THE TREATMENT OF SLEEP DISORDERS WITH MELATONIN

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Since sleep requires neurological control, it is not surprising that disorders of the brain may be associated with severe sleep disturbance (Okawa *et al.* 1986). Neurologically multiply disabled children can experience chronic sleep–wake rhythm difficulties (Okawa *et al.* 1987, Quine 1991), which often respond poorly to strict bedtime scheduling, various psychological measures and sedatives. In fact sedatives may cause agitation or provide the desired effect for only a few days, and physicians often cannot offer successful treatment. Some of these children have difficulty falling asleep, some sleep in a totally fragmented fashion for minutes or hours, while others seem to require only a few hours of sleep. When they are awake they tend to fuss, cry, play and demand attention from their exhausted parents, to the point where the sleep disturbance itself can become the major reason for parental exhaustion and the introduction of foster care.

The prevalence of chronic neurological disabilities has significantly increased during the last decade, because markedly preterm infants and children with severe brain damage have survived due to advances in medical care (Alberman *et al.* 1992, Robinson and Jan 1993). Sleep disorders have also appeared to be increasing in this population.

Melatonin plays an important role in the induction of sleep. It is produced by pinealocytes in the pineal gland. Tryptophan is converted to serotonin then to N-acetylserotonin and finally to melatonin (N-acetyl-5-methoxytryptamine). The secretion of melatonin is controlled by an endogenous rhythm-generating system in the brain which is synchronised by the light–dark cycle, so that melatonin levels are high in darkness and low in light; this is why it is called the 'hormone of darkness' (Utinger 1992). The process begins at the retina, from where the signal goes to the suprachiasmatic nucleus of the hypothalamus, the reticular system, the spinal cord, cervical ganglia and through the postganglionic sympathetic fibres to the pineal gland (Rusak 1977). Recently, the suprachiasmatic nucleus has been found to be a major sleep regulator, and melatonin appears to influence this structure (Cassone *et al.* 1986, Vanecek *et al.* 1987). When it is damaged, as demonstrated in studies with rodents, sleep difficulties develop which are intensified in a darkened environment.

Melatonin has been synthesised, and the oral form is now available for investigational use. Its usefulness in regulating sleep has been noted for shift-workers (Weitzman *et al.* 1981), jet-lag (Arendt 1987), chronic insomnia (MacFarlane *et al.* 1991) and delayed sleep-phase syndrome (Dahlitz *et al.* 1991). Blind adults with

free-running sleep–wake rhythms may also benefit from it (Sack *et al.* 1991). Voordouw *et al.* (1992) gave 300mg of melatonin daily for four months to women, and found that it inhibited ovarian function. Yet even with such large doses, adverse side-effects were not noted by these or any of the other investigators.

We became interested in melatonin treatment on compassionate grounds because a blind, neurologically multiply disabled child was referred to the Visually Impaired Program with a severe and chronic sleep disorder which did not respond to conventional treatment. His parents were sleep-deprived and in crisis. The treatment was successful, so we began to use it for other children with and without visual impairment.

Method

This study was carried out by co-ordinators of the Children's Hospital Visually Impaired Program at British Columbia's Children's Hospital and staff at the Department of Neurology at the Royal Liverpool Children's Hospital, Liverpool, England. Only children with the most severe sleep disorders were accepted for melatonin treatment. A chronic sleep disorder was considered to be severe when the child failed to respond to conventional management, resulting in a family crisis. Most subjects were multiply disabled. Children were excluded from the study if their sleep disturbance was thought to be due to obstructive apnoea, pain, emotional distress or nocturnal seizures causing repeated arousals.

After a detailed history the children had physical and neurological examinations, including EEG, CT and haematological tests (complete blood count, platelets, urinalysis with microscopy, blood urea nitrogen, thyroid and liver function studies). Subsequently the caregivers were requested to record the child's 24-hour sleep pattern for seven to 10 days. This was a difficult task, but these children usually awakened the caregivers by their crying, screaming, talking or banging.

Once a child was felt to be a candidate for treatment, oral melatonin (2·5 to 5mg) or a placebo was given at the desired bedtime for seven to 10 days each, in a double-blind, crossover randomised fashion. There was also a wash-out period of four or five days between the treatment phases. Standardised sleep charting was completed throughout all study phases, with detailed recording of the behaviour. After the trial the results were decoded and analysed. On six occasions, due to family crises, the children were given melatonin immediately after the baseline sleep charting. When the treatment had been proven to be successful, it was continued. The parents were always instructed to awaken their child at the same time each morning and to reduce the afternoon naps.

