A qualitative approach of the neuronal control of the lower urinary tract

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including the paper:

"NEURONAL CIRCUITRY OF THE LOWER URINARY TRACT:
ITS STEERING BY CENTRAL AND PERIPHERAL CONTROL MECHANISMS:
A REVIEW."

M.V. Kinder\textsuperscript{1,2}, E.H.C. Bastiaanssen\textsuperscript{2,4}, R.A. Janknegt\textsuperscript{1}, E. Marani\textsuperscript{2}.

\textsuperscript{1} Department of Urology, Academic Hospital Maastricht.
\textsuperscript{2} Neuroregulation Group, Dept. of Physiology, Medical Faculty, University of Leiden.
\textsuperscript{3} Faculty of Mechanical Engineering, Eindhoven University of Technology.
\textsuperscript{4} Medical Informatics, Medical Faculty, University of Leiden, The Netherlands.

M.V. Kinder  
Report: **WFW 94.041**  
Eindhoven University of Technology  
Biomedical Engineering  
FOREWORD

This report, "A qualitative approach of the neuronal control of the lower urinary tract", gives you a closer look at the work that I have done during the fulfilment of my final project.

It serves as a compulsory part of my Master's Degree Program to acquire an Engineering Degree in Biomedical Engineering at the Eindhoven University of Technology.

The final project has been realised in about 16 months, from 8 December 1992 to 14 April 1994, as a cooperation of: the Eindhoven University of Technology, Faculty of Mechanical Engineering, Division of Fundamentals of Mechanical Engineering; the Academic Hospital of Maastricht, Department of Urology; the University of Leiden, Medical Faculty, both Medical Informatics and Department of Physiology, Neuroregulation Group.


I would like to thank all of my mentors for their participation, time and very pleasant cooperation during this period.

This applies for all people in Eindhoven, Maastricht and Leiden who took somehow part in the realisation of this report.

A special thanks to Frank van Leeuwen, who made the flow charts possible and of course to my parents, who always supported me.

I dedicate my work to all the people in this world that never had a chance in life.
SUMMARY

The functioning of the lower urinary tract has been studied in several ways: (neuro-)anatomical and structural research, urodynamical measurements and pharmacological studies have been performed.

In this context the following problems can be discerned:

1. Studies considering the central and peripheral connections to the lower urinary tract overlap only partially and also contain conflicting data. No complete and structurally organized model can be found.
2. Descriptions of muscle morphology in the lower urinary tract are still controversial, resulting in inconsistent nomenclature.
3. Broad individual and intersexual variability of the pathways is present within the peripheral connections.
4. Only a modest amount of data on relay stations in the pathways between the spinal cord and the target organs is available.

By comparison of data available in the literature, four qualitative models are derived, which constitute neuronal circuitry for control of the lower urinary tract. De Groat integrates animal experiments to support parts of his description of pathways and their function; Bradley uses a "loop concept" to describe the peripheral and central circuitry; Blaivas' main article arises from a clinical study, the results of which were compared to models of De Groat and Bradley, leading to his own representation. The most extensive study on connections related to the micturition center in the brain stem has been published by Holstege.

The four models are portrayed in the same way: firstly, by a description of the neuronal circuitry itself and secondly by a description of the functional interpretation of this circuitry.

The neuronal circuitries as described by the different authors are compared and integrated in this report to suggest a complete model, which represents the general central and peripheral control mechanisms. Several publications filling in details or parts of the circuitry were consulted in order to complete the neuronal control overview.

It is concluded that the proposed reflex arcs and supraspinal connections involved in micturition and continence are different and sometimes contradictory. Little is known about how autonomic information of the lower urinary tract is relayed to supraspinal structures. Information about supraspinal interconnections and their function in micturition control is still fragmentary. The function of both the pelvic floor musculature and the peripheral nervous system in the control of the lower urinary tract is probably underestimated.

Two applications of the proposed neuronal circuitry are discussed: a reduced version can be used for neural network simulations and the proposed circuitry provides an approach for future research in neurostimulation of the uropoetic system.
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ITS STEERING BY CENTRAL AND PERIPHERAL CONTROL MECHANISMS:
A REVIEW.

M.V. Kinder1,2, E.H.C. Bastiaanssen3,4, R.A. Janknegt1, E. Marani2.

1 Department of Urology, Academic Hospital Maastricht.
2 Neuroregulation Group, Dept. of Physiology, Medical Faculty, University of Leiden.
3 Faculty of Mechanical Engineering, Eindhoven University of Technology.
4 Medical Informatics, Medical Faculty, University of Leiden, The Netherlands.

ABSTRACT

Four qualitative models, which constitute neuronal circuitry for control of the lower urinary tract, are derived from literature. Using these models, and additional publications to fill in details or parts of the circuitry, one model representing general central and peripheral control mechanisms was designed. It is concluded that the proposed reflex arcs and supraspinal connections involved in micturition and continence are different and sometimes contradictory. Little is known about how autonomic information from the lower urinary tract is relayed to supraspinal structures. Information about supraspinal interconnections and their function in micturition control is still fragmentary. The role of both the pelvic floor musculature and the peripheral nervous system in the control of the lower urinary tract is probably underestimated. Two applications of the proposed neuronal circuitry are discussed: a reduced version can be used for neural network simulations and the proposed circuitry provides an approach for future research in neuromodulation and neurostimulation of the urological system.

INTRODUCTION

The human system of bladder, urethra and pelvic floor has to satisfy two contradictory needs: its function is to store urine, thereby offering complete continence, whereas it is also responsible for the controlled evacuation of urine. The functioning of the lower urinary tract has been studied in several ways: (neuro-)anatomical research, urodynamic measurements and pharmacological studies have been performed. This paper reviews the literature on the neuronal pathways controlling the lower urinary tract. It does not concern conflicting data on the structure of the bladder and its neck, nor does it discuss differences between the female and male urethrae.

The studies considering the central and peripheral nervous connections involved in the control of the urological system overlap only partially and also contain conflicting data (Baljet, 1981; Baljet and Drukker, 1979; Blaivas, 1982, 1985, 1988; Bradley, 1978;

De Groat integrates animal experiments to support parts of his description of pathways and their function in human (De Groat and Lalley, 1972; De Groat, 1975; De Groat et al. 1979ab; De Groat and Steers, 1990). Bradley uses a "loop concept" to describe the peripheral and central circuitry of the lower urinary tract (Bradley et al., 1974; Bradley, 1978; Fletcher and Bradley, 1978). Blaivas' main article arises from a clinical study, the results of which were compared to models of De Groat and Bradley, leading to his own representation of the neuronal connections of the uroperic system (Blaivas, 1982). His description of pathways has been updated in 1990. The most extensive study on connections related to the micturition center in the brain stem has been published by Holstege (1989) and Holstege and Griffiths (1990).

The neuronal circuitries as described by De Groat, Bradley, Blaivas and Holstege are chosen to be discussed in this paper, because these authors consider both peripheral and central connections and discuss the function of these connections in the control of the lower urinary tract. These four theories are compared and integrated in this paper to suggest one model of the neuronal control of the lower urinary tract. Several other publications filling in details or parts of the circuitry were consulted in order to complete the neuronal control overview (e.g. Bradley, 1969; Bradley and Conway, 1966; Bradley and Teague, 1968a, 1969abc; De Groat and Saum, 1971, 1972; Dixon and Gosling, 1987; Elbadawi, 1988; Gosling, 1985; Marani et al., 1993; Morisson, 1987abcd; Raz, 1978).
PROCEDURE

The procedure used to model the neuronal circuitry of the lower urinary tract is as follows:

1. Inventarisation of the existing theories and models.
2. Integration of the described connections, reflexes and functional mechanisms from one author into his qualitative model.
   Four qualitative models, derived from the literature, are portrayed in the same way: firstly by a description of the neuronal circuitry itself and secondly by a description of the functional interpretation of this circuitry.
3. Comparison of the models.
4. Realisation of one qualitative model based on the available data, which represents the general central and peripheral control mechanisms.
5. Applications of this qualitative model:
   The qualitative model is reduced to a version that can be used in neural networks (see Bastiaanssen et al., 1993).
   The extended qualitative model provides an approach for future research in neuromodulation and neurostimulation of the uroepithelial system.

The models are presented as flow charts (see figs. 1 to 13) and in each case the layout is principally the same.

The flow charts should be read from the top to bottom. The blue printed upper part of the flow chart consists of the *afferent* or sensory system, connecting effector structures to spinal and/or supraspinal structures. The *supraspinal* structures are located at the black coloured mid-portion of the flow chart. The green coloured lower part shows the *efferent* or motor system, receiving information from the central nervous system.

The flow charts can also be interpreted from left to right, showing structures belonging to the *somatic*, *parasympathetic* and *sympathetic* nervous system in that order.

A *block* represents a nervous structure or a muscle effector. Sensors or receptors are anatomically located inside or very near the muscular tissue. There are no special blocks reserved for sensors; they are thought to be integrated in the effector blocks. A nervous structure can be located at the peripheral nervous system or at the spinal part of the central nervous system. *Supraspinal structures* in the central nervous system are represented by a circle.

The *arrows* in the flow chart denote the connections between the different structures. Peripheral structures are connected to each other by nerves, indicated in the descriptions by their anatomical names. Central connections are named as tracts. Each connection is described in the section "Circuitry". Here the appropriate text is linked to its flow chart by a reference between square brackets.
Sometimes plus and minus signs are present in the flow charts to indicate the functional mechanisms. The plus sign denotes an excitatory effect and the minus denotes an inhibitory effect. Flow charts that represent a functional mechanism show thick red lines for the activated pathway(s) and structures; not activated pathways and structures are shown by thin black lines.

The coloured bars placed in the left side of the flow charts enables the reader to compare quickly the amount of attention that is being paid to specific structures. The three basic colours can be found again: blue for the afferent part, black for the supraspinal part and green for the efferent part. The little circles code muscular or nervous structures in the following way: red for muscular tissue, orange for nervous structures of the peripheral nervous system and yellow for nervous structures inside the spinal cord. The coloured circles refer to the structures in the flow chart on the same vertical level.

The signal flow within the flow charts is as follows:

1. In case of a supraspinal reflex, the afferent pathway originates in a muscle effector on top of the flow chart and terminates in a supraspinal nervous structure (represented by a circle located at the mid-portion of the flow chart). Along this afferent pathway several other synapses can occur, which will not always be depicted, e.g. because the author does not mention it.

   The efferent pathway originates in the supraspinal nervous structure(s) and provides two functions. A muscle effector can be affected or another nervous structure, supraspinal, spinal or peripheral, can be modulated.

2. In case of a spinal reflex, supraspinal structures in the mid-portion of the flow chart are not involved. The afferent pathway terminates in a spinal nervous structure on the upper half of the flow chart. The efferent pathway originates in the same spinal nervous structure located on the down half of the flow chart and can have two functions. A muscle effector can be affected or another nervous structure can be modulated.

For all structures, the nomenclature used by the cited author in his papers is taken over. One should note, that even in the papers of one and the same author the nomenclature varies. In such a case a global and consistent nomenclature is used here and, when necessary, the nomenclature used in the referred paper is mentioned as well.
RESULTS

THE MODEL OF DE GROAT

Circuitry (see fig. 1.1)

Musculature of the lower urinary tract
Within the lower urinary tract the following muscular structures are described: striated urethral musculature, referred to as the external urethral sphincter [EXTERNAL URETHRAL SPHINCTER]; the bladder, consisting of the smooth detrusor muscle [BLADDER]; the trigone and its connected smooth urethral muscles [TRIGONE & SMOOTH URET. MUSC.].

Sympathetic connections
Tension receptors inside the bladder wall are connected to afferent fibres, which are conveyed by the pelvic nerve. These fibres enter the sacral spinal cord to terminate on sympathetic neurons inside the thoracolumbar cord (De Groat and Lalley, 1972; De Groat et al., 1979; De Groat and Steers, 1990) [BLADDER → TH-L]. A descending spinal tract originates in the pontine micturition center and projects to the thoracolumbar spinal cord segments (De Groat et al., 1979; De Groat and Steers, 1990) [PONTINE MICTUR. CENTER ~ TH-L].

Sympathetic efferent fibres are presented from a functional point of view (see fig. 1.1) as originating in the thoracolumbar spinal cord, synapsing in pelvic ganglia [TH-L → PELVIC PLEXUS], on the detrusor muscle [TH-L → BLADDER] and the bladder base and the smooth musculature of the urethra (De Groat and Steers, 1990; De Groat et al., 1979) [TH-L → TRIGONE & SMOOTH UR. MUSC.].

Somatic connections
Afferent input from tension receptors inside the bladder wall in De Groat’s model travels in the pelvic nerve to Onuf’s nucleus, a circumscribed somatic motor region in the ventral horn of the sacral spinal cord [BLADDER → ONUF’s NUCLEUS]. Afferent nerve fibres from the external urethral sphincter and other urethral afferents reach through the pudendal nerve the sacral spinal cord, where they terminate in several layers of the sacral dorsal horn (De Groat and Steers, 1990) [EXTERNAL URETHRAL SPHINCTER → SACRAL DORSAL HORN]. The sensory endings of these pudendal nerve afferents transmit, among other information, the sensation of urine flow in the urethra.

The pontine micturition center is connected by a direct descending spinal tract to Onuf’s nucleus [PONTINE MICTUR. CENTER → ONUF’s NUCLEUS]. In the cat fibres coming from other supraspinal structures first synapse in the pontine micturition center before they terminate on Onuf’s nucleus (De Groat and Steers, 1990) [CORTEX DIENCEPHALON → PONTINE MICTUR. CENTER → ONUF’s NUCLEUS].

Efferent nerve fibres originating in Onuf’s nucleus are conveyed to the external urethral sphincter by the pudendal nerve [ONUF’s NUCLEUS → EXTERNAL URETHRAL SPHINCTER].
Parasympathetic connections
Tension receptors inside the bladder wall project to neurons in laminae I, V, VII and X of the sacral spinal cord via the pelvic nerve [BLADDER → SACRAL DORSAL HORN]. From here, ascending neurons terminate in the pontine micturition center (De Groat and Steers, 1990) [SACRAL DORSAL HORN → PONTINE MICTUR. CENTER].
An efferent tract, originating in the pontine micturition center, projects to the sacral autonomic nucleus, an intermediolateral cell group at sacral spinal cord segments S₂-S₄ [PONTINE MICTUR. CENTER → SACRAL AUTONOMIC NUCLEUS]. From the sacral autonomic nucleus, preganglionic neurons send axons in the pelvic nerve to ganglion cells, which are situated inside the pelvic plexus [SACRAL AUTONOMIC NUCLEUS → PELVIC PLEXUS] and bladder wall (De Groat and Steers, 1990) [SACRAL AUTONOMIC NUCLEUS → BLADDER]. The pelvic ganglia send parasympathetic nerve fibres to innervate the urinary bladder [PELVIC PLEXUS → BLADDER]. Efferent fibres leaving the sacral detrusor nucleus to innervate the bladder presumably give off collaterals, which probably return to interneurons near the sacral autonomic nucleus (De Groat et al., 1979b; De Groat and Lalley, 1972). In figs. 1.1 and 1.2 this recurrent connection is thought to be integrated in the block [SACRAL AUTONOMIC NUCLEUS].

Functional mechanisms (see fig. 1.2)

Storage
During the filling phase of the urinary bladder, tension receptors inside the bladder wall note the distension of the bladder wall and produce low-level firing in pelvic nerve afferents. Afferent fibres of the pelvic nerve convey this information to the sacral spinal cord, connect to Onuf’s nucleus or ascend to the thoracolumbar segmental levels.

