Enuresis – Background and Treatment

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Nocturnal urinary continence is dependent on 3 factors: 1) nocturnal urine production, 2) nocturnal bladder function and 3) sleep and arousal mechanisms. Any child will suffer from nocturnal enuresis if more urine is produced than can be contained in the bladder or if the detrusor is hyperactive, provided that he or she is not awakened by the imminent bladder contraction.

Urine production is regulated by fluid intake and several interrelated renal, hormonal and neural factors, foremost of which are vasopressin, renin, angiotensin and the sympathetic nervous system. Detrusor function is governed by the autonomic nervous system which under ideal conditions is under central nervous control. Arousal from sleep is dependent on the reticular activating system, a diffuse neural network that translates sensory input into arousal stimuli via brain stem noradrenergic neurons.

Disturbances in nocturnal urine production, bladder function and arousal mechanisms have all been firmly implicated as pathogenetic factors in nocturnal enuresis. The group of enuretic children are, however, pathogenetically heterogeneous, and two main types can be discerned: 1) Diuresis-dependent enuresis – these children void because of excessive nocturnal urine production and impaired arousal mechanisms. 2) Detrusor-dependent enuresis – these children void because of nocturnal detrusor hyperactivity and impaired arousal mechanisms. The main clinical difference between the two groups is that desmopressin is usually effective in the former but not in the latter.

There are two first-line therapies in nocturnal enuresis: the enuresis alarm and desmopressin medication. Promising second-line treatments include anticholinergic drugs, urotherapy and treatment of occult constipation.

Key words: Enuresis, Urine production, Detrusor hyperactivity, Arousal, Desmopressin.

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1 INTRODUCTION

The focus of this text is the pathogenesis and treatment of bedwetting. Although this is an extremely common disorder, having a large psychological impact on those affected and posing an economic burden on their families, treatment success is still unimpressive. One of the main reasons for this is that research regarding both the causes and treatment of enuresis has historically been almost exclusively psychiatrically focused, causing old misconceptions to linger and new ones to arise. Luckily, this state of affairs has seen some change for the better during the last decades as endocrinological and neurological factors, as well as bladder function, have been shown to be pathogenically important, and treatment modalities with proven efficacy have been developed. Furthermore, it has been shown that psychological problems in enuretic children usually are the consequences, not the causes, of the bedwetting.

Still, many doctors confronted with enuretic children persist in either telling the families that bedwetting is trivial and should not be treated, or implicating behavioural, social or psychological causes as the root of the problem. The truth is that enuresis is only trivial if the child and the family regard it as trivial, otherwise it should certainly be treated. More information about the results of modern enuresis research is obviously needed.

The aim of this text is twofold; first: to summarize the present state of enuresis research, and second: to draw conclusions and hypothesize from what is known and present the authors' views on the aetiology, pathogenesis and treatment of enuresis. The intention is that the book should serve the double purpose of introducing the reader to the field of enuresis research while providing practical guidance in the evaluation and treatment of bedwetting children.

The text is intended primarily for paediatricians, urologists, urotherapists, child psychiatrists and general practitioners, although medical students and other professionals with a special interest in enuresis might find use for it as well.

Established facts, common beliefs and personal hypotheses will all be presented and our aim is to clearly distinguish between them.

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When trying to explain why some children wet their beds, we first ask: why not? The fact that many children voluntarily postpone micturition for ten hours or more every night, although they often find it hard to wait for a few minutes during daytime, would be surprising if we weren't used to it. Thus, before being able to formulate hypotheses about the pathogenesis of enuresis, we need to understand why most of us do *not* wet our beds at night.

The ability to have dry nights presupposes 1) that nocturnal urine production does not exceed bladder capacity and 2) that the bladder does not contract when not told to do so *or* 3) that the sleeper is awakened by bladder filling or detrusor contractions. Thus, urine production, bladder function (and volume) and sleep and arousal mechanisms are all crucial for the attainment of nocturnal dryness.

Not surprisingly, the most influential current theories of the pathogenesis of enuresis involve these three factors. It has been claimed that bedwetting children wet their beds because of 1) nocturnal polyuria, 2) nocturnal detrusor hyperactivity and 3) "deep" sleep. It is our belief that all these explanations contain parts of the truth and that much of the controversy in the field of enuresis research stems from not taking this pathogenetical heterogeneity into account. If the large group of bedwetting children can be subdivided into clinically relevant subgroups, the treatment can be individualized and more children can be helped to achieve nocturnal dryness.

For reasons mentioned above, we will start by discussing the mechanisms of nocturnal dryness in chapters 2, 3 and 4. After that, central terms in the field of enuresis research will be defined and a short epidemiological background will be provided in chapter 5, and the genetics of enuresis is reviewed in chapter 6. The main hypotheses of the pathogenesis of enuresis are then presented (chapters 7–10), followed by an attempt to reconcile the different theories and to provide a subdivision into clinically relevant subgroups in chapter 11. An overview of treatment options is provided in chapter 12, after which a strategy for the evaluation and treatment of different groups of enuretic children is presented in chapter 13. Finally, in chapter 14, hints of a possible common disturbance responsible for the different kinds of bedwetting are presented.

2 REGULATION OF URINE PRODUCTION

2.1 General considerations

The first step in urine production is the formation of primary urine by ultrafiltration in the glomeruli. This fluid is isoosmolar to plasma. Most of the water and sodium chloride is subsequently reabsorbed in the proximal or distal tubules and the collecting ducts. The amount of water and solute that is reabsorbed is determined by the glomerular filtration rate (GFR) and by several hormones and local mediators acting on different parts of the nephron.

Extracellular volume is regulated through changes in sodium excretion by the kidneys, which are brought about by several interrelated humoral, neural and local renal mechanisms that control solute diuresis. This influences urine production to a great extent. Foremost among the mechanisms of solute diuresis is the tubuloglomerular feedback system (see below), which is regulated by several endocrine and nonendocrine factors, among which the renin-angiotensin-aldosterone system, atrial natriuretic peptide, the sympathetic nervous system and the local production of prostaglandins by the kidneys deserve special mention.

Plasma osmolality is regulated through thirst and the actions of the hormone vasopressin. Through these mechanisms, deviations from isoosmolality result in changes in water intake or water diuresis. This, obviously, influences urine production to an equally great extent.

The factors regulating water and solute diuresis are summarized in a highly simplified way in Fig. 1.

Urine production varies greatly both inter- and intraindividually (1) among normal children. It usually varies during the day as well, with a night-time decrease compared with daytime urine production.

Since it is obvious that fluid intake influences urine output, thirst mechanisms will first be reviewed in this chapter. The proximal nephron and the factors regulating solute diuresis will then be considered. Water diuresis and vasopressin, the central osmoregulatory hormone, will be discussed in some detail in the last part of the chapter. A lengthy elaboration on this topic is warranted since vasopressin has – rightly or wrongly

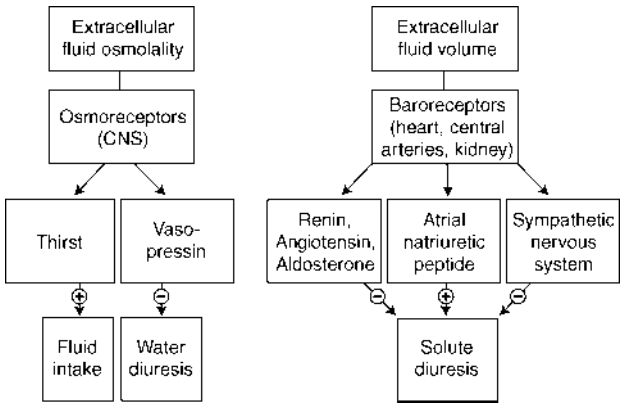

Fig. 1. Central factors governing urine production in response to changes in plasma osmolality or extracellular fluid volume.

– been assigned a role in the pathogenesis of enuresis, and the synthetic vasopressin analogue desmopressin is successfully used in enuresis treatment.

2.2 Fluid intake and thirst mechanisms

Obviously, if you drink a lot you need to pee a lot. It would be considered normal for a school child to drink between 500 and 1 500 ml per day. However, fluid intake varies greatly from day to day, and is often governed by habit, social factors and personal preferences more than by thirst as such. Further, the intake of both water and solutes usually exceeds requirements, and the regulation of renal losses has a much greater physiological importance than the control of intake. Generally speaking, intake and output are proportional to each other, but the relationship becomes less clear when looking at individual days (2). These are circumstances that should be kept in mind when discussing thirst as a determinant of urine output.

The sensation of thirst is perceived when plasma osmolality exceeds a threshold value (usually somewhere between 280 and 290 mOsm/kg), and the intensity of thirst rises in a linear manner as osmolality increases. Both the threshold value and the slope of the thirst-osmolality curve vary between individuals, but are fairly stable when repeated measurements are performed in the same person (3).

The CNS receptors that constitute the link between hyperosmolality and thirst sensation are located in the organum vasculosum of the lamina terminalis – one of the so-called circumventricular organs that are located outside the blood brain-barrier – and in the neighbouring medial preoptic area of the hypothalamus (4, 5). These structures are situated at the ventral surface of the third ventricle (Fig. 2). Locally released angiotensin II is reported to be the neurotransmitter involved in the perception of thirst (6).

2.3 Solute diuresis

Since extracellular fluid volume is determined by body salt content, regulation of urine production cannot be explained without discussing sodium homeostasis. At least three main effector systems are worth considering in this context: the renin-angiotensin-aldosterone system, the atrial natriuretic peptide, and the sympathetic nervous system. It should be noted, however, that: 1) these factors act mainly by strengthening or inhibiting the coupling between tubular solute flow and GFR, that is, by adjusting tubuloglomerular feedback (see below), 2) all these factors influence each other in a complex and incompletely understood way, and 3) renal prostaglandins and other local mediators are deeply involved as crucial intermediate steps and regulators of the effects of the other factors.

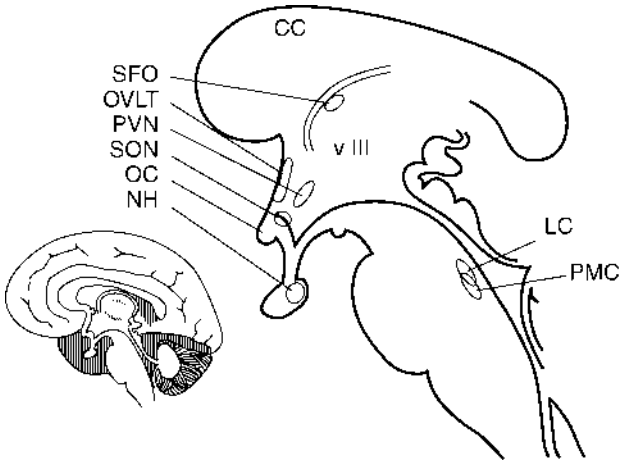

Fig. 2. Central nervous structures involved in thirst sensation and osmoregulation. Sagittal section in the median line. For orientation, see inset. CC = Corpus callosum, PMC = pontine micturition centre, LC = locus coeruleus, v III = third ventricle, PVN = paraventricular nucleus, SON = supraoptic nucleus, OVLT, organum vasculosum of the lamina terminalis, SFO = subfornical organ, NH = neurohypophysis, OC = optic chiasm.

Tubuloglomerular feedback. Central in the regulation of extracellular volume is the tubuloglomerular feedback (TGF) mechanism, that is, the ability of the kidney to adjust glomerular filtration rate (GFR) in response to changes in solute content in the distal tubule (7). This is brought about via the macula densa (MD), a highly specialized area of the distal tubular epithelium that is in close contact with the afferent and efferent arterioles of the glomerulus belonging to the same nephron as the MD cells themselves. The MD responds to changes in tubular sodium chloride concentration by adjusting: 1) the diameter of the efferent arteriole – and, thereby, GFR, and 2) renin secretion (8). The first of these effects – the TGF proper – is active on a minute-by-minute basis and has a stabilizing effect on GFR (7). As an illustration; a rapid increase in glomerular filtration will increase tubular flow and, as a consequence, decrease proximal tubular sodium reabsorption. This will result in an increased sodium chloride concentration at the MD, which, through TGF, will cause vasoconstriction of the efferent glomerular arteriole and thus a reflex decrease in GFR. Renin secretion, on the other hand, is adjusted much more slowly (over hours or days) and is important for regulating electrolyte excretion during states of altered body sodium content. The processes by which the MD accomplishes the two effects mentioned above are not fully understood, but the local production of adenosine, prostanoids and nitrogen monoxide appear to be crucial intermediate steps (7).

The purpose of TGF is to ensure that transitory

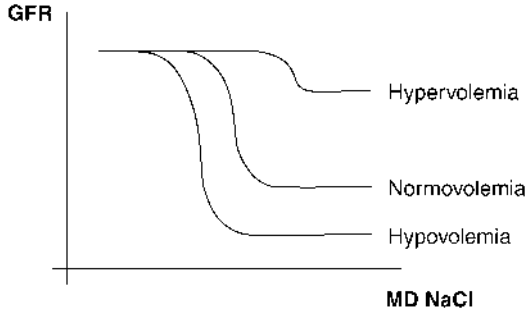

Fig. 3. Illustration of the tubuloglomerular feedback mechanism, and its adjustment by influences such as changes in extracellular fluid volume. GFR = glomerular filtration rate; MD NaCl = sodium chloride concentration at the macula densa. In the hypovolemic state, the set-point and the gain of the tubuloglomerular feedback mechanisms are adjusted so that a small increase in tubular flow (via an increased MD NaCl) will result in a large decrease of filtration, thus preserving body fluid volume. On the other hand, during hypervolemia even large increases of tubular flow will not greatly reduce GFR.

perturbations of GFR, such as those brought about by fluctuations in arterial pressure, do not result in changes in solute excretion (7). It is, however, important that the TGF mechanisms can be adjusted or over-ridden in situations of altered body solute content, such as dehydration or hypervolemia (9). Thus, the factors governing solute diuresis (described below) act chiefly as resetters or adjusters of TGF (10), see Fig. 3.

The actions of TGF and the systems regulating its sensitivity are difficult to disentangle from each other, but they all control natriuresis and, thus, urine production. The importance of these mechanisms is underlined by the fact that minimum and maximum urine production are determined not by the water requirements but by the need to retain or excrete electrolytes. The time factor is also important to keep in mind; while a large extra intake of water will be lost in the urine after a few hours, the same volume of saline will not be excreted until perhaps a day has passed.

The renin-angiotensin-aldosterone system (RAAS). The RAAS plays a central role in protecting the organism against sodium and volume loss. It is also the principal regulator of TGF (10, 11).

Renin is a hormone produced by the juxtaglomerular cells of the afferent glomerular arteriole in the kidney. There are three principal stimuli for renin release: 1) decreased blood pressure in the afferent arteriole (12), 2) decreased sodium chloride delivery to the MD cells of the distal tubule (as explained above) (8, 13), and 3) sympathetic stimulation through the renal nerve (13–16). Additional influences on renin secretion are provided by vasopressin (17), atrial natriuretic peptide (ANP) (18) and prostaglandins (19, 20). The central effect of circulating renin is the cleavage of inactive angiotensinogen to angiotensin I, which is then further modified by angiotensin converting enzyme to the active hormone angiotensin II. Thus, the long-term goal of TGF (as opposed to short-term adjustments of GFR) can be said to be the provision, via renin, of an angiotensin II level that is adequate for body salt requirements (7).