All children had repeated haematological tests and urinalysis at approximately three and six months after the treatment began. They were also examined at these times. The caregivers were telephoned repeatedly, especially during the initial treatment phase, and were interviewed on each occasion about possible side-effects.

In British Columbia there is no paediatric sleep disorder clinic to do polysomnographic studies, and the laboratories are not equipped to analyse serum or urine melatonin levels. These tests would anyway be extremely difficult to perform on multiply disabled children, even in optimum conditions.

Melatonin is an investigational drug. In Canada, permission for its use has to be obtained from the Canadian Health Protection Branch and also from the US Food and Drug Administration. The drug is supplied by Sigma Company, St. Louis, Missouri, USA.

Case reports

CASE 1

This severely delayed and cortically blind eight-year-old boy was born with multiple dysmorphic features due to a chromosome anomaly. He had slept extremely poorly from birth, despite various types of sedation and rigid bedtime scheduling. Almost every night he awoke several times and demanded attention by crying, screaming and banging the side of his bed (Fig. 1a).

A three-day course of melatonin (2·5mg), given at bedtime, induced night-long sleep within 30 to 45 minutes (Fig. 1a). After several months the dosage was increased to 5mg. He became more alert during the day and his afternoon naps gradually disappeared. The educators noted improved mood, together with increased alertness and interest in his environment. These changes were most obvious during the first two or three weeks. No adverse side-effects were observed after one year of treatment.

CASE 2

This 14-year-old multiply disabled boy had sustained a hypoxic-ischaemic insult after birth. He now has spastic quadriplegia, marked mental retardation, cortical blindness, shunted hydrocephalus and epilepsy, which is well controlled on valproic acid.

His sleep pattern had been fragmented since infancy, despite strict bedtime scheduling and various sedations, which tended to make him agitated (Fig. 1b).

Melatonin (2·5mg at bedtime) helped him within three days, but did not fully normalise his sleep (Fig. 1b). He became more alert during the day, his afternoon naps decreased and his irritability and lethargy disappeared. When he awoke during the night he seemed content and no longer cried or banged the side of his bed. No side-effects were observed after 10 months of treatment.

CASE 3

This four-year-year-old severely multiply disabled male child was born with trisomy 18 syndrome. He had gastro-oesophageal reflux, with vomiting up to 20 times a day and seizures consisting of 10 to 20 myoclonic body-jerks daily. His sleep pattern had been markedly fragmented since birth (Fig. 1c). Sedatives, strict bedtime routines and forced interruption of daytime naps did not help. His parents were unable to cope, and placed him in foster care.

Melatonin (2·5mg at bedtime) improved his night sleep and reduced his daytime naps (Fig. 1c). Unexpectedly, his reflux and seizures subsided. He became more alert and happier, and his development began to improve. Adverse side-effects were not noted.

CASE 4

This five-year-old boy had developed nystagmus at nine months of age. Head CT scan showed a large optic nerve glioma involving the chiasm and hypothalamus and partially involving both optic radiations. Endocrine studies were normal, and chemotherapy was started. At four years, due to tumour growth and progressive loss of sight, his tumour was debulked and chemotherapy was restarted. Postoperatively he became totally blind and developed multiple endocrine deficiencies and a fragmented type of sleep (Fig. 1d). The sleep disturbance, which created a major family crisis, failed to respond to sedatives, strict bedtime schedules or to various psychological measures. He did not respond to 2·5mg of melatonin given each night, but his mood and functioning improved when the dose was doubled (Fig. 1d). There were no adverse side-effects. After six months of treatment, the melatonin became ineffective even with larger doses (20mg), and therefore it was phased out.

