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Influence of Stress Due to Circumcision on Sleep State Organization in the Neonate

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by

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VITA

The author, Miss Dalma Kalogjera was born in Zagreb, Yugoslavia on February 11, 1954. She is the daughter of Ing. Jaksa Kalogjera and Mrs. Biserka Kalogjera neé Erak.

Miss Kalogjera attended elementary school in Zagreb, Yugoslavia from 1960 to 1968 and high school (Gymnasium) from 1968 to 1972. Her high school curriculum entailed the usual liberal arts background as well as an additional emphasis on mathematics, chemistry, biology, physics and solid geometry. She matriculated in 1972 and was, as a valedictorian, absolved from the matriculation examination. The title of her matriculation thesis was "Zen and Japanese Culture." Upon graduation she attended the University of Zagreb (1972-1973) where she studied Comparative Literature and The English Language and Literature. After successful completion of her first year she emigrated to the U.S. where she continued her undergraduate schooling at Milwaukee Area Technical College (1973-1974) with a major in psychology. In May of 1974 she received the Chemistry Award. At that time she was offered an academic scholarship at Pepperdine University, Malibu, California and transferred to Los Angeles where she continued with her degree in psychology. Following a summer term at UCLA she returned to the Midwest in the autumn of 1975 in order to work with Dr. Roger Ulrich (an experimental psychologist noted for his experiments in elicited aggression) at Western Michigan University, Kalamazoo, Michigan. She completed her undergraduate studies (major in Experimental Psychology; minor in Philosophy) and graduated summa cum laude in December of 1977. She spent the remaining eight months prior to the entry to the M.A. program in Clinical Psychology at Western taking advanced courses in German. In spring of 1978 she received a grant to work with Dr. Hermann Teichert of the German Department as his assistant, collaborating on the workbook for his courses and tutoring students. She also continued her work as a tutor of foreign languages (German, Russian, French, and Croatian at the Center for Educational Opportunity).

During the academic year 1978-1979 she was enrolled in the M.A. program in Clinical Psychology at Western Michigan. In April of 1979 she terminated her studies at Western and in August of 1979 enrolled in the Ph.D. program in Clinical Psychology at Loyola University of Chicago. During her first year at Loyola she was an assistant to Dr. Deborah Holmes and participated in her reserach on the long-term effects of prematurity and illness on infants' social and cognitive functioning. In September of 1980 she passed the Ph.D. Qualifying Exam with distinction. In the course of her studies at Loyola she was granted two additional assistantships with Dr. Thomas Petzel (1980-1981) and Dr. Frank Kobler (1982-1983). Ms. Kalogjera took her pre-internship clinical training at Hines V.A. Hospital (Clerkship I in 1981 and Clerkship II in 1982) where she worked with Drs. Trimakas, Graham, and Doyle.

The work presented in this paper is a result of an effort which spanned nearly two and a half years and entailed an intensive study of literature on various sleep phenomena as well as active experimentation.

A summary of the present investigation as well as a general overview of sleep research will be presented by Miss Kalogjera at the Clinical Psychiatric Conference at Loyola University School of Medicine in April of 1983.

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INTRODUCTION

Our current knowledge of sleep states in infants, including their structural components, function, and the factors which affect them is still rather incomplete, particularly with respect to the effects of stress stimulation on the organization of sleep states. In the absence of definitive data, there are two competing hypotheses in the area of stress effects on sleep which lead to different empirical predictions. According to one of them, developed by Emde and his associates (1971), stress as a result of circumcision leads to an increase in the proportion of quiet (NREM) sleep without changes in wakefulness. This phenomenon is viewed by Emde as an indication of the infant's "executive control of stress". Emde's position was challenged by Anders (1974) who, on the basis of his own experimental findings, concluded that the primary effect of stress was manifested in the increase in wakefulness and that putative changes in REM/NREM ratio were ancillary.

The purpose of the present research is two-fold. It attempts to provide an answer to the specific experimental question which can be stated briefly in the following manner: Does stress due to circumcision lead to an increase in the proportion of NREM (quiet) sleep without the concomitant changes in the amount of wakefulness (as predicted by Emde), or to an increase in the level of wakefulness without modifications of sleep state proportions (consistent with Anders' findings)? The second goal of the study is to contribute to our knowledge of various sleep states, especially the functions of REM and NREM sleep in infancy. Before examining the specific experimental problem, let us briefly discuss general features of sleep state organization and development.

Awareness and its bio-behavioral concomitants can be conceptualized in terms of at least three states: wakefulness, REM (active) sleep, and NREM (quiet) sleep. State, itself can be described as a "constellation of certain functional patterns and physiological variables which may be relatively stable and which seems to repeat itself" (Prechtl et al., 1968). Sleep in the human neonate which constitutes the focus of the present investigation includes two states: active sleep and quiet sleep (Delange et al., 1962; Jouvet, 1963; Petre-Quadens, 1974; Roffwarg et al., 1964). The former has been alternatively referred to as REM, paradoxical sleep (Jouvet, 1962), "activated sleep" (Dittrichova, 1962), and "irregular sleep" (Wolff, 1959). The quiet sleep (Parmelee et al., 1961) is equivalent to NREM and slow wave sleep (Jouvet, 1963; Petre-Quadens, 1974).

