figure 64 which also shows the effect on transcutaneous oxygen tension. This infant had successive apnoeic episodes lasting between 5 and 11 seconds. $PtcO_2$ always fell after the first apnoeic episode, heralding a periodic breathing pattern. This was observed in other patients with metabolic alkalosis.

Figure 64

Periodic breathing and associated changes in $PtcO_2$



This patient had mild metabolic alkalosis.
Periodic breathing was observed in AS and QS

Figure 65 is a record of $PtcO_2$ in the same infant. Each abrupt fall in oxygen tension represents an apnoeic episode within a periodic breathing cluster. $PtcO_2$ ranges from 57 to 70 mmHg. Periodic breathing was observed mainly in active sleep and, to a lesser extent, in quiet sleep. With clinical recovery, these changes were no longer observed. This infant did not have prolonged central apnoea. Figure 66 shows prolonged central apnoea (15.2 seconds) in another infant with pyloric stenosis (Case 44).

Case 66 (GF) - Sibling - upper respiratory infection

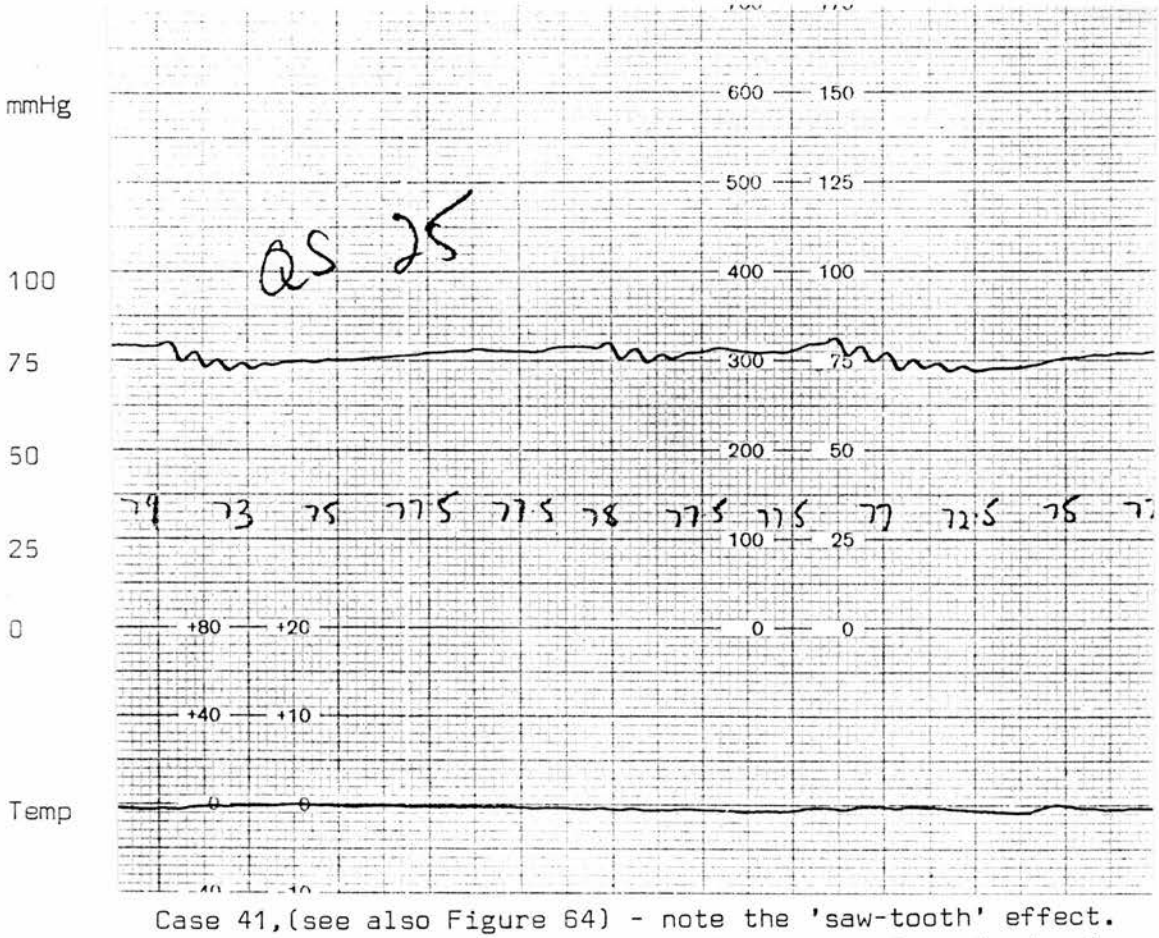
A sibling of a previous SIDS victim born at 40 weeks gestation and of birthweight 3.50kg was monitored at 6 weeks of age. At that time he was well and healthy apart from 'snuffles' due to an associated upper respiratory infection.

Polygraphic sleep studies showed several episodes of obstructive apnoea. Figure 67 illustrates an episode of mixed central and obstructive apnoea occurring during active sleep. There is a decrease in heart rate and $PtcO_2$ falls from 75 to 60 mmHg. Figure 68 shows the corresponding $PtcO_2$ tracing which indicates the desaturation caused by that particular episode. On subsequent monitoring following apparent clinical recovery, brief obstructive apnoea was again observed.

No infant in the siblings group had prolonged central apnoea.

Figure 65

Transcutaneous oxygen ($PtcO_2$) record during QS



Case 41,(see also Figure 64) - note the 'saw-tooth' effect. Each abrupt fall in $PtcO_2$ represents an apnoeic episode of a periodic breathing cluster. Throughout the study $PtcO_2$ ranged from 57 to 77 mmHg.

1 minute

Figure 66

Prolonged central apnoea in QS in pyloric stenosis (Case 44)

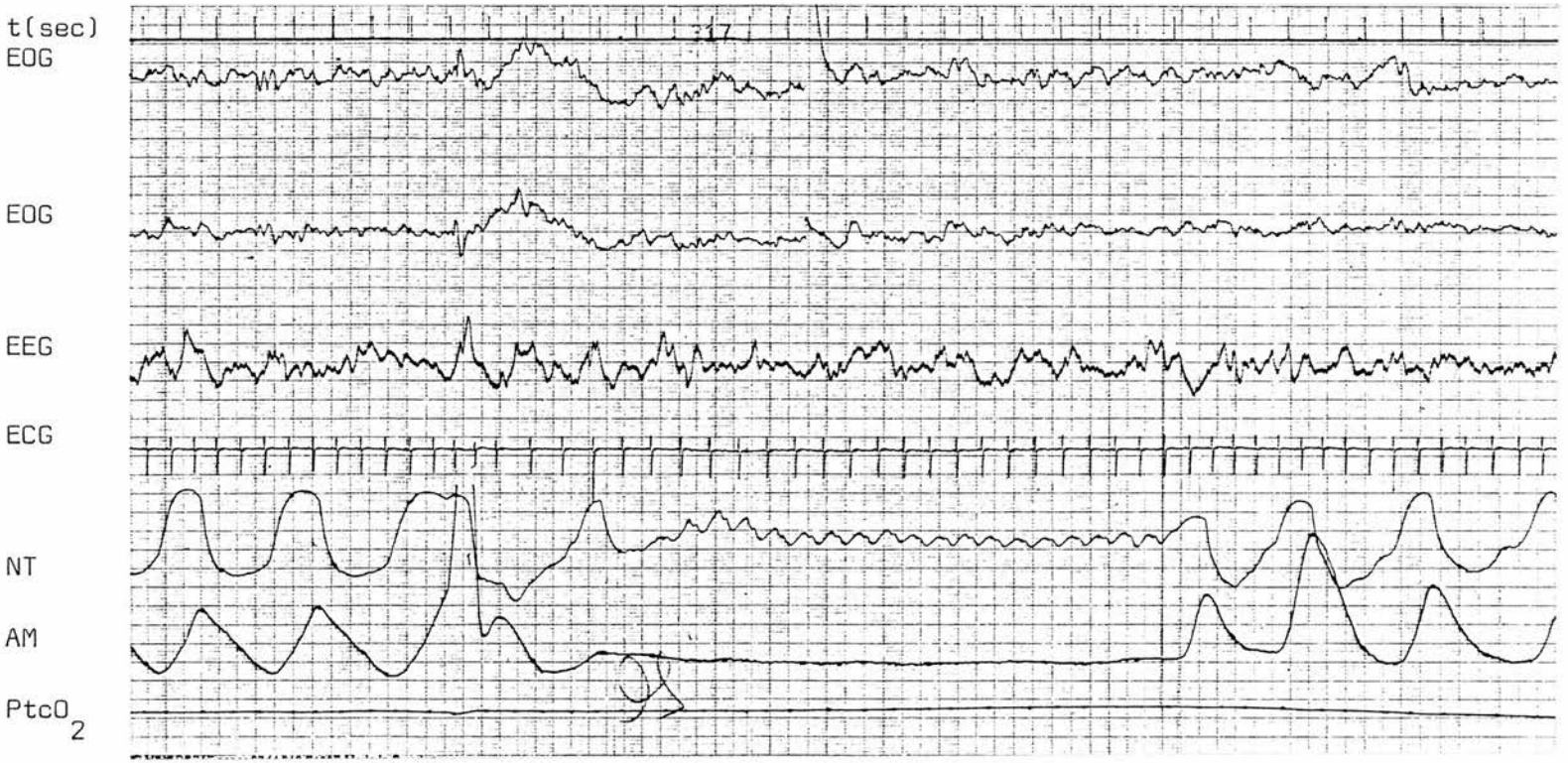
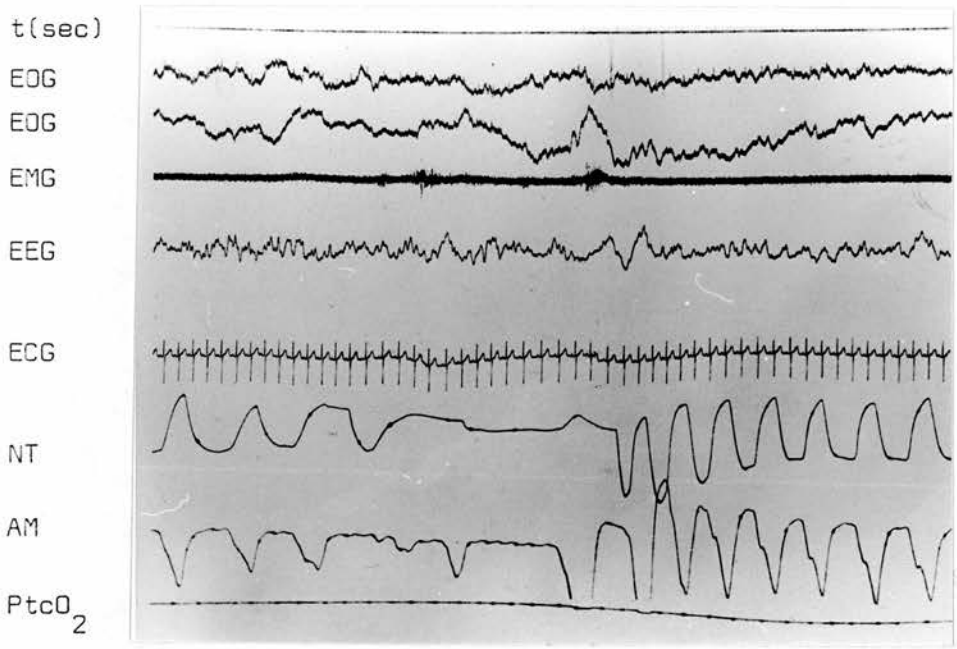


Figure 67

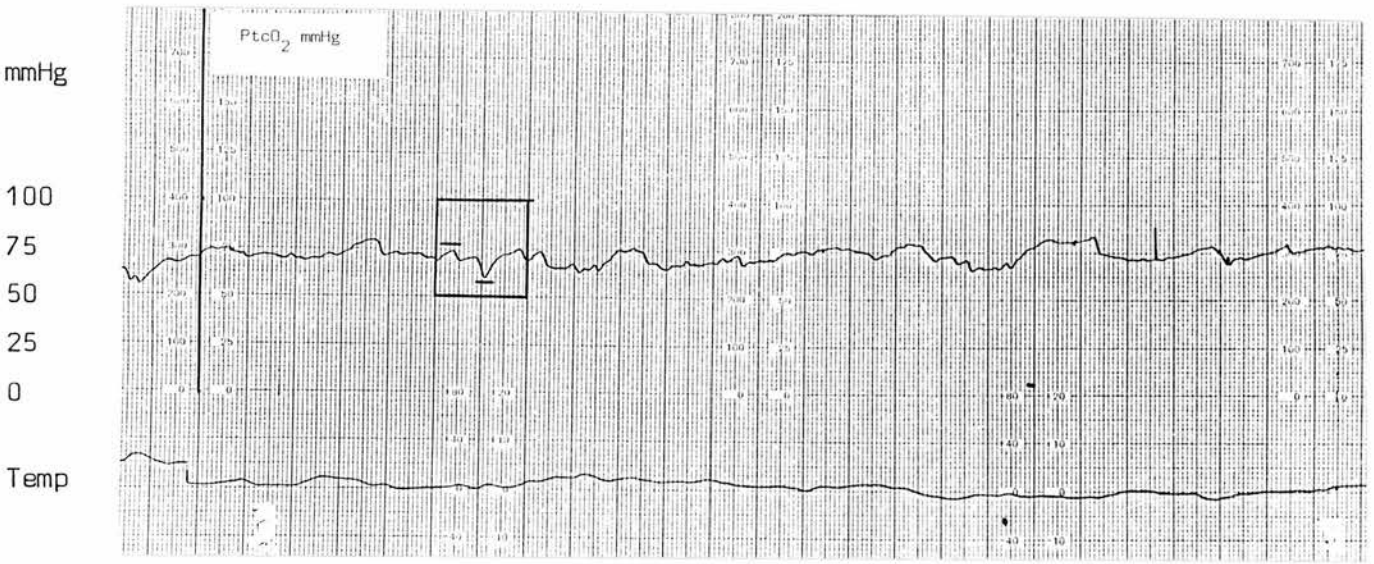
Mixed central and obstructive apnoea



Fall in heart rate. $PtcO_2$ falls from 75 to 60 mmHg.
Case 66.

Figure 68

Transcutaneous oxygen ($PtcO_2$) record in subsequent sibling with upper respiratory infection (URI)



The square shown refers to change occurring during episode illustrated in Figure 67.

⌊⌋ 1 minute

Case 73 (SS) - 'Near-miss'

A female infant born to a mother who had lost an infant (diagnosed as SIDS) from a previous marriage. She was born at 38 weeks gestation and weighed 3.04 kg. During late pregnancy there had been several episodes of threatened premature labour for which ritodrine infusions were given. There were no birth or neonatal problems. There had been a history of feeding difficulties since birth. Mother was of the opinion that sucking, swallowing, and breathing were not properly co-ordinated, and she evolved the technique of letting baby have several sucks and then breaking the seal between lips and teat in order to let her breathe and swallow. With this technique she avoided the tendency for baby to choke at feed times. From time to time baby had breathed noisily between feeds. She had episodes of apnoea and cyanosis on the day of admission which increased in frequency and severity. She was admitted to hospital after one particularly severe episode.

She had apparently recovered by the time of admission but became slightly cyanosed from time to time. This was accompanied by mild stridor and breathing difficulty. Spontaneous extension of the head would lead to resolution of these difficulties within seconds. Clinical examination was normal between episodes but she developed signs of upper respiratory tract infection. On investigation, the

main 'abnormality' found was in barium swallow. The swallowing mechanism seemed normal with no aspiration of barium into the trachea. There was, however, a prominent impression during swallowing at the level of the crico-pharyngeal muscle. There was no evidence of an H-shaped tracheo-oesophageal fistula. Blood TSH was marginally elevated (11.4 m units per litre).

Polygraphic studies during sleep revealed brief episodes of obstructive apnoea. On follow-up these diminished as symptoms of upper respiratory tract infection resolved. There were no further choking episodes in hospital and at discharge, two weeks later, she was generally well, feeding normally, and gaining weight. At follow-up the inco-ordination of breathing and swallowing had also resolved.