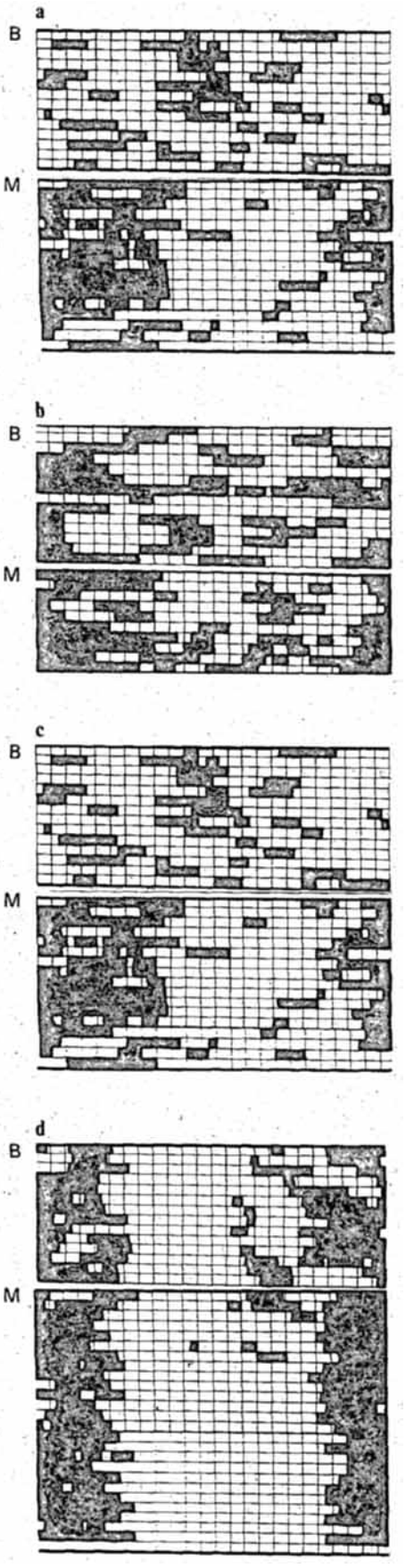

Fig. 1. Fragmented sleep patterns. Sleep charts were recorded by caregivers before (B) and during first week of melatonin (M) treatment. 24 horizontal squares indicate hours from midnight to midnight. Vertical divisions represent days. Black spaces show when child was asleep.

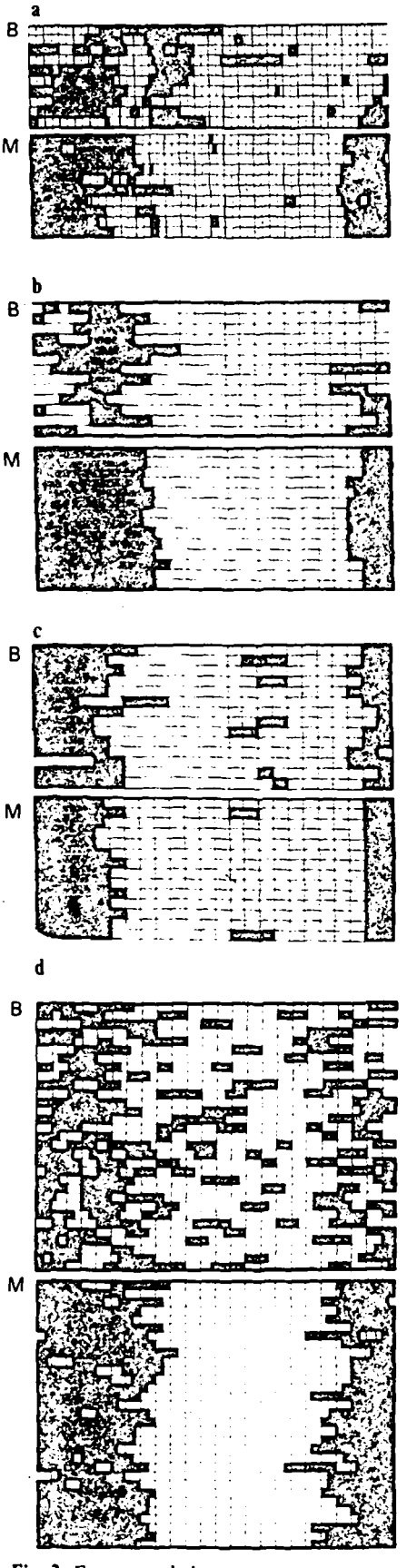

Fig. 2. Fragmented sleep.

CASE 5

This 5½-year-old severely multiply disabled boy sustained hypoxic-ischaemic brain damage at birth. He had severe microcephaly, spastic quadriplegia, epilepsy, mental retardation and cortical visual impairment. His severe sleep disturbance had been present since early infancy and did not respond to any type of management. He had been put in foster care. The sleep pattern was fragmented (Fig. 2a).

Oral melatonin (5mg) greatly improved his sleep pattern (Fig. 2a). His night sleep appeared to be less restless and slight noises no longer awakened him. His behaviour was more pleasant, with fewer temper tantrums. His seizure control also significantly improved without changes in his anticonvulsant treatment. There were no adverse side-effects.

CASE 6

This cranky and hostile 14-year-old boy with Down syndrome had temper outbursts due to a severe and fragmented sleep disturbance (Fig. 2b). Previous attempts at improving his sleep had failed. He was a frequent bed-wetter.

Melatonin (2·5mg at bedtime) normalised his sleep within 24 to 48 hours (Fig. 2b). There were no apparent adverse side-effects. The temper tantrums and bed-wetting disappeared, his attention span improved and he became inquisitive and friendly. These behavioural changes were strikingly rapid, occurring within a few days of treatment. During the next 12 months the parents stopped the treatment on two occasions but the sleep disorder returned within two or three days. Later the dose of melatonin was increased to 5mg.