REM Sleep

Neurophysiological and EEG properties of REM state are summarized as follows. Olga Petre-Quadens (1974) distinguishes two stages of REM in infants: "a" and "d". The maturationally less complex stage "a" includes: isolated eye movements, sucking, and irregular respiration. Stage "d" can be described in terms of electro-cortical activation consisting of fast,"low amplitude EEG waves similar to the EEG during arousal," bursts of rapid eye movements, small body movements, and cardiac irregularities (Petre-Quadens, 1974). EMG hypotonia, which is a typical feature of adult REM cannot always be detected in the neonate (Petre-Quadens, 1974). Compared to NREM, REM is a developmentally earlier form of sleep. It is already present at birth and can be discerned as early as 28 weeks of gestational age (Dreyfus-Brisac, 1967). Control of REM state has traditionally been attributed to various brainstem structures such as nucleus reticularis pontis caudalis (Jouvet, 1962), tegmental giant cells of the pontine reticular formation (McCarley & Hobson, 1971; McCarley et al., 1972), and vestibular nuclei (Morrison & Pompeiano, 1966) which regulate rapid eye movements. The involvement of the frontal cortex has also been suggested (Hernandez-Peon, 1965).

The newborn spends on the average 50% of his entire sleep time in REM state (Roffwarg et al., 1966). The precise function of REM, however, and the reasons for its preponderance in neonatal sleep are unclear. Several possibilities have been considered. Roffwarg and his associates (1966) have suggested that

> REM sleep affords intense stimulation to the CNS, stimulation turned on periodically from within by a mechanism capable of stimulating the rest of the central nervous system. The intervals of intense activity would be available in great quantities to the developing organism in utero and later in its early extrauterine life when stimuli are limited.

In addition to its growth enhancing value, sleep in general and REM especially may be needed in order to allow the organism to deal with the experience without sensory overstimulation which would otherwise ensue were the organism exposed to stimuli which its adaptive processes are too primitive to manage (Gaarder, 1966). REM is thus seen ontogenetically either as an agent of stimulus integration or a state in which stimulation is provided in a controlled way and in accordance with the processing limitations of the organism. Snyder (1966) approached the question of REM function from an evolutionary perspective. He conceptualizes active sleep as a derivative of the occasional periods of vigilance which were incorporated into sleep in order to maintain defensive capabilities of the organism with an additional advantage of conservation of energy. Dement (as cited in Snyder) who examined Snyder's hypothesis citing both supporting and disconfirming evidence concluded that "ontogenetic" and "evolutionary" positions were both viable although they had differential importance at different stages of development. The former is associated with early development, especially late prenatal and early neonatal period, whereas the latter becomes significant in later development. On a more molecular level, Berger (1969) emphasized the role of REM in the development of occulomotor control.

In subsequent stages of development, REM is thought to fulfil multiple functions or at least to provide favorable conditions for a number of diverse processes involved in learning, cognition and mood states (in Hartmann, 1970). Animal studies that have employed operant paradigms indicate the importance of REM in both the acquisition stage (Pegram, 1968; Rust, 1962; Stern, 1969, 1970), as well as the consolidation phase of learning (Stern, 1969, 1970). REM state appears to play a significant role in human learning as well, in particular the type of learning which Greenberg (1970) refers to as "emotionally meaningful learning" and which entails processing and integration of information which is emotionally stimulating or relevant to the organism and may require an adaptive effort (Fiss & Kline, 1968; Lewin, 1972; Zimmerman, Stoyva, & Metcalf, 1969). In addition to fostering learning, REM seems to be associated with memory processes as well, both in animals and in humans. The evidence for the importance of REM in animal memory stems from the studies in which REM deprivation is shown to lead to memory loss (Fishbein, 1969; Pearlman & Greenberg, 1968). Impact of REM in the realm of human memory is seen in the observed correlations between decreases in REM sleep and memory deficits in certain pathological conditions such as Korsakoff's psychosis (Greenberg et al., 1968), encephalitis (Torda, 1969), and chronic brain syndrome (Feinberg, 1968; Hartmann, 1973).

Furthermore, a good deal of experimental evidence has accumulated which suggests that REM is functionally linked to the so-called "Norepinephrine Dependent Systems" (NE-dependent) which regulate such functions as maintenance of wakefulness (Jones, 1969; Weiss & Latties, 1962), acquisition of operant learning tasks (Seiden & Petersen, 1968), achievement (Evans & Smith, 1964), and directed attention (Hartmann, 1970; Weiss & Latties, 1962). They have also been associated with positive reinforcement circuits (Olds, 1958) and mood (Davis & Klerman, 1965; Hartmann, 1970; Kety et al., 1967; Schildkraut, 1965; Schildkraut, Davis, & Klerman, 1965; Schildkraut & Hartmann, 1969; Schildkraut et al., 1967). The precise manner in which REM state is linked to the NE-dependent systems is not entirely understood. Hartmann, for example, postulated that the following relationship obtains: "There is a feedback mechanism connecting catecholamine systems and REM such that conditions characterized by low catecholamine levels produce increased REM and REM in turn restores catecholamine levels and maintains the integrity of the catecholamine systems" (Hartmann, 1970). The hypothesis of reciprocity is primarily based on studies in which chemical manipulations that alter the level of catecholamines have been shown to affect REM sleep in the expected direction (Baekeland & Lundwall, 1971; Cohen & Dement, 1966; Hartmann, 1966, 1970; Hartmann et al., 1971).

