

ENURESIS IN CHILDREN

KELM HJÄLMÅS

Section of Pediatric Urology, Göteborg University, Göteborg, Sweden

ABSTRACT

Recent demographic studies report a prevalence of nocturnal enuresis in at least 5 - 10% of six to seven year old children, most often boys, and in 0.5% of the adult population. Bedwetting is the most common chronic problem in childhood next to allergic disorders.

Nocturnal enuresis is still perceived as a shameful condition and kept as a secret. But there is nothing shameful about bedwetting. It is caused by a delay in maturation of the somatic mechanisms responsible for sleeping dry all night. This delay is most often hereditary in nature. With few exceptions, nocturnal enuresis is not caused by psychosocial factors; but it generates psychological problems for the child, especially evident as a deterioration of self-esteem.

Nocturnal enuresis results from nocturnal polyuria and/or reduced bladder capacity and, in addition, the child's inability to wake up as a response to an over-full bladder.

With this background, the treatment for nocturnal enuresis is based on enuresis alarm, which is meant to induce arousal, and/or desmopressin (Minirin®, DDAVP) which reduces the amount of urine produced. The alarm may be the first choice but needs a strong support from both the prescribing physician and the parents. Desmopressin is used when the alarm fails or is not accepted by the family and it is increasingly becoming the first choice. Desmopressin in long-term treatment may, like the alarm, give lasting cure of nocturnal enuresis, in particular if medication is preceded with some weeks with bladder training (urotherapy). Thus, the advice to the medical profession is to identify nocturnal enuresis and prescribe treatment when the patient wants to sleep dry.

Key words: enuresis; urinary incontinence; urination disorders; voiding dysfunction

Braz J Urol, 28: 232-249, 2002

INTRODUCTION

Introductory Note on Terminology

The term "enuresis" in this text is synonymous with "nocturnal enuresis" according to the recommendations issued by ICCS (International Children's Continence Society) (1). Nocturnal enuresis (NE) or bedwetting, is the only kind of childhood urinary incontinence that takes place as a complete incontinent micturition. All other kinds of urinary leakage in children, whether daytime only or both day and night should simply be denoted "urinary incontinence" (UI).

The medical profession has not regarded bedwetting as an exciting disorder. It is non-fatal and has a good prognosis. For those families who ask for help, some will meet physicians who share the traditional view on nocturnal enuresis as a marginal problem, requiring little attention and no treatment. The standard answer from a physician to a family searching help for their bedwetting son has often been "he will grow out of it". But this is not true for at least 5 per cent of children with nocturnal enuresis (NE) who will remain enuretic for the rest of their lives. In addition, recent investigations have shown

that NE is a very significant handicap for the affected child. Nocturnal enuresis is still perceived as a shameful condition and kept as a secret. But there is nothing shameful about bedwetting. As will be shown in the following, NE is caused by a delay in maturation of the somatic mechanisms responsible for sleeping dry all night. This delay is most often hereditary in nature. With few exceptions, nocturnal enuresis is not caused by psychosocial factors; but it generates psychological problems for the child, especially evident as a deterioration of self-esteem.

The typical bedwetter is a little boy who, while asleep, is doing something wrong, but he does not know what, and definitely does not know what to do about it. His self-esteem is gradually broken down and he sees himself as an inferior person. This occurs at an age when intact self-esteem is extremely important for an optimal personality development. So there is no doubt that bedwetting requires the physician's attention. The doctor's door should be open for enuretic children and they should receive adequate therapy as soon as they are motivated for treatment, usually at an age around 6 - 7 years.

A new window to an improved understanding of NE was opened in 1985 when a Danish research group discovered a somatic disorder, nocturnal polyuria, in a group of bedwetting children (2). The nocturnal polyuria was due to absence of the normally occurring increase of antidiuretic hormone (aVP, arginine vasopressin) in plasma during the night. This finding was in accordance with previous, largely overlooked studies by Poulton (3) and the Indian researcher Puri (4) who had shown larger nocturnal diuresis, and lower nocturnal urinary concentrations of antidiuretic hormone, respectively, in enuretic as compared to non-enuretic children.

In addition, nocturnal bladder overactivity has also been found a significant cause in at least one third of bedwetters (5). Moreover, some kind of arousal defect (or premature activation of the micturition reflex) must be operative to allow the voiding to take place during sleep. The need to empty the bladder during the night is quite common in childhood, since nocturia (waking up from sleep to void) is even more prevalent in school children than bedwetting (6).

DEFINITIONS

Nocturnal Enuresis

Enuresis is defined as a complete or near-complete micturition in the bed during sleep. The most common form of bedwetting is monosymptomatic nocturnal enuresis (MNE) meaning that there are no daytime symptoms pointing to bladder dysfunction. Thus, the child has no pronounced urgency, no very frequent nor infrequent voidings and, most important, no daytime incontinence. MNE is usually not a great problem for children under the age of 5 years (7). Most children with MNE have primary enuresis; i.e. there has never been a dry period of at least 6 months, in which case the enuresis is said to be secondary. This review deals primarily with primary monosymptomatic nocturnal enuresis (PMNE).

The number of wet nights required in order to regard nocturnal enuresis as a clinical problem is now generally considered to be between 1 and 3 per month, because this is the threshold for most affected children to be concerned and thus for most parents to seek help (8).

Incontinence versus Enuresis

All forms of wetting other than enuresis, isolated bedwetting, should be categorized as incontinence, i.e. the loss of small amounts of urine, never a complete void. The distinction between the terms enuresis and incontinence has been found necessary for scientific as well as clinical reasons. From the scientific viewpoint, monosymptomatic nocturnal enuresis is a well-circumscribed entity and should not be mixed up in research with other urine-losing conditions such as combined night- and daytime incontinence. Research on such a mixed bag of conditions has been common in the past resulting in studies lacking in scientific validity. From the clinical viewpoint, traditional wisdom tells that the term enuresis denotes an essentially innocent condition because everybody knows that most enuretic children become dry as time goes by. "Enuresis" became almost synonymous with urinary incontinence in childhood. Therefore, many children with urinary incontinence due to organic conditions in the nervous system or the lower urinary tract have been labeled "enuretics" by less careful

clinicians and sent home with a “wait and see” message instead of getting immediate diagnostic attention. This has caused unnecessary delay and sometimes even a worsening of prognosis for the individual child. The more somber term incontinence makes the clinician more attentive so time has now come to stop using the word “enuresis” for every wetting child.

Outcome of Treatment of Nocturnal Enuresis

The normal annual resolution rate of MNE (15 to 17% per year) (9) should be accounted for when cure rates are reported. The outcome of drug treatment for MNE is expressed as either full or partial response while on the medication. Full response is defined as a reduction in wet nights of more than 90% while partial response is defined as a reduction in the number of wet nights of between 50% and 90%. Less than 50% reduction in wet nights is considered to be non-response. A lasting cure is defined as a full response still present 6 months or longer after discontinuation of pharmacotherapy (1). It is obvious that these definitions of response require that the child’s nighttime wetting is carefully recorded during at least 2 weeks before treatment. The 90% cut-off point has been chosen in order to allow for the occasional wetting that can occur up to 2 years after otherwise successful treatment during a night when the child is running a fever or sleeps very deeply after a tiring day.

In all studies on outcome of treatment of MNE, it should be reported whether nighttime wetting was replaced with nocturia (1).