CASE 7

This multiply disabled 11-year-old boy was born totally blind, due to bilateral optic nerve hypoplasia, and had profound mental retardation, spastic quadriplegia and epilepsy.

The sleep disorder, present since infancy, was characterised by fragmentation (Fig. 2c). When he was awake he demanded attention by crying and screaming. Night-time sedatives made him agitated and his physicians failed to offer any useful advice. Oral melatonin (2·5mg at bedtime) helped him to fall asleep within 30 to 40 minutes, but the sleep charts, which we feel were recorded inaccurately, did not show an improvement. Nevertheless, the treatment was continued at the family's insistence (Fig. 2c). After a few days the child became happier and more alert, and the seizures decreased, even though occasional early-morning awakening was still a problem. A few months later the dosage of melatonin was increased to 5mg. Side-effects were not noted. After about eight months the treatment was phased out and the sleep pattern remained reasonable.

CASE 8

This six-year-old boy with developmental delay and autistic behaviour had had a severe sleep disturbance for three years. His sleep was fragmented and on average he slept only 2½ to three hours a night. Various medications had failed to help him. Melatonin (5mg at bedtime) improved his sleep without adverse side-effects. His autistic behaviour remained unchanged, but his parents were now able

to sleep and the child's care became easier. After several months the treatment was stopped and the child's sleep pattern remained acceptable to the parents.

CASE 9

This severely multiply disabled three-year-old boy had been born with lissencephaly. He was microcephalic, with epilepsy, spastic quadriplegia and cortical visual impairment. From two years of age his sleep pattern had deteriorated, while his epilepsy and reflux had come under control. There was no obvious sleep-wake cycle and his sleep was markedly fragmented (Fig. 2d). Numerous sedating drugs, used either singly or in combination, had no effect apart from making him more irritable during the day.

At 2½ years of age, five days after the introduction of melatonin (2mg at 7 p.m.), a distinct and almost uninterrupted sleep-wake cycle returned, with periods of sleep lasting for up to 12 hours (Fig. 2d). When the patient did awaken during the night, it was for brief periods only and not accompanied by screaming or restlessness. The patient was more alert during the day and appeared to respond in a preschool environment. Withdrawal of melatonin was followed by rapid deterioration of his sleeping pattern, as well as marked daytime irritability and an apparent increase in seizure frequency. Following the reintroduction of treatment, the sleep-wake cycle returned to normal. The patient has remained on melatonin for the past six months, with sustained effect. The parents had been reluctant either to discontinue treatment or to allow a placebo *vs.* melatonin trial, in view of the child's improvement. Adverse side-effects were not noted.

CASE 10

This totally blind five-year-old boy had bilateral retinopathy of prematurity. His development was mildly delayed, with hyperactive, self-abusive behaviour and frequent temper tantrums. After the family moved to another location, a severe delayed sleep onset developed (Fig. 3a). At night he appeared to be unable to fall asleep for several hours, in spite of numerous medications, psychological measures, extra physical activity in the daytime and forced early-morning awakenings. His daytime behaviour markedly deteriorated and a family crisis developed.

Melatonin (5mg at bedtime) normalised his sleep pattern within three days (Fig. 3a). His behaviour improved greatly. He became a pleasant child, eager to go to school, in contrast to his behaviour before treatment. His self-abusive behaviour disappeared, and his attention span and his school performance improved. Side-effects were not noted. After three months the treatment was withdrawn but the child has continued to sleep normally. On rare occasions, the parents still give melatonin when he exhibits difficulties falling asleep.

CASE 11

This three-year-old girl with Down syndrome had developed infantile spasms which only partially responded to anticonvulsants. Initially she had been cortically blind, but within several months she partially regained her sight. The child's sleep disorder had been present since 18 months of age