Case 77 (JC) - 'Near-miss'

A female infant born at 39 weeks gestation, with a birthweight of 3.15 kg. A previous sibling had died suddenly and unexpectedly in infancy and his death had been attributed to SIDS. She had had a cyanotic episode on the first day of life and polygraphic studies on the fourth day showed brief episodes of central apnoea, none of which exceeded 10 seconds. An apnoea monitor was issued at the time of discharge from hospital. Baby remained well apart from occasional 'snuffles' until her readmission to hospital at

6 weeks. On the morning of the day of admission she had seemed well. Following a breast-feed at mid-day she was slow to settle. At 1 p.m. she finally settled on her side. Some 30 minutes later the apnoea alarm sounded. She was found pale and unresponsive with the eyes glazed. There were no breathing movements. She was picked up by her mother who squeezed her chest. The only sound was the passive expulsion of air. An Ambu bag (issued at the time of discharge from hospital) was applied and after 3 to 4 puffs baby cried and her colour improved. There were no jerking movements of the limbs. She was admitted to hospital immediately by which time she had recovered. She was 'snuffly' and rather pale. She was afebrile with a pulse rate of 120 per minute and respiration rate of 40 per minute. Her weight and length were each on the 10th centiles for age. Arterialised capillary pH was 7.33, PCO_2 34 mmHg, and standard bicarbonate 18.8 mmol per litre, and base excess -6.8 mmol per litre. Barium studies revealed marked gastro-oesophageal reflux. Extensive investigations were otherwise negative.

Polygraphic sleep studies on the night of admission revealed many episodes of central apnoea, simultaneous transcutaneous oxygen tension varied between 50 and 60 mmHg. She was subsequently observed carefully but no further apnoeic episodes were noted. Her feeds were thickened and parents

advised to nurse her propped up at home. Her progress during the first year of life was uneventful. At 13 months her height and weight remained on the tenth centile for age (her mother was only 4 feet 11 inches). Developmentally she was normal.

Case 81 (CM) - 'Near-miss'

A male infant, born at 41 weeks gestation by elective caesarian section on account of cephalo-pelvic disproportion. He weighed 3.63 kg at birth. There were no neonatal problems and at discharge he was feeding normally on Cow and Gate Premium milk. During the early weeks of life, he 'possetted' frequently. He was admitted to hospital where he was noted to have blood-staining in his vomit. He was found to be anaemic with a haemaglobin of 8.8 gm per dl, and enteropathic E. coli were isolated from stool culture. He recovered and was said to be thriving at discharge.

His first admission to RHSC occurred at 11 weeks following an episode of choking, cyanosis and breathing difficulty. It was not clear whether he was apnoeic but he had been noted to become blue, then white and finally limp. He was also sweating unduly. This occurred within half an hour of completing a feed. His mother, thinking he had choked, turned him over and banged his back. Thereafter he recovered.

On admission he looked well and his growth was satisfactory. His haemoglobin was 9.3 g per dl. Extensive investigations were negative. Polygraphic sleep recording did not reveal prolonged central, mixed or obstructive apnoea. He continued to 'posset' and gastro-oesophageal radionuclide scan demonstrated reflux. There was one brief respiratory pause during reflux, without associated change in colour. He was nursed upright and his feeds thickened. There was no further vomiting and he was discharged home.

From the outset, social problems had complicated the picture. The family lived in a mobile home of adequate size, but parents had hoped for a baby girl and were disappointed that he was a boy. His mother had expressed the wish to give baby to her own mother to look after so that she could return to work. She also reported feelings of wanting to injure her baby. The family doctor suspected that she was suffering from post-natal depression and arranged to provide support in the home at the time of discharge from hospital.

Baby was readmitted to hospital at 16 weeks of age at the family doctor's request, principally because of mother's aggressive urges towards her son and because of an acute episode during which she tried to smother him with a pillow. Mother reported hearing two voices coming from inside her; one telling her to choke her baby and the other saying 'No, don't be stupid. This is your boy'. She did put a pillow over his head for about two minutes and it was only

then that she called for help. This led to urgent hospital admission. The infant was well-nourished and thriving and there was no evidence that the episode described had caused him harm. His mother was admitted to hospital for psychiatric assessment and treatment. As she improved, she and her baby were nursed together at the mother-and-baby unit within the psychiatric hospital. He continued to posset periodically but overall his growth and development were normal over the ensuing months.

Case 84 (RM) - 'Near-miss'

A male infant born at 40 weeks gestation weighing 2.83 kg following a normal pregnancy and delivery. There was no evidence of birth asphyxia. His mother was a healthy 31-year old whose previous child by a different father was normal. Within a few days of birth baby began vomiting after feeds and on occasion this was associated with nasal regurgitation and choking. This led to his admission to hospital between 3 and 4 weeks after a particularly severe episode. On examination he was a thriving infant with a slightly odd appearance due to a rather small jaw and low-set ears. He had no other dysmorphic features and clinical examination was normal. In particular, palate and nose appeared normal, a naso-gastric tube was easily passed on both sides, there were no obvious cranial nerve or other neurological abnormalities, body

temperature was normal,and a triple response to scratching the skin was easily elicited.

His symptoms persisted and a variety of investigations was performed. The results of the following were normal: FBC and ESR, blood film, blood urea and electrolytes, serum calcium, blood gas tensions and pH, amino acid profile, ganglioside screen, ECG, infection screen, skull X-ray, ultrasound examination of the kidneys, and chromosome studies. Chest X-ray showed increased lung markings, cine-radiography during barium swallow revealed a wide gastro-oesophageal junction, a sliding hiaitus hernia and reflux. There was little or no movement of the soft palate on phonation and inefficient closure of the naso-pharynx during swallowing. In addition a persistent concentric area of narrowing in the upper oesophagus was demonstrated. There was nasal regurgitation of barium but no evidence of aspiration into the lungs. Polygraphic monitoring during sleep was first carried out at the age of six weeks. Both central apnoea and obstructive apnoea were noted. During four hours of monitoring, he had 30 episodes of obstructive apnoea lasting between 6 and 18 seconds; 23 occurred during active sleep, 11 were associated with a fall in $PtcO_2$ and he awoke on two occasions when $PtcO_2$ fell to its lowest value of 42 and 52 mmHg. None of the central apnoeas was longer than 6 seconds. Figures 69 and 70 illustrate an episode of severe obstructive apnoea and the associated fall in $PtcO_2$ of 30 mmHg.

Figure 69

Episode of prolonged obstructive apnoea (Case 84)

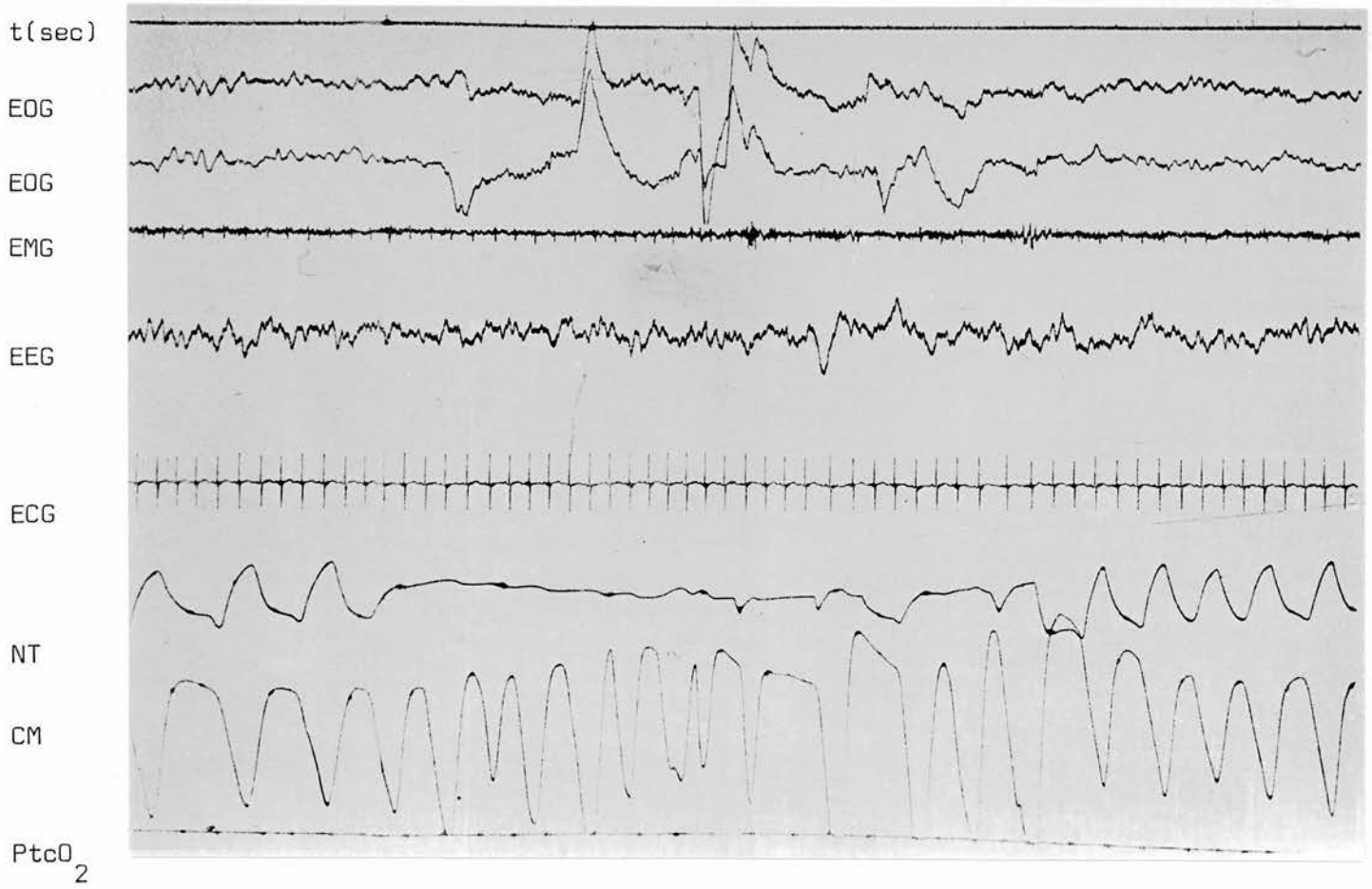
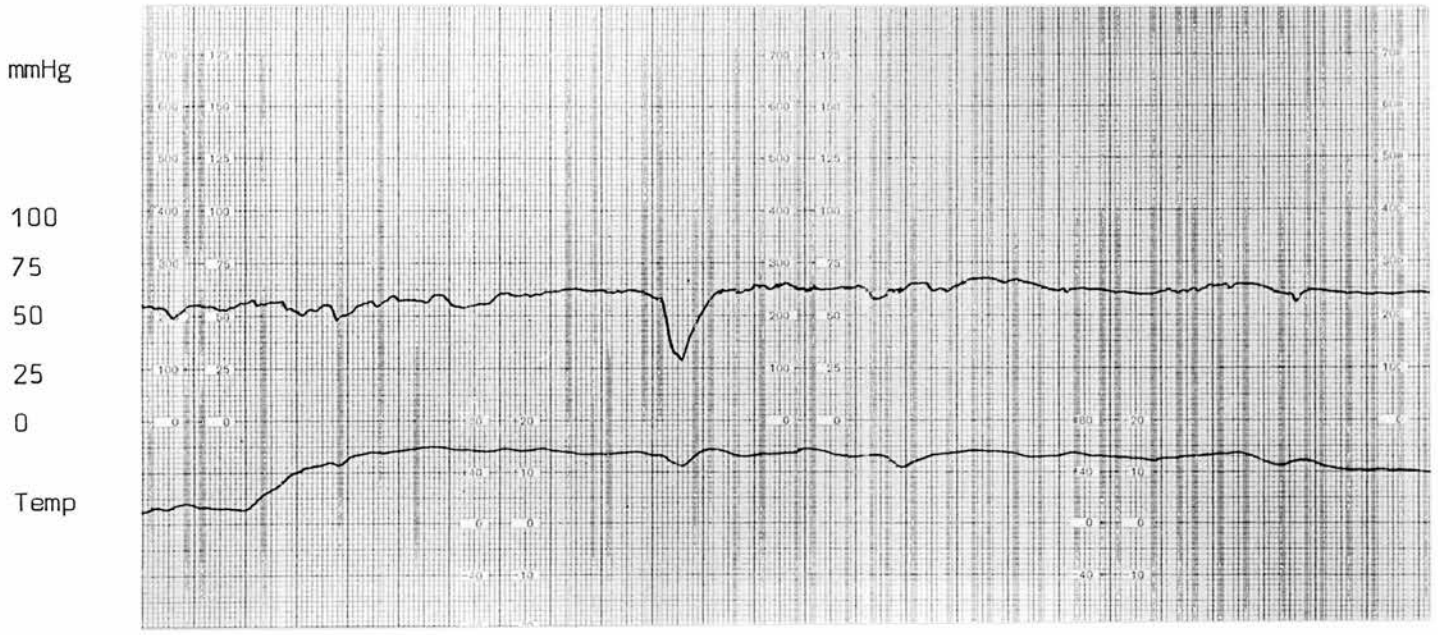


Figure 7C

Dip in transcutaneous oxygen tension ($PtcO_2$) following prolonged obstructive apnoea (Case 64)



His gastro-oesophageal reflux was treated 'medically' by thickening feeds. Vomiting diminished, his choking stopped, and he thrived. In spite of the alarming respiratory pattern found in the sleep laboratory, there were no incidents at home. By four months of age, obstructive apnoea had disappeared and polygraphic studies revealed no abnormalities. Follow-up barium studies suggested that his gastro-oesophageal reflux was no longer a problem but his swallowing remained abnormal. At the age of a year, his developmental status was normal but his vocalisations had a nasal quality.

Case 92 (BF) - Pre-term 'Near-miss'

A male infant born in hospital at 34 weeks gestation following a pregnancy complicated by slight bleeding at 29 weeks and spontaneous rupture of membranes at 33 weeks by dates. Delivery was spontaneous, by the vertex and he weighed 1.98 kg at birth. There was no birth asphyxia or early neonatal problems. He developed mild jaundice and received photo-therapy for 24 hours. There were no apnoeic episodes in the neonatal period. He was discharged home at three weeks of age, bottle-fed on no treatment, and weighing 2.27 kg.

During the following week at home he fed well without vomiting or choking. He remained well until the evening of admission

to hospital at five weeks of age. Whilst apparently asleep in his pram he was heard to scream and was found awake, blue, and not breathing. His mother lifted him and patted his back. His chest then started to heave and he turned white. Within 4 minutes he seemed completely normal.

He was admitted to hospital almost immediately where he was found to have prolonged respiratory pauses. Between these he was afebrile, pink and well-looking. External features were consistent with a pre-term baby nearing term. There were no signs of inflammation in the ears or throat. Respiration rate was 40 per minute and there were no signs of respiratory distress. The chest was clear on auscultation. Pulse rate was 140 per minute and regular. Both heart sounds were audible and no murmurs were noted. Peripheral pulses were normal and there were no signs of cardiac failure. Examination of other systems was unrevealing.

Extensive investigations were carried out, most of which were negative. Chest and skull X-rays were normal. Barium swallow showed some regurgitation of barium into the naso-pharynx during swallowing but was otherwise normal. A full infection 'screen' including lumbar puncture was normal. Within hours of admission polygraphic monitoring demonstrated frequent episodes of prolonged central apnoea associated with bradycardia, cyanosis, and dips in transcutaneous oxygen tension between 35 and 40 mmHg. These episodes

responded slowly to stimulation. 25% oxygen was administered with no apparent improvement and aminophylline was started at a dose of 3.5 mg per kg intravenously t.i.d. This resulted in a serum theophylline level of 77 umol/L which is below the range usually considered therapeutic. Apnoeic episodes continued for 36 hours after admission.

Within 12 hours of admission he developed 'snuffles', an increase in respiration rate and mild intercostal indrawing. The clinical picture was consistent with mild bronchiolitis. Symptoms persisted for 5 days and latterly were not associated with apnoea. Virological studies were negative and the possibility of undetected bacterial infection was covered by the administration of ampicillin and cloxacillin. At the time of discharge 10 days following admission he was normal clinically. A monitor to detect apnoea was provided for use in the home. Parents were instructed in cardio-pulmonary resuscitation techniques, and arrangements were made for frequent home visits.