In addition to its inferred specific link to the NE-dependent systems, REM sleep, especially its phasic (i.e., short-lasting) events, has also been conceptualized as a "nocturnal or secondary drive discharge mechanism which is regulated by serotonin and which allows the drive systems to remain active at night without disrupting sleep" (Dement as cited in Webb, 1973). This putative function of REM is consistent with the empirical finding that REM deprivation potentiates the expression of drive behaviors such as hunger, aggression, and libido (Dement, 1965a, 1965b; Morden et al., 1968a, 1968b). It is likewise consistent with the observation that the depletion of serotonin which is purportedly involved in chemical control of drive systems, leads to an indiscriminate and intense erruption of PGO spikes ("high amplitude sharp waves from the pons and other areas"), aggression and other concomitants of pathological drive potentiation into wakefulness (Dement as cited in Webb, 1973).

NREM Sleep

NREM (quiet) sleep is an ontogentically later state which is first discernable in a very primitive form at 36 weeks of gestational age (Dittrichova, 1969; Stern et al., 1969). Quiet sleep is still inchoate at birth and undergoes rapid development in the course of the first six months past term (Paul & Dittrichova, 1974). This process reflects and is contingent upon forebrain maturation (Allison, 1973). NREM is mediated by structures in the lower brainstem (Moruzzi, 1964), upper brainstem (Villablanca, 1966), and forebrain mechanisms (Sterman, 1972; Sterman & Clemente, 1962), especially the basal forebrain area (McGinty & Sterman, 1968). In contrast to a physiologically more variable REM state, NREM is characterized by a "greater degree of quiescence in several variables": cardiac and respiratory functioning are more regular and eye movements are rare although their absence does not necessarily signify quiet sleep (Paul & Dittrichova, 1974). Motor activity is generally suppressed with the exception of periodic isolated movements of the extremities (Petre-Quadens, 1974).

Petre-Quadens (1974) conceptualizes NREM in infants in terms of two phases, "b" and "c" which differ mainly in their EEG properties. The EEG pattern of stage "b" entails "6 Hz waves against a slow background tracing" whereas stage "c" contains spindles of 12 to 14 Hz (Petre-Quadens, 1974). Quiet sleep in infants is not directly analogous to NREM state in adults. The overall pattern of greater quiescence during stages "b" and "c" in infant sleep is consistent with adult trends in NREM (Sterman in Clemente, Purpura, & Mayer, 1972), although differences along several dimensions exist (e.g., absence of spindles as well as lack of pituitary hormone secretions) which caution against equating NREM in neonates and adults (Finkelstein et al., 1971; Hrbek et al., 1969; Rose, 1971; Sterman in Clemente, Purpura, & Mayer, 1972).

Our present knowledge of the significance of NREM sleep in the neonatal period is fairly inchoate. With the exception of the already discussed role of quiet sleep in the context of the infant's stress response mechanism and Oswald's (1970) hypothesis of the role of NREM in the "growth and repair of peripheral tissues," few functions have been elaborated. The importance of NREM in adult development has also not been clearly established although several possibilities have been suggested. In general, NREM seems responsive to the conditions of physical exertion and trauma (Hartmann, 1973) such as colds, flu (Brewer & Hartmann, 1973), starvation diet (Oswald, 1972), exercise (Hobson, 1968; Matsumoto, 1968), hyperthyroidism (Dunleavy & Oswald, 1972), and sexual activity (Boland & Dewsbury, 1971), all of which tend to be accompanied by an increase in the amount of NREM.

On the basis of these and other studies, Hartmann (1973) concluded that "NREM primarily fulfills an anabolic function, i.e., it enables restoration of somatic systems after exercise, apin, physical exertion, and excessive catabolism" (Hartmann, 1973).

Changes in State Organization with Development

Maturational factors determine both the characteristics of individual states as well as state organization. Before discussing changes in specific states, it would be useful to consider global features of neonatal physiology. Somatic functioning of the inant (EEG, autonomic measures, etc.) is regulated by "bio-periodicity," i.e., ultradian cyclical fluctuations in the levels of variables of 40-60 min duration which are referred to as basic rest-activity cycles or BRACs (Kleitman, 1963; Sterman as cited in Drucker-Colin, Shkurovich, & Sterman, 1979). These are already apparent at 24 weeks of gestational age (Sterman, 1967; Sterman & Hoppenbrouwers, 1971). The BRACs, which are initially mediated by the brainstem mechanisms (Sterman in Drucker-Colin, Shkurovich, & Sterman, 1979), constitute the rudiments of state organization (Sterman, 1972; Sterman & Hoppenbrouwers, 1971).

Global state differentiation which reflects and is made possible by forebrain maturation proceeds according to the following sequence, delineated by Sterman (as cited in Drucker-Colin, Shkurovich, & Sterman, 1979):

> Periods of generalized arousal, which originally occurred briefly at 3-4 hour intervals, lengthen dramatically (Parmelee et al., 1964) as motor and social learning during

> these periods give rise to the state of wakefulness. Periods of quiescence within the rest-activity cycle also lengthen significantly and become associated with specific EEG patterns that are characteristic of adult quiet sleep (Parmelee & Stern, 1972; Sterman et al., 1977). Finally these periods of quiescence, still modulated by relatively unchanged periods of nonspecific activation (REM) shift progressively into the nocturnal phase of the circadian cycle. By six months of age, a circadian rhythm of diurnal waking and nocturnal sleep becomes stabilized (Kleitman & Engelmann, 1953). (Sterman as cited in Drucker-Colin, Shkurovich & Sterman, 1979).