Low-level afferent firing results in activation of a complex vesicosympathetic reflex, which is organised as a sacrolumbar intersegmental spinal pathway. An effect of sympathetic activity during storage is the inhibition of bladder activity by stimulation of β-adrenoceptors, which are located in the bladder wall. Another effect is the inhibition at the pelvic ganglionic level of parasympathetic neurons, which mediate the micturition reflex. Finally, closure of the bladder neck is realised: the trigone and the smooth urethral muscular fibres are brought to contraction via their α-adrenoceptors. These sympathetic reflexes are generally accepted in animals, but in humans their existence is still debated (De Groat and Steers, 1990).

A similar organization results in contraction of the striated urethral sphincter during the filling phase (De Groat and Steers, 1990). Onuf’s nucleus receives low-level input from tension receptors in the bladder wall via the pelvic nerve. From Onuf’s nucleus, the striated urethral musculature is stimulated to contract.

These two spinal segmental reflexes, stimulation of sympathetic and somatic nerve outflow during bladder filling by low-level afferent activity, are referred to as "guarding reflexes" which promote continence.
Figure 1.1: integrated circuitry based on neuronal connections as described by De Groat and associates.
Recurrent inhibition of the sacral parasympathetic outflow is possible, probably by inhibition of interneurons on the excitatory pathway to the parasympathetic neurons (De Groat et al., 1979; De Groat and Lalley, 1972), but no functional mechanisms is being discussed (De Groat et al., 1979). Recurrent inhibition is presumed to be present during storage and absent during micturition (De Groat, 1975).

Micturition
At the initiation of micturition, sympathetic and somatic activity is depressed. Intense activity of tension receptors inside the bladder wall is passed by pelvic nerve afferents to the sacral dorsal horn and is projected to the pontine micturition center. From here, the two "guarding reflexes" are overruled.

1. Sympathetic vesicomotoneurons inside the thoracolumbar spinal cord are inhibited by the pontine micturition center. Sympathetic influence on the trigone, smooth urethral musculature, bladder wall and the pelvic ganglia is eliminated. The bladder neck opens.

2. The somatic motoneurons inside the sacral spinal cord (Onuf's nucleus) are inhibited by the pontine micturition center and probably indirectly by the cerebral cortex and diencephalon as well. The excitatory activity of Onuf's nucleus on the striated urethral muscles is inhibited, which results in relaxation of these muscles.

Micturition is established and maintained by a supraspinal circuit involving tension receptors inside the bladder wall, which produce intense afferent activity, and an afferent tract to the pontine micturition center. From the pons, excitatory influence on the sacral autonomic nucleus is generated, which is sent through the pelvic ganglia to the detrusor muscle. This excitatory influence is responsible for detrusor contraction. During micturition detrusor contraction is reinforced by urine flow in the urethra, which results in activity of pudendal nerve afferents. Signals are conveyed to the dorsal sacral spinal cord and excitatory signals reach the bladder, but the relay station is not known.

End of micturition
Higher centres in the cerebral cortex and diencephalon are involved in voluntary control of micturition; the external urethral sphincter can be contracted or inhibited voluntarily by cortical control, but no specific functional mechanism is noted. Contraction of the striated urethral musculature results in bladder relaxation, but the pathways are not known (De Groat and Steers, 1990). It has been suggested, that a part of the circuit responsible is formed by a descending tract from the cortex to the pontine micturition center, which terminates in Onuf's nucleus (De Groat and Steers, 1990).
Figure 1.2: functional mechanisms during storage and micturition as described by De Groat and associates.
BRADLEY's "LOOP CONCEPT"

Circuitry (see fig. 2.1)
Bradley's "loop concept" (Bradley et al., 1974; Bradley, 1978), consisting of several interconnected sub-loops, has been integrated into one circuit.

Musculature of the lower urinary tract
Within the lower urinary tract the following muscular structures are described: the smooth detrusor muscle [BLADDER], a urinary sphincter [URINARY SPHINCTER] and the pelvic floor [PELVIC FLOOR]. The urinary sphincter is defined as the striated muscle portion of the urethra, located at a mid-urethral segment, in combination with a striated external circular urethral muscle (Bradley et al., 1974).

Sympathetic connections
No sympathetic connections, nor any functional influence of the sympathetic nervous system are integrated in Bradley's "loop concept", although Bradley does describe the course of sympathetic nerve fibres innervating the lower urinary tract (Bradley et al., 1974, Bradley, 1978, Fletcher and Bradley, 1978):

According to Bradley et al. (1974) sympathetic bladder afferents are carried in the pelvic nerve, enter the sacral spinal cord and pass rostrally to synapse on sympathetic vesicomotoneurons in the first two segments of the lumbar spinal cord. Efferent fibres originating in the lumbar spinal cord travel via the hypogastric nerve and are organized threefold:

1. The pelvic ganglia are innervated.
2. Others innervate the individual smooth muscle cells of the proximal urethra.
3. The vascular cushion situated in the submucosa of the bladder epithelium at the bladder neck is innervated (Bradley et al., 1974).

Ablation of the sympathetic system, however, has no effect on detrusor reflex function (Van Kerrebroeck, 1993).

As a consequence no sympathetic nervous structures are shown in the flow charts of figs. 2.1 and 2.2.

Somatic connections
Proprioceptive sensory axons originating in the detrusor muscle are carried in the pelvic nerve and connect to the pudendal nucleus [BLADDER → PUDENDAL NUCLEUS]. The pudendal nucleus consists of somatic motoneurons situated in the anterior gray horn of spinal cord segments S₂-S₄. Sensory axons emanating from the urinary sphincter (referred to as periurethral striated muscle) and pelvic floor musculature travel in the pudendal nerve to terminate on the pudendal nucleus [URINARY SPHINCTER → PUDENDAL NUCLEUS and PELVIC FLOOR → PUDENDAL NUCLEUS]. Part of the sensory endings are muscle spindles, but it remains to be clarified whether there are muscle spindles present in both the urinary sphincter (also referred to as striated external urethral musculature, periurethral striated muscle) and the pelvic floor musculature (Bradley et al., 1974; Bradley, 1978; Fletcher and Bradley, 1978).
A supraspinal circuit is also described: "The supraspinal innervation consists of sensory impulses from the muscle spindles passing cranially in the posterior columns. These axons send collaterals to the cerebellum and thalamus to terminate in the sensorimotor cortex of the frontal lobes. The motor neurons in Layer V of the sensorimotor cortex send impulses down the corticospinal tract that end by synapsing on motor neurons in the pudendal nucleus in the ventral horn of the sacral spinal cord" (Bradley, 1978) [UREINARY SPHINCTER → CORTEX; PELVIC FLOOR → CORTEX and CORTEX → PUDENDAL NUCLEUS]. Although the thalamus is specifically named, neither a clear function in micturition control is given, nor is the structure integrated in the functional "loop concept" (Bradley, 1978; Bradley et al., 1974). Therefore it is not integrated in figs. 2.1 and 2.2. The pudendal nucleus innervates the urinary sphincter and the pelvic floor musculature by pudendal nerve efferents [PUDENDAL NUCLEUS → URINARY SPHINCTER and PUDENDAL NUCLEUS → PELVIC FLOOR].

Parasympathetic connections
Urine flow in the urethra is noted by stretch receptors in periurethral striated muscle, which are probably connected to the detrusor nucleus in the sacral spinal cord (Bradley, 1978) [UREINARY SPHINCTER → SACRAL DETRUSOR NUCLEUS]. The sacral detrusor nucleus consists of parasympathetic neurons in the intermediolateral cell column of the sacral gray matter. Proprioceptive sensory nerve endings inside the detrusor muscle send signals through the pelvic nerve to the sacral spinal cord. From here the afferent fibres ascend in the posterior columns to the brain stem detrusor nucleus [BLADDER → B-STEM DETRUS NUCL.]. In this context it is noted, that "These axons do not synapse but rather 'long route' to the brain stem." (Bradley, 1978). Similar remarks can also be found in: Bradley et al., 1974; Bradley, Conway, 1966.

Descending spinal tracts from the brain stem detrusor nucleus synapse on the sacral detrusor nucleus [B-STEM DETRUS NUCL. → SACRAL DETRUSOR NUCLEUS]. From here, axons of vesicomotoneurons travel in the pelvic nerve to innervate the pelvic ganglia [SACRAL DETRUSOR NUCLEUS → PELVIC GANGLIA], from which pelvic nerve efferents innervate the detrusor muscle [PELVIC GANGLIA → BLADDER]. Efferent fibres leaving the sacral detrusor nucleus to innervate the bladder give off collaterals, which form a recurrent connection. This recurrent connection could also consist of vesical afferent fibres, entering the anterior roots of the sacral spinal cord, instead of recurrent inhibitory collaterals of efferent fibres (Fletcher and Bradley, 1978). In figs. 2.1 and 2.2 this recurrent connection is thought to be integrated in the block [SACRAL DETRUSOR NUCLEUS].

Supraspinal connections
A lot of attention is being paid to supraspinal structures, such as the gray matter of the cerebral cortex, the thalamus, the basal ganglia, the locus coeruleus and the cerebellum. The locus coeruleus is referred to as brain stem detrusor nucleus and: "The brain stem detrusor nucleus is located on the border between the pons and midbrain in a dorsal position. It is called the nucleus locus coeruleus." (Bradley, 1978). Three interconnected supraspinal structures, of which their supraspinal cooperation is not totally clear, are integrated in the "loop concept" for the coordination of the micturition process: the cortex, the cerebellum and the brain stem detrusor nucleus [CORTEX → B-STEM DETRUS NUCL. → CEREBELLUM].

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Figure 2.1: Integrated circuitry based on neuronal connections as described by Bradley and associates.
Functional mechanisms (see fig. 2.2)

Storage
During the filling phase of the urinary bladder the urinary sphincter (striated musculature) (Bradley et al., 1974) and the pelvic floor musculature are contracted (Bradley, 1978). Muscle spindles, located in the striated musculature, continuously send signals to the pudendal nucleus. This afferent activity results in a state of tonic contraction of the urinary sphincter and pelvic floor musculature, thereby promoting continence.

Micturition
Intense vesical activity and the thereupon following bladder contraction stimulates predominantly free unspecialized nerve endings inside the bladder wall. Sensory information is conveyed to the sacral spinal cord by pelvic nerve afferents. Their synapses impinge upon the pudendal nucleus, resulting in an inhibitory signal proportional to the intensity of stimulation of the pelvic nerve afferents (Bradley et al., 1974; Bradley, 1978). As a consequence the urinary sphincter and the pelvic floor musculature relax (Bradley, 1978).

Micturition is established and maintained by a supraspinal pathway. Sensory endings of pelvic nerve afferents send signals concerning the condition of the bladder to the sacral spinal cord, where the afferent fibres are "long routed" to the brain stem detrusor nucleus and higher structures (Bradley et al., 1974; Bradley, 1978; Bradley and Conway, 1966). Here, the sensory information is processed and excitatory signals are sent to the detrusor nucleus in the sacral spinal cord. The sacral detrusor nucleus sends excitatory signals to the pelvic ganglia, which leads to bladder contraction (Bradley, 1978). During voiding the detrusor contraction is sustained by positive feedback of urethrovessical reflexes. Urine passing the urethra stimulates stretch receptors inside the urethral wall and inside the urinary sphincter (referred to as periurethral striated muscle), which pass their signals probably to the detrusor nucleus in the sacral spinal cord. The sacral detrusor nucleus stimulates the bladder to sustain the contraction until the bladder is completely emptied.

End of micturition
Negative feedback regulates the output of the sacral detrusor nucleus and helps to terminate the detrusor reflex (Bradley et al., 1974).

A supraspinal and a spinal reflex are discerned which both result in the contraction of the urinary sphincter and the pelvic floor musculature, therefore terminating the micturition reflex. Pudendal nerve afferents send information about the condition of the urinary sphincter and pelvic floor not only to the cortex, but also, as a spinal reflex, to the pudendal nucleus in the spinal cord. The pudendal nucleus receives additional excitatory influence from the cortex. The urinary sphincter and pelvic floor musculature are stimulated by the pudendal nucleus to contract (Bradley, 1978).
Figure 2.2: functional mechanisms during storage, micturition and the end of micturition as described by Bradley and associates.
THE MODEL OF BLAIVAS

Circuitry (see fig. 3.1)

Musculature of the lower urinary tract
Within the lower urinary tract the following separate muscular structures are described: the vesical neck and proximal urethra (constituting an internal sphincter mechanism (Blaivas, 1985)) [VESICAL NECK & PROX. UR.]; the smooth detrusor muscle of the bladder [BLADDER] and striated urethral and pelvic floor muscles (Blaivas, 1985) [STRIATED URETHRAL MUSCUL. and PELVIC FLOOR].

Sympathetic connections
Sympathetic afferents originating from the vesical neck and proximal urethra and inside the bladder wall are conveyed by the hypogastric nerve. The sympathetic afferents terminate inside the thoracolumbar spinal cord, but no function in micturition control is mentioned (Blaivas, 1985, 1990). These connections are therefore not integrated in the circuitry of fig. 3.1.
Sympathetic bladder afferents are conveyed by the hypogastric nerve to synapse inside the thoracolumbar spinal cord (Blaivas, 1982) [BLADDER → TH-L].
The pontine micturition center connects to the sympathetic vesicomotoneurons inside thoracolumbar spinal cord segments by a descending spinal tract (Blaivas, 1982) [PONTINE MICTUR. CENTER → TH-L].
Efferent sympathetic axons emanating from vesicomotoneurons inside the thoracolumbar spinal cord travel in the hypogastric nerve to innervate the smooth musculature of the proximal urethra and vesical neck [TH-L → VESICAL NECK & PROX. UR.]. The detrusor body and the pelvic ganglia are innervated similarly (Blaivas, 1982, 1985, 1990) [TH-L → BLADDER and TH-L → PELVIC ganglia].

Somatic connections
Pudendal nerve afferents travelling from the pelvic floor and striated urethral musculature to Onuf's nucleus in the anterior horn of the sacral spinal cord are discerned, but no function in micturition control is mentioned (Blaivas, 1985, 1990).
Pelvic nerve afferents from the bladder wall connect to Onuf's nucleus (Blaivas, 1982, 1990) [BLADDER → ONUF'S NUCLEUS].
A corticospinal tract connects the frontal cortex to Onuf's nucleus, which sends efferent pudendal nerves to innervate the external urethral sphincter and the pelvic floor (Blaivas, 1982, 1985) [CORTEX → ONUF'S NUCLEUS; ONUF'S NUCLEUS → PELVIC FLOOR and ONUF'S NUCLEUS → STRIATED URETHRAL MUSCUL.].
The pontine micturition center projects to Onuf's nucleus by a descending spinal tract (Blaivas, 1982) [PONTINE MICTUR. CENTER → ONUF'S NUCLEUS].

Parasympathetic connections
Tension receptors inside the bladder wall send signals in pelvic nerve afferents, which synapse on the pelvic nucleus inside the spinal cord [BLADDER → PELVIC NUCLEUS], while other afferents "long route" to the pontine micturition center (Blaivas, 1982, 1985, 1990) [BLADDER → PONTINE MICTUR. CENTER]. The pelvic nucleus is located in an
intermediolateral cell column of spinal cord segments $S_2$-$S_4$ (Blaivas, 1982, 1985).