Bladder Capacity

The important variable is functional bladder capacity (FBC) which is defined as the volume in the bladder when the individual feels a genuine desire to void (DV). This is why it is difficult in children to decide functional bladder capacity. Before 4 to 5 years of age, or in older children with bladder dysfunction, the child is uncertain about how to interpret signals from the bladder. A great up to 10-fold variation of voided volumes is found even in older children with normal bladders when the voidings are not supervised. “The normal child voids when it is convenient, not always when the bladder is full” (6). When we try to decide the FBC of a child in a hospital setting, a com-

mon source of error is the child’s wish to please the investigator (and to shorten the time spent in the laboratory) by performing several small voidings with volumes well below the true bladder capacity. It is therefore important to supervise the child, ask repeatedly “are you sure that you need to void right now, or can you wait a little longer?”, and allow voidings only when the child feels a genuine desire to void.

Because it is problematic to define a child’s functional bladder capacity in the laboratory, the variable may be better defined operationally. This is done by letting the family fill in a voiding diary for at least a couple of days and define FBC as the largest measured voiding excluding the morning voiding. The latter is a measure of the nocturnal FBC after a dry night and is larger than any daytime micturition volume (6). In enuretic children, nocturnal FBC can be measured at home by weighing diapers.

With FBC defined in this way, it will be found that normal daytime FBC for age complies well with the simple formula:

$$\text{voided volume (ml)} = [30 \times (\text{age in years} + 1)]$$

meaning that the newborn baby has a bladder capacity around 30 ml and that the capacity increases with 30 ml per year until adult capacity is reached at age 15. Nocturnal capacity in a non-enuretic child (i.e., the volume of the first morning void) will be larger. The daytime FBC is significantly reduced when it does not reach more than 65 per cent of the formula value (10).

ETIOLOGY

Genetics

Nocturnal enuresis is a hereditary disorder. Since long, it has been observed that bedwetting often occurred in several members of the same family that has since been confirmed in an often cited twin study (11). The mode of inheritance is autosomal dominant so if both parents were enuretic as children, the risk for their offspring is 77%, while if only one parent had NE, the risk is about 45%. Sporadic bedwetting with no affected relatives occur in a little more of 30% of enuretic children, but this figure may

include polygenic or autosomal dominant inheritance with low penetrance.

An interesting development is that genetic aberrations leading to nocturnal enuresis are now becoming identified with molecular genetic methods. Linkage analysis has shown foci on chromosomes 13 (12), 12 (13), 8, and 22 (14). This is however only the beginning of the process of genetic mapping of NE. With increasing knowledge, a picture of pronounced heterogeneity of both genotype and phenotype is emanating (15), so the etiology of NE is characterized by a complex interaction of genetic and environmental factors.

EPIDEMIOLOGY

Children usually become dry by day before they become dry during sleep. The prevalence of nocturnal enuresis has now been studied in many populations all over the world (Table-1) (16-22). Only one study is longitudinal (16) while all the rest are cross-sectional studies. In the French study by Lottmann (21), the severity and consequences of enuresis were studied in a sub-sample of 228 children (out of the 349 who had reported enuresis). In the sub-sample, 66% had more than one wet night per month, 37%

more than one wet night per week, and 22% wet the bed every night. Regarding consequences, 42% of the 228 were “bothered a lot” while 15% were “not bothered at all” by their enuresis. In contrast, 92% of the 228 mothers declared that the enuresis had no effect on family life or the child’s behavior at school. Fourteen per cent of mothers punished their child and only 13% intended to seek treatment for their child.

As is evident from the table, the figures are not easy to compare because different selection criteria have been used, especially regarding age and frequency of enuresis. Also, only one study (18) reports on monosymptomatic enuresis while the others include all patients with bed-wetting, hence even non-monosymptomatic patients with NE and additional daytime symptoms (urgency, frequency, some also day incontinence).

In early childhood, NE is more common in boys than in girls but this gender difference disappears before adolescence. Prevalence of NE at age 7 is significant since many children then start school meaning more exposure to the environment and thus a greater awareness of the problem. As a general rule it can be said that between 5% and 10% of all 7-year-old children wet their beds often enough to be motivated to receive active treatment. This makes NE, next

Table 1 - Prevalence of nocturnal enuresis.

Study (reference #) year	Age years	Frequency	N	Boys	Girls
Fergusson, New Zealand (16) 1994	7	any time	1,265	10.3%	
Järvelin, Finland (17) 1988	7	<1/10 to ≥7/10 nights	3,206	8.6%	6.4% 3.9%
Hellström, Sweden (18) 1990 (MNE)	7	≥1/3 months	3,556	7.0	2.8
Hellström, Sweden (18) 1990 (all NE)	7	≥1/3 months	3,556	11.9	7.1
Watanabe, Japan (19) 1994	5 11		2,033	19% 6%	
Bower, Australia (20) 1996	5-12	overall ≥1/week	2,292	18.9% 5.1%	
Lottman, France (21) 1999	5-10	overall >1/week	3,803	9.2% 3.4%	
ADULTS: Hirsasing Holland (22) 1997	18-64	≥1/4 weeks	13,081	0.5%	

to allergic conditions, the most common chronic health problem in children in Western countries.

Recently the first reliable study on the prevalence of NE in otherwise healthy adults has been published (22) (Table-1). It should be noted that a prevalence of 0.5% in adults (with half of them having primary NE) and 5% in children means that no less than 5% of children with NE are at risk for life-long enuresis if they are not treated successfully during the childhood years.

PATHOPHYSIOLOGY

Why do some children wet their beds during sleep? The remarkable fact is that the great majority of children sleep dry for 8 - 9 hours or more while sometimes finding it hard to wait for only a couple of hours during daytime. Thus, nocturnal dryness requires functions that are not present during daytime. These are (i) reduction of nocturnal urine production so that it does not exceed bladder capacity; and/or (ii) that the bladder detrusor muscle is efficiently inhibited and relaxed; and (iii) that the sleeping child is awakened by a full bladder, alternatively that the micturition reflex is well inhibited so that the child is allowed sufficient time to wake up before micturition ensues.

Thus, the basic pathophysiology of NE is simple in that the bladder gets filled to capacity during sleep and needs to be emptied. There are two main factors, working singly or in combination, causing the bladder to become full. One is nocturnal polyuria because urine production is not reduced during sleep as in the normal case. The other factor is reduced nocturnal bladder capacity. The full bladder needs to be emptied and then the important question is: does the child wake up? If he wakes up, he walks to the bathroom and performs the socially acceptable act of nocturia. If he does not wake up, the socially unacceptable bedwetting ensues. Nocturia and enuresis share the same pathophysiological background, a mismatch between diuresis and available bladder storage space, with arousal or lack of arousal as the key difference.

Nocturia is even more common than NE in children. Of healthy school-children 7 - 15 years of

age, 35.2% reported occasional nocturia, 3.6% nocturia at least once a week and 4.1% habitual (every night) nocturia (23). With the addition of the 5 - 10% of children who were nocturnal enuretics (7.9% in the cited study) (23), night-time micturitions, asleep or after waking up, seem to occur in around 50% of otherwise healthy school children.

Nocturnal Polyuria

Normal subjects have a marked circadian variation in urine output leading to a significant reduction of urine excretion and a corresponding increase of urine osmolarity during sleep (24). Decrease of renal urine production during the night allows for sleep not disturbed by a full bladder. The circadian variation is present in normal subjects regardless of age and has been attributed to nocturnal increase of antidiuretic hormone (plasma vasopressin) (25) which is, however, true only in childhood. In adolescence and adult age, the reduction of nocturnal urine production occurs mainly due to a decrease in urinary sodium excretion (24,26,30).