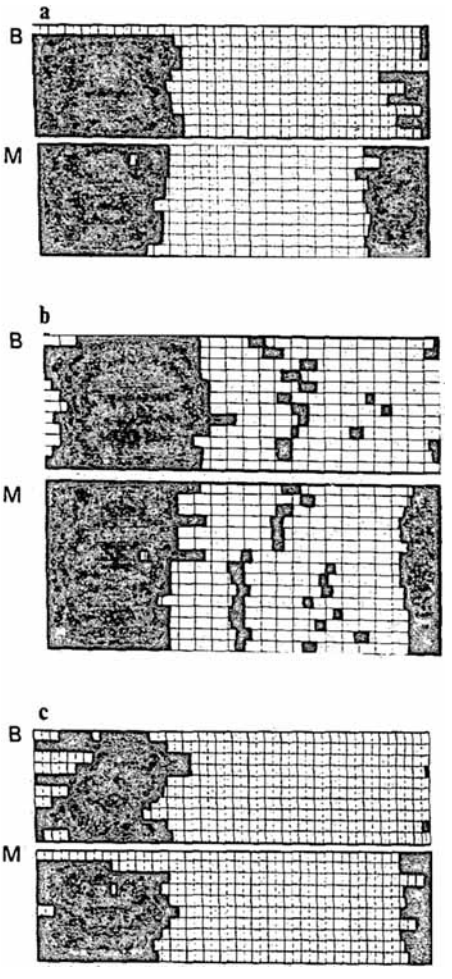

Fig. 3. Delayed sleep-onset.

(Fig. 3b). She could not fall asleep, but cried and fussed for three to six hours. In the morning she was exhausted and remained irritable throughout the day. Bedtime sedatives made her agitated, behaviour modification techniques did not help and her two daytime naps continued in spite of efforts to abolish them.

Melatonin (2·5mg at bedtime) resulted in immediate alteration of her sleep pattern (Fig. 3b). She fell asleep 30 to 45 minutes after the medication was given. After a week she began to wake up in the mornings smiling rather than irritable. Her myoclonic seizures unexpectedly decreased from 40 to between two and seven per day, without a change in her anticonvulsants. The afternoon naps spontaneously decreased to 15 or 20 minutes once a day. There was evidence of increased alertness; she gained 1kg in two months, due to better appetite, and her development began to improve. After several weeks her parents increased the melatonin to 5mg. The impact on the family was striking, and the chronically exhausted mother was transformed into a happy individual. On two separate occasions the melatonin was phased out, but the sleep disturbance quickly returned. After a year of treatment, adverse side-effects had not been noted.

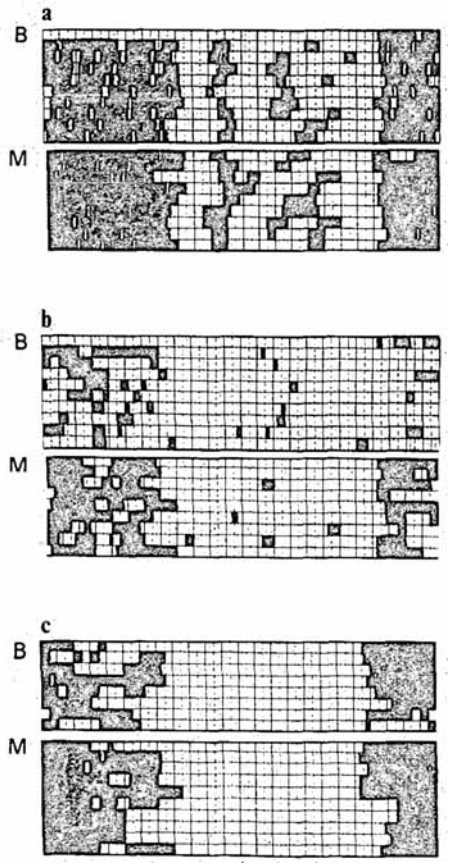

Fig. 4. Non-specific sleep disturbance.

CASE 12

This 12-year-old boy had severe behavioural difficulties. He was an aggressive, hostile, hyperactive, attention-seeking and at times violent child, by now in his 23rd foster home. While he had no health problems, he did have a severe and chronic sleep disorder, which did not respond to treatment (Fig. 3c). For years he had been unable to fall asleep at night until 2 to 3 a.m., and during the days he tended to be tired. His caregivers considered his sleep difficulty to be the greatest problem in his management.

Melatonin (5mg at bedtime) generally induced sleep within 30 minutes to an hour (Fig. 3c). His chronic tiredness disappeared, with some immediate improvement in his behaviour. Several weeks later the dose of melatonin was increased to 10mg. No adverse side-effects were noted.

CASE 13

This six-month-old male infant had a severe congenital sleep disorder (Fig 4a). He generally awoke seven or eight times during the night, resulting in such stress on the family that the referring paediatrician was worried about the sleep-deprived mother committing suicide. There was no explanation for the sleep disorder, because the infant had been born after a normal pregnancy without complications, but his mother had also had a severe sleep disorder in her early childhood. He was healthy and his development was age-appropriate.