It seems likely that this pre-term infant had a 'near-miss' episode during the incubation period of a viral infection which resulted in bronchiolitis. The initial scream is difficult to explain. It seems likely that he was apnoeic and cyanosed when found by parents. Investigations confirmed prolonged episodes of central apnoea, such as that illustrated

on Figure 71. These preceeded the clinical manifestations of mild bronchiolitis and persisted during the early stages of that illness. Figure 72 shows the corresponding $PtcO_2$ trace.

He was readmitted to hospital when he was 8 weeks old with symptoms of respiratory infection. On examination, his temperature was 37.6^{o}C, pulse rate 120 per minute, and respiration rate 36 per minute. He had a clear nasal discharge and his throat was slightly reddened. No other abnormalities were detected.

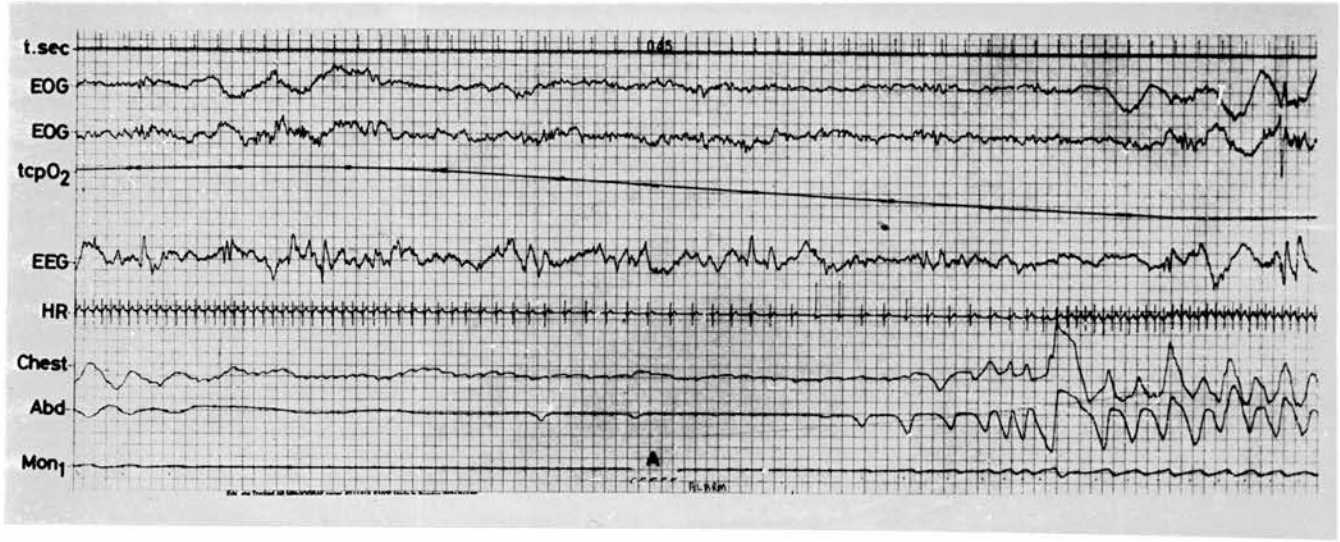
Initially he received no specific treatment for his upper respiratory tract infection, but within 48 hours he developed fever and purulent nasal discharge and was treated with antibiotics.

Polygraphic monitoring again demonstrated prolonged central apnoea, and also obstructive apnoea. Within days, apnoeic episodes were no longer clinically apparent. His subsequent progress was carefully supervised. At eight months his growth and development were progressing normally.

On two occasions during the early months of life this child developed prolonged central apnoea during the course of upper respiratory tract infections. Following recovery, a normal breathing pattern was observed. Table 53 gives details of sequential sleep studies.

Figure 71

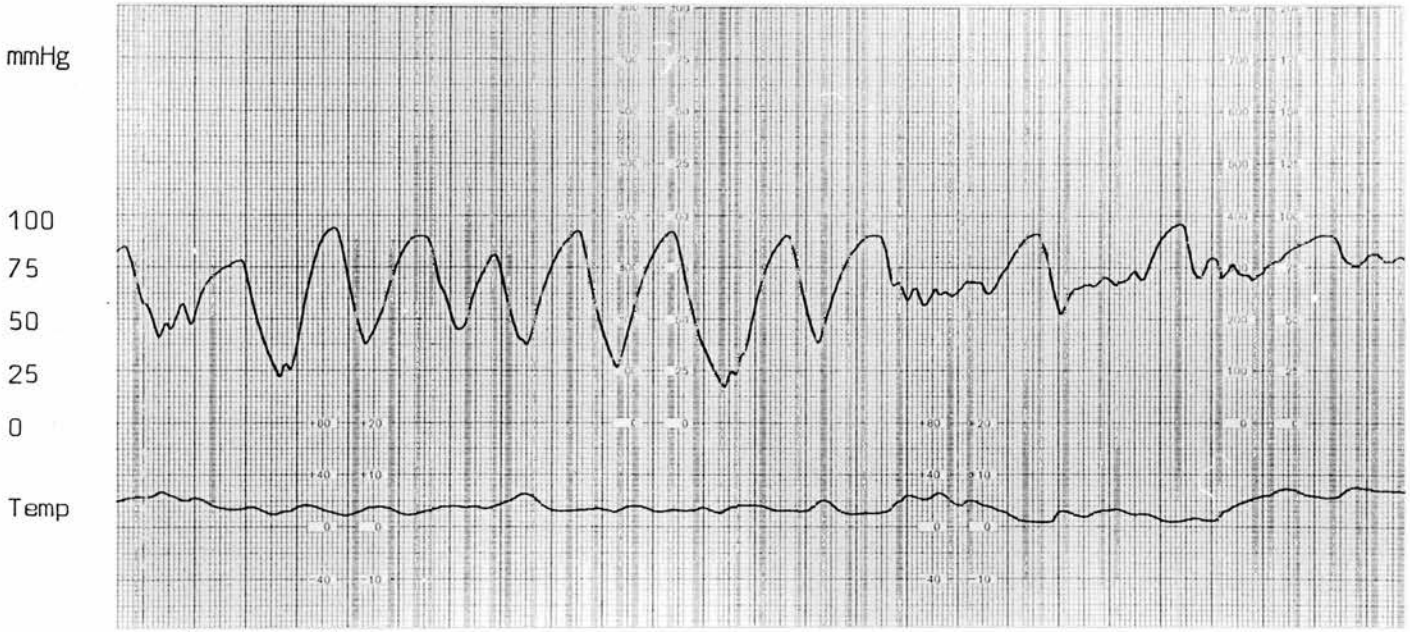
Prolonged central apnoea in prodromal phase of bronchiolitis (Case 92)



There is cessation of chest and abdominal movements for greater than 30 seconds accompanied by increasing bradycardia and a decrease in $PtcO_2$. Monitor alarms after 20 seconds of central apnoea. Episode is terminated spontaneously.

Figure 72

Transcutaneous oxygen tension ($PtcO_2$) in infant with recurrent episodes of central apnoea



Dips in $PtcO_2$ sometimes exceeding 50 mmHg are seen

⟷ 1 minute

Table 53

Apnoea variables, percent sleep, respiration and heart rate between 5 and 21 weeks chronological age in Case 92

Variable	Sleep State	Chronological age (weeks) 5*	>5	6	8*	21
Apnoea Index	AS	7.98	0.97	0.00	3.00	0.30
	QS	24.30	0.63	0.34	4.60	0.00
	IS	5.54	0.00	0.49	1.02	0.00
	T	13.78	0.69	0.19	3.50	0.11
Apnoea Attack rate	AS	0.56	0.12	0.00	0.22	0.04
	QS	0.97	0.07	0.04	0.32	0.00
	IS	0.56	0.00	0.05	0.11	0.00
	T	0.72	0.08	0.02	0.25	0.01
Apnoea %	AS	15.50	3.66	0.00	6.52	1.16
	QS	28.20	2.09	1.27	9.58	0.00
	IS	13.70	0.00	1.64	3.44	0.00
	T	20.00	2.51	0.69	7.57	0.44
Mean Duration of apnoea	AS	14.03	7.90	0.00	13.82	7.80
	QS	25.06	8.97	8.05	14.46	0.00
	IS	9.88	0.00	9.10	8.85	0.00
	T	19.10	8.22	8.40	13.83	7.80
Episode of longest duration	AS	35.5	11.8	0.0	27.2	9.6
	QS	51.5	11.6	9.1	28.8	0.0
	IS	26.4	0.0	9.1	11.7	0.0
	T	51.5	11.8	9.1	28.8	9.6
% Sleep	AS	45	48	49	29	38
	QS	38	36	37	53	53
Heart rate	AS	152	146	144	146	113
	QS	150	141	139	137	105
Respiration rate	AS	37	46	39	50	28
	QS	39	45	37	50	27

*During the course of upper respiratory infection

CHAPTER 7

DISCUSSION

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DISCUSSION

These results present an opportunity to discuss i) the respiratory status during sleep of normal healthy control infants, ii) the pattern of breathing observed during and after relatively minor illnesses capable of stressing respiratory control mechanisms before the attainment of full stability (Fleming and Levine 1982) iii) the respiratory patterns exhibited by siblings and 'near-miss' infants - groups widely considered to be at increased risk for SIDS, iv) sleep related trends in $PtcO_2$ with post-conception age, and the effects on $PtcO_2$ of the abnormal breathing patterns observed, and to comment on the possible significance of these findings in relation to the Sudden Infant Death Syndrome.

7.1 Healthy normal controls (C)

The studies described were not designed to examine sequential changes in apnoea variables, respiration rate and heart rate with increasing post-conception age in normal full-term infants. This would have required more stringent planning and standardisation of the timing of studies for the group as a whole. In the light of this limitation it is not surprising that significant trends with post-conception

age were not observed for any of the variables presented. However, it is of interest to compare the group mean value of each variable, adjusted to both 50 and 55.5 weeks post-conception age (See Table 17), with published data.

There have been several polygraphic studies of normal infants during the first six months of life designed to observe the changes which occur with age. Hoppenbrouwers et al (1977) reported the incidence of apnoea and periodic breathing in nine neurologically normal infants in the first week of life, and monthly for the remaining six months, based on sequential 12-hour overnight polygraphic recordings. Their results at three months are similar to those presented here. The findings for apnoea density and the duration of apnoeic pauses are in broad agreement. In both series apnoeic pauses between 6 and 10 seconds duration were more numerous than longer ones, and occurred with equal frequency in active and quiet sleep. There were no episodes of central apnoea $>$ 15 seconds.

Gould et al (1977) have also reported the sleep characteristics of sleep apnoea in a group of 36 twins at 38-52 weeks post-conception age. At 40, 44, and 52 weeks post-conception, each infant's sleep and respiration were recorded polygraphically for 2-4 hour periods during the day. All respiratory pauses were referred to as apnoea and subdivided according to duration. None of the infants had central apnoea $\geq$15 seconds and

apnoea of 10 seconds or longer was uncommon. These results are confirmed in the present study. The same authors noted that the effect of maturation on apnoea varied with sleep state. Over the period 40-52 weeks, quiet sleep apnoea was unchanged. Active sleep apnoea of 5-10 seconds duration decreased between 40 and 44 weeks, and active sleep apnoea of 10 seconds or longer decreased from 27% at 40 weeks to 0% at 52 weeks. This suggested that during active sleep, apnoea 'turn-on' and turn-off' mechanisms are operative. Studies in the home using impedance methods to monitor respiration also indicate that prolonged apnoea $\geq$ 15 seconds is unusual in normal infants (Stein et al 1979).

The results for respiration rate in normal control infants are most comparable to those reported by Carse et al (1981), who studied breathing and heart rates during the first six months of life in ten normal infants. Their studies were carried out from 9 a.m. for a complete inter-feed nap. At three months, they report a mean respiration rate of 36 ± 2.42 in active sleep and 33 ± 1.9 in quiet sleep - values almost identical with the present findings but slightly higher than those observed by Hoppenbrouwers et al (1978 and 1980) at the same post-conception age. The latter studies were conducted over a 12-hour period during the night in infants who were not totally unrestrained. The computation of respiration rate was based on an analysis of a complete overnight record, so that our findings are not directly

comparable. Curzi-Dascalova et al (1981) have also reported respiratory frequencies of sleeping infants during the first month of life, and reviewed current literature.

The present findings for heart rate at three months of age are also comparable with those of Carse et al (1981). These authors report slightly higher values - $134^{+}3.58$ in active sleep, and $128^{+}3.0$ in quiet sleep. In both studies heart rate is higher in active sleep than in quiet sleep, confirming the findings of Katona, Frasz, and Egbert (1980) who observed a higher heart rate in active sleep at all ages in infancy.

In brief polygraphic studies, it is difficult to know whether estimates of sleep percent for active and quiet sleep reflect values which would be obtained over a 24-hour period. The increase in time spent in quiet sleep at 3 months of age is in agreement with previous reports (Dittrichova 1966).

The results for periodic breathing and gross body movements are given in Table 19. The amount of periodic breathing was variable. It occurred more frequently and was of longer duration in active sleep than in quiet sleep confirming previous reports (Hathorn 1975; Hoppenbrouwers et al 1977). Comparable findings have been reported by Carse et al (1981).

Gross body movements were more frequent in active than in quiet sleep in the present study. This confirms previous reports. The findings for both active and quiet sleep are similar to those reported by Dittrichova (1966) who reported sequential studies in 7 children up to six months of age. Movements remained fairly constant during the first four months of life. Guilleminault and Coons (1983) have reported that the percent of movement time during 24-hour sleep gradually decreases between 3 weeks and 3 months in the normal infant.

It seems therefore that the findings reported for normal healthy control infants (and also control infants recovered from previous respiratory infection) are in broad agreement with published reports.

7.2 Symptom groups

7.2.1 Bronchiolitis

The infants studied were slightly to moderately affected and were monitored during the latter days of illness before discharge. Perhaps for that reason, prolonged episodes of apnoea such as herald the onset of bronchiolitis in a few infants, especially those of low birthweight (Bruhn et al 1977) were not observed. The increases in respiration rate and heart rate in active sleep compared with quiet sleep agrees with the known relationships in normal subjects.

The highly significant relationship between the relative amounts of active sleep and quiet sleep and the age of the infants suggests that the decreased amount of active sleep found in recovery is primarily related to normal maturation and that other possible factors (such as a regression of the sleep pattern during illness, or an incomplete adaptation during the second recording) are negligible.

During the course of bronchiolitis apnoeic pauses did not exceed 15 seconds which compares with the findings in normal term infants in the early months of life. When apnoeic episodes between 6 and 15 seconds were observed in paired studies, their mean duration and episodes of longest duration were similar. It seems unlikely, therefore, that hypoxaemia during bronchiolitis had influenced the duration of apnoea, which contrasts with the findings in the newborn period (Rigatto and Brady 1972) where apnoea and periodic breathing have been shown to increase as a result of hypoxaemia.

Several investigators have used the terms 'apnoea index' and 'apnoea attack rate' and 'apnoea percent' in their analysis of respiratory patterns (Gould et al 1977; Hoppenbrouwers et al 1977; Steinschneider 1977). Unfortunately the duration of apnoea upon which calculations of these variables is based varies from one study to another. Normal values vary with age and maturity (Hoppenbrouwers et al 1980) and the length of sleep studied (Hoppenbrouwers

et al 1977). Limited sleep studies of less than 4 hours may underestimate their values compared with 12-hour studies (Guilleminault et al 1981). For these reasons, findings have not been related to 'normal' data but compared with those obtained after recovery from bronchiolitis. Apnoea index, apnoea attack rate, and apnoea percent were all significantly increased in QS but not in AS during the course of an infection. It is not known whether the frequency or duration of apnoeic episodes or an increase in the above variables increase the risk of SIDS. It has been suggested that infants susceptible to prolonged sleep apnoea and possibly to SIDS have an increase in respiratory pauses exceeding 6 seconds compared with controls (Steinschneider 1977).