Blaivas (1985) notes: "The 'micturition reflex' is integrated in the rostral brain stem in an area designated as the 'pontine micturition center' which is connected to the 'sacral micturition center' via spinal pathways in the posterior and lateral columns." Besides the descending tract mentioned from the pons to Onuf's nucleus (see somatic connections), we assume (although not specific noted in the cited text), that the pons projects to the pelvic nucleus in the sacral spinal cord as well [PONTINE MICTUR. CENTER $\rightarrow$ PELVIC NUCLEUS].

The pelvic nucleus sends preganglionic parasympathetic nerve fibres via the pelvic nerve to synapse on postganglionic parasympathetic nerve fibres inside the pelvic ganglia [PELVIC NUCLEUS $\rightarrow$ PELVIC GANGLIA]. The postganglionic nerve fibres innervate the bladder (Blaivas, 1982, 1985, 1990) [PELVIC GANGLIA $\rightarrow$ BLADDER].

**Supraspinal connections**

Blaivas (1982, 1990) notes facilitatory and inhibitory influences of suprapontine brain structures on the pontine micturition center during the micturition cycle. The influence of higher brain structures is symbolically portrayed by the connection between the cortex and the pontine micturition center in fig. 3.1, because no exact structures and circuits are elucidated for this purpose [CORTEX $\rightarrow$ PONTINE MICTUR. CENTER].

**Functional mechanisms** (see fig. 3.2)

**Storage**

During the filling phase of the bladder sympathetic afferents convey signals from the bladder body to neurons inside the thoracolumbar spinal cord. The resulting efferent sympathetic influence on the lower urinary tract during urine storage is threefold:

1. Closure of the vesical neck and proximal urethra is realised by direct stimulation of $\alpha$-adrenoceptors.
2. The transmission of signals from the pre- to postganglionic parasympathetic nerve fibres, which mediate the micturition reflex, is inhibited.
3. Stimulation of $\beta$-adrenoceptors inside the bladder wall results in inhibition of detrusor activity.

Bladder distension produces activity in pelvic nerve afferents, which stimulate, probably via an interneuron, Onuf's nucleus. Stimulation of Onuf's nucleus is responsible for the contraction of the striated urethral and periurethral musculature, the latter being a part of the pelvic floor. This reflex is seen as a guarding reflex.

During filling, sensors inside the bladder wall also send signals in pelvic nerve afferents to the pelvic nucleus inside the sacral spinal cord. From here, parasympathetic outflow is mediated through the pelvic nerve and is blocked at a ganglionic level by sympathetic influences (Blaivas, 1990).
Figure 3.1: integrated circuitry based on neuronal connections as described by Blaivas.
Micturition

Two major reflex pathways are discerned, both of which have an excitatory influence on the detrusor muscle: a brain stem reflex (Blaivas, 1982, 1985) and a reflex pathway organized on a sacral spinal level (Blaivas, 1985).

The brain stem reflex is responsible for a coordinated micturition and results in normal voiding. Pelvic nerve afferents originating in the bladder send signals to the pontine micturition center. Descending spinal tracts fulfill two functions. One is inhibition of reflexes underlying the storage function:

1. Inhibition of the sympathetic vesicomotoneurons in thoracolumbar spinal cord segments opens the bladder neck, stops the direct inhibition of the detrusor body and ends the inhibition of parasympathetic efferent activity on a pelvic ganglionic level.

2. Inhibition of Onuf’s nucleus activity results in relaxation of the external urethral sphincter. Micturition is initiated by a sudden and complete relaxation of striated urethral and pelvic floor musculature.

The second function of descending spinal tracts is the stimulation of the pelvic nucleus, resulting in bladder contraction.

The sacral reflex arc mediates a parasympathetic reflex. Pelvic nerve afferents originating in the bladder synapse in the pelvic nucleus. The signals sent through pelvic nerve efferents are no longer blocked at ganglionic level by sympathetic influence (Blaivas, 1990).

End of micturition

To end the micturition phase the cortex stimulates the pudendal nucleus via a direct corticospinal pathway. This results in efferent pudendal nerve activity and consequently in contraction of the striated muscles. The end of micturition is probably a complex neurological event, of which the above reflex is a part. Other connections have not yet been elucidated (Blaivas, 1982).
Figure 3.2: functional mechanisms during storage, micturition and the end of micturition as described by Blaivas.
THE MODEL OF HOLSTEGE

Circuitry (see fig. 4.1)

Musculature of the lower urinary tract
Within the lower urinary tract the following muscular structures are described: smooth musculature of the bladder base and the urethra \( [\text{SMOOTH URETHRAL MUSCUL.}] \), the bladder, consisting of smooth detrusor muscle \( [\text{BLADDER}] \), and the pelvic floor, including the intrinsic external urethral sphincter \( [\text{PELVIC FLOOR \& SPHINCTER}] \).

Sympathetic connections
A spinal vesicosympathetic reflex is discerned. After entering the sacral spinal cord through the dorsal roots, bladder afferents project to lumbar spinal cord segments. It is suggested that the bladder afferents synapse on a sacral intermedio medial cell group \( [\text{BLADDER} \rightarrow \text{SACRAL SPINAL CORD} \rightarrow \text{SACRAL INTERMEDIOMEDIAL}] \), which on its turn connects to a lumbar mediolateral (sympathetic) cell group (Holstege and Griffiths, 1990) \( [\text{SACRAL INTERMEDIOMEDIAL} \rightarrow \text{L1-L4}] \). This suggestion is based on the following considerations:

the sacral intermedio medial cell group is innervated by both dorsal root afferents and the medial region of the pontine micturition center, called the M-region. During micturition the vesicosympathetic reflex is inhibited, possibly via projections from the M-region to the sacral intermedio medial cell group \( [\text{M} \rightarrow \text{SACRAL INTERMEDIOMEDIAL}] \): neither the M- nor the L-region directly project to the lumbar intermediolateral (sympathetic) cell group. Therefore the sacral intermedio medial cell group could be the missing link in the vesicosympathetic reflex pathway (Holstege and Griffiths, 1990).

Axons of sympathetic vesicomotoneurons, located in the intermediolateral cell group inside the lumbar cord, are carried in the pelvic and hypogastric nerve. These sympathetic fibres innervate the smooth musculature of the urethra and the bladder base \( [\text{L1-L4} \rightarrow \text{SMOOTH URETHRAL MUSCUL.}] \), terminate inside the bladder wall \( [\text{L1-L4} \rightarrow \text{BLADDER}] \) and connect to the paravesical ganglia of the parasympathetic system (Holstege and Griffiths, 1990) \( [\text{L1-L4} \rightarrow \text{PARAVESICAL GANGLIA}] \).

Somatic connections
Afferent nerve fibres from the pelvic floor, including the intrinsic external urethral sphincter, enter the sacral spinal cord through the dorsal roots \( [\text{PELVIC FLOOR \& SPHINCTER} \rightarrow \text{SACRAL SPINAL CORD}] \). The sacral intermedio medial cell group receives dorsal root afferents (Holstege and Griffiths, 1990), but it remains unclear if afferent fibres from the pelvic floor project to the sacral intermedio medial cell group. The efferent somatic pathway origins in the lateral region of the pontine micturition center and is therefore called L-region. From the L-region, a descending spinal tract to the nucleus of Onuf in the sacral spinal cord exists \( [\text{L} \rightarrow \text{ONUF’s NUCLEUS}] \). Onuf’s nucleus relays to the intrinsic external urethral sphincter and the pelvic floor \( [\text{ONUF’s NUCLEUS} \rightarrow \text{PELVIC FLOOR \& SPHINCTER}] \).
Parasympathetic connections
Bladder afferents enter the sacral spinal cord through the dorsal roots (Holstege and Griffiths, 1990; Holstege, 1989) [BLADDER → SACRAL SPINAL CORD]. It is not noted what type of afferents are involved. No other relevant bladder afferents, besides those of the vesicosympathetic reflex, are described.
A supraspinal bladder to bladder reflex pathway is mentioned, but no complete circuitry is elucidated (Holstege and Griffiths, 1990). Information about the degree of bladder filling is conveyed to supraspinal structures, "...but specific sacral projections to the pontine micturition center have not been demonstrated. On the other hand, neurons in the sacral cord project very strongly to specific portions of the caudal half of the periaqueductal gray (PAG) (Blok et al., in preparation)." (Holstege, 1989) [SACRAL SPINAL CORD → P-AQUADUCTAL GRAY]. Note that the periaqueductal gray is a subcortical structure. The M-region projects to the sacral intermediolateral cell group and to the sacral intermediomedial cell group (Holstege and Griffiths, 1990) [M → INTERMEDIOLATERAL and M → INTERMEDIOMEDIAL]. Preganglionic parasympathetic neurons, located in the sacral intermediolateral cell group, use the pelvic nerve to innervate the bladder via paravesical ganglia [SACRAL INTERMEDIOLATERAL → PARAVESICAL GANGLIA → BLADDER].

Supraspinal connections
In the cat, the preoptic area, lying just rostral to the hypothalamus, seems to receive no afferent input. Although it is suggested that structures rostral to the pons receive information from the sacral spinal cord, no spinal tract is mentioned (De Groat and Steers, 1990). The output of the preoptic area is aimed towards the periaqueductal gray, i.e. a structure inside the mesencephalon, and the M-region of the pons [PREOPTIC AREA → PERIAQUADUCTAL GRAY and PREOPTIC AREA → M]. The periaqueductal gray only projects to the M-region of the pons [PERIAQUADUCTAL GRAY → M]. The M- and L-region of the pons are reciprocally connected [L ↔ M].

Functional mechanisms (see fig. 4.2)
A mechanism of major importance during the micturition cycle is the reciprocal inhibitory effect of the M-region and the L-region on each other, both being regions of the pontine micturition center (Holstege, 1989). This mutual inhibitory effect is suggested by Holstege and Griffiths (1990), based on a study of Griffiths et al. (1989), but awaits further confirmation by physiological or anatomical data.

Storage
Bladder filling activates the complex spinal vesicosympathetic pathway. Bladder afferents pass their signals through the sacral dorsal roots and synapse on the sacral mediolateral cell group, which connects to a lumbar intermediolateral (sympathetic) cell group. Efferent sympathetic nerve activity originating in the lumbar cord inhibits bladder contraction and stimulates contraction of the smooth musculature of the urethra and bladder base, thereby promoting continence. This way an increase in bladder pressure results in an increase of the sympathetic inhibitory activity, allowing the bladder to collect more fluid.
Figure 4.1: integrated circuitry based on neuronal connections as described by Holstege and associates.
During the filling phase of the bladder continuous activity of the L-region excites Onuf's nucleus, thereby preventing urethral relaxation, which would be followed by detrusor contraction, and thus promoting continence (Holstege and Griffiths, 1990; Holstege, 1989). Urethral closure is realised by contraction of the pelvic floor and intrinsic external urethral sphincter and detrusor inhibition is probably realised by the inhibitory influence of the L-region on the M-region.

Micturition
Specific projections from neurons in the sacral cord to the caudal half of the periaqueductal gray are reported (Holstege, 1989; Holstege and Griffiths, 1990). It is suggested, that information about the condition of the bladder is conveyed to the periaqueductal gray and other structures rostral to the pontine micturition center as well. The preoptic area and a portion of the periaqueductal gray project to the M-region in the cat. Stimulation of these two structures results in micturition or micturition-like contractions of the bladder. These areas possibly determine the onset of micturition (Holstege, 1989).

The onset of micturition takes place, when the M-region excites the sacral parasympathetic motoneurons, which causes bladder contraction. Simultaneously, the L-region, which is partly responsible for the closure of the urethra, is inhibited by the increased activity of the M-region. This results in relaxation of the intrinsic external urethral sphincter and the pelvic floor.

The inhibitory influence of the vesicosympathetic reflex is eliminated by the M-region activity. The M-region sends signals to the sacral intermediomedial cell group, which forms a part of the vesicosympathetic reflex pathway. This opens the bladder neck and stops the inhibition of the detrusor body.

End of micturition
No circuitry or functional mechanisms are mentioned that could be responsible for the termination of voiding.
Figure 4.2: functional mechanisms during storage and micturition as described by Holstege and associates.
DIFFERENCES BETWEEN THE FOUR THEORIES

In this paragraph, the differences between the presented theories are discussed. The discussion is supported by using the flow charts (figs. 1 to 8).

Differences in circuitry

Musculature of the lower urinary tract
Little consistency can be found in the used nomenclature for the muscular units described by the four authors. Moreover, in most cases two authors are using the same terminology for a muscular structure, they refer to (slightly) different anatomical structures. The correct interpretation has to be found in the context of the paper, but often no anatomical description of the used term is presented. Apart from differing anatomical interpretation of muscular tissue, also variation in its functional interpretation exist.

The following global comparison can be made (see fig. 5):
all authors discern a smooth detrusor muscle and striated urethral musculature. The smooth muscle sphincter constitutes one functional unit rather than an anatomical one and consists of smooth musculature from the proximal urethra, the trigone and/or the vesical neck. Bradley doubts the function of such a smooth muscle sphincter in promoting continence (Fletcher and Bradley, 1978).
All authors, except De Groat, discern a role for the pelvic floor musculature in the function of the lower urinary tract, but the anatomical interpretation of the pelvic floor musculature varies. De Groat mentions periurethral striated musculature in a recent paper briefly (De Groat and Steers, 1990), but this structure is thought complementary to the external urethral sphincter.

Sympathetic connections
Two views are presented for the most important sympathetic afferent connections.

1. According to De Groat (De Groat and Lalley, 1972; De Groat et al., 1979b; De Groat and Steers, 1990), Bradley (Bradley et al., 1974) and Holstege (Holstege and Griffiths, 1990), bladder afferents enter the sacral spinal cord and ascend to thoracic and/or lumbar segments. This is the afferent part of an intersegmental spinal vesicosympathetic reflex arc. De Groat (De Groat and Lalley, 1972; De Groat et al., 1979b; De Groat and Steers, 1990) and Bradley (Bradley et al., 1974) suggest that bladder afferents are carried in the pelvic nerve. Holstege suggests that the bladder afferents, which enter in the sacral dorsal horn, connect to a sacral intermediomedial cell group, before they ascend to higher spinal levels (Holstege 1989; Holstege and Griffiths, 1990).
2. According to Blaivas, no intersegmental spinal reflex occurs. Bladder afferents directly connect to thoracolumbar spinal cord segments by the hypogastric nerve.

Afferents from the vesical neck and proximal urethra (Blaivas, 1985, 1990) and from the bladder and urethra (De Groat and Steers, 1990) are also directly connected to

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thoracolumbar spinal cord segments by the hypogastric nerve, but no function in micturition control is demonstrated. These connections are therefore not integrated in figs. 1.1 and 3.1 (see fig. 5 as well).

In De Groat’s and Blaivas’ opinion, the pons projects to sympathetic vesicomotoneurons, which are located inside the thoracolumbar spinal cord. Holstege denies the existence of a connection between the pons and sympathetic vesicomotoneurons on a (thoraco-)lumbar spinal level. Holstege suggests that pontine structures (the M-region) project to a sacral intermediomedial cell group instead, which will take part in the intersegmental vesicosympathetic circuitry.

According to De Groat and Blaivas lower thoracic and higher lumbar spinal cord segments contain vesicosympathetic vesicomotoneurons, whereas Bradley and Holstege suggest lumbar segments only.