These changes reflect a general developmental trend toward greater quiescence, integration, and synchronization (Parmelee & Stern, cited in Clemente, Purpura, & Mayer, 1972).

During the first six months past term, individual states as well as their patterns and constellations undergo significant changes. In the course of the first 16 postnatal weeks, the total amount of sleep per day decreases (Parmelee et al., 1964). Additionally, the number of state changes is reduced during this period as the infant becomes able to sustain longer periods of both sleep and wakefulness (Parmelee et al., 1964). Moreover, during the first three weeks, a developmental trend emerges which is characterized by a decline in REM and the proportional increase in NREM with an eventual predominance of NREM around the 4th postnatal week (Anders & Hoffman, 1973). Maturational changes are evident in the sequencing of states as well. Early sequencing approximates the pattern described by Campbell & Raeburn, 1973):

> The first passage of sleep may fall into any of the four

> sleep states (i.e., REM, NREM, transitional REM, transitional NREM), although REM entries are common. The first passage is followed by an unpatterned interchange among different categories. Around the 40th minute, the first substantial episode of REM occurs, followed by the appearance of regular cycles.

In contrast to this early fairly indiscriminate pattern of sleep entry, the infant at the age of 3 months, begins sleep with NREM (Metcalf, 1971). In general, the period between the 3rd and 4th month is characterized by an overall maturation of state components, an increase in the duration of states (Stern, Parmelee, & Harris, 1973) and a decrease in transitional sleep (Parmelee et al., 1967). REM/NREM cycles increase in duration (Stern et al., 1969) which is consistent with Hartmann's observation of a positive correlation between the maturational status of the organism and the length of his sleep cycles (Hartmann, 1968).

Environemtnal Influences on Sleep States

In addition to developmental factors just described, infant sleep is sensitive to a variety of environmental influences. In general, their effects are complex and rarely involve only one aspect of sleep, but rather tend to affect distribution and patterning of states as well as short-term changes in the duration of specific sleep components. Food intake, for example, especially the scheduling of feed periods, has been found to induce changes in the state distribution and short-term variations in the duration of REM (Harper et al., 1977). State monitoring procedures, themselves, often affect sleep. Bernstein, Emde and Campos (1973) found that the infants were observed in the laboratory where polygraph measurement was used showed a lower proportion of REM sleep in comparison with infants who were observed at home where no polygraph measures were taken. Monotonous stimulation in modalities such as the sound of heartbeat, light, swaddling, and ambient temperature at 32C (Brackbill, 1971) tends to have a soporiphic effect, i.e., it induces sleep and leads to an increase in quiet sleep (Backbill, 1970, 1971).

As was indicated earlier, sleep states in the early postnatal period show a great deal of variability even within a single day. REM, for instance, has been found to be diurnally unstable (Thoman, Korner, & Kraemer, 1976), whereas NREM is comparatively less influenced by the time of day (Thoman, Korner, & Kraemer, 1976). Distribution of sleep states is further influenced by such external manipulations as selective state interruption and sleep deprivation (Anders & Roffwarg, 1973). Exclusive interruption of a specific state, however, is more complicated in infants than in adults and its impact is complex. Total sleep deprivation is usually followed by an increase in the overall sleep time as well as an increase in NREM (Anders & Roffwarg, 1973).

The environmental factor of particular relevance to the present study is stress. The precise nature of infant's stress mechanism is not fully understood. However, experimental findings suggest that stressful stimuli affect several aspects of functioning including endocrine processes and sleep. An important aspect of the endocrine stress reaction is an increase in the level of plasma cortisol ("the adrenocortical response") which is activated by a variety of stimuli: respiratory distress (Klein, Baden, & Giroud, 1973); crying (Anders et al., 1970); injections of ACTH (Hillman & Giroud, 1965); and circumcision (Talbert et al., 1976). Physical noxae which threaten neurological intactness of the organism also affect sleep, particularly the quality and the amount of REM. For example, maternal heroin addiction and overall "at risk for CNS impairment" status of the infant have been shown to be associated with abnormally active REM and defective NREM (Schulman, 1969). Head trauma was also found to depress the percentage of NREM and lead to an increase in REM (Lenard & Penningstorff, 1970). The pattern of reactions to these influences probably represents regressive processes, i.e., interference or blocking of the inhibitory controls which accompany maturation.

Stress has also been found to influence the organization of sleep states in neonates. The nature of this influence has varied across studies, however, with resulting differences in theoretical conclusions. According to one theoretical orientation, formulated by Emde (1971) and based on his own observations and experiments as well as investigations of other researchers, the infant's response to stress entails an increase in the proportion of NREM sleep without proportional changes in wakefulness. Emde's pilot study (1971) in which behavioral observations were used showed that stress as defined by the circumcision procedure lead to an increase in the reported levels of NREM in 4 out of 6 subjects. In his 1971 experiment in which polygraphic recordings were used, Emde and his associates again observed a "significant increase in the proportion of NREM after circumcision, a decreased latency to the first NREM episode, an increased number of NREM episodes, an increase in the number of very long NREM episodes and no changes in wakefulness" all of which strongly suggested that NREM sleep was affected in some significant way. Emde interpreted the observed changes in NREM not as an isolated or random occurrence but as the "organismic substrate of the behaviorally oriented conservation-withdrawal syndrome which is indicative of early executive control in times of stress" (Emde et al., 1971). The concept of conservation-withdrawal pattern was developed by Engel (1962). He postulated that "the CNS is organized to mediate two opposite response systems in the presence of stress: 1) an active (fight or flight) pattern characterized by increased motor activity, and 2) a conservation-withdrawal pattern which entails an increased sensory threshold, withdrawal of attention and sleep. The two systems are neurally and anatomically distinct" (Engel, 1962). Engel supported his contention by clinical observations of several authors who found that infants responded with sleep to a variety of frustrating circumstances such as withdrawal of the nipple (Fries & Woolf, 1953), "inadequate mothering" (Ribble, 1943), and physical pain (Burton & Derbyshire, 1958).