$PtcO_2$ was lower during bronchiolitis than after recovery in each case. This is consistent with observations on arterial hypoxaemia in acute bronchiolitis (Reynolds 1963). However, the finding that $PtcO_2$ was similar in active sleep and quiet sleep, both during and after bronchiolitis contrasts with findings (Martin et al 1979) in the newborn period where $PtcO_2$ is lower in active sleep.

SIDS occurs most often during sleep and there has been speculation concerning the sleep phase during which death might occur. It is not known whether the infants

are more vulnerable during active sleep or quiet sleep. The mechanisms underlying respiratory disturbance during sleep are unlikely to be defined without knowledge of the normal behaviour of the respiratory control system during sleep. This has been investigated systematically in dogs (Phillipson 1978) where it has been shown that in quiet sleep ventilation is regulated by 'automatic' respiratory control system (chemical inputs and respiratory reflexes), whereas breathing movements during active sleep are fairly insensitive to classical respiratory stimulae with the exception of hypoxaemia. This suggests that the mechanism of apnoeic episodes in quiet sleep and active sleep might be different. In studies of experimental hypoxia in kittens (Baker and McGinty 1977), it has been shown that hypoxia reduces the proportion of active sleep to quiet sleep. It is argued that the kitten is more vulnerable to hypoxia during quiet sleep and, by extrapolation, it is suggested that SIDS in infancy is more likely to occur in that phase of sleep. Other investigators (Tonkin 1975) have inferred that vulnerability is greatest in active sleep.

The most significant changes in our patients occurred in quiet sleep. It may be that stretch receptor stimulation in the lungs during the course of bronchiolitis had an inhibitory effect on respiration in quiet sleep leading to an increase in apnoea. A reflectory component of the

apnoeas might also explain the fact that the number did not increase during active sleep.The inflation reflex, like many others, seems to be inhibited (Finer et al 1976) during this phase of sleep. An interaction between the metabolic and behavioural control of breathing has been suggested (Martin et al 1979) for the origin of periodic breathing, often seen in drowsiness, and light non-REM sleep. A new adjustment of the breathing control has to be postulated also for the transient wakenings from quiet sleep. A higher incidence of apnoeic pauses or other irregularities can be expected on these occasions, particularly at an age when maturation of the mechanism underlying quiet sleep has not been completed. In our subjects, many apnoeic episodes in quiet sleep and in indeterminate sleep were initiated by a sigh or movement, behavioural signs suggesting a change of state or, possibly, a response to a stimulus. In addition, the periods of indeterminate sleep which can be expected to occur during a transition from one stable state to another showed a higher incidence of apnoeic episodes than in either quiet sleep or active sleep.

It seems therefore that bronchiolitis (in the degree studied) increases physiological 'weak spots' in breathing but is not a major cause of transition from a physiological to pathological apnoea. It is tempting to speculate that in certain infants, this causes an increased vulnerability, perhaps during their indeterminate sleep or quiet sleep

which may be decisive if there is an associated difficulty in ventilatory control as has been suggested (Shannon et al 1977) in victims of SIDS.

7.2.2 Upper Respiratory Tract Infection

The association between upper respiratory tract infection and SIDS has been well documented by the epidemiological and pathological studies described in Chapter 2. Several authors have reported that prolonged apnoeic episodes occur more frequently during upper respiratory infection in infants thought to be at increased risk for SIDS (Steinschneider 1975; Brady et al 1978; and Stevens 1965).

In the present study, at a mean post-conception age of 47 weeks no differences were observed between indices of apnoea during and following recovery from infection. Prolonged central apnoea was not observed but brief episodes of obstructive apnoea were present which did not significantly affect heart rate or transcutaneous oxygen tension. None of the infants studied was thought to be at increased risk for SIDS; the one pre-term infant (Case 32), birthweight 1.29 kg, did not show increased apnoea during the course of infection.

In a retrospective study of hospital charts of 274 infants under 6 months of age with proven respiratory syncytial

virus infection, Bruhn et al (1977) reported an association between respiratory infection caused by this virus and prolonged apnoea. The association was strongest during the first month of life and in infants born prematurely. Mitchell et al (1983) reported a prospective study of the frequency and severity of apnoea in respiratory tract infections in infancy. In 9 infants with upper respiratory infection there were 121 episodes of apnoea exceeding 10 seconds (assessed by impedence pneumography) and in 8% their duration exceeded 20 seconds. Severe bradycardia was sometimes observed unrelated to central apnoea. It is interesting to speculate that these bradycardic episodes might have resulted from obstructive apnoea, not detected by the methods employed.

Gould et al (1980) have described the effects of upper respiratory tract infection in twins studied polygraphically in the early months of life, during 2-3 hour inter-feed periods of sleep. Infants with colds exhibited sleep state specific alterations in sleep apnoea. At 40, 44, and 48 weeks post-conception, the number of respiratory pauses of 2-4.9 seconds and of 5-9.9 seconds duration per 100 minutes of state were decreased during active and indeterminate sleep. This phenomenon did not occur at 52 weeks post-conception suggesting that it had been modified by maturation. The authors hypothesise that the response described during the early weeks following birth was adaptive but for infants

at risk for SIDS it could be overwhelmed, resulting in increased apnoea and sometimes Sudden Infant Death.

Gross body movements were increased during the course of respiratory infection in relation to total sleep time (Table 24); no differences were observed between infection and recovery values during quiet sleep. Thus arousal (as indicated by gross body movements) was unaffected during quiet sleep by upper respiratory infection. In the infants studied $PtcO_2$ remained within the normal limits observed in control (C) infants (Figures 48 and 49).

7.2.3 Congenital laryngeal stridor

The results for apnoea variables, percent sleep, respiration rate and heart rate were similar to those obtained in matched case controls (Table 25). Gross body movements were also comparable, both in quiet sleep and in total sleep (Table 26). However, 5 of the 7 infants studied showed no periodic breathing; this relative absence of periodic breathing was statistically significant at the 5 percent level (see Table 48). The mean ages at which studies were carried out in the stridor and healthy control groups of infants were almost identical - 50 and 48 weeks post-conception respectively. The occurrence of periodic breathing in infants with stridor was less than in other index subgroups of infants, perhaps

due to alterations in feedback loops which influence the activity of the central respiratory controller (See review, Phillipson 1978).

In their review of congenital stridor in infancy, Kahn et al (1977) reported an infant in whom tracheomalacia had been diagnosed, who died suddenly and unexpectedly at 4 to 5 months of age. In this condition stridor is predominantly expiratory and not inspiratory as in the present cases. Guilleminault et al (1979) reported the sudden death of a 5-month old infant who presented as a 'near-miss' for SIDS at 3 months of age. 24-hour polygraphic sleep monitoring was carried out within 30 hours of her death. The data obtained were compared with those from healthy control infants and other infants with 'near-miss' for SIDS who were of similar age. The number of mixed and obstructive respiratory events was abnormally high in the case described. The finding of obstructive apnoea in 3 of the 7 infants in the present series (See Figure 62) suggests that in such infants superimposed respiratory infection might increase the hazard of obstructive apnoea and its attendant adverse effects on heart rate and oxygenation. It is of interest that the case described by Guilleminault et al (1979) had less periodic breathing than the controls selected. Detailed histological study of this case revealed fibrillary gliosis in the raphe nuclei of the pons and medulla.

7.2.4 Pyloric stenosis

In the five infants with pyloric stenosis, apnoea variables were significantly increased in both active and quiet sleep, and respiration and heart rates decreased in quiet sleep (Table 27) during the acute phase of illness, when each infant had mild to moderate metabolic alkalosis. Metabolic alkalosis of varying degree is nearly always present in such infants prior to surgical treatment (Degn et al 1974).

In this situation, the metabolic stimulus to breathing is reduced and any resulting abnormality in breathing pattern should be most obvious in quiet sleep. Potentially lethal, prolonged central apnoea might then result from loss of stimulus to wakefulness and/or a defect in metabolic control affecting central or peripheral chemoreceptor mechanisms. Prolonged central apnoea exceeding 15 seconds was observed in two infants in this group of patients, in both active and quiet sleep. Any defect in arousal in quiet sleep is potentially hazardous. However, gross body movements were increased during illness in these infants, not only in relation to total sleep time, but also in quiet sleep (Table 28) suggesting that arousal mechanisms were intact. The increase in central apnoea in active sleep is more difficult to explain; it could have resulted from activity in cerebral REM 'centres', reflex inhibition (e.g. laryngeal or chest wall), or possibly impaired hypoxic chemosensitivity. However, mean $PtcO_2$ was not reduced when compared with normal data (Figures 58,59), though

fluctuations up to 10 mmHg did occur in relation to striking periodic breathing patterns observed in all sleep states during the acute phase of illness (Figure 65). Four of the five infants studied also had episodes of obstructive apnoea during active sleep, perhaps due to loss of upper airway tone, possibly exaggerated by depletion of intra-cellular potassium, or a latent tetanic 'increase in tone' of pharyngeal constrictor muscles.

The extent to which infants exhibiting the breathing patterns and associated fluctuations in $PtcO_2$ observed in pyloric stenosis are 'vulnerable' and perhaps potential SIDS victims is not known. However, it is of interest that one infant (Case 40) also suffered a 'near-miss' episode and is included in the 'near-miss' index subgroup. He had associated upper respiratory infection which could have provided an additional respiratory'stress'. It is conceivable that summation of several stresses, perhaps of little significance individually, might destabilise respiratory control so as to initiate the sequence which culminates in Sudden Infant Death. It may not be necessary to postulate a fundamental defect in respiratory or other control mechanisms as a necessary prerequisite for SIDS.

7.3 Infants at increased risk

7.3.1 Subsequent siblings of SIDS

Indices of apnoea were similar in subsequent siblings and healthy control (C) infants when compared at 55.5 and 50 weeks post-conception age (Table 31). Respiration rate was significantly decreased in subsequent siblings when compared with control values, though the ranges of respiratory frequency observed were similar in both groups (Figure 42). In their carefully controlled 12-hour overnight studies referred to previously, Hoppenbrouwers et al (1978 and 1980) found that subsequent siblings had an increased mean and variability of respiration rate, and a decrease in brief apnoeic pauses. Obstructive apnoea was rare. They found also that once asleep subsequent siblings were more likely to remain asleep than control infants. They postulated that the higher respiration rate observed at 3 months in their series might have resulted from mild chronic hypoxaemia in subsequent siblings, a view supported by observations on transcutaneous oxygen tension in subsequent siblings and controls at 3 months of age (Hoppenbrouwers et al 1982). Monod et al (1983) also found that subsequent siblings had an increased frequency of brief apnoeic episodes between birth and the thirteenth week of life in a study conducted during morning naps. However, Kahn et al (1982) found no difference in the frequency of apnoeic pauses between subsequent siblings and controls. In the present series the only difference observed, based on a small number of case/control comparisons was at 56 weeks post-conception

(Table 32). An increase in indices of apnoea was observed, not seen in the other index/control comparisons presented. Brady et al (1981) examined the response of subsequent siblings to mild hypoxia (17 percent oxygen) and observed that after six weeks of age, subsequent siblings developed an increased number of apnoeic pauses and a greater change in respiratory rate relative to controls.

In the infants reported here, periodic breathing and gross body movements were comparable in subsequent siblings and controls (C). Kelly et al (1980) recorded respiration and heart rate in the homes of 48 subsequent siblings and a similar number of controls between the ages of 2 days and 2 months. They found that the frequency and duration of periodic breathing were increased in the subsequent sibling group, a finding not substantiated by Hoppenbrouwers et al (1980). Thus controversy concerning the respiratory status of sibling of SIDS victims continues. The possible causes for lack of consistency between studies comparing subsequent siblings and normal control infants have been reviewed by Steinschneider (1983). These relate to population differences, methodology and terminology, ambient conditions, sample size, and also variable criteria in defining the index case. In the present series, there is no obvious explanation for the lower respiration rates found in subsequent siblings when compared to controls.

Subsequent siblings had significantly less active sleep than healthy controls at 50 weeks post-conception age (Table 31); the corresponding increase in quiet sleep was not statistically significant. Hoppenbrouwers et al (1980) showed that subsequent siblings exhibited evidence of a circadian influence upon respiration and heart rates earlier than in control infants. In the development of the EEG between 4 and 8 weeks, siblings showed an accelerated increase in power of 12-15 Hz activity during quiet sleep and 4-7 Hz activity during active sleep (Sterman et al 1979). It seems possible that a transient acceleration in maturation occurs, perhaps as a consequence of some undetermined physiological deficit (?hypoxia). This possibility is supported by studies on stresses which operate during pregnancy (Gould et al 1977; Gluck et al 1977). An abnormal stimulus might upset the normal process of development and cause an 'overshoot' in some functional systems. The accelerated maturation in circadian influences and in EEG in siblings might represent such a response. This response, though initially adaptive, may 'deplete' the infant's reserves. The observation that quiet sleep is being acquired more rapidly in siblings than in healthy controls lends support to this view. It also fits the sleep hypothesis of Gould (1983) which may be summarised as follows - at two to three months of life, infants' sleep becomes prolonged and the quiet sleep predominates.

The maintenance of homeostasis by reflex mechanisms in quiet sleep is then a major challenge to the developing infant. Minor failure in homeostasis during quiet sleep, compounded by ineffective arousal mechanisms, could lead to further central nervous system depression and death. The notion of a transient overshoot is consistent with the observation that siblings once asleep tend to maintain sleep longer than controls (Hoppenbrouwers et al 1980), a possible precursor of arousal failure.

7.3.2 'Near-miss' for SIDS

In the present series, the diagnosis 'near-miss'for SIDS was made on the basis of the 'near-miss' event and exclusion of obvious causes, e.g. pneumonia, meningitis. This process of exclusion was not rigidly applied to infants in whom certain investigations were positive, e.g. the isolation of a virus or the detection of gastro-oesophageal reflux. A firm policy of excluding such infants would have reduced the series to 5. In these, the event itself was no different from the others. Scrutiny of their records did not reveal adverse birth or developmental factors and none gave a previous history of Sudden Infant Death or a family history of epilepsy. Most of the 29 'near-miss' infants were studied within 48 hours of admission to hospital, and at least once thereafter during the following weeks. In these two

respects, namely, the designation of 'near-miss' and the timing of initial studies, the series differs from most published reports. Definitions have been more restrictive (Gould and James 1979; Guilleminault and Korobkin 1979; Shannon and Kelly 1982), and the timing of studies unstated or more remote from the 'near-miss' event.

The modes of presentation of the full-term and pre-term 'near-miss' infants have been described in Chapter 4 and their clinical details, including results of investigations, summarised in Tables 35 and 36. The group was clinically heterogeneous. Within it there were one or more infants with upper respiratory infection, 'prodromal' bronchiolitis, gastro-oesophageal reflux, swallowing inco-ordination, stridor, suspected allergy, pyloric stenosis, urinary tract infection, and possibly child abuse. Each of the symptom subgroups discussed, was'represented' in the 'near-miss' for SIDS series. The possibility that a seizure was responsible for the 'near-miss' event applied to most infants. However, there was scant support from EEG investigations, or at follow-up. Only one infant had a seizure (febrile convulsion) during the following year. The combination of apparently minor problems was not uncommon in individual infants, e.g. upper respiratory tract infection plus gastro-oesophageal reflux plus infantile larynx (Case 76, Table 35). The age of presentation, antecedent symptoms,

higher than expected proportion of pre-term infants (17%) in this series is reminiscent of most SIDS series. Had any infant died, the question arises whether an adequate explanation of death would have been found at post mortem. Although this can not be answered, it seems unlikely that evidence of gastro-oesophageal reflux, swallowing inco-ordination, or respiratory infection of sufficient degree to explain death would have been present. Such deaths, unexpected and probably unexplained, would have been attributed to SIDS. During the three-year period of study, three additional infants presented at hospital with apparent 'near-miss' episodes. However, they could not be resuscitated and all three died within 24 hours despite vigorous resuscitative measures and mechanical ventilation. Following detailed post-mortem examinations, these deaths were attributed to SIDS. This suggests an overlap between 'near-miss' and SIDS (vide infra). The finding that four 'near-miss' cases were from families with a previous history of Sudden Infant Death suggests also that the 'near-miss' and siblings groups overlap. Pathologists recognise that a small minority of infant 'cot' deaths are non-accidental and that the post-mortem findings can be identical with those seen in SIDS. Very occasionally child abuse presents as 'near-miss for SIDS' (Berger 1979), and this possibility could not be excluded in one of the cases reported (Case [81]). If SIDS is comprised of a spectrum

of conditions, one or more genetically predisposed subgroup could be at risk for either 'near-miss' events or SIDS. This would explain recurrences or the varying pattern of presentation in certain families.