Relative nocturnal polyuria has been operationally defined as a day/night urine ratio of < 1 which has been shown to exist in around two thirds of children with PMNE. As mentioned previously, a Danish research group in Aarhus looked at nocturnal urine production and plasma vasopressin in children with NE and found a virtual absence of day/night variation of vasopressin accompanied by nocturnal polyuria (2,27). Thus, for the first time, a coherent physiological explanation for NE, or at least a large part of the NE population, had been presented. The new findings generated quite intense research resulting in, as expected, both validating (28) and conflicting (29) data. This conflict has been subsequently resolved by the mentioned finding that lack of nocturnal increase in vasopressin ceases to be operative for the nocturnal polyuria in enuretics at the beginning of adolescence (when it seems to be due to nocturnal natriuresis). Presently, there is a consensus that relative nocturnal polyuria is an important pathogenetic factor in around two thirds of MNE patients regardless of age (those are the patients responding to desmopressin, DDAVP® or Minirin®) while the remaining third has inadequate nocturnal bladder storage.

Bladder Dysfunction in Nocturnal Enuresis

Previously, bladder function was thought to be normal in enuretic patients. Recently, however, evidence about the pathophysiological role of the bladder for NE has accumulated so it can safely be said that the Bladder is Back in Business in NE (5,31-33). As many as one third of all enuretic children, or even more, have a nocturnal detrusor overactivity that will need specific treatment in order for the enuresis to resolve. Especially non-polyuric bed-wetters, those who do not respond well to desmopressin, should be suspected to have a malfunctioning bladder with reduced capacity (34). Even children believed to have monosymptomatic enuresis, that is no daytime symptoms, may have an overactive bladder. Firstly, the bladder may be overactive only during sleep. Secondly, experience tells that history taking is notoriously difficult in enuretic children so that a negative history does not always exclude day symptoms with absolute certainty.

Detrusor overactivity is revealed as pressure peaks during cystometry. How does this finding translate into an inadequate storage function of the bladder? The relevant fact is that an overactive detrusor is not properly relaxed. Since the bladder is a muscle bag, it cannot make use of its "true" capacity without a well functioning inhibition of spontaneous detrusor activity during the filling phase.

In this context, it is interesting to note that there is an association between childhood NE and adult detrusor overactivity. In a retrospective study of 1000 urodynamic case records, 10% of the male subjects were found to have idiopathic detrusor overactivity. Of these, 63% had suffered from childhood bedwetting (35). Corresponding figures for females were 29% with bladder overactivity of whom 38% had been nocturnal enuretics, which probably reflects the gender difference in childhood bedwetting.

Convincing data on the role of daytime and/or nighttime bladder dysfunction in NE have recently been published (5). Forty-one children (33 boys and 8 girls), mean age of 10.4 years, with PNE (3 or more wet nights weekly) had resisted previous treatment attempts with desmopressin with or without an enuresis alarm. The enuresis was considered to be mono-

symptomatic. All children were studied with daytime cystometry, continuous natural fill cystometry and electroencephalography during sleep, and recording of daytime and nighttime urinary output. Almost none of the patients had nocturnal polyuria. All had a functional bladder capacity smaller than expected for age. All 41 children were found to have abnormal bladder function during sleep (detrusor overactivity or frequent high-pressure small voidings) while 18 (44%) had normal urodynamics at daytime. Thus, this study provides strong evidence that bladder dysfunction is an important pathogenetic factor for NE, especially in children resistant to conventional treatment with desmopressin and/or alarm. Also, that several children with "monosymptomatic" NE, that is a normal bladder during the day, may have nocturnal bladder dysfunction as a cause for their enuresis.

Sleep and Arousal

Relative nocturnal polyuria and/or reduction of the nocturnal bladder capacity due to an overactive bladder cannot explain why the enuretic child does not wake up to the sensation of a full or contracting bladder so that the shameful enuresis could be transformed into the acceptable act of nocturia. This is certainly something the enuretic child himself would like to happen.

Sleep and arousal remain the least understood factors in the pathophysiology of enuresis. Countless numbers of parents have told physicians that their enuretic child is very difficult to arouse (36) or rather, as the parents put it, "sleeps very deeply". Until recent years, medical research has been largely unsuccessful in confirming this opinion of parents, not least because research on sleep and arousal is extremely difficult. However, we have to question our scientific methodology before drawing conclusions that conflict with what the parents tell us. And today some modern studies seem to support the parent's view about abnormal sleep and arousal in enuretic children. By using auditory signals (37), computerized EEG analysis (38), or inquiries (39), a defect in arousal seems to be confirmed. Sophisticated EEG energy analysis has indicated both greater depth of sleep and impaired arousal in enuretics (40). Another recent study shows that the locus coeruleus, one of

the brain areas most responsible for arousal, is activated by bladder distension only when the patient is in deep sleep, not in light sleep (41). This finding agrees well with the results of EEG overnight monitoring in Yeung's enuretic children where EEG either did not show any change at the enuretic event or a change from deep to lighter sleep with the enuresis occurring in an aroused state but without actual full awakening (5).

Parent's opinion about abnormal sleep and arousal in children with NE are thus gradually confirmed. It should be added, however, that even a child with perfectly normal sleep and arousal may experience NE if there is an inadequate inhibition of the micturition reflex due to an impaired processing of inhibitory signals in the brain stem (42).

NE Pathophysiology According to Watanabe

Nocturnal polyuria, arousal disorders and detrusor overactivity have been integrated in a classification system for NE proposed by Watanabe & Azuma (43). Based on overnight simultaneous monitoring of electroencephalography and cystometry in several hundred enuretic children, three main types of NE have been identified. Type I is the most common (57% of patients) and regarded as an isolated mild arousal disorder. Type II a (9%) shows an EEG that does not seem to respond at all to a full bladder, thus an overt arousal defect, while in Type II b (34%) there is, in addition to an arousal defect, continuous detrusor overactivity in the cystometry during sleep.

OTHER CAUSES OF ENURESIS

Upper Airway Obstruction

Surgeons have sometimes experienced that NE resolves after the child had large adenoids or tonsils removed. One study reports significant decrease or complete cure of NE in 87 (76%) of 115 enuretic children (of whom 103 with primary NE) after surgical removal of upper airway obstruction (44). The pathophysiology here is not clear. Disturbed sleep may be a plausible explanation.

Constipation

Constipation may cause secondary NE or make primary NE persist (33,45). A hypothetical explanation is that fecal retention in the sigmoid colon and rectum exerts pressure on the bladder thus reducing the storage capacity. The important implication is that constipation has to be identified and treated in every child with NE.

Diabetes mellitus and Insipidus

The polyuria in these conditions increases the risk for NE, which is most often of the secondary type.

Minor Neurological Dysfunction and ADHD

Children with minor neurological dysfunction are more prone to NE, particularly if belonging to a lower social class (46). Children with attention deficit hyperactivity disorders (ADHD) are 2.7 times more likely to have enuresis than the general child population (47). The combination of ADHD and NE constitutes one of the rare indications for treatment of NE with tricyclic antidepressants.

Sexual Abuse

We have become aware that sexual abuse must count among factors that may lead to NE (most often secondary and non-monosymptomatic). A strong suspicion would prompt full investigation (48).