The sympathetic efferent fibres are conveyed by only the hypogastric nerve, according to Bradley and Blaivas. De Groat and Holstege include the pelvic nerve also in conveying sympathetic fibres to the lower urinary tract. Blaivas and De Groat describe anatomically the routing of the hypogastric nerve to the lower urinary tract extensively, but in the description of micturition control, a pure functional design of pathways is applied. Sympathetic nerve fibres in all four theories synapse in the parasymptomatic ganglia. Blaivas specifically notes an (urogenital) short neuron system (Blaivas, 1990). The smooth urethral musculature, the base of the bladder and/or the trigone are innervated by sympathetic nerve fibres. De Groat, Blaivas and Holstege mention sympathetic fibres that innervate β-adrenoceptors located inside the bladder wall.

Bradley summarizes some sympathetic connections, but does not integrate them in his "loop concept".

**Somatic connections**

De Groat, Bradley and Blaivas describe bladder afferents, which are conveyed by the pelvic nerve to terminate on Onuf’s nucleus inside the sacral spinal cord. This connection is based on functional considerations (De Groat and Steers, 1990) and electrical stimulation experiments with cats (Bradley and Teague, 1969). The pelvic floor musculature (except for De Groat as remarked before) and striated urethral musculature are connected to the sacral spinal cord by pudendal nerve afferents. Once the fibres enter the sacral spinal cord, two different views are present. According to De Groat and Holstege, the afferents synapse somewhere in the dorsal horn. Bradley and Blaivas describe that the afferent fibres terminate on Onuf’s nucleus, indicating a myotatic reflex arc. Blaivas notes that this connection has no function in micturition control and it is therefore not integrated in fig. 3.1. Bradley also discerns afferent (somatic) fibres from the urethra, which probably travel to the sacral detrusor nucleus.

The connection between the cortex and Onuf’s nucleus inside the sacral spinal cord is a point of discussion (see fig. 5). Only Bradley mentions an ascending tract: sensory information from the pelvic floor and urinary sphincter passes cranially in the posterior columns of the spinal cord to finally terminate in the cortex.
Bradley and Blaivas discern a direct corticospinal tract involved in guiding Onuf's nucleus, whereas De Groat formulates an indirect corticospinal tract, which synapses in the pontine micturition center. Blaivas notes, besides a direct corticospinal tract, an additional connection between the pons and Onuf's nucleus. Holstege mentions a similar tract from the L-region in the pons to Onuf's nucleus. Holstege notes that a direct cortical projection to Onuf’s nucleus has not been convincingly demonstrated yet, but he mentions no alternative circuit that could be responsible for the voluntary control of the striated urethral musculature (Holstege, 1989; Holstege and Griffiths, 1990).

All four authors agree that the peripheral innervation of the striated urethral musculature and, where appropriate, the pelvic floor musculature originates in Onuf's nucleus inside the sacral spinal cord. The striated urethral and pelvic floor musculature is innervated in their view by only the pudendal nerve and not by the pelvic nerve.

Parasympathetic connections
The most essential afferent pathway in micturition control gives rise to discussion (see fig. 5). Bladder afferents are noticed which are conveyed by the pelvic nerve to the sacral spinal cord, entering through the dorsal roots. From this point, different opinions are present.

Bradley and Blaivas mark "long-routed" afferents, i.e. afferents which enter the spinal cord, do not synapse, but rather ascend in the spinal cord to terminate in the pontine micturition center. Blaivas also notes a spinal circuit: a part of the afferent fibres do synapse on the sacral pelvic nucleus, i.e. the sacral intermediolateral cell group.

De Groat does not share the view that the afferents are "long-routed" to the pons. In his opinion, the afferents first synapse in the sacral dorsal horn, before they ascend to the pons.

Holstege mentions the bladder afferents entering the sacral spinal cord in the dorsal horn, but describes no synapses. Holstege remarks that no specific projection from the sacral spinal cord to the pontine micturition center has been demonstrated yet. Instead, he mentions a connection between the sacral spinal cord and the periaquaductal gray of the cat. Both the periaquaductal gray and the preoptic area project to the pontine micturition center (M-region).

The efferent parasympathetic circuitry is the same for all four theories. From the pons, a projection is found to the sacral parasympathetic nucleus. This cell group sends parasympathetic preganglionic fibres through the pelvic nerve to synapse on neurons, constituting postganglionic fibres, inside ganglia of the pelvic plexus or inside ganglia, that are located closer to the bladder. In this context, De Groat mentions efferent fibres that originate from the sacral parasympathetic nucleus and terminate in the bladder without synapses in ganglia of the pelvic plexus.

Supraspinal connections
According to De Groat's theory, the cerebral cortex and diencephalon fulfil a function in the voluntary control of micturition. A short review is given in a recent paper, focusing on Holstege's ideas about supraspinal control of the micturition process (De Groat and Steers, 1990). These ideas are not integrated in De Groat's circuitry, but are in this paper dealt with in the description of Holstege's theory.

Bradley not only pays attention to cortical structures, but also to the cerebellum. Although cerebellar organization of the micturition reflex is proposed (Bradley et al., 1974), the
connections and the functional role of this area during the micturition control remain unclear. Blaivas only discerns the cortex as an important supraspinal structure for micturition control, besides the pontine micturition center. Holstege divides the pontine micturition center in a lateral region (L-region) and medial region (M-region), both with different connections and functions. Holstege also discerns the preoptic area and the periaqueductal gray as supraspinal structures involved in the control of the lower urinary tract in cat.

In three theories supraspinal structures without incoming connections can be discerned, e.g. the cortex according to De Groat and Blaivas and the preoptic area according to Holstege. Control theory does not allow this isolation: such a system would not work properly. Every muscular structure on the efferent side that is under indirect or direct supraspinal control has to sent sensory information on the afferent side to supraspinal structures in order to close the circuit. Although the afferent somatic pathway as proposed by Bradley may be quite exotic from an anatomical point of view, the requirement that somehow information has to be passed to supraspinal structures is met.
Figure 5: circuitries as described by De Groat, Bradley, Blaivas, Holstege and associates.
Differences in functional mechanisms

Storage (see fig. 6)
A high degree of bladder filling is possible due to the existence of several mechanisms which prevent urine to flow through the urethra and thus realise continence.

Bradley describes only the role of the somatic nervous for promoting continence. No sympathetic influence can be found in his "loop concept", because ablation of the sympathetic system has no effect on detrusor reflex function. There is no internal sphincter (smooth muscle sphincter), trigone or bladder neck mechanism mentioned that could contribute in maintaining continence during the filling phase (Bradley, 1978), although a circular layer of urethral smooth musculature is partly responsible for regulating urethral resistance (Bradley et al., 1974). The proximal urethra is mainly occluded by the inherent tonicity of collagen and elastic fibres.

De Groat, Blaivas and Holstege note that the sympathetic nervous system has considerable influence during bladder filling. During urine storage, the sympathetic nervous system employs only spinally organized mechanisms. The smooth musculature of the proximal urethra, bladder neck and/or trigone is contracted. Inhibition of the parasympathetic neurons, which mediate the micturition reflex, by the sympathetic nervous system on pelvic ganglionic level is mentioned by De Groat and Blaivas. Holstege, De Groat and Blaivas note direct inhibitory influence on bladder activity by the stimulation of β-adrenoceptors inside the bladder wall. Holstege also suggests an inhibition of the detrusor muscle by fibres that synapse in paravesical ganglia of the parasympathetic system.

The somatic mechanisms employed in this context differ. De Groat and Blaivas discern bladder afferents being carried to Onuf's nucleus in the pelvic nerve and being activated during storage. This results in contraction of striated urethral and, where appropriate, pelvic floor musculature on the efferent side (see figs. 1.2, 3.2 and 6). To fulfil the same motor function Bradley employs pudendal nerve afferents instead, which originate in the urinary sphincter and pelvic floor and project to the pudendal nucleus. Holstege suggests more influence of the pontine micturition center. Here, the L-region is the most rostral integrative structure during the filling phase. It inhibits the M-region, which is a for the micturition reflex important supraspinal structure, and it also activates the striated pelvic floor and sphincter muscles.
Storage as described by De Groat et al. (see fig. 1.2).

Storage as described by Bradley et al. (see fig. 2.2).

Storage as described by Blaivas (see fig. 3.2).

Storage as described by Holstege et al. (see fig. 4.2).

Figure 6: functional mechanisms during storage as described by De Groat, Bradley, Blaivas, Holstege and associates.
**Micturition process** (see fig. 7)

**Termination of guarding reflexes**
Before micturition can fully develop, the sympathetic and somatic guarding reflexes that promote continence during the filling phase of the bladder have to be eliminated in order to realize relaxation of all striated and smooth urethral muscles. According to De Groat, Bradley and Blaivas, bladder afferents send information about the degree of bladder filling to the pontine micturition center. Holstege describes that this information is being sent to the periaqueductal gray first, before it is transferred to the M-region of the pontine micturition center.

In De Groat's and Blaivas' theories, just before micturition the pontine micturition center develops an inhibitory influence on vesicomotoneurons inside the thoracolumbar spinal cord and on Onuf's nucleus. De Groat mentions an additional inhibitory influence of the cortical/diencephalic structures on Onuf's nucleus.

Holstege claims that the M-region of the pontine micturition center eliminates the effect of the sympathetic nervous system by inhibition of the sacral intermediodiomedial cell group. Inhibition of the somatic nervous system happens on a supraspinal level only. The M-region of the pontine micturition center inhibits the L-region, which controls the pelvic floor musculature and the striated urethral musculature.

Bradley needs to explain the inhibition of only the somatic nervous system. He claims a sacral spinal reflex mechanism, where high-level activity of bladder afferents results in inhibition of the pudendal nucleus and therefore relaxation of the urinary sphincter and pelvic floor shortly before and during micturition (see figs. 2.2 and 7). Note that Bradley uses for this mechanism the same pathways as described by De Groat and Blaivas to explain the contraction of the striated musculature during storage. No supraspinal structures are involved.

**Micturition**
Once the pelvic floor and striated urethral musculatures are relaxed and the urethra has opened, micturition can fully develop. The pontine micturition center plays a central role in the development of micturition. The used mechanisms are principally the same for all theories (see fig. 7). The pontine micturition center stimulates the parasympathetic motoneurons, located in the sacral spinal cord. The resulting parasympathetic efferent activity stimulates the detrusor to contract.

De Groat and Holstege discern a sacral spinal micturition reflex system, that is functionally non-existent in humans and animals with an intact neuraxis (De Groat, 1975; De Groat *et al.*, 1979; De Groat and Steers, 1990; Holstege, 1989; Holstege and Griffiths, 1990). Blaivas notes a sacral spinal parasympathetic pathway, of which the activity during the filling phase is inhibited by sympathetic discharges on ganglionic level.

De Groat and Bradley discern a "second reflex wave" initiated by urine flow in the urethra, which reinforces micturition.
Micturition as described by De Groat et al. (see fig. 1.2).

Micturition as described by Bradley et al. (see fig. 2.2).

Micturition as described by Blaivas (see fig. 3.2.).

Micturition as described by Holstege et al. (see fig. 4.1).

Figure 7: functional mechanisms during micturition as described by De Groat, Bradley, Blaivas, Holstege and associates.
End of micturition (see fig. 8)
The pathways and the functional mechanisms underlying the termination of voiding remain unclear. De Groat and Bradley propose recurrent inhibition of sacral parasympathetic preganglionic neurons as a mechanism, which takes part in the termination of the micturition reflex. However, no anatomical evidence for the existence of recurrent collaterals from sacral parasympathetic fibres, which mediate the micturition reflex, has been found yet.
Bradley and Blaivas formulate a direct corticospinal tract, which makes voluntary control of the pelvic floor and striated urethral musculature possible. By contracting the pelvic floor and striated urethral musculature, an unknown reflex is activated, which results in relaxation of the detrusor muscle.
Bradley also notes that the connection between the cortex and the pontine micturition center is used to terminate voiding, but no detailed explanation is given.
End of micturition as described by Bradley et al. (see fig. 2.2)

End of micturition as described by Blaivas (see fig. 3.3).

Figure 8: functional mechanisms during the end of micturition as described by Bradley, Blaivas and associates.
DISCUSSION

INTRODUCTION

In this paper we deliberately do not discuss the controversies in muscles morphology in the lower urinary tract (for reviews see Dixon and Gosling, 1987; Elbadawi, 1987, 1988, 1991; Van Arsdalen and Wein, 1991; a.o.). The discussion will focus on the pathways used in the peripheral nervous system to reach the target organs and the linking up of the central nervous system to the peripheral connections.

Within the peripheral connections an obstacle for this study is the broad variability of the pathways present, e.g. the constitution of a peripheral nerve in the cauda equina is recently shown to contain a greater variability than expected (Mersdorf et al., 1993). This also holds for the sacral ventral rami.

After passing the sacral foramina the ventral rami constitute the sacral plexus. Within the sacral plexus the interconnections of the upper ventral rami fluctuate as to interconnections between S1 and S2 and between S2 and S3, both for male and female (Marani et al., 1993).

Another distorting factor is that the branches of the ventral rami contributing to the pelvic plexus differ greatly, both individually and intersexually (Marani et al., 1993). The relay stations in the pathways between the spinal cord and the target organs are difficult to study. Using acetylcholinesterase in total stainings as used by the former Amsterdam Baljet group (Baljet and Drukker, 1979; Baljet, 1981) only demonstrates the overall nerve paths, but can not discern on the relay stations. Tract tracing in the peripheral nervous system is seldom reported in literature, with the consequence that convergency and divergency are badly understood in the peripheral innervation of the lower urinary tract.

Moreover, the pudendal nerve complex causes in its definition confusion. Two definitions are used: a functional one and an anatomical one. The functional one describes the pudendal nerve as the somatic axons of the sacral plexus and includes subsequently the autonomic axons belonging to the pelvic plexus (Jueneman et al., 1988; Tanagho et al., 1982). The anatomical definition, found in classical literature (Cunningham, 1972; Gray 1985; Morris, 1942; Paturet, 1964; Pernkopf, 1941; Piersol, 1930) defines the pudendal nerve as a major trunk originating from the sacral plexus, which leaves the pelvis by the infrapiriform foramen and enters laterally, via the lesser sciatic foramen, into the ischiorectal fossa.

It is, of course, important to be aware of the wide range of branches, including interconnections between the ventral rami of the sacral nerves, which are involved in the formation of the pelvic plexus, when decisions have to be made concerning the strategy of neurostimulation and the extent of a dorsal rhizotomy to be performed on bladder stimulation patients.
Circuitry (see figs. 9, 10 and 11)

Musculature of the lower urinary tract
Functionally, the following muscular structures are controlled by the nervous system: the smooth musculature of the detrusor (including the deep trigonal muscle); the smooth musculature of the vesical neck, the superficial trigonal muscle and smooth musculature of the urethra, which can be seen as one functional unit; all to the urethra connected striated musculature, i.e. all striated urethral musculature and that part of the pelvic diaphragm, which lies adjacent to the urethra; and the pelvic floor musculature, seen as a from the urethra independent muscular structure.
The trigone consists of two muscles: the deep trigonal muscle and the superficial trigonal muscle. The muscle cells of the deep trigonal muscle are indiscernible from those of the detrusor and receive the same autonomic innervation (Dixon and Gosling, 1987; Gosling, 1986). Therefore, they are functionally integrated with the smooth detrusor muscle.