The results of polygraphic sleep studies show that for full-term infants no differences were detected between 'near-miss' cases and controls with respect to indices of central apnoea, percent sleep, respiration, or heart rate (Table 39). Obstructive apnoea was observed mainly during initial studies in infants with respiratory infection, gastro-oesophageal reflux, and swallowing inco-ordination. No such abnormalities were detected in cases where investigations were negative. Periodic breathing was similar in both index groups and control groups, but gross body movements were increased in 'near-miss' cases in relation to total sleep time (Figures 46 and 47). There was no increase in gross body movements in quiet sleep.

The findings for indices of central apnoea, respiration rate, and heart rate are in agreement with those of Hoppenbrouwers et al (1978). These investigators did not find an increase in brief obstructive apnoea in 'near-miss' infants; in this respect the findings described here are in agreement with those of Guilleminault et al (1979). The timing of studies may be relevant; in the present study, obstructive apnoea

had either diminished or disappeared on follow-up suggesting that its detection is most likely soon after 'near-miss' events. A variety of abnormalities in sleep-related respiratory behaviour has been reported in 'near-miss' infants. Steinschneider (1972) first reported prolonged apnoea during active sleep; Shannon et al (1977) emphasised the occurrence of central apnoea during quiet sleep. In the series reported by Guilleminault et al (1979), neither prolonged apnoea nor an increase in central apnoea were observed. Monod et al (1976) found no increase in either obstructive or central apnoea in 'near-miss' infants compared to controls. A trend towards decreased apnoea and increased respiration rate in 'near-miss' infants had been reported by Navelet et al(1979) and Haddad et al (1981). An increase in periodic breathing has been reported by Kelly and Shannon (1979) but has not been confirmed by other groups (Guilleminault et al 1979). Thus, from the information available, no common pattern of respiratory behaviour has emerged which identifies the full-term 'near-miss' infant. Obstructive apnoea in 'near-miss for SIDS', first reported by Guilleminault (1979) and confirmed here, is not specific for 'near-miss' infants and may be found during minor illnesses in infants who do not experience 'near-miss' events. The difference may be one of degree; in 'near-miss' cases, obstructive episodes may be more pronounced (See Case 84, Figure 69). The findings for gross body movements are in agreement with those of

Guilleminault and Coons (1983) who report an increase in relation to total sleep time, but not in quiet sleep.

The uncontrolled observations presented for pre-term 'near-miss' infants (Tables 41,44) indicate that prolonged central apnoea is not uncommon and that periodic breathing and gross body movements exceed those seen in full-term 'near-miss' cases (Figures 44,45). The studies were repeated in these infants following recovery from colds and associated illnesses. The findings were similar to those in healthy full-term controls. In one infant, further respiratory infection had a marked effect on all indices of apnoea (Case 92, Table 53).Thus for the 'near-miss' group as a whole, certain infants exhibit obstructive apnoea, others prolonged central apnoea or apparently excessive periodic breathing. Such abnormalities are more likely to be detected the nearer the acute event that infants are studied. When inter-group comparisons are made between full-term 'near-miss' infants (combining initial and follow-up data) and controls, the similarities are more striking than the differences.

The follow-up findings do not fully confirm previous reports in that abnormalities of breathing pattern had usually resolved on follow-up recordings. Hodgman et al (1982) report that half of their infants had no recurrence

of apnoea, either in hospital or at home. One fifth had repetitive apnoea for several weeks or months. Guilleminault et al (1984) have reported five 'near-miss for SIDS' cases and the subsequent development of obstructive sleep apnoea syndrome. Each case was followed up with repeat polygraphic monitoring from the early weeks of life to four years of age. The five developed heavy snoring at night and symptoms of obstructive sleep apnoea. Four had adenoidectomies and this significantly improved their conditions. Although the cases reported here were only followed for one year, night snoring was not a feature during that time. Three developed severe allergies, and one breath-holding attacks. Neurological development was normal in 28 cases; one infant showed mild developmental retardation which had been noted before initial presentation.

The exact risk for 'near-miss' infants of subsequent death from SIDS is unknown (See Chapter 2). The highest incidence of subsequent death in a large series has been reported by Kelly et al (1978), in which 4 of 84 infants died (4.8%). These deaths occurred in infants monitored for apnoea in home, and all had 'required' repeated positive pressure resuscitation. Studies of 'near-miss' infants which have attempted to detect underlying defects have failed to reveal convincingly vulnerability in sleep, cardio-respiratory control,or autonomic function. Read and Jeffery (1983)

suggest that neuro-chemical investigations deserve attention, in particular, the rôle of thiamine and endogenous opiates. They postulate that infants at risk are vulnerable to asphyxial insults such as apnoea (central or obstructive), gastro-oesophageal reflux, and infection. The unimpressive mortality of surviving infants, (most such cases are nowadays carefully supervised) and the failure to identify underlying defects have increased scepticism concerning the relevance of 'near-miss' infants as a possible model for SIDS. One prominent epidemiologist has coined the term 'near-myth' syndrome. Whilst acknowledging this view, it is also possible that 'near-miss' infants who survive have simply been fortunate enough to have been discovered in time. With recovery from associated illness or appropriate treatment of attendant abnormality, e.g. gastro-oesophageal reflux, the risk of recurrence is diminished;increasing maturation with age could reduce the risk still further. This would be the expected sequence if the increased risk for SIDS between 2 and 3 months of age were shared by all infants. The results presented do not answer the following questions: (i) do 'near-miss' infants have subtle defects rendering them potentially vulnerable to asphyxial insult and possibly SIDS?, or (ii) is the 'near-miss' infant a suitable model for the study of SIDS? However, evidence has been presented which suggests an overlap between subsequent SIDS, 'near-miss for SIDS', and SIDS. Moreover,

a random group of symptomatic infants studied between 1 and 6 months exhibit during relatively mild illnesses respiratory patterns comparable to but less severe than those occurring in some 'near-miss' cases with similar illnesses. Why one infant may develop an uncomplicated cold, another a 'near-miss' episode in association with a cold, and yet another die during the course of a cold remains a mystery. Are the differences due to the magnitude of the stress, host factors, fortuitous aggregation of stresses which together cause profound functional abnormalities during sleep, or a critical combination of stress and host factors. Of the various alternatives, the notion that SIDS is the result of a mystery illness (or illnesses) without distinctive symptoms, and not diagnosable during life, with a single end point (death) and for which (by definition) there is no pathological explanation, is the least appealing. Such a disease(s) would probably be unique in medicine.

7.4 Transcutaneous oxygen tension

The technique of estimating arterial oxygen tension by a skin electrode which monitors $PtcO_2$ has widened the range of physiological measurements that can be made non-invasively in normal babies. The reliability of this technique has been reported in the newborn period (Huch et al 1974), in older children (Bompard et al 1979) and also in adults

(Kleinheinz et al 1979). Its value for monitoring oxygen therapy in neonates is widely but not universally accepted, but there have been few reports of its use in healthy babies during the early months of life (Carse et al 1981). The site of application of the sensor has also been shown to be important; in general thoracic application gives slightly higher values than abdominal attachment regardless of post-natal age (Whyte et al 1983).

The observations in 11 healthy control infants relate to post-conception ages between 39 and 57 weeks with one exception - 63 weeks (Case 4). Curvilinear analyses show that oxygen tension rises most steeply in the early weeks after birth, and more gradually thereafter (Figures 48 and 49). The finding of similar mean values for $PtcO_2$ during active sleep and quiet sleep at 50 weeks post-conception age confirms the findings of Carse et al (1981). The quadratic curves described predict lower arterial oxygen tension measured transcutaneously in active sleep and quiet sleep in the early weeks of life, an observation previously reported by Martin et al (1979). Loss of intercostal muscle tone during active sleep in newborn infants is associated with a decrease in thoracic volume which results in lower oxygen stores (Henderson-Smart and Read 1979). Duration of sleep over which $PtcO_2$ is computed may also be important. Sleep is not homogeneous in the newborn or young infant, either within or between sleep cycles. In active sleep, periods

of rapid eye movements and postural muscle relaxation are interspersed with periods of movements and brief arousals (Roffwarg et al 1966). Although quiet sleep is more homogeneous with a less variable pattern than in seen in active sleep, respiration rate decreases from the beginning to the end of each quiet sleep period, a phenomenon also associated with changes in EEG activity (Paul et al 1973). Ideally the normal range of oxygen tension in young infants during sleep should be ascertained by monitoring continuously throughout unbroken sleep periods for several hours as variations in $PtcO_2$ between different sleep cycles makes the interpretation of different mean values difficult. The analytical methods described (Chapter 5, page 150) in the present study attempted to overcome this problem and provide data for $PtcO_2$ which accurately reflected events during the second hour of sleep.

The results of the present study are comparable at 50 weeks post-conception age with those reported by Carse et al (1981) and Hoppenbrouwers et al (1982) for 3-month-old infants. The increase in $PtcO_2$ during the early months, in both active and quiet sleep, at a time of increasing skin thickness might be expected to result in spuriously low levels indicates improved respiratory function during this period. Whether this is due changes in the mechanical properties of the lungs and chest wall, to better matching of ventilation and perfusion, or improvement in control mechanisms is uncertain.

The results for linear analysis (Table 49) indicate that in active sleep, significant differences are observed between groups with a rate of increase in $PtcO_2$ with age. This applied particularly to subsequent siblings. However, curvilinear analysis revealed no differences between groups either in active sleep or in quiet sleep. Although two infants in the 'near-miss' subgroup (Cases 70 and 90) were hypoxaemic on presentation, subsequent measurements following recovery fell within the normal control range. There is therefore no support for the view that siblings suffer mild chronic hypoxaemia. Similarly, 'near-miss' infants as a group show no evidence of chronic hypoxaemia following recovery from illnesses associated with acute 'near-miss' events. The studies in symptomatic infants lead to similar conclusions. Those with bronchiolitis were initially hypoxaemic (Table 51, Figures 56, 57) but not following clinical recovery. In the remaining symptom groups, no infant had even mild hypoxaemia, relative to controls.

Dips in transcutaneous oxygen tension usually occurred in association with obstructive apnoea or prolonged central apnoea. The most profound dips were observed in a small number of 'near-miss' cases, particularly during active sleep. As most apnoeic events (obstructive or central) occurred during active sleep, it is tempting to suggest that vulnerability is greatest in that sleep state. This

conflicts with the earlier suggestion implicating quiet sleep as potentially the more hazardous. 'Weak' spots in defence are predictable in both sleep states, making it unlikely that infants die exclusively in one sleep state.

7.5 Conclusions

The studies reported are not necessarily relevant to Sudden Infant Death, as all of the infants survived. At least, they provided further insights on how babies breathe during sleep, especially during illnesses which are not usually regarded as life-threatening. The studies of infants considered to be at increased risk for SIDS demonstrated the same high degree of inter-subject variability which characterised all the data on breathing in healthy control infants. No one physiological marker has been found consistently which identifies a subsequent sibling or a 'near-miss' infant. How far do the studies reported answer the initial questions posed?(See Chapter 3). These answers can be summarised as follows:

1. Normal healthy control infants do not have episodes of obstructive apnoea or prolonged (>15 seconds) central apnoea during sleep. They do exhibit periodic breathing which varies widely in frequency and duration between infants.

2. A significant number ofotherwise normal infants admitted to hospital with relatively minor illnesses which 'stress' respiratory control mechanisms show abnormalities of breathing pattern (brief and prolonged obstructive apnoea, increased indices of central apnoea, prolonged central apnoea) during illness, but seldom following clinical recovery. Periodic breathing, when present, is increased during these illnesses.

3. There is little evidence that subsequent siblings of SIDS victims exhibit an increase in apnoea when compared to healthy control infants. Brief or prolonged obstructive apnoea is uncommon and occurs almost exclusively with associated upper respiratory infection. Prolonged central apnoea is not present. Mean respiration rate is decreased in siblings though the ranges of respiration rate for siblings and controls were similar. There is also a significant decrease in active sleep and a trend towards an increase in quiet sleep in siblings when compared with controls.

4. Full-term 'near-miss' infants are not distinguishable from healthy controls in respect of indices of central apnoea, percent time in each sleep state, respiration rate or heart rate. Brief or prolonged obstructive apnoea was seen in a minority of infants, usually during

active sleep, when associated symptoms were present (upper respiratory infection, recurrent vomiting, feeding difficulties). These abnormalities of breathing patterns diminished or disappeared in all but three infants when studied subsequently.

Pre-term 'near-miss' infants may exhibit prolonged central apnoea, prolonged obstructive apnoea, or periodic breathing above the upper limit observed in full-term control infants. These abnormalities diminish or disappear on recovery from associated illness.

5. Gross body movements are usually increased in relation to total sleep time during illness in symptom and 'near-miss' subgroups of infants. There was no evidence that gross body movements were diminished in quiet sleep in any of the groups studied. No gross deficit in arousal mechanism was apparent.

6. Transcutaneous oxygen tension was similar in active and quiet sleep for each group studied. Mean $PtcO_2$ at 50 weeks post-conception age was comparable in control, sibling, and 'near-miss' groups in active sleep and in quiet sleep. A lower mean value for siblings than in controls at this age was not statistically significant.

Infants with bronchiolitis, and a minority of 'near-miss' cases were hypoxaemic on presentation. Dips in $PtcO_2$ occurred in association with prolonged central or obstructive apnoea and were most striking in a minority of 'near-miss' infants.

Thus, in the complete absence of symptoms, no infant in the present series exhibited prolonged obstructive or prolonged central apnoea, or significant dips in $PtcO_2$ during sleep. The risk for SIDS in infants exhibiting abnormalities of breathing patterns cannot be stated, as all survived. In functional terms, a minority of 'near-miss' infants would seem to have been at greater risk than others included in the study.

The SIDS puzzle might be approached within the broad framework of post-perinatal mortality studies, which could provide clues to improve predictions of 'risk', and permit strategies to be devised which prevent or limit risk. Concurrent studies of known 'risk' groups are also indicated, for example, the epidemiological characteristics of 'near-miss' for SIDS cases have yet to be defined. The 'vulnerability' factor alluded to repeatedly throughout this thesis merits further attention by the study of 'normal' pre- and post-natal developmental processes. Insights on the impact of illnesses on the relatively immature host (and on the processes themselves)

can be gained in the clinical arena with its huge investigative potential. The pathologist also, might profitably extend his role beyond the descriptive, to an elucidation of the mechanisms concerned in sudden death, e.g. the detection of pharmacological mediators when anaphylaxis is suspected. Fresh open minded approaches are needed on a broad front to solve the mysteries which surround Sudden Infant Death.

APPENDICES

Appendix 1

Details of healthy control infants.