The opposite theoretical position, represented by Anders and his colleagues, questions the existence of the executive control of stress in the neonate. In 1974, they conducted an investigation of the effects of circumcision induced stress on sleep patterns in the infant. They assessed state patterns of a group of full-term male neonates by means of behavioral observations on three separate occasions: prior to circumcision, during the hour immediately following circumcision surgery, and "during the first interfeeding period subsequent to circumcision." Contrary to Emde's results, Anders found no significant change in REM/NREM proportions. He did, however, observe a "significant increase in wakefulness immediately following circumcision as well as a decrease in sleep onset latency during the recovery hour." Anders concluded that circumcision induced stress "mainly affected wakefulness and that any shifts in REM/NREM proportions, if indeed they could be reliably demonstrated, were secondary to changes in wakefulness" (Anders et al., 1974). He consequently rejected the notion of specific significance of NREM in executive control of stress on the grounds of insufficient evidence.

Differences in interpretive conclusions between the two studies could have been due in part to differences in methodology. These methodological differences were summarized by Anders (1974) and they refer to: the nature of circumcision procedure, the method of determining state, and the duration and distribution of observation periods. Regarding circumcision, the most relevant difference between the two techniques refers to the degree of stress imposed on the infant. Anders' method is more stressful. Consequently, the NREM increase observed by Emde would be expected to be especially pronounced. This, however, did not occur. The second difference which entails the method of assessing state (Emde relied on polygraphic measures, and Anders used behavioral observations) is particularly important because it has direct relevance for the REM/NREM ratio. Namely, polygraphic monitoring of state has been shown to be stressful and to depress REM (Bernstein, Emde, & Campos, 1973), a fact which could have contributed to the proportional increase in NREM sleep in Emde's experiment. Furthermore, the studies differed with respect to the length and distribution of observation intervals. Anders used three one-hour periods which were distributed throughout the day, sometimes as widely as six hours, whereas Emde's observations were longer and concentrated into two 10-hour blocks. Anders assumed no diurnal variation in REM and NREM, yet studies have indicated that REM varies throughout the day (Thoman, Korner, & Kraemer, 1976). It is possible that diurnal variation in REM state obscured the changes in REM/NREM proportions. Finally, experimental design was different in each study. Emde's design entailed comparison between the experimental group of infants who underwent circumcision and the controls who did not, whereas Anders applied the "Within Subjects" design. Since Emde and his colleagues (1975) have shown differences in REM and NREM sleep during the first few days of life, this confound is potentially a serious one.

In the present study it was possible to deal with some of the problematic methodological issues which lead to interpretive ambiguities. These included method of observations, length of observation periods, and method of circumcision. State was assessed by means of behavioral observation. This was done for several reasons. Firstly, Bernstein, Emde and Campos (1973) showed that behavioral observations were as adequate as polygraphic recordings. Secondly, polygraphic measures may be stressful to the infant (Bernstein, Emde, & Campos, 1973) which is problematic ethically as well as methodologically since stress related to the use of an instrument may confound the effects of stress due to circumcision. Finally, polygraphic recording depresses REM (Bernstein, Emde, & Campos, 1973). Use of behavioral observations would thus preclude the confounding as well as spurious increases in NREM due to artifactual depression of REM, all of which would tend to strengthen the finding of NREM increase should it occur.

The length of the observation period (2 hours and 45 minutes) was determined by the length of the standard interfeeding period at Evanston Hospital. Two hours and 45 minutes is considerably longer than one-hour periods used by Anders (1974), yet it cannot match ten-hour observation blocks used by Emde (1971). The latter would have been ideal but was not feasible. Nevertheless, it was felt, on the basis of pilot observations carried out by the experimenter prior to the beginning of the study that 2 hours and 45 minutes was a sufficient length of time to allow some indication of sleep patterns and sequences of states to emerge. Circumcision procedure utilizing the Gomco Clamp was employed. This method is similar in several respects to the method used by Anders and his colleagues. In particular, it is an essentially brief (15 minutes) "acute" method and very likely more painful to the infant than the Plastibel technique employed by Emde. Consequently, one might expect a stronger stress response and a pronounced NREM increase.

Unfortunately, it was not possible to control for age. As was the case in Anders' study, post-circumcision observations were carried out on older subjects. Since Emde et al. (1975) have found a decline in NREM sleep during the first few days of life, it was not possible to determine whether changes in NREM sleep were due to circumcision or an increase in age.

METHOD

Subjects

The subjects were ten full-term, healthy male infants with a mean age of 25 hours. They were products of normal pregnancies and uncomplicated deliveries.