Sympathetic connections
See fig. 9. In cats a spinal intersegmental pathway is discerned (De Groat and Lalley, 1971) and a functional mechanism is proposed by Holstege (1990) and by De Groat and Steers (1991). Tension and stretch receptors inside the bladder and urethral wall connect to ganglia on the surface of and within the bladder and urethra (juxta- and intramural ganglia) [DETRUSOR... → JUXTA...] and to pelvic nerve afferents. The pelvic nerve afferents synapse in or pass through the pelvic plexus, which is also known as the inferior hypogastric plexus or plexus of Frankenhäuser [JUXTA... → PELVIC PLEXUS and DETRUSOR... → PELVIC PLEXUS]. After leaving the pelvic plexus, the pelvic nerve afferents enter the sacral spinal cord through the dorsal roots and probably terminate in the sacral intermediomedial cell group (Holstege and Griffiths, 1989) [PELVIC PLEXUS → SACRAL INTERMEDIOMEDIAL; JUXTA... → SACRAL INTERMEDIOMEDIAL and DETRUSOR... → SACRAL INTERMEDIOMEDIAL]. Afferent fibers that synapse in the pelvic plexus give rise to extraspinal pathways, i.e. some afferent fibers possibly connect in peripheral structures to efferent fibers, do not reach the spinal cord and influence that way the neuronal control of the lower urinary tract (Bradley and Teague, 1968a; Elbadawi, 1987b; Morrison, 1987a).
In the sacral intermediomedial cell group, the terminating bladder afferents connect to ascending fibres, which presumably project to the vesicomotoneurons inside the thoracolumbar spinal cord (Holstege and Griffiths, 1989; De Groat and Lalley, 1971) [SACRAL INTERMEDIOMEDIAL → THORACIC 11...].

Sympathetic afferent fibres emanating from the bladder and urethra take two routings to reach the thoracolumbar spinal cord. One circuitry runs through the hypogastric nerve (Morrison, 1987b). A smaller part of the sympathetic afferent fibres coming from the lower urinary tract is carried in the pelvic nerve (De Groat and Steers, 1990; Holstege and Griffiths, 1990; Morrison, 1987a), which conveys predominantly parasym pathetic nerve fibers.
Routing via hypogastric nerve. Sympathetic afferents originating in the bladder and urethra that are conveyed by the hypogastric nerve and course to the sympathetic chain as follows: The sympathetic afferents pass or connect to the juxta- and intramural ganglia [DETRUSOR... → JUXTA...] and synapse in or traverse the pelvic plexus [JUXTA... → PELVIC PLEXUS and DETRUSOR → PELVIC PLEXUS]. They take part in the short neuron system and on this level an extraspinal control mechanism might occur. Afferent fibers leave the mesh-like area of the pelvic plexus as left and right hypogastric nerve. Reaching the lumbosacral area anterior to the aorta, both constitute a plexiform nerve arrangement, which is in fact a caudal extension of the superior hypogastric plexus. Unlike in animals, nerve fibers coursing to the hypogastric plexus do not synapse in the inferior mesenteric ganglion (it is rudimentary or thought absent in humans). The afferent fibers course to the hypogastric plexus and synapse or traverse it [PELVIC PLEXUS → SUPERIOR HYPOGAST. PLEXUS; JUXTA... → SUPERIOR HYPOGAST. PLEXUS and DETRUSOR... → SUPERIOR HYPOGAST. PLEXUS]. Leaving the hypogastric plexus, fibers enter via the gray rami communicantes the sympathetic chain, which consists of interconnected paravertebral ganglia [SUPERIOR HYPOGAST. PLEXUS → SYMPATHETIC CHAIN; PELVIC PLEXUS → SYMPATHETIC CHAIN; JUXTA... → SYMPATHETIC CHAIN and DETRUSOR... → SYMPATHETIC CHAIN]. Now each fiber follows one out of the three used pathways:

1. Fibres synapse on the thoracolumbar level of entry in a paravertebral ganglion.
2. Fibres ascend or descend in the sympathetic chain before they synapse in a paravertebral ganglion.
3. Fibres traverse the sympathetic chain without synapsing.

Inside the sympathetic chain fibres may synapse more than once. Fibers synapsing in ganglia of the hypogastric plexus or paravertebral ganglia of the sympathetic chain, give rise to extraspinal circuits.

Routing via pelvic nerve. Sympathetic afferent fibers that are conveyed by the pelvic nerve pass or connect to the juxta- and intramural ganglia [DETRUSOR → JUXTA...], synapse in or traverses the pelvic plexus [JUXTA... → PELVIC PLEXUS and DETRUSOR → PELVIC PLEXUS] and course to the sacral spinal cord. Once the pelvic nerve trunks come near the sympathetic chain, the sympathetic fibers exit, enter the sympathetic chain and ascend to a thoracolumbar level, synapsing once or more on paravertebral ganglia along the way [PELVIC PLEXUS → SYMPATHETIC CHAIN; JUXTA... → SYMPATHETIC CHAIN and DETRUSOR... → SYMPATHETIC CHAIN]. Considering both possible routings, it is noted that sympathetic afferent fibres, emanating from the lower urinary tract, connect to the paravertebral ganglia on levels L₅-S₃. Both described routings merge and use the same pathways when they leave the sympathetic chain and travel to the thoracolumbar spinal cord segments. The afferent sympathetic fibres leave the sympathetic chain by the white rami communicantes, which connects to the spinal nerve again. The spinal nerves are thought to enter the upper lumbar and lower thoracic spinal cord, presumably being concentrated on levels Th₁-L₂ (Van Arsdalen and Wein, 1991) [SYMPATHETIC CHAIN → THORACIC 11...; SUPERIOR HYPOGAST. PLEXUS → THORACIC 11; PELVIC PLEXUS → THORACIC 11; JUXTA... → THORACIC 11 and DETRUSOR... → THORACIC 11] and might synapse on
dorsal column nuclei. Now two ways are followed:

1. Collaterals enter the dorsal horn and connect, possibly via interneurons, on sympathetic vesicomotoneurons.
2. Ascending fibres connect presumably via the dorsal column nuclei, to the thalamus (see fig. 11) [THORACIC... → THALAMUS], which on its turn projects to the cortex [THALAMUS → PREOPTIC A...], to terminate in the nucleus paraventricularis hypothalami [THALAMUS → PARAVENTRICULARIS]. The development and existence of a spinal tract between the sympathetic vesicomotoneurons, located at the thoracolumbar intermediolateral cell group, and the paraventricularis nucleus in the hypothalamus is demonstrated by Lakke and Hinderink in the rat (1989).

In the rat the development and the presence of projections from the hypothalamus (paraventricular hypothalamic nucleus) to thoracic spinal cord segments has been demonstrated (Lakke and Hinderink, 1989) [PARAVENTRICULARIS → THORACIC 11]. Holstege has demonstrated by autoradiography a descending tract from the M-region of the pontine micturition center to the sacral intermediomedial cell group, which connects to the thoracolumbar vesicomotoneurons (Holstege and Griffiths, 1990) [M → SACRAL INTERMEDIATE].

A descending spinal tract has been discerned by cutting the spinal cord on a thoracic level in functional experiments with cats (De Groat and Lalley, 1972). Neither the exact starting point in the brain nor the termination site in the spinal cord are known. Holstege claims the tract from the M-region to the sacral intermediomedial cell group to be identical with the unknown tract found in De Groat’s experiments. Activity of the latter, which inhibits sympathetic influence, strongly correlates with activity of the descending micturition tract, which starts in the M-region and ends in the sacral intermediolateral cell group. This is one argument for Holstege to present the intermediomedial cell group as the missing sacral link of an intersegmental vesicosympathetic circuit, which is active during bladder filling. Whether the functional tract found by De Groat coincides with the tract found by Lakke or Holstege remains to be established.

Efferent sympathetic fibres, innervating the lower urinary tract, presumably originate in the thoracolumbar intermediolateral cell group of spinal cord segments Th₁₋₂ (see fig. 10). From every corresponding spinal segment efferent fibres arise, leaving the spinal cord through the ventral roots, split from the spinal nerve via the white rami communicantes and travel to the sympathetic chain [THORACIC 11 → SYMPATHETIC CHAIN]. Once fibres enter the sympathetic chain three connections occur:

1. Fibres synapse on the level of entry in a paravertebral ganglion and leave the sympathetic chain by the gray rami communicantes, which connects to the spinal nerve again.
2. Fibres ascend or descend in the sympathetic chain before they synapse in a paravertebral ganglion. Sympathetic fibres leaving thoracolumbar spinal cord segments are able to descend to a sacral level this way.

Inside the sympathetic chain fibres may synapse more than once. Sympathetic efferent fibres, innervating the lower urinary tract, emanate from the paravertebral
ganglia on levels L₃-S₃.
Fibres coming from the rostral part traverse or synapse once or more in the superior hypogastric plexus [SYMPATHETIC CHAIN \rightarrow SUPERIOR HYPOGAST. PLEXUS], the pelvic plexus [SYMPATHETIC CHAIN \rightarrow PELVIC PLEXUS and SUPERIOR HYPOGAST. PLEXUS \rightarrow PELVIC PLEXUS], and the juxta- and intramural ganglia [SYMPATHETIC CHAIN \rightarrow JUXTA...; SUPERIOR HYPOGAST. PLEXUS \rightarrow JUXTA... and PELVIC PLEXUS \rightarrow JUXTA...], before they terminate on the detrusor muscle and urethra [SYMPATHETIC CHAIN \rightarrow DETRUSOR...; SUPERIOR HYPOGAST. PLEXUS \rightarrow DETRUSOR...; PELVIC PLEXUS \rightarrow DETRUSOR... and JUXTA... \rightarrow DETRUSOR...].
Fibres originating in a more caudal part of the sympathetic chain are not conveyed to the superior hypogastric plexus, but to the pelvic plexus instead, where they continue their way to the lower urinary tract as described above. Part of these sympathetic fibres are carried in the pelvic nerve.

3. Fibres traverse the sympathetic chain ganglia and synapse within the superior hypogastric plexus (a prevertebral ganglion) [THORACIC 11 \rightarrow SUPERIOR HYPOGAST. PLEXUS], the pelvic plexus [THORACIC 11 \rightarrow PELVIC PLEXUS], both plexi or neither one. They course to the bladder and the urethra as described above.

Once the sympathetic efferent fibres have reached the bladder and urethra, the following view is generally accepted (Dixon and Gosling, 1987; Gosling, 1986): sympathetic efferent fibres innervate the smooth musculature of the bladder neck, the urethra and the superficial trigonal muscle. In male this region receives rich sympathetic innervation (Raz, 1978), which is sparse in female (see "Functional mechanisms, storage"). The detrusor muscle and deep trigonal muscle have the same autonomic innervation, being rich in parasympathetic supply and less abundant in sympathetic supply. Sympathetic efferent fibres could also play a role in the muscular control of the bladder by β-adrenoceptors, which are located inside the bladder wall of humans (Andersson, 1986) and cats (De Groat, 1975).

The juxta- and intramural ganglia form together with the ganglia of the pelvic plexus a short neuron system, of which the existence and function was postulated by Elbadawi (1984, 1986, 1991). The ganglia of this short neuron system are innervated by either sympathetic nerve fibres, parasympathetic nerve fibres or both (Bradley and Teague, 1986a).

Besides synapses of efferent axons from one autonomic nervous system on dendrites and cell bodies inside ganglia of the other autonomic nervous system, also direct axoaxonal contacts between both autonomic nervous systems have been discerned on the bladder base and proximal urethra (Elbadawi, 1986). Despite postganglionic sympathetic fibres that emanate from thoracolumbar spinal cord segments, from paravertebral ganglia inside the sympathetic chain, from prevertebral ganglia or from the superior hypogastric plexus, the actual autonomic innervation of the lower urinary tract is derived predominantly from the peripheral ganglia adjacent to or within the bladder and urethra (the short neuron system).

**Somatic connections** (see fig. 11)
Afferent fibres of the pelvic nerve in cats, probably being parasympathetic fibres from tension receptors within the bladder wall, pass or connect to ganglia of the short neuron system (i.e. ganglia of the pelvic plexus, juxta- and intramural ganglia). Synapses in the short neuron system give rise to extraspinal pathways. Leaving the short neuron system,
the pelvic nerve afferents enter the sacral dorsal horn and travel via a medial collateral pathway to the dorsal gray commissure (Morrison, 1987a). At this site contact with somatic motoneurons is possible. This collection of pathways is simplified represented in fig. 11 by [DETRUSOR → ONUF’s NUCLEUS]

Somatic afferents from the striated urethral musculature and urethral mucosa are conveyed by the pelvic nerve to the sacral spinal cord. The somatic afferents traverse the ganglia of the short neuron system, but it is not known if they also synapse. The somatic afferents continue their course to the spinal cord and enter on sacral levels S₁-S₄.

Somatic afferents from the pelvic floor musculature are conveyed by the pudendal nerve to the sacral spinal cord. The pudendal afferents coming from the lower urinary tract meet other trunks of the pudendal nerve, merge to one single trunk and pass Alcock’s canal. Near the spinal cord the pudendal nerve splits in several trunks. The fibers originating from the pelvic floor musculature enter the spinal cord on levels S₁-S₃, but use predominantly S₂.

When the described somatic afferent fibres, which are carried in the pelvic and pudendal nerve, enter the sacral spinal cord via the dorsal roots, two ways are followed (see fig. 11):

1. Somatic afferent fibres enter the dorsal horn and terminate mainly near the intermediolateral cell group, where pelvic vesicomotor neurons and dendrites of pudendal motoneurons are located. The somatic afferent fibres probably synapse on both the somatic motoneurons (Fletcher and Bradley, 1978; Morrison 1987a) [STRIATED URETHRA → ONUF’s NUCLEUS and PELVIC FLOOR → ONUF’s NUCLEUS] and parasympathetic motoneurons (Bradley and Teague, 1968b; Morrison, 1987a) [STRIATED URETHRA → SACRAL INTERMEDIOLATERAL]. Evidence for synapses of somatic afferents, coming from the urethra, on pelvic vesicomotoric neurons can be found by HRP-tracing in animals (e.g. Morrison, 1987a).

2. The somatic afferent fibres synapse in the posterior column nuclei [STRIATED URETHRA → POSTERIOR COLUMN NUCLEI and PELVIC FLOOR → POSTERIOR COLUMN NUCLEI], ascend as a spinal tract on the ipsilateral side, cross the mid-line on a higher spinal level and continue to terminate in the thalamus [POSTERIOR COLUMN NUCLEI → THALAMUS]. The thalamus projects to cortical and subcortical structures [THALAMUS → PREOPTIC A. & CORTEX]. Sensations from the urethra and pelvic floor are transmitted (Morrison, 1987a).

The projection of somatic afferents to Onuf’s nucleus in animals is described by Morrison (1987a): dendrites of somatic motoneurons extend dorsally towards the intermediolateral cell group and the dorsal gray commissure in the cat. Here somatic afferents may synapse directly or via interneurons on dendrites of the pudendal motoneurons, indicating a sacral reflex arc.

After entering the sacral spinal cord, pudendal nerve afferents in monkeys synapse just dorsal to the sacral parasympathetic nucleus, which would be a perfect site to contact interneurons of the micturition reflex pathway (Morrison, 1987a). In cats, somatic afferents originally arising from the striated urethral musculature synapse in the sacral parasympathetic nucleus after they have entered the spinal cord (Bradley and Teague, 1968b).
The pelvic floor and other striated musculature of the lower urinary tract are under voluntary control, which points out the involvement of a corticospinal tract. A descending tract has been identified by magnetic stimulation of the motor cortex as well (Ingram, 1982). It is a point of discussion whether this connection consists of a direct projection between the cortex and Onuf's nucleus or an indirect projection with synapses in thalamus, brain stem and probably other structures. Morrison (1987a) suggests that both, a direct and indirect connection, are present. Recent research by Iwatsubo et al. (1990) suggests however, that the human nucleus of Onuf has predominantly indirect and virtually no direct corticospinal connections. This suggests an important role for the L-region of the pons, which projects to Onuf's nucleus, in voluntary control (Holstege, 1989; Holstege and Griffiths, 1990) [PREOPTIC A. & CORTEX → L and L → ONUF'S NUCLEUS].