Six different night-time sedatives failed to help the child, who remained exhausted, whiny and irritable, and exhibited frequent temper tantrums. Melatonin (2·5mg at bedtime) reduced the awakenings by 50 per cent within three days, without side-effects (Fig. 4a). Behavioural improvements were observed immediately. The medication was discontinued four months later and the child's sleep disorder, while not resolved completely, was more manageable than before.

CASE 14

This three-year-old boy had been born after a normal pregnancy and delivery. His development and health were normal, but he slept for only two or three hours a day (Fig. 4b). There was no apparent reason for his sleep disturbance, as he did not have seizures or apnoeic spells. His mother claimed that the sleep disturbance was present even before birth, because he was so restless during the pregnancy. He was hyperactive and whiny, and at times he was reported to 'walk around like a zombie'.

Melatonin (5mg at night) partially improved his sleep pattern (Fig. 4b). His attention span improved, he calmed down and became more or less like a typical three-year-old. The parental stress diminished and there were no apparent side-effects from the treatment. After about six months the melatonin was phased out and the child's sleep pattern, while not perfect, remained acceptable to the parents.

CASE 15

This eight-year-old girl had a chronic sleep disturbance (Fig. 4c) and severe attention deficit disorder. Her care was exceedingly difficult because of her extreme hyperactivity and her sleep disorder. During the night she required constant supervision, because she wandered around the house, often destroying things. Approximately 20 foster homes had failed to cope, and she was finally placed in a group home. Over the years more than 15 night-time medications had been prescribed, but her sleep difficulties continued. Otherwise she was healthy. No abnormalities were noted on physical or neurological examinations, an EEG or various metabolic tests.

She minimally responded to 5mg melatonin at bedtime (Fig. 4c). Although she was calmer, her behavioural difficulties continued. Several weeks later the melatonin was increased to 10mg. Later a small dose of a sedative was added and the child's sleep became satisfactory.

The clinical profiles of the 15 subjects are shown in Table I. As a humanitarian gesture, we treated two other children outside the study. One was frequently awakened by recurring pain and the second child's myoclonic seizures kept him awake at night. Melatonin treatment had no effect on their sleep disturbances. Since this article was first submitted for publication, we have successfully treated another four children: two who are blind,

TABLE I
Clinical profiles of children treated (N = 15)

Case	*Age (yrs)*	*Sex*	*Sleep disorder**	*Visual impairment*	*Mental retardation*	*Cerebral palsy*	*Epilepsy*	*Diagnosis*
1	8	M	Fr	Cortical	+	–	–	Chromosomal abnormality
2	14	M	Fr	Cortical	+	+	+	Birth asphyxia
3	4	M	Fr	Cortical	+	+	–	Chromosomal abnormality
4	5	M	Fr	Ocular	–	–	–	Optic nerve glioma
5	5·5	M	Fr	Cortical	+	+	+	Birth asphyxia
6	14	M	Fr	–	+	–	–	Chromosomal anomaly
7	11	M	Fr	Ocular	+	+	+	Brain maldevelopment
8	6	M	Fr	–	+	–	–	Autism
9	3	M	Fr	Cortical	+	+	+	Brain maldevelopment
10	5	M	D	Ocular	–	–	–	Preterm birth
11	3	F	D	Cortical	+	–	+	Chromosomal anomaly
12	12	M	D	–	–	–	–	Attention deficit disorder
13	0·5	M	N	–	–	–	–	Congenital sleep disorder
14	3	M	N	–	–	–	–	Congenital sleep disorder
15	8	F	N	–	–	–	–	Attention deficit disorder

*Fr = fragmented; D = delayed sleep onset; N = non-specific.

one sighted multiply disabled child with delayed sleep-onset and one blind infant with a free-running sleep-wake rhythm.

Discussion

The endogenous sleep-wake rhythms of humans under time-cue free-running conditions is about 25 hours. This is well demonstrated by cave experiments, where individuals live in total darkness. Their sleep cycle shifts approximately one hour daily, so that periodically they are awake at night and sleep during the day. Adults totally blinded by ocular disorders frequently have similar sleep difficulties, which cause them considerable hardship. It was a blind man who was first successfully treated with oral melatonin (Miles *et al.* 1977). Subsequently the benefits of melatonin for blind people have been confirmed (Folkard *et al.* 1990, Sack *et al.* 1991).

Although it is the retinal response to darkness which gives a signal to the pinealocytes for increased melatonin production, it is our experience that severe sleep disorders are exceptional in neurologically normal blind children. Free-running sleep-wake rhythms in young blind children are also rare, maybe because melatonin levels are much higher in the younger age-group (Iguchi *et al.* 1982).