Procedure

Infants were observed by the investigator in the Normal Newborn Nursery. Observations were conducted on two occasions: a) during an interfeeding period (two hours and 45 minutes, approximately) on the day prior to circumcision, and b) during the first interfeeding period immediately following the circumcision procedure. Due to the scheduling of circumcision surgery which was beyond the examiner's control, some infants were observed twice on the same day, i.e., pre- and post-observations were carried out on the same day. For most infants, however, pre- and post-observations were carried out on two consecutive days. Observations were conducted during morning hours (approximately between 10 A.M. and 1:45 P.M.) or in the afternoon (between 2 P.M. and 4:45 P.M.). Only one observation block was obtained during the evening interfeeding period (6 P.M. to 8:45 P.M.).

States were determined on the basis of behavioral observations made by the experimenter every 20 seconds. A modification of Thoman's

(1975) and Holmes and Nagy's (in press) classification scheme was used. The modified version includes the following states:

Quiet Sleep (NREM). Respiration is regular. The infants eyes are closed and still. There is little motor activity, possibly a startle or an isolated movement of one limb.

Active Sleep (REM). Shallow and irregular respiration. The infant's eyes are closed (although they may open briefly) and rapid eye movements (singly or in bursts) occur during the 20 sec epoch. Motor activity may or may not be present. Significant motor activity alone or bursts of rapid eye movements alone are sufficient for REM classification. Any combination of the above features is also characterized as REM.

Drowsy REM

Rapid eye movements, usually in bursts are detectable while the eyelids are opening and closing.

Alert Inactivity. The infant's eyes are wide open, focused bright and shining (Wolf, 1966). Motor activity is usually absent, but may be present if it is involved with the infant's looking behavior (e.g., infant slowly moves hand across field of view while following with eyes).

Alert Activity. The infant's eyes are open and motor activity is present.

Crying. The infant's eyes may be open or closed, and intense motor activity is present. Two or more cry bursts occur during the 20 sec epoch.

Drowsy. The infant's eyes may be partially or fully open but dazed in appearance. Motor activity may or may not be present.

Data Reduction Procedures (According to Holmes et al., in press and Swartz, 1981)

Each infant's predominant state was originally recorded every 20 seconds onto computer scored optical scan sheets. The use of such a short recording interval (20 seconds) in conjunction with the general disorganization of state in young infants resulted in an excessive movement in and out of the different states. Many of these state transitions appeared to be artifacts of the short recording epoch. In order to avoid this problem we decided to consider only those transitions as "real" in which the infant remained in the same state for the duration of one minute.

This requirement was implemented by a computer program that automatically smoothed and scored the raw data. In short, this computerized smoothing procedure was programmed to reduce extraneous variability in state transitions in a purely objective and consistent statistical manner. The result of this smoothing procedure was a revised data stream, showing fewer state transitions, clean and unambiguous transitions between states, and longer within state epochs.

These results were achieved by defining the occurrence of a state epoch as a minimum of three consecutive observations in that state. State observations not falling into an epoch by this definition were recorded and appended to the preceding epoch or prefixed to the subsequent epoch. Recording was accomplished through a decision hierarchy based upon the similarity and temporal proximity of non-epoch observations and adjacent epochs, as well as within subject estimates of transition likelihood. Once smoothed and recoded according to the procedures just described, the data were then summarized in terms of the percentage of total observation time spent in each sleep and waking state.

RESULTS

To determine how state patterns are affected by the impact of stress, analyses were conducted on the percentage of time spent in each state category: 1) % of Quiet Sleep, 2) % of Active Sleep, 3) % of Drowsy REM, 4) % of Drowsy, 5) % of Alert Inactivity, 6) % of Alert Activity, and 7) % of Crying. In addition, analyses were conducted on a number of computed states (i.e., various combinations of single states). This was done, firstly, in order to clarify whether stress leads to changes in overall amounts of specific states or to changes in proportional amounts. The latter changes are particularly relevant since the experimental question deals primarily with changes in patterning and constellation of sleep states, especially changes in REM/NREM ratio. Secondly, computed states such as waking time, total sleep time, etc., can offer useful information about possible stress-related changes in the overall state organization. The computed states were as follows: 1) % of total sleep time (Quiet Sleep + Active Sleep); 2) % of total sleep time spent in Quiet Sleep (Quiet Sleep/total sleep time); 3) % of total sleep time spent in Active Sleep (Active Sleep/total sleep time); 4) % of waking time (Drowsy + Drowsy REM + Alert Inactivity + Alert Activity + Crying); 5) % of waking time (Alternative definition which includes Alert Inactivity, Alert Activity and Crying); 6) % of waking time in Alert Inactivity (Alert Inactivity/Alert Inactivity + Alert Activity + Crying): 7) %

of waking time spent in Crying (Crying/Drowsy REM + Drowsy + Alert Inactivity + Alert Activity + Crying), and 8) % of waking time spent in Drowsy (Drowsy + Drowsy REM/Drowsy + Drowsy REM + Alert Inactivity + Alert Activity + Crying).

Three separate statistical procedures were applied to these measures. These included: 1) t-test for correlated data (α = .01) to determine if the percentage of each one of the measures referred to above changes significantly from pre to post circumcision; 2) A descriptive index was taken for the measures indicated below in order to determine the pattern of change regardless of its statistical significance. This index simply referred to the direction of change, i.e., an increase or a decrease. For the sake of uniformity, data for all states included were reported in terms of an increase (see Table 1). This information was obtained on the following states only: Quiet Sleep, Active Sleep, Wakefulness (both definitions), total sleep time, total skeep time in Quiet Sleep, total sleep time in Active Sleep); 3) These data were further treated with the Binomial Test in order to establish if the proportion of subjects who evidenced an increase (or a decrease) in a given single or computed state subsequent to circumcision was statistically significantly different from the expected frequency of 50%: 50% at .01 level of significance.