Number	Unit Number	Initials	Sex	Date of Birth	Study 1			Study 2			Study 3			Study 4		
					Code	Date	Ref	Code	Date	Ref	Code	Date	Ref	Code	Date	Ref
1	232854	SML	M	28/ 1/81	C1a - 41	31/ 1/81	70	C1b - 46	6/ 3/81	49	C1c - 54	28/ 5/81	52			
2	233016	SP	M	3/ 2/81	C2a - 47	20/ 3/81	186	C2b - 58	14/ 6/81	62						
3	233017	GO	M	21/ 2/81	C3a - 38	26/ 2/81	179	C3b - 44	2/ 4/81	177	C3c - 56	1/ 7/81	61			
4	233641	LH	F	5/ 4/81	C4a - 40	9/ 4/81	178	C4b - 46	17/ 5/81	64	C4c - 57	2/ 8/81	54	C4d - 63	19/ 9/81	63
5	233642	RB	M	8/ 4/81	C5a - 40	11/ 4/81	180	C5b - 46	20/ 5/81	50	C5c - 56	31/ 7/81	59			
6	234988	MMD	M	3/ 6/81	C6a - 39	10/ 6/81	185	C6b - 46	18/ 7/81	48	C6c - 57	7/10/81	175			
7	234897	COD	F	9/ 6/81	C7a - 40	12/ 6/81	184	C7b - 45	16/ 7/81	66	C7c - 56	28/ 9/81	176			
8	236038	AB	M	28/ 7/81	C8a - 41	2/ 8/81	183	C8b - 46	2/ 9/81	51	C8c - 56	12/11/81	174			
9	235985	JC	F	3/ 8/81	C9a - 41	5/ 8/81	182	C9b - 46	13/ 9/81	65	C9c - 56	22/11/81	96			
10	236039	AR	F	30/ 7/81	C10a - 41	1/ 8/81	181	C10b - 46	8/ 9/81	60	C10c - 56	16/11/81	95			
11		AF	M	7/ 6/81	C11a - 63	6/ 9/81	55									

Symbols:

C Control
a-d Studies 1-4
- Post-conception age in weeks
Ref Laboratory reference number

Details of 'control' infants with previous upper respiratory tract infections or bronchiolitis.

Number	Unit Number	Initials	Sex	Date of Birth	Post-infection		
					Code	Date	Ref
96	224711	RS	M	22/11/79	B18b - 51	30/ 1/80	41
97	224663	LMD	F	21/ 6/79	B17b - 69	25/ 1/80	42
12	220558	MAC	F	10/ 4/79	B1b - 50	21/ 6/79	221
14	219424	KH	F	29/ 1/79	B3b - 54	11/ 5/79	225
15	219961	RY	M	24/ 2/79	B4b - 56	1/ 6/79	227
16	220023	JW	M	21/ 2/79	B5b - 50	25/ 5/79	229
17	219877	SJ	F	31/ 1/79	B6b - 56	21/ 5/79	231
18	220599	KM	M	6/ 3/79	B7b - 48	28/ 6/79	233
19	221002	SAP	F	20/ 3/79	B8b - 59	18/ 7/79	235
20	220020	LAS	F	26/ 1/79	B9b - 58	30/ 5/79	237
22	220438	RW	M	22/ 1/79	B11b - 54	15/ 6/79	241
28	233914	SB	M	29/ 3/81	U1b - 47	18/ 5/81	21
29	222882	LS	F	22/ 8/79	U2b - 52	13/11/79	31
30	232025	JW	M	2/12/80	U3b - 51	15/ 2/81	32

Symbols:
- B Bronchiolitis
- U Upper respiratory tract infection
- b Second studies
- \- post-conception age
- Ref Laboratory reference number

Appendix 3

Details of infants studied during and following recovery from acute bronchiolitis.

Number	Unit Number	Initials	Sex	Date of Birth	Gestation	During			Recovery		
						Code	Date	Ref	Code	Date	Ref
12	220558	MAC	F	10/ 4/79	40	B1a - 47	31/ 5/79	220	B1b - 50	21/ 6/79	221
13	219034	AH	F	2/ 1/79	40	B2a - 49	6/ 3/79	222	B2b - 53	4/ 4/79	223
14	219424	KH	F	29/ 1/79	40	B3a - 49	2/ 4/79	224	B3b - 54	11/ 5/79	225
15	219961	RY	M	24/ 2/79	42	B4a - 52	4/ 5/79	226	B4b - 56	1/ 6/79	227
16	220023	JW	M	21/ 2/79	37	B5a - 47	2/ 5/79	228	B5b - 50	25/ 5/79	229
17	219877	SJ	F	31/ 1/79	39	B6a - 51	25/ 4/79	230	B6b - 56	21/ 5/79	231
18	220599	KM	M	6/ 3/79	32	B7a - 45	5/ 6/79	232	B7b - 48	28/ 6/79	233
19	221002	SAP	F	20/ 3/79	42	B8a - 55	22/ 6/79	234	B8b - 59	18/ 7/79	235
20	220020	LAS	F	26/ 1/79	39	B9a - 53	1/ 5/79	236	B9b - 58	30/ 5/79	237
21	218806	SS	M	16/ 1/79	40	B10a- 54	22/ 4/79	238	B10b- 58	22/ 5/79	239
22	220438	RW	M	22/ 1/79	33	B11a- 51	26/ 5/79	240	B11b- 54	15/ 6/79	241
23	221148	JS	M	10/ 1/79	41	B12a- 66	1/ 7/79	242	B12b- 69	22/ 7/79	243
24	221132	BR	M	28/12/78	37	B13a- 63	27/ 6/79	244	B13b- 66	20/ 7/79	245
25	220755	DW	F	4/12/78	40	B14a- 67	11/ 6/79	246	B14b- 69	29/ 6/79	247
26	219246	MJ	M	22/ 8/78	40	B15a- 70	20/ 3/79	248	B15b- 73	11/ 4/79	249
27	219896	SS	M	28/ 8/78	35	B16a- 69	24/ 4/79	251	B16b- 74	28/ 5/79	252

Symbols: B Bronchiolitis
a and b First and second studies respectively
- Post-conception age in weeks
Ref Laboratory reference number

Appendix 4

Details of infants studied during and following recovery from 'colds'.

Number	Unit Number	Initials	Sex	Date of Birth	During			Recovery		
					Code	Date	Ref	Code	Date	Ref
28	233914	SB	M	29/ 3/81	U1a - 44	28/ 4/81	24	U1b - 47	18/ 5/81	21
29	222882	LS	F	22/ 8/79	U2a - 45	29/ 9/79	25	U2b - 52	13/11/79	31
30	232025	JW	M	2/12/80	U3a - 48	30/ 1/81	35	U3b - 51	15/ 2/81	32
31	231557	LR	M	3/11/80	U4a - 49	3/ 1/81	34	U4b - 51	16/ 1/81	23
32	236040	CS	M	2/ 6/81	U5a - 44	11/ 9/81	68	U5b - 47	1/10/81	67

Symbols U - upper respiratory tract infections ('colds')

a - study during infection

b - study following recovery

_ - post-conception age in weeks

ref- laboratory reference number

Appendix 5

Details of infants with stridor, and matched case controls.

Number	Unit Number	Initials	Sex	Date of Birth	During			Matched Control		
					Code	Date	Ref	Code	Date	Ref
33	228038	GH	M	4/ 5/80	St1 - 47	25/ 6/80	72	C1b - 46	6/ 3/81	49
34	229074	MH	M	29/ 6/80	St2 - 47	17/ 8/80	75	C5b - 46	17/ 5/81	50
35	220570	JM	M	15/ 4/79	St3 - 48	7/ 6/79	74	C6b - 46	18/ 7/81	48
36	220470	LA	F	2/ 4/79	St4 - 49	9/ 6/79	71	C4b - 46	17/ 5/81	64
37	230434	KS	F	20/ 8/80	St5a- 50	31/10/80	76	B1b - 50	21/ 6/79	221
38	221505	DS	F	22/ 4/79	St6 - 53	22/ 7/79	78	B3b - 54	11/ 5/79	225
39	226472	DL	M	29/12/79	St7 - 55	13/ 4/80	73	B7b - 48	28/ 6/79	233

Symbols St - stridor

B - bronchiolitis (post-recovery).

a - first study

b - second or post-recovery study

__ - post-conception age in weeks

Ref - laboratory reference number

Appendix 6

Details of infants studied during and following recovery from recurrent vomiting, and matched case controls.

Number	Unit Number	Initials	Sex	Date of Birth	During			Recovery			Matched Control		
					Code	Date	Ref	Code	Date	Ref	Code	Date	Ref
40	221994	TW	M	22/ 7/79	P1a - 39	14/ 8/79	10	P1b - 41	28/ 8/79	94	C1a - 41	3/ 1/81	70
41	234414	ST	F	28/ 4/81	P2a - 43	21/ 5/81	28	P2b - 45	2/ 6/81	29	C5b - 46	20/ 5/81	50
42	232601	CD	M	9/ 1/81	P3a - 46	21/ 2/81	69	P3c - 50	18/ 3/81	27	U3b - 51	15/ 2/81	32
43	230880	SMG	M	9/10/80	P4a - 46	19/11/80	3	P4b - 47	26/11/80	30	C8b - 46	2/ 9/81	51
44	234718	GW	M	16/ 4/81	P5a - 47	5/ 6/81	33	P5b - 48	10/ 6/81	36	C1b - 46	6/ 3/81	49

Symbols
- P - repeated vomiting (pyloric stenosis)
- a - first study
- b - study following recovery
- __ - post-conception age in weeks
- ref - laboratory reference number
- c - control
- u - upper respiratory tract infection

Siblings of SIDS - post-mortem details of infants who died

Number	Initial	Post-Mortem	Death Certificate	Microscopic Studies
45	SM	Yes	SIDS	No
46	PMK	Yes	SIDS	NK
47	AH	Yes	SIDS	Yes
48	DMD	Yes	SIDS	Yes
49	AS	Yes	SIDS	No
50	DM	Yes	SIDS	Yes
51	KD	Yes	SIDS	Yes
52	MK	Yes	SIDS	NK
53	JJ	Yes	SIDS	Yes
54	EC	Yes	SIDS	No
55	SG	Yes	SIDS	No
56	HG	Yes	SIDS	Yes
57	VC	Yes	SIDS	Yes
58	TR	Yes	SIDS	Yes
59	SF	Yes	SIDS	Yes
60	JD	Yes	SIDS	Yes
61	LC	Yes	SIDS	Yes
62	JL	Yes	SIDS	Yes
63	SS	Yes	SIDS	Yes
64	JY	Yes	SIDS	Yes
65	AML	Yes	SIDS	Yes
66	GF	Yes	SIDS	Yes
67	IH	Yes	SIDS	Yes
68	CB	No	SIDS	No

Appendix 8

Details of siblings of SIDS victims, and matched case controls.

Number	Unit Number	Initials	Sex	Date of Birth	Study (a)			Matched Control			Study (b)		
					Code	Date	Ref	Code	Date	Ref	Code	Date	Ref
45	232823	SM	F	12. 2.81	S1a - 43	5. 3.81	45	C7b - 45	16. 7.81	66	S1b - 44	9. 3.81	254
46	224861	PMK	F	26.11.79	S2a - 44	14. 1.80	43	C4b - 46	17. 5.81	64	S2b - 49	21. 2.80	158
47	225974	AH	M	22. 2.80	S3a - 45	3. 4.80	16	C1b - 46	6. 3.81	49	S3b - 56	20. 6.80	15
48	225352	DMD	M	23. 1.80	S4a - 45	23. 2.80	20	C5b - 46	20. 5.81	50	S4b - 60	4. 6.80	159
49	229564	AS	M	29. 8.80	S5a - 46	13.10.80	6	C6b - 46	18. 7.81	48	S5b - 58	4. 1.81	151
50	224047	DM	M	23.10.79	S6a - 46	8.12.79	1	C8b - 46	2. 9.81	51	S6b - 53	21. 1.80	5
51	225975	KD	M	15. 2.80	S7a - 48	11. 4.80	12	U1b - 47	18. 5.81	21	S7b - 52	12. 5.80	157
52	228504	MK	F	12. 5.80	S8a - 50	23. 7.80	22	B1b - 50	21. 6.79	221	S8b - 61	4.10.80	14
53	223885	JJ	M	28.10.79	S9 - 51	31. 1.80	19	U3b - 51	15. 2.81	32			
54	224002	EC	F	25. 4.81	S10a - 41	2. 5.81	165				S10b - 46	4. 6.81	9
55	233361	SG	F	23. 3.81	S11a - 40	30. 3.81	170				S11b - 46	8. 5.81	173
56	225973	HG	F	22. 2.81	S12a - 47	9. 4.80	17				S12b - 57	22. 2.80	2
57	224874	VC	F	23. 5.81	S13a - 46	6. 7.81	167				S13b - 58	26. 9.81	46
58	219196	TR	M	8. 3.79	S14a - 41	16. 3.79	149				S14b - 45	14. 4.79	37
59	216377	SF	M	5. 9.78	S15a - 66	1. 3.79	11				S15b - 69	26. 3.79	18
60	214339	JD	F	15. 5.78	S16 - 73	19. 1.79	166						
61	212859	LC	F	17. 2.78	S17 - 92	24. 2.79	171						
62	217889	JL	F	4. 7.78	S18 - 74	17. 2.79	172						
63	219896	SS	M	28. 8.78	S19a - 69	24. 4.79	250				S19b - 74	28. 5.79	251
64	219647	JY	M	26. 3.79	S20a - 45	28. 4.79	161				S20b - 83	19. 1.80	160
65	220607	AML	M	18. 5.79	S21 - 54	31. 8.79	4						
66	225676	GF	M	6. 2.80	S22a - 46	20. 3.80	8				S22b - 49	8. 4.80	40
67	227251	IH	M	26. 3.80	S23 - 46	8. 5.80	150						
68	233259	CB	F	31. 3.81	S25a - 42	6. 4.81	154				S25b - 46	7. 5.81	162

Matched Control			Study (c)			Matched Control			Study (d)			Matched Control		
Code	Date	Ref	Code	Date	Ref	Code	Date	Ref	Code	Date	Ref	Code	Date	Ref
			S1c - 46	25. 3.81	253				S1d - 57	12. 6.81	44	C4c - 57	2. 8.81	54
C5c - 56	31. 7.81	59												
C1c - 54	28. 5.81	52												
			S7c - 56	4. 6.80	168									
C9c - 56	22.11.81	96												
C9b - 46	13. 9.81	65	S10c - 55	12. 8.81	39	C10 c - 56	16.11.81	95						
			S11c - 56	27. 7.81	13	B6b - 56	21. 5.79	231						
B8b - 59	18. 7.79	235												
B9b - 58	30. 5.79	237												
			S14c - 65	29. 8.79	7	C11 a - 63	6. 9.81	55						
			S22c - 58	9. 6.80	38									
			S25c - 51	8. 6.81	148									

Symbols:

s	Siblings
c	Controls
B	Bronchiolitis
u	Upper Respiratory Tract Infection
a-d	Studies 1-4
-	Post-conception age in weeks
Ref	Laboratory reference number

Appendix 9

Details of 'near miss' for SIDS infants and matched case controls.