Efferent somatic fibres originate in Onuf's nucleus, which is predominantly located in spinal cord segment S2, with extensions to levels S1 and S3. The efferent somatic fibres leave the spinal cord through the corresponding ventral roots and are conveyed to the pelvic floor musculature by the pudendal nerve (Elbadawi, 1987b; Blaivas, 1985; Holstege, 1990) [ONUF'S NUCLEUS → PELVIC FLOOR] and to the striated urethral musculature by the pelvic nerve (Donker, 1986, Gil Vernet, 1964; Gosling et al., 1983; Marani et al., 1993) [ONUF'S NUCLEUS → STRIATED URETHRA]. The efferent somatic fibres carried in the pudendal nerve converge to one single trunk after they have left the spinal cord. Several branches arise from the pudendal nerve not earlier than after it has passed Alcock's canal. The pudendal nerve with its branches innervates, among other structures, the pelvic floor musculature. The routing of the pelvic nerve is described later.

The nerve supply of striated urethral musculature by somatic afferent and efferent fibres is a point of discussion in literature. Some authors suggest an innervation by the pelvic plexus (Donker, 1986; Gil Vernet, 1964, Gosling et al., 1983, Marani et al., 1993), others favour an innervation by the pudendal nerve (Juenemann et al., 1988; Gray, 1985; Morris, 1942; Tanagho et al., 1982).

Parasympathetic connections
Pelvic nerve afferents, coming from the bladder and smooth urethral musculature, traverse or synapse in the ganglia of the short neuron system. Synapses in the short neuron system give rise to extraspinal pathways. Reaching the sacral spinal cord the pelvic nerve fans out in visceral branches of the sacral dorsal roots, enter it and synapse on parasympathetic vesicomotoneurons, located in a lateral band of the gray matter (intermediolateral cell group) (Morrison, 1987a; Fletcher and Bradley, 1978) [DETRUSOR... → SACRAL INTERMEDIOLATERAL, ETC.].

The discussion how information about the degree of bladder filling is conveyed to supraspinal structures is delicate. The "long-routing" of bladder afferents as described by Bradley and Blaivas seems very unlikely. Holstege denies the existence of an ascending tract between the sacral spinal cord and the pontine micturition center and suggests an indirect projection to higher brain structures.

To complete the afferent parasympathetic circuitry of our model, Holstege's theory is applied: an ascending tract between the sacral spinal cord and suprapontine brain structures is integrated in fig. 11 [SACRAL INTERMEDIOLATERAL → PREOPTIC A. & CORTEX].
Figure 9: proposed afferent parasympathetic and sympathetic peripheral pathways.

- : this symbol indicates that the pathway does not connect to the following block.

- : this symbol indicates that the pathway does connect to the following block.

For further description see text.
An efferent pathway originates in the M-region, medial to the locus coeruleus in the pontine tegmental field. The pathway connects the M-region to the parasympathetic vesicomotoneurons in the sacral cord (Holstege, 1989; Holstege and Griffiths 1990) [M \rightarrow SACRAL INTERMEDIOLATERAL]. Lakke et al. (1987) and Oudega et al. (1993) have demonstrated a descending projection of the nucleus tegmentalis laterodorsalis (TLD), located adjacent to the locus coeruleus, to target cells in the L4-S2 intermediolateral gray matter in the rat. The pontine nucleus TLD might coincide with Holstege's M-region: it mediates bladder contraction upon electrical stimulation. Holstege and Lakke demonstrate that not the locus coeruleus constitutes the pontine micturition center, but structures located close to it.

Efferent parasympathetic fibres originate in an intermediateolateral cell group (sacral parasympathetic nucleus) of spinal cord segments S2-S4, being concentrated in S3, and are carried in the pelvic nerve. The pelvic nerve carries mainly parasympathetic fibres. It arises by linking up visceral branches of sacral ventral roots and consists of two to three trunks in the human (Marani et al., 1993). Please note that all parasympathetic fibres of the pelvic nerve synapse very near their target organ in the short neuron system for the first time. The fibres synapse in or traverse the pelvic plexus, which for the routing of the pelvic nerve can functionally be divided in two different parts, and synapse and/or terminate in the juxta- and intramural ganglia. The smooth detrusor muscle, including the vesical neck and deep trigonal muscle, and the smooth urethral musculature receive rich parasympathetic supply (Dixon and Gosling, 1987; Gosling, 1986) [SACRAL INTERMEDIOLATERAL \rightarrow DETRUSOR...].

A recurrent inhibitory pathway on parasympathetic preganglionic neurons has been based on electrical stimulation experiments (Bradley, 1969; De Groat, 1975), but the anatomical basis remains to be established (Morrison, 1987).
Figure 10: proposed efferent parasympathetic and sympathetic peripheral pathways.

- O: this symbol indicates that the pathway does not connect to the following block.

- ➔: this symbol indicates that the pathway does connect to the following block.

For further description see text.
Supraspinal connections
The M- and L-region of the pontine reticular formation are supposed to reciprocally inhibit each other (Holstege, 1989; Holstege and Griffiths, 1990). In the cat the M-region is innervated by the preoptic area and the periaqueductal gray (PAG) (Holstege and Griffiths, 1990).
Figure 11: integrated circuitry of the proposed model.
Functional mechanisms

Problems arise when functional mechanisms are proposed for the micturition process in human. Several reflexes are known to occur in animals, but their existence in humans is still uncertain.

Storage

During the filling phase of the bladder a vesicosympathetic reflex and a somatic reflex act as guarding reflexes, thus promoting continence (Bradley et al., 1974; Bradley, 1978, De Groat and Steers, 1991; Holstege and Griffiths, 1990).

1. In case of the vesicosympathetic reflex, bladder and urethral afferents of both the pelvic and hypogastric nerve send signals to the thoracolumbar (sympathetic) intermediolateral cell group.

Pelvic nerve afferents use a spinal intersegmental pathway, where fibres synapse in the dorsal horn of the sacral spinal cord and connect to ascending fibres that project to the thoracolumbar intermediolateral cell group (De Groat and Lalley, 1971; De Groat and Steers, 1991; Holstege and Griffiths, 1990).

Hypogastric nerve afferents synapse in thoracolumbar spinal cord segments (Fletcher and Bradley, 1978; Morrison, 1987). Here they probably project to the intermediolateral cell group. According to all four authors these sympathetic afferent fibres do not contribute to micturition control. With the rather complex and badly understood afferent sympathetic circuitry, the possible extraspinal pathways and the spinal tract from thoracolumbar spinal cord segments to the paraventricularis nucleus in the hypothalamus in mind (see figs. 10 and 11), it seems very unlikely that these fibres have no function in micturition control. The exact role of these hypogastric afferents in the control of the lower urinary tract remains to be established, but they appear to transmit information about the degree of bladder filling (Morrison, 1987).

Efferent sympathetic neurons inside the thoracolumbar cord are excited by the described two activated afferent pathways. The effects are fourfold:

1. In all ganglia where the sympathetic nervous system meets the parasympathetic nervous system, the latter is inhibited (De Groat et al., 1979; De Groat, 1975). The short neuron system is under sympathetic control and transmission of parasympathetic excitatory signals is inhibited on ganglionic level (De Groat et al., 1979; De Groat, 1975; De Groat and Saum, 1971) and probably also by direct axoaxonal contacts (Elbadawi, 1986).
2. The detrusor activity is inhibited by β-adrenoceptors inside the bladder wall (De Groat, 1975, cats).
3. A smooth muscle sphincteric mechanism is activated. Smooth urethral musculature, the trigone and the vesical neck are brought under tension by activation of α-adrenoceptors (De Groat et al., 1979; Elbadawi, 1984; Mattiasson et al., 1984). Elbadawi introduced for this purpose the
functional concept of a lissosphincter, constituting of smooth
musculature from the bladder base, proximal urethra and a periureteral

4. The vascular bed of the mucosa is affected (Fletcher and Bradley,
1978).

These effects are present in animals under unphysiological conditions. The
importance of either these elements under more physiological conditions in the
human remains unclear.

2. In case of the somatic reflex, afferents from the striated urethral musculature and
from the pelvic floor musculature send signals to Onuf’s nucleus. Collateral
somatic afferents relay information to the cortex. Possibly by both a spinal and a
supraspinal circuit the motoneurons of Onuf’s nucleus bring the striated urethral
musculature and pelvic floor musculature under strain.
The supraspinal influence comes from the L-region. The L-region continuously
excites Onuf’s nucleus. The L-region also reciprocally inhibits the M-region,
which results in a stable bladder.

Bladder afferents enter to the sacral spinal cord and connect to Onuf’s nucleus (Morrison,
1987'). This circuitry might be active during storage to excite the striated sphincters or it
might be active when micturition is about to happen to inhibit Onuf’s nucleus, resulting in
relaxation of the striated sphincters. Until now neither function has been demonstrated
convincingly yet, therefore in our opinion it might be functionally non-existent in human.

The pelvic floor contributes to urethral closure by contraction of striated muscle fibres
adjacent to the urethra, especially when a sudden rise in abdominal pressure as during
coughing or sneezing appears (Fowler and Fowler, 1987).
The importance of the pelvic floor as a from the urethra separated muscular structure in
the micturition process however, is often underestimated or not recognised. Clinical
evidence in the treatment of refractory detrusor instability and stress urinary incontinence
by neurostimulation and neuromodulation suggests that the pelvic floor has considerable
effect on micturition control (Dijkema et al., 1992; Fall, 1984, Schmidt and Tanagho
1990; Tanagho et al., 1989; Thon et al., 1991; Siegel, 1992). Both contraction and
relaxation of the pelvic floor probably activate several unknown functional mechanisms,
which affects the bladder stability during storage (Mayo, 1978) and both the initiation and
termination phase of voiding.
Besides neuronal effects of the pelvic floor, structural influence is present too. The pelvic
floor maintains a correct bladder-to-urethra position during the filling phase, thereby
facilitating the closure of the proximal urethral.

The anatomical differences in male and female urethra (Awad and Downie, 1976; Dixon and Gosling, 1987;
Droes, 1972) have their effect on functioning. In contrast with the rich sympathetic innervation of the bladder
neck, superficial trigonal muscle and proximal urethra in male human subjects, in female subjects this
sympathetic innervation is less abundant (Dixon and Gosling, 1987; Venema, 1990). Moreover a smooth
muscle sphincter can be difficult discerned in female subjects: smooth urethral muscle fibres have a
predominant longitudinal orientation throughout the whole urethra and circular or helical orientated fibres are
sparse (Gosling, 1986; Hickey et al., 1982).
Figure 12: proposed functional mechanisms, which probably enhance the storage capacity of the bladder and contribute to continence.
This seems contradictory with the functional mechanisms that promote continence during bladder filling by contraction of smooth musculature from the vesical neck, superficial trigone, proximal urethra and more caudal parts of the urethra. However the same functional mechanisms contribute to the closure of the urethra and vesical neck in male and female, but the importance of the occurring mechanisms vary intersexually (Awad and Downie, 1976; Venema 1990).

The material characteristics of the urethral tissue contribute considerably in the closure of the urethra during bladder filling. In this paper only contributions of muscular tissues in the closure of the vesical neck and urethra will be discussed.

**Micturition**

Critical bladder distension produces high-level firing of bladder (parasympathetic and sympathetic) afferents. The parasympathetic and probably sympathetic bladder afferents that are carried in the pelvic and hypogastric nerve send their signals to the thalamus, from where the cortical (possibly the preoptic area in the cat) and subcortical structures (possibly the nucleus paraventricularis in the hypothalamus and the periaquaductal gray) are stimulated. These suprapontine structures, the cortex, the periaquaductal gray and the nucleus paraventricularis might determine the onset of voiding. The paraventricular hypothalamic nucleus probably inhibits the sympathetic vesicomotoneurons inside the spinal cord (Coote et al., 1982).

The cortex indirectly inhibits the nucleus of Onuf, resulting in a starting relaxation of the pelvic floor and striated urethral musculature.

Both, cortex and periaquaductal gray, stimulate the M-region in the pontine tegmental field. The M-region activity results in three simultaneous occurring effects:

2. The M-region reciprocally inhibits the L-region. This results in relaxation of striated urethral and pelvic floor musculature (Holstege and Griffiths, 1990; Holstege, 1989).
3. The M-region influences the sacral intermediomedial cell group, which somehow results in the inhibition of the vesicosympathetic guarding reflex (Holstege, 1989). This means the opening of the bladder neck and urethra; the termination of inhibitory sympathetic influence on the detrusor muscle; the end of the sympathetic control of the urogenital short neuron system.

Micturition reflex duration and amplification in cats is realised by central and peripheral control structures. The continual afferent discharge of tension receptors during micturition remains a stimulus for bladder contraction.

Centrally, the brain stem reticular formation and the sacral parasympathetic nuclei, located in the sacral spinal cord, both endure and amplify the micturition reflex (Bradley, 1969a; De Groat, 1975). Peripherally, the ganglia of the short neuron system, especially the pelvic ganglia inside the pelvic plexus, amplify and elongate the micturition reflex (Bradley, 1969a; Bradley and Teague, 1968a; De Groat, 1975; De Groat et al., 1979b). Under unphysiological conditions, an output of these ganglia can be measured, several minutes after the input has faded. These ganglia play an essential role in the control of the lower urinary tract, both during storage and micturition. A high pass filter behaviour has been noted, i.e. low-level parasympathetic input does not pass, while repetitive high level input...
results in a stronger gain (De Groat, 1975; Morrison, 1987b). The connection between somatic afferent fibres and parasympathetic vesicomotoric neurons (Morrison, 1987b; see fig. 11) is supposed to start a second reflex wave as noted by De Groat and Bradley. De Groat and Bradley suggest that this reflex reinforces detrusor contraction and is activated by urine flow in the urethra. This reflex is known to be present in animals (Bradley and Teague, 1968b; Elbadawi, 1991; Morrison, 1987d), but urodynamic measurements in human do not show such a second reflex wave (Griffiths, 1987; Torrens, 1987), indicating that if it does exist, the effects are neglectable.

**End of micturition**

The end of the micturition reflex remains to be clarified. The striated musculature, that can be contracted voluntary, plays an important role. However, the supraspinal organization is not clear: indirect corticospinal tracts influence Onuf's nucleus and thereby are able to contract the striated urethral and pelvic floor musculature. This activates an unidentified reflex arc, which inhibits and terminates further contraction of the detrusor (Blaivas, 1982; De Groat and Steers, 1990).
Figure 13: proposed functional mechanisms during micturition.
APPLICATIONS

Based on the experimental data as described in the paper, applications have been developed for understanding the steering of the uropoetic system or for clinical solutions to impairment of this system. Two applications will be considered: neural networks, neurostimulation and neuromodulation.