Non-monosymptomatic Enuresis

Although this review deals primarily with primary monosymptomatic nocturnal enuresis (PMNE), it should be added that children with urinary tract infection, infravesical obstruction, neurogenic bladder, serious psychiatric disorders, and other conditions may be wetting their beds. Their nocturnal incontinence is, however, with very few exceptions combined with daytime symptoms, in particular day wetting. One possible exception is congenital infravesical obstruction in boys (posterior urethral valves) who sometimes present with primary NE without daytime symptoms. It is, however, wise to remember that PMNE with isolated bedwetting as the only symptom is a well circumscribed condition that should be identified when present, thus avoiding clinical

confusion generated by the huge number of childhood disorders that may have bedwetting as one of its symptoms.

PSYCHOLOGICAL ASPECTS

Fortunately, it is now long since PNE was looked upon as a disorder of the mind. "Pediatricians should treat PNE as a common biobehavioral problem without a psychiatric component" (49). While it seems clear that psychopathology is not, with few exceptions, the cause of PNE, research has lately been focused on the sometimes serious psychological consequences caused by enuresis. Several recent studies have been unanimous in reporting that PNE generates substantial feelings of shame and inferiority in the enuretic child, in particular evident as depression of the child's self-esteem and self-image (17,50-51). There is a small but significant risk for psychiatric disorders and problems with social adjustment in enuretic children beyond the age of 10 years (17). This circumstance certainly constitutes a strong indication for starting active treatment as soon as the child is ready to receive it, especially since it has been shown that the child's self-esteem becomes normal within 6 months after successful treatment (51).

Most parents feel tolerant towards their enuretic child with the understanding that the child cannot control the problem. However, up to one third of parents is less understanding and intolerant, and they may even punish their child (52). Parental intolerance is strong predictor that any attempts to treat the enuresis will fail.

INVESTIGATION

For the management of a child with NE, the most important diagnostic procedure is to identify monosymptomatic enuresis by history. Once the history has classified the child as monosymptomatic by the exclusion of pronounced urgency, frequency or infrequent voidings, and in particular daywetting, only minimal additional diagnostic work is needed.

History

Pediatric history taking is never easy and the enuretic child is certainly not an exception. Most of the history is filtered through the parents who often tend to give answers they believe to be the right answers, not necessarily the correct answers. Also, the references used by the parents are the child's siblings and friends. If there happens to be a high prevalence of urgency and frequency among these children, the parents may look upon their 7-year-old son's speedy and frequent rushes to the toilet as normal behavior. Also, NE is still looked upon as a shameful condition by many parents and children alike which will add bias to the history taking. Finally, history taking often involves teaching parents and children to understand the actual meaning of the concepts of urgency and frequency.

Urgency

Urgent desire to void is present in no less than 22% (imperative urgency in 16%) of healthy 7-year-old schoolchildren in Sweden (18). What the physician needs to know is whether the child has pronounced urgency with last-minute races to the bathroom threatening to produce urge incontinence. It is also of value to find out if the urgency is due to holding the urine to the last minute (so called voiding postponement) or to a sudden imperative detrusor contraction. The voiding postponers are relatively easy to identify because they are intensely occupied in play while giving bodily signals that they feel a genuine desire to void, such as crossing their legs and wriggling while sitting.

Frequency and Infrequent Voiding

The normal range in 7-year-olds is 3 to 7 micturitions daily (18). Detrusor overactivity (unstable bladder) leads to eight or more voidings a day. But it is equally important to recognize infrequent voiding with three or less voidings due to detrusor underactivity. The latter is most often caused by bladder distension as a sequel of long-standing detrusor-sphincter dyscoordination, which is a sign of serious bladder-sphincter dysfunction.

Daywetting

This is the most important symptom to exclude in order to classify the enuresis as monosymptomatic but it is also quite often the most difficult to elucidate, due to the parent's and the patient's understandable tendency to subdue information which they are ashamed of. However, the history has to penetrate this question carefully. "Wetting" may be denied while a question about "dampness" may receive a positive response. If there is any amount of daytime incontinence present, the enuresis is definitely not monosymptomatic. The child's daytime and nighttime incontinence is most probably caused by detrusor overactivity and will need specific investigation and therapy.

Symptoms Pointing to Bladder Emptying Problems

Difficulty to empty the bladder points to bladder-sphincter dysfunction or organic, anatomical or neurogenic, disorders of the lower urinary tract and is present in 1% of an unselected population of 7-year-olds in Sweden (18). Such conditions, if present, do not allow the child's bedwetting to be classified as monosymptomatic. The child may experience that it is difficult to start the voiding or has to strain with the abdominal muscles or press with the hand against the suprapubic area during voiding. The urine stream may be weak and can be labeled "non-competitive" in a boy voiding together with friends. Finally, a healthy child always empties the bladder in one portion. A micturition divided in several discrete portions is a sure sign of an underactive detrusor and/or infravesical obstruction of whatever cause.

Voiding Diary

The voiding diary is included here in the History section because the diary supplements the history in an invaluable way. When first asked about frequency of daytime voidings or the number of enuretic events per week, most parents cannot give a reliable answer. Time is saved if the parents can receive the diary by mail before the first office visit and bring it duly filled in at the first visit. The voiding diary should be maintained for at least one week and will give a clear picture of the child's micturition

pattern including any daytime wetting or "dampness" and the number of wet nights. The parents should be asked to observe whether there is more than one enuretic event during a wet night. A baseline is thus established to be compared with the results of subsequent therapy.

Diet

The pattern of food and fluid intake during an ordinary day has to be looked into. It is quite common to find that the child takes massive amounts of soft drinks just before going to bed, a habit which in itself can lead to enuresis.

Emotional Impact

One of the physician's first questions to the child should be "Do you know why you visit me today?" or even "Is there anybody in this room wanting to stop wetting the bed?". Even if a shy child does not give a verbal response, the child's body language may tell a lot about the perceived impact of the enuresis. Children who do not seem to bother about these questions probably do not bother much about their enuresis either, so they may not yet be motivated to receive treatment. Most often, however, enuretic children clearly react in a distressful way to the questions and some even say in plain language that they would very much like to get rid of their bedwetting. Since it is important to assess the emotional impact on the child, questions to child and parents should follow whether there has been any teasing from family and schoolmates and if the child avoids sleeping over in a friend's home or participate in school trips. It is important to tell the child, at this stage, that NE is a very common condition. The enuretic child feels very much alone with his problem which he and all other affected children keep as a shameful secret. The child feels enormous relief when understanding that he is not alone, after all.

Primary or Secondary Enuresis?

The history has to include this question which is not, however, of any great consequence. Secondary enuresis presenting before age 4 to 5 years as a rule has the same characteristics as primary enuresis. When presenting later, secondary enuresis may be due

in some children to psychological trauma or urinary tract infection. It is then seldom monosymptomatic NE but rather nighttime and daytime incontinence.

Physical examination

An ordinary physical examination should be performed at the first office visit. In order to exclude neuropathy, the lower back, legs and feet should be inspected and tendon reflexes tested. Genitals should be examined since the only part of the urinary tract visible to the naked eye is the urethral meatus. A rectal exploration should be performed in order to check the tonus of the anal sphincter and exclude fecal retention in the rectum.

Urinalysis

A dip stick will exclude protein, glucos, hematuria and most urinary pathogens. If there is a history of previous UTI, urinary culture should be added.