Angiotensin II – the principal effector of the RAAS – has mainly hypertensive and sodium-retaining effects. The latter accomplished both by direct effects on the nephron and by the stimulation of aldosterone release (17). The direct renal effects are exerted both by increasing sodium reuptake in the proximal tubule (21, 22), and by adjusting TGF at the level of the MD (11), and these effects are considered more important for fluid homeostasis than those that are mediated by aldosterone release (23–26). Furthermore, angiotensin II has been shown to have functions in the central nervous system, such as mediating the sensation of thirst (see above) and salt appetite (27, 28), stimulating the release of various hormones (including vasopressin) (29) and increasing the activity of the sympathetic nervous system (30). The sympathetic tone is also stimulated through direct effects on peripheral adrenergic synapses (31, 32). Angiotensin II has also been implicated in the regulation of renal prostaglandin production (33, 34).

Aldosterone is released by the adrenal cortex in response to circulating angiotensin II (17) or to increased potassium levels (35, 36). Its main function is to retain sodium and excrete potassium (37, 38). These effects are exerted mostly at the collecting ducts (39).

Atrial natriuretic peptide (ANP). ANP is released by the cardiac atria in response to atrial stretch (40, 41). ANP has diuretic and natriuretic effects and plays a crucial role in the regulation of interstitial fluid volume (42). The hormone has been described as a necessary but not alone sufficient factor for natriuresis (43), and it exerts its effects partly through increased glomerular filtration rate (18, 44), inhibition of tubular sodium reabsorption (45) (46) and antagonism of renin (18, 47), aldosterone (48, 49) and vasopressin (43, 50–54). It has been suggested that the diuretic (as opposed to natriuretic) effects of ANP are largely determined by its inhibition of vasopressin effects in the renal collecting ducts (55).

Analogous to the case of vasopressin (see below) a circadian rhythm has been sought and found for the plasma concentration of ANP in man. The results have been conflicting, however (56–58). Interestingly, ANP has been found not to give the same degree of diuresis at night as during the day (59). ANP receptors are found in the CNS as well, mainly in the circumven-

tricular organs, the hypothalamus and in cardiovascular pontine centres (60).

Neural factors. The efferent renal innervation comes exclusively from the sympathetic nervous system and from dopaminergic fibres. Postganglionic sympathetic axons from the splanchnic nerves (61) reach all parts of the nephron through the renal nerves (62–64). Renal sympathetic tone has been shown to be stimulated by angiotensin II (32, 65) and inhibited by vasopressin (66), prostaglandins (67) and cardiac atrial stretch (68).

The overall consequences of renal nerve stimulation are antinatriuresis and antidiuresis (69–73), whereas renal denervation has opposite effects (74). Possibly, the sympathetic nervous system acts mainly by influencing other regulators of fluid and electrolyte balance, such as renin (13, 14, 72, 75, 76), vasopressin (77), prostaglandins (78, 79) and ANP (80). It appears that sympathetic stimulation is most important for fluid homeostasis in situations of hypovolemia or salt depletion (81).

Prostaglandins. The vasodilatory prostaglandins PGE_2 and PGI_2 (prostacyklin) are produced by all parts of the nephron (82). They are autacoids and, as such, exert most of their effects locally, at their site of production. This makes them ideally suited to act as tissue-or organ-specific modulators or mediators of the hemodynamic effects of other substances. For instance: the stimulation of renin release by increased glomerular capillary blood pressure and by decreased electrolyte flow in the distal tubule are both probably mediated by local prostaglandin production (83, 84).

Although the role played by prostaglandins in protecting the renal microcirculation in response to stress (85), sympathetic stimulation (86) or vasoactive hormones such as angiotensin II (33) (87) and vasopressin (88) is established, their function in sodium and fluid homeostasis is less clear. As mentioned above, prostaglandin production at the MD is probably an important intermediate step in the stimulation of renin release during states of sodium depletion (7). The possible effects of prostaglandins on water diuresis are reported to be secondary to vasopressin antagonism at the collecting ducts (89, 90). Prostaglandins are also thought to be involved in the reflex natriuresis that follows distension of the renal pelvis (70).

Other factors, circadian influence. Bradykinin and the kallikrein-kinin cascade has natriuretic effects through increased GFR (91) and decreased tubular sodium reabsorption (92). These effects are probably mediated by local prostaglandin release (93).

The renal production of nitrogen monoxide has lately been shown to be an important intermediate step in TGF (94).

Stimulation of the chemoreceptors of the carotid artery, such as in hypoxia, has been shown to cause natriuresis and diuresis (95). This might explain the nocturnal polyuria observed among patients with sleep apnoeas (96).

Finally, a circadian rhythmicity of urine production is usually detected, with a decrease during the night independent of body position, fluid intake and sleep (97). Both glomerular and tubular mechanisms are involved in this rhythmicity (97).

2.4 Vasopressin and water diuresis

The neurohypophyseal hormone vasopressin, or arginine-vasopressin, is identical to the antidiuretic hormone (ADH), and is the main endocrine regulator of urine production in man. Although the hormone has hypertensive effects as well, these are of minor importance at physiological concentrations (98).

Vasopressin – production and release. Vasopressin is a peptide consisting of 9 amino acids (99) encoded by a gene located on the short arm of chromosome 20 (100). The translation product of the gene is a long precursor molecule including vasopressin and a so-called neurophysine (101). The hormone vasopressin is produced by the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus, but rendered biologically active by cleavage of the precursor molecule during axonal transport in the hypophyseal stalk (102) (see Fig. 2). Vasopressin storage and release is a function of the neurohypophysis.

Vasopressin effects. The central role of vasopressin is to diminish water diuresis through increased water permeability in the distal nephron. The hormone also has neurotransmitter functions in the central nervous system and peripheral hypertensive effects.

Most vasopressin effects have been reported to be mediated through one of two receptors: the V1 and the V2 receptor (103). The osmoregulatory renal effects are exerted mainly via the V2 receptor, a 40 kD membrane-spanning protein located in the collecting ducts (104). Maximal antidiuresis is accomplished if 2.5% or more of the renal V2 receptor sites are occupied (105).

On a cellular level, the activation of V2 receptors leads to the synthesis of cyclic adenosine monophosphate (cAMP), which, in turn, results in the translocation of intracellular aquaporin type 2 to the apical cell membrane (106, 107). Aquaporin type 2 belongs to a group of water channel-forming proteins and is the molecule directly responsible for the vasopressin-induced water permeability in the collecting duct

(108). The net result of this process is that water is reabsorbed from the collecting ducts in the hyperosmolar environment of the renal medulla, and the urine becomes more concentrated (109).

Renal V1 receptors may also play a role in osmoregulation, via glomerular effects (110) or prostaglandin production in the medulla (111). The situation is, however, confused by the recent discovery that there there are two kinds of V1 receptors, V1a and V1b, with different distributions and binding properties (112, 113).

Vasopressin functions in the central nervous system have also aroused some interest. When discussing this it must first be noted that vasopressin does not cross the blood brain-barrier (114) and that peripheral and central release of vasopressin are independent of each other (115), although hyperosmolality is reported to stimulate both (116).

Vasopressin has neurotransmitter functions, exerting its CNS effects mainly via the V1 receptors (116) (although other types of receptors may be involved as well (117)). Vasopressinergic fibres innervate most parts of the neuraxis, especially limbic and hypothalamic structures (115). Centrally released vasopressin has been assigned possible roles in memory processes (118), concentration (119, 120), avoidance behaviour (121) sleep regulation (122) and arousal mechanisms (123). Interestingly, vasopressin periodically synthesized by the main "internal pace-maker" of the brain – the suprachiasmatic nucleus – and vasopressin concentrations in the cerebrospinal fluid both exhibit a synchronized circadian rhythmicity with a day-time peak and a nocturnal trough (124), the significance of which is unclear.

Osmotic stimuli for release. The main stimulus for peripheral vasopressin release is hyperosmolality. The relationship between plasma osmolality and vasopressin secretion is quite similar to that between plasma osmolality and thirst perception (125, 126). Thus, below a threshold level of plasma osmolality vasopressin release is minimal, but for higher osmolality values the relationship is roughly linear. Both threshold and slope of the curve vary interindividually but are fairly stable over time in the same subject (3, 127). This is genetically influenced (128). In a normal population, the threshold osmolality for vasopressin release is between 282 and 289 mOsm/kg and the slope is 0.2–0.69 pmol per mOsm/kg (129). Maximum antidiuresis is obtained at a vasopressin concentration above 5 pg/ml, which is usually reached at a plasma osmolality above 293 mOsm/kg.

The parallel between vasopressin and thirst is neuroanatomically evident as well. The osmoreceptors that initiate vasopressin release are also located in the organum vasculosum of the lamina terminalis, outside the blood brain-barrier (130) (see Fig. 2).

Table 1. *Factors influencing vasopressin release*

Vasopressin release stimulators	Vasopressin release inhibitors
Important physiological influences	*Important physiological influences*
Hyperosmolality	Hypoosmolality
Hypovolemia	Hypervolemia
Nausea	
Possible/minor influences	*Possible/minor influences*
Upright body position	Atrial natriuretic peptide
Bladder distention?	Drinking?
Parasympathetic suppression?	
Sleep?	
Pharmacological substances	*Pharmacological substances*
Lithium	Ethanol, carbamazepine, opioids
	Clonidine

Other factors regulating vasopressin release. Although osmolality is the main regulator of vasopressin release, other factors are known to influence the hormone, such as blood volume, orthostatic factors, nausea and certain drugs. Still other factors may be operative under certain conditions (see Table 1).

Hypovolemia has been shown to increase vasopressin levels by increasing the osmotic sensitivity of the vasopressin-releasing neuron circuit (i.e. moving the vasopressin-osmolality curve to the left), and hypervolemia acts in the opposite way (131). By the same mechanisms, the upright body position has been shown to increase vasopressin concentrations (131, 132). These changes are brought about through activation of cardiac and arterial baroreceptors (133). A strong stimulus for vasopressin release is provided by nausea, regardless of cause (127, 134). The mechanism behind this is unclear.

The finding that plasma levels of vasopressin drop almost instantaneously when drinking (135), before plasma osmolality has decreased, has led to the suggestion that drinking *per se* exerts an inhibiting effect on vasopressin release, possibly mediated by oropharyngeal receptors (136, 137).

ANP has also been reported to inhibit vasopressin release (50, 55, 138), although the physiological importance of this has been debated (139–141).

Some drugs are known to influence vasopressin levels: lithium increases osmotically induced vasopressin release (142, 143), while ethanol (144), carbamazepine (145), opioids (146) and clonidine (147) have the opposite effect.

Interestingly, bladder distention has been proposed as a stimulus for vasopressin release (148), although contradictory findings have been reported (149).

The autonomic nervous system has also been assigned a regulatory role, since studies have indicated that suppression of parasympathetic tone increases vasopressin secretion (150, 151) and noradrenergic impulses from the brainstem have a similar effect (126, 152). Central norepinephrine may be important for both osmotic and hypovolemic stimulation of vasopressin release (153). Finally, sleep has been described as a factor stimulating vasopressin release (154–156).

Vasopressin is, like other hypophyseal hormones, released in a pulsatile manner (157). A pulse length of 6–24 minutes has been reported (158). A circadian rhythmicity, with a nocturnal peak and a diurnal trough, has also been demonstrated (159), although conflicting results regarding non-enuretic adults have been published (160). Furthermore, vasopressin levels are probably influenced by age. According to Rascher *et al*. the vasopressin levels are elevated at birth and decrease gradually until adult levels are reached at the age of one year (134). The slope of the vasopressin-osmolality curve (i.e. the osmosensitivity of the hormone) is reported to double from early adulthood to middle age (161).

Vasopressin analogues. Although several synthetic analogues of vasopressin have been produced, the only one that has proven clinically useful is desamino-8-*D*-arginine vasopressin, or desmopressin (162). This drug is a V2 receptor agonist without any cardiovascular effects (163). Interestingly, it has been demonstrated to have V1b-agonistic properties as well (164). Desmopressin has long been used with great success as a treatment for central diabetes insipidus (165), as a test of renal concentrating capacity (166), and in the management of various coagulation disorders (167), although the initial reports of beneficial effects on memory and learning (168, 169) have so far not proven clinically useful. As will be discussed in greater detail below, a definite role for desmopressin has been found in the treatment of nocturnal enuresis.

It should be clear by now that the regulation of solute diuresis (that is, the regulation of sodium homeostasis), is more complex than the regulation of water diuresis (that is, the regulation of plasma osmolality). While hypoosmolar polyuria can usually be explained by looking into the actions of vasopressin and thirst, solute polyuria might involve several interrelated humoral, neural and local renal mechanisms.

3 BLADDER FUNCTION

The role of the bladder is to store and release urine in a physiologically and socially acceptable way. Ideally, the detrusor should be completely relaxed during storage, bladder size should allow for several hours' postponement of micturition, and voiding should be characterised by coordinated detrusor contraction and sphincter relaxation resulting in a complete emptying of the bladder (170).

In this chapter, after describing the urodynamics and neurology of the normal, continent bladder, the maturation of bladder function during growth, and detrusor hyperactivity, will be discussed.

3.1 Normal bladder function

Definitions and normal values. A few words about definitions are appropriate at this stage since urodynamic terminology is often somewhat confusing, especially when measurements of bladder volumes are concerned. *Functional bladder capacity* (FBC) denotes spontaneous bladder volume as measured from a home voiding chart, *maximal FBC* means voided volume when micturition has been maximally postponed voluntarily, and *cystometric bladder capacity* (CBC) is the maximum bladder volume as measured by cystometry. These definitions were chosen to conform with the recommendations of the International Children's Continence Society (171). The disturbing lack of a good definition of FBC stems from the fact that children void when it suits them and not necessarily because the bladder is "full". Asking the child to postpone mixturition maximally will yield highly variable volumes, since the sensation of bladder filling is very subjective. Furthermore, the first morning voiding (after a dry night) denotes *nocturnal* bladder capacity, which differs from daytime FBC. Consequently, the best way to determinine maximal FBC would probably be to measure the largest single voiding, excluding first morning micturition, during several days of home recording.

Normal CBC in children can be approximated with the formula CBC = 30+ (30× age in years) ml (170).

Bladder stability means that the detrusor is relaxed during the storage phase, that is, it contracts only as part of a micturition reflex involving coordinated relaxation of the sphincter and the expulsion of urine.

Innervation of the lower urinary tract. All three major neural systems – somatic, sympathetic and parasympathetic – converge to the lower urinary tract. We have, in fact, an organ system with largely autonomous innervation which is under complete cortical control. Thus, viscero-somatic integration is essential for normal function.