Neural network
To understand the principles underlying information processing in the complex neuronal system for the control of the lower urinary tract, mathematical modelling might be useful. One approach to this problem is the application of techniques from artificial neural networks. Several neural networks have been developed to describe parts of the nervous system of invertebrates (for example Getting, 1989). The neurons in these networks are modelled as electronic circuits like the description by Hodgkin and Huxley (1952). The electrical membrane potential during time can be calculated and compared with electrophysiological measurements. This approach is not applicable to the human nervous system underlying the control of the lower urinary tract: too many neurons are involved and electrophysiological measurements from individual cells is extremely difficult. However, many details of single nerve cells may be unimportant for an understanding of the collective behaviour of a network of cells (Hertz et al., 1991). In physiological nervous systems, features can be recognized (like transmission of signals by threshold units, associative memory, excitatory and inhibitory connections, etc.), which can be modelled in a simplified way in artificial neural networks. Computer simulations of neural networks can be used to predict the behaviour of a neural control system under normal and pathological circumstances (for example the effect of broken connections).

A neural control model for the urinary bladder based on the qualitative model of Holstege, has been developed, see fig. 14 (Bastiaanssen et al., 1993). The main structures are the nucleus of Onuf, the parasympathetic motoneurons, the sympathetic motoneurons, the intermediomedial cell group in the sacral spinal cord, the micturition centre in the brain stem and the preoptic area in the cortex. It would be too complicated to include all anatomical structures and their connections involved in the control of the lower urinary tract. Therefore, only the most important relay stations in the qualitative model were represented as layers in the neural network, whereas the urethral sphincter and its innervation were initially excluded. The neural pathways are represented as connections between the neurons in the different layers. The fire frequencies of the inhibitory and excitatory motoneurons are the inputs for the mechanical bladder model. The mechanical aspects of the bladder, like the development of tension and pressure, and the flow of urine are described in the bladder model. The output of a sensor in the bladder wall, which is described as the nonlinear response to the strain in the wall, feeds back into the neural network.
Figure 14: Simplified neural circuitry that can be used in the neural network simulations. Thick lines: part of the neural circuitry used in neural network simulations as discussed in Bastiaanssen et al. (1993). In this simplification, the relay stations in the afferent pathways from the muscle structures to the cortex are excluded and replaced by direct connections.
For the control of the urinary bladder, the fire frequencies of the motoneurons seem to be of more interest than the precise potential fluctuations. The fire frequency of an individual neuron is influenced by its current fire frequency and the incoming excitatory and inhibitory inputs from neurons of previous layers. Dependent on the importance of the connections between different neurons, the weighted sum of all input signals is determined. The response on the weighted sum of inputs can be described by an activation function. For this activation function is a sigmoid (the fire frequency is close to maximal if the sum exceeds a certain threshold, almost zero if the sum is low and somewhere between these values if the sum is near the threshold) is chosen. The neurons can have different time constants, representing slow and fast responding cells. The fire frequency of the neuron will change rapidly as a result of a change in the incoming signals if its time constant is small. In contrast, a slow neuron (with a large time) constant will show a more moderate and lasting response on a change in input. The parameters in the neural network are the time constants and the weights of the connections. The optimal values of these parameters are searched during the learning phase of the neural network. After the learning phase, the trained network shows a behaviour as close as possible to the desired behaviour. In this particularly case, the neural network can control the bladder model to mimic a prescribed filling and emptying behaviour.

In this way, transmission of signals by slow and fast responding threshold units with excitatory and inhibitory connections can be modelled in a quantitative model based on a qualitative description. Such a description of neural network simulations can be helpful to understand the collective behaviour of the neural system underlying the control of the lower urinary tract.

Neurostimulation and neuromodulation.

Some new methods of treatment for refractory detrusor instability and stress urinary incontinence are based on reflexly orientated interactions between the pelvic floor and the lower urinary tract. Biofeedback, where the patient gets aware of pelvic floor activity again and regains conscious control of the pelvic floor, can result in a reflexly inhibition of an instable detrusor muscle. Externally applied electrostimulation of the pelvic floor by means of a vaginal or rectal electrode can back up this process (Dijkema et al., 1992). The functional mechanisms behind this treatment are not yet defined. Spinal reflex mechanisms seem to influence the pelvic floor and detrusor muscle during electrical stimulation, but long term cure of incontinence probably involves the central nervous system (Fall, 1984).

In case of neuromodulation, the sacral spinal nerve near S3 or the ventral root near S3 is directly stimulated. Treatment is realised by implantation of an electrode in the sacral foramina and a stimulator in an abdominal pocket (for the applied method, see Schmidt and Tanagho, 1990; Tanagho et al., 1989; Thon et al., 1991; Siegel, 1992; Dijkema et al., 1992). A high stimulus level activates autonomic fibres and results in a contraction of the detrusor muscle and the urethral sphincter. Low-level stimulation mainly activates somatic fibres, and no contraction of the detrusor muscle is noted. Instead, a continuous state of contraction of mainly the ventral levator ani muscle and the external urethral sphincter is realised. Reflexly, the detrusor muscle is inhibited via the same reflex mechanism as in case of external stimulation. Detrusor and urethral instabilities are depressed and sphincteric and pelvic floor spasms are corrected. When the stimulator is turned of in
presence of a filled bladder, the pelvic floor will relax and the micturition reflex will be activated (Dijkema et al., 1992).

Exact knowledge about the activated functional mechanism and fibres is not present yet. It is suggested, that afferent and efferent fibres are activated, probably of both the pelvic and pudendal nerve. Sympathetic efferent fibres are probably not excited. Neuromodulation in animals can help to elucidate some of the underlying functional mechanisms. Here, a qualitative model that represents the neuronal control circuitry of the lower urinary tract as presented in this review has its value in objective judgement of the possibly activated pathways. This way more insight can be gained in the overall functioning and dysfunctioning of the urinary tract with respect to neuronal control disorders.
CONCLUSION

The review given in this paper on the anatomy and function of the uropoetic system demonstrates:

1. The proposed reflex arches and supraspinal connections in literature involved in micturition and continence are different and sometimes contradictory.
2. From the known literature a measured judgement on circuitries proposed has been made and a general scheme of the uropoetic neuronal circuitry proposed.
3. Little is known about how autonomic information of the lower urinary tract is relayed to supraspinal structures.
4. Information about supraspinal interconnections and their function in micturition control is still fragmentary.
5. The role of the pelvic floor musculature during the micturition process is probably underestimated.
6. The function of the peripheral nervous system, especially the short neuron system, in the control of the lower urinary tract is probably underestimated.
7. Application of this general circuitry in a summarized form is proposed in neural network simulations and its implications for neurostimulation and neuromodulation shown.

Future research on the mentioned subjects will be necessary to gain more insight in the micturition process and to develop a continual improving qualitative model. New developments in neural network theory will become available and offer promising perspectives.
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1.1 INTRODUCTION.

The purpose of appendix 1 is to summarize and explain medical terms and physiological backgrounds which will allow one to gain more insight in complex biological control systems. Recurrent inhibition, transformation functions, filters, amplification, control strategies, etc., occur in the control of the micturition cycle, but insight in the biologic "version" is necessary to recognize them as such and to abstract them into technical terms.

Neurons are the smallest functional units of the system and play an important role in signal transmission and conduction. Therefore, attention will be paid to them. Existing relationships and functional mechanisms will be described from a technical point of view in § 1.2 and § 1.3. In § 1.4 and § 1.5 a closer look will be taken at the elicited relationships by focusing on physiology and anatomy. Nevertheless limitation in describing these subjects is necessary. This summary is therefore incomplete and it merely introduces one to some subjects. For a good and comprehensive illustration of biologic functioning, see fundamental physiology books, especially the work of J.A. Bernards and L.N. Bouman (1988). A used medical terminology is explained partly in the enclosed vocabulary.

1.2 CONTROL LOOP.

The control loop in figure 1.1 illustrates human functioning in a simplified way.

![Diagram of human control loop](image)

Figure 1.1: human control loop.

We can discern a global controller, the central nervous system, which processes information obtained by several sensors to control functions in the human body. The purpose of these functions is to react on the changing in- and external environment. Control actions often aim to keep certain body values in a narrow range, as for example the body temperature. On the other hand, quick and big changes can be necessary, for example in case of body movement. Successively all the elements of the control loop will be closer examined.
1.2.1 SENSORS.

Three different types of sensors can be discerned:

1. Extero-sensors are sensors which generate information about the outside world.
2. Proprio-sensors give information about motoric aspects, like posture, movement, position in space.
3. Intero-sensors generate information about the condition of internal systems, like organs and other structures.

A sensor is able to translate a non-electric stimulus from the periphery (for example a mechanical stimulus such as pressure on the skin) into an electrical signal. The induced signal is conveyed to the controller by afferent pathways (see fig. 1.1). Biologically a sensor consists of a specialized nerve cell.

1.2.2 AFFERENT AND EFFERENT PATHWAYS: A NEURON.

Sensoric information is conveyed by afferent pathways from the periphery (organs, skin, muscles, etc.) towards the central nervous system. Vice versa, efferent pathways exist, which connect the central nervous system to the periphery (subsystems named "process" in fig. 1.1). Inside the central nervous system neuronal pathways enable signal conduction and transmission.

Neuronal pathways are formed by a large collection of nerve cells called neurons. A neuron gives of a long thin thread known as an axon, which is able to convey signals over a long distance, sometimes up to one meter and a half. Inside the nervous system neurons are shaped in several ways. Figure 1.2 shows two examples of neurons inside the central nervous system.

![Neuron Diagram](image)

A. Interneuron inside the spinal cord; B. Neuron from the motor cortex inside the cerebrum.

Figure 1.2: Two different neuron types inside the central nervous system; dendrites, soma and the sprouting axon are shown.

The axon is an elongated part of the cell body (soma) and is responsible for signal conduction. The cell body (soma) with his dendrites (i.e. shorter and more numerous elongations of the soma compared to an axon) connected to it constitute the receptive area of a neuron. Signals arriving from another neuron (for example an interneuron or a sensor) are noticed here.
On the other end of the axon a transmissive area can be discerned; the axon fans out in branches, terminating in synapses. Via these synapses signals are transmitted to a next neuron or effector organ, i.e. muscular or glandular tissue, by special designed structures. The connective area between two neurons is called synapse; a junction is defined as a connection between a neuron and an effector organ. The intra-cellular and the extra-cellular fluid of a neuron both function as a conductor and the plasmamembrane as an isolator. Technically, this results in an isolated wire with a grounded and conducting network on the outside.

1.2.3 THE CENTRAL NERVOUS SYSTEM.

The central nervous system (defined as neural structures inside the brain and the spinal cord) acquires information about the condition of the body through sensors and neuronal pathways. It acts as a controller and sends control instructions to various effector structures through efferent neuronal pathways.

A neuronal pathway from a sensor to an effector structure consists of two or more neurons. At least one afferent neuron and one efferent neuron has to be involved. In most cases more than two neurons constitute the pathway between sensor and effector.

Most of the afferent nerves enter the central nervous system through the spinal cord. A synapse on another neuron takes place at the segmental level of entry, at higher or lower segmental levels (see fig. 1.3). Now two global pathways can be followed:

1. Efferent nerves leave the spinal cord without being connected to supraspinal structures: a spinal pathway.
2. Axons ascend to synapse in supraspinal structures, which send descending axons to terminate inside the spinal cord. From here efferent fibres leave the spinal cord. This is called a supraspinal pathway.

All neuronal pathways outside the central nervous system (connections of the brain and spinal cord) belong to the peripheral nervous system. According to a functional organization a somatic (or animal) and an autonomic nervous system can be discerned. The autonomic nervous system can be divided in an (ortho)sympathetic and a parasympathetic system and effects smooth muscles and glands. In figure 1.4 the functional organization of the nervous system is shown.
The signals of the sympathetic and parasympathetic nervous system have opposite effects. Both systems influence the metabolism of the organism. The sympathetic system stimulates catabolism and inhibits anabolism, while the parasympathetic system inhibits catabolism and stimulates anabolism. Catabolism means, that the potential energy of the metabolically produced substance(s) is less than the potential energy of the substances that took part in the reaction process. In case of anabolism, things are reversed: the resulting amount of potential energy is larger.

The somatic nervous system processes sensory information such as posture, movement, pain, temperature, pressure, etc. and generates control actions, which mainly serve motor functions of striated muscles. This is known as animal or senso-motory integration. We are aware of most actions initiated by this system, while the actions initiated by the autonomic nervous system mainly take place unconsciously.

1.2.4 PROCESSES.

The controller innervates two types of tissue: muscular and glandular tissue. Glandular tissue will not be dealt with.

Two muscle types will be considered:

1. Striated musculature.
   This consists of skeletal musculature, i.e. muscles that posses one or more attachments to the skeleton. Contraction often results in motion of the body or body parts (motor functions). These muscles are also described as somatic (animal) muscles, according to their innervation. Take for example the striated pelvic floor musculature.
   The fibres of the skeletal musculature can be divided in so called slow-twitch and fast-twitch fibres. Fast-twitch fibres are able to react very quickly, but get fatigued early. Slow-twitch fibres react slower, but are almost indefatigable. No attention is payed to other types of striated musculature.

2. Smooth musculature.
   This type of musculature mainly appears in internal organs. Contraction of smooth musculature happens unconsciously (autonomic nervous system), slowly and often serves to change the diameter of a hollow organ.
1.3 NEURONAL CONDUCTION AND TRANSMISSION OF SIGNALS.

Theoretically and on a small scale, a neuron is able to conduct a signal in two directions. Practically, seen on a larger scale, the conduction of a signal in an axon takes place in only one direction, from the receptive to the transmissive area of the neuron. By stimulating the receptive area, a signal can be generated (it will be considered later what conditions and type of stimulus are necessary to elicit a signal). The receptive area of a neuron consists of the cell body and his dendrites. The dendrites are in fact processes of the cell body, which increase the receptive surface remarkably. Stimulus duration and intensity applied to the receptive surface do not influence the amplitude of the resulting signal: the amplitude of the signal is always the same. So modulation of amplitude for information transfer is not possible. Frequency modulation is: the number of signals per second can be varied.

In general, signal transmission is realised by a neurotransmitter. This is called indirect transmission. A neurotransmitter is a chemical substance that is released as soon as a signal passes the axon and reaches the transmissive area of the neuron. The neurotransmitter chemically stimulates receptors, which are located inside the cell wall of the receptive area belonging to the next neuron or effector organ (see figure 1.5).

Figure 1.5: several effects of a neurotransmitter.

Chemical stimuli are translated by receptors in changes of cell membrane characteristics. The cell membrane can be "triggered". Further explanation is given in the next paragraph. The amount of released neurotransmitter is correlated to the appearance of signal transmission. You can interpret this as a filter function. If the neurotransmitter exceeds a certain concentration, the cell membrane is triggered and signal transmission occurs. In case the concentration of neurotransmitter is not sufficient to trigger the cell membrane, the signal simply ends at this synapse. There are several types of neurotransmitters known and some of them can even inhibit signal transmission. Every terminal branch of a neuron can only release one type of neurotransmitter or more substances at the same time. A neurotransmitter can inhibit his own release or the release of other substances (see fig. 1.5).

Signal transmission is possible between sensor-neuron, neuron-neuron and neuron-effector organ. Former and latter generally occur in the peripheral nervous system. A neuron-neuron synapse occurs in so called ganglia of the peripheral nervous system or inside the central nervous system. A ganglion consists of a collection of cell bodies from neurons, positioned outside of the central nervous system. Several types of ganglia can be
discerned. It is possible for a neuron to pass through a ganglion without synapsing.