Other Investigations

If the history has clearly identified monosymptomatic NE there is presently no indication for additional investigations. This situation may change in the future since the mode of management will depend on the relative importance of nocturnal polyuria, bladder dysfunction, and arousal disorder, for the pathogenesis of the individual child's enuresis. Some specialized enuresis centers have already started to assess nocturnal urine production by weighing diapers, and bladder function by measurement of urinary flow and post-void residual. For the evaluation of arousal there is as yet no clinically useful test available. However, most physicians taking care of enuretic children still use an *ex juvantibus* approach to this diagnostic question. For example, polyuria is probably an important factor and bladder dysfunction less important for the child who responds well to desmopressin, and vice versa.

Ultrasound of kidneys and bladder is an optional examination that is quite often used but very seldom gives any information in a child with monosymptomatic NE. The situation is quite different, of course, if the child has combined daytime and nighttime incontinence in which case a full neuro-urological investigation is always indicated.

TREATMENT

Management of NE is based on 4 principles:

- a)- Verify the child's motivation to be treated and exclude confounding psychosocial factors;
- b)- Information and instruction about daily habits underlining the importance of having regular fluid intake and voidings and relaxed routines at bedtime;
- c)- Enuresis alarm;
- d)- Antidiuretic medication (desmopressin, DDAVP®, Minirin®).

This section will also cover other pharmacological therapy (detrusor relaxing agents, tricyclic antidepressants, and prostaglandin synthesis inhibitors), urotherapy, prevention of relapses, choice of treatment, and how to handle non-responders.

Motivation

It is not uncommon for a 4 - 5 year old bedwetter to be brought to the physician's office because the parents are concerned about the bedwetting while the child is not. NE often requires a long course of treatment that may last for one or several years. It is therefore important that the enuretic child is at least moderately motivated to receive treatment and mature enough to understand that he/she is expected to participate actively, and that it will take time to become dry. The child's motivation is checked with the simple question "Do you want to become dry at night?".

Confounding Psycho-Social Factors

Broken homes, social misery, intolerant parents and child behavioral problems should be identified. These factors predict treatment failures.

Regulating Daily Habits

Today, school children often delay most of their eating and drinking until after school hours. Girls in particular often avoid to visit the busy and sometimes unsafe and not-so-clean school toilets. Consequently, many school children do not void at all between the morning micturition and the time when they return back home from school. The risk for bedwetting increases when the bladder has not been emptied for 8 hours during daytime and then is exposed to in-

creased urine production during evening hours. Quite a few enuretic children stop wetting their beds just by establishing a regular drinking and voiding schedule during the day. Such a schedule will often need to be discussed with and supervised by the child's teacher and school nurse.

Enuresis Alarm

The enuresis alarm is an effective way to treat monosymptomatic NE although not quite as effective as described in older literature. A well done meta-analysis reports lasting cure in 43% of patients (53). Bed mats and body-worn alarms are equally effective. Alarm treatment is slow in the start so it should continue for at least 6 to 8 weeks before being considered ineffective. However, alarm treatment requires that the parents participate actively especially in the initial stages of therapy. Thus, compliance remains a problem with drop-out rates seldom reported in the studies. In a study of 88 adults who had been treated with enuresis alarm 10 to 20 years earlier, 3 had not ceased bedwetting until age 20 to 36 and 4 were still having NE. Of the cured, 16 remembered the alarm as awkward and embarrassing (54). Failure of alarm treatment is predicted by lack of supervision during the treatment period, inconsistent or incorrect use of the alarm, technical problems with the alarm or, most often, that the child does not wake up when the alarm sounds (55). The rest of the family usually does, verifying the arousal disorder in NE.

The mode of action of the alarm has been believed to be an improvement of arousal when the bladder is full. This may be true but lacks scientific proof. An interesting recent finding is that the alarm increases the nocturnal bladder capacity in those children who become dry. This may explain why children, after successful alarm treatment, are often able to sleep dry with no nocturia (56).

A modern development of the alarm method is by monitoring bladder volume during the night using a miniaturized ultrasonic transducer which is carried on a belt over the suprapubic area of the sleeping child. At a predetermined bladder volume, a sound signal is emitted intending to wake the child before the enuresis occurs (57).

Desmopressin, dDAVP

Placebo-controlled studies have shown that the anti-diuretic drug desmopressin (dDAVP) is significantly more effective against NE than placebo (58). Around 62% of patients become dry or reduce the number of wet nights with at least 50% (59) which agrees well with the 69% of enuretic children found by Poulton to have nocturnal polyuria. In a long-term home-based study monitoring nocturnal urine production and enuretic episodes, the responders to desmopressin treatment were those with nocturnal polyuria (60). Relapse after short-term treatment is rather the rule while long-term treatment may yield better cure rates (61). In order to elucidate the effect of long-term desmopressin, a large multi-center prospective study (the Swedish Enuresis Trial, SWEET) was performed (59), comprising 393 children aged 6 - 12 years with monosymptomatic NE and 10 or more wet nights during 4 weeks. Intranasal desmopressin in titrated dose 10 - 40 µg was given until at least a 50% reduction in the number of wet nights occurred which happened for 245 (62%) of the children. The 245 responders started a 1-year treatment period which resulted in 75 (31%) becoming completely dry while still on desmopressin and another 75 (31%) cured without medication. Most of the full responders became dry during the first 6 months of treatment. An intention-to-treat analysis thus showed lasting cure in 75 of the original 393 children, that is 23% which is only marginally better than spontaneous resolution. The lesson learnt from the SWEET study is that among children who had an initial response of > 50% reduction of wet nights (and these are probably the children with nocturnal polyuria as their main pathogenesis), 31% were dry and continued to be dry after stopping desmopressin treatment.

Besides polyuria, predictors of response to desmopressin are fewer wet nights (≤ 3 per week), only one enuretic event per night, age 8 years or more, and a lasting response to a small dose of desmopressin (20 µg intranasal or 0.2 mg per os). In addition, daytime bladder capacity in the normal range (that is the capacity expected for age), measured as the largest voiding in a 2 day voiding diary, predicts good response to desmopressin (32,33). In contrast, morning urine osmolarity or heredity for NE does not have any predictive value.

Side effects are moderate headache or abdominal pain in 3% of patients (59), seldom severe enough to interrupt treatment. Since desmopressin is a potent antidiuretic drug there are rare accounts of severe water retention with hyponatremia and convulsions (62) but none with a lethal outcome. The patient should not drink any fluids for 2 hours before taking desmopressin.

Combined Treatment with Alarm and Desmopressin

Enuresis alarm and desmopressin are not antagonists. They are rather synergistic when used together, so a combined treatment should be tried when monotherapy with alarm and desmopressin has been unsuccessful. After around 6 weeks, desmopressin is discontinued and alarm continued until NE is cured. The fast action of desmopressin is believed to facilitate the child's adaptation to the alarm. Compared to monotherapy with desmopressin and alarm, the combination has been found to be particularly effective for children with psychosocial problems (63).

Other Pharmacological Therapy

Detrusor Relaxing Drugs

Detrusor overactivity, at least during nighttime, is an important pathogenetic factor even for monosymptomatic NE (5), especially in children who do not show a satisfactory response to alarm and/or desmopressin. This condition can be diagnosed with overnight cystometry which is hardly feasible in everyday clinical practice. It is permissible, therefore, to try a detrusor relaxing drug *ex juvantibus* in addition to the ongoing therapy with alarm and/or desmopressin. Oxybutynine is used in dosage of 5-mg bid to children 7 - 10 years of age. A recent alternative is tolterodine which in adults seems to have the same effect on the overactive detrusor as oxybutynine but with fewer side effects such as dry mouth and blurred vision. Tolterodine is not yet approved for use in children, but a recent study in children 5 to 10 years of age with overactive bladder has shown good effect of tolterodine with a virtual absence of side effects. The dosage in children was 1-mg bid, which is half of the recommended dose for

adults (64). It should be noted that detrusor relaxing drugs given as monotherapy are not efficient against NE. They have their place as adjuncts to urotherapy (see below) and enuresis-specific therapy such as alarm and/or desmopressin.