The neural input to the bladder is predominantly cholinergic (172). These fibres inhibit urethral smooth muscle and initiate detrusor contractions during mic-

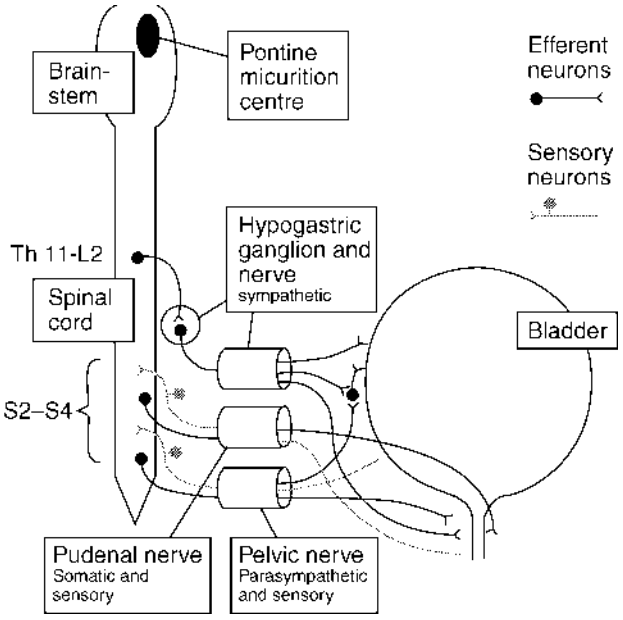

Fig. 4. Innervation of the lower urinary tract. Note that signal pathways within the central nervous system are omitted in this highly simplified illustration.

turition (173), and constitute part of a reflex arch involving the pelvic nerves, the pontine micturition centre and the sacral branch of the parasympathetic nervous system (174). The parasympathetic input to the bladder is quiescent during urine storage.

The thoracolumbar sympathetic branch of the autonomic nervous system reaches the bladder via the hypogastric and pelvic plexa and mediates sphincter contraction and detrusor relaxation during urine storage (175). Sympathetic fibres also directly inhibit parasympathetic excitatory input to the bladder (176). Somatic efferents and afferents of the urethra and bladder travel through the pudendal nerve (173, 177).

Thus, micturition is a mainly parasympathetic phenomenon, while the sympathetic nervous system facilitates urine storage during bladder filling. The innervation of the lower urinary tract is schematically outlined in Fig. 4.

CNS centres for bladder control. The spinal centres for bladder control are under constant influence from cell groups in the brainstem. The pontine micturition centre was first found by Barrington in the early twenties (178), and has since then been described in closer detail (179, 180). This centre consists of neuron groups in the rostral pons, within or in the immediate surroundings of the locus coeruleus, that have been shown to elicit or inhibit detrusor contractions when stimulated (181, 182). The neurons of the pontine micturition centre increase their firing rate in response to both bladder distension and detrusor contractions (180).

The influence of higher nervous centres on bladder function is a complicated and incompletely understood matter, and virtually all parts of the neuraxis have been implicated (for reviews of this subject, see (183) and (184)).

The storage phase. During storage of urine the smooth muscle of the internal sphincter is tonically contracted through alfa-adrenergic stimulation in the urethra (185), to prevent leakage of urine. At the same time a reflex arch, involving the pelvic nerve and the sympathetic fibres of the hypogastric and pelvic plexa, tonically inhibits excitatory input to the detrusor muscle (186) via beta-adrenergic receptors in the corpus and fundus of the bladder. The spinal motoneurons innervating the striated muscle of the external sphincter are also tonically active during filling.

Micturition. During voluntary micturition, input from higher brain centres inhibits the spinal storage reflexes and activates the parasympathetic excitatory outflow to the bladder. The signals for initiating voluntary micturition are transmitted from the pontine micturition centre to the sacral motoneurons innervating the external sphincter (173, 187), and to the parasympathetic neurons innervating the detrusor (177). On the bladder level, voiding starts with relaxation of the sphincter and pelvic floor, immediately followed by reflex detrusor contraction (188–191). The presence of urine in the urethra then facilitates continuing detrusor contraction and sphincter relaxation, so that emptying will be complete (177, 192). Glutamate is the major excitatory neurotransmitter involved in the initiation of micturition by the CNS (193).

Conscious interruption of micturition is accomplished in the following way: Signals originating from the motor cortex, via the pudendal nerve, elicit the forceful contraction of the striated muscle of the external sphincter and the pelvic floor, and this contraction initiates a spinal reflex that inhibits further bladder contractile activity. The voluntary inhibition of involuntary detrusor contractions is a similar process.

3.2 Maturational aspects of bladder function

Several lines of evidence suggest that the micturition reflex is under higher central nervous system control already at the foetal and neonatal stage (194). For instance, intrauterine micturition seems to occur almost exclusively while the foetus is awake, and is not randomly distributed over the behavioural states (195, 196). It has been observed that micturition can be elicited by acoustic stimulation (197). Furthermore,

the central neural pathways controlling micturition in the adult rat can be detected in the newborn animal, before the micturition reflex has become functional (198). Animal data even suggest that the adult micturition reflex is functional, but tonically inhibited, at birth (198). The development of functional voiding and storage reflexes involves the selective suppression or stimulation of the proliferation of the synapses of different pathways in the evolving nervous system (199).

Incomplete co-ordination of the detrusor and sphincter, resulting in residual urine, is not uncommon in the infant (200), and in well-designed studies it has been shown that – in contrast to common belief – the infantile bladder tends to be stable and that the infant usually only voids while awake (201).

Bladder capacity increases by approximately 400% during the first 3–4 years (202). The first step towards social continence is usually taken during the second or third year, when the child becomes somewhat aware of bladder distension. By this time voiding is usually fully co-ordinated and residual urine has disappeared. The final steps are taken when, around the age of four or five, the child has learned to postpone micturition and is able to initiate micturition even when the bladder is not full. For a review on this subject, see (170).

Micturition habits are highly variable among normal, dry children. Studies involving home measurements have shown voiding frequencies between 2 and 8 times daily (2, 203), with a peak around 5–6 (204, 205) and no gender differences (203, 205). Children with urgency symptoms (see below) go to the toilet more often than other children (203). The prevalence of nocturia in the normal night-dry population is incompletely known. In an Australian study approximately 80% of 5–12 year-olds ($n = 2292$) "occasionally" needed to wake up and go to the toilet at night (206), while our survey of 1 413 children of approximately the same age group indicated that 38% had nocturia at least every month (207). When asked to complete a 24 hour micturition diary approximately 6% of 1127 children (age 7 to 8 years) reported nocturia (204).

*3.3 Detrusor hyperactivity**

Detrusor hyperactivity denotes the presence of involuntary detrusor contractions during the storage phase. Such detrusor contractions are commonly associated with urgency, i.e. the experience of sudden and intense feelings of bladder filling and the desire to void. Although detrusor hyperactivity is a major cause of day-time urinary incontinence (208, 209), many children with hyperactive bladders can prevent urinary leakage by contracting the external sphincter or performing other maneuvers that elicit reflex inhibition of detrusor contractions, such as standing on their toes or crouching and pressing the heel onto the perineum.

The prevalence of detrusor hyperactivity in the continent population is not known, since the only way to examine this would be to examine a large group of healthy individuals with cystometry. However, since approximately 20% of seven year-olds experience urgency symptoms (203, 204, 207), it can be assumed that detrusor hyperactivity is not uncommon in this age group. There are no clear differences between boys and girls in this respect (203, 204, 207).

The causes of detrusor hyperactivity among otherwise healthy persons are also incompletely known. It is, however, interesting to note that the involuntary bladder contractions of the hyperactive bladder are preceded by a decrease of urethral pressure, just as during normal micturition (210, 211).

4 SLEEP AND AROUSAL MECHANISMS

In this chapter, a brief overview of sleep physiology will first be provided, after which arousal mechanisms and the factors that influence them will be addressed. Finally, the sleep habits and sleep problems of normal children will be described.

4.1 Human sleep; basic facts

Although the subdivision of our time into waking time and time spent asleep is intuitively appealing, it is neurophysiologically more correct to talk about three fundamentally different human behavioural states: wake, rapid eye movement (REM) sleep, and non-REM sleep. With just a slight exaggeration it can be stated that the only thing that REM sleep and non-REM sleep have in common is the reduced awareness of the outside world.

Non-REM sleep. Non-REM sleep is neurophysiologically defined by electroencephalographic (EEG) characteristics, by the presence of resting electromyographic activity, and by the absence of eye movements (212). Further subdivision into superficial non-REM sleep (sleep stages 1 and 2) and deep non-REM sleep (sleep stages 3 and 4) or delta sleep is often useful, with the EEG of the deeper stages dominated by slow, synchronized delta rhythms. Increasing depth of sleep usually corresponds to higher arousal thresholds.

The regulation of basal functions such as respiration, heart rate, blood pressure and body temperature during non-REM sleep is under stable, homeostatic control.

*Note that the use of the terms "bladder instability" and "detrusor instability" will be avoided in this text, since they originally denoted the presence of detrusor contractions on cystometric provocation and not during normal circumstances.

The activity of the autonomic nervous system is dominated by high parasympathetic tone (213–216), and this is especially true among children, although there are interindividual differences in this respect (217). Vivid dreams are scarce or non-existent (218). This behavioural state has probably mainly restorative functions.

REM sleep. Recurring periods of eye movements during sleep, accompanied by an EEG pattern closely resembling that of the waking state, was first described by Aserinsky and Kleitman in the fifties (219), and has since then been identified as dreaming sleep (218).

Apart from the dreams, this behavioural state is peculiar in several ways. The dreamer is effectively paralysed: except for respiration and eye motility, there is a general atonia of striated muscles (220, 221). Homeostatic control of basal body functions during REM sleep is much more lax, resulting in large variations of heart rate (222), respiration (223–225) and body temperature (226, 227). High phasic activity of the sympathetic branch of the autonomic nervous system characterises REM sleep (213–216, 228). Penile erection, although parasympathetically mediated, is a common feature of this sleep stage in males (229). The physiological purpose of REM sleep is incompletely known (as is, by the way, the purpose of sleep as such), but one purpose is probably memory consolidation (230, 231).

As an illustration, Parmeggiani has suggested that if the cerebral cortex governs our behaviour during the waking state, then the hypothalamus is in charge during non-REM sleep, and during REM sleep the organism is controlled on a brainstem level (232). The unresponsiveness to the outside world, characteristic of both REM and non-REM sleep, is caused by thalamic inhibition of sensory input (233).

Sleep architecture. REM and non-REM sleep usually alternate periodically during the night, with a cycle length of approximately 90 minutes, starting with non-REM sleep at sleep onset. During the first hours of sleep delta sleep (stage 3 and 4) dominates and REM periods are short, but REM periods become longer and non-REM periods become more superficial as the night progresses. Thus, most of the dreams are experienced during the morning hours, and the sleeper is most difficult to arouse during the first hours of sleep. Short moments of arousal into the waking state are usually interspersed throughout the night, most of them too short to be remembered in the morning (Figure 5) (234) provides a good review on this subject). Furthermore, normal sleep is characterised by short, recurring bouts of accelerated pulse, EMG- and EEG-activation, and bodily movements,

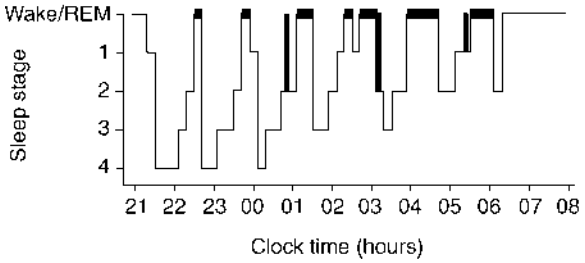

Fig. 5. Schematic polysomnogram of a normal school child. Time of night is shown on the x axis and sleep stages on the y axis. REM sleep is represented by thick lines.

even though the sleeper does not become fully awake. These arousals and "micro-arousals" are supposed to serve a "periscopic" function, providing the sleeper with the possibility to semi-consciously scan the surroundings for signs of danger (235).

Paediatric normal values of common neurophysiological sleep parameters, adapted from Coble (236) are provided in Table 2. As can be seen in the table, there is a general tendency for the deep stage 4 non-REM sleep, and total sleep time, to decrease, as the child grows.

Chronobiology, biological rhythms. The alternation between sleep and the waking state represents one of the most obvious circadian biological rhythms in man. Other physiological functions have been shown to vary in similar ways, synchronised either with the time of day or with behavioural state (REM sleep, non-REM sleep or awake), or both. The rhythmicity of functions that are linked to circadian phase – that is, to the time of day – is governed by internal "clocks" in the central nervous system; these are neural circuits with an inherent periodicity that is constantly corrected by external cues, such as light, to correspond with a 24 hour schedule. Foremost

Table 2. *Normal polysomnographic values for children aged 6–15 years. Values obtained during the second and third consecutive night spent at the sleep laboratory.*

	6–7 years	8–9 years	10–11 years	12–13 years	14–15 years
Stage 1 (%)*	7.7	7.7	6.9	8.1	6.9
Stage 2 (%)*	47.2	48.3	52.0	50.5	53.7
Stage 3 (%)*	6.3	6.5	7.0	8.3	8.6
Stage 4 (%)*	17.6	15.3	14.0	12.6	8.9
REM sleep (%)*	20.7	22.0	19.8	20.2	21.9
REM latency (min)*	142.3	129.5	132.5	119.3	106.1
Awake time (min)*	8.2	4.3	3.7	5.6	4.8
Number of arousals*	3.2	2.7	1.6	2.5	2.4
Total sleep time (min)*	546.6	513.7	467.2	451.1	422.6

* Percentages refer to the time spent asleep. REM latency is the time elapsed between falling asleep and the first REM sleep period. Awake time refers to time spent awake between falling asleep in the evening and waking up in the morning.

among these internal clocks is the suprachiasmatic nucleus in the hypothalamus (237).

Adrenocortical activity is tightly linked to circadian phase (238) and the same is true for the pineal gland and melatonin synthesis (239). Melatonin also gives important feedback to the rhythm-generating neural centres by providing a "darkness signal" and preparing the organism for sleep (240). Growth hormone secretion, on the other hand, is mainly regulated not by circadian phase but by behavioural state, with the largest peaks in plasma concentration occurring during delta sleep (241–243). Vasopressin is regulated in a similar way, with peak levels during sleep (159), regardless of circadian phase (154). Body temperature represents a middle road between these two kinds of rhythmicity, being influenced both by circadian phase and behavioural state (244), as is the case for thyroid-stimulating hormone (245) and prolactin (246) as well. Views are conflicting as to whether there is any circadian rhythmicity of the atrial natriuretic hormone (57, 247). Interestingly, for a majority of the hormones that are under circadian control, this control is exerted via vasopressinergic neurons in the suprachiasmatic nucleus (248).

It is also clear that not only can sleep affect hormone secretion but hormones can also affect sleep. Growth hormone-releasing hormone (GHRH) promotes sleep, and delta sleep in particular (249, 250), cortisol reduces REM sleep and increases delta sleep (251) and vasopressin is reported to reduce REM sleep (122).