Severe chronic sleep disorders in multiply disabled children with or without blindness are common (Okawa *et al.* 1986, Quine 1991). A review of the literature revealed only one case report of

a multiply disabled, visually impaired child treated with melatonin (Palm *et al.* 1991). This mentally retarded nine-year-old boy with ocular blindness had a chronic and free-running sleep–wake rhythm disorder, due to a 24·75-hour circadian rhythm. His sleep shifted 30 to 60 minutes daily, leading to times when he only slept during the day and was awake all night. Melatonin (0·5mg) given orally at night normalised his sleep.

Due to the selection criteria of this study, we have treated only children with severe sleep disorders whose families were in crisis. We have treated nine children with fragmented sleep patterns, three children with delayed sleep-onset and three others with non-specific sleep disturbance of unclear aetiology (see Table I). Since none of the subjects had previously responded to any type of sleep management, melatonin treatment offered enormous benefits for them and their families. It is unclear why 13 of the 15 were males. Nine patients had ocular or cortical visual impairment, which is a bias because the study was carried out by a programme for the visually impaired. The role of visual loss (ocular or cortical) in the aetiology and treatment of sleep disorders needs to be explored further.

Fragmented sleep patterns appear to be the result of a disturbed sleep–wake circadian rhythm (Okawa *et al.* 1986). Our patients with fragmented sleep had been resistant to conventional treatment yet readily responded to melatonin, which presumably influenced the suprachiasmatic nucleus of the hypothalamus (Cassone *et al.* 1986). This structure is known to be the 'pacemaker' of the sleep–wake rhythm. Only case 4 showed obvious evidence of a hypothalamic disturbance, so the destruction of the suprachiasmatic nucleus is unlikely to have been the cause of the other subjects' sleep disorders. Rather, the quick response would suggest that for some reason the multiply disabled children had particular difficulty in formulating appropriate cerebral signals for melatonin release. Case 4 also responded to melatonin for a short time. His sleep disorder and multiple endocrine deficiencies followed a debulking procedure for bilateral optic nerve glioma which almost certainly destroyed his suprachiasmatic nucleus. Entrainment of free-running rhythm by melatonin in rats does not occur after lesions of the suprachiasmatic nucleus (Cassone 1986). It is interesting that he nevertheless responded to melatonin, although after a few months the melatonin treatment became ineffective.

Children with delayed sleep-onset significantly benefited because of the phase-setting action of melatonin. It is well known that multiply disabled individuals and those with attention deficit disorder often have trouble falling asleep.

Three other neurologically normal children with non-specific sleep disorders were also helped by the treatment, but their response was the least obvious. The pathophysiology of their sleep difficulties was unclear.

The optimum dosage of melatonin has not been established for children. Palm *et al.* (1991) used 0·5mg for a nine-year-old child. Our study suggests that the dosage needs to be adjusted on an individual basis. Most of the caregivers administered 5mg as the optimum dosage, since higher dosages of melatonin seemed to yield little or no additional benefit.

After oral administration, the peak plasma concentration occurs within 60 minutes (Waldhauser *et al.* 1990); indeed, most of our subjects fell asleep within 30 to 60 minutes of receiving their medication. Of course these dosages produce supraphysiological levels (Aldhous *et al.* 1985) but, because of the short half-life, the levels tend to remain elevated for only a few hours. For this reason, we occasionally gave a second dose to some children during the night, but this had no effect. It would make sense to give melatonin only at bedtime, but perhaps in a slow-release form.

In most instances, melatonin had a beneficial effect from the first dose, and certainly within three days, but minimal improvements in the sleep pattern were observed for several weeks. None of our subjects demonstrated sedation or a 'hangover' effect, even when they awoke during the night. Melatonin is not a hypnotic (Waldhauser *et al.* 1990), but it has a phase-setting action. We have not noted any adverse side-effects in any of our patients, and the benefits have been

numerous. Improved mood and disposition have been the rule. Irritability has greatly decreased and age-inappropriate temper tantrums have disappeared. The children have tended to become more alert and more sociable, and developmental gains have often been noted. Increased appetite and weight gains have occasionally been seen. Bed-wetting disappeared in one case, and gastro-oesophageal reflux subsided in another child. Three subjects with epilepsy almost immediately showed an improvement in their seizure control—it is unclear whether this was due to more adequate sleep and less tiredness or to the anticonvulsant action of melatonin (Brailowsky 1976, Golombek *et al.* 1992).

This study clearly shows that adequate sleep is critically important for multiply disabled children and that health and behaviour are closely connected with sleep. Furthermore, sleep difficulties, like other chronic disorders, affect the well-being of the entire family.