Now let us focus to a synapse positioned in the central nervous system, e.g. a motor anterior horn cell (motoneuron), that is characterised by its receptive area which possesses thousands (!) of synapses. One signal arriving from an afferent fibre does not release enough neurotransmitter to accomplish signal transmission. There are two possible mechanisms available to accomplish signal transmission:

1. Using a higher stimulus frequency (summation of time).
2. Activating more synapses (summation of place).

Both mechanisms increase the amount of released neurotransmitter and therefore affect the presynaptic neuron, i.e. the neuron that releases the neurotransmitter. In the former case an excitatory neurotransmitter, which is able to accomplish signal transmission, has been discussed. Not all neurotransmitters act excitatory; some have inhibitory effects on signal transmission. Again the amount of released neurotransmitter can be increased by summation of time and place. Two possible inhibitory mechanisms can be discerned:

1. The receptors of a postsynaptic neuron will be manipulated in such a way that a greater amount of neurotransmitter is necessary to trigger the postsynaptic cell membrane (fig. 1.5: effect of T1 on R3).
2. The inhibitory transmitter selectively reduces the release of an excitatory transmitter of a close presynaptic neuron (fig. 1.5: effect of T1 on T2).

In the second case, the receptors of the postsynaptic cell are not influenced and can still be stimulated by free neurotransmitters inside the synaptive space. Terminal branches of several axons can terminate on one next neuron: convergence. Divergence is also possible: the terminal branches of one axon contact two or more other neurons.

Summary: more or less simultaneous stimuli in combination with a lot of synapses are necessary to excite a motoneuron. Stimulation with just one axon terminal does not affect the postsynaptic cell membrane enough to realise signal transmission. The site where a lot of synapses occur can function as a controller. Such a "switch-board" can act amplifying, can increase the duration of a transmitted signal and/or can function as a filter.
1.4 PHYSIOLOGY.

Mechanisms and relations have been discussed globally without loss of understanding due to medical terms. Nevertheless it is of major importance to take a closer look at the underlying physiological ideas.

1.4.1 THE NEURON.

A neuron, especially an axon, can be interpreted as an electric wire. There exists an electric potential over the cell membrane.

The occurrence of a membrane potential depends on very complex mechanisms. Besides an electric gradient a concentration gradient of charged ions is involved as well. These two gradients are responsible for an equilibrium state. The characteristics of the cell membrane, especially its permeability, plays a major role too. It is not possible in this context to explain the involved mechanisms in detail. Below a very simplified and incomplete version is presented, mainly to elucidate some characteristic properties in signal conduction of neurons. For a better and complete description it is referred to fundamental physiology books.

The membrane potential is confined to an area very close to the cell membrane. The inner side of the cell membrane is locally charged negative compared to the outer side of the cell membrane. This negative membrane potential is present over the whole neuron: the inner cell membrane of dendrites, soma, axon and terminal branches are all negatively charged compared to the outer side. The membrane potential can be changed, for example by a chemical stimulus such as a released neurotransmitter. A neurotransmitter affects the receptive area of a neuron. It can increase or decrease the membrane potential, which is dependant on the neurotransmitter-receptor combination.

To achieve an increase of the membrane potential, the permeability of the cell membrane is increased by opening specific so called ion-channels. This makes it easier for positive charged ions, which are abundantly present in the extracellular fluid, to pass through the membrane. This influx of positive charged ions makes the membrane potential less negative. When the membrane potential reaches a certain critical threshold value, locally all "gates" in the membrane are opened wide for the passage of positive charged ions. A local and sudden reversion of the membrane potential occurs. The membrane potential increases explosively and becomes positive: an action potential has been provoked (see fig. 1.6). The speed and amount of this leap in potential is independent of both stimulus duration and intensity.

If the stimulus is to faint to reach the excitatory threshold of the membrane, there will be no potential leap of the membrane at all. But that "inadequate" stimulus results in a minor increase of the membrane potential (the membrane potential gets less negative). This effect is called depolarisation. In case of depolarisation a less intense next stimulus is necessary in order to elicit an action potential. If a number of stimuli, which individually are too faint to provoke an action potential, arrive with an adequate frequency, there appears to be a summation effect, based on depolarisation. This eventually results in an action potential (summation of time).

After an action potential took place, repolarisation occurs: the original state is being restored. Positive ions leave the cell through specific channels. After an action potential
A stimulus S applied to neuron results in a local action potential (AP). Passive conductance results in two AP’s on both sides of the stimulated site. A. intracellular area; b. extracellular area.

A2. The process of A1 is repeated: active conduction. The site where the former AP took place is not excited again, because of the refractory period (R).

B. An AP in a neuron of the octopus.

Figure 1.6: occurrence of an action potential.

took place it is (almost) not possible for some time to provoke another action potential. This period exceeds the repolarisation phase and is called the refractory period (see fig. 1.6). The refractory period can be subdivided in an absolute refractory period, in which under no circumstances an action potential can be elicited, and a relative refractory period, in which a stronger stimulus as usual is necessary to provoke an action potential.

A decrease of the membrane potential (the membrane potential gets more negative), for example by the injection of current with an intracellular electrode, makes stronger stimuli necessary to reach the excitatory threshold of the membrane. This phenomenon is called hyperpolarisation. Passive conductance along a neuron means that small deviations of the membrane steady-state potential, as they occur in case of de- and hyperpolarisation, are conducted along the neuron without ever reaching the excitatory threshold. In this case the conducted signal decreases in time because of current leakage over the isolating membrane that covers the intracellular fluid: conduction with loss.

If an adequate stimulus elicits an action potential, there occurs on both sides of the stimulated site an local circular current (passive conduction). This elicits another action potential on both sides of the stimulated site. This is an iterative process which is called active conduction of an action potential. The first stimulated site can not be excited again, because of the refractory period (see fig. 1.6).

In case of active conduction no loss of signal appears, because every time a new action potential is elicited: the domino principle.

The velocity of active conduction differs and depends on the type of neuronal fibre.
exist for example very fast conducting fibres, which combine the much faster passive conduction principle with the signal-keeping active conduction principle. This is called saltatoric conduction.

Generally the statement holds that the thickness of the fibre is proportional to the conduction velocity.

The manipulation of information can be described this way: Outside the central nervous system a peripheral neuron is activated by stimuli, originating from the milieu interieur or exterieur. Conduction to the central nervous system takes place. Here signal transmission between two neurons will only occur, if the receptive neuron is stimulated sufficiently, possibly also by other afferent neurons. Inside the central nervous system one or two transmission sites are present. Finally, the peripheral efferent neurons are able to activate the effector organs (glandular or muscular tissue).
1.4.2 THE NERVES.

The spinal nerves, which form the peripheral nerves,emanate fromthe spine through a
hole between the spinal elements.

The spine is divided in as many segments as emanating spinal nerves. The segment are
named after the vertebra under which the spinal nerves leave the spine:

- Th(oracic)$_1$ t/m Th$_{12}$;
- L(umbar)$_1$ t/m L$_5$ and
- S(acral)$_1$ t/m S$_5$.

The cervical segments are named slightly
different: C$_1$ belongs to the nerve that
emanates between the skull and the first
cervical vertebra and C$_8$ belongs to the
site of the nerve that emanates between
the seventh and eighth cervical vertebra
(see figure 1.7).

Although the spinal nerves exit separated
from each other, some intermingle outside
the spinal cord to form a network or
plexus. From this plexus the final
peripheral nerves emanate.

Figure 1.7: organization of the spine.
A cross section of the spinal cord shows the grey H-shape in a surrounding white substance: the grey and white substance (fig. 1.8).

The grey substance can be divided in an anterior horn, a posterior horn and, at the thoracic level, a lateral horn. The grey substance mainly consists of cell bodies from neural elements (neurons and interneurons) and their dendrites: here synapses are present and signal transmission between nerve fibres takes place. Synapses can be found in ganglia and supra-spinal structures as well.

The white substance possesses nerve fibres that are orientated longitudinal throughout the spine. The nerve fibres belong to the ascending and descending nerve tracts. Lateral, dorsal and ventral columns can be discerned.

The peripheral sensoric nerve fibres originate from the sensors and often converge with fibres emanating from other sensors to form the afferent part of a spinal nerve, which eventually enters the spinal cord through the dorsal nerve roots (see fig. 1.9).

The peripheral motoric nerve fibres have their cell bodies and dendrites in the anterior horn (motoric anterior horn cells). Efferent fibres or axons leave the spinal cord at the ventral nerve roots. A number of the efferent nerve fibres join each other on segmental level and represent the efferent part of a spinal nerve. The axons end with a lot of terminal branches in the musculature.

The major part of the nerves are "mixed": they consist of afferent and efferent nerve
fibres. A nerve fibre is an axon from a neuron. A nerve is a collection of numerous nerve fibres. A plexus consists of a network of nerves.
1.5 THE BRAIN.

A control centre for the storage and expulsion of urine lies in the brain; in the cortex and in the reticular formation of the pons and the mesencephalon (the pontine micturition centre) to be more specific. It is of importance to be at least a bit familiar with the existing nomenclature of the brain. Figure 1.10 gives a global view.

![Brain diagram]

The former mentioned reticular formation (formatio reticularis) can be found throughout the whole brain stem (truncus cerebri) and consists of a diffuse area of short, almost web-like interconnecting neurons, which expand from the spine to the midbrain. This area possesses many important transmission and control centres. The cerebellum serves mainly the control of motor functions and is part of a complex control loop. The cerebral cortex (cortex cerebri) serves, besides other functions, the awareness and coordination of feelings: here a lot of signals emanating from sensors terminate here. The thalamus is a very extensive relay station for sensory pathways.

1.6 EXPERIMENTS WITH ANIMALS.

A lot of existing data and theories concerned with the micturition process are based on animal experiments and therefore are not directly comparable. Data based on experiments or research with humans are very limited available. Data of animal experiments should be interpreted carefully when extrapolation to the human situation takes place. Where necessary, the compatibility of animal data to the human situation will be elucidated.
VOCABULARY OF APPENDIX 1

Extero-sensors: Sensors which ceaselessly record stimuli from the outside world.

Intero-sensors: Sensors which ceaselessly record stimuli from internal organs.

Proprio-sensors: Sensors which ceaselessly record stimuli from the motoric apparatus.

Motor apparatus: Skeleton, joints and attached muscles (skeletal muscles). These muscles are responsible for movement.

Receptors: In the cell membrane anchored structures (mostly proteins) which are able to generate signals if they are connected with certain substances (like hormones, neurotransmitters, pharmacy, etc.).

Nervous system: The system that conducts electric signals is anatomically divided as:

1. Central nervous system
   The parts inside the bony shell of the skull and the spinal canal form together the central nervous system, as there are: the brain - cerebrum, cerebellum and brain stem (truncus cerebri)- and the spinal cord (medulla spinalis).

2. Peripheral nervous system:
   The collection of the nerve fibres that carry the sensoric information from extero- intero- and proprio-sensors to the central nervous system (the afferent nerves) and the collection of nerve fibres that carry the motoric information from the central nervous system to the musculature (the efferent nerves), are called the peripheral nerves. The peripheral nerves can be subdivided in 12 pairs of cranial nerves and 30 pairs of spinal nerves.

A functional division of the nervous system is:

1. Animal or somatic nervous system:
   The basis of the somatic nervous system consists of information exchange: the ability to react to changes of the environment, starting at a cellular level. Keywords are: sensitivity (reception), stimulus operation (discerning stimulus conduction and stimulus transmission) and movement (motor).
2. Vegetative or autonomic nervous system:
The basis consists of the material exchange between the cell and the environment. Keywords are: metabolism, resorption, excretion and secretion.

Ganglion:
Collection of cell bodies from neurons outside the central nervous system. A ganglion is a nervous structure capable to conduct electric signals.

Neuron:
Can be seen as a connecting element, the smallest functional unit of the nervous system and often possesses a very long branch. Consists of a cell body, dendrites (both with a receptive function) and an axon (a long branch, which has a conductive function). Transmission to other neurons takes place by indirect and direct mechanisms; innervation of striated musculature for example happens by motor end-plates.

Synapse:
Connective space: site of signal transmission between two neurons.

Junction:
Connective space: site of signal transmission between a neuron and an effector organ.

Neurotransmitter:
Substance that is released at the terminal end of an axon by stimulation of the neuron. Functions as a way of indirect chemical signal transmission. Receptors react on the transmitter substance. There are several transmitter substances known: one substance is not a specific element of the somatic or autonomic nervous system.
APPENDIX 2: "CLOSURE AND OPENING OF THE URETHRA."

Additional information about intersexual variation of urethral anatomy and its consequences for urethral closure is given in this section. The relevant text is quoted first:

The anatomical differences in male and female urethra (Awad, Downie, 1976; Droes, 1972) have their effect on functioning. In contrast with the rich sympathetic innervation of the bladder neck, superficial trigonal muscle and proximal urethra in male human subjects, in female subjects this sympathetic innervation is less abundant (Venema, 1990). Moreover no smooth muscle sphincter can be discerned in female subjects; smooth urethral muscle fibres have a predominant longitudinal orientation throughout the whole urethra and circular or helical orientated fibres are sparse (Gosling, 1986; Hickey, Phillips, Hukins, 1982). This seems contradictory with the functional mechanisms that promote continence during bladder filling by contraction of smooth musculature from the vesical neck, superficial trigone, proximal urethra and lower parts of the urethra. However the same functional mechanisms contribute to the closure of the urethra and vesical neck in male and female, but the importance of each mechanism varies intersexually. The characteristics of the urethral tissue contribute considerably in the closure of the urethra during bladder filling as well.

Comments
Awad en Downie (1976), see figure 3.1, consider for the closure of the canine urethra neural components more important in male than in female. Non-neuronal contributions are about equal to sympathetic contribution in female, whereas somatic contribution plays a minor role. In male canines neuronal contributions are the most important factor in closure of the urethra, constituting about 75% of the urethral pressure profile.

<table>
<thead>
<tr>
<th></th>
<th>percentage of control</th>
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<tbody>
<tr>
<td></td>
<td>sympathetic component</td>
</tr>
<tr>
<td>males</td>
<td>45 ± 6</td>
</tr>
<tr>
<td>females</td>
<td>40 ± 7</td>
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</tbody>
</table>

Figure 3.1: components of the high pressure region of the urethral pressure profile.

Research on the arrangements of collagen fibrils and muscle fibres in the female urethra and their implications for the control of micturition by Hickey, Phillips and Hukins indicates collagen to be the major structural component of the female urethra. No abundant elastic fibres are observed in the human urethra, making it unlikely for urethral elastic fibres to have a marked effect on the closure of the urethra.
After relaxation of urethral sphincteric musculature has occurred shortly before micturition emanates, contraction of the detrusor, which is connected to the urethra by descending longitudinal smooth muscle fibres, initiates the opening of the urethra by simultaneous contraction of these longitudinal muscle fibres. Once the lumen has opened and is filled with urine, distension will occur because of the way it is reinforced with collagen. When urine ceased to flow the urethra closes by its own elasticity until the longitudinal muscles are contracted again. This mechanism can be demonstrated if the following assumptions are made. Consider the urethra to be a thin walled flexible tube with following characteristics:

- $l_0$: initial length,
- $C_0$: initial cross-sectional circumference, not necessarily circular,
- $t$: thickness of the wall,
- $V$: volume of material in the wall of the tube.

The volume of material in the wall of the tube can be determined by:

$$V = l_0 \times C_0 \times t$$

Contraction of the longitudinal urethral fibres will not appreciably change $V$ or $t$, but will shorten $l_0$ to a new length $l$, while the circumference will change to:

$$C = C_0 \times (l_0/l)$$

So the circumference increases and the lumen opens. The circumferential stress in a pipe containing fluid under pressure is known to be twice the longitudinal stress. This little exercise supports the described mechanism for opening of the urethral lumen.