4.2 Arousal mechanisms and arousal thresholds

Arousal, basic neurophysiology. Although opinions differ as to why we need to sleep, everyone agrees that it is important to be able to wake up. A sleeping organism is vulnerable, and during both REM and non-REM sleep there must be mechanisms at work that will result in arousal and awakening in response to urgent external or internal stimuli. (Reviews: (252–254))

A necessary role in arousal is played by the reticular activating system (RAS), whose anatomical substrate is the reticular formation, a diffuse network of neurons spanning the whole neuraxis caudal to the telencephalon. The role of the RAS is to produce general arousal and wake up the organism in response to any external or internal stimulus that is strong or threatening. The reticular formation receives collaterals from afferent sensory pathways (255) and projects diffusely to the whole cerebral cortex. Thus, activation of the RAS by sensory input results in general cortical arousal (256) and EEG rhythms typical for the waking state (257). On the other hand, the destruction of the rostral part of reticular formation results in severe sleepiness and synchronisation of the EEG as in sleep (258). The RAS responds in a uniform way regardless of the provoking sensory stimuli. To put it another way: we need the sensory pathways for the perception of specific stimuli, but without the RAS we would not respond to anything at all.

The locus coeruleus (LC) in the rostral pons is the principal nucleus of the central noradrenergic system (259) and, as such, has crucial functions within the RAS. Under the influence of signals from the LC the cortical target neurons will tend to ignore weak sensory input and respond more readily to stronger stimuli, thus making the cortex more selective (260–263). LC neurons are most active during the waking state or during arousal reactions, whereas they fire less during non-REM sleep and are completely quiet during REM sleep (264). Changes in LC neuron firing rate precede EEG changes, with the exception of the change from REM sleep to the waking state (264).

In many ways the central noradrenergic system can be considered the CNS branch of the sympathetic nervous system; the two systems are activated by the same stimuli and their activities are usually synchronised (265–267). It has been stated that the LC and the central adrenergic system provide the cognitive complement to sympathetic activation (268). Since the sympathetic nervous system plays a major role in the organism's defence against outside threat, it should come as no surprise that it is deeply involved in arousal as well. Arousal from sleep is characterised by an increase in sympathetic tone, concomitant with parasympathetic inhibition (269, 270). This is reflected by typical changes in heart rate, blood pressure etc., and these changes appear before changes of the EEG (215). Furthermore, it has been demonstrated that the burst of sympathetic activity during arousal reactions is disproportionally intense, accompanied by much greater physiological changes than would be needed for just waking up and rising from bed (270). This reaction probably has survival value; when waking from sleep the organism has to be prepared for whatever may come.

The bladder as an arousal stimulus. Cystometric studies have confirmed that bladder distention or detrusor contractions – not surprisingly – cause arousal in healthy humans (271). Both bladder distention and detrusor contractions (272) do, in similar ways, result in increased firing of LC neurons, followed by EEG changes and arousal (271, 273). In analogy to other arousal stimuli, LC activity has been shown to be a necessary link between these bladder stimuli and cortical arousal (274). And, as with arousal from other causes, the bladder-related awakening from sleep is accompanied by increased activity of the sympathetic nervous system (70). The nucleus paragigantocellularis of the medulla oblonga-

ta is the proposed link between spinal bladder afferents and the LC (273).

Arousal thresholds. Although it is well known that some people are easy to arouse from sleep while others sleep soundly in very noisy environments, research regarding arousal thresholds – and how they differ between subjects – has been scarce.

Arousal thresholds are usually higher during delta sleep (non-REM sleep stages 3 and 4) than during superficial non-REM sleep (275–277), while REM sleep is less uniform in this respect, with both high (278) and low (277) arousability reported. The arousal thresholds tend to diminish, regardless of sleep stage, during the night's sleep, so that the sleeper is most difficult to arouse during the first hours of sleep (275–277, 279). It has also been shown that thresholds are higher after sleep deprivation (277) and that arousability may, paradoxically, decrease if the sleep is fragmented by frequent disruptions such as sleep apnoeas (280).

The study of individual arousal thresholds is a complicated matter, since the interindividual differences are great (275) and subjects with similar sleep EEG recordings may have different arousal thresholds (281). The sleep EEG gives information regarding sleep architecture and sleep stages but is of very limited help when trying to differentiate between "deep" and "superficial" sleepers. To measure arousal thresholds objectively one needs to apply quantifiable arousal stimuli during well-defined sleep stages and then measure effects such as changes in EEG, heart rate and behaviour (277), and this would still only give data relevant to the sensory modality tested (i.e. auditory, tactile, pain etc).

In a recent survey of 1413 school children aged 6–10 years, the subjective arousal thresholds were estimated by asking the families "how easy or difficult are you to awaken from sleep at night?" (207). The distribution of answers is shown in Fig. 6. Contrary to common belief, most children were considered, by themselves and their parents, to be fairly easy to arouse. It has objectively been shown, however, that children are more difficult to arouse from sleep than adults (282).

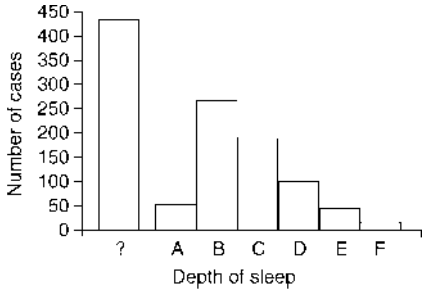

Fig. 6. Distribution of answers to the question "how easy or difficult are you to arouse from sleep at night?" among 1413 children aged 6 to 10 years. A = Very easy, B = easy, C = not easy and not difficult, D = difficult, E = very difficult, F = almost impossible, ? = don't know, never tested.

4.3 Epidemiology of sleep

Most school children sleep around 10 hours per night, with no clear differences between boys and girls (207, 283, 284). Sleep requirements understandably diminish with age (283, 285).

Although most children sleep well (286), sleeping problems are not uncommon. Traditionally, problems of sleep are divided into parasomnias and other sleep-related problems. The former category usually includes reasonably well-defined and strictly nocturnal abnormalities such as somnambulism (sleep-walking), somniloquy (sleep-talking), confused arousals (night-terrors and related behaviours), bruxism (tooth-griding) and the rhythmic movement disorder (body-rocking, head-banging), while the latter category is less well-defined and usually includes nightmares, bedtime fears and struggles, "growing pains", night-time awakenings and snoring. This subdivision is not altogether clear. Table 3 provides an overview of the prevalence of different sleep problems in a representative group of school children aged 6–10 years.

Typical for the parasomnias are that they are usually not associated with psychopathology or day-time psychological problems. The classical parasomnias somnambulism and night-terrors have been shown to occur almost exclusively during non-REM sleep and are described as representing the defective arousal from delta sleep (287). Interestingly, enuresis has been proposed to belong to this group of sleep problems as well (287).

Snoring, often caused by enlarged tonsils or adenoids, is a common problem in childhood (288–291). If severe, it may result in sleep apnoeas and day-time symptoms of inadequate sleep, such as headache, stomachache or sleepiness (291, 292).

Other sleep or night-time problems, such as bedtime fears, onset insomnia, nightmares and interrupted sleep are often components of psychological or behavioural problems and are not specific to sleep as such.

5 ENURESIS: DEFINITIONS AND EPIDEMIOLOGY

5.1 Definitions

The scientific word for bedwetting is nocturnal enuresis. Some confusion exists regarding the terminology in this field of research. According to the suggestions provided by the ICCS, *enuresis* is defined as "the urodynamically normal voiding of urine at an inap-

Table 3. *Frequencies of sleep factors in 1413 children aged 6–10 years*

	n	Every day %	Every week %	Every month %	Never/seldom %	Previously %
Bedtime struggles, afraid of night	1403	5.4	8.6	27.2	58.5	0.3
Bone pains ("growing pains")	1406	0.1	2.6	27.5	69.1	0.6
Hypnagogic myoclonias	1371	1.1	2.0	15.8	81.1	0.0
Onset insomnia	1407	2.5	11.4	38.4	47.6	0.1
Bruxism (tooth grinding)	1395	1.1	4.4	14.6	79.1	0.7
Rhythmic movement disorder	1407	1.4	1.2	5.7	91.7	0.0
Somnambulism (sleepwalking)	1406	0.3	0.7	6.3	92.7	0.1
Somniloquy (sleeptalking)	1406	0.6	4.7	35.9	58.8	0.0
Confused arousals	1403	0.2	1.4	9.0	88.2	1.1
Enuresis	1409	1.3	1.9	5.0	87.8	4.1
Nocturia	1406	5.3	6.2	28.7	59.3	0.6
Snoring	1404	1.4	4.1	17.5	76.4	0.6
Confused when awoken at night*	914	4.3	7.3	18.5	69.9	0.0
Nightmares	1380	0.5	4.9	51.8	42.6	0.2
Bodily movements during sleep	1406	1.4	5.1	19.4	73.9	0.2
Interrupted sleep	1406	4.6	8.7	36.6	49.4	0.6
Day-time sleepyness	1401	0.4	3.6	37.2	58.7	0.1
Headache, stomachache	1404	0.1	4.9	30.8	64.0	0.1

* On this item the alternative "don't know" was also given. It was chosen by 454 families.

propriate location and at the age of five years or more" (171). However, the assumption that all bedwetting episodes occur as urodynamically normal voidings has been challenged (293–295) and if nocturnal cystometries are required before being able to state that a child who pees in his or her bed suffers from nocturnal enuresis, then the definition is in our opinion not very useful. Thus, we will use the term nocturnal enuresis (or just enuresis) simply as denoting bedwetting, that is, the passing of urine in bed while asleep, in a child whose age and neurological maturity suggest that he or she should be dry. With this exception, we will adhere to the terminology suggested by the ICCS.

The socially acceptable habit of waking at night in order to go to the toilet and urinate is called nocturia.

The ambiguous term diurnal enuresis should be avoided (or it could be reserved for involuntary micturitions occurring during day-time naps). In this text the involuntary leakage of urine during day-time or while awake will consistently be called daytime urinary incontinence, or simply incontinence.

Onset enuresis, or secondary enuresis, denotes bedwetting that affects a child that has previously been dry for at least 6 months without treatment, whereas in primary enuresis no such intervening period of dryness has occurred. Monosymptomatic enuresis means enuresis without day-time incontinence. Enuretic children with day-time bladder symptoms such as urgency (see below) are still said to suffer from monosymptomatic enuresis as long as they do not wet their clothes. This is, obviously, illogical, and a change of definition would be very welcome. Anyway, in this text the above-mentioned definition will, reluctantly, be used.

Urgency is the experience of a strong and sudden desire to void. This symptom is often, but not always, associated with incontinence. The experience of urgency is the subjective hallmark of detrusor hyperactivity.

Encopresis denotes the involuntary diurnal or nocturnal faecal soiling of sheets or underclothes in a child without known neurological or anatomical abnormalities, usually in the presence of functional constipation (296, 297).

5.2 Epidemiology of enuresis

Enuresis is a common problem among children and adolescents. Many studies regarding the prevalence of bedwetting have been published, yielding somewhat different results because of different inclusion criteria and different definitions. However, if a problem frequency of at least one accident per month is taken into account, the prevalence of nocturnal enuresis is probably above 10% among 6 year-olds (203, 298), around 5% among ten year-olds (207, 299–302), and 0.5–1% among teenagers and young adults (302, 303). The natural history of enuresis is difficult to assess, but a spontaneous cure rate of 15% per year is often quoted (304, 305).

Monosymptomatic enuresis in children is 1.5–2 times as common among boys than girls (203, 206, 207). Among children with combined day-and night-time wetting problems and among adults no such gender differences are found (203, 207, 303). Day-time incontinence is more common among girls (203, 207).

6 HEREDITY OF ENURESIS

Enuresis has long been known to be strongly influenced

by hereditary factors, as shown by twin studies (306) and numerous epidemiological surveys (207, 307–312).

The discovery a few years ago of a gene on chromosome 13 responsible for the dominant inheritance of enuresis (313) caused much excitement. However, not much later a second gene was localised on chromosome 12 (314), and it did not take long for the third enuresis gene to show up, this time on chromosome 22 (315). Obviously, enuresis is not caused by one single gene.

Furthermore, in a recent study on a material of 167 children with different kinds of enuresis (i.e. monosymptomatic nocturnal enuresis, combined enuresis/incontinence, primary enuresis and secondary enuresis) it was found that although enuresis could be linked to chromosomes 8, 12 or 13 in different families there was no clear correspondence between phenotype (subtype of enuresis) and genotype (316).

Thus, it seems that different genes can result in a single symptom, and different symptoms can be caused by a single gene. This makes the search for "the enuresis gene" somewhat elusive.

Since it can be suggested that enuresis is the result of a combination of osmoregulatory or urodynamic disturbances and disorders of arousal (this will be discussed in greater detail below) it could also be hypothesised that these different defects might be inherited separately. Some support for this view has been provided by epidemiological data showing that not only enuresis, but also nocturia and subjectively high arousal thresholds are common in the families of enuretic children (207).

7 PATHOGENESIS OF ENURESIS: NOCTURNAL POLYURIA

The discovery, made by investigators in Aarhus, Denmark, that there is a group of enuretic children and adolescents with polyuria secondary to a nocturnal deficiency of vasopressin, has rightly been considered a break-through in enuresis research. It was shown that this group of bedwetting children lacked the physiological nocturnal peak of vasopressin secretion and had a nocturnal urine production exceeding their functional bladder capacity (317, 318). This provided an explanation for the beneficial effects of desmopressin against bedwetting, since it is assumed that desmopressin acts by reducing nocturnal urine output to a volume that can be contained in the child's bladder (this assumption has, however, been questioned, as will be discussed in chapter 12.7).

The finding of nocturnal polyuria among enuretic children has since then been repeated by other investigators (160, 319, 320), and support for the hypothesis was also provided when it was shown that enuresis-like accidents could be provoked in normal, night-dry children simply by increasing fluid intake before bed-time (321). However, in other studies no nocturnal polyuria or vasopressin deficiency was found (322–327), and it has been argued that it would be strange if the normal osmotic regulation of vasopressin secretion were disabled only at night (327).

A contributing explanation for the conflicting results regarding vasopressin values could be the fact that this hormone is released in a pulsatile manner (157, 158). Accurate measurements of circadian profiles would call for measurements every 15 minutes, which has to our knowledge only been done once in this population, and in this case without normal controls (328). The results of that particular study did not imply a clear-cut vasopressin deficiency among enuretic children.

A problem with the polyuria hypothesis is the finding that nocturnal polyuria is not a phenomenon exclusive to bedwetters. It has been shown that 12% of dry children produce more urine during the night than during daytime (1), and adults who need to go to the toilet at night often lack circadian rhythmicity of vasopressin secretion although they do not suffer from enuresis (329). The fact that nocturia is a common phenomenon among dry children (206, 207, 330) indicates that nocturnal polyuria may be common as well.

The possibility has also been put forward that the polyuria is not necessarily caused by vasopressin deficiency, as solute diuresis has been found instead of water diuresis in enuretic children with nocturnal polyuria (320, 331). The reason for this finding is, as yet, unclear, and other renal or endocrine mechanisms may be involved. No disturbance of ANP secretion has been found in enuretic children (332) and other factors responsible for solute diuresis (such as angiotensin, aldosterone, prostaglandins or the sympathetic nervous system) have almost never been compared between enuretic and dry children. Suppressed levels of aldosterone or angiotensin II have recently been suggested to be the reason behind the nocturnal polyuria of some enuretic children (333). As has been demonstrated in chapter 2, the investigation of the causes behind solute diuresis is a very complicated task.