Number	Unit Number	Initials	Sex	Date of Birth	Study (a)			Matched Control			Study (b)		
					Code	Date	Ref	Code	Date	Ref	Code	Date	Ref
69	224586	CB	M	22. 8.79	N1a - 55	23.12.79	83	B7 - 48	28. 6.79	233	N1b - 63	2. 2.80	87
70	224497	LS	M	13.11.79	N2a - 46	22.12.79	86	C6b - 46	18. 7.81	48	N2b - 53	9. 2.80	90
71	227821	RG	M	24.10.79	N3 - 73	11. 6.80	156						
72	230838	JM	M	17.11.80	N4a - 53	18. 2.81	109				N4b - 54	25. 2.81	155
45	232823	SM	F	12. 2.81	N5a - 43	5. 3.81	45				N5b - 44	9. 3.81	254
73	227852	SS	F	11. 4.80	N6a - 48	18. 6.80	152				N6b - 56	13. 8.80	153
74	234059	BW	M	24. 4.81	N7a - 42	3. 5.81	156(b)				N7b - 45	23. 5.81	98
75	231410	AA	F	26.11.80	N8a - 48	25. 1.81	58	C9b - 46	13. 9.81	65	N8b - 53	26. 2.81	93
76	228240	KS	M	12. 6.80	N9a - 51	11. 8.80	128				N9b - 60	15.10.80	257
77	231638	JC	F	25.12.80	N10a - 45	1. 2.81	135				N10b - 55	16. 4.81	137
78	230760	LS	F	4. 9.80	N11a - 51	16.11.80	88	B1b - 50	21. 6.79	221	N11b - 60	12. 1.81	56
79	230486	KL	M	26.10.80	N12 - 62	23. 3.81	147						
80	235253	RA	M	24. 5.81	N13a - 47	2. 7.81	136				N13b - 51	4. 9.81	107
81	235556	CM	M	1. 5.81	N14a - 52	21. 7.81	169				N14b - 57	21. 8.81	97
82	221130	SA	F	8. 6.79	N15a - 43	2. 7.79	140				N15b - 51	23. 8.79	139
83	221149	JE	M	9. 6.79	N16a - 43	3. 7.79	133				N16b - 51	25. 8.79	132
84	225952	RM	M	8. 2.80	N17a - 47	21. 3.80	164				N17b - 61	30. 6.80	163
85	218191	AL	M	30. 8.78	N18a - 60	21. 1.79	79	B11b - 54	15. 6.79	241	N18b - 74	27. 4.79	47
86	218541	SB	F	11. 9.78	N19a - 58	3. 2.79	80	C4c - 57	2. 8.81	54	N19b - 63	10. 3.79	82
87	218796	JF	F	19. 1.79	N20a - 44	23. 2.79	84	C7b - 45	16. 7.81	66	N20b - 49	28. 3.79	91
88	225423	SL	M	24.12.79	N21a - 44	6. 2.80	85	C5b - 46	20. 5.81	50	N21b - 57	2. 5.80	53
89	229568	SD	M	8. 9.80	N22a - 39	16. 9.80	123				N22b - 39	18. 9.80	114
90	226887	DA	M	29. 1.80	N23 - 53	21. 4.80	57	B4b - 56	1. 6.79	227			
91	229756	MW	M	8. 8.80	N24a - 48	21. 9.80	258				N24b - 49	23. 9.80	259

Matched Control			Study (c)			Matched Control			Study (d)			Matched Control		
Code	Date	Ref	Code	Date	Ref	Code	Date	Ref	Code	Date	Ref	Code	Date	Ref
C11a - 63	6. 9.81	55												
B5 - 50	25. 5.79	229												
			N5c - 46	25. 3.81	253				N5d - 57	12. 6.81	44			
			N7c - 55	3. 8.81	134									
B3 - 54	11. 5.79	225	N8c - 57	24. 3.81	92									
B9b - 58	30. 5.79	237												
			N15c - 73	24. 1.80	141									
			N16c - 72	17. 1.80	126									
B17 - 69	25. 1.80	42												
C4d - 63	19. 9.81	63	N19c - 77	19. 6.79	144									
U2b - 52	13.11.79	31	N20c - 60	18. 6.79	108				N20d - 69	17.08.79	116			
C3c - 56	1. 7.81	61												
			N22c - 44	21.10.80	81	C8b - 46	2. 9.81	51	N22d - 54	8. 1.81	89	C1c - 54	28. 5.81	52
			N24c - 59	8.12.80	260									

Symbols:

N	'Near-miss' (full-term)
C	Control
B	Bronchiolitis
U	Upper respiratory tract infection
a-d	Studies 1-4
-	Post-conception age in weeks
Ref	Laboratory reference number

Appendix 10

Details of premature 'near-miss' SIDS victims

Number	Unit Number	Initials	Sex	Date of Birth	Code	Study (a) Date	Ref	Code	Study (b) Date	Ref	Code	Study (c) Date	Ref
40	221994	TW	M	22.07.79	N25a-39	14.08.79	10	N25b-41	27.08.79	94	N25c-45	22.09.79	278
92	228729	BF	M	26.06.80	N26a-38	28.07.80	280	N26b-38	30.07.80	277	N26c-39	05.08.80	113
93	232132	SH	F	14.12.80	N27a-46	20.02.81	118	N27b-48	13.03.81	119	N27c-58	14.05.81	115
94	227465	GT	M	19.02.80	N28a-45	02.06.80	281	N28b-50	07.08.80	279			
95	228621	DC	F	27.06.80	N29a-38	29.07.80	127	N29b-38	31.07.80	145	N29c-38	03.08.80	130

Symbols:
- N — 'Near-miss' (pre-term)
- a-f — Studies 1-6
- \- — Post-conception age in weeks
- Ref — Laboratory reference number

Code	Study (d) Date	Ref	Code	Study (e) Date	Ref	Code	Study (f) Date	Ref
N25d-61	12.01.80	131						
N26d-41	24.08.80	122	N26e-50	24.10.80	124	N26f-54	17.11.80	125
N29d-43	03.09.80	110	N29e-50	27.10.80	129			

APPENDIX 11

'NEAR-MISS' INVESTIGATIONS

X-RAYS

Chest
Skull
Skeletal survey (selected cases)
Barium swallow
Swallowing
Fistulae
Reflux

HAEMATOLOGY

Hb
WBC
Differential WBC
Film

BIOCHEMISTRY

Sodium
Chloride
Potassium
BUN
CO_2
Ca
P
Alk. Phosp.
Serum Osmolality
Blood Amino Acids

URINE

Urinalysis
Microscopy
Culture
Amino Acid Chromotography

INFECTION SCREEN

Nasal and Throat swab

Urine culture

Virological studies

Blood cultures (selected cases)

Lumbar puncture (selected cases)

ECG (All leads)

EEG

EMI Scan

IMMUNOGLOBULINS

IgA

IgG

IgM

IgE

TSH

T4

OTHER

Indices of apnoea of 'control' infants
with previous upper respiratory tract infections or bronchiolitis.

Number	Code	Apnoea index				Apnoea attack rate				Apnoea %			
		AS	QS	IS	T	AS	QS	IS	T	AS	QS	IS	T
96	B18b - 51	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
97	B17b - 69	0.68	0.00	0.00	0.34	0.09	0.00	0.00	0.04	2.60	0.00	0.00	1.30
12	B1b - 50	0.00	0.00	0.44	0.08	0.00	0.00	0.07	0.01	0.00	0.00	2.08	3.80
14	B3b - 54	0.00	0.30	0.00	0.17	0.00	0.05	0.00	0.03	0.00	1.46	0.00	0.83
15	B4b - 56	0.17	0.00	0.41	0.14	0.02	0.00	0.06	0.02	0.68	0.00	1.85	0.57
16	B5b - 50	0.00	0.22	0.00	0.11	0.00	0.03	0.00	0.01	0.00	0.98	0.00	0.49
17	B6b - 56	1.23	0.38	3.84	0.64	0.17	0.06	0.05	0.09	5.19	1.69	1.69	2.75
18	B7b - 48	0.00	0.11	0.00	0.06	0.00	0.02	0.00	0.01	0.00	0.56	0.00	0.33
19	B8b - 59	0.31	0.00	0.00	0.12	0.05	0.00	0.00	0.02	1.44	0.00	0.00	0.56
20	B9b - 58	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
22	B11b - 54	0.00	0.26	0.00	0.12	0.00	0.03	0.00	0.01	0.00	0.94	0.00	0.44
28	U1b - 47	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
29	U2b - 52	0.59	1.03	0.00	0.88	0.10	0.14	0.00	0.13	2.94	4.30	0.00	3.78
30	U3b - 51	2.33	0.97	2.36	1.41	0.25	0.09	0.30	0.15	7.50	2.78	9.09	4.40

Indices of apnoea of 'control' infants

with previous upper respiratory tract infections or bronchiolitis.

Number	Code	Episode of longest duration				Mean duration				% Sleep	
		AS	QS	IS	T	AS	QS	IS	T	AS	QS
96	B18b - 51	0.0	0.0	0.0	0.0	0.00	0.00	0.00	0.00	54.2	37.2
97	B17b - 69	9.4	0.0	0.0	9.4	7.85	0.00	0.00	7.85	50.0	44.2
12	B1b - 50	0.0	0.0	6.4	6.4	0.00	0.00	6.40	6.40	46.0	35.0
14	B3b - 54	0.0	6.5	0.0	6.5	0.00	6.23	0.00	6.23	25.0	57.0
15	B4b - 56	7.4	0.0	6.7	7.4	7.40	0.00	6.70	7.05	43.0	42.0
16	B5b - 50	0.0	6.9	0.0	6.9	0.00	6.80	0.00	6.80	40.0	50.0
17	B6b - 56	7.9	7.3	6.8	7.9	7.15	6.70	6.80	6.97	30.0	46.0
18	B7b - 48	0.0	6.1	0.0	6.1	0.00	6.10	0.00	6.10	36.0	59.0
19	B8b - 59	6.4	0.0	0.0	6.4	6.35	0.00	0.00	6.35	39.0	48.0
20	B9b - 58	0.0	0.0	0.0	0.0	0.00	0.00	0.00	0.00	32.0	54.0
22	B11b - 54	0.0	8.4	0.0	8.4	0.00	8.40	0.00	8.40	31.0	46.0
28	U1b - 47	0.0	0.0	0.0	0.0	0.00	0.00	0.00	0.00	52.2	36.1
29	U2b - 52	6.0	8.5	0.0	8.5	6.00	7.20	0.00	6.96	25.8	70.5
30	U3b - 51	11.5	13.2	7.8	13.2	9.33	10.47	7.80	9.60	25.2	67.9

Indices of apnoea of 'control' infants with previous upper respiratory tract infections or bronchiolitis.

Number	Code	Respiration rate		Heart rate	
		AS	QS	AS	QS
96	B18b - 51	32.7	28.4	134.0	129.8
97	B17b - 69	33.6	32.8	130.0	128.1
12	B1b - 50	42.0	30.8	124.8	113.7
14	B3b - 54	38.0	28.3	131.5	92.9
15	B4b - 56	21.7	22.0	117.0	117.3
16	B5b - 50	39.0	31.1	115.0	110.6
17	B6b - 56	29.9	29.4	128.1	129.3
18	B7b - 48	36.6	31.0	119.8	99.0
19	B8b - 59	41.1	33.3	119.2	117.3
20	B9b - 58	35.4	30.7	135.1	134.6
22	B11b - 54	26.9	25.0	117.9	106.5
28	U1b - 47	50.7	49.1	144.3	145.5
29	U2b - 52	34.7	31.3	134.0	126.3
30	U3b - 51	30.0	28.8	120.7	114.3

Gross body movements and periodic breathing in relation to sleep phase in 10 healthy control (c) infants

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
1	t(min)	11.42	2.80	9.97	8.47	0.00	0.00	0.00	0.00
	n	39	27	26	33	0	0	0	0
	t(min)	1.02	0.58	29.13	2.65	0.00	0.00	0.00	0.00
	n	6	5	117	13	0	0	0	0
2	t(min)	1.45	0.00	57.78	2.47	0.78	0.00	0.00	0.32
	n	8	0	150	8	3	0	0	1
3	t(min)	6.88	0.00	63.63	4.82	4.85	0.00	0.00	1.83
	n	33	0	153	18	12	0	0	5
4	t(min)	11.68	0.47	46.42	7.98	4.22	2.68	0.00	3.20
	n	39	3	123	25	7	3	0	4
	t(min)	1.80	0.00	50.60	6.43	1.95	0.00	0.00	0.87
	n	13	0	113	18	5	0	0	2
	t(min)	0.61	0.28	30.10	2.78	11.42	2.35	1.88	5.15
	n	4	1	100	10	19	4	6	9
6	t(min)	4.70	0.15	39.47	7.95	6.92	0.72	0.00	3.58
	n	21	1	84	22	16	2	0	8
7	t(min)	6.28	0.42	30.68	4.85	4.20	0.00	0.00	1.90
	n	31	3	83	21	11	0	0	5
8	t(min)	3.47	0.23	66.13	7.12	0.35	1.12	0.00	0.73
	n	17	1	143	20	1	4	0	2
9	t(min)	6.17	1.73	48.57	11.65	2.00	0.00	0.00	0.93
	n	37	14	147	47	3	0	0	1
	t(min)	5.02	0.32	31.52	3.85	3.98	0.00	0.00	1.53
	n	33	3	122	21	8	0	0	3
10	t(min)	1.81	0.20	33.73	3.32	2.72	0.00	0.00	1.30
	n	14	1	100	14	7	0	0	3
	t(min)	1.92	0.12	44.87	2.70	1.33	0.45	18.33	2.35
	n	10	1	167	12	4	1	17	3
11	t(min)	1.40	0.12	8.33	0.63	1.55	0.85	0.00	1.03
	n	10	1	50	5	6	1	0	3

Gross body movements and periodic breathing in relation to sleep phase in 14 control (c') infants with previous respiratory tract infection or bronchiolitis

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
96	t(min)	4.80	2.37	26.95	5.02	1.62	0.00	0.00	0.82
	n	30	22	89	30	4	0	0	2
97	t(min)	7.93	1.40	49.35	9.07	0.00	0.00	0.00	0.00
	n	45	8	179	43	0	0	0	0
12	t(min)	4.17	1.58	31.05	7.72	0.00	0.00	0.00	0.00
	n	24	9	158	41	0	0	0	0
14	t(min)	1.77	2.03	20.55	5.62	1.33	0.55	0.00	0.63
	n	13	17	100	33	4	2	0	2
15	t(min)	4.28	1.53	25.77	6.52	1.17	0.00	0.00	0.40
	n	48	14	136	46	3	0	0	1
16	t(min)	5.42	2.38	28.75	6.42	0.00	0.00	0.00	0.00
	n	34	11	136	33	0	0	0	0
17	t(min)	1.10	0.82	21.72	5.67	12.50	0.00	0.77	4.20
	n	13	10	115	35	15	0	3	5
18	t(min)	6.18	0.75	25.48	3.93	0.73	0.00	0.00	0.25
	n	36	8	82	22	2	0	0	1
19	t(min)	1.27	0.67	31.55	4.60	3.63	0.00	0.00	1.45
	n	13	5	110	21	9	0	0	3
20	t(min)	1.01	1.07	29.73	4.92	0.00	0.00	0.00	0.00
	n	17	9	91	23	0	0	0	0
22	t(min)	0.58	1.55	19.38	6.22	0.42	0.00	0.00	0.12
	n	2	13	94	33	3	0	0	1

Appendix 14 (continued)

Gross body movements and periodic breathing in relation to sleep phase in 14 control (c) infants with previous respiratory tract infection or bronchiolitis

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
28	t(min)	0.57	1.05	33.43	4.58	0.00	0.00	0.00	0.00
	n	4	8	97	16	0	0	0	0
29	t(min)	1.37	0.28	6.67	0.82	0.00	0.60	0.00	0.42
	n	6	2	40	5	0	2	0	2
30	t(min)	1.33	0.90	32.12	3.17	0.00	0.75	0.00	0.52
	n	5	11	73	14	0	2	0	1

Gross body movements and periodic breathing in relation to sleep phase in 16 infants during and after bronchiolitis

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
12	t(min)	5.17	2.17	37.20	5.50	1.70	3.83	0.00	2.63
	n	30	14	96	26	4	7	0	5
	t(min)	4.17	1.58	31.05	7.72	0.00	0.00	0.00	0.00
	n	24	9	158	41	0	0	0	0
13	t(min)	3.03	0.27	33.80	6.98	1.37	0.00	0.00	0.50
	n	31	4	115	33	4	0	0	2
	t(min)	1.68	0.27	30.20	5.37	3.07	0.00	0.00	0.90
	n	11	3	100	20	8	0	0	2
14	t(min)	6.48	0.87	27.52	8.45	0.00	1.67	1.08	0.95
	n	35	6	121	40	0	4	2	2
	t(min)	1.77	2.03	20.55	5.62	1.33	0.55	0.00	0.63
	n	13	17	100	33	4	2	0	2
15	t(min)	3.05	1.08	39.70	6.22	0.00	0.00	0.00	0.00
	n	40	8	184	38	0	0	0	0
	t(min)	4.28	1.53	25.77	6.52	1.17	0.00	0.00	0.40
	n	48	14	136	46	3	0	0	1
16	t(min)	2.27	0.37	32.65	4.85	3.52	0.88	1.23	1.70
	n	19	7	157	29	8	2	4	4
	t(min)	5.42	2.38	28.75	6.42	0.00	0.00	0.00	0.00
	n	34	11	136	33	0	0	0	0
17	t(min)	2.32	0.22	30.77	3.70	2.57	1.98	0.00	2.07
	n	22	2	138	22	9	5	0	7
	t(min)	1.10	0.82	21.72	5.67	12.50	0.00	0.77	4.20
	n	13	10	115	35	15	0	3	5
18	t(min)	4.10	3.98	46.97	10.03	0.00	0.63	0.00	0.28
	n	29	23	159	44	0	1	0	1
	t(min)	6.18	0.75	25.48	3.93	0.73	0.00	0.00	0.25
	n	36	8	82	22	2	0	0	1