Tricyclic Antidepressants

Imipramine and other members of the same drug family are still widely used for treatment of enuresis. However, they cannot be generally recommended for treatment of this non-fatal disorder because of their potentially lethal side-effects with deaths reported both in patients and their younger siblings (65). Also, the reported lasting cure rate of only 17% (66) after imipramine therapy restricts the use of these drugs. However, for a small group of very carefully selected patients with NE, tricyclic antidepressants may be of value. Adolescent boys with ADHD and persistent NE belong to this group. Given the adverse effects, especially the cardiomyotoxicity, and the individual variability in plasma levels, responsible use of such medication includes careful monitoring by the prescribing clinician, preferably a child psychiatrist.

Inhibitors of Prostaglandin Synthesis

As mentioned, nocturnal polyuria in adolescent and adult patients with NE is as a rule caused by an increase in nocturnal excretion of solutes, especially sodium (26). This may be the explanation that cyclo-oxygenase inhibitors (such as diclofenac) which are known to reduce urinary solute excretion were effective against NE in a double-blind placebo-controlled trial (67). The future role of these drugs for treatment of NE remains to be elucidated.

Urotherapy ("Bladder Training")

For enuretic children not responding to either of alarm, desmopressin, or the combination, the bladder may be the culprit even if historical data have allowed the enuresis to be classified as monosymptomatic. For nonresponders to conventional treatment, detrusor relaxing drugs should be considered, as already mentioned, but non-pharmacological management with bladder-specific treatment, urotherapy, should always be the first step. This is particularly

true for children with border-line urgency, frequency, or infrequent voiding. Urotherapy is cognitive training which makes use of the fact that the normal bladder is under complete cortical, voluntary control in the healthy individual. Urotherapy involves information about what is normal and abnormal concerning the lower urinary tract, instruction about regular habits as regards drinking, voiding and sleeping, and a schedule with voidings at predetermined times. In addition, the child is coached repeatedly that he or she will really become able to take control of the bladder. This regimen is not magic but it puts the onus of responsibility where it belongs, on the owner of the bladder, and where it next belongs, on the parents. The schedule with voidings at predetermined times is the most efficient part of the training program. The child seems to be greatly impressed when he or she succeeds, for the first time, to start a voiding at will without having felt a prior desire to void: "I may be able to become Boss of my Bladder, after all". It has been shown in several studies that with these simple measures, the symptoms of an overactive or underactive bladder will disappear in 65% to 75% of the patients.

Especially children with bladder distension and infrequent voidings need a strict micturition regimen supervised by a urotherapist in order to increase the number of regular voidings during the day. Twenty-two children with therapy-resistant NE were initially considered to be monosymptomatic although, when the history was carefully revised, they were shown to have "lazy bladders" with infrequent voidings. After having attained a normal number of daytime voidings, 20 of the 22 were cured of their bedwetting, either without further treatment or with the help of desmopressin or alarm (68). Since bladder problems are so difficult to exclude with history, a most useful option is to let all enuretic children start treatment with a few weeks of urotherapy as described, subsequently adding specific anti-enuretic therapy.

Prevention of Relapse

Neither of the commonly used management modalities for NE can claim to be really successful. Less than half of affected children achieve perma-

nent cure of their NE. New management strategies are certainly needed. As a promising example, a structured withdrawal program at the end of desmopressin or alarm treatment is reported to reduce relapses substantially. A key factor here is said to be, in the psychologist's language, "internalization of the child's success" (55). These words seem to mean, in the child's own language "I am dry, not because I have been treated but because I am dry".

Choice of Treatment

A sensible recommendation for treatment would require a thorough analysis of the relative importance of the different pathogenetic factors and their causes in the individual child with NE, that is nocturnal polyuria, bladder dysfunction, arousal disorder, and possible psycho-social confounders. While this may be the ultimate goal it is clearly not yet a practical suggestion. There are some predictors available as mentioned above regarding desmopressin and alarm, i.e.

- 1)- alarm should not be used in families living under stress or where there is parental intolerance towards the child;
- 2)- alarm should be preferred if the child has frequent NE (>3 per week) or when there is a strong suspicion of reduced bladder capacity;
- 3)- desmopressin is the treatment of choice where nocturnal polyuria has been established (which will need weighing of diapers).

But by and large our present knowledge does not allow us to identify "the right treatment" for any child with NE. When the rationale is not there we will have to do with Treatment Strategies of which a useful one is presented in Table-2. This strategy proposes to let the child and the family choose mode of therapy themselves after having received full information about the options (69). Whatever first step is taken does not matter much because sequential switching between different treatments will be the rule for children who do not respond.

How to Handle Non-responders

Even with sequential treatment over and over again some children do not get rid of their

Table 2 - Treatment strategy for nocturnal enuresis.

-
- Exclude daytime incontinence, imperative urgency and frequency (8 or more voidings per day) to establish the diagnosis of monosymptomatic NE.
 - Assess the child's motivation.
 - Explain NE to the family and emphasize that NE is not a psychogenic disorder.
 - History, simple physical examination, urinalysis. Voiding diary for ≥ 2 weeks.
 - Treat constipation and airway obstruction, if present.
 - "Sign a contract" with the family that they will endure a long treatment period and comply with instructions and regular follow-up.
 - If there is any suspicion, however slight, that the child may have daytime problems, prescribe an initial 4 weeks of urotherapy (timed voiding schedule).
 - Describe alarm treatment and desmopressin, respectively. Let the family decide which treatment they want to try first.
 - If beginning with alarm, instruct the parents that they will have to participate actively. Discontinue alarm treatment if ineffective (less than 50% reduction of the number of wet nights) after 6-8 weeks. Switch over to desmopressin.
 - If alarm is effective, continue until the child is dry 14 nights in a row.
 - If beginning with desmopressin (i.n. 10-40 μg , or p.o. 0.2-0.6 mg at bedtime). Discontinue after 12 weeks if ineffective (see above). Switch over to alarm.
 - If the number of wet nights is reduced with at least 50%, continue with desmopressin for 6-12 months, whereafter stepwise discontinuation.
 - If monotherapy with alarm and desmopressin has not been effective, try the combined treatment with desmopressin and alarm.
 - If still not successful, review the history on day symptoms and consider adding anticholinergics (oxibutynine or tolterodine) to desmopressin & alarm.
 - Do not use tricyclic antidepressants.
 - If the child is still not dry, he or she is now frustrated by the treatment failures and may need a 3-6 months "time out" before starting new therapeutic attempts.
 - Start a new sequence of treatments with desmopressin – alarm – combination – urotherapy.
 - The child who is still wetting the bed when approaching adolescence should be referred to pediatric urology for complete uro-neurological investigation.
 - Never give up your enuretic patient.
-

bedwetting. It then becomes evident that the concern felt by the 7-year-old grows into an immense burden for the enuretic adolescent ready to take the first steps into an independent life. Among adult bedwetters the majority consider the enuresis to be their most significant life problem (22) and many avoid the opposite sex and stay unmarried in fear of revealing their shameful secret. For the adolescent enuretic it is of huge importance that he is not rejected by his physician but instead is met by an op-

timistic attitude and always feels welcome to discuss other lines of action.