An objection to the polyuria hypothesis has been that the causal relationship between vasopressin deficiency and enuresis might go in the opposite direction, since there are data indicating that bladder distention is a stimulus for vasopressin release (148). The following argument is presented: the bladder of the enuretic child will be less distended at night than that of the dry child, since urine is not stored in the bladder but voided in the bed; thus, the enuretic child will not secrete as much vasopressin as the dry child (330). However, recent

Table 4. *Cystometric studies in* monosymptomatic *nocturnal enuresis. Studies on children with nocturnal and diurnal wetting are only included in the list if the recordings from monosymptomatically enuretic children can be evaluated separately.*

Study	N	Children with uninhibited contractions	%	Comments
Arena *et al.* 1996	46	17	37%	
Booth & Gosling 1983	4	2	50%	
El-Sadr *et al.* 1990	10	5	50%	
Hindmarsh & Byrne 1980	13	5	38%	
Karaman *et al.* 1992	31	6	19%	
Ishigooka *et al.* 1992	17	6	35%	
Kosar *et al.* 1999	29	11	38%	
Mahony *et al.* 1981	18	3	17%	
Mayo & Burns 1990	24	5	21%	
Medel *et al.* 1998	33	16	48%	
Torrens & Collins 1975	22	14	64%	
Whiteside & Arnold 1975	13	2	15%	
Bugge-Nielsen *et al.* 1984*	14	14	100%	Nocturnal, natural filling
Nørgaard *et al.* 1989	40**	19**	47%	Nocturnal
Nørgaard *et al.* 1989	52**	6**	<12%	Nocturnal, natural filling
Watanabe & Azuma 1989	204	57	28%	Nocturnal
Yeung *et al.* 1999***	41	>28	>69%	Nocturnal, natural filling

* All children included had vesico-ureteral reflux. No difference between children with and without enuresis
** Numbers shown are numbers of recordings, not of children. Same children in both studies.
*** All children were non-responders to desmopressin treatment.

studies have failed to find support for this argument (149).

There is evidence indicating that nocturnal polyuria is common among enuretic children, and that nocturnal vasopressin deficiency may be causing this polyuria at least in some of the children. All bedwetting children do not, however, have polyuria. There are many reasons to believe that there are bedwetting children who have nocturnal polyuria and there are those who don't. And, importantly, the polyuria hypothesis does not explain why the children do not wake up to void.

8 PATHOGENESIS OF ENURESIS: DETRUSOR HYPERACTIVITY

Although it is clear that detrusor hyperactivity is the major cause of day-time incontinence, and that the overlap between the groups of bedwetting and incontinent children is great (203, 206, 207, 303, 310), the pathogenic role of detrusor hyperactivity in monosymptomatic nocturnal enuresis is still a controversial issue. This is in our opinion somewhat surprising. It would be strange if two disorders that are so closely interrelated clinically were totally distinct from a pathogenic point of view.

Watanabe *et al.*, in Kyoto, Japan, performed sleep cystometries in a large number of children with monosymptomatic nocturnal enuresis, and found frequent uninhibited detrusor contractions during sleep in a third of them although they had stable bladders while awake (293). Similar results have been reported by others (208, 294). Not surprisingly, in studies in which subjects with combined day-and nighttime wetting as well as monosymptomatic bedwetters are included, the finding of urodynamic abnormalities is even more common (287, 334, 335). Table 4 provides a summary of cystometric studies in monosymptomatic nocturnal enuresis. Note that only data from children without daytime incontinence is included in the table. Studies in which no distinction is made between monosymptomatic enuresis and combined day-and nighttime wetting are not included. The data presented in the table indicates that 1) uninhibited detrusor contractions are probably quite common, affecting perhaps about 30% of children with monosymptomatic enuresis, and 2) the distinction between normal and pathological bladder activity is unclear. More nocturnal cystometric studies with standardised procedures and well-defined patient populations (as well as, ideally, normal controls) are badly needed.

The elegant study by Yeung and colleagues deserves special mention (336). In a well-defined group of 41 children with severe primary monosymptomatic enuresis, none of whom had responded to desmopressin therapy, nocturnal and diurnal cystometries were performed. *All* of these children had pathological cystometrograms during sleep, with nocturnal detrusor hyperactivity, dysfunctional voidings and/or obstruction.

A hyperactive bladder is usually a small bladder. It has been noted for several decades that the bladder capacity of enuretic children tends to be smaller than that of dry children (334, 336–341), and the small bladder capacity has been put forward as a possible cause of enuresis. Troup and Hodgson compared enuretic and dry children and found that the spontaneous functional bladder capacity was smaller in the former group, whereas cystometric bladder capacities did not differ, indicating that the difference was functional, not anatomical (342). Further support for the detrusor hyperactivity hypothesis is also provided by the finding that children with enuresis go to the toilet more often (205, 343), and that urgency symptoms are more common in this group (207). This observation has been made as early as in the beginning of the 19th centrury (344). Furthermore, it has been shown that

some children with monosymptomatic enuresis can be successfully treated with anticholinergic or smooth muscle relaxant drugs (345).

Indirect support for the detrusor hyperactivity hypothesis is also provided by the observation that children with therapy-resistant enuresis do not delay the moment of nocturnal bladder voiding when given antidiuretic medication at bed-time (345). If they emptied their bladders when full, in a urodynamically normal manner, this would surely happen later at night if urine production were diminished.

The fact that not all children successfully treated with the enuresis alarm (see below) subsequently need to wake up and urinate in the toilet (346), and the observation by Oredsson that bladder capacity increases during alarm treatment (347), can in our opinion also be taken as an argument supporting the detrusor hyperactivity hypothesis. The alarm treatment possibly helps the child recognize and inhibit detrusor contractions while asleep. As described above, arousal reactions are characterized by large bursts of sympathetic activity, which would help to inhibit the parasympathetically mediated detrusor contractions even if the sleeper does not become fully awake (or wakes, but only briefly and doesn't remember it afterwards). This is, however, a hypothesis that has, as yet, not been tested.

Opposition to the detrusor hyperactivity hypothesis is based on studies in which normal diurnal bladder function has been cystometrically demonstrated in enuretic children (348, 349). This view is also expressed in the definition of enuresis quoted above, proposed by the ICCS (171).

It is also argued that we know very little about the nocturnal bladder function in normal dry children, since they are not usually cystometrically examined. In a recent evaluation of children without symptoms of lower urinary tract malfunction, who underwent cystometry during abdominal surgery, uninhibited bladder contractions during the late filling phase was detected in 11% (however, many of these children had gross upper urinary tract or intestinal malfunction) (350). In the study by Bugge-Nielsen and co-workers, who performed nocturnal cystometries in children with vesico-ureteral reflux, no differences were found between children with and without enuresis (351). Furthermore, it is not clear that a small bladder necessarily means an hyperactive bladder.

In analogy to the case of the polyuria hypothesis, it seems reasonable to suspect that there is a subgroup of enuretic children in which nocturnal detrusor hyperactivity is a pathogenetic factor. It has to be borne in mind, however, that this is also an incomplete hypothesis, since it does not explain why the children do not wake up from the detrusor contractions.

The dysfunctional elimination syndrome. At this point a few words have to be said about the possible link between constipation and detrusor hyperactivity (352). It has been shown that constipation and encopresis is common among children with incontinence (353) or enuresis (354–356), and that enuretic children often become dry when treated for constipation (356, 357). Furthermore, constipated children with enuresis and/or incontinence have been shown cystometrically to exhibit detrusor hyperactivity (356). The mechanism behind this link is not totally clear, but it has been argued that the bowel may compress the bladder, making it more prone to contraction (358, 359), and that the frequent and forceful contractions of the pelvic floor that occur in detrusor hyperactivity cause constipation (171). The term "dysfunctional elimination syndrome" has been introduced, to denote the association between disturbances of bladder and bowel function (360).

Bladder "immaturity". Enuresis is commonly regarded as a kind of maturational delay of the mechanisms responsible for continence. It is argued that the enuretic child is neurologically or psychiatrically immature, i. e. that his or her bladder function has remained on an infantile level. The obvious argument in support of this notion is that enuresis tends to disappear spontaneously with age. Recent research into bladder function in infancy does, however, not favour this concept, since, as mentioned earlier in this text, it has been shown that infants only very seldom micturate while asleep (201). Hypothetically, it would perhaps be possible to distinguish the future enuretic child by studying the sleeping infant. Such prospective studies have, as yet, not been performed.

Although it is probable that there are maturational aspects of the pathogenetic mechanisms behind enuresis the statement that the enuretic child "stays on an infantile level of bladder control" is probably an oversimplification, stained by old ideas of enuresis as a kind of regressive behaviour.

9 PATHOGENESIS OF ENURESIS: IMPAIRED AROUSAL MECHANISMS

The idea that enuretic children are "deep sleepers" is not new (361). Many parents report that their bed-wetting children are almost impossible to awaken from sleep at night and if they are forcibly aroused, they still will not become fully awake but are led in a drousy state to the toilet. This subjectively low arousability has been reported in numerous epidemiological studies (335, 354, 362–366), and has also been observed in clinical research (367, 368). The common observation by parents to children being treated with the enuresis

alarm, that the whole family wakes up from the sound of the alarm *except* the child that is using it, is also well known to clinicians in the field. It is noteworthy that this observation involves a "control group" – i.e. the rest of the family – as well.

A common objection to the hypothesis of the deeply sleeping bedwetting children has been that perhaps *all* children are difficult to arouse from sleep, but the arousability of dry children is not tested since there is usually no need to try and wake those children at night (369). In our recent epidemiological survey this argument was accounted for by giving participating families the option to refrain from assessing the arousal thresholds of their child. When discounting the families that chose to do so the subjective depth of sleep was still found to differ greatly between bedwetting and dry children. Furthermore, most of the dry children were considered relatively easy to arouse from sleep (207).

Indirect support for the hypothesis has been provided by investigators who recorded sleep EEG of enuretic children and found the bladder voiding to be temporally linked to nonREM sleep, especially delta sleep (368, 370–374). A pioneer in this field is Broughton, who saw the bladder voiding as an event occurring during the incomplete arousal from delta sleep, and coined the expression "disorder of arousal" to describe enuresis, sleepwalking and night terrors (287). But these findings have been contradicted by well-conducted studies in which the enuretic event was found to be randomly distributed across the night, with no fixed relationship to sleep stages (375–377). Thus, the question whether the involuntary nocturnal micturitions are linked to events of the EEG or not is still not answered.

Studies on objective arousal thresholds of enuretic children have been scarce. The problem here, as described above, is that the mere recording of sleep EEG gives no information regarding differences in arousal thresholds between subjects. Older studies, with semi-quantitative measurements of arousability, have generally supported the idea of the deeply sleeping bedwetters (363, 378), but these studies have been afflicted with methodological shortcomings and they have been contradicted by other investigators (380). However, in the elegant study by Wolfish and co-workers (380) it could be quite clearly shown that children with severe enuresis were significantly more difficult to arouse from sleep, by auditory stimulation, than controls. The findings of Ornitz, who detected subtle signs of defect brainstem processing of sensory signals in enuretic children (381), and Hunsballe, who showed increased delta wave activity in the sleep EEG of enuretic children (382), point in the same direction.

In conclusion, there is experimental support for the notion of the deeply sleeping enuretic children. Furthermore, it seems logical for sleep to play at least a permissive role in the pathogenesis of enuresis, since neither bladder overfilling nor detrusor contractions would fail to arouse a lightly sleeping person.

The snoring bedwetters might constitute a special subgroup in which arousability plays a pathogenetic role. There is a group of bedwetters who snore, and who will become dry when the snoring has been treated (373). Frequent disruption of sleep, such as occurs in heavy snorers, has been associated with high arousal thresholds (280, 383). Note, however, that snoring or sleep apnoeas are associated with nocturnal polyuria as well (96).

10 ENURESIS AND PSYCHIATRY

The old opinion that enuresis mainly is a psychiatric disorder (384) has been largely abandoned today, since the behaviour problems among enuretic children, as expected from psychiatric explanation models, were not found (385, 386), and no differences regarding stressful family events or toilet training were detected (387). This has been shown in prospective studies as well (388), and the prevalence of enuresis has not been found to differ between children with and without psychosocial problems (284). Psychotherapy has not been shown superior to treatment with, for instance, the enuresis alarm (see below), and there is no tendency for symptom substitution among successfully treated children (389).

There are some studies in which enuresis has been found to be weakly associated with emotional immaturity, behaviour problems or anxiety (364, 387, 390, 391). However, when differentiating between subgroups of enuretic children, it can be noted that the association between psychological problems and enuresis is strongest among children suffering from combined day-and nighttime incontinence or those with secondary enuresis (392, 393). Children with primary, monosymptomatic nocturnal enuresis are usually psychologically well-adjusted and have capable and caring parents.

Still, it would probably be to go too far to conclude that psychological or psychiatric factors are without any importance in enuresis. Bedwetting can be a heavy burden for a growing person, and the social and psychological consequences can be grave. In the study by Hägglöf and associates it was clearly demonstrated that enuretic children suffer from low self-esteem compared with dry children, and that this difference disappeared when the children became dry (394). Thus, many of the psychiatric or psychological abnormalities attributed to enuretic children in the past are probably consequences of the bedwetting in stead of causes.

Enuresis is reported to be common among children

with attention-deficit hyperactivity disorder (ADHD) (395–397). These children often have combined day- and nighttime wetting with a marked variation both in symptom frequency and in voided volumes, and the involuntary day-time voidings are reported to be urologically normal (171). Possibly, these children represent a pathogenetically distinct subtype of enuresis, although there is a disturbing lack of literature to support or reject this clinical impression.

11 PATHOGENETIC SUBTYPES OF ENURESIS

11.1 The heterogeneity of enuresis

As has been explained above, enuresis is a clinically and genetically heterogeneous disorder. We have every reason to suspect that it is also pathogenetically heterogeneous. Different groups of bedwetting children have different underlying defects and require different treatments to become dry. It is thus important to find a way to subdivide the large group of enuretic children into clinically relevant subgroups.

There are at least three theories of the pathogenesis of enuresis whose proponents can point to reasonably firm scientific evidence: 1) the polyuria hypothesis, 2) the detrusor hyperactivity hypothesis and 3) the disorder of arousal hypothesis. If one subscribes to the opinion that all of these theories describe parts of the truth (which the authors of this text do), the important question is this: how do we differentiate between the polyuric, the "detrusor hyperactive" and the deeply sleeping children? It is of course quite possible (and, indeed, probable) that these groups overlap, but we still need means to differentiate between groups with more or less different pathogenetic mechanisms. Enuresis research will continue to yield conflicting results and treatment success will continue to be unimpressive as long as we do not take the heterogeneity of the disorder into account.

Enuretic children with nocturnal polyuria. Continuing research by the Aarhus group has quite convincingly shown that nocturnal polyuria is characteristic of children with enuresis that responds favourably to desmopressin treatment (160, 326, 398, 399). Work at our centre has corroborated these results by showing that the desmopressin responders tend to concentrate urine poorly and that they produce larger amounts of more dilute urine, compared with the non-responders (400).