Results of the statistical analyses indicate the following. The t-test analyses which are summarized in Tables 2 and 3 yielded no

Table 1

Summary of the Binomial Test Examining Percentage of Subjects Showing Increase in State

Variable	% of Subjects Who Showed Increase in % of State*
State 1 (Quiet Sleep)[a]	40
State 2 (Active Sleep)[b]	80
Total Sleep Time (1+2)	60
% of Sleep in Quiet Sleep ($\frac{1}{1+2}$)	40
% of Sleep in Active Sleep ($\frac{2}{1+2}$)	60
Waking Time (3+4+5+6+7)[c]	30
Waking Time (4+5+6)	30

*Critical value of P = 10% or 90%, α = .05
= 0% or 100%, α = .01

[a]1 = Quiet Sleep

[b]2 = Active Sleep

[c]3 = Drowsy REM; 4 = Alert Inactivity; 5 = Alert Activity; 6 = Crying; 7 = Drowsy

Table 2

Summary of t-Tests for Correlated Measures Examining Changes in States

	% OF TIME IN SINGLE STATES						
	Quiet Sleep (NREM)	Active Sleep (REM)	Drowsy REM	Alert Inactivity	Alert Activity	Crying	Drowsy
Pre-Circumcision							
Mean	38.769	43.044	2.149	.119	1.326	6.973	7.619
Post-Circumcision							
Mean	36.679	47.163	.043	.348	.551	6.322	4.519
Change	2.09	-4.119	2.106	-.229	.775	.651	3.1
t obtained*	-.4299	.669	-1.613	.1576	1.0558	-.153	-.996

$\alpha = .01$

df = 9

*None of the t's achieved the critical value of 3.25

Table 3

Summary of t-Tests for Correlated Measures Examining Changes in Computed States

	% OF TIME IN COMPUTED STATES							
	1+2[a]	$\frac{1}{1+2}$	$\frac{3+7}{3+4+5+6+7}$ [d] [b]	$\frac{6}{3+4+5+6+7}$	3+4+5+6+7	4+5+6[c]	$\frac{2}{1+2}$	$\frac{4}{4+5+6}$
Pre-Circumcision								
Mean	81.813	47.407	45.582	39.821	18.186	8.418	52.589	.00586
Post-Circumcision								
Mean	83.842	45.418	45.334	25.827	11.783	7.221	54.581	.1206
Change	-2.029	1.989	.248	13.994	6.403	1.197	-1.992	-.11474
t obtained*	.225	-.399	-.00485	-1.141	-.879	-.269	.3996	1.1935

= .01
df = 9

*None of the t's achieved the critical value of 3.25.

1 = Quiet Sleep
2 = Active Sleep
3 = Drowsy REM

4 = Alert Inactivity
5 = Alert Activity
6 = Crying
7 = Drowsy

[a] 1+2 = total sleep time
[b] 3+4+5+6+7 = waking time (1st definition)
[c] 4+5+6 = waking time (alternative definition)
[d] 3+7 = drowsy (overall drowsy)

significant results for any of the measures at either the .01 or .05 level of significance.

The descriptive data yielded the following picture. After circumcision the percentage of Quiet Sleep (NREM) decreased in 60% of the subjects. Subject 6 evidenced the greatest decrease whereas Subject 4 showed the largest increase. The percentage of total sleep time in Quiet Sleep also decreased in 60% of the infants with the largest decrease in Subject 6 and the largest increase in Subject 2. The percentage of Active Sleep (REM) increased in 80% of the subjects, maximally in Subject 7. Percentage of toal sleep time in Active Sleep increased in 60% of the subjects, with Subject 6 showing the largest increase. This was the state in which the greatest number of infants showed a change in the same direction. Total sleep time increased in 60% of the subjects. Subject 3 showed the largest increase. A decrease in wakefulness (defined as a composite of Drowsy REM, Alert Inactivity, Alert Activity, Crying, and Drowsy) was observed in 70% of the subjects with the maximal decrease in Subject 3. The percentage of wakefulness (based on the alternate formula which includes Alert Activity, Alert Inactivity, and Crying) also decreased in 70% of the subjects with the largest decrease occurring in Subject 3.

In order to establish whether the observed frequencies of increase and decrease for each state were statistically significant, the Binomial test was applied. As Table 1 indicates, none of the states thus analyzed showed statistically significant changes at either the .01 or .05 level.

DISCUSSION

The data obtained from this experiment can be approached from two different points of view: a) pattern and direction of change, and b) magnitude of change. On the basis of the information pertaining to the statistical analyses of the extent of change, we may conclude that the stress induced by circumcision procedure does not lead to a significant change either in the overall percentage of each state considered (single or computed) or in the proportional amount of any given state.