Appendix 15 (continued)

Gross body movements and periodic breathing in relation to sleep phase in 16 infants during and after bronchiolitis

		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
19	t(min)	2.98	0.43	40.87	6.47	4.67	0.00	0.00	1.88
	n	33	5	241	46	11	0	0	4
	t(min)	1.22	0.67	31.55	4.60	3.63	0.00	0.00	1.45
	n	13	5	110	21	9	0	0	3
20	t(min)	5.90	0.25	31.38	7.22	0.00	0.00	0.00	0.00
	n	45	5	130	40	0	0	0	0
	t(min)	1.02	1.07	29.73	4.92	0.00	0.00	0.00	0.00
	n	17	9	91	23	0	0	0	0
21	t(min)	0.73	0.68	20.10	2.00	7.08	1.10	6.35	3.88
	n	15	10	194	25	16	2	19	10
	t(min)	4.35	2.83	27.20	10.17	0.00	0.00	0.00	0.00
	n	42	19	176	70	0	0	0	0
22	t(min)	4.35	0.53	21.83	4.82	0.00	0.00	0.00	0.00
	n	26	2	78	20	0	0	0	0
	t(min)	0.58	1.55	19.38	6.22	0.42	0.00	0.00	0.12
	n	6	13	94	33	3	0	0	1
23	t(min)	0.65	1.92	29.75	4.53	0.00	0.00	0.00	0.00
	n	12	14	158	29	0	0	0	0
	t(min)	3.40	1.90	32.10	4.85	0.00	0.00	0.00	0.00
	n	31	17	141	31	0	0	0	0
24	t(min)	1.95	0.98	19.82	3.58	10.57	0.28	8.93	4.45
	n	20	9	104	24	14	1	22	7
	t(min)	3.50	1.40	24.50	3.27	7.58	0.00	0.00	1.83
	n	37	9	140	23	17	0	0	4
25	t(min)	1.25	2.05	16.30	2.98	2.77	0.75	0.00	1.20
	n	17	11	135	23	8	3	0	4
	t(min)	1.62	0.57	19.52	2.07	7.50	11.03	11.48	10.43
	n	13	7	142	17	26	16	25	18

Appendix 15 (continued)

Gross body movements and periodic breathing in relation to sleep phase in 16 infants during and after bronchiolitis

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
26	t(min)	2.48	1.55	23.58	5.17	15.45	5.47	4.15	8.20
	n	34	23	97	37	22	9	8	13
	t(min)	1.20	0.42	10.83	1.22	7.38	0.72	2.95	2.25
	n	14	4	80	11	16	2	7	5
27	t(min)	1.02	0.47	20.08	2.18	4.28	0.23	0.00	1.60
	n	12	6	132	18	8	1	0	3
	t(min)	1.27	1.95	24.22	4.30	0.00	0.00	0.00	0.00
	n	25	10	95	23	0	0	0	0

Appendix 16

Gross body movements and periodic breathing in relation to sleep phase in 5 infants during and following recovery from upper respiratory tract infection

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
28	t(min)	1.55	0.00	31.95	4.57	0.00	0.00	0.00	0.00
	n	7	0	125	18	0	0	0	0
	t(min)	0.57	1.05	33.43	4.58	0.00	0.00	0.00	0.00
	n	4	8	97	16	0	0	0	0
29	t(min)	12.98	1.82	40.02	19.12	0.00	0.00	0.00	0.00
	n	67	11	164	60	0	0	0	0
	t(min)	1.37	0.28	6.67	0.82	0.00	0.60	0.00	0.42
	n	6	2	40	5	0	2	0	2
30	t(min)	4.13	0.88	73.30	12.17	0.00	0.00	0.00	0.00
	n	22	7	169	35	0	0	0	0
	t(min)	1.33	0.90	32.12	3.17	0.00	0.75	0.00	0.52
	n	5	11	73	14	0	2	0	1
31	t(min)	3.28	0.70	68.32	12.10	0.52	3.60	0.65	1.93
	n	21	3	173	36	1	7	3	4
	t(min)	1.62	0.27	70.87	5.05	4.47	1.67	0.00	2.93
	n	8	1	122	8	15	6	0	10
32	t(min)	6.48	0.00	77.47	16.02	1.37	2.52	2.30	1.83
	n	23	0	97	40	4	8	3	5
	t(min)	2.52	0.63	52.43	6.48	2.07	1.13	2.92	1.75
	n	13	4	103	18	4	4	11	5

Gross body movements and periodic breathing in relation to sleep phase in 7 infants with stridor

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
33	t(min)	5.33	0.57	33.93	6.67	0.00	0.00	0.00	0.00
	n	33	5	123	32	0	0	0	0
34	t(min)	3.33	1.78	67.12	12.80	0.00	0.00	0.00	0.00
	n	23	39	131	46	0	0	0	0
35	t(min)	2.37	0.87	39.30	5.42	3.78	1.03	0.00	2.00
	n	13	6	121	21	11	2	0	5
36	t(min)	1.35	7.60	35.00	12.27	1.33	1.05	0.00	0.88
	n	14	66	127	69	3	4	0	3
37	t(min)	4.62	0.30	56.23	8.57	0.00	0.00	0.00	0.00
	n	24	2	149	30	0	0	0	0
38	t(min)	1.72	0.17	86.95	2.20	0.00	0.00	0.00	0.00
	n	14	2	467	14	0	0	0	0
39	t(min)	6.15	0.67	39.12	5.37	0.00	0.00	0.00	0.00
	n	40	4	100	23	0	0	0	0

Appendix 18

Gross body movements and periodic breathing in relation to sleep phase in 5 infants during and following recovery from recurrent vomiting

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
40	t(min)	2.98	1.55	31.52	9.47	45.02	64.83	30.98	45.83
	n	23	13	229	70	46	47	47	46
	t(min)	4.02	0.65	55.93	14.32	2.48	4.18	1.35	2.72
	n	28	3	148	47	6	5	3	5
41	t(min)	4.03	0.68	42.07	5.55	25.85	5.17	23.03	18.43
	n	17	10	153	24	36	10	47	27
	t(min)	3.38	2.00	45.37	8.17	0.00	0.00	0.00	0.00
	n	22	13	117	30	0	0	0	0
42	t(min)	7.40	1.77	98.07	16.77	8.78	34.63	3.33	5.88
	n	40	15	144	43	9	8	8	8
	t(min)	5.72	0.87	32.07	5.05	1.07	0.00	5.98	0.87
	n	31	4	129	25	5	0	24	4
43	t(min)	2.82	0.00	52.85	5.97	9.48	0.42	4.72	4.87
	n	8	0	69	10	22	1	11	11
	t(min)	5.48	0.10	44.38	6.90	0.00	0.00	0.00	0.00
	n	24	1	88	20	0	0	0	0
44	t(min)	4.18	2.63	56.85	5.02	5.43	1.37	0.00	3.23
	n	30	19	778	29	12	3	0	7
	t(min)	3.22	0.58	39.32	4.37	6.10	0.00	0.00	2.95
	n	19	4	118	19	13	0	0	6

Appendix 19

Gross body movements and periodic breathing in relation to sleep phase in 24 siblings of sudden infant death syndrome victims

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
45	t(min)	2.63	0.87	47.95	6.20	5.53	6.50	4.38	5.80
	n	15	7	114	21	11	11	11	11
	t(min)	0.15	0.50	9.18	1.13	4.57	5.65	5.15	5.05
	n	3	9	51	9	7	12	6	9
46	t(min)	2.23	0.53	45.57	4.68	4.93	3.07	0.00	3.85
	n	15	3	143	19	15	9	0	11
47	t(min)	7.22	0.67	63.83	13.52	0.42	0.00	0.00	0.23
	n	31	4	111	34	1	0	0	1
	t(min)	8.93	2.08	62.08	14.63	7.22	9.27	1.98	7.28
	n	63	29	170	65	12	12	6	11
48	t(min)	6.85	0.55	60.40	7.90	0.00	0.00	0.00	0.00
	n	42	5	161	23	0	0	0	0
49	t(min)	4.93	0.63	58.42	6.22	0.00	0.00	0.00	0.00
	n	17	7	168	22	0	0	0	0
50	t(min)	3.15	0.90	43.30	7.40	0.00	0.00	0.00	0.00
	n	25	7	98	23	0	0	0	0
	t(min)	3.33	0.55	74.00	6.40	5.38	0.57	0.00	2.23
	n	19	5	140	19	15	1	0	6
51	t(min)	6.00	1.73	44.57	9.33	0.00	0.00	1.17	0.17
	n	35	14	152	41	0	0	9	1
52	t(min)	5.78	0.05	39.17	5.32	0.00	0.00	0.00	0.00
	n	22	1	117	18	0	0	0	0
	t(min)	4.15	0.42	56.55	5.10	1.83	0.30	0.00	0.72
	n	31	4	156	21	2	1	0	1

Appendix 19 (continued)

Gross body movements and periodic breathing in relation to sleep phase in 24 siblings of sudden infant death syndrome victims.

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
53	t(min)	4.48	4.42	55.55	9.42	2.95	0.00	0.00	1.15
	n	26	30	347	40	8	0	0	3
54	t(min)	4.28	0.72	62.30	8.25	1.10	0.00	0.00	0.55
	n	25	4	156	29	2	0	0	1
	t(min)	3.03	1.33	30.00	4.67	0.33	0.70	0.00	0.45
	n	25	9	124	27	1	3	0	2
55	t(min)	2.60	1.60	27.87	3.50	0.72	0.00	1.53	0.35
	n	23	14	144	25	1	0	8	1
56	t(min)	2.65	0.37	62.08	7.12	0.00	0.00	0.00	0.00
	n	19	3	183	25	0	0	0	0
57	t(min)	2.98	1.10	33.07	3.90	0.00	0.55	0.00	0.37
	n	26	13	152	27	0	2	0	1
58	t(min)	6.33	0.18	23.47	2.35	0.00	0.67	5.00	0.77
	n	31	2	77	10	0	2	15	2
59	t(min)	3.37	0.18	8.02	1.95	0.98	0.00	3.25	0.63
	n	27	3	52	15	3	0	10	2
60	t(min)	2.42	0.53	0.00	0.87	0.00	0.00	0.00	0.00
	n	28	5	0	9	0	0	0	0
61	t(min)	2.00	0.62	26.02	3.58	0.98	0.00	0.00	0.30
	n	21	4	125	24	3	0	0	1
62	t(min)	6.08	2.75	28.92	5.25	0.00	0.55	0.00	0.33
	n	49	21	173	39	0	1	0	1

Appendix 19 (continued)

Gross body movements and periodic breathing in relation to sleep phase in 24 siblings of sudden infant death syndrome victims

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
63	t(min)	1.02	0.47	20.08	2.18	4.28	0.23	0.00	1.60
	n	12	6	132	18	8	1	0	3
64	t(min)	0.87	1.15	19.25	5.37	0.00	0.00	0.00	0.00
	n	6	9	68	22	0	0	0	0
65	t(min)	4.45	1.37	62.27	6.18	0.00	0.95	0.00	0.50
	n	34	8	129	26	0	3	0	2
66	t(min)	4.03	0.00	63.02	8.75	0.78	0.00	0.00	0.47
	n	27	0	146	31	2	0	0	1
67	t(min)	4.55	0.67	39.57	8.60	1.97	2.10	2.17	2.03
	n	28	11	67	28	4	3	4	4
68	t(min)	2.23	0.00	61.57	7.23	0.57	0.00	3.43	0.65
	n	13	0	103	18	2	0	6	2

Gross body movements and periodic breathing in relation to sleep phase in 24 'near-miss' for SIDS infants

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
69	t(min)	2.93	3.33	64.60	12.57	0.00	0.00	0.00	0.00
	n	16	26	185	47	0	0	0	0
70	t(min)	3.22	0.00	40.83	6.30	1.37	0.00	0.00	0.68
	n	25	0	138	28	6	0	0	3
71	t(min)	3.22	0.47	29.05	1.75	0.00	0.00	0.00	0.00
	n	22	5	57	10	0	0	0	0
72	t(min)	3.58	0.00	51.90	8.30	0.00	0.00	0.00	0.00
	n	17	0	118	23	0	0	0	0
45	t(min)	2.63	0.87	47.95	6.20	5.53	6.50	4.38	5.80
	n	15	7	114	21	11	11	11	11
73	t(min)	4.20	0.57	58.88	15.58	0.00	2.38	0.00	0.77
	n	32	3	105	39	0	7	0	2
74	t(min)	4.67	0.72	36.08	4.88	0.48	0.97	0.00	0.60
	n	25	6	120	24	1	1	0	1
75	t(min)	3.97	0.65	29.05	3.75	11.47	1.32	4.37	6.32
	n	21	5	133	20	22	3	10	12
76	t(min)	0.70	0.37	22.72	2.42	0.00	0.00	0.00	0.00
	n	7	5	96	14	0	0	0	0
77	t(min)	8.57	0.22	29.27	7.20	28.85	20.17	0.00	22.67
	n	33	1	70	24	33	19	0	25
78	t(min)	3.30	0.37	43.52	5.08	10.70	0.67	7.27	6.18
	n	36	3	228	36	21	2	17	13
79	t(min)	3.10	1.28	25.40	4.93	0.00	0.00	0.00	0.00
	n	28	14	109	31	0	0	0	0

Gross body movements and periodic breathing in relation to sleep phase in 24 'near-miss' for SIDS infants

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
80	t(min)	2.63	0.13	0.00	1.57	2.37	0.18	0.00	1.43
	n	17	2	0	10	7	1	0	4
81	t(min)	9.17	0.68	40.92	8.77	0.00	0.00	0.00	0.00
	n	43	4	98	32	0	0	0	0
82	t(min)	4.08	1.87	64.08	7.55	0.00	0.00	0.00	0.00
	n	33	16	190	36	0	0	0	0
83	t(min)	1.25	1.72	29.70	4.15	0.00	0.00	0.00	0.00
	n	12	15	133	25	0	0	0	0
84	t(min)	2.32	3.42	32.43	5.58	0.00	0.00	0.00	0.00
	n	23	14	91	23	0	0	0	0
85	t(min)	2.15	1.13	36.67	3.18	6.95	0.00	0.00	1.77
	n	29	10	114	20	17	0	0	4
86	t(min)	6.37	0.32	17.78	4.23	0.43	0.00	0.00	0.18
	n	28	3	65	18	2	0	0	1
87	t(min)	3.75	0.58	42.37	7.48	3.60	0.00	0.00	1.67
	n	27	8	100	29	6	0	0	3
88	t(min)	2.15	0.00	53.27	8.35	0.00	3.78	2.87	1.85
	n	16	0	135	26	0	9	9	5
89	t(min)	4.27	1.20	56.58	9.88	0.00	0.00	0.00	0.00
	n	43	20	203	54	0	0	0	0
90	t(min)	4.85	1.50	57.45	9.70	0.43	0.00	0.00	0.18
	n	35	10	168	39	2	0	0	1
91	t(min)	1.60	1.13	43.42	9.73	0.00	0.00	0.00	0.00
	n	11	12	116	32	0	0	0	0

Appendix 21

Gross body movements and periodic breathing in relation to sleep phase in 5 premature 'near-miss' for SIDS infants

Number		Movements/100 min sleep				Periodic Breathing/ 100 min sleep			
		AS	QS	IS	T	AS	QS	IS	T
40	t(min)	2.98	1.55	31.52	9.47	45.02	64.83	30.98	45.83
	n	23	13	229	70	46	47	47	46
92	t(min)	3.08	2.00	38.01	8.60	9.80	19.15	6.57	12.82
	n	19	16	97	31	15	23	11	18
93	t(min)	6.02	0.62	44.05	9.90	1.32	0.00	0.00	0.38
	n	44	7	160	45	4	0	0	1
94	t(min)	3.83	1.57	46.95	8.78	0.45	0.40	0.00	0.37
	n	32	21	164	45	2	1	0	1
95	t(min)	4.85	0.32	49.10	4.63	3.77	3.90	7.47	4.00
	n	25	4	185	22	6	10	15	9

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