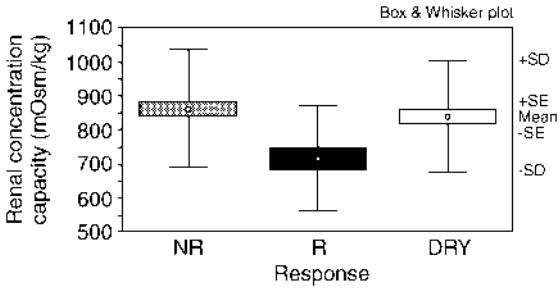

Fig. 7. Renal concentrating capacity after 14 h thirst provocation in dry children, desmopressin responders R and desmopressin non-responders NR. $p < 0.05$.

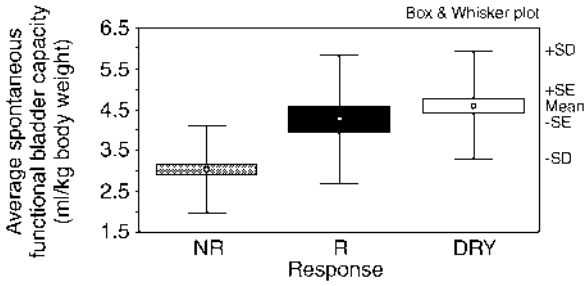

Fig. 8. Functional bladder capacity (average voided bladder volumes during two days) in dry children, desmopressin responders R and desmopressin non-responders NR. $p < 0.05$.

It has been suggested that desmopressin responders have a lower morning urine osmolality than the non-responders (401), but numerous studies have since then failed to repeat these findings (324, 402–405). Obviously, the simple measurement of morning urine osmolality is too blunt an instrument to be of prognostic value. However, more is possibly gained by performing a thirst provocation test, since it has been shown that the desmopressin responders do not achieve the same urinary concentration as the non-responders (400, 406, 407), again indicating an osmoregulatory defect in the former. In on-going studies, in which responders, non-responders and dry children are compared, the responders concentrate significantly less than the rest of the children, as shown in Fig. 7.

Although it is possible that this osmoregulatory defect involves vasopressin deficiency, measurement of the hormone in desmopressin responders and non-responders have yielded ambiguous results (324, 328, 400, 408). Perhaps the measurement of vasopressin in morning urine would be more useful for the assessment of this episodically released hormone (409, 410), but – apart from the small pioneer investigation by Puri in 1980 (411) – such measurements have not yet been reported in enuretic children.

Vasopressin deficiency or not, it is fair to suggest that the children with nocturnal polyuria are to be found in the desmopressin-responding group. But we still need to explain why they don't wake up.

Enuretic children with detrusor hyperactivity. Unfortunately, no comparative cystometric study on desmopressin responders and non-responders has so far

been done, but indirect evidence suggests that detrusor hyperactivity is to be found mainly in the non-responder group.

First: several comparisons between desmopressin responders and non-responders have indicated that the functional bladder capacity of the latter is smaller than that of the former (400, 402, 412–414). On-going studies including dry children as well confirm those findings (Fig. 8)

Second: if the opposite hypothesis were true, namely that the non-responders voided with full, stable bladders at night, the administration of antidiuretic drugs such as desmopressin at bedtime would delay the enuretic event. This has been demonstrated not to be the case (345). Apparently, in desmopressin non-responders urine volume seems not to be the main factor determining when the enuretic event occurs.

Third: desmopressin non-responders often respond favourably to anticholinergic treatment with oxybutynin (especially when combined with desmopressin) (345), as do children with combined day-and nighttime incontinence (415, 416). In contrast, in children with stable bladders and in unselected children with monosymptomatic enuresis the response to oxybutynin is poor (417, 418). A favourable antienuretic effect of oxybutynin has been linked to cystometrically detectable detrusor hyperactivity (419).

In the previously mentioned study by Watanabe it was found that 28% of 204 children with monosymptomatic enuresis exhibited nocturnal detrusor hyperactivity (293). Although the desmopressin response of these children was not examined, it is tempting to suggest that the group of children with nocturnal detrusor hyperactivity and the desmopressin non-responder group are one and the same. As mentioned below, desmopressin is effective in approximately two thirds of bedwetting children. Furthermore, the study by Yeung *et al*. mentioned above, in which all children exhibited detrusor hyperactivity or other cystometric pathology at night, included only desmopressin non-responders (336). In this study it was also found that the children did not have nocturnal polyuria.

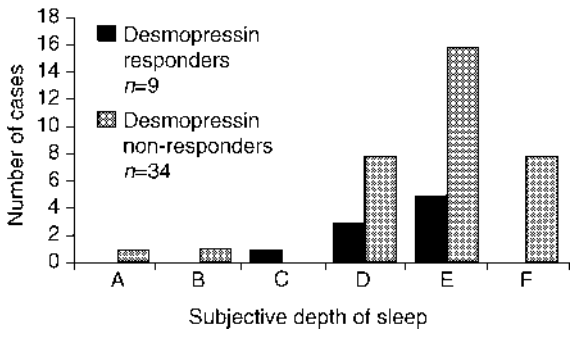

Fig. 9. Subjective arousal thresholds of enuretic children with good or poor desmopressin response. The letters represent answers to the question "how easy are you to arouse from sleep at night?". A = very easy, B = easy, C = not easy and not difficult, D = difficult, E = very difficult, F = almost impossible.

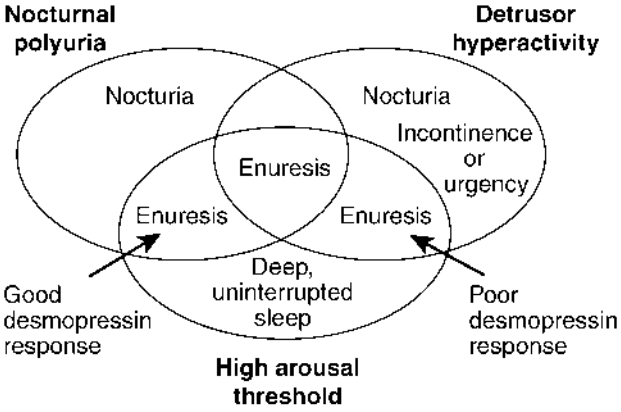

Fig. 10. Suggested interaction of factors relevant in the pathogenesis of enuresis.

In our view, the evidence today indicates that nocturnal detrusor hyperactivity is a pathogenetic factor in a subgroup of enuretic children and that this subgroup more or less coincides with the group of children not responding to desmopressin treatment. But, again, we still need to explain why they don't wake up.

Enuretic children with high arousal thresholds. Since both detrusor contractions and bladder distention are arousal stimuli and neither the polyuria hypothesis nor the detrusor hyperactivity hypothesis offers any explanation for the children not waking up, it would be logical to suggest that both groups share a disorder of arousal.

This remains to be proven. All studies on arousal thresholds of enuretic children so far have examined these children as one group. In no published material has the arousal thresholds, subjective or objective, of desmopressin responders and non-responders been compared. During the course of other investigations at our centre we asked participating children about how easy or difficult they are to awaken from sleep at night. We found no clear differences between desmopressin responders and non-responders in this respect: they all tend to answer that they sleep very deeply (Fig. 9). The only difference between the sleep of these two groups that we have found is that the responders often empty their bladders during the first hours of sleep, whereas the nonresponders void during any part of the night (374). This implies that the sleep of these children perhaps does not differ as much from dry children as that of the non-responders, since all children – wet or

dry – are difficult to arouse from sleep during this part of the night (420).

A proposed subdivision. Supported by the arguments presented above we believe that it is possible and clinically relevant to subdivide the large group of bedwetting children into two pathogenetically distinct groups that roughly correspond to the responders and non-responders to desmopressin treatment. In the former group, nocturnal polyuria is a probable cause of enuresis, and detrusor hyperactivity is the major culprit in the latter group, while both groups share high arousal thresholds as an additional pathogenetic factor. We have chosen to call the enuresis "diuresis dependent" and "detrusor-dependent", and these groups will be presented in more detail below. The proposed subdivision is visualized graphically in Fig. 10.

11.2 "Diuresis dependent enuresis": enuresis because of nocturnal polyuria and low arousability.

The term diuresis dependent enuresis* denotes those children who void with full, stable bladders at night. This corresponds roughly to the group of bedwetting children who respond favourably to desmopressin treatment.

Pathogenesis. It has been quite firmly established that many children with enuresis have nocturnal polyuria (317, 318). The bladder of these children is emptied in a urodynamically stable manner when it is full (421). Since nocturnal polyuria and/or nocturia is not uncommon among dry children (1, 207), sleep factors must be involved as well. Thus, these children wet their beds because their bladders are full and they sleep too deeply to recognize it.

Some children with diuresis dependent enuresis produce exceedingly large amounts of urine during the earliest part of the night, although the total nocturnal urine output may be normal, (422). In accordance with this stands the recent finding that many desmopressin responders void during the first two hours of sleep (374).

Aetiology. The nocturnal polyuria of diuresis dependent enuretic children has in some, but not all, groups been associated with nocturnal vasopressin deficiency (317, 320, 324). It has been suggested that the hereditary influence is stronger in desmopressin responders than in nonresponders (423), but this has not been confirmed. The finding that nocturia is common among siblings and parents of bedwetting children is also an indication of a hereditary influence (207).

Characteristics. Most of the children with diuresis dependent enuresis respond to desmopressin treatment (326). They may show signs of defective renal concentrating ability (341), their functional bladder capacity is usually in the normal range (341), and they are not more prone to urgency symptoms than the general population. A history of bladder voidings in the bed during the first hour of sleep is suggestive of diuresis dependent enuresis (374).

11.3 "Detrusor dependent enuresis": enuresis because of uninhibited detrusor contractions and low arousability

The children with detrusor-dependent enuresis are those who void not because the bladder is full, but because of failure to suppress detrusor contractions. The majority of these children are non-responders to desmopressin treatment.

Pathogenesis. We believe that there is a large number of enuretic children who void because of uninhibited hyperactive detrusor contractions at night. This belief is based on the large overlap between children suffering from enuresis and those suffering from day-time incontinence or urgency (203, 207), the cystometric registration of nocturnal detrusor hyperactivity in enuretic children (293, 336), and the observation that enuretic children have smaller bladder capacity than dry children (338, 341).

But, in analogy with diuresis dependent enuresis, sleep and arousal factors are probably involved as well. Because urgency symptoms, and even day-time incontinence, do occur among night-dry children (203, 207), it can be suspected that detrusor hyperactivity does as well. Thus, the children suffering from detrusor-dependent enuresis wet their beds because of micturition contractions that are not inhibited and that fail to awaken the child from sleep.

It could also be argued that perhaps it is not the arousal process that is abnormally slow among these children, but the micturition reflex that is abnormally quick.

Aetiology. The mechanisms behind detrusor hyperactivity are unclear. It has been hypothesised that detrusor hyperactivity is caused by hyperexcitability of the smooth muscle cells in the bladder wall secondary to denervation caused by excessive intravesical pressure (359). The interesting cystometric observations by Low contradict this hypothesis. In this study it was found that involuntary detrusor contractions were preceded by a fall in urethral pressure

*The concept "volume dependent enuresis" that was introduced in the earlier works of the authors of this text has the same meaning as the now proposed "diuresis dependent enuresis". The wording has been changed in order to lessen the confusion regarding urine volumes and bladder volumes.

in just the same way as happens before normal micturition (210). This favours the suspicion that detrusor hyperactivity is caused by central disinhibition.

A disturbed balance of the autonomic nervous system, with parasympathetic dominance and sympathetic inadequacy, might be involved here (this will be discussed in some detail in chapter 14). Perhaps the sleep of these children is not only subjectively "deeper" than that of dry children, but also characterised by exaggeration of the normally high nocturnal parasympathetic tone. This would fit well with our observation that the enuretic event is linked to the parasympathetically dominated non-REM sleep (374), although this is admittedly hypothetical.

Genetic factors are probably influential in this group of children as well as among desmopressin responders (424). This was recently illustrated by the demonstration of dominant inheritance of urge incontinence and/or enuresis in a large four generation family (Eiberg H, paper presented at the 2nd congress of the International Children's Continence Society, August 22–24, 1999, Denver, USA).

Characteristics. Detrusor-dependent enuresis is probably associated with a poor response to desmopressin treatment, although some response to the drug even in these children can be attributed to possible desmopressin effects on sleep and arousal and to the beneficial effect of a decreased urine flow into the hyperactive bladder. These children usually have smaller functional bladder capacity than other enuretic children (341, 412, 413), and their kidneys concentrate urine normally (341). The presence of urgency symptoms or day-time incontinence is common in this group (Schaumburg S, Rittig S, Djurhuus JC, paper presented at the 10th annual meeting of the European Society for Paediatric Urology, April 15–17, 1999, Istanbul, Turkey), and concomitant constipation or encopresis would not be a surprising finding.

11.4 Possible exceptions and special subgroups

Although it is proposed in this text that the division of bedwetting into diuresis dependent and detrusor-dependent varieties is clinically useful and pathogenetically relevant, it is not suggested that *all* enuretic children can be neatly assigned a place in one of these two subgroups. All subdivisions of heterogeneous clinical entities are more or less artificial, and perhaps it would be better to view detrusor dependency and diuresis dependency as two ends of a clinical spectrum.

Children with combined detrusor – and diuresis dependency. Since both nocturnal polyuria and detrusor hyperactivity can be supposed to be quite common, the combination of the two is probably not rare. Some children may share the characteristics of volume- and detrusor-dependent enuresis, or change from one type to the other. For instance, some children may concentrate urine poorly and suffer from combined day-and night-time wetting problems. Or they may start with enuresis that responds to desmopressin treatment, but then become therapy-resistant and finally achieve dryness with anticholinergic treatment.

Furthermore, an interaction between urine flow and detrusor hyperactivity has been recognised: an increased urine flow through the ureter is in itself a stimulus for detrusor contractions (425), and the hyperactive bladder becomes still more hyperactive when diuresis is increased (426).

Children with neuropsychiatric disturbances and enuresis. Children with ADHD have enuresis and/or day-time incontinence more often than other children (395–397). Their possibly somewhat atypical symptoms (171) might reflect a distinct pathogenesis. It is conceivable that the involuntary bladder voidings of these children are secondary to their disturbance of attention or to suggested disturbances of the autonomic nervous system (427–429), although more research is needed to support or reject these suspicions.

Bedwetting children who snore. Snoring is common among healthy children (207, 286, 288–290) and is considered harmless if there are no sleep apnoeas and the child is not suffering from excessive day-time sleepiness. There is no strong epidemiological association between snoring and enuresis (207, 290), but there is possibly a higher prevalence of enuresis among children with obstructive sleep apnoeas than in the general population (430), and it has been elegantly shown by Weider and co-workers that there are children who snore and wet their beds, who become dry when the upper airway obstruction has been removed (373).

The enuresis of heavily snoring children could be explained either by low arousability or by nocturnal polyuria (or a combination of the two). In Weider's study the children were observed to be difficult to arouse from sleep (373), and in other investigations it has been shown that the frequent disruption of sleep that occurs in snorers is associated with elevated arousal thresholds (280, 383). Sleep apnoeas have been shown to cause nocturnal polyuria (96, 431, 432). The snoring bedwetter may thus often belong to the diuresis dependent group.