It is also important to remember that a few patients have an organic cause for even monosymptomatic NE. After one year or more of failed treatment attempts it is therefore imperative to refer the patient to a full uro-neurological investigation including cystometry, voiding urethrocytography and urethrocytscopy in addition to careful neurological examination.

FUTURE RESEARCH PRIORITIES

The main priority for future clinical research is to try to find ways out of the present rather gloomy situation regarding treatment. The honest view is that we lack a really efficacious therapy for this very common disorder. As always, this depends on a lack of understanding of the basic mechanisms underlying the heterogeneous condition, or rather symptom, of NE. If polyuria, poor arousal, and bladder dysfunction were the only important pathogenetic factors in NE, how comes that we do not cure all patients with NE? There is a large space available here for new and original thinking around the etiology of enuresis.

Further studies are needed on the role of urinary solute excretion and its regulation by hormones and prostaglandins, and on treatments aiming at reducing nocturnal solute excretion and, thereby, polyuria.

Hopefully, molecular genetic research will be able to open new avenues by identifying the genes at fault and their gene products. The gene product is an enzyme that will induce the synthesis of a protein that may eventually turn out to be a neural transmitter involved in the conversation between different centers in the pontine area: the micturition center, the arousal center and the noradrenergic nucleus responsible for the control of vasopressin output. Once we know a little more about how the faulty genes express themselves in the phenotype we may be able to help those enuretic children who are presently unresponsive to our treatment attempts. Our ultimate goal must be to prevent nocturnal enuresis to persist in adult age.

REFERENCES

1. Nørgard JP, van Gool JD, Hjälmås K: Standardization and definitions in lower urinary tract dysfunction in children. *Brit J Urol*, 81: Suppl 3: 1-16, 1998.
2. Nørgaard JP, Pedersen EB, Djurhuus JC: Diurnal anti-diuretic-hormone levels in enuretics. *J Urol*, 134: 1029-1031, 1985.
3. Poulton EM: Relative nocturnal polyuria as a factor in enuresis. *Lancet*, 2: 906-907, 1952.
4. Puri VN: Urinary levels of antidiuretic hormone in nocturnal enuresis. *Indian Pediatr*, 17: 675-676, 1980.
5. Yeung CK, Chiu HN, Sit FK: Bladder dysfunction in children with refractory monosymptomatic primary nocturnal enuresis. *J Urol*, 162: 1049-1054, 1999.
6. Mattsson S, Lindström S: Diuresis and voiding patterns in healthy school children. *Brit J Urol*, 76: 783-789, 1995.
7. Bloom DA, Seeley WW, Ritchley ML: Toilet habits and continence in children: an opportunity sampling in search of normal parameters. *J Urol*, 149: 1087-1090, 1993.
8. Butler RJ: Establishment of working definitions in nocturnal enuresis. *Arch Dis Child*, 66: 267-271, 1991.
9. Forsythe WI, Redmond A: Enuresis and spontaneous cure rate - study of 1129 enuretics. *Arch Dis Child*, 49: 259-263, 1973.
10. Hjälmås K: Micturition in infants and children with normal lower urinary tract. *Scand J Urol Nephrol*, 12: Suppl 37: 1-130, 1976.
11. Bakwin H: Enuresis in twins. *Arch Pediatr Adolesc Med*, 121: 222-225, 1971.
12. Eiberg H, Berendt I, Mohr J: Assignment of dominant inherited nocturnal enuresis (ENUR1) to chromosome 13q. *Nat Genet*, 10: 354-356, 1995.
13. Arnell H, Hjälmås K, Jägervall M: The genetics of primary nocturnal enuresis: inheritance and suggestion of a second major gene on chromosome 12q. *J Med Genet*, 34: 360-365, 1997.
14. von Gontard A, Eiberg H, Hollman E: Molecular Genetics of Nocturnal Enuresis: Linkage to a Locus on Chromosome 22. In: Djurhuus JC, Hjälmås K, Jørgensen TM (eds.). *Proceedings, Fourth International Workshop, International Research Center, Aarhus*. *Scand J Urol Nephrol*, 33: (Suppl 202): 76-80, 1999.
15. von Gontard A, Eiberg H, Hollman E: Molecular genetics of nocturnal enuresis: clinical and genetic heterogeneity. *Acta Paediatr*, 87: 571-578, 1997.

16. Fergusson DM, Horwood LJ: Nocturnal enuresis and behavioral problems in adolescence: a 15 year longitudinal study. *Pediatrics*, 94: 662-668, 1994.
17. Järvelin MR, Vikeväinen-Tervonen L, Moilanen I: Enuresis in seven-year-old children. *Acta Paediatr*, 77: 148-153, 1988.
18. Hellström A-L, Hanson E, Hansson S: Micturition habits and incontinence in 7-year-old Swedish school entrants. *Eur J Pediatr*, 149: 434-437, 1990.
19. Watanabe H, Kawauchi A, Kitamori T: Treatment system for nocturnal enuresis according to an original classification system. *Eur Urol*, 25: 43-50, 1994.
20. Bower WF, Moore KH, Shepherd RB: The epidemiology of childhood enuresis in Australia. *Brit J Urol*, 78: 602-606, 1996.
21. Lottmann H: Enuresis treatment in France. *Scand J Urol Nephrol*, 33 (Suppl 202): 66-69, 1999.
22. Hirasings RA, van Leerdam FJ, Bolk-Bennink L: Enuresis nocturna in adults. *Scand J Urol Nephrol*, 31: 533-536, 1997.
23. Mattsson S: Urinary incontinence and nocturia in healthy school children. *Acta Paediatr*, 83: 950-954, 1994.
24. Rittig S, Matthiesen TB, Hunsballe JM: Age-related changes in the circadian control of urine output. *Scand J Urol Nephrol*, 29 (Suppl 173): 71-74, 1995.
25. George PLC, Messerli FH, Genest J: Diurnal variation of plasma vasopressin in man. *J Clin Endocr Metab*, 41: 332-338, 1975.
26. Rittig S, Matthiesen TB, Pedersen EB: Sodium regulating hormones in enuresis. *Scand J Urol Nephrol*, 33 (Suppl 202): 45-46, 1999.
27. Rittig S, Knudsen UB, Nørgaard JP: Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol*, 256: F664-671, 1989.
28. Aikawa T, Kasahara T, Uchiyama M: Circadian variation of plasma arginine vasopressin concentration or arginin vasopressin in enuresis. *Scand J Urol Nephrol*, 33 (Suppl 202): 47-49, 1999.
29. Läckgren G, Neveus T, Stenberg A: Diurnal plasma vasopressin and urinary output in adolescents with monosymptomatic nocturnal enuresis. *Acta Paediatr*, 86: 385-390, 1997.
30. Hunsballe JM, Hansen TK, Rittig S: The efficacy of DDAVP is related to the circadian rhythm of urine output in patients with persisting nocturnal enuresis. *Clin Endocrinol*, 49: 793-801, 1998.
31. Kirk J, Rasmussen PV, Rittig S: Micturition habits and bladder capacity in normal children and in patients with desmopressin-resistant enuresis. *Scand J Urol Nephrol*, 29 (Suppl 173): 49-50, 1995.
32. Rushton H, Belman AB, Zaontz M: The influence of small bladder capacity and other predictors on the response to desmopressin in the management of monosymptomatic nocturnal enuresis. *J Urol*, 156: 651-655, 1996.
33. Eller DA, Homsy YL, Austin PF: Spot urine osmolality, age and bladder capacity as predictors of response to desmopressin in nocturnal enuresis. *Scand J Urol Nephrol*, 31(Suppl 183): 41-45, 1997.
34. Nevéus T, Hetta J, Cnattingius S: Depth of sleep and sleep habits among enuretic and incontinent children. *Acta Paediatr*, 88: 748-752, 1999.
35. Moore KH, Richmond DH, Parys BT: Sex distribution of adult idiopathic detrusor instability in relation to childhood bedwetting. *Br J Urol*, 68: 479-482, 1991.
36. Wille S: Nocturnal enuresis: sleep disturbance and behavioural patterns. *Acta Paediatr*, 83: 772-774, 1994.
37. Wolfish NM, Pivik RT, Busby KA: Elevated sleep arousal thresholds in enuretic boys: clinical implications. *Acta Paediatr*, 86: 381-384, 1997.
38. Kawauchi A, Imada N, Tanaka Y: Changes in the structure of sleep spindles and delta waves on electroencephalography in patients with nocturnal enuresis. *Br J Urol*, 81(Suppl 3): 72-75.
39. Nevéus T, Läckgren G, Stenberg A: Sleep and night-time behaviour of enuretics and non-enuretics. *Br J Urol*, 81 (Suppl 3): 67-71, 1998.
40. Hunsballe JM: Sleep studies based on electroencephalogram energy analysis. *Scand J Urol Nephrol*, 33 (Suppl 202): 28-30, 1999.

