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Pharmacology of Lower Urinary Tract Smooth Muscles and Penile Erectile Tissues*

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I. Introduction

The smooth muscles of the human lower urinary tract are generally divided into the detrusor (bladder dome), the trigone, and the bladder neck and urethra. They work as a functional unit, and this is a prerequisite for normal voiding and continence. Unfortunately, these muscles have been studied much less intensively than many other types of smooth muscle. However, the mechanisms underlying the basic functions of the bladder, to store urine at a low pressure and to empty its contents at regular intervals, have been the subject of much research during the last decade. Thus, our knowledge of the central regulation of micturition has increased considerably (Maggi and Meli, 1986; de Groat, 1990; Maggi, 1991b;

Steers, 1992; de Groat et al., 1992), as has information concerning factors of importance for micturition control at the bladder level (Brading, 1987; Andersson, 1990a; Van Arsdalen and Wein, 1991). Much new information has also been obtained regarding the morphology, physiology, and pharmacology of penile erectile tissues (Lue and Tanagho, 1987; Krane et al., 1989; Andersson and Holmquist, 1990; Andersson et al., 1991d). Most of the literature concerns animal work, and because of the many well-established differences between species, the information is not always valid for humans.

In this review, the peripheral regulation of lower urinary tract and penile erectile smooth muscles will be discussed. Much of the presented information was obtained from animal studies. However, when possible, the discussion will focus on human tissues.

II. Detrusor

A. Anatomy

Details concerning the innervation and morphology of detrusor smooth muscle can be found in recent reviews (Burnstock, 1990; Dixon and Gosling, 1990; Elbadawi, 1991), and only a few aspects will be discussed here.

In the human detrusor, bundles of muscle cells of varying size are surrounded by connective tissue containing much collagen. The bundles are arranged in a complicated pattern, but from a functional viewpoint, the detrusor comprises an integrated unit of interconnected muscle bundles. In smaller animals, e.g., rabbit, the bundles are less complex and the patterns of arrangement simpler. Gap junctions between detrusor cells can be found in the guinea pig and rabbit (Gabella, 1981) but not in the rat (Gabella and Uvelius, 1990). The guinea pig detrusor was shown to possess cable properties, i.e., the smooth muscle cells have electrical connections such that the detrusor acts as single-unit smooth muscle (Creed, 1971a). True gap junctions seem to be absent from human detrusor (Daniel et al., 1983; Dixon and Gosling, 1990). If spread of excitation occurs, "the regions of close approach," a frequently observed junction between detrusor cells (Dixon and Gosling, 1990), may represent the morphological feature that enables this physiological event to take place (see section II.C).

B. Mechanical Properties

The bladder can accommodate large volumes of urine without an increase in intravesical pressure (Coolsaet, 1985), and detrusor smooth muscle cells have the ability to change length without marked changes in tension. It is hard to define the resting length of a strip of detrusor muscle, and above a certain elongation, passive tension increases quite steeply (Uvelius, 1976). The relationship between length and tension and between force and velocity have been extensively studied in animal detrusor tissue (Bissada and Finkbeiner, 1980; Uvelius, 1980; Finkbeiner and O'Donnell, 1990; Longhurst et al., 1990), whereas the information concerning human tissue is limited (Uvelius et al., 1990a; Malmqvist et al., 1991). The maximal active force of human detrusor strips was similar to that found in detrusor muscle from rat and rabbit, and the maximal shortening velocity corresponded well with data from rabbit tissue (Uvelius, 1977).

The lack of pressure increase during normal filling and distension of the bladder was originally ascribed to reflex mechanisms, but later, experimental evidence suggested that natural filling occurs independently of extrinsic innervation (Klevmark, 1977) and that inherent properties of the detrusor muscle play an important role. However, whether or not this is the case is still an unsettled question.

As the bladder is filled, the thickness of the wall decreases (Uvelius and Gabella, 1980). The length of the individual muscle cells increases linearly with bladder radius over normal functional volumes, the mean length increasing nearly 4-fold in the guinea pig (Uvelius and Gabella, 1980). There was a proportional decrease in the diameter of both cells and bundles. The results suggest that both single cells and bundles are simply stretched as the bladder fills without cells slipping longitudinally past each other.

Another characteristic of detrusor smooth muscle is the ability to contract efficiently over a wide range of volumes. Over a range of cell lengths, corresponding to filling volumes of 25 to 75% of bladder capacity, the active force was nearly maximal (Uvelius and Gabella, 1980). At maximum capacity, the active force was 75% of its maximal value, and in an empty bladder, it was approximately 25%. Maximal intravesical pressure on activation was obtained at much lower volumes and declined to about 30% of maximum when the bladder was fully distended.

C. Electrophysiology

Most available electrophysiological information regarding detrusor muscle has been obtained from tissues of a few animal species (Mostwin, 1988, 1991; Brading, 1992). Information concerning human detrusor is scarce. Because conventional intracellular recording was impossible in this tissue, recordings were made using the whole cell patch-clamp technique on cells obtained by collagenase digestion of bladder biopsy specimens (Montgomery and Fry, 1992). In the guinea pig bladder dome, a resting membrane potential value of -37.3 ± 5.2 mV was reported (Creed, 1971a); the corresponding value in the rabbit was -37.5 ± 3.9 mV (Callahan and Creed, 1986). In isolated human detrusor cells, the resting membrane potential, recorded by conventional 3 M KCl-filled microelectrodes, was -47.2 ± 16.7 mV (Montgomery and Fry, 1992).

Spontaneous action potentials, associated with slow waves of depolarization, have been demonstrated by several investigators in detrusor tissue from guinea pig and

rabbit (Ursillo, 1961a; Creed, 1971a,b; Creed et al., 1983; Mostwin, 1986). Similar action potentials have been described in human detrusor cells (Montgomery and Fry, 1992). In the guinea pig detrusor, the passive and active electrical properties did not change significantly with the growth of the animal (Seki et al., 1992a). The spontaneous electrical activity of the guinea pig detrusor is usually single spikes occurring at regular intervals, but occasionally bursts of spikes can be recorded (Creed, 1971a). The frequency of the spontaneous action potentials is voltage sensitive, depolarization increasing and hyperpolarization decreasing the rate of firing. In detrusor tissue from the guinea pig, intracellularly recorded action potentials have a duration of about 10 ms. They have no plateau phase and have an overshoot of approximately 15 to 18 mV. Corresponding values from isolated human detrusor cells were approximately 40 to 60 and 0 to 20 mV (Montgomery and Fry, 1992). In guinea pig detrusor, the action potentials exhibit a pronounced afterhyperpolarization, which may last for 500 ms (Mostwin, 1986). The rising phase is generated by an inward Ca^{2+} current, as suggested by the failure of TTX† (blocking Na^+ channels) to block elicited action potentials (Creed, 1971b) and as demonstrated by Klöckner and Isenberg (1985a,b) using voltage clamp of isolated guinea pig detrusor cells. Also in the human detrusor, the depolarizing phase of the action potential occurs by an inward Ca^{2+} current (Montgomery and Fry, 1992). Repolarization probably involves inactivation of the Ca^{2+} current and activation of an outward K^+ current that is partially Ca^{2+} dependent (Mostwin, 1986; Montgomery and Fry, 1992).

Under normal circumstances, there would appear to be little cell to cell conduction in detrusor muscle due to a high longitudinal resistance (Brading et al., 1989; Brading and Inoue, 1991; Brading, 1992). However, this may well vary between species, and indirect evidence suggests that, in the pig detrusor, the smooth muscle cells are less well connected than in the guinea pig (Fujii, 1988; Brading and Inoue, 1991; Brading, 1992). Changes in detrusor morphology, such as those occurring in the hypertrophic detrusor, may change cell to cell transmission of excitation. Seki et al. (1992b,c) studied the changes in electrical properties of guinea pig smooth muscle membrane by experimental bladder outflow obstruction and found significant changes. There was a reduction of the membrane constants (space constant and time constant) and of spontaneously occurring electrical activity. The membrane potential was unchanged, but there was a greater amount of ouabain-sensitive membrane hyperpolarization after application of K^+-free solution and a greater membrane depolarization evoked by a low extracellular chloride concentration solution. It was suggested that there was a suppression of the cell to cell transfer of electrical activity and activation of a membrane electrogenic Na^+-K^+ pump mechanism in the obstructed and hypertrophied guinea pig detrusor.

D. Excitation-Contraction Coupling

The exact mechanism underlying excitation-contraction coupling in the detrusor is unknown. As in other types of smooth muscle, an increase in the intracellular free Ca^{2+} concentration is a crucial step in the activation of contraction. This increase is due to influx from the extracellular space and/or release from intracellular stores (Isenberg et al., 1992). In single smooth muscle cells of the guinea pig urinary bladder held under voltage clamp, Ganitkevich and Isenberg (1991) recorded $[Ca^{2+}]_i$ by means of the Ca^{2+} indicator Indo-1. They concluded that Ca^{2+} influx through voltage-operated Ca^{2+} channels is the key event in depolarization-mediated changes in $[Ca^{2+}]_i$. The voltage dependence of peak $[Ca^{2+}]_i$ was bell shaped, which supported the idea that $[Ca^{2+}]_i$ is controlled by Ca^{2+} influx through Ca^{2+} channels and that Ca^{2+} influx via the Na^+-Ca^{2+} exchanger is insignificant. They also concluded that depolarization-induced influx of Ca^{2+} through L-type Ca^{2+} channels induces a release of Ca^{2+} from intracellular stores, which constitutes a major portion of the phasic $[Ca^{2+}]_i$ transient (Ganitkevich and Isenberg, 1992).

When contracted by high K^+ solutions or prolonged application of agonists, the detrusor muscle has an inability to sustain the contraction, and the response fades rapidly. Brading (1992) suggested that this may be due to a transient increase in the membrane permeability to Ca^{2+}, the Ca^{2+} channels closing even in the face of persistent depolarization. A well-developed Ca^{2+}-induced inactivation of the channels may account for the phasic nature of the detrusor contraction and its inability to sustain tone.

In the urinary bladder, the Ca^{2+} channels seem to be mainly, if not exclusively, of the L type. For example, in guinea pig detrusor cells, the contribution of Ca^{2+} influx via T-type channels is of no importance (Isenberg et al., 1992). Extracellular Ca^{2+} removal and L-type Ca^{2+} channel blockers slow the rate of rise, decrease the amplitude of the action potential (Mostwin, 1986), and reduce the contractile amplitude (Andersson and Forman, 1986). Because the smooth muscle of the urinary bladder generates action potentials spontaneously, Ca^{2+} influx

† Abbreviations: ACE, angiotensin-converting enzyme; ATP, adenosine triphosphate; AVP, arginine vasopressin; At, angiotensin; BK, bradykinin; $[Ca^{2+}]_i$, intracellular calcium concentration; cGMP, cyclic guanosine-3′,5′-monophosphate; CGRP, calcitonin gene-related peptide; carbachol, carbamyl choline chloride; ET, endothelin; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine, serotonin; I_{Ca}^{2+}, inward calcium current; NADPH, β-nicotinamide adenine dinucleotide phosphate; NANC, nonadrenergic, noncholinergic; L-NMMA, N^G-monomethyl-L-arginine; L-NNA, N^G-nitro-L-arginine; D-NNA, N^G-nitro-D-arginine; NO, nitric oxide; NOS, nitric oxide synthase; NK, neurokinin; NPY, neuropeptide Y; PG, prostaglandin; SIN-1, 3-morpholino-sydnonimin hydrochloride, linsidomine; SP, substance P; TX, thromboxane; TTX, tetrodotoxin; VIP, vasoactive intestinal polypeptide.

through voltage-operated Ca^{2+} channels can be regulated through the amplitude, duration, and frequency of the action potentials. However, the cells may also generate slow depolarizations due to stretch or under the influence of neurotransmitters or hormones. The sources of Ca^{2+} used for contraction induced by acetylcholine or carbachol in detrusor smooth muscle are of particular interest because of the possible use of drugs with Ca^{2+} channel-blocking effects in the management of bladder hyperactivity.

Several studies of animal detrusor tissue demonstrated the importance of extracellular Ca^{2+} entry through dihydropyridine-sensitive Ca^{2+} channels and mobilization of intracellular Ca^{2+} (Mostwin, 1985; Huddart and Butler, 1986; Batra et al., 1987b; Maggi et al., 1988c; Kishii et al., 1992). In addition, carbachol was suggested to increase the sensitivity of the contractile machinery to Ca^{2+} (Kishii et al., 1992). Which of these mechanisms is the most important has not been established. In the human detrusor (Fovaeus et al., 1987a), extracellular Ca^{2+} seems to play a major role in the activation process. In line with this view, Maggi et al. (1989c), who found that different agonists used different Ca^{2+} sources to various degrees, suggested that in the human bladder carbachol-induced activation involved dihydropyridine-sensitive Ca^{2+} channels but not T- or N-type channels. Carbachol can mobilize a calcium pool (either extracellular or located at the membrane level) that is $LaCl_3$ sensitive and nifedipine resistant. In addition, carbachol can mobilize an intracellular Ca^{2+} pool independently from membrane depolarization.

It is of interest that phorbol esters, which are activators of protein kinase C and may produce contraction of smooth muscle without activation of myosin light chain kinase, caused a concentration-dependent contraction of rabbit bladder dome (Yoshida et al., 1992). It was proposed that protein kinase C activation may contribute to agonist-induced contraction in this tissue.

E. Mechanisms of Activation

1. Myogenic activity. The spontaneous electrical activity demonstrated in detrusor muscle in vitro is associated with contractions that are resistant to TTX and cannot be blocked by hexamethonium, atropine, and α-adrenoceptor blockers, suggesting a myogenic origin. Supporting such a view is the observation that the contractions can be effectively inhibited by L-type Ca^{2+} channel blockers and K^+ channel openers (Andersson and Forman, 1986; Fovaeus et al., 1987a). They can also be increased by agents that decrease K^+ permeability, such as procaine (Kurihara, 1975) and tetraethylammonium ions (Mostwin, 1986). It has been suggested that the activity is under the control of PGs produced by the tissues because PG synthesis inhibitors may have an inhibitory effect (Downie and Slack, 1983; Satake et al., 1984).

Increasing extracellular Mg^{2+} reduced spontaneous contractile activity and attenuated the inward Ca^{2+} current associated with the action potential. It was proposed that the spontaneous contractile activity was related to generation of spontaneous action potentials or to alteration of the ability of intracellular organelles to regulate intracellular calcium (Montgomery et al., 1992).

The frequency of the spontaneous mechanical activity of isolated detrusor tissue seems to vary among species (Sibley, 1984), being more frequent in the rabbit (100%) than in pig and human (20%), but is probably also dependent on experimental factors, e.g., the duration of the equilibration period in the organ bath. The characteristics of spontaneous contractile activity have been studied in detail in detrusor tissue from pigs (van Duyl, 1985; Hak et al., 1988; van Duyl et al., 1990) and rabbits (Potjer and Constantinou, 1989). Levin et al. (1986a) pointed out that the frequency and amplitude of the spontaneous contractions of, for example, the rabbit detrusor are extremely variable among strips of the same bladder. They found no spontaneous contractile activity in the isolated whole rabbit bladder or in the catheterized bladder in vivo and suggested that the spontaneous activity observed in isolated strips has no physiological significance in normal bladder functioning.

It is obvious that the observations on the mechanical activity of an isolated tissue cannot be immediately translated into functions exerted by the whole organ. Myogenic activity may contribute to tone in many types of smooth muscle (Rüegg, 1971), including the urinary bladder. In vivo, such activity may be exaggerated in conditions in which an increased afferent activity leads to conditions of bladder hyperactivity. Thus, Kinder and Mundy (1987) found that spontaneous contractile activity developed more often in muscle strips from hyperactive than normal bladders. Detrusor cells may have automacity, i.e., spontaneous generation of action potentials. This may not necessarily mean that some cells have a pacemaker role in the initiation of detrusor contractions leading to bladder emptying. It seems unlikely, considering the morphological and electrophysiological information available, that a bladder contraction leading to micturition can occur without efferent nervous activity coordinated via the micturition reflex.

2. Cholinergic mechanisms. a. MUSCARINIC RECEPTORS. In most animal species, bladder contraction is mediated by both cholinergic and NANC mechanisms (Ambache and Zar, 1970; Taira, 1972). In isolated guinea pig and rabbit detrusor muscle, acetylcholine produced slight depolarization, initiated spike generation, increased the frequency of action potentials, and contracted the muscle (Creed, 1971a; Callahan and Creed, 1981; Creed et al., 1983). The isolated human detrusor also is contracted by acetylcholine. These contractions are enhanced by cholinesterase inhibitors and abolished by atropine and, thus, must be mediated by stimulation of muscarinic

receptors. In the normal human detrusor, the emptying contraction in vivo and the contraction evoked by electrical stimulation of nerves in vitro have been suggested to be mediated mainly, if not exclusively, through muscarinic receptor stimulation (Sjögren et al., 1982b; Sibley, 1984; Kinder and Mundy, 1985a; Craggs et al., 1986), because these responses can be more or less completely blocked by atropine. In support of this hypothesis, atropine (Cullumbine et al., 1955) and other anticholinergic drugs produce an almost complete paralysis of the bladder when injected intravenously in normal humans.

The role of an NANC mechanism in the contractile activation of the human bladder is still disputed. In strips of human detrusor, Hindmarsh et al. (1977) found that electrically induced contractions were partially resistant to atropine. They concluded that acetylcholine was the main, but not the sole, motor transmitter in the human detrusor. Support for such a view was given by Cowan and Daniel (1983), who found that acetylcholine was responsible for approximately 50% of the electrically induced contraction in strips of the normal human detrusor. In contrast, Sjögren et al. (1982b), who investigated morphologically normal detrusor samples from patients undergoing bladder surgery for different reasons, found that atropine caused >95% inhibition of electrically evoked contractions.

Sibley (1984) compared the effects of atropine on contractions induced by electrical field stimulation in isolated detrusor preparations from rabbit, pig, and humans. He found that in human preparations, obtained from patients undergoing lower urinary tract surgery for different disorders or donor nephrectomy, atropine abolished nerve-mediated contractions. He concluded that nerve-mediated contractile activity in human detrusor is exclusively cholinergic. This was supported by the results of Kinder and Mundy (1985a), who found that atropine caused an almost total inhibition of the electrically induced contraction in human detrusor tissue taken from patients with urodynamically normal bladders. Craggs et al. (1986), investigating the effects of atropine on bladder contractions evoked by sacral ventral root stimulation in paraplegic humans, also arrived at the conclusion that the parasympathetic innervation of the human bladder is exclusively cholinergic.

These apparently conflicting data may partly be explained by differences in the tissues investigated and by varying experimental approaches. Most probably, normal human detrusor muscle exhibits little "atropine resistance." This does not exclude that atropine resistance may exist in morphologically and/or functionally changed bladders. Sjögren et al. (1982b) found that, in detrusor strips from male patients with a diagnosis of unstable bladder, and in particular from patients with bladder hypertrophy, an atropine-resistant component of up to 50% of the electrically induced contraction could be demonstrated. Nergårdh and Kinn (1983) found a varying degree of atropine resistance (0 to 65%) in isolated detrusor preparations from male patients, most of them having prostatic hypertrophy. Sibley (1984) verified the occurrence of atropine resistance in hypertrophic bladder muscle but also showed that the atropine-resistant response was resistant to TTX, suggesting that it was not nerve mediated but was caused by direct muscle stimulation.

Even if part of the detrusor response to electrical stimulation is mediated by noncholinergic mechanisms, there is evidence from experiments with isolated whole rabbit bladder preparations suggesting that muscarinic receptor stimulation is responsible for the main part of bladder emptying (Levin et al., 1986b; Chancellor et al., 1992). This seemed also to be the case in vivo in the guinea pig. A highly significant correlation was found between the potencies of anticholinergic agents to inhibit isolated guinea pig detrusor muscle contraction and peak intravesical bladder pressure in the cystometrogram in vivo (Noronha-Blob et al., 1989).

Muscarinic receptors consist of several subpopulations, and at least five different subtypes (m_1 to m_5) have been cloned. Pharmacologically, three different subtypes (M_1 to M_3) have been defined using subtype-selective agonists and antagonists (Hulme et al., 1990; Richards, 1991). In the human detrusor, muscarinic receptor agonists were found to recognize more than one population of receptor sites, whereas muscarinic receptor antagonists were bound to a virtually uniform population of sites (Nilvebrant et al., 1985). Results of functional (Adami et al., 1985; Zappia et al., 1986) and receptor-binding experiments (Batra et al., 1987a; Ruggieri et al., 1987; Levin et al., 1988), using pirenzepine for subclassification of muscarinic receptors as M_1 or M_2, have suggested that the receptors of the detrusor in rats and humans are of the M_2 type. Experiments with the selective M_1 receptor-blocking drug, telenzepine, seem to rule out any significant occurrence of M_1 receptors in the human detrusor (Poli et al., 1992b). In sheep ureterovesical junction, evidence was presented for the occurrence of M_1, M_2, and M_3 receptor subtypes, all mediating contraction (Rivera et al., 1992). In the rat detrusor, van Charldorp et al. (1985) suggested the occurrence of a heterogenous population of M_2 receptors. Other investigators identified a small proportion of glandular muscarinic receptors (M_2), which could represent the functional receptor responsible for muscarinic agonist-induced contraction. It was proposed that this receptor subtype should be called M_3 (Monferini et al., 1988). A systematic subclassification of the muscarinic receptors of the human bladder remains to be done, but indirect evidence suggests that the human detrusor also contains muscarinic receptors of the M_3 subtype (Poli et al., 1992b).

In rabbits, the mechanical detrusor response to carbachol required a much lower concentration than that needed for stimulation of ^{45}Ca uptake or for occupying

binding sites for [^{3}H]quinuclidinyl benzilate-binding sites, and there appeared to be about a 150-fold muscarinic receptor excess (Anderson and Marks, 1982). These results are in conflict with those of Levin et al. (1984b), who found the rabbit bladder to have few spare muscarinic receptors. If there are no spare receptors, there should be a direct relation between the contractile response to muscarinic receptor stimulation and the receptor density. Such a direct relation is not always found. Batra and Andersson (1989) demonstrated in the rabbit detrusor that, despite a 90% reduction in muscarinic receptor number after 4 weeks of estrogen treatment, there was no significant effect on the concentration-response curve for carbachol.

Muscarinic receptors, which when stimulated inhibit transmitter release, have been demonstrated on adrenergic nerve terminals in detrusor tissue from rabbit, cat, dog, and humans (Mattiasson et al., 1987a; Mutoh et al., 1987; Somogyi and de Groat, 1990) and on cholinergic nerves in rat bladder (d'Agostino et al., 1986; Somogyi and de Groat, 1992). In rat urinary bladder, three types of cholinergic receptors were demonstrated to affect acetylcholine release (Somogyi and de Groat, 1992). M_2 inhibitory receptors dominated in untreated preparations, whereas in physostigmine-treated bladder strips, in which the concentrations of acetylcholine were elevated, facilitatory M_1 and nicotinic receptors were also demonstrated. Physostigmine had a biphasic effect, causing inhibition of acetylcholine release at low (M_2) and facilitation at high (M_1) concentrations. The authors suggested that, even if muscarinic inhibitory receptors appear to be the only type activated by acetylcholine released by electrical stimulation under normal conditions, facilitatory receptors may be activated by the high-frequency parasympathetic nerve discharge that occurs during micturition. Particularly in pathological conditions, such as the neurogenic hyperreflexic bladder, such a mechanism may contribute to changes in bladder function.

The subtype(s) of receptor involved in acetylcholine release in human bladder has not been clarified. Presynaptic modulation seemed to exclude M_1 receptors (Poli et al., 1992b), but this was not systematically investigated.

The coupling between the muscarinic receptors and intracellular messenger systems in the human detrusor has not been extensively studied. Carbachol was found to inhibit adenylate cyclase in both rabbit and human urinary detrusor muscle (Ruggieri et al., 1987). Both carbachol and acetylcholine were able to stimulate production of inositol phosphates in human detrusor (Andersson et al., 1989, 1991c; Iacovou et al., 1989, 1990). However, the functional role of inositol phosphates in human bladder contraction has not been established. In the guinea pig, on the other hand, the inositol phosphate mechanism was considered a main mediator of bladder contraction (Noronha-Blob et al., 1987, 1989; Iacovou et al., 1990). If this is the case, it would be reasonable to suppose that lithium, which is known to inhibit phospholipid hydrolysis (Godfrey et al., 1989), would affect muscarinic receptor-mediated contraction. This was not found in the rat bladder (Lucchelli et al., 1992).

It is known that parasympathetic denervation or decentralization leads to an impaired ability of the bladder to empty. The bladder may be distended by residual urine, and the bladder wall hypertrophies. These changes can be prevented by urinary diversion. The denervated/decentralized bladder exhibits an increased responsiveness to muscarinic receptor stimulation, which has been the basis for the use of bethanechol or carbachol as a test to diagnose neurogenic bladder disorders (Lapides et al., 1962; Glahn, 1970). It has been suggested that this supersensitivity may be related to an increase in the density of muscarinic receptors in detrusor muscle (Raz, 1983), but the mechanisms involved have not been identified. Short-term, partial obstruction of the rabbit bladder resulted in a marked decrease in muscarinic receptor density (Levin et al., 1984a). Whether or not significant changes in muscarinic receptor densities can be found after long-term obstruction does not seem to have been investigated.

In decentralized cats, Mattiasson et al. (1984c) were unable to demonstrate any supersensitivity to muscarinic receptor stimulation, provided that the urine was diverted and the bladder did not hypertrophy. In the denervated rat bladder, Nilvebrant et al. (1986) found no changes in the muscarinic receptor density that could explain supersensitivity. They found an increase in receptor density in hypertrophied bladders, whereas the receptor density decreased when the development of hypertrophy was prevented by urinary diversion. It was suggested that the regulation of the receptor levels was influenced by the functional state of the bladder.

In pigs with experimental outflow obstruction, Sibley (1987) found that, although the response to intramural nerve stimulation was decreased, there was a supersensitivity of the detrusor muscle, including a leftward displacement of the concentration-response curve for acetylcholine. He suggested that this was due to partial denervation of the bladder as a result of the obstruction and that the supersensitivity may manifest as detrusor instability. Such a denervation had previously been claimed to occur in the obstructed pig and human detrusor (Gosling et al., 1986; Speakman et al., 1987). Support for the presence of cholinergic denervation in the bladders of patients with obstruction and bladder instability was presented by Harrison et al. (1987). They found that, in muscle strips from patients with bladder instability, the acetylcholine concentration-response curve demonstrated a significant leftward shift, suggesting an increased sensitivity to acetylcholine. There was a depression of the responses to electrical stimulation. In con-

trast, Yokoyama et al. (1991) found that there was a displacement to the right of the concentration-response curve for acetylcholine obtained in detrusor strips from patients with obstruction and benign prostatic hyperplasia compared to the curve obtained in preparations from controls without obstruction, suggesting a decreased sensitivity to acetylcholine. The responses to acetylcholine of detrusor strips from patients with bladder instability were not significantly different from those without (Yokoyama et al., 1991). The reasons for these conflicting results are unclear.

It might be assumed that the muscarinic receptor functions change also in nonobstructed bladders showing hyperactivity. Kinder et al. (1985b) and Kinder and Mundy (1987) compared detrusor muscle from human normal, idiopathic unstable, and hyperreflexic (neurological damage) bladders. They found no significant differences in the degree of inhibition of electrically induced contractions by TTX and atropine between detrusor strips from any of these bladders and no significant differences in the concentration-response curves for acetylcholine. In hyperactive bladders, without associated neurological disorders, a decreased number of muscarinic receptors has been demonstrated (Restorick and Mundy, 1989), but the relation to hyperactivity remains unclear. Also, in patients with neurogenic bladder dysfunction, small-capacity bladders, and detrusor instability, the density of muscarinic receptors was lower than in normal controls (Lepor et al., 1989). The lower density in neurogenic bladders was suggested to represent down regulation of muscarinic receptors or a replacement of smooth muscle by fibrosis.

b. NICOTINIC RECEPTORS. Nicotine induces an atropine-resistant increase in intravesical pressure in cats (Koley et al. (1984), and in isolated strips of the urinary bladder of guinea pigs and rabbits, it causes a phasic concentration-related contraction (Hisayama et al., 1988; Kizawa et al., 1988). The mechanism of this action in the guinea pig was analysed (Hisayama et al., 1988, 1989). It was suggested that nicotine induced contraction by an interaction with nicotinic receptors on nerve terminals, involving parasympathetic cholinergic (acetylcholine), sympathetic nonadrenergic (possibly tachykinins), and nonsympathetic purinergic nerves (ATP). In addition, intramural PG release, initiated by ATP, may contribute to the response. The nicotine response was insensitive to TTX, suggesting that it was produced mainly through an Na^+ action potential-independent mechanism. Tachykinins, probably released from sympathetic nerves, were suggested to enhance nicotine's ability to release acetylcholine through stimulation of NK-2 receptors (Shinkai et al., 1993). Nicotine-induced contractions were reduced following chronic treatment with nicotine, possibly due to a reduction in the number of nicotine receptors (Kizawa et al., 1988, 1990)

3. Adrenergic mechanisms. a. α-ADRENOCEPTORS. In detrusor muscle from several species, including humans, β-adrenoceptors have been shown to preponderate over α-adrenoceptors. Creed (1971b) showed in guinea pig bladder that the frequency of spontaneous action potentials was decreased by adrenaline and noradrenaline. However, in most species, it is possible to evoke detrusor contraction with drugs stimulating α-adrenoceptors (Salimi et al., 1969; Nergårdh and Boréus, 1972; Awad et al., 1974; Elmér, 1974a; Raezer et al., 1973; Sundin and Dahlström, 1973; Downie et al., 1975; Sundin et al., 1977; Levin and Wein, 1979a; Levin et al., 1980a, 1981b; Johns, 1983; Honda et al., 1985, 1987; Honda and Nakagawa, 1986; Åmark et al., 1986; Mattiasson et al., 1987b), preferentially with those acting on α_1-adrenoceptors (Honda et al., 1985, 1987; Honda and Nakagawa, 1986).

The role of the sympathetic nervous system in human bladder function has been much discussed, partly because of the paucity of the adrenergic innervation of human detrusor muscle. There is no doubt, however, that noradrenaline is released when human bladder tissue is electrically stimulated (Mattiasson et al., 1987a) and that the normal response to released noradrenaline is relaxation (Perlberg and Caine, 1982; Åmark et al., 1986). Drugs stimulating α-adrenoceptors have hardly any contractile effects in isolated, normal human detrusor muscle, but both trigonal and urethral smooth muscle respond with contraction.

There are reasons to believe that the predominating postjunctional α-adrenoceptor subtype in the human lower urinary tract is α_1 (Levin et al., 1988). α_2-Adrenoceptors have been demonstrated on adrenergic nerve terminals in both detrusor and urethral smooth muscle, which when stimulated by noradrenaline inhibit further release of the amine (Mattiasson et al., 1984a, 1985a, 1987a). However, postjunctional α_2-adrenoceptors probably have little functional importance. In rat detrusor, clonidine produced concentration-dependent inhibition of contractions evoked by electrical field stimulation (Santicioli et al., 1983; Maggi et al., 1985b). This effect was suggested to be due to stimulation of α_2-adrenoceptors located on postganglionic nerve endings, leading to reduced output of excitatory neurotransmitters.

Even if the α-adrenoceptors have no significant role in normal bladder contraction, there is evidence that this may change after, for example, bladder outlet obstruction and parasympathetic decentralization and in hyperactive bladders. Detrusor tissue from patients with bladder hyperactivity (without neurological disorders) had an almost 4-fold increase in the density of α-adrenoceptors compared to the density in normal persons (Restorick and Mundy, 1989). The importance of this finding for bladder hyperactivity is, however, unclear (Andersson, 1990b).

Rohner et al. (1978) found that in isolated dog detrusor muscle, which normally responds to noradrenaline with relaxation, contraction could be demonstrated in seven

of 12 dogs after bladder outlet obstruction was established. This was suggested to be dependent on a decrease in β-adrenoceptor function rather than an increased α-adrenoceptor function. Perlberg and Caine (1982) found that noradrenaline caused contraction instead of the normal relaxant response in bladder strips from 11 of 47 patients with benign prostatic obstruction. They proposed that there was a correlation between the response to stimulation, on one hand, and bladder instability and irritative symptoms, on the other. It has been observed that, in patients with benign prostatic hyperplasia treated with α-adrenoceptor blockers, bladder hyperactivity (bladder instability) disappears during treatment (Caine, 1985, 1986). Taken together, these observations suggest that there may be an increased α-adrenoceptor function associated with the morphological changes occurring in bladder hypertrophy. On the other hand, Mattiasson et al. (1987b) found that the number of α-adrenoceptors in the detrusor, as determined by [^{3}H]dihydroergocryptine binding was decreased in rats with bladder outflow obstruction. At the same time, α-adrenoceptor-mediated contraction was impaired. Saito et al. (1993b) found that, in mildly obstructed rats, there was an increased detrusor response to phenylephrine, suggesting an enhanced α-adrenoceptor function. It cannot be excluded that factors such as the degree and duration of obstruction have an important influence on α-adrenoceptor-mediated responses in the detrusor.

Sundin and Dahlström (1973) found that, in parasympathetically decentralized cat bladder, there was a change in adrenoceptor-mediated function with a shift from a β-adrenoceptor-dominated relaxant influence in the normal bladder to an α-adrenoceptor-dominated response after decentralization. However, more recently, investigators were unable to confirm this finding (Malkowicz et al., 1985; Andersson et al., 1991a). It is possible that, in the study of Sundin and Dahlström (1973), there was bladder hypertrophy with an increased α-adrenoceptor function and that this may explain the discrepancy in results.

However, there are clinical observations in agreement with the view that neurological damage may be associated with a change in α-adrenoceptor functions in the detrusor. In a study on patients with bladder hyperactivity and neurological disorders (bladder hyperreflexia), Jensen (1981) found that treatment with prazosin decreased the hyperreflexia and increased bladder capacity. This was confirmed by other investigators (Petersen et al., 1989), but the results were not impressive. In children with myelomeningocele and detrusor hyperactivity, phentolamine injected intramuscularly decreased tone and bladder hyperactivity (Åmark and Nergårdh, 1991). It cannot be excluded that an effect of the α-adrenoceptor blockers on the central nervous system contributed to these actions.

b. β-ADRENOCEPTORS. Many functional, as well as receptor binding, studies have demonstrated the occurrence of β-adrenoceptors in detrusor muscle from various animals (Dhasmana et al., 1970; Gregg et al., 1970; Elmér, 1974b; Dave and Dhattiwala, 1976; Ganguly and Vedasiromoni, 1976; Larsen, 1979; Levin and Wein, 1979a,b; Wein and Levin, 1979; Khanna et al., 1981; Maggi and Meli, 1982; Anderson and Marks, 1984; Morrison et al., 1986; Morita et al., 1986, 1990; Labadia et al., 1988; Levin et al., 1988; Li et al., 1992), as well as from humans (Todd and Mack, 1969; Awad et al., 1974; Ek et al., 1977; Nergårdh et al., 1977; Larsen, 1979; Perlberg and Caine, 1982; Åmark et al., 1986). In most species, β_2-adrenoceptors seem to predominate. However, in guinea pig detrusor, which contains both β_1- and β_2-adrenoceptors, the relaxant effect was mediated mainly by β_1-adrenoceptors (Li et al., 1992).

In humans, the β-adrenoceptors of detrusor muscle were shown to have functional characteristics typical of neither β_1- nor β_2-adrenoceptors, because they could be blocked by propranolol but not by practolol or butoxamine (Nergårdh et al., 1977; Larsen, 1979). On the other hand, receptor-binding studies in which subtype-selective ligands were used suggest that the β-adrenoceptors of the human detrusor are primarily of the β_2 subtype (Levin et al., 1988).

There are much evidence suggesting that the sympathetic nervous system contributes to the urine storage function by inhibiting the reflex activation of the detrusor muscle during bladder filling (Learmonth, 1931; Edvardsen, 1968; de Groat and Saum, 1972; de Groat, 1975; de Groat and Theobald, 1976; de Groat and Booth, 1980; Ohtsuka et al., 1980; Maggi et al., 1985e; Rudy and Downie, 1988). It may be expected that this occurs via β-adrenoceptor stimulation (Perlberg and Caine, 1982; Åmark et al., 1986). However, the role of β-adrenoceptor-mediated detrusor relaxation has been questioned, particularly in humans (Klevmark, 1977; Nordling, 1983; Andersson, 1986). One argument is that β-adrenoceptor blockade seems to have no effect on normal detrusor function. Thus, the functional importance of β-adrenoceptors for normal detrusor function remains to be settled.

It cannot be excluded that bladder relaxation during filling may be obtained by activation of α-adrenoceptors. α-Adrenoceptor stimulation can inhibit excitatory neurotransmission in the pelvic ganglia, as described in cats (de Groat and Theobald, 1976; de Groat and Booth, 1980; Keast et al., 1990), but also in ganglia within the bladder wall and at the nerve terminal level (Mattiasson et al., 1984a; Åmark et al., 1986).

It may be speculated that, in bladder hyperactivity, there is a lack of the inhibitory β-adrenoceptor-mediated noradrenaline response. However, detrusor muscle from patients with bladder instability was reported to show a similar degree of inhibition in response to isoprenaline as normal detrusor (Eaton and Bates, 1982), even if the

inhibitory effect of isoprenaline on the response to electrical stimulation was less in unstable muscle. No differences in the density of β-adrenoceptors were revealed by receptor-binding studies between normal and hyperactive bladders (Restorick and Mundy, 1989).

4. Nonadrenergic, noncholinergic mechanisms. It has been known for a long time that, in most mammalian species, part of the neuronally induced bladder contraction is resistant to atropine (Langley and Anderson, 1895; Henderson and Roepke, 1934; Edge, 1955; Ursillo and Clark, 1956; Ursillo, 1961b; Chester and Thorpe, 1965; Hukovic et al., 1965; Dumsday, 1971; Carpenter, 1977; Downie and Dean, 1977; Johns and Paton, 1977; Krell et al., 1981; Longhurst et al., 1984). Several explanations for this phenomenon have been proposed (Taira, 1972), one being the occurrence of an NANC transmitter (Ambache and Zar, 1970; Burnstock et al., 1972, 1978a,b; Dean and Downie, 1978a; Krell et al., 1981). The proportion of NANC-mediated response to the total contraction varies with species and the frequency of stimulation. Thus, in rats and guinea pigs, atropine has little effect on the response to single nerve stimuli, but at 20 Hz, it inhibits about 25% of the response. Corresponding figures for rabbit and pig are 40 and 75%, respectively (Brading and Inoue, 1991). The only species in which the occurrence of NANC transmission has been questioned is the human urinary bladder (see section II.E.2).

Luheshi and Zar (1990b) investigated whether the reported full atropine sensitivity of the human detrusor was due to a genuine absence of a noncholinergic element in its motor transmission or was dependent on the experimental protocols, which in most investigations involve prolonged electrical stimulation. They used an experimental protocol with which field stimulation was limited to the minimum required to elicit consistent and reproducible contractions and found that part of the electrically induced response (about 30%) was resistant to atropine. With a more conventional stimulation protocol involving long trains of pulses, however, the responses were enhanced by physostigmine and fully blocked by atropine. Atropine-resistant, TTX-sensitive contractions evoked by electrical stimulation in normal human detrusor tissue also have been reported by other investigators and have been suggested to be caused by ATP (Hoyle et al., 1989; Ruggieri et al., 1990). However, the contribution of purinergic neurotransmission to bladder excitation in humans, and also in pigs, seems to be small.

These results suggest that there is an NANC component contributing to motor transmission in the isolated human detrusor and that no obvious qualitative difference exists between humans and other mammalian species. The importance of the NANC component for detrusor contraction in vivo, normally, and in different micturition disorders remains to be established.

a. ADENOSINE 5′-TRIPHOSPHATE. Stimulation of NANC nerves in the guinea pig bladder evokes contractions that can be mimicked by exogenous ATP, and studies of the NANC component of bladder contraction in this species (Burnstock et al., 1978a,b; Westfall et al., 1983) suggested that the excitatory transmitter is ATP. Excitatory purinergic responses have been reported in bladders from rabbit (Downie and Dean, 1977; Dean and Downie, 1978a; Levin et al., 1981a; Hoyle and Burnstock, 1985; Sneddon and McLees, 1992), rat (Burnstock et al., 1972; Brown et al., 1979; Dahlén and Hedqvist, 1980), mouse (Acevedo and Contreras, 1985; Holt et al., 1985), ferret and marmoset (Moss and Burnstock, 1985), and cat (Theobald, 1983, 1986). It was suggested that ATP interacts with P_{2x}-purinoceptors, because the contractions were blocked by desensitization with β,γ-methylene ATP (Brown et al., 1979; Hourani et al., 1985; Nicholls et al., 1992). The results of several investigations support the view that ATP is an NANC transmitter in the guinea pig bladder (Kasakov and Burnstock, 1983; Levin et al., 1986b; Fujii, 1988; Brading and Mostwin, 1989; Brading and Williams, 1990; Inoue and Brading, 1990; Creed et al., 1991; Schneider et al., 1991). Activation of P_{2x}-purinoceptors depolarizes the cells, increases the spike frequency, and causes contraction (Brading and Inoue, 1991). However, ATP may not be the only NANC transmitter. Based on their findings in rabbit and guinea pig bladders, Creed et al. (1991) suggested that either the desensitization with α,β-methylene ATP is not complete or other noncholinergic, nonpurinergic nerves contribute to the innervation of the guinea pig bladder.

This may also be the case in the rat bladder (Bo and Burnstock, 1990; Parija et al., 1991), in which it is possible, by single-pulse stimulation, to separate the cholinergic (slow) and noncholinergic (fast) contractile components distinctly (Maggi et al., 1985d; Bhat et al., 1989). The slow component could be abolished by atropine, and the fast component could be reduced, but not abolished, by α,β-methylene ATP (Parija et al., 1991; Maggi, 1991a). Maggi (1991a) showed that ω-conotoxin-sensitive voltage-dependent calcium channels played a more important role in determining the cholinergic, rather than the noncholinergic, putatively purinergic, component of the response. The action of ω-conotoxin was likely to be exerted on N-type rather than L-type calcium channels.

Luheshi and Zar (1990a) found that the responses to electrical stimulation in the rat bladder were reduced following α,β-methylene ATP desensitization but that a sizable proportion of the response persisted (in the presence of atropine and indomethacin). They concluded, therefore, that ATP is unlikely to be the sole noncholinergic motor transmitter in the rat detrusor. Choo and Mitchelson (1980), using ATP as the desensitizing nucleotide, had previously arrived at a similar conclusion. Also, in the rabbit, there was a residual response to nerve stimulation in the presence of atropine and desensitiza-

tion of P_2-purinoceptors, which could be blocked by TTX (Chen, 1990).

In the cat, two distinct bladder responses to parasympathetic nerve stimulation were demonstrated (Theobald, 1986). The initial response was a sharp transient increase in intravesical pressure, and the second consisted of a tonic maintenance during stimulation. Theobald (1986) reported that the photoaffinity analogue of ATP, arylazido aminopropionyl ATP, which blocked ATP-induced contractions, partially blocked the first phase, and atropine, which had no effect on the first response, blocked the second phase of the contraction. Also, these results may be interpreted as suggesting that ATP and acetylcholine are the main contractile activators of the cat detrusor, but they do not exclude that another NANC transmitter may contribute to the first contractile response to parasympathetic nerve stimulation.

Based on their observations on the isolated, whole rabbit bladder model, in which a biphasic contractile response to electric field stimulation was found, Levin et al. (1986b) suggested that purinergic stimulation may play a role in initiating micturition, whereas bladder emptying appears to be primarily a result of muscarinic receptor stimulation. This suggestion was supported by the results of Chancellor et al. (1992) using the same model.

Igawa et al. (1993a) found that, in the normal, unanaesthetized rat, both exogenous ATP and carbachol were able to empty the bladder. Micturition was still possible after desensitization with α,β-methylene ATP or after blockade of the muscarinic receptors with atropine. However, in the presence of atropine, α,β-methylene ATP produced dribbling incontinence in all animals tested. This is in agreement with previous findings in vitro showing that, given separately, neither atropine nor α,β-methylene ATP were effective inhibitors of electrically evoked contractions, but given together, they abolished the responses (Brading, 1987; Brading and Mostwin, 1989; Peterson and Noronha-Blob, 1989; Brading and Williams, 1990). When the micturition reflex was blocked after intrathecal morphine injection, neither ATP and α,β-methylene ATP nor carbachol were able to empty the bladder (Igawa et al., 1993a). This suggests that these drugs, by increasing the tone of the detrusor muscle cells, elicit a micturition reflex leading to synchronized detrusor contraction and outlet relaxation with consequent bladder emptying. Such a mechanism was previously suggested for the bladder emptying induced by bethanechol (Downie et al., 1983).

Whether or not ATP is involved in the contractile response of the human bladder to electrical stimulation has not been settled. Husted et al. (1983) found that ATP produced a concentration-dependent contraction in isolated human detrusor muscle, but they also reported that ATP influenced the responses to transmural nerve stimulation, probably by both prejunctional and postjunctional effects. Evidence has been presented (Hoyle et al., 1989; Ruggieri et al., 1990) that the atropine-resistant contractile component evoked in human detrusor by electrical stimulation can be abolished by α,β-methylene ATP, suggesting that the NANC mediator is ATP. Inoue and Brading (1991) showed that the properties of the ATP-induced current in human and pig detrusor, and the current intensity, were similar to those in guinea pig detrusor. The smooth muscle cells of the three species all have a high density of ATP receptors. The variation in the purinergic component of the excitatory innervation in bladder muscle from different species thus could not be explained by differences in the properties of the postsynaptic purinoceptors. On the other hand, in the feline detrusor muscle, Theobald (1992) found evidence for the presence of novel purinoceptors and/or the presence of multiple purinoceptors. This suggests the possibility of species-specific purinergic responses of detrusor muscle.

Nifedipine abolished the NANC-mediated contractile component in rabbit (Andersson et al., 1986b) and rat detrusor (Bo and Burnstock, 1990; Zar et al., 1990). If it is assumed that ATP is responsible for the NANC component of the contraction, this suggests that voltage-sensitive L-type calcium channels play an important role in the excitatory mechanical action of ATP in the urinary bladder of rats and rabbits. Also, in the guinea pig urinary bladder, it was found that nifedipine inhibited both ATP-induced contraction and the simultaneous elevation of intracellular Ca^{2+} (Katsuragi et al., 1990). However, Schneider et al. (1991), studying single smooth muscle cells from the guinea pig detrusor with whole cell patch-clamp combined with microspectrofluometry, found that nitrendipine did not block the ATP-induced inward current or the ATP-induced $[Ca^{2+}]_i$ transient. They suggested that ATP activates (via membrane depolarization) a dihydropyridine-sensitive inward Ca^{2+} current in the multicellular specimen but not in the isolated myocyte.

Available results suggest that ATP may contribute to the NANC-mediated excitatory neurotransmission. Whether or not it is the sole transmitter mediating this response is unclear, but most probably other factors may contribute. Because ATP may be released from nerves in the bladder, and because it is readily metabolized to adenosine in this tissue (Cusack and Hourani, 1984), Acevedo et al. (1992) proposed that adenosine may have a modulatory role as an endogenous regulator of NANC transmission. In the mouse urinary bladder, they found that adenosine (and related structural analogues) inhibited the responses to transmural electrical stimulation as well as the responses to exogenous ATP. Both of these responses were increased by 8-phenyltheophylline (Acevedo et al., 1992). It was suggested that endogenous adenosine may modulate bladder neurotransmission, possibly by acting both prejunctionally (A_1 receptors)

and postjunctionally (A_2 receptors). In the rat bladder, Nicholls et al. (1992) suggested that the P_1-purinoceptors inhibiting contraction were of the A_2 type (A_{2b} subclass).

In the human detrusor muscle, in which the contribution of the NANC mechanism has been questioned, Husted et al. (1983) found that adenosine and dipyridamole reduced responses to electrical stimulation, whereas theophylline augmented these responses. This may be taken as further support of the hypothesis advanced by Acevedo et al. (1992).

b. NITRIC OXIDE. The mechanism underlying the bladder relaxation during filling is not fully understood. It has been attributed to the physical properties of the bladder (Nesbit et al., 1947; Tang and Ruch, 1955) and also to inhibition of the parasympathetic (Sherrington, 1915; Klevmark, 1977) or sympathetic (Edvardsen, 1968; de Groat, 1975; Maggi et al., 1985e) bladder nerves. NO has been suggested to be a mediator of adaptive relaxation in the stomach, i.e., to accommodate food or fluid (Desai et al., 1991). Theoretically, an increased activity of NO-releasing inhibitory nerves to the detrusor could be a factor keeping the bladder relaxed during the filling phase.

NO is synthesized from L-arginine by two main classes of NOS. The one occurring in peripheral nerves is a constitutive, Ca^{2+}-calmodulin-dependent enzyme, which releases picomoles of NO in response to receptor stimulation (Förstermann et al., 1991; Moncada, 1992). It was shown that NO synthase and neuronal NADPH diaphorase are identical in brain and peripheral tissues, and it was suggested that NADPH diaphorase histochemistry should provide a specific marker for neurons producing NO (Dawson et al., 1991; Hope et al., 1991). NADPH diaphorase-positive fibres and thick nerve branches were found in or around the muscular bundles of the pig detrusor, trigone, and urethra. The nerve fibres in the trigone and urethra were thinner and more dispersed within the muscle than those of the detrusor. There was a distinct staining of the urothelium (Larsson et al., 1992; Persson et al., 1993). Conflicting results have been reported concerning the NADPH diaphorase staining of the detrusor of different species. No NADPH diaphorase staining was observed in the rat detrusor by Keast (1992), whereas McNeill et al. (1992) and Grozdanovic et al. (1992) found staining in the rat and mouse detrusor, respectively.

Immunohistochemistry, with antisera produced in rabbits against COOH- and NH_2-terminal fragments (Alm et al., 1993) of a cloned NOS from rat cerebellum (Bredt et al., 1991), revealed a difference in the distribution of NOS-positive nerves among pig detrusor, trigone, and urethra. Thus, the density of NOS immunoreactivity was higher in trigonal and urethral tissue than in the detrusor (Persson et al., 1993). This corresponds well with the ability to respond with NO-mediated relaxation in response to nerve stimulation, which was distinct in the trigone and the urethra but not in the detrusor (Persson and Andersson, 1992). There was no NOS staining of the urothelium, which contrasts to the results with NADPH diaphorase. This may be due to a high specificity for the NOS of nerves exhibited by the antisera used or to the fact that NADPH diaphorase histochemistry visualizes other enzymes in addition to NOS. The data obtained by immunohistochemistry and NADPH diaphorase staining suggest that NOS is localized in nerve fibres of the lower urinary tract, including the detrusor, but predominantly in the outflow region.

In pig detrusor muscle, an NANC-mediated relaxation preceded by a contraction, and which was blocked by TTX, was demonstrated by Klarskov (1987a). In the human detrusor, Klarskov (1987a) claimed to have found an occasional NANC-mediated relaxation, but the evidence for this was not convincing. James et al. (1991) found that, in isolated preparations of the human detrusor contracted by 20 mM K^+, in the presence of atropine, electrical stimulation evoked relaxations sensitive to L-NNA but insensitive to TTX. They suggested that NO might be generated from the detrusor muscle and could be an important factor for bladder relaxation during the filling phase.

It was not possible to convincingly reproduce these results in human, pig, or rat detrusor. In human detrusor strips contracted by 35 mM K^+ or ET-1, in the presence of atropine and after desensitization with α,β-methylene ATP, no relaxation could be evoked by electrical stimulation (K. Persson and K.-E. Andersson, unpublished results). In pig detrusor muscle contracted by K^+ (35 mM), after pretreatment with atropine and α,β-methylene ATP, no response or small contractions were found. If, instead, contraction was induced by ET-1 in a concentration that induced a tension near that evoked by high K^+ (124 mM), a small relaxation was seen in some preparations that was sensitive to L-NNA but partly insensitive to TTX (Persson and Andersson, 1992). Electrical stimulation of the precontracted rat detrusor in the presence of atropine and after desensitization with α,β-methylene ATP did not produce relaxation—only further contraction (Persson et al., 1992).

In the pig detrusor, the NO donor SIN-1 and NO (stimulating guanylate cyclase) relaxed carbachol- and ET-1-contracted preparations by approximately 60%. However, isoprenaline (stimulating adenylate cyclase) was about 1000 times more potent than SIN-1 and NO and caused complete relaxation (Persson and Andersson, 1992). Nitroprusside, SIN-1, and NO were only moderately effective in relaxing isolated rat detrusor muscle, compared to their effects on the urethral muscle (Persson et al., 1992). These results agree well with those of Morita et al. (1992), who found that, in rabbits, cGMP is mainly related to urethral relaxation and cyclic adenosine-3′,5′-monophosphate is mainly related to urinary bladder relaxation.

The possible role of the L-arginine/NO pathway as a neuromodulator of the excitatory response in the pig isolated detrusor has been studied (Persson et al., 1993). L-NNA caused a nonsignificant enhancement of the contractile response to electrical field stimulation. L-Arginine, but not D-arginine, decreased the electrically evoked contractions by 25 to 30%. This effect of L-arginine was reversed by L-NNA. Propranolol did not affect the decrease in amplitude caused by L-arginine, excluding the possiblity that the observed effect was due to (indirect) β-adrenoceptor stimulation. Furthermore, L-arginine had no effect on NANC contractions in the presence of scopolamine, indicating that the inhibitory response was associated with the cholinergic component of the contraction. Concentration-response curves to carbachol or contractions induced by carbachol were not influenced by L-arginine, demonstrating that L-arginine has no postjunctional effects on the detrusor muscle. Therefore, the results support the view that NO may act prejunctionally to inhibit acetylcholine release.

Taken together, these results do not suggest that NO has a role as a neurotransmitter causing direct relaxation of the detrusor smooth muscle. However, NO may exert its action prejunctionally and influence the bladder tone by modulation of acetylcholine release. It is still unsettled to what extent the L-arginine/NO pathway may be involved in muscle relaxation responses in the detrusor.

c. NEUROPEPTIDES. The functional roles of the many neuropeptides that have been demonstrated to be synthesized, stored, and released in the human lower urinary tract (de Groat and Kawatani, 1985; Burnstock, 1990; Maggi, 1991b) have not been established. These peptides, which are present in sensory nerves, include SP, NKA, VIP, CGRP, somatostatin, enkephalins, NPY, BK, galanin, and the ETs. As discussed by Maggi and Meli (1986) and Maggi (1991b), neuropeptide-containing, capsaicin-sensitive primary afferents in the bladder and urethra may not only have a sensory function but also may have a local effector or efferent function. In addition, they may play a role as neurotransmitters and/or neuromodulators in the bladder ganglia and at the neuromuscular junctions. As a result, the peptides may be involved in the mediation of various effects, including micturition reflex activation, smooth muscle contraction, potentiation of efferent neurotransmission, and changes in vascular tone and permeability. Evidence for this is based mainly on experiments in animals. Studies of isolated human bladder muscle strips have failed to reveal any specific local motor response attributable to a capsaicin-sensitive innervation (Maggi, 1991b). However, cystometric evidence that capsaicin-sensitive nerves may modulate the afferent branch of the micturition reflex in humans has been presented (Maggi et al., 1989a). In a small number of patients suffering from bladder hypersensitivity disorders, intravesical capsaicin produced a long-lasting, symptomatic improvement.

It has been much discussed whether neuropeptides are involved in various forms of bladder hyperactivity, and it has been demonstrated that obstruction, which is often associated with hyperactivity, causes a reduction in the density of neuropeptide-containing nerves (Chapple et al., 1992). On the other hand, in bladder tissue from women with idiopathic detrusor instability, there was a significant increase in the density of subepithelial, presumptive sensory nerves compared to stable controls (Moore et al., 1992). Capsaicin-sensitive afferents may be a part of a spinal, vesico-vesical excitatory (short-loop) reflex, providing a neurogenic mechanism for unstable and/or hyperreflexic detrusor contractions (de Groat et al., 1990; Maggi, 1991b).

Evidence in support of a role of capsaicin-sensitive nerves in the pathogenesis of detrusor hyperreflexia in humans was given by Fowler et al. (1992). They found that intravesical capsaicin improved the control of detrusor hyperreflexia in four of five patients with multiple sclerosis.

i. Vasoactive intestinal polypeptide. VIP was shown to inhibit spontaneous contractile activity in isolated detrusor muscle from several animal species (Levin and Wein, 1981; Finkbeiner, 1983a; Kihl et al., 1985; Sjögren et al., 1985) and from humans (Larsen et al., 1981; Klarskov et al., 1984; Kinder and Mundy, 1985b; Sjögren et al., 1985) but to have little effect on contractions induced by muscarinic receptor stimulation or by electrical stimulation of nerves (Sjögren et al., 1985). In isolated rat bladder, VIP had no effect (Andersson et al., 1988c; Igawa et al., 1993c), whereas in isolated guinea pig bladder, VIP produced contraction (MacKenzie and Burnstock, 1984). However, if the low-amplitude myogenic contractile activity demonstrated in human (Sibley, 1984), as well as animal (Sibley, 1984; van Duyl 1985; van Duyl et al., 1990; Potjer and Constantinou, 1989), bladders is of primary importance for the genesis of reflex bladder contraction, direct inhibitory effects of VIP on bladder smooth muscle should not be neglected. The findings that VIP levels were markedly reduced in patients suffering from idiopathic detrusor instability (Gu et al., 1983b; Chapple et al., 1992) or detrusor hyperreflexia (Kinder et al., 1985a) were interpreted to suggest that VIP (or rather lack of it) may be involved in some forms of bladder hyperactivity.

Stimulation of the pelvic nerves in cats increased the VIP output from the bladder and increased bladder blood flow, although moderately (Andersson et al., 1987c). VIP injected intravenously into dogs induced a relaxation of the urinary bladder (Andersson et al., 1990). On the other hand, VIP given intravenously to patients in a dose causing increases in heart rate had no effect on cystometric parameters (Klarskov et al., 1987). This may, of course, be due to a too low concentration of VIP reaching the bladder, but plasma concentrations of VIP were obtained that, in other clinical investigations, had been

sufficient to cause relaxation of smooth muscle (Klarskov et al., 1987). In rats with infravesical outflow obstruction, bladder hypertrophy, and bladder hyperactivity (Malmgren et al., 1987), the concentrations of VIP in the middle and lower parts of obstructed bladders were higher than in controls (Andersson et al., 1988c). Neither in the hypertrophic nor in the normal isolated rat bladder did VIP have relaxant or contractant effects, and the peptide did not influence contractions induced by electrical stimulation (Andersson et al., 1988c; Igawa et al., 1993c). This does not support the view that lack of VIP is associated with bladder hyperactivity, at least not in the rat.

ii. Tachykinins. Falconieri Erspamer et al. (1973) showed that SP and various related peptides had contractile effects in the isolated bladder smooth muscle from various species. They suggested that biogenic peptides may interfere in the physiological control of bladder motility and tone. The potential role of SP in the atropine-resistant component of the contractile response induced by electrical stimulation was studied by several investigators (Husted et al., 1981; Leander et al., 1981; Johns, 1982; Sjögren et al., 1982a; Norlén et al., 1983; Hourani, 1984; Longhurst et al., 1984; Mackenzie and Burnstock, 1984; Meldrum and Burnstock, 1985; Dveksler et al., 1985; Berggren et al., 1988). With few exceptions, these studies did not favor the view that SP, released from postganglionic nerve terminals, has an excitatory transmitter role. Evidence has been presented, on the other hand, that SP may play a role in the afferent, sensory branch of the micturition reflex (Sharkey et al., 1983; Maggi et al., 1985h, 1986, 1987c, 1988a, 1991b; Holzer-Petsche and Lembeck, 1984).

Several tachykinins are present in sensory nerves of the urinary bladder in rat and other mammalian species, including humans (Maggi, 1991b; Keast and de Groat, 1992). Receptor subtypes were identified in urinary bladders of several mammals, both in vitro and in vivo (Mizrahi et al., 1985a; Burcher et al., 1986; Maggi et al., 1986). In the rat urinary bladder, three receptor types, classified as NK_1, NK_2, and NK_3, have been demonstrated, as evidenced by radioligand binding, autoradiographic, and functional experiments (Burcher and Buck, 1986; Maggi et al., 1987d, 1988d; Dion et al., 1987; Hall et al., 1992; Nimmo et al., 1992; van Giersbergen et al., 1992).

Maggi et al. (1986) suggested the existence of two different receptors for tachykinins in the rat bladder, whose activation was responsible for initiation of the micturition reflex and direct smooth muscle contraction, respectively. In a later study by the same group, however, evidence was presented that, at the peripheral level, neither NK_1 nor NK_2 receptors have any importance to normal initiation of the micturition reflex in the rat (Lecci et al., 1993). This does not exclude that they have such a role in, for example, detrusor hyperreflexia induced by irritants.

Thiorphan, an inhibitor of endopeptidase 24.11 (enkephalinase), was found to potentiate and prolong the contractile response to tachykinins on strips of guinea pig isolated urinary bladder in the presence and absence of the mucosal layer (Maggi et al., 1990a). Endopeptidase 24.11 activity was found in both the mucosal and muscular layers, although it was more concentrated in the former. It was suggested that endopeptidase 24.11 terminates the activity of tachykinins and modulates the intensity of the biological response produced after their release from peripheral nerve endings. In the dog bladder, Saban et al. (1992) found that removal of the mucosa, or treatment with the metalloproteinase inhibitor phosphoramidone, increased the sensitivity to NKA. They suggested that NKA was degraded by enkephalinase in the mucosa.

In the guinea pig, Shinkai and Takayanagi (1990) found that both NK_1 and NK_2 receptors mediated contraction; the NK_3 receptor-selective agonist senktide had no effect. Longmore and Hill (1992) confirmed this conclusion. In the rat, both NK_1 and NK_2 receptors mediate contraction; multiple tachykinins activating these receptors were shown to be coreleased by capsaicin (Maggi et al., 1991b). The dog bladder also may have a mixture of NK_1 and NK_2 receptors (Dion et al., 1987; Saban et al., 1992).

Maggi et al. (1991b) presented evidence for the involvement of SP and NKA (or other NKA-related peptides preferentially acting at NK_2 receptors) as cotransmitters in rat detrusor muscle and that, in addition to acetylcholine and ATP, tachykinins must be considered as excitatory transmitters in this organ. Intravenous administration of tachykinins caused dose-dependent increases in vascular permeability in the rat lower urinary tract, and this effect was suggested to be mediated by NK_1 receptors (Abelli et al., 1989). Nimmo et al. (1992) found that NK_2-binding sites appeared to be present on the peripheral terminals of capsaicin-sensitive visceral afferent fibres and that the density of these binding sites may increase following bladder outlet obstruction. Their results suggested that NK_3-binding sites were present on the peripheral terminals of nerves that have their cell bodies in the pelvic ganglia.

Tachykinins also have contractile effects in the human bladder (Erspamer et al., 1981; Kalbfleisch and Daniel, 1987; Dion et al., 1988; Maggi et al., 1988e, 1989e). The potency of NKs was shown to be NKA > NKB >> SP (Dion et al., 1988; Maggi et al., 1989e). This, and results with subtype-selective agonists (Maggi et al., 1989e), suggested that the tachykinin receptor mediating contraction in the human bladder is of the NK_2 type.

A specific functional role for the tachykinins in the lower urinary tract of animals or humans has not been demonstrated. However, as mentioned previously, cys-

tometric evidence that capsaicin-sensitive nerves may modulate the afferent branch of the micturition reflex in humans has been presented (Maggi et al., 1989a). This may also be the case in, for example, rats and guinea pigs, in which a selective agonist for NK_2 receptors, administered intravesically, stimulated micturition (Maggi et al., 1991a).

iii. Neuropeptide Y. NPY-containing nerves were shown to be present in abundance in the rat detrusor (Mattiasson et al., 1985c; Iravani and Zar, 1988; Keast and de Groat, 1989). Iravani and Zar (1988) found that exogenously added NPY contracted strips of rat detrusor and potentiated the noncholinergic motor transmission. The effects were blocked by nifedipine, and it was concluded that the abundant presence of NPY-like immunoreactive nerve fibres in the detrusor muscle was consistent with a motor transmitter function of the peptide in the rat bladder. These results are not in agreement with those of Zoubek et al. (1993), who found that porcine NPY did not induce any direct contractile effect in isolated strips of rat detrusor. On the other hand, porcine NPY had a marked inhibitory effect on the cholinergic component of electrically induced contractions in rat bladder strips, particularly at low (<10 Hz) frequencies of stimulation. In the isolated guinea pig detrusor, NPY had no effects per se but decreased the electrically induced NANC response (Lundberg et al., 1984).

Even if the available information regarding the effects of NPY on the rat detrusor is conflicting, it cannot be excluded that NPY may have an important role in the neural control of the lower urinary tract in this species.

iv. Arginine vasopressin. In detrusor from rabbits and humans, higher levels of of AVP-like immunoreactivity were detected than those normally found in plasma (Holmquist et al., 1991b). Vasopressin receptors were identified in rat urinary bladder (Thibonnier et al., 1986), and the peptide was shown to have potent contractile effects especially in the isolated rabbit (Angelucci et al., 1974; Crankshaw, 1989; Falconieri Erspamer et al., 1981), but also in the rat, bladder (Abdel-Hakim et al., 1983; Falconieri Erspamer, 1973; Uvelius et al., 1990b); AVP had little effect on the isolated human bladder (Erspamer et al., 1981; Holmquist et al., 1991b). In the rabbit bladder, the contractions were effectively inhibited by a V_1 receptor-selective antagonist. However, the antagonist had no effect on contractions induced by electrical field stimulation (Holmquist et al., 1991b).

Radioligand membrane-binding studies, using [^{3}H] AVP as the ligand, revealed the existence of a single population of binding sites in the rabbit bladder, and displacement experiments indicated that the receptor was of the V_1 subtype. By autoradiography, [^{3}H]AVP-binding sites were found in the rabbit bladder, both in the smooth muscle layers and in the submucosa. Neither binding experiments nor autoradiography revealed any specific [^{3}H]AVP-binding sites in the human bladder (Holmquist et al., 1991b). It was concluded that, in both rabbit and human bladder, AVP seems to be synthesized locally and/or extracted from the circulation. It is unlikely that AVP is the NANC transmitter in rabbit detrusor, and the functional importance of the hormone in the lower urinary tract can only be speculated on.

In bladders from rats with hereditary diabetes insipidus due to lack of hypothalamic AVP (Sokol et al., 1982), the total amount of AVP immunoreactivity was the same as in normal controls, but the concentration was lower (Uvelius et al., 1992). It was suggested that this AVP was synthesized locally; it did not seem to be responsible for NANC-mediated contraction.

v. Calcitonin gene-related peptide. Among the sensory neuropeptides from capsaicin-sensitive nerves, CGRP has been proposed as a determinant of certain responses in the urinary tract (Hua, 1986; Maggi et al., 1987b; Stief et al., 1990; for review, see Maggi et al., 1992b). CGRP-immunoreactive nerves distribute to smooth muscle, around blood vessels, and may form a dense suburothelial plexus with some nerve fibres penetrating within the urothelium. Binding sites for the peptide were demonstrated in the mucosa both in rat (Nimmo et al., 1988) and human bladders (Edyvane and Marshall, 1990). CGRP was colocalized with tachykinin-like immunoreactivity in primary sensory neurones of the bladder in several species (Ghatei et al., 1985b; Su et al., 1986; Yokokawa et al., 1986), and a physiological antagonism was suggested to occur beween the tachykinins and CGRP (Maggi and Meli, 1986; Maggi et al., 1992b).

Even if the CGRP content of the bladder is of primary afferent origin, CGRP may have an efferent function when released, including relaxation of smooth muscle and vasodilation. However, as Maggi et al. (1992b) pointed out, the action of CGRP is of different intensity in different regions of the urinary tract of the same species, and for the same region of the urinary tract, the effect of CGRP may vary with the species investigated. Thus, in the guinea pig, the relaxant action of CGRP is much more intense in the bladder neck than in the bladder dome (Maggi et al., 1988f). In guinea pig and canine urinary bladder, CGRP is a potent relaxant agent. However, in the rat bladder, CGRP had little or no effect on either bladder motility or vascular permeability (Maggi et al., 1987b), and it had no effect on contractile activity in the human bladder (Maggi et al., 1989e). In agreement with these findings, Persson et al. (1991a) found no functionally important mechanical effects in isolated pig detrusor strips, but the peptide was a potent dilator of vesical arteries through an endothelium-independent mechanism. It has been reported that CGRP increases blood flow in the cat bladder (Andersson, 1989), but whether or not CGRP has any importance for bladder function through this action remains to be established.

Maggi et al. (1992b) presented evidence that CGRP is

a neurotransmitter regulating motility in the mammalian urinary tract. There is hardly enough data to support that this is the case in, for example, the normal human bladder. However, it cannot be excluded that CGRP and tachykinins, released by different noxious stimuli from capsaicin-sensitive afferents, may contribute to symptoms in different disorders of the lower urinary tract, particularly those with damage of the urothelium due to inflammation, trauma, or cancer (Maggi et al., 1992b).

vi. Somatostatin. Hökfelt et al. (1978) demonstrated somatostatin in the lower urinary tract of various species. Sjögren et al. (1982a) found that, in the rabbit detrusor, somatostatin caused a concentration-dependent, slowly developing increase in tension that was unaffected by TTX and or physostigmine. The peptide had a low potency, and it was considered unlikely that it had any transmitter function in the lower urinary tract.

vii. Enkephalins. By immunohistochemistry, enkephalins have been demonstrated in parasympathetic ganglia on the surface of the urinary bladder (Hökfelt et al., 1978; Alm et al., 1981; de Groat et al., 1981, 1983; Kawatani et al., 1983; de Groat and Kawatani 1989), where they are suggested to be involved in δ-receptor-mediated inhibitory mechanisms (de Groat and Kawatani, 1989). Both methionine and leucine enkephalin were found to inhibit electrically evoked contractions in human detrusor and pig lower urinary tract smooth muscle, probably by a prejunctional effect (Klarskov, 1987b). In guinea pig urinary bladder, neither methionine nor leucine enkephalin had any prominent direct action on the smooth muscle, nor did they significantly modify the cholinergic or noncholinergic components of the contractile response to electrical stimulation of nerves (Mackenzie and Burnstock, 1984).

An involvement of opioid mechanisms in the peripheral control of detrusor muscle was suggested by Berggren et al. (1992). They found in isolated rat and human detrusor muscle that naloxone caused a significant facilitation of the response to electrical field stimulation, which was counteracted by morphine and the synthetic δ-receptor agonist D-ala^2-D-leu^5-enkephalin. Morphine and D-ala^2-D-leu^5-enkephalin had by themselves no effect on the electrically induced contractions, which is in agreement with previous findings in mouse urinary bladder (Acevedo et al., 1986). The authors suggested that there was a tonic, inhibitory action on the detrusor contraction elicited by electrical field stimulation exerted via μ- and, possibly, δ-receptors. Whether or not a peripheral action complements the central depressant effects on micturition exerted by morphine (Dray and Metsch, 1984), and the stimulatory effects of naloxone (Vaidyanathan et al., 1981a; Murray and Feneley, 1982), is an open question.

viii. Bradykinin. BK can contract the detrusor of several animal species with a wide range of relative potencies (Falconieri Erspamer et al., 1973). In isolated dog bladder muscle, where BK was a potent contractile agonist (Regoli et al., 1986; Steidle et al., 1990) the response was mediated by B_2 receptors. Albert et al. (1970) found that BK had a contractile effect on human detrusor muscle but that the sensitivity to the peptide varied widely. Confirming these observations, BK was found to contract isolated human detrusor muscle (Andersson et al., 1992b). However, it was considerably less potent and effective than AtI and AtII. The contractile effect was significantly increased after pretreatment with captopril or enalaprilate, which suggests that ACE inhibitors may reduce the degradation of BK in the human detrusor also. These results are again in contrast with findings in the dog bladder (Steidle et al., 1990), where BK caused a contraction, which at a concentration of 10^{-6} M was >150% of that induced by 150 mM KCl; the effect was not enhanced by ACE inhibition.

In guinea pig urinary bladder, in which BK was found to have a rather low relative potency (Falconieri Erspamer et al., 1973), binding of [^{3}H]BK was located to the subepithelial lamina propria; it was absent over the muscle layers (Manning and Snyder, 1986). Therefore, it was suggested that BK had an indirect action on urinary tract smooth muscle. Supporting such a view, several investigators found that the effect of BK in the rabbit bladder could be inhibited by PG synthesis inhibitors, and they concluded that part of the effect was mediated by prostanoids (Downie and Rouffignac, 1981; Nakahata et al., 1987). It cannot be excluded that, in the human detrusor, also, part of the response to BK is mediated by prostanoids (Andersson et al., 1992b).

Maggi et al. (1989d) found that multiple mechanisms were involved in the motor responses of the guinea pig isolated bladder to BK. They found that BK-induced contraction involved activation of both B_2 receptors and prostanoid synthesis. In addition, they found that in carbachol-contracted detrusor strips BK produced relaxation. This response involved activation of B_2 receptors and opening of apamine-sensitive K^+ channels. Maggi et al. (1989d) also found that BK stimulated sensory nerves in the bladder, mainly by prostanoid production.

Even if the role for BK in normal detrusor function is unclear, it cannot be excluded that it may contribute significantly to lower urinary tract symptoms in, for example, inflammatory conditions.

ix. Bombesin. The tetradecapeptide bombesin was found to induce concentration-dependent contractions of human, rat, and guinea pig urinary bladder smooth muscle (Falconieri Erspamer et al., 1973, 1988; Erspamer et al., 1981; Abdel-Hakim et al., 1981; Mizrahi et al., 1985b; Regoli et al., 1988; Rouissi et al., 1991; Watts and Cohen, 1991; Maggi et al., 1992a). There was no tachyphylaxis to the effects of the peptide, which were unaffected by antagonists to several putative transmitters. However, the effects of bombesin were inhibited by some tachykinin antagonists (Mizrahi et al., 1985b).

The effects of bombesin seem to be produced by direct activation of bombesin receptors on the smooth muscle cells and not via release of other endogenous agents. The bombesin receptors may not be the same in guinea pig and rat urinary bladder (Rouissi et al., 1991). Using a potent antagonist of bombesin receptors, Maggi et al. (1992a) found no effect against the NANC response to electrical stimulation or to capsaicin-induced contractions in the isolated guinea pig bladder.

Even if bombesin-like immunoreactivity occurs in the rat urinary bladder (Ghatei et al., 1985a), and bombesin has a potent contractile effect on the bladder of several species, a physiological role for the peptide in bladder function has not been demonstrated.

x. Galanin. By immunohistochemistry, the 29-amino acid peptide galanin has been demonstrated in nerves of the rat and human urinary tract (Bauer et al., 1986). The peptide contracts rat urinary bladder (Rokaeus, 1987). Maggi et al. (1987f) showed that galanin concentration-dependently caused a pronounced reduction of the responses to electrical stimulation in human detrusor strips. Its action was restricted to the atropine-sensitive, neurally mediated bladder contractility, and a prejunctional site of action was suggested. Because the human bladder is contracted mainly by an atropine-sensitive mechanism (see section II.E.2), a possible neuromodulator role of galanin in the human urinary bladder was proposed. However, its functional role, if any, in the lower urinary tract remains to be established.

xi. Endothelins. ET-1 is known to induce contraction in rabbit (Secrest and Cohen, 1989; Garcia-Pascual et al., 1990; Saenz de Tejada et al., 1992; Traish et al., 1992), guinea pig and rat (Wiklund et al., 1989), and human detrusor muscle (Maggi et al., 1989b, 1990b; Saenz de Tejada et al., 1992). Garcia-Pascual et al. (1990) showed that, in isolated rabbit detrusor muscle, ET-1 caused concentration-related, slowly developing contractions that were difficult to wash out. There was a marked tachyphylaxis to the effects of the peptide. The ET-1-induced contractions were not significantly affected by scopolamine or indomethacin but could be abolished by incubation in a Ca^{2+}-free solution, and nifedipine had a marked inhibitory action. These results were confirmed by Saenz de Tejada et al. (1992). On the other hand, in human detrusor, the ET-1-induced contractions were resistant to Ca^{2+} channel blockade by nifedipine (Maggi et al., 1989b), illustrating species variation in the activation mechanisms.

In the rabbit bladder, ET-1 was found to have no significant effect on the responses induced by electrical stimulation, but it did increase basal tension (Garcia-Pascual et al., 1990). However, Saenz de Tejada et al. (1992) demonstrated that ET-1 caused a small, but consistent, attenuation of the atropine-resistent contraction, whereas it had no effect on the atropine-resistant component.

Garcia-Pascual et al. (1990) found ^{125}I-ET-1-binding sites mainly in the outer longitudinal muscle layer, in vessels, and in the submucosa of the rabbit bladder. The highest density of binding sites appeared to be in vessels and the outer muscle layer. These findings were extended by Saenz de Tejada et al. (1992). They demonstrated, in both human and rabbit bladder, ET-like immunoreactivity in the transitional epithelium, serosal mesothelium, vascular endothelium, smooth muscles of the detrusor (nonvascular) and vessels, and in fibroblasts. This cellular distribution was confirmed in in situ hybridization experiments. The authors suggested that ET may act as an autocrine hormone in the regulation of the bladder wall structure and smooth muscle tone and that it may regulate cholinergic neurotransmission by a paracrine mechanism.

Maggi et al. (1990b) demonstrated that ET-1, as well as ET-3, produced concentration-dependent contractions of the human isolated urinary bladder. ET-3 was less potent than ET-1. In rabbit bladder, Traish et al. (1992) found that ET-1, ET-2, and ET-3 all caused concentration-dependent contractions. The threshold concentrations of ET-3 to initiate contraction were higher than for ET-1 and ET-2. Traish et al. (1992) also characterized the ET receptor subtypes in the rabbit bladder and suggested that at least two subtypes exist in rabbit bladder tissue, ET-1 and ET-2 binding to one subpopulation and ET-3 to another. These receptors may be involved in the modulation of smooth muscle tone.

xii. Angiotensins. AtII was reported to contract the urinary bladder of several species, including rat, guinea pig, rabbit, dog, cat, and monkey, but with a wide range of relative potencies (Falconieri Erspamer et al., 1973). Anderson et al. (1984) demonstrated the occurrence of AtII receptors in the rabbit urinary bladder and confirmed that AtII was able to contract the bladder smooth muscle. However, exogenous AtII had a delayed onset of action, and saralasin was not able to block completely the atropine-resistant component of electrically induced contractions. It was, therefore, suggested that, if AtII is involved in neurotransmission, it may be as a neuromodulator.

Erspamer et al. (1981) reported that among several peptides, AtII was the most potent contractant agent in human detrusor muscle. Renin-At systems and the ACE have been demonstrated in several peripheral tissues, including human (van Sande et al., 1985; Dzau, 1988). In vascular smooth muscle and in the heart, these systems have been suggested to have a trophic effect and be involved in the cardiovascular changes associated with hypertension (Dzau, 1988). A similar role in the lower urinary tract has not been established.

In the human detrusor, AtII was a potent and effective contractile agent (Andersson et al., 1992b; Saito et al., 1993a). The onset of action was rapid and the amplitude of contraction similar to that obtained with 124 mM K^+.

This is in contrast to the findings in dog bladder, where the responses to both AtII and AtI were minor or lacking (Steidle et al., 1990), illustrating the wide variation in response to the peptide between species. There was a marked tachyphylaxis to the effects of AtII, which made it difficult to characterize its actions (Andersson et al., 1992b). Notably, the contractile effect was very sensitive to removal of extracellular calcium but less so to calcium antagonists, which suggests that calcium influx may occur through pathways in addition to L-type calcium channels. Also, AtI caused concentration-dependent contractions in the human detrusor, which, like those evoked by AtII, could be blocked by saralasin. This suggests that the actions of both AtI and AtII were mediated through stimulation of AtII receptors. It was, therefore, surprising that the effects of AtI could not be blocked by the ACE inhibitors captopril and enalaprilate (Andersson et al., 1992b). The ability of captopril and enalapril to block the AtI-induced contractions under similar experimental conditions was verified in rabbit mesenteric arteries, where both ACE inhibitors markedly reduced or abolished the responses induced by AtI (Andersson et al., 1992b). In contrast to these findings, Saito et al. (1993a) reported that AtI-induced contractions in the isolated human detrusor were completely blocked by captopril. However, they used only one relatively low (10^{-7} M) concentration of AtI.

ACE is not the sole enzyme able to convert AtI to AtII (Cornish et al., 1979; Oliver and Sciacca, 1984). In dog isolated renal artery without endothelium, the AtI-induced relaxation was not significantly attenuated by ACE inhibition, suggesting that AtII-generating enzyme(s) other than ACE exist in vascular tissue (Okunishi et al., 1984; Okamura et al., 1990). This may be the case also in the human detrusor. Further experiments on isolated membranes from the human detrusor have shown the presence of an enzyme (or enzymes) other than ACE that is able to convert AtI to AtII, most probably a serine proteinase (Lindberg et al., 1993). Such an enzyme (or enzymes) has been demonstrated to convert AtI to AtII in the human heart in the presence of captopril (Urata et al., 1990a,b).

Previous investigations (van Sande et al., 1985) demonstrated the occurrence of ACE in the human bladder. The amounts were low compared to the levels found in other parts of the urogenital tract, e.g., the normal prostate. Notably, very high concentrations were found in the hypertrophic prostate (Yokoyama et al., 1980, 1982; van Sande et al., 1985). Because bladder hypertrophy is common in patients with benign prostatic hyperplasia, it cannot be excluded that the bladder renin-At system may be different from normal in this condition. Further studies on the effects of AtI and AtII on human bladder muscle, as well as on the characteristics of possible AtII-generating enzymes other than ACE, in normal and hypertrophic human bladder seem necessary.

d. PROSTANOIDS. The importance of prostanoids in the regulation of detrusor function has attracted considerable interest, and the topic has been the subject of several reviews (Andersson and Forman, 1978; Andersson and Sjögren, 1982; Pavlakis et al., 1983; Mikhailidis et al., 1987; Maggi, 1992). Prostanoids are known to be generated locally by physiological stimuli such as stretch of the detrusor smooth muscle (Gilmore and Vane, 1971; Ghoneim et al., 1976; Poggesi et al., 1980) but also injuries of the vesical mucosa (Downie and Karmazyn, 1984), nerve stimulation (Khalaf et al., 1979; Alkondon and Ganguly, 1980; Dveksler et al., 1989), and agents such as ATP and mediators of inflammation, e.g., BK (Nakahata et al., 1987; Maggi et al., 1989d), and the chemotactic peptide N-formyl-methionyl-leucyl-phenylalanine (Giuliani et al., 1991) may initiate prostanoid generation.

Both during contraction (Bultitude et al., 1976; Khalaf et al., 1980; Klarskov, 1987c) and under basal conditions (Brown et al., 1980; Poggesi et al., 1980), E-type PGs were found to be synthesized and released by the bladder of various species. That the major prostanoid produced by the rabbit bladder was PGE_2 was confirmed by Leslie et al. (1984). They also showed that the rabbit bladder was capable of releasing PGI_2, $PGF_{2\alpha}$, and TXA_2. In rat bladder, on the other hand, PGI_2 was the principal prostanoid, with smaller amounts of PGE_2 and TXA_2 being produced (Jeremy et al., 1984). Biopsies of human urinary bladder mucosa were demonstrated to release the same prostanoids as the rabbit bladder, but the quantitative order was $PGI_2 > PGE_2 > PGF_{2\alpha} > TXA_2$ (Jeremy et al., 1987). Obviously, there seems to be marked species variation in the spectrum of prostanoids and their relative amounts synthesized and released by the urinary bladder (Larsson, 1980).

Several investigators have shown that $PGF_{2\alpha}$, PGE_1, and PGE_2 contract isolated human, as well as animal, detrusor muscle, whereas $PGF_{2\alpha}$ contracts and PGE_1 and PGE_2 relax or have no effect on the urethra (Ambache and Zar, 1970; Abrams and Feneley, 1976; Persson, 1976; Andersson et al., 1977, 1978b; Khanna et al., 1978; Khalaf et al., 1979; Klarskov et al., 1983a; Maggi et al., 1984a, 1985a, 1988b; Ueda et al., 1985; Gotoh et al., 1986a; Poli et al., 1992a). Misoprostol, a stable PGE_1 derivative, had no effect on human bladder, whereas other derivatives of this PG had contractile effects comparable to those of the parent compound (Poli et al., 1992b). Prostanoids may affect the excitation-contraction coupling in the bladder smooth muscle in two ways: directly by effects on the smooth muscle and/or indirectly via effects on neurotransmission.

The membrane potential of guinea pig and rabbit smooth muscle cells was unchanged by low concentrations of PGE_2 (up to 10^{-6} M), but higher concentrations depolarized the cells and increased the frequency of spontaneous action potentials. It was concluded that

prostanoids are not normally released by the nerves to the guinea pig urinary bladder but are able to facilitate excitation-contraction coupling, possibly by mobilizing Ca^{2+} (Creed and Callahan, 1989). The response of bladder smooth muscle to prostanoids is slow, and it is unlikely that these agents are directly involved in the evacuation of the bladder by exerting direct effects on the bladder smooth muscle (Andersson and Sjögren, 1982). The prostanoids may affect the excitation-contraction coupling in lower urinary tract smooth muscle by indirect effects, leading to a modulation of the efferent and/or afferent neurotransmission. When physostigmine was added to the rabbit bladder, spontaneous contractions and basal tone increased. Because these effects were inhibited by indomethacin, and the inhibition was counteracted by $PGF_{2\alpha}$, it was suggested that there was a connection between the effects mediated by acetylcholine and by prostanoids in the bladder (Bultitude et al., 1976). This suggestion was supported by Borda et al. (1982), who found that, in the human bladder, endogenous prostanoids facilitated the action of acetylcholine through an increase in its concentration, probably by an inhibition of the acetylcholinesterase activity. Johns and Paton (1977) found that contractions elicited by transmural electrical stimulation of rabbit and monkey detrusor were moderately reduced when the preparations were exposed to atropine or indomethacin but that the inhibition was marked when both agents were present simultaneously. The potential NANC transmitter ATP is degraded to ADP, which causes release of prostanoids. In turn, these may contribute to tone, spontaneous contractions, and modulation of excitatory neurotransmission (Choo and Mitchelson, 1977; Dean and Downie, 1978b; Andersson et al., 1980; Husted et al., 1980b,c; Downie and Larsson, 1981; Anderson, 1982; Kasakov and Vlaskovska, 1985).

Available results thus suggest a role for the prostanoids as modulators of efferent neurotransmission.

Capsaicin-sensitive afferents in the bladder are chemosensitive and can be activated by prostanoids to increase the afferent input produced by a given degree of bladder filling. Maggi et al. (1988b) and Maggi (1992) suggested that prostanoids may be the link between detrusor muscle stretch produced by bladder filling and activation of capsaicin-sensitive afferents by bladder distension. Evidence for this was produced in the rat urinary bladder, where intravesical instillation of PGE_2 lowered the threshold for reflex micturition, and topical application of PGE_2 and TXB_2 on the serosal surface activated reflex micturition. Both effects were prevented by systemic capsaicin desensitization. Indomethacin pretreatment and systemic capsaicin increased the micturition threshold without affecting the amplitude of the micturition contraction. Because intravesical PGE_2 did not reduce the residual urine volume in capsaicin-pretreated animals, it was suggested that endogenous prostanoids enhance voiding efficiency through an action, direct or indirect, on sensory nerves (Maggi et al., 1988b; Maggi, 1992).

Prostanoids may also be involved in the pathophysiology of different bladder disorders. As pointed out by Maggi (1992), in cystitis there may be an exaggerated prostanoid production leading to intense activation of sensory nerves, increasing the afferent input. In addition, through the "efferent" function of capsaicin-sensitive bladder afferents, there may be a neurogenic contribution to the overall inflammatory process. Supporting this view, Abelli et al. (1992) found that SP injected intravenously in rats, via stimulation of NK_1 receptors, promoted plasma exudation in the urinary bladder by release of cyclooxygenase metabolites of arachidonic acid. This release may be caused by SP interacting with mast cells and was suggested to amplify the direct effect of SP on the permeability of postcapillary venules.

In view of the evidence for a role of prostanoids in the function of the lower urinary tract, it is not surprising that these agents, and drugs interfering with their synthesis, have been used therapeutically (Andersson, 1988). Bultitude et al. (1976) gave PGE_2 intravesically to women with difficulties in micturition and with various degrees of urinary retention. They found a decrease in the bladder volume at which voiding was initiated, an increase in bladder pressure, and a decrease in residual urine in two-thirds of their patients ($n = 22$). Most interestingly, the effects were reported to last for several months. These results were confirmed in a prospective study by the same group (Desmond et al., 1980). Also, other investigators have found beneficial effects of intravesical prostanoids in, for example, patients with neurogenic bladder dysfunction (Vaidyanathan et al., 1981c) and patients with partial or complete urinary retention after surgery for female stress incontinence (Tammela et al., 1987). However, other investigators have not demonstrated any such effects, either in patients with chronic retention (Delaere et al., 1981) or in postoperative patients (Wagner et al., 1985). Both PGE_2 and sulprostone (a derivative of PGE_2), instilled intravesically, caused a strong urgency sensation, resulting in reduced bladder capacity and bladder instability (Schüssler, 1990).

Thus, the clinical value of prostanoids in the treatment of urinary retention is controversial. If prostanoids are involved in the genesis of bladder hyperactivity, use of inhibitors of their synthesis would be a logical treatment alternative. In the few controlled studies published, both flurbiprofen (Cardozo et al., 1980) and indomethacin (Cardozo and Stanton, 1980) produced symptomatic relief in patients with bladder instability but had little effect on urodynamic parameters, and the incidence of side effects was high.

e. 5-HYDROXYTRYPTAMINE (SEROTONIN). 5-HT has been shown to contract the bladder or isolated bladder smooth muscle from several species (Gyermek, 1962;

Hukovic et al., 1965; Matsumura et al., 1968; Ambache and Zar, 1970; Saum and de Groat, 1973; Creed and Tulloch, 1978; Saxena et al., 1985; Andersson et al., 1987b; Chen, 1990; Cohen, 1990), although its potency seems to vary with the species investigated. 5-HT also potentiates the contractions induced by electrical field stimulation of isolated urinary bladder of mouse and man (Holt et al., 1986; Clean et al., 1989; Hindmarsh et al., 1977). The response to the amine may be caused by direct actions on the smooth muscle cells or by indirect effects on the autonomic innervation of these organs. Saxena et al. (1985) suggested that both actions were implicated in the effects of 5-HT on the cat bladder, but in general, there is evidence in favour of predominating indirect effects.

Cohen (1990) found that, in isolated strips of bladder tissue from dogs, but not rats, 5-HT had potent contractile effects. These effects were mimicked by the 5-HT_2 selective agonist α-methyl serotonin, but not by 8-hydroxy-2-(di-*n*-propylamino)tetraline, acting on 5-HT_{1A} receptors and 2-methyl serotonin acting on 5-HT_3 receptors. Furthermore, the effect of both 5-HT and α-methyl serotonin could be blocked by a selective 5-HT_2 receptor antagonist. Based on her data, Cohen (1990) suggested that the contractions induced by 5-HT in the dog bladder were mediated by 5-HT_2 receptors.

In mouse bladder, the potentiating action of 5-HT has been analysed, and the activation of facilitatory 5-HT_{1B} and 5-HT_2 receptors, located on intrinsic nerves, was demonstrated (Holt et al., 1986; Clean et al., 1989). Hindmarsh et al. (1977) found that the potentiating effect of 5-HT could be demonstrated at very low concentrations and was unaffected by methysergide and morphine.

In the isolated rabbit bladder, Chen (1990) found that the contraction induced by 5-HT was concentrationdependently inhibited by 5-HT_3 receptor antagonists {1-αH-3α-5αH-tropan-3-yl-3,5-dichlorobenzoate, (3-α-tropanyl)^{1}H-indole-3-carboxylic acid ester, N^8-[3-(4-indolyloxy)-2-hydroxypropyl]-N^1-(propidoyl-(*z*)-1.8-diamino-*p*-methane-granisetron, endo-N-(methyl-9-azabicyclo-[3.3.1]-non-3-yl)-1-methyl-indazol-3-carboxamide} but not by 5-HT_1 (metitepine) or 5-HT_2 (methysergide, ketanserin) receptor antagonists. 5-HT_3 receptor blockade had no effect on the electrically induced contraction. Like electrically induced contractions, the responses to 5-HT were also inhibited by α,β-methylene ATP and atropine, and it was suggested that 5-HT, through stimulation of 5-HT_3 receptors, mediated release of ATP and acetylcholine from nerve terminals. This effect was not sensitive to blockade with TTX. There was, however, a residual contractile response to 5-HT that could not be blocked by 5-HT_1, 5-HT_2, or 5-HT_3 receptor antagonists.

In human (Todd and Mack, 1969; Klarskov and Hørby-Petersen, 1986) and pig (Klarskov and Hørby-Petersen, 1986) detrusor tissue, 5-HT produces concentration-dependent contractions. These contractions were partly blocked by ketanserin, methysergide, and cyproheptadine, but the antagonists had no effects on contractions induced by electrical stimulation of nerves (Klarskov and Hørby-Petersen, 1986). Corsi et al. (1991) found that, in the human urinary bladder, 5-HT had two opposite effects on the contractile response to electrical field stimulation. A potentiating effect at low concentrations was due to an interaction with an atypical receptor different from the classical 5-HT_1, 5-HT_2, or 5-HT_3-receptor subtypes. This receptor was probably prejunctional and controlled release of acetylcholine. An inhibitory effect at higher concentrations was probably due to an interaction with 5-HT_1-like receptors.

5-HT-immunoreactive cells can be demonstrated in human urinary tract tissue (Fetissof et al., 1983), but the importance of 5-HT to bladder function in humans is not known. The 5-HT_2 receptor antagonist ketanserin was found to have little effect on bladder function, as judged by urodynamic investigation, but did reduce intraurethral pressure (Hørby-Petersen et al., 1985; Andersson et al., 1987b; Delaere et al., 1987). This was, however, attributed mainly to ketanserin's blocking effect on urethral α-adrenoceptors. In patients with neurogenic bladder dysfunction, administration of clomipramine, which inhibits 5-HT uptake, decreased the intravesical volume where the first detrusor reflex activity was observed and reduced residual urine (Vaidyanathan et al., 1981b). Whether this observation reflects effects exerted by 5-HT can only be speculated on, and the importance of this observation remains to be established.

f. HISTAMINE. Because histamine is a known mediator of allergic and acute inflammatory reactions, and because such reactions may occur in the lower urinary tract, the mechanical actions of the amine on isolated urinary tract smooth muscle have been studied by several investigators. In the rabbit and guinea pig urinary bladder, histamine was suggested to produce contraction through H_1 receptors located on the smooth muscle (Fredericks, 1975; Khanna et al., 1977; Poli et al., 1988). In the rabbit bladder, part of the contraction may be mediated by release of acetylcholine, because the histamine-induced contraction was effectively inhibited by atropine or propantheline (Fredericks, 1975). Kondo et al. (1985) verified the contractant effect of the amine in the guinea pig and characterized, by means of radioligand binding, the H_1 receptor involved in the response. In strips of sheep ureterovesical junction, histamine produced a concentration-dependent contraction through activation of H_1 receptors, with no apparent involvement of H_2 receptors (Benedito et al., 1991). Part of the contraction was possibly mediated via a cholinergic mechanism, because scopolamine had an inhibitory effect on the contractions induced by the amine.

Interestingly, in the guinea pig bladder, histamine was

found to inhibit noncholinergic contraction through stimulation of H_2 receptors (Taniyama et al., 1984). However, these results have not been confirmed (Poli et al., 1988). Instead, it was suggested that prejunctional histamine receptors also are of the H_1 subtype and that there is a heterogeneity in the H_1 receptor population, the prejunctional receptors differing from the postjunctional (Poli et al., 1988).

g. γ-AMINOBUTYRIC ACID. GABA seems to have complex effects on the lower urinary tract. It is a major inhibitory transmitter in the central nervous system, and, as pointed out by Maggi et al. (1987a), there is considerable evidence indicating that GABA can inhibit the reflex-activated bladder motility by acting through at least five distinct sites: at the supraspinal level by inhibiting activation of neurons in the pontine micturition center (Satoh et al., 1978; Sillén et al., 1979), at the spinal level by reducing afferent input from the detrusor or by inhibiting the neurons of the sacral parasympathetic nucleus (de Groat et al., 1981; Maggi et al., 1987a,e), at the pelvic ganglionic level by inhibiting excitatory neurotransmission (de Groat, 1970; Maggi et al., 1985c), and/or at the postganglionic level by reducing neurotransmitter release from neurons innervating the detrusor (Maggi et al., 1985f,g; Taniyama and Tanaka, 1986; Chen et al., 1992).

Evidence has been presented suggesting that GABAergic neurons are present in the vesical ganglia of the guinea pig urinary bladder and that they are involved in the control of bladder motility (Taniyama and Tanaka, 1986; Erdö et al., 1989). GABA and the $GABA_A$-selective agonist muscimol, but not baclofen acting on $GABA_B$ receptors, produced concentration-related phasic contractions of isolated strips from the guinea pig bladder dome (Maggi et al., 1985f). This effect was believed to be produced by a burst release of neurotransmitters from intramural postganglionic elements in the bladder wall, because it was almost abolished by TTX and partially antagonized by atropine. In the urinary bladder from guinea pigs, rabbits, and newborn rats, prejunctional $GABA_B$ receptors were found to reduce the cholinergic component of the postganglionic excitatory neurotransmission to the detrusor muscle (Maggi et al., 1983, 1984b, 1985f,g; Santicioli et al., 1984). In the mouse urinary bladder, GABA inhibited cholinergic, as well as NANC, components of the postganglionic excitatory innervation through stimulation of prejunctional $GABA_B$ receptors (Santicioli et al., 1986) and in the rabbit bladder GABA, acting via $GABA_B$ receptors, inhibited detrusor contraction (Chen et al., 1992). This was attributed, at least partly, to a direct effect on detrusor muscle cells, because both GABA and baclofen inhibited carbachol-induced muscle contractions, and these effects were not inhibited by TTX (Chen et al., 1992). Alternatively, GABA may cause the release of substance(s) inhibiting bladder smooth muscle contraction (Maggi et al., 1985g). On the other hand, $GABA_A$ receptors also were found to be involved in the regulation of motility in the guinea pig isolated bladder through a modulatory effect on both cholinergic and NANC components of the postganglionic excitatory innervation (Taniyama et al., 1983; Kusunoki et al., 1984; Maggi et al., 1985f,g). Thus, GABA was found to inhibit the release of acetylcholine from postganglionic nerve terminals, an effect mimicked by muscimol (Kusunoki et al., 1984). The release of GABA from GABAergic neurons may be enhanced by SP (Shirakawa et al., 1989).

Activation of $GABA_A$ and $GABA_B$ receptors by muscimol and baclofen, respectively, reduced and increased release of CGRP-like immunoreactivity from capsaicin-sensitive afferents in the guinea pig urinary bladder; this indicated an ability of GABA receptors to modulate the efferent function of afferent nerves (Santicioli et al., 1991).

In the normal, unanaesthetized rat, muscimol and baclofen, injected intraarterially near the bladder, had little affect on micturition. Only in high doses, for which central nervous effects of the drug could not be excluded, were inhibitory effects recorded. It was, therefore, concluded that in vivo muscimol and baclofen have insignificant peripheral effects on the lower urinary tract but depress micturition by actions on the central nervous system (Igawa et al., 1993b).

These partly conflicting data make it difficult to assess the importance of peripheral GABA receptors for controlling bladder motility. GABA analogues, probably because of their central nervous system effects, have a potential for treatment of bladder hyperactivity, both in patients with idiopathic detrusor instability (Taylor and Bates, 1979) and in patients with neurogenic voiding disturbances (Kiesswetter and Schober, 1975; Hachen and Krucker, 1977; Florante et al., 1980), particularly when given intrathecally (Nanninga et al., 1989; Steers et al., 1991, 1992).

F. Inhibition of Activation Mechanisms

1. Membrane hyperpolarization—potassium channel openers. Even if the relationship of action potential to contraction is not completely understood, control of membrane excitability may prove useful in the control of bladder contractility. As mentioned previously, the frequency of spontaneous action potentials is voltage sensitive. Therefore, hyperpolarization of the detrusor muscle cell membrane would be a means of decreasing action potential firing and associated contraction. Drugs are available that produce hyperpolarization by the opening of K^+ channels and subsequent efflux of K^+. Examples of such drugs are cromakalim, pinacidil, and nicorandil (Weston and Abbott, 1987; Cook, 1988; Robertson and Steinberg, 1990; Andersson, 1992; Longman and Hamilton, 1992).

Cromakalim reduced the spike frequency in isolated

guinea pig bladder. In high concentrations (10^{-6} to 10^{-5} M), it abolished the spikes, and there was a concentration-dependent hyperpolarization of the cell membrane (Fujii, 1987; Foster et al., 1989a). Spontaneous contractile activity was abolished. Similar effects have been demonstrated with pinacidil (Seki et al., 1992d). Cromakalim opened a K^+ channel having properties similar to those of the delayed rectifier K^+ channel responsible for spike repolarization. This channel is also similar to the ATP-dependent K^+ channels in vascular smooth muscle (Fujii et al., 1990). Supporting such a view, the relaxant effects of several K^+ channel openers in the rat detrusor were antagonized by glibenclamide (Edwards et al., 1991). Grant and Zuzack (1991) also concluded from their results that cromakalim opens ATP-sensitive K^+ channels in the guinea pig detrusor. They found marked stimulatory effects of charybdotoxin and iberiatoxin, which were used as probes for investigation of the large conductance, Ca^{2+}-activated K^+ channels, and concluded that these channels may be involved in the control of basal tension and possibly the membrane potential of detrusor cells.

Studies of isolated human detrusor muscle (Andersson et al., 1988a; Foster et al., 1989b; Fovaeus et al., 1989) and bladder tissue from several animal species (Andersson et al., 1988a; Foster et al., 1989a,b; Malmgren et al., 1990; Edwards et al., 1991; Levin et al., 1992; Soares de Moura et al., 1993) have shown that K^+ channel openers reduce not only spontaneous contractions but also contractions induced by electrical stimulation, carbachol, and low, but not high, external K^+ concentrations. The drugs also increase the outflow of ^{86}Rb or ^{42}K in preloaded tissues, further supporting the view that they relax bladder tissue by K^+ channel opening and subsequent hyperpolarization. The K^+ channel openers were particularly effective in hypertrophic rat bladder muscle in vitro (Malmgren et al., 1990) and effectively suppressed bladder hyperactivity in rats with bladder outflow obstruction (Malmgren et al., 1989). Pinacidil given intravesically significantly reduced bladder "hyperreflexia" induced by penile ligation in anesthetized rabbits (Levin et al. (1992). However, available K^+ channel openers were approximately 8 times more potent as inhibitors of the spontaneous contractions of the rat portal vein than of K^+-induced contractions of the rat detrusor (Edwards et al., 1991).

No effects of pinacidil on the bladder were found in a pilot study of patients with detrusor instability secondary to outflow obstruction caused by benign prostatic hyperplasia (Hedlund et al., 1991). The potential clinical usefulness of presently available K^+ channel openers in states of bladder hyperactivity remains to be established (Andersson, 1992).

2. Inhibition of calcium influx—calcium antagonists. As discussed previously, activation of detrusor muscle, both through cholinergic and NANC pathways, seems to require influx of extracellular Ca^{2+} through dihydropyridine-sensitive Ca^{2+} channels, as well as via mobilization of intracellular Ca^{2+} (Forman et al., 1978; Khanna et al., 1983; Mostwin, 1985, Huddart and Butler, 1986; Batra et al., 1987b; Fovaeus et al., 1987a; Maggi et al., 1988c, 1989c).

There seems to be an age dependence in the sensitivity to extracellular Ca^{2+}. Thus, the ED_{50} for Ca^{2+} was lower in isolated bladder preparations from 1-day- and 1-week-old rabbits than in mature 8-week-old rabbits (Zderic et al., 1991). Similarly, when bladder tissue from young (six months old) and aged (16 and 24 months old) rats were compared, the contractile response to Ca^{2+} was significantly less in preparations from old than from young rats (Saito et al., 1991). It was suggested that this was dependent on a decreased membrane permeability with age. Supporting this view, neonatal bladder showed a much greater sensitivity to diltiazem than did adult bladders (Zderic et al., 1991). It is unclear whether the age-related sensitivity to extracellular Ca^{2+} can be linked to detrusor hyperreflexia with impaired contractility in elderly patients (Resnick and Yalla, 1987; Resnick et al., 1989). If there is an increased Ca^{2+} influx in detrusor hyperreflexia, one would expect changes in, for example, the binding or functional properties of the voltage-dependent Ca^{2+} channels. In bladders from children with myelodysplasia, in whom detrusor hyperreflexia is a common phenomenon, this was not found (Shapiro et al., 1991). Saito et al. (1989) found that the supersensitivity to Ca^{2+}, demonstrated in rabbit bladder after denervation achieved by bilateral sacral rhizotomy, could be effectively inhibited by a Ca^{2+} antagonist, and it was hypothesized that there was a hyperpermeability to Ca^{2+} responsible for this phenomenon. If so, this would be in agreement with the finding of an increased sensitivity to depolarizing stimuli in the hypertrophic rat bladder (Malmgren et al., 1988).

Considering the importance of Ca^{2+} influx for contractile activation, blockade of L-type Ca^{2+} channels seems to be an attractive way of inhibiting bladder contraction. By voltage clamp, nifedipine was shown to decrease $I_{Ca}{}^{2+}$ in guinea pig urinary bladder smooth muscle cells (Kura et al., 1992), which is in line with the finding that, irrespective of the mode of activation, nifedipine inhibited detrusor contraction in isolated human detrusor preparations (Forman et al., 1978). Nifedipine also abolished the NANC-mediated contractile component in rabbit (Andersson et al., 1986b) and rat detrusor (Bo and Burnstock, 1990; Zar et al., 1990), and the atropine-resistant contractile component in hypertrophic human detrusor muscle (Sjögren et al., 1982b).

Several other studies have shown that Ca^{2+} antagonists have potent inhibitory effects on contraction of isolated detrusor muscle from various animal species, including humans (Sjögren and Andersson, 1979; Husted et al., 1980a; Finkbeiner, 1983b; Mostwin, 1985; Yousif et al., 1985, Gotoh et al., 1986b; Hassouna et al., 1986; Batra

et al., 1987b; Fovaues et al., 1987; Maggi et al., 1988c, 1989c; Acevedo and Contreras, 1989; Faustini et al., 1989; Lowe and Noronha-Blob, 1991; Latifpour et al., 1992. They also inhibit bladder contractions under in vivo conditions (Diederichs et al., 1992) and clinically in patients with bladder hyperactivity without and with neurogenic lesions (Rud et al., 1979; Palmer et al., 1981; Faustini et al., 1989).

Using [^{3}H]nitrendipine as a ligand, Yousif et al. (1985) demonstrated high-affinity binding sites in bladder membranes from the guinea pig. They also found that nifedipine and D-600 were noncompetitive inhibitors of detrusor muscle contractions induced by K^+ and muscarinic receptor stimulation. The tonic component of contraction was more sensitive to inhibition than was the phasic. The [^{3}H]nitrendipine binding was sensitive to displacement with other dihydropyridines, paralleling their pharmacological activities. Latifpour et al. (1992) compared the density of binding sites in the rabbit bladder dome, bladder base, and urethra. Their data showed that the density of binding sites for the ligand (+)-[^{3}H]isopropyl-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-methoxy-carbonyl-pyridine-3-carboxylate was significantly higher in the urethra than in the bladder dome. They also found that the contractile responses to carbachol were in parallel with the dihyropyridine receptor densities and concluded that the urethra is functionally more sensitive to dihydropyridine agonists and antagonists than the bladder dome. This conclusion may not be interpreted to mean that urethral function is affected at lower dihydropyridine antagonist concentrations than detrusor function. In sheep urethral smooth muscle, the effect of nifedipine on noradrenaline-induced contraction was not impressive (Garcia-Pascual et al., 1991b), and in humans, nifedipine caused no effect on intraurethral pressure at doses having effects on the bladder (Forman et al., 1978).

Nifedipine belongs to the agents interacting selectively with binding sites on L-type calcium channels (Spedding and Paoletti, 1992). In contrast, terodiline is a nonspecific calcium antagonist which, in addition, has muscarinic receptor-blocking properties (Husted et al., 1980a; Østergaard et al., 1980; Larsson-Backström et al., 1985; Andersson et al., 1988b; Noronha-Blob et al., 1991). This profile of action should be of particular interest for inhibition of bladder contraction, and indeed, terodiline was shown to be clinically effective in the treatment of motor urge incontinence (Andersson, 1988; Langtry and McTavish, 1990). In isolated guinea pig urinary bladder, Kura et al. (1992) demonstrated that terodiline blocked not only the $I_{Ca}{}^{2+}$ but also the Ca^{2+}-independent outward K^+ current. Terodiline reduced the overshoot and maximum upstroke velocity of the action potential by inhibiting $I_{Ca}{}^{2+}$ in a use- or frequency-dependent way. It also prolonged the action potential by inhibition of the outward K^+ current.

The complex interactions of terodiline with Ca^{2+}, K^+, and possibly other ion channels may be responsible for the recently discovered cardiac side effects of the drug; terodiline caused polymorphic ventricular tachycardia (torsade de pointes) in some patients (Connolly et al., 1991; Stewart et al., 1992) and has, therefore, been withdrawn from clinical use.

Several other drugs used for treatment of bladder hyperactivity are thought to have calcium antagonistic properties (Andersson, 1988). A comparison of the calcium antagonist properties of imipramine, oxybutynin, and flavoxate suggested that only imipramine had calcium antagonistic actions (Malkowicz et al., 1987). Whether or not this action of imipramine has any relevance for its effectiveness in the treatment of bladder hyperactivity (Andersson, 1988) is unclear.

G. Effects of Sexual Hormones

1. Estrogen and progesterone. Estrogen receptors have been demonstrated in detrusor muscle from animals (Lindskog et al., 1982; Urner et al., 1983; Weaker et al., 1983) as well as in detrusor and trigonal muscle from humans (Iosif et al., 1981; Saez and Martin, 1981). The effects of estrogen on autonomic nervous control of the urinary bladder have been examined in different studies (Levin et al., 1980b; Ghoneim et al., 1983; Shapiro, 1986; Batra and Andersson, 1989; Elliott et al., 1992a,b). Levin et al. (1980b) found that when immature female rabbits were treated with estrogen (estradiol) a marked increase was induced in the response to stimulation of α-adrenoceptors and muscarinic receptors and to ATP in the bladder body and midbladder but not in the bladder base. There were no changes in the response to isoprenaline or K^+. In the bladder body and midsection, but not the base, there was a significant increase in the number of α-adrenoceptors and muscarinic receptors. Shapiro (1986) reported that treatment of mature female rabbits with estradiol led to a significant decrease in muscarinic receptor density. This observation was confirmed by Batra and Andersson (1989) who also found that the decrease in muscarinic receptor number had little effect on the responses to carbachol and electrical stimulation.

Elliott et al. (1992a) found a decreased sensitivity to acetylcholine, carbachol, and electrical stimulation, but not to K^+, in isolated detrusor tissue from female rats treated with estradiol. Addition of diethylstilbestrol further reduced these responses, an effect previously investigated by the same group and attributed to a reduction of calcium influx into the detrusor cells (Elliott et al., 1992b). In male rats treated with diethylstilbestrol, there was a decrease in the response to electrical stimulation (Ghoneim et al., 1983).

Taken together, these results show that estrogens can modify the responses of the detrusor to autonomic nervous influences. Some of the discrepancies in results may be attributed to differences in experimental approach.

The results also suggest that estrogens may have a role in the treatment of motor urge incontinence, even if their place in therapy is unclear (Miodrag et al., 1988).

Progesterone receptors have been demonstrated in the lower urinary tract of rabbits previously treated with estrogen (Batra and Iosif, 1987). However, their functional importance has not been established, even if it has been suggested that progesterone may enhance the effects of β-adrenoceptor stimulation on the detrusor (Miodrag et al., 1988).

2. Testosterone. A significant increase in the density of muscarinic receptors in bladder tissue was demonstrated in rabbits treated with testosterone (Anderson and Navarro, 1988). There was, however, no change in the maximal response to carbachol, and no change in the EC_{50} value. Testosterone treatment did not affect the density of α- or β-adrenoceptors; it increased the ratio of the bladder to total body weight (Anderson and Navarro, 1988).

3. Pregnancy. Pregnancy may be associated with changes in bladder function (Andriole, 1975). The length-tension curves obtained in bladder strips from pregnant and virgin rabbits did not differ (Levin et al., 1991). In the presence of bethanechol, bladder strips from pregnant rabbits generated 50% less tension in response to calcium than those from nonpregnant rabbits (Zderic et al., 1990). The isolated whole bladder from pregnant animals responded to low-frequency stimulation and to ATP with a greater increase in intravesical pressure than did preparations from virgin rabbits, whereas the response to bethanechol was greater in the virgin rabbits (Levin et al., 1991). Receptor-binding studies in bladder tissue from pregnant animals revealed a significantly reduced muscarinic receptor density (50%), corresponding to the decrease in response to bethanechol of the whole bladder. The results were interpreted to mean that pregnancy induced an increase in the purinergic, and a decrease in the cholinergic, component of the urinary bladder response to field stimulation (Levin et al., 1991).

In the rabbit, there was a decrease in the response to α-adrenoceptor stimulation in the midsegment and base of the bladder from pregnant as compared to virgin animals (Tong et al., 1992b). It was speculated that such an effect would be beneficial, because a relaxation of the outlet region would compensate for a decreased contractile strength of the bladder body.

III. Trigone

The traditional view has been that the superficial trigone is adrenergically innervated, whereas the deep trigone has the same properties as the detrusor muscle (Dixon and Gosling, 1987). There are, however, few investigations of the electrical and mechanical properties of trigonal smooth muscles.

Speakman et al. (1988) dissected muscle strips from the two layers of the human trigone and compared their responses to those of strips from the detrusor. They found that the superficial trigone produced its maximal response to α-adrenoceptor stimulation (phenylephrine) but also produced 40% of maximal response to muscarinic receptor stimulation (carbachol). In the deep trigone, the maximal response was obtained by carbachol, whereas there the response to phenylephrine was about 20%. Detrusor strips responded, as expected, maximally to carbachol but did not contract in response to phenylephrine. Electrical stimulation of superficial trigone preparations revealed three excitatory components, one α-adrenoceptor-mediated (blocked by phentolamine), one muscarinic receptor mediated (blocked by atropine), and one mediated by an NANC mechanism. In addition, a relaxant response to electrical stimulation could be demonstrated in 40% of the strips. This response could not be blocked by propranolol, and it was enhanced by atropine and phentolamine, which suggested that it was NANC mediated. Similar relaxant effects were previously demonstrated in human and pig trigonal muscle (Klarskov et al., 1983b; Hills et al., 1984; Klarskov, 1987a).

In pig trigonal muscle, NADPH diaphorase-positive fibres and thick nerve branches were found in or around the muscular bundles. The nerve fibres were thinner and more dispersed within the trigonal muscle than those of the detrusor (Larsson et al., 1992; Persson et al., 1993). Immunohistochemistry revealed that the density of NOS immunoreactivity was higher in trigonal and urethral tissue than in the detrusor (Persson et al., 1993). In isolated trigonal strips from pigs, precontracted by noradrenaline, carbachol, or ET-1 and relaxed by electrical stimulation, exposure to L-NNA concentration-dependently reduced the relaxant response (Persson and Andersson, 1992). L-NNA abolished all relaxation and unmasked a contractile component; D-NNA had no effect. Maximal relaxation was increased after pretreatment with L-arginine, and the inhibitory effect of L-NNA was prevented. Incubation of the preparations with methylene blue had no effect on relaxations elicited at frequencies <6 Hz, but a small inhibition was observed at higher frequencies. NO induced concentration-dependent relaxations in preparations contracted by noradrenaline, ET-1, or carbachol. These results suggest that NANC-mediated relaxation, involving the L-arginine/NO pathway, can be demonstrated in the pig trigonal smooth muscle. The functional importance of this is, however, unclear.

IV. Bladder Neck and Urethra

A. Anatomy

In the male, the urethra comprises four regions, the preprostatic, the prostatic, the membranous, and the penile urethra. Anatomical details can be found elsewhere (Dixon and Gosling, 1987; Elbadawi, 1987), but it should be stressed that there are disagreements about

the architecture of the proximal urethra and the exact arrangements of the smooth musculature and intrinsic striated muscle or rhabdosphincter, both in males and females. It seems, however, that the proximal sphincter in the male is a sexual sphincter, preventing retrograde ejaculation, and that the sphincter mechanism maintaining continence is confined to the membranous and distal prostatic urethra. In the female, the urethra has sphincteric functions throughout its length.

Many factors have been suggested to contribute to urethral closure (Rud et al., 1980; Torrens, 1987; Delancey, 1990), including urethral smooth muscle tone and the properties of the urethral lamina propria. The relative contribution to intraurethral pressure of the various factors are still a matter of different opinions. For example, Rud et al. (1980) suggested that in humans a vascular factor contributed to approximately one-third of the intraurethral pressure. This was not supported by the experiments of Downie and Lautt (1986), who found that in cats urethral constriction produced by hypogastric nerve stimulation could be produced without any change in urethral vascular resistance. There is ample pharmacological evidence, however, supporting the view that the smooth muscle component has an important role in maintaining intraurethral pressure.

B. Electrophysiology

The resting membrane potential of the smooth muscle of the guinea pig urethra was found to be -42.2 ± 4.0 mV (Callahan and Creed, 1981), and similar values (-40.1 ± 3.1 mV) were found in the rabbit (Ito and Kimoto, 1985). Spontaneous electrical activity was recorded from all regions of the organ (Callahan and Creed, 1981). Excitatory and inhibitory junction potentials have been recorded in the rabbit urethra (Ito and Kimoto, 1985). The excitatory junction potentials were found to have a fast and a slow component. Only the slow component was blocked by atropine; the fast component was partially, but not completely, blocked by guanethidine and phentolamine. The inhibitory junction potentials were not affected by adrenergic or cholinergic antagonists, suggesting that they were generated by stimulation of NANC nerves.

C. Mechanisms of Activation

1. Myogenic activity. Even if spontaneous electrical activity was recorded from all regions of the isolated guinea pig urethra (Callahan and Creed, 1981), spontaneous mechanical contractions were rarely observed. In isolated human urethra, spontaneous motor activity was infrequently seen; when observed, it was irregular and of low amplitude (Mattiasson et al., 1985a; Parlani et al., 1990). The middle part of the pig urethra develops tone spontaneously. This preparation can be relaxed by a high extracellular K^+ concentration, an effect attributed to closing of voltage-sensitive Ca^{2+} channels (Brading and Chen, 1990).

2. Adrenergic mechanisms. a. α-ADRENOCEPTORS. There is evidence that a substantial part of urethral tone, which is an important factor for the maintenance of intraurethral pressure, is mediated through stimulation of α-adrenoceptors in the urethral smooth muscle by released noradrenaline (Persson and Andersson, 1976; Awad and Downie, 1976; Andersson et al., 1978b; Levin and Wein, 1979a; Hassouna et al., 1983; Mattiasson et al., 1984a; Poirier et al., 1988; Azuma et al., 1989; Garcia-Pascual et al., 1991a,b,d). In the rabbit urethra, incubated with [^{3}H]noradrenaline, electrical stimulation of nerves caused a release of ^{3}H which was decreased by noradrenaline and clonidine and increased by rauwolscine. It was also increased by scopolamine and markedly reduced by carbachol (Mattiasson et al., 1984a). In the isolated guinea pig urethra, [^{3}H]noradrenaline secretion was suggested to be regulated by presynaptic α_{2A}-adrenoceptors, which may be coupled to a 4-aminopyridine-sensitive K^+ channel (Alberts, 1992).

Clonidine is known to reduce intraurethral pressure in humans (Nordling et al., 1979). This may be attributed partly to a peripheral effect on adrenergic nerve terminals, leading to decreased noradrenaline release. More probable, however, this effect is exerted on the central nervous system with a resulting decrease in peripheral sympathetic nervous activity. Supporting this view, clonidine produced a decrease in plasma noradrenaline concentration (Nordling et al., 1979). Furthermore, in cats, clonidine was able to depress firing in the hypogastric nerves innervating the bladder, possibly by a spinal site of action (Krier et al., 1979).

α-Adrenoceptor agonists induce bursts of spikes in the guinea pig urethra (Callahan and Creed, 1985) and contract isolated urethral smooth muscle. Radioligand binding and functional studies have demonstrated that there are significant amounts of both α_1- and α_2-adrenoceptors in the rabbit urethra (Larsson, 1983; Andersson et al., 1984a; Ueda et al., 1984; Honda et al., 1985; Tsujimoto et al., 1986; Yablonsky et al., 1986; Kimoto et al., 1987; Morita et al., 1987; Latifpour et al., 1990; Yoshida et al., 1991; Yamaguchi et al., 1993). The density of α-adrenoceptor-binding sites was higher in urethral than in detrusor smooth muscle (Levin and Wein, 1979a,b; Johns, 1983).

Andersson et al. (1984a) showed that the female rabbit urethra contains a preponderance of α_2-adrenoceptors (approximately 25% α_1- and 75% of α_2-adrenoceptors), a finding that has been confirmed by some investigators (Morita et al., 1987; Latifpour et al., 1990) but not by others (Tsujimoto et al., 1986). Interestingly, in the male rabbit urethra, α_1-adrenoceptors seem to predominate (Ueda et al., 1984; Honda et al., 1985; Kimoto et al., 1987; Yamaguchi et al., 1993). Yamaguchi et al. (1993) suggested different functions for the α-adrenoceptor subtypes in the rabbit urethra, α_1-adrenoceptors mediating a fast response dominating in males and α_2-adrenocep-

tors mediating a slow and prolonged response, essential for urinary continence in female rabbits.

Latifpour et al. (1990) determined the α_2-adrenoceptor subtypes in the rabbit urethra and provided evidence for a preponderance of the α_{2A} subtype. In human urethral smooth muscle, both functional studies and receptor-binding studies have shown that the predominating postjunctional α-adrenoceptor subtype is α_1 (Kunisawa et al., 1985; Levin et al., 1988). Levin et al. (1988) found that the distribution of α_1-adrenoceptor subtypes in the human bladder base was approximately 80% α_1 and 20% α_2.

Both α_1- and α_2-adrenoceptors seem to be involved in contractile responses (Yoshida et al., 1991). Contractions mediated by α_1-adrenoceptors were mediated through both α_{1A} and α_{1B} subtypes (Yoshida et al., 1991). Comparing the α-adrenoceptors of young (6 months) and old (4.5 to 5 years) female rabbits, Yoshida et al. (1991) found smaller ED_{50} values for phenylephrine and clonidine but otherwise no age-dependent differences. In the pithed rat, neurally evoked (stimulation of hypogastric spinal outflow) urethral constriction was found to involve mainly postjunctional α_1-adrenoceptors. However, stimulation of extrasynaptic, postjunctional α_2-adrenoceptors by circulating catecholamines may also increase tone in the proximal urethra (Willette et al., 1989, 1990).

In the isolated urethra, the noradrenaline-induced contraction seemed to be dependent on both influx of extracellular calcium and on release of intracellular calcium (Larsson et al., 1984c; Garcia-Pascual et al., 1991b). Calcium influx for contractile activation and refilling of extracellular stores seemed to occur through membrane channels that could only partly be blocked by calcium antagonists. More than one type of potential dependent calcium channel may be operating (García-Pascual et al., 1991d). The contraction mediated by α_2-adrenoceptors in the female rabbit urethra was found to be almost entirely dependent on extracellular calcium, whereas a_1-adrenoceptor-mediated responses were dependent on both intra- and extracellular calcium (Yoshida et al., 1991).

Patients with a parasympathetically decentralized lower urinary tract have been suggested to develop an urethral supersensitivity to α-adrenoceptor agonists (Koyanagi, 1978, 1979; Koyanagi and Tsuji, 1979). This suggestion was based on the finding that patients with lower motor neuron lesions responded to a single dose of an α-adrenoceptor agonist with a greater increase of the maximum urethral pressure than did normal patients. It was further proposed that this could be used as a test for damage of the autonomic innervation of the lower urinary tract. However, Mattiasson et al. (1984b) found that the maximal urethral pressure at rest was significantly lower in patients with parasympathetically decentralized lower urinary tract than in normal persons. Noradrenaline dose-dependently increased the maximal urethral pressure in all subjects. The absolute increase was greater in the patients with parasympathetically decentralized lower urinary tracts, but they had no increased sensitivity to noradrenaline.

b. β-ADRENOCEPTORS. Both α- and β-adrenoceptors can be demonstrated in isolated urethral smooth muscle from animals (Persson and Andersson, 1976; Latifpour et al., 1990) as well as humans (Ek et al., 1977). The density of α-receptor-binding sites was similar to or somewhat greater than the density of β-receptor-binding sites (Levin and Wein, 1979a,b), the ratio being dependent on which binding site for [^{3}H]dihydroergocryptine (high or low affinity) was used for calculation (Johns, 1983). The β-adrenoceptors are probably of the β_2 subtype, as shown by receptor-binding studies using subtype-selective antagonists (Levin et al., 1988; Latifpour et al., 1990).

The functional importance of urethral β-adrenoceptors has not been established, but they are potential targets for therapeutic interventions. Thus, in humans, selective β-adrenoceptor agonists have been shown to reduce intraurethral pressure (Laval and Lutzeyer, 1978; Rao et al., 1981; Vaidyanathan et al., 1980; Bapna et al., 1981; Thind et al., 1993). β-Adrenoceptor blockers, on the other hand, have not been shown to influence intraurethral pressure acutely (Donker and van der Sluis, 1976; Whitfield et al., 1976; Thind et al., 1993), and although it can be expected that β-adrenoceptor blockade would increase the α-adrenoceptor-mediated effects of noradrenaline on the urethra, this has not been shown to be an effective therapeutic principle in women with stress urinary incontinence (for review, see Andersson, 1988).

3. Cholinergic mechanisms. The number of muscarinic receptor binding sites in the rabbit urethra was lower than in the bladder (Johns, 1983). Muscarinic receptor agonists contract isolated urethral smooth muscle from several species, including humans, but these responses seem to be mediated mainly by the longitudinal muscle layer (Nergårdh and Boréus, 1972; Persson and Andersson, 1976; Hassouna et al., 1983; Mattiasson et al., 1990; Hashimoto et al., 1992). Resistance to flow in the urethra was only increased by high concentrations of acetylcholine (Persson and Andersson, 1976; Andersson et al., 1978b). In humans, tolerable doses of bethanechol (Ek et al., 1978) and emepronium (Ulmsten and Andersson, 1977) had little effect on intraurethral pressure.

Prejunctional muscarinic receptors may influence the release of both noradrenaline and acetylcholine in the bladder neck/urethra. In urethral tissue from both rabbits and humans, carbachol decreased and scopolamine increased concentration-dependently the release of [^{3}H] noradrenaline from adrenergic, and of [^{3}H]choline from cholinergic, nerve terminals (Mattiasson et al., 1988).

4. Nonadrenergic, noncholinergic mechanisms. The normal pattern of voiding in humans is characterized by an initial decrease in urethral pressure followed 5 to 15

seconds later by an increase in intravesical pressure (Tanagho and Miller, 1970; Asmussen and Ulmsten, 1976; Low, 1977; McGuire, 1978; Rud et al., 1978; Low et al., 1989). The mechanism of this relaxant effect has not been established. One possibility is that the decrease in intraurethral pressure is caused by stimulation of muscarinic receptors on noradrenergic nerves, diminishing noradrenaline release and, thereby, tone in the proximal urethra (Mattiasson et al., 1987a). Another possibility is that an NANC mechanism mediates this response (Andersson et al., 1983b; Klarskov et al., 1983b; Hills et al., 1984; Klarskov, 1987b; Ito and Kimoto, 1985).

Slack and Downie (1983) analysed the mechanical responses of the cat urethra to autonomic nerve stimulation and to intraarterial acetylcholine injection. Sacral ventral root stimulation produced an atropine-sensitive constriction when basal urethral resistance was low but dilation when resistance was high. The latter response was reduced, but not abolished, by atropine. When urethral constriction had been produced by phenylephrine, injection of acetylcholine produced a consistent decrease in urethral resistance, which was not reduced by atropine. It was suggested that parasympathetic dilation of the urethra may be mediated by an unknown NANC transmitter released from postganglionic neurons.

a. NITRIC OXIDE. NADPH diaphorase-positive fibres were found in or around the muscular bundles of the pig urethra and were frequently seen around arteries but not veins (Larsson et al., 1992; Persson et al., 1993). In the female rabbit lamina propria, numerous NADPH diaphorase-positive, fine varicose nerve fibres were demonstrated around arteries and in and around smooth muscle fibres. There was also staining of nerves in the connective tissue and staining of the endothelium of small arteries. The urothelium stained intensively (Zygmunt et al., 1993). NOS-positive nerves were demonstrated with immunohistochemistry in the bladder neck and membranous urethra of rats (Burnett et al., 1992) and in the pig urethra (Persson et al., 1993). There was no NOS staining of the urothelium, which contrasts to the results with NADPH diaphorase. In the rat urethra, high NOS activity was found, as revealed by the ability of urethral tissue to convert [^{3}H]arginine to [^{3}H]citrulline (Burnett et al., 1992).

Andersson et al. (1991b, 1992a) demonstrated that the NANC nerve-mediated relaxation induced in the isolated female rabbit urethra, contracted by noradrenaline, ET-1, AVP, or electrical stimulation, could be inhibited concentration-dependently by L-NNA. D-NNA had no effect. Maximal relaxation was increased after pretreatment with L-arginine, and the inhibitory effect of L-NNA was counteracted. NO also induced concentration-dependent relaxations in preparations contracted by noradrenaline or carbachol. These results were confirmed by Dokita et al. (1991), who also showed that a selective cGMP-phosphodiesterase inhibitor potentiated, and methylene blue reduced, the relaxation.

Nerve-induced relaxation of the rabbit urethra increases the smooth muscle content of cGMP. Inhibition of NOS by L-NNA prevented both the urethral relaxation and the increase in cGMP content. Furthermore, in the presence of the cGMP phosphodiesterase inhibitor, zaprinast, the increase in cGMP level was more pronounced (Persson and Andersson, 1993). Thus, it seems that cGMP has a role as a second messenger in the rabbit urethra and that this system is activated during NANC nerve-mediated relaxation.

The involvement of the L-arginine/NO pathway in relaxation of isolated urethral and bladder neck smooth muscle has now been demonstrated by several investigators in various species, including sheep (Garcia-Pascual et al., 1991c; Thornbury et al., 1992), rat (Persson et al., 1992), pig (Persson et al., 1991b; Persson and Andersson, 1992), dog (Hashimoto et al., 1993), and humans (Andersson et al., 1992a). Hashimoto et al. (1992) demonstrated in the dog that the relaxation response to electrical stimulation had more than one peak and suggested that more than one relaxing component was involved. The first, transient component of relaxation could be inhibited by L-NNA but not the second, slow component (Hashimoto et al. (1993).

These results suggest that NANC-mediated relaxation, involving the L-arginine/NO pathway, can be demonstrated in bladder neck/urethral smooth muscle, but they do not exclude that other NANC transmitters can be involved.

Hindmarsh et al. (1983) suggested that the origin of detrusor instability was to be found in the urethra, and Chalfin and Bradley (1982) showed that, by local anesthesia of the hyperplastic prostate, detrusor instability in patients was inhibited. Persson et al. (1991c, 1992) showed that, in the unanesthetized rat, inhibition of the L-arginine/NO pathway led to bladder hyperactivity and decreased bladder capacity. They suggested that continuous activity in this pathway is one of the factors keeping the bladder relaxed during filling. Because the NANC-mediated relaxant response to electrical stimulation was found in the trigone and the urethra of several species, but not in the detrusor muscle, this may reflect the localization of such activity and lends support to the view that bladder hyperactivity (unstable detrusor contractions) may be initiated from the bladder outlet.

Isolated preparations of the rabbit urethral lamina propria, contracted by noradrenaline, produce frequency-dependent, NANC relaxations in response to electrical field stimulation and to acetylcholine (Mattiasson et al., 1985b; Zygmunt et al., 1993). It was shown (Zygmunt et al., 1993) that electrically induced relaxations were possible to evoke even in preparations in which acetylcholine-induced relaxation was poor or absent. Pretreatment with L-NNA reduced the maximum relaxation obtained

at 30 Hz to 12% of the control response. D-NNA had no effect. The effects of L-NNA were antagonized by addition of L-arginine. Acetylcholine relaxed noradrenaline-precontracted strips by 36%; VIP reduced the contraction by 95%. L-NNA, but not D-NNA, abolished and reversed acetylcholine-induced relaxations but failed to reduce the relaxations produced by VIP. The NO donor, SIN-1, relaxed lamina propria preparations contracted by noradrenaline in a concentration-dependent way. This effect was not influenced by L-NNA (Zygmunt et al., 1993).

The results show that, in the rabbit urethral lamina propria, both nerve- and acetylcholine-induced relaxations sensitive to inhibition of the L-arginine/NO pathway can be produced but do not exclude the occurrence of other relaxation-mediating factors.

b. NEUROPEPTIDES. Abelli et al. (1991) produced mechanical irritation by a catheter inserted into the urethral meatus of urethane-anesthetized rats and measured the result as microvascular permeability changes. The increase in permeability produced could be reduced by previous pretreatment with capsaicin, and when combined with pelvic ganglionectomy, it was virtually abolished. It was suggested that the increase in vascular permeability produced by mechanical irritation was nerve mediated and that both capsaicin-sensitive afferents and capsaicin-insensitive nerves passing through the pelvic ganglia contributed to the response. Neuropeptides have also been suggested to be involved in both contraction and relaxation of urethral smooth muscle.

i. Vasoactive intestinal polypeptide. One of the agents suggested to be the relaxation-producing NANC transmitter in urethral smooth muscle is VIP (Andersson et al., 1983b; Klarskov et al., 1983b). Larsen et al. (1981) reported that the peptide had inhibitory effects on isolated feline urethra contracted by noradrenaline. Such a relaxant effect on isolated cat urethra could not be confirmed by Abdel-Hakim et al. (1983). A relaxant effect of the peptide on pig trigone, bladder neck, and urethra was reported by Klarskov et al. (1984). Sjögren et al. (1985) showed that VIP had a marked inhibitory effect on isolated female rabbit urethra contracted by noradrenaline or electrical stimulation of nerves. No effect was found on noradrenaline release. In human urethral smooth muscle, relaxant responses were less consistent, but a modulatory role in neurotransmission could not be excluded (Sjögren et al., 1985). Infusion of VIP in amounts that caused circulatory side effects had no effects on urethral resistance (Klarskov et al., 1987). Plasma concentrations of VIP were obtained that in other clinical investigations had been sufficient to cause relaxation of the lower esophageal sphincter and to depress uterine contractions (Klarskov et al., 1987). Therefore, the physiological importance of VIP on the lower urinary tract in humans was questioned (Klarskov et al., 1987).

ii. Tachykinins. Tachykinins produced powerful contractions of isolated rat, guinea pig, and human urethral smooth muscle (Maggi et al., 1988d; Parlani et al., 1990; Maggi and Patacchini, 1992). The contractile effects were not influenced by TTX, favouring the view that the receptors for the peptides are localized on the urethral smooth muscle cells. In rat proximal urethra, both NK_1 and NK_2 receptors seem to be present (Maggi et al., 1988d). In human urethral tissue the rank order of potency was found to be NKA > NKB >> SP, suggesting that NK_2 receptors are the dominating species. This was supported by results obtained with receptor-selective synthetic peptide agonists (Parlani et al., 1990). On the other hand, in guinea pig isolated proximal urethra, NK_1 receptors were found to be the main, if not the only, mediator of tachykinin-mediated responses (Maggi and Patacchini, 1992), illustrating differences between species. Capsaicin-induced contractions were inhibited by a selective NK_1 receptor antagonist.

It may be speculated that tachykinins, locally released by chemical or mechanical irritation of the primary sensory afferent nerves, may have a role in the genesis of abnormal urethral contractions (urethral instability) seen in humans (Maggi and Patacchini, 1992). However, it should be stressed that the role, if any, for tachykinins in urethral function remains to be established.

iii. Neuropeptide Y. In the isolated female rabbit urethra, NPY reduced the electrically induced contraction of the longitudinal muscle, probably by selectively inhibiting the release of acetylcholine. It had no effect on circular muscle preparations. In the rabbit urethra, the peptide did not appear to have any significant postjunctional effects or to interfere with the release or effects of noradrenaline or NANC transmitters (Sjögren et al., 1988). However, in the spirally cut rat urethra, Zoubek et al. (1993) found that NPY exhibited a nearly maximal inhibition (90 to 100%) of electrically induced contractions over a broad range of stimulus frequencies (1 to 20 Hz). This finding suggests that NPY, at least in some species, may affect also the release of noradrenaline in the urethra.

iv. Endothelins. Garcia-Pascual et al. (1990) showed that, in isolated urethral smooth muscle, ET-1 caused concentration-related, slowly developing contractions. There was a marked tachyphylaxis to the effects of the peptide. The ET-1-induced contractions were not significantly affected by phentolamine or indomethacin, suggesting that they were produced by a direct effect on the smooth muscle cells. Incubation for 30 minutes in a Ca^{2+}-free solution abolished the ET-1-induced contractions, but nifedipine had no effect. In the presence of ET-1, Ca^{2+}-induced contractions were not significantly blocked by nifedipine. ET-1 stimulated phosphoinositide hydrolysis in the rabbit urethra. The formation of inositol phosphates was dependent on extracellular Ca^{2+}. The

Ca^{2+} entry pathway used was Ni^{+} sensitive and nifedipine resistant (Garcia-Pascual et al., 1993).

Pretreatment with ET-1 produced a significant increase in the contractions induced by electrical stimulation but had no significant effect on contractions induced by exogenous noradrenaline. ET-1 did not affect spontaneous or stimulation-induced efflux of [^{3}H]noradrenaline (Garcia-Pascual et al., 1990).

^{125}I-ET-1-binding sites in the urethra were found mainly in the outer longitudinal muscle layer, in vessels, and in the submucosa. The highest density of binding sites appeared to be in vessels and the outer muscle layer (Garcia-Pascual et al., 1990).

The functional significance of the ET-1 actions on the urethra are not known. It may be speculated that, if the effects on mechanical activity are of any importance, it may be in long-term regulation of smooth muscle tone.

c. PROSTANOIDS. Persson (1976) showed that PGE_1 and PGE_2 decreased, but $PGF_{2\alpha}$ increased, the perfusion pressure in the isolated, perfused cat urethra. This was also found in the isolated, perfused human fetal urethra (Andersson et al., 1978b). Strips of human urethral smooth muscle were contracted by $PGF_{2\alpha}$ but not by PGE_1 and PGE_2. However, preparations contracted by noradrenaline, adrenaline, or $PGF_{2\alpha}$ were effectively relaxed by by PGE_1 and PGE_2. The relaxation was not affected by TTX, propranolol, phenoxybenzamine ($PGF_{2\alpha}$-contracted preparations), or atropine (Andersson et al., 1977). In dogs, PGE_2 produced a reduction of intraurethral pressure (Ghoneim et al., 1976; Khalaf et al., 1981). Such an effect was also demonstrated in female patients receiving PGE_2 intravesically or intraurethrally; a decrease in the maximum urethral pressure and a reduction of the closure pressure were found (Andersson et al., 1978a). In rabbit urethral preparations at resting tension, $PGF_{2\alpha}$, but not PGE_2, caused contraction (Khanna et al., 1978); PGI_2, in high concentrations ($>10^{-6}$ M), also had a weak contractile effect (Gotoh et al., 1986a).

Even if the dual direct effects of PGE_2 on bladder and urethral smooth muscle may seem appropriate for bladder emptying, the importance of prostanoids for urethral function have not been clarified. Because the bladder, trigone, and urethra form a functional unit, it may be that the function of prostanoids in these structures is the same and primarily involves local modulation of afferent nerve activity.

d. 5-HYDROXYTRYPTAMINE (SEROTONIN). In search of transmitter candidates mediating the NANC relaxation of bladder neck and urethra, Hills et al. (1984) found that, in the isolated pig bladder neck preparation, 5-HT produced concentration-dependent relaxations. The effect was antagonized by methysergide, but the relaxant response to electrical nerve stimulation was not. In the rabbit trigonal and urethral muscle strips, 5-HT produced a concentration-dependent contraction (Chen, 1990). Although no detailed data for the urethra were presented, it was concluded that, like in the bladder, the 5-HT_3 receptor was involved in the mediation of the response.

D. Effects of Sexual Hormones

1. Estrogen and progesterone. The urethra, as well as the detrusor, seems to be a target for estrogen action, and estrogen receptors have been demonstrated in urethral smooth muscle from animals and humans (Iosif et al., 1981; Lindskog et al., 1982; Batra and Iosif, 1983, 1992). After 1 week of estrogen treatment, there was a 5-fold increase in urethral weight and a simultaneous increase in peroxidase activity. There was also a significant decrease in both cytosolic and nuclear estrogen receptor content.

Treatment with estrogens per se was claimed to increase the intraurethral pressure in women (Faber and Heidenreich, 1977). This finding was confirmed, but even after high doses, it was small, and its clinical significance may be questioned. There seemed to be no effect on intraurethral pressure during long-term treatment (Iosif, 1992). The transmission of intraabdominal pressure to the urethra increased (Rud, 1980; Iosif, 1992), an effect considered of importance. An improved urethral sphincter mechanism was also demonstrated after estrogen treatment of the castrated female baboon