Children with constipation and bedwetting. The not uncommon association between constipation and en-

uresis (352) has also been mentioned in this text. As explained above, it can be argued both that constipation may cause detrusor hyperactivity and that detrusor hyperactivity may cause constipation. Regardless of the causal relationship there is a strong case for the epidemiological association of detrusor hyperactivity, urge incontinence and constipation (353–356). It is fair to suggest that the enuresis of the constipated child is detrusor dependent rather than diuresis dependent.

12 TREATMENT: THEORETICAL CONSIDERATIONS

Although success has been claimed for several methods, only a few antienuretic treatment modalities have stood the test of controlled trials. Desmopressin and the enuresis alarm are presently the only therapies that can be recommended for routine use. There are, however, other methods, new and old, that show some promise and may be of use for specific groups of bedwetting children.

12.1 Historical methods

Numerous therapies have been tried against enuresis. Hedgehog testicles, prayers to saint Catherine of Alexandria, arsenic, porcine bladder, Belladonna, hare shot after sundown, lizard meat, the application of sacral blisters and physical punishment have all been tried with varying success, and historical accounts of enuresis therapy make for amusing reading (344, 433, 434). Because enuresis has a high tendency for spontaneous resolution the proponents of many treatment modalities have been able to claim success. The subcutaneous injection of sterile water has been reported to cure 87% of enuretic children (435), and the same kind of anectdotal success has been reported for amphetamine (436, 437), self-hypnosis (438) and psychotherapy (439), among others.

The long-lived tradition to treat enuresis with psychoanalysis and related therapies will not be penetrated in this text since they have not in controlled studies been shown to be effective and since, for reasons stated earlier, we do not consider enuresis to be a psychiatric disorder.

12.2 The enuresis alarm

Although an ingenious (but frightening) apparatus that delivered an electrical shock to the bedwetting child at the moment of bladder voiding was described as early as 1830 (440), the first functional enuresis alarm, using an auditory awakening stimulus, was constructed in the middle of this century (441). The alarm device consists of a urine detector – placed either in the child's underclothes or beneath the sheets – that is connected to an alarm clock that emits a strong wake-up signal when the detector is activated. For the alarm treatment to be successful both child and parents need to be motivated, since the sleep of the whole family might be disrupted and the treatment usually must be continued for several weeks without interruption.

The success rate of the alarm treatment is reported to be around 60–70% (305, 346, 347, 442, 443). A serious problem here is the disturbing lack of evaluations of alarm treatment success performed on an "intention to treat"-basis. Patients failing to comply or dropping out of treatment are seldom accounted for. Relapse after successful treatment occurs in 5–30% of children (305, 444, 445). Intensified treatment, involving the consumption of large quantities of fluid during the evenings to provoke enuresis after primary success has been achieved, may reduce this risk (444).

The enuresis alarm works by a simple principle: by waking the child from sleep at the moment of enuresis, he or she will gradually learn to recognise the imminent bladder voiding and to wake up instead and go to the toilet. However, this explanation is flawed by the fact that not all children successfully treated with the alarm experience nocturia after they have been cured (346, 347). A suggested explanation, that the alarm treatment helps the child to recognise and inhibit detrusor contractions while asleep or half-awake, has been provided above in chapter 8. It has recently been suggested that the time of night when the child is to be awakened is of minor importance (446), although this has to be confirmed with further studies (see "dry bed training" below).

12.3 Behavioural interventions, biofeedback

Apart from the alarm treatment, various other behavioural intervention techniques have been used. The so-called dry bed training, which includes regular waking of the child at night as the central therapeutic intervention, is recommended by an influential Dutch expert panel (447). It is reported to be a good addition to the alarm treatment (448), although opinions differ regarding this (449), and, as yet, no controlled study has confirmed that the waking schedule is a better treatment than placebo.

Biofeedback training, aiming at improving the ability to inhibit detrusor contractions, have shown some promise (450), but more studies are needed to confirm this.

In Japan a device has been constructed that is supposed to recognise the EEG patterns signalling imminent bladder emptying and wake the child before this takes place (451, 452). Although this idea is attractive, the success has, in our opinion, not been convincing, and we doubt the possibility of reliably predicting the moment of bladder emptying through

the EEG. It would be interesting to see if this apparatus has a higher success rate than a random waking schedule.

More promising is, in our view, the so-called "bladderscan" (453, 454), an ultrasound sensor that is worn on the lower abdomen and wakes the child when the urinary bladder volume is approaching a "critical" level. This apparatus has only been tested in pilot investigations as yet and controlled trials are eagerly expected.

12.4 Bladder distention exercises, urotherapy

Urotherapy is the recognised treatment of choice in day-time incontinence (455). Standard urotherapy rests on several principles, and a full description of these is beyond the scope of this text. Shortly, the urotherapist helps the child to adjust fluid intake and to achieve sound micturition habits by teaching how and when to void and helping him or her to recognise bladder sensations. Urotherapy has also shown some promise in the treatment of nocturnal enuresis (456), especially when combined with daytime incontinence.

Bladder distention exercises, when the child by gradually delaying micturition learns to augment functional bladder capacity, was introduced into the therapeutic arsenal by Starfield in the early seventies (457), although described a hundred years earlier (361). Since then there have been a few studies indicating a favourable effect in nocturnal enuresis (with or without day-time incontinence) (458, 459) and some investigations that did not show any such effects (460, 461). Modern research indicates that the main role of bladder distention exercises in the treatment of enuresis is as a reenforcement of conditioning or pharmacological therapies (462–464), or as a means of preventing relapse (465). The method requires a high degree of motivation and cooperation from the child, and non-compliance is associated with poor self-esteem or behaviour problems (462).

12.5 Other non-pharmacologic interventions

As mentioned in chapter 8, constipated children with enuresis often become dry when successfully treated for their constipation (356, 357). This is not surprising, given the association between constipation and detrusor-hyperactivity (356). Standard treatment of constipation or encopresis includes laxatives, diet changes and behavioural interventions (466, 467).

Analogously, heavy snorers with enuresis can get rid of both problems when their upper airway obstruction is removed (373, 468). Orthodontic corrections have also been reported to be beneficial (469, 470), supposedly by similar mechanisms. It has to be borne in mind, however, that most bedwetters do not snore (207).

Food allergies have been suggested to be over-represented among enuretic children (413), and treatment with hypoallergenic elimination diet has in one controlled study proven effective against enuresis (471).

There are a few reports about beneficial effects of acupuncture in the treatment of enuresis (472), an effect that may be dependent on an increased bladder capacity (Watanabe H, paper presented at the 2nd congress of the International Children's Continence Society, August 22–24, 1999, Denver, USA).

Another possibly effective therapy is anal or vaginal electrical stimulation in children with detrusor hyperactivity. This has in one study been demonstrated to be better than placebo even in children without day-time incontinence (473). Obviously, more studies are needed.

12.6 Tricyclic antidepressants

Since the early sixties tricyclic antidepressant drugs, and imipramine in particular, have been suggested as worth-while treatment methods of enuresis (474). A large number of studies, several of them placebo-controlled, have shown that roughly 50% of enuretic children were helped by imipramine (305, 475–479), although it was likewise clear that relapse after treatment was common (480–484), and that some children may develop tolerance to the drug (485).

Although it is clear that imipramine has a beneficial effect in some bedwetting children, the reasons for this are unclear. In fact, virtually every proposed pathogenetic factor may possibly be modulated by imipramine. Anticholinergic and smooth muscle relaxant effects have been suggested (486–488), as well as sympathomimetic or central noradrenergic mechanisms (475), leading to decreased detrusor irritability and increased bladder capacity (477, 489). The drug is also known to have some influence on sleep, resulting in arousal and suppression of REM sleep (377). Finally, another possible mechanism of antienuretic action is suggested by the finding that imipramine decreases urine production (326, 490), possibly through stimulation of vasopressin release (491). The suspicion favoured by the authors of this text is that the antienuretic potential of imipramin resides in central noradrenergic facilitation, since the drug may in selected cases be useful in children who have not responded to either alarm, antidiuretic or anticholinergic treatment.

Side-effects of imipramine treatment (nausea, anticholinergic side effects) are usually minor (484), but the substance is cardiotoxic in high doses and lethal reactions have been reported (492).

Even though imipramine as a treatment against enuresis is still common in some parts of the world,

it has today largely been abandoned in favour of more effective and safe treatment modalities, notably desmopressin and the enuresis alarm.

12.7 Desmopressin

As mentioned above, desmopressin was designed as a vasopressin analogue devoid of pressor effects but with intact antidiuretic action and with a longer plasma half-life than the hormone (163, 493).

In the late seventies it was found that desmopressin could be successfully used in the treatment of enuresis (401, 494, 495). Since then many studies have been performed (305, 365, 404, 412, 496–507), and reported success rates have varied between 40 and 80%. Most children relapse after treatment, so the curative effect is low (497, 502). There are, however, results that indicate some curative effects of the drug (502) and it has been suggested that the probability of cure in children responding favourably to desmopressin treatment increases if the drug is discontinued gradually (Butler RJ, paper presented at the 2nd congress of the International Children's Continence Society, August 22–24, 1999, Denver, USA).

There is a small group of children who do not respond to desmopressin in ordinary dosage (20–40 μg intranasally or 0.2–0.4 mg orally at bedtime) but who will become dry when the dose is doubled (345).

Desmopressin, by virtue of its V2 receptor-agonistic properties, acts by decreasing urine output and thus delaying the moment of bladder overfilling until the night has passed. At least this has always been the general view. Recently, some doubt has been thrown on this explanation by the researchers led by dr Eggert in Kiel, Germany. They have described an enuretic boy with nephrogenic diabetes insipidus secondary to a mutation in the V2 receptor gene, who consequently had no antidiuretic effect of desmopressin but who nevertheless became dry when given the drug (508). Central nervous system effects of desmopressin, possibly mediated via the V1b receptor, might be more important than previously thought in this respect. Note, however, that desmopressin has not been shown to cross the blood-brain barrier (114, 509, 510).

Treatment with desmopressin is generally considered safe and side-effects are rare, provided that the patient does not consume large amounts of liquids while taking the drug (511, 512). If desmopressin is combined with large fluid intake there is a significant risk of hyponatremia with convulsions or unconsciousness (513).

12.8 Anticholinergics and smooth muscle relaxants

Foremost among parasympatholytic substances used in urological practice is oxybutynin, a drug with both anticholinergic and smooth muscle relaxant properties (514), that has proven to be effective in the treatment of day-time incontinence caused by detrusor hyperactivity (455). Some investigators have treated enuresis with oxybutynin and have reported some success (415, 417, 515, 516). In these studies incontinent children were included as well, and not only children with monosymptomatic nocturnal enuresis. The only controlled study in which only children with monosymptomatic nocturnal enuresis were included, yielded no significant difference between oxybutynin treatment and placebo (418). The recent study by Kosar and colleagues deserves special mention (419): they found that 16 of 36 enuretic children responded favourably to oxybutynin treatment, when given a total maximum dose of 20 mg daily, that all these responders had cystometrical signs of detrusor hyperactivity, and that response was associated with a dramatic increase in bladder capacity. Of these 16 children, 11 had monosymptomatic enuresis.

We have recently described a selected group of children with monosymptomatic enuresis resistant to desmopressin and the enuresis alarm in which more than 50% became greatly improved when given combined treatment with desmopressin and oxybutynin (345).

The toxicity of oxybutynin is low (517) but side effects – mainly dryness of the mouth, constipation and vertigo – may limit its usefulness (518). Especially constipation may pose a problem, since – as has been explained above – children with detrusor hyperactivity are often constipated from the start, and the development of constipation may aggravate detrusor hyperactivity and thus counteract the beneficial effects of the drug. Furthermore, children using oxybutynin should be examined regularly to exclude the accumulation of residual urine, since this is possibly associated with a risk of bacterial colonization and urinary tract infection (519).

The novel anticholinergic and smooth muscle relaxant drug tolterodine has, in adults, shown a more favourable therapeutic profile, with the same clinical efficacy and a lesser frequency of side-effects (520–525). Preliminary data indicate that it is useful in the paediatric population as well (Hjälmås K, personal communication) and a fair guess is that many of the children that would today receive oxybutynin therapy will in the not too distant future be given tolterodine.

12.9 Other pharmacologic treatment modalities

Case reports and isolated studies on various other treatment modalities have been published, only three of which will be mentioned here: androgens, pseudoephedrine and prostaglandin synthesis inhibitors.

During the 1930s and 40s several investigators

claimed favourable effects of androgens in enuresis (526–528). These results did not result in any changes in treatment strategies, but lately one placebo-controlled study showed promising effects of mesterolone in a group of boys with monosymptomatic enuresis (529) (but the pre-announced two year follow-up report has not yet appeared).

In a small patient material the sympathomimetic drug pseudoephedrine gave better treatment success than indomethacin or oxybutynin (530). A success rate of 86% was reported in one larger study, in which, however, the treatment and control groups were poorly defined (531). Flavoxate, a drug with central and peripheral relaxing effects on the detrusor (532), has in one uncontrolled study shown some promise in the treatment of children with detrusor hyperactivity and enuresis (533).

Since prostaglandins are involved in the regulation of urine production it is not surprising that prostaglandin synthesis inhibitors have been tested as therapeutic alternatives against nocturnal enuresis. Indomethacin has been reported to be useful in combination with imipramine (534), and diclophenac was judged to be better than placebo in a small controlled study (535). In an other study, indomethacin was not shown to be effective (530).

12.10 Treatment summary

Although many methods have been tried, there are today only two safe treatment modalities with proven efficacy against enuresis: the enuresis alarm and desmopressin treatment. The advantages of the former are that it is safe and that it has a curative potential, while the advantages of the latter are that it is simple to use and that the beneficial effects appear without delay. However, the enuresis alarm is awkward to use and requires good motivation, and desmopressin has only minor curative potential.

Since the alarm and desmopressin are effective against different pathogenetic mechanisms (sleep and urine production) they may be combined for greater efficacy. Consequently, it has been shown that the combination of alarm treatment and desmopressin can be a more effective alternative than either treatment used alone (536), but the large number of children that do not respond to either treatment still constitute a major clinical, psychological and social problem. There is a widespread clinical impression that approximately 75% of bedwetting children respond to either of these two treatment modalities, but there are no firm epidemiological data to confirm this observation.

Treatment with anticholinergic or smooth muscle relaxant drugs is worth-while in some enuretic children, and there is probably still a place for the use of antidepressants in selected groups of children with therapy-resistant enuresis. Furthermore, some of the many alternative methods that have been described may find a role in the antienuretic treatment repertoire, but controlled studies in well-defined patient populations are urgently needed. Particularly, studies are needed in which hints can be given about what to do with the children that do not respond to desmopressin or the enuresis alarm.

13 TREATMENT: PRACTICAL CONSIDERATIONS

In this chapter suggestions will be given about how to evaluate and treat children with enuresis. The proposed treatment strategies are based on both the available evidence and the hypotheses that are presented above, and thus represent the views (as of the year 2000) of the Enuresis Research Group of Uppsala, Sweden. The recommendations given in this text coincide largely with those given by Läckgren *et al*. in reference (537).

13.1 Initial evaluation and treatment

Evaluation. The primary evaluation of the enuretic child is simple and straight-forward. History and a thorough physical examination will usually suffice to exclude those organic disorders that may present with bedwetting as a symptom – urinary tract infection, diabetes mellitus and neurological abnormalities in particular.

The history should include questions regarding the type of enuresis (primary or secondary enuresis, monosymptomatic enuresis or combined day-and nighttime wetting) frequency of wetting accidents, and daytime voiding habits. Urgency symptoms and signs of urinary tract infection (UTI) should be asked for, as well as symptoms suggesting constipation, such as encopresis. Parents should be asked about the presence of enuresis in the family and about the arousability of the child at night. It is also important to find out whether the child regards the enuresis as a serious problem and if it affects his or her life greatly.

The physical examination should include inspection of the genitals and a standard neurological examination. A rectal examination should be performed if constipation is suspected, since the presence of stool in the rectum (without the child sensing a need to go to the toilet) is strongly indicative of faecal impaction (538).

Blood samples or other invasive investigations are not needed at this stage if the case history and physical examination both indicate primary monosymptomatic nocturnal enuresis. Even the need for urine examinations can be questioned if the child has never been reliably dry, since it would be strange for bedwetting to

be the sole manifestation of diabetes mellitus or urinary tract infection for several years. In secondary enuresis, however, urinary analyses are certainly needed.

If concomitant day-time incontinence is present, measures should be taken to treat this before specific treatment of the enuresis starts. This means that bladder training is started, preferably with the help of a urotherapist. Pharmacological treatment of day-time incontinence is indicated if bladder training alone doesn't succeed; oxybutynin is then the drug of choice today (455), although tolterodine will possibly replace oxybutynin in this role in the near future. Urodynamic investigations may also be needed in these children, but seldom at this early stage, unless there are symptoms or signs suggestive of outlet obstruction (i.e. weak urinary stream), aberrant ureter (i.e. continuous leakage) or other urological conditions requiring specific treatment.

Symptomatic UTIs in boys or recurrent symptomatic UTIs in girls should prompt (antibiotic treatment and) radiological investigation without delay.

Treatment. When organic disease is not suspected, and the child suffers from monosymptomatic nocturnal enuresis that he or she considers a significant problem (usually by the approximate age of six years) it should be treated. Initial treatment will usually be the enuresis alarm or desmopressin, and our recommendation is to leave this choice to the child and his or her family.

The advantages of desmopressin are that it is easy to administer and that effects appear without delay. The major drawback is the low curative potential. The usual dose is 0.2–0.4 mg orally or 20–40 μg intranasally at bedtime. Since the response or non-response to this drug will be evident quite immediately there is no reason to treat for more than, say, two weeks if the child experiences no beneficial effects of the drug. For children responding to this treatment, the decision to take medication continuously or just on "important" nights should be left to the families. The one important thing to remember when prescribing desmopressin is to tell the family that large amounts of liquid should not be consumed on nights when the drug is taken. It has been suggested that, to eliminate the risk of hyponatremia, the child should not be allowed to drink more than 240 ml, or 30 ml/kg, during evenings and nights when the drug is taken (539, 540). One practical approach is to allow one glass to drink at dinner and at most half a glass at bedtime. If desmopressin treatment is successful and the child chooses to medicate every night a one-week interruption is recommended every three months in order to see if the problem has disappeared. It has recently been shown that the chances of permanent cure may increase adopting a "structured withdrawal program". This implies the gradual discontinuation of the drug and positive reenforcement of dry nights without medication (Butler RJ, paper presented at the 2nd congress of the International Children's Continence Society, August 22–24, 1999, Denver, USA).

The advantages of alarm treatment are that it has a definite curative potential and that it is completely harmless. To many families the prolonged use of hormonal substitution is not an attractive option, and to them the alarm is often a better alternative. It does, however, require a high degree of compliance and motivation from both the parents and the child to be effective. Children with infrequent wetting episodes are not suitable candidates for alarm treatment, and neither are children who are considered extremely difficult to arouse from sleep by their parents. Families using this treatment should be instructed to help the child to awaken and go to the toilet immediately when the alarm sounds. This usually means that one parent should sleep in the same room as the child. Furthermore, it is imperative that the treatment be continuous; thus, no interruptions during week-ends should be allowed. However, the child should not be awakened more than once per night, since too much sleep disruption could impair day-time alertness. Treatment should be continued until either 14 consecutive dry nights have been achieved or more than a month has passed without signs of effect. To decrease the risk of relapse the use of an "overlearning" method has been advocated; this involves the consumption of large fluid volumes during the evening after primary success has been achieved until once again 14 consecutive dry nights have passed (443, 444).

Children not responding to desmopressin should usually be offered the alarm, and vice versa.

Psychological aspects. Although most parents nowadays do not reproach or punish their bedwetting children, many children nevertheless think that bedwetting is, in one way or an other "their own fault". One of the duties of health care professionals is to tell him or her that this is not the case. I usually tell the child that "you wet your bed because your bladder is not as smart as you are" or "the reason that you pee in your bed is that your kidneys make too much pee during the night, and that is not your fault". Another common problem is that the child thinks that he or she is (almost) the only bedwetting person in the world. This misconception is strengthened by the fact that most bedwetting children keep their problem top secret even from their closest friends. This dark secret can make the child terribly lonely. Some children even report that because of that eternal hidden knowledge, they can never feel really happy.

Consequently, the doctor should also inform the child that enuresis is a very common disorder, and that it can be successfully treated. Furthermore, a good piece of advice to the children is that they tell their best friends about their problem; this will usually – in contrast to the child's belief – not result in teasing and bullying, and it will lessen the child's sense of loneliness.

Although the mainstay of anti-enuresis treatment is somatically oriented, the mind should not be forgotten. Enuretic accidents should (of course) not be punished, but the reward of dry nights strengthens the child's self-esteem and can be expected to hasten the cure. The success of the structured withdrawal program mentioned earlier is attributed to the "internalization" of the dry nights, that is, to the child's explicit knowledge that he or she herself, not the medication, should be given the credit for many of the dry nights that are achieved.

13.2 Therapy-resistant enuresis

Secondary evaluation. Children with enuresis that do not respond to the alarm or to desmopressin in ordinary dosage, and non-responders to desmopressin in whom the alarm is considered unsuitable, should receive the attention of a specialist, usually a paediatrician with a specific interest in voiding problems or a paediatric urologist.

The urodynamic and renal status of these children should be evaluated with extra care. The children are asked to complete a home voiding chart for a few days, so that functional bladder capacity can be documented and cases of excessive urine production can be detected. Uro-flow measurements are performed to detect signs of outlet obstruction and raise possible suspicions of detrusor hyperactivity, and residual urine is assessed with a simple ultrasound examination. A thirst provocation test, to assess renal concentrating capacity, may also be useful, in order to detect osmoregulatory defects and gain prognostic information regarding further treatment. The rectum should be examined for the presence of stool and, if this examination turns out negative, a plain x-ray of the abdomen should be considered. It is our opinion that cystometry, cystoscopy and further radiologic evaluation of the kidneys and urinary tract are not necessary at this stage, provided that the above-mentioned examinations do not reveal signs of neurological disturbances, renal damage or bladder outlet obstruction. Nor will blood tests give much useful information.

Secondary treatment, diuresis dependent enuresis. Children with diuresis dependent enuresis usually respond to desmopressin (or alarm) treatment. However, in a minority of the children not responding to this treatment, diuresis-dependency can still be suspected, for instance: children with a partial desmopressin response, children who void during the earliest part of the night and children with low renal concentrating capacity. In these children treatment with desmopressin 0.8 mg orally at bedtime could be tried, since it has been shown that there are some enuretic children who need high desmopressin doses to achieve dryness (345). During high-dose desmopressin treatment it is imperative that the child does not consume large amounts of fluids during the evening and night.

Secondary treatment, detrusor dependent enuresis. The majority of desmopressin non-responders suffer from detrusor-dependent enuresis. Many of these children experience urgency symptoms, have small bladder capacity, go to the toilet often and/or have current or previous incontinence as well, and they are often constipated.

The appropriate second-line treatment for these children is oxybutynin (or tolterodine) orally. Our practice is to give 5 mg of oxybutynin in the morning and 5–15 mg in the evening, starting with half that dosage during the first week. The morning tablet is probably not necessary if there is no concomitant daytime incontinence. Treatment success is estimated after approximately two months. If response is partial, the addition of desmopressin in standard dosage may be beneficial. Our experience is that responders to oxybutynin therapy usually need to continue this mediciation for 6–12 months. During this treatment the child should try to develop sound, regular voiding habits and the family should watch out for signs of constipation or urinary tract infection. If oxybutynin is used more than a few months residual urine should be measured regularly and, if present, prompt temporary withdrawal of the drug.

Tertiary treatment. If desmopressin, alarm and anticholinergic treatment have all been tried without success or have been judged unsuitable, the cautious use of imipramine might be warranted. This is, however, a matter for specialist clinics and not for the general paediatrician. It is our experience that imipramine is helpful in approximately 50% of cases unresponsive to first-and second-line treatment.

13.3 Treatment of special subgroups

Enuretic children with neuropsychiatric disorders. It is our impression that enuretic children with ADHD seldom respond to desmopressin therapy and seldom comply with alarm treatment. Furthermore, oxybutynin treatment is associated with a tendency for psychological side-effects (aggressive behaviour) in

this group, whereas imipramine often has a beneficial effect both against the bedwetting and the hyperactivity. This is, however, a clinical impression that needs to be tested in controlled trials before general recommendations can be made.

Snoring bedwetters. In a bedwetting child who is reported to snore heavily and/or experience nocturnal apnoeas, tonsillectomy and/or adenoidectomy should be considered as a possible treatment, at least if ordinary antienuretic treatment fails.

Constipated bedwetters. Constipation should always be kept in mind in children with therapy-resistant enuresis, especially if they also have encopresis. Note, however, that many children with constipation defecate every day and have no definite bowel complaints. Still, the diagnosis of constipation is not very difficult to ascertain. Manual rectal examination has a high positive predictive value, and a plain x-ray examination will verify uncertain cases (538).

Treatment of these children should be aimed at the bowel first. This usually means laxatives and the institution of regular, daily bowel habits. If enuresis persists after the constipation has been eradicated, the enuresis alarm would be a good choice, since constipated bedwetters can be suspected to be detrusor dependent rather than diuresis dependent. A good second-line therapy would be oxybutynin (or tolterodine) medication, but only in the evening and with continued use of laxatives of the non-irritant type given at breakfast.

14 TOWARDS A UNIFYING THEORY: HYPOTHESIS OF A COMMON AETIOLOGY

Throughout much of this text the heterogeneity of nocturnal enuresis has been stressed. Children with enuresis can and should be evaluated and treated individually, and clinically and pathogenetically meaningful subgroups can be discerned. Still, further research might show that these different kinds of enuresis share a common disturbance. A hypothesis implying such a common aetiology will be presented in this chapter. We are well aware that, in doing so, we are leaving the firm ground of established fact and the not so secure area of clinical experience and are entering the misty field of enthusiastic speculation.

The reason for suggesting such a unifying hypothesis is threefold: 1) The clinical overlap between detrusor dependent and diuresis dependent enuresis. 2) The observation that there is no clear link between genotype and phenotype in enuresis. 3) The fact that many of the different mechanisms underlying nocturnal dryness rely heavily on the autonomic nervous system and on neurons in one small area in the brainstem.

The locus coeruleus (LC) has been mentioned several times in this text. This is a small, circumscribed area in the rostral pons, containing roughly half of the noradrenergic neuron population, or 70% of the norepinephrine, in the central nervous system (259). The efferent network of this nucleus is uniquely wide, including virtually all parts of the central nervous system (541, 542), and providing the sole noradrenergic innervation of, for instance, the hippocampus and other parts of the cerebral cortex (262, 543). Accordingly, to quote Dr Aston-Jones “The noradrenergic locus coeruleus (LC) system has been proposed to be involved in almost as many brain and behavioral phenomena as there are investigators who study this structure” (268).

As mentioned previously, the LC plays a crucial role in arousal and attention. This is an important part of the reticular activating system, and it responds with increased firing during arousal reactions caused by either the external environment or by internal stimuli such as bladder distension or detrusor contractions (273). And attention, which involves ignoring weak or irrelevant stimuli and reenforcing strong or relevant stimuli, is a function of the LC as well (544). The bulk of the evidence assigns a central role for the LC in vigilance, i.e. to prepare the brain for new or relevant information (268).

Children with ADHD have been shown to have an unbalanced basal activity in the central noradrenergic system (427), of which the LC is the principal nucleus. It is also worth noting in this context that the main binding site for desipramine, the active metabolite of imipramine, is the LC (545), and that an intact LC is required for the central nervous effects of this drug (546).

The pontine micturition center and the LC overlap to a large extent, as described above, and the firing of LC neurons has been clearly shown to influence bladder function (181, 547). It is also true that bladder distention increases the firing of LC neurons (272, 273, 548, 549), and destruction of this nucleus may cause all kinds of micturition disturbances in man (550). Thus, a possible deficient inhibition of the micturition reflex among enuretic or incontinent children could certainly have brainstem-related causes.

A link between the LC and water homeostasis also is possible. There are direct and indirect connections between the noradrenergic LC neurons and the vasopressin-producing cells of the hypothalamus (551–556), and stimulation of the LC neurons has been shown to cause vasopressin release (557). Interestingly, a reciprocal vasopressinergic innervation of the LC from the hypothalamus has also been described

(264), and vasopressin stimulates the activity of LC neurons (558). Furthermore the LC has been reported to cause natriuresis (559) and bilateral destruction of this nucleus in rats have been associated with polydipsia (560).

The hypothesis put forward is that disturbances in the region of the LC might result in enuresis secondary to nocturnal polyuria, detrusor hyperactivity or decreased arousal thresholds, or combinations of these. Small differences – structural or biochemical – in these disturbances could account for clinical differences in enuresis phenotype.

Support for this hypothesis can be found when looking at the role of the LC in the function of the autonomic nervous system. As has been mentioned earlier in chapter 4.2, the LC may be regarded as the principal nucleus of the central nervous system branch of the sympathetic nervous system. It has also been explained that

1) parasympathetic suppression may cause antidiuresis via vasopressin release
2) sympathetic activity in the renal nerve has antidiuretic effects
3) the sympathetic nervous system is active during the urine storage phase
4) the parasympathetic nervous system is active during the voiding phase
5) the parasympathetic nervous system is active during non-REM sleep
6) the sympathetic nervous system is active during arousal from sleep.

The suspicion that arises from these observations is that the enuretic child – regardless of whether the bedwetting is caused by nocturnal polyuria, detrusor hyperactivity and/or low arousability – may be characterized by parasympathetic hyperactivity or sympathetic inhibition. Of course, this remains to be proven.

To our knowledge the only investigator to date that has touched upon this question is Yakıncı, who, in a pilot investigation found enuretic children to exhibit signs of parasympathetic hyperactivity compared to dry children (561). More research in this field is needed.

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