41. Watanabe H, Kawauchi A: Locus coeruleus function in enuresis. *Scand J Urol Nephrol*, 33: (Suppl 202): 14-17, 1999.
42. Ornitz EM, Russel AT, Hanna GL: Prepulse inhibition of startle and the neurobiology of primary nocturnal enuresis. *Biol Psychiatry*, 45: 1455-1466, 1999.
43. Watanabe H, Azuma Y: A proposal for classification system of enuresis based on overnight simultaneous monitoring of electroencephalography and cystometry. *Sleep*, 12: 257-264, 1989.
44. Weider DJ, Sateia MJ, West RP: Nocturnal enuresis in children with upper airway obstruction. *Otolaryngol Head Neck Surg*, 105: 427-432, 1991.
45. Loening-Baucke V: Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. *Pediatrics*, 100: 228-232, 1997.
46. Lunsing RJ, Hadders-Algra M, Touwen BC: Nocturnal enuresis and minor neurological dysfunction at 12 years: a follow-up study. *Dev Med Child Neurol*, 33: 439-445, 1993.
47. Robson WLM, Jackson HP, Blackhurst D: Enuresis in children with attention deficit hyperactivity disorder. *SMJ*, 90: 503-505, 1997.
48. Forbes FC: Children with enuresis. Nowadays, a strong suspicion of sexual abuse would prompt full investigation. *BMJ*, 316: 777, 1998.
49. Friman PC, Handwerk ML, Swearer SM: Do children with primary nocturnal enuresis have clinically significant behavior problems? *Arch Pediatr Adolesc Med*, 152: 537-539, 1998.
50. Schulpen TWJ: The burden of nocturnal enuresis. *Acta Pædiatr*, 86: 923-926, 1997.
51. Hägglöf B, Andrén O, Bergström E et al: Self-esteem before and after treatment in children with nocturnal enuresis and urinary incontinence. *Scand J Urol Nephrol*, 31 (Suppl 183): 79-82, 1997.
52. Butler RJ, Brewin CR, Forsythe WI: Maternal attributions and tolerance for nocturnal enuresis. *Behaviour Res Ther*, 24: 307-312, 1986.
53. Houts AC, Berman JS, Abramson H: Effectiveness of psychological and pharmacological treatments for nocturnal enuresis. *J Consult Clin Psychol*, 62: 737-745, 1994.
54. Bengtsson B, Bengtsson M: Childhood Enuretics in Adult Age: A Long-term, Retrospective Follow up of 88 Children. In Nørgaard JP, Djurhuus JC, Hjälmsås K (eds.). *Proceedings of the Third International Children's Continence Symposium*. Royal Tunbridge Wells, Wells Medical, pp. 61-63, 1996.
55. Butler RJ: Annotation – night wetting in children: psychological aspects. *J Child Psychol Psychiat*, 39: 453-463, 1998.
56. Oredsson AF, Jørgensen TM: Changes in nocturnal bladder capacity during treatment with the bell and pad for monosymptomatic nocturnal enuresis. *J Urol*, 160: 166-169, 1998.
57. Petrican P, Sawan MA: Design of a miniaturized ultrasonic bladder monitor and subsequent evaluation on 41 enuretic patients. *IEEE Trans Rehabil Eng*, 6: 66-74, 1998.
58. Terho P: Desmopressin in nocturnal enuresis. *J Urol*, 145: 818-820, 1991.
59. Hjälmsås K, Kruse S, Hellström A-L: Long term desmopressin treatment of children with primary monosymptomatic nocturnal enuresis: an open multicentre study. *Brit J Urol*, 82: 704-709, 1998.
60. Rittig S, Schaumburg H, Schmidt F: Long-term home studies of water balance in patients with nocturnal enuresis. *Scand J Urol Nephrol*, 31: Suppl 183: 25-26, 1997.
61. Miller K, Klauber GT: Desmopressin acetate in children with severe primary nocturnal enuresis. *Clin Ther*, 12: 357-366, 1990.
62. Robson WLM, Nørgaard JP, Leung AKC. Hyponatremia in patients with nocturnal enuresis treated with DDAVP. *Eur J Pediatr*, 155: 959-962, 1996.
63. Bradbury MG, Meadow SR: Combined treatment with enuresis alarm and desmopressin for nocturnal enuresis. *Acta Pædiatr*, 84: 1014-1018, 1995.
64. Hjälmsås K, Hellström A-L, Mogren K, Läckgren G, Stenberg A: The overactive bladder in children: a potential future indication for tolterodine. *BJU Int*, 87: 569-574, 2001.

65. Geller B, Reising D, Leonard HL: Critical review of tricyclic antidepressant use in children and adolescents. *J Am Acad Child Adolesc Psychiatry*, 38: 513-516, 1999.
66. Von Gontard A, Lehmkuhl G: Drug therapy of enuresis. *Z Kinder Jugendpsychiatr*, 24: 18-33, 1996.
67. Al-Waili NS: Diclofenac sodium in the treatment of primary nocturnal enuresis: double-blind cross-over study. *Clin Exp Pharmacol Physiol*, 13: 139-142, 1986.
68. Kruse S, Hellström A-L, Hjälhmås K: Daytime bladder dysfunction in therapy-resistant nocturnal enuresis. A pilot study in urotherapy. *Scand J Urol Nephrol*, 33: 49-52, 1999.
69. Monda JM, Husman DA: Primary nocturnal enuresis: a comparison among observation, imipramine, desmopressin acetate and bedwetting alarm systems. *J Urol*, 154: 745-748, 1995.

Received: September 17, 2001

Accepted: October 12, 2001

Correspondence address:

Dr. Kelm Hjälhmås
 Berzeliigatan 26
 SE-412 53 Göteborg, Sweden
 Fax: ++ (46) (31) 778-9468
 E-mail: kelm@kelm.se