The response to melatonin was varied in our subjects. In cases 2 and 7 the sleep charts showed only minimal improvement, yet the parents refused to stop the treatment because of the improved behaviour. They felt that, since other forms of treatment were associated with adverse side-effects (unlike melatonin), there could only be improvement. Further studies are required to analyse the benefits and whether they are due to more adequate sleep or perhaps to some additional properties of melatonin.

Some of the subjects have already been receiving treatment for a year, yet melatonin has remained effective. However, a longer follow-up is needed to see whether tolerance may develop. After several months the caregivers tried to phase out the treatment at our request, but in 10 children the sleep difficulties returned within two or three days. In four other children the unmedicated sleep pattern became acceptable, while in case 4 melatonin ceased to help. It should be emphasised that, because the response to melatonin is often incomplete, it needs to be used in conjunction with other conventional measures.

Sleep disorders in children, especially in multiply disabled individuals, are sadly neglected and very difficult to treat. This pilot study has been rewarding because of the surprisingly good outcome and the gratitude of the caregivers. We believe that melatonin, which is at present an investigational drug, will offer hope especially to those who have sleep-wake rhythm disturbances. These are seen mainly in those with neurological disabilities. Further clinical and laboratory investigations must be performed before melatonin can be released for general use, and to this end we are in the process of organising an international multicentre study.

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SUMMARY
Fifteen children (most of whom were neurologically multiply disabled) with severe, chronic sleep disorders were treated with 2 to 10mg of oral melatonin, given at bedtime. Nine had fragmented sleep patterns, three had delayed sleep onset and three others had non-specific sleep disturbance of unclear aetiology; all had failed to respond to conventional management. Nine patients had ocular or cortical visual impairment. The health, behavioural and social benefits of treatment were significant, and there were no adverse side-effects. While the response was not always complete, the study clearly showed that melatonin has an important role in the treatment of certain types of chronic sleep disorders.

RÉSUMÉ
La traitement des troubles du sommeil par la mélatonine
Quinze enfants (la plupart d'entre eux présentant des incapacités neurologiques multiples) avec des troubles du sommeil sévères et chroniques, furent traités par 2 à 10mg de mélatonine orale,

administrés au moment du coucher. Neuf enfants présentaient une allure fragmentée du sommeil, trois avaient un début de sommeil retardé et les trois autres présentaient des troubles du sommeil non spécifiques et d'origine inconnue: l'échec du traitement conventionnel était manifeste dans tous les cas. Neuf patients présentaient des troubles visuels ou cortico-visuels. Les bénéfices du traitement sur la santé, le comportement et la relation sociale furent significatifs et il n'y ey pas d'effets secondaires désagréables. Bien que réponse au traitement n'ait pas été toujours complète, l'étude montre clairement que la mélatonine a un rôle important à jouer dans le traitement de certains types de troubles chroniques du sommeil.

ZUSAMMENFASSUNG

Die Behandlung von Schlafstörungen mit Melatonin

15 Kinder (die meisten hatten multiple neurologische Störungen) mit schweren chronischen Schlafstörungen wurden mit 2-10mg Melatonin oral vor dem Schlafengehen behandelt. Neun hatten fragmentierte Schlafmuster, drei hatten Einschlefstörungen und drei weitere hatten unspezifische Schlaftstörungen unklarer Ätiologie; bei allen waren die üblichen Behandlungsmethoden erfolglos geblieben. Neun Patienten hatten okuläre oder corticale visuelle Störungen. Der Nutzen der Behandlung für Gesundheit, Verhalten und für den sozialen Bereich war signifikant und es wurden keine negativen Nebenwirkungen beobachtet. Wenn auch nicht immer eine hundertprozentige Wirkung erzielt wurde, so konnte die Studie doch eindeutig zeigen, daß Melatonin für die Behandlung bestimmter Formen der chronischen Schlafstörungen eine wichtige Rolle spielt.

RESUMEN

Tratamiento de las alteraciones del sueño con melatonina

Quince niños (la mayoria de los cuales tenían múltiples incapacidades neurológicas), con alteraciones del sueño graves y crónicas fueron tratados con 2 a 10mg de melatonina oral al acostarse. Nueve tenían un patrón de sueño fragmentado, tres tenían un inicio del sueño retardo y otros dos tenían alteraciones del sueño no especificas de etiologia no clara; todos habían fracasado a tratamientos convencionales. Nueve pacientes tenían alteraciones visuales oculares o corticales. Los beneficios del tratamiento sobre la salud, comportamiento y factores sociales fueron significativos y no hubo efectos secundarios. Si bien la respuesta no siempre era completa, el estudio mostró claramente que la melatonina tiene un papel importante en el tratamiento de ciertas formas de alteraciones crónicas del sueño.

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