The results are more suggestive, however, if the pattern is considered. Analysis of the direction of change within each state while failing to achieve statistical significance, is congruent with certain aspects of both Emde's and Anders' findings. In addition, it offers some new information. NREM (Quiet) Sleep, for example, decreased in 60% of the subjects. This clearly contradicts Emde's finding of a significant increase in Quiet Sleep subsequent to circumcision. Furthermore, the proportion of total sleep time in Quiet Sleep also suggested a decline. Although neither of these measures achieved statistical significance, the direction of change was consistent in both cases and argues against Emde's finding of NREM increase. On the other hand, the observed increase in total sleep time is consistent with Emde's data, although it did not reach statistical significance. Similarly, the percentage of wakefulness (defined both as a combination of Drowsy REM, Alert Activity, Alert Inactivity, Drowsy, and Crying as well as the alternate formula which included only Alert Activity, Alert Inactivity and Crying) showed a decrease in 70% of the subjects which is also in accord with Emde's data and contrary to Anders' findings. The difference in the direction of change for this variable, however, may be more apparent than real due to certain methodological differences between Anders' experiment and the present study. Anders was able to monitor the level of wakefulness immediately following circumcision. This was not possible in the present study because the subjects were not available at that time. Had the subjects been observed for the first hour directly following circumcision, it is possible that an analogous trend would have emerged.

The most surprising finding in this study concerns the changes in Active Sleep (REM). As summarized in the Introduction, Anders observed no significant changes in the proportion of REM while Emde found a decrease in REM in five out of eight subjects in whom he found an increase in Quiet Sleep. In the present experiment, the total percentage of Active Sleep increased in 80% of the subjects and 60% of the subjects showed an increase in the proportion of total sleep time spent in Active Sleep. This finding is thus inconsistent with both Emde and Anders and is, at this time, difficult to account for. One possible interpretation of the observed tendency in Active Sleep is in terms of Dewan's hypothesis (1969) which maintains that

"REM facilitates the processing and programming of information which the organism has absorbed during wakefulness" (Dewan, 1969). Thus, if the stress induced by circumcision is viewed as an addition to the stimulus load which necessitates an increase in the processing activity, one might expect a post-circumcision increase in the amount of Active Sleep, such as was suggested here.

Unforunately, none of the trends described above achieved statistical significance. This is most likely due to error variability. First, pre- and post-observations were not carried out at the same time of day as had been originally planned, a problem which was brought about by the fact that the scheduling of circumcision surgery was impossible to predict with any degree of accuracy. Thus, the time of day effect could have augmented error variability. Second, pre- and post-observations were usually carried out on two consecutive days. Consequently, the difference in subject's age at the time of pre- and post-observation could have further increased error variance. Finally, neonates are neurologically highly variable. Quiet Sleep, in particular, is inchoate during this period which makes it difficult to detect specific and unidirectional changes with such a small sampling of subjects and time.

The overall response constellation, however, suggests orderly changes. Most subjects showed an increase in Active Sleep, a decrease in Quiet Sleep as well as an increase in total sleep time and a decrease in waking time. This pattern, although not statistically significant suggests that: a) stress may indeed tend to intensify the need for sleep (consistent with the conservation withdrawal syndrome); and b) that Active Sleep with its putative information management function may play a significant role in the neonatal stress response. This particular function of Active Sleep should be investigated further. Future studies in this area, however, would need to impose stringent controls for the time of day as well as age differential. Larger sample size is definitely recommended in order to compensate for error variability which is particularly troublesome in neonatal research.

SUMMARY

The research reported in the present paper is concerned with the effect of stress induced by circumcision on sleep state organization in neonates. It attempted to clarify the experimental problem previously dealt with by two groups of researchers: Emde and his associates (1971) and Anders and his colleagues (1974). The former group found a significant proportional increase in NREM (Quiet) sleep with no changes in wakefulness, whereas the latter found no significant changes in the proportion of NREM and a short-term significant increase in the proportion of wakefulness following circumcision. In the present study, 10 full-term, health male neonates (mean age of 25 hours) were studied on two separate occasions: during a three-hour interfeeding period prior to circumcision and during the interfeeding period subsequent to circumcision. Behavioral observations were used. The infant's behavior was described in terms of single states which included Quiet sleep (NREM), Active sleep (REM), Drowsy REM, Drowsy, Alert Activity, Alert Inactivity, and Crying as well as computed states which entailed percentage of total observation time spent in sleep (total sleep time), percentage of total sleep time spent in Quiet sleep, percentage of total sleep time spent in Active sleep, percentage of waking time (based on two definitions), percentage of waking time spent in Alert Inactivity, percentage of waking time spent in Drowsy and percentage of waking time spent in Crying. No

statistically significant changes in any of the above states, either single or computed, were found. Qualitative analysis of pattern and direction of state change, however, revealed orderly although non-significant changes manifested in the increase in total sleep time, increase in Active (REM) sleep, a decrease in waking time, and a decrease in Quiet sleep (NREM). This constellation represents a departure from both Emde's and Anders' positions. Possible reasons for this discrepancy were attributed to methodological differences between the present experiment and the referenced studies. The unanticipated increase in Active (REM) sleep following circumcision was interpreted tentatively in the context of Dewan's (1969) hypothesis of the "reprogramming" function of REM.

In conclusion, the results of the present investigation of the effects of stress on sleep state organization in neonates suggest no significant post-cicumcision changes in any of the states, either single or computed. This finding is thus discrepant with both Emde's observation of a significant NREM increase as well as Anders' finding of an increase in wakefulness. Qualitative analysis of the pattern and direction of change, however, revealed a non-significant increase in total sleep time and Active (REM) sleep as well as a decrease in Quiet (NREM) sleep and wakefulness.

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APPROVAL SHEET

The thesis submitted by Dalma Kalogjera has been read and approved by the following committee:

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The final copies have been examined by the director of the thesis and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the thesis is now given final approval by the Committee with reference to content and form.

The thesis is therefore accepted in partial fulfillment of the requirements for the degree of Master of Arts.

March 16, 1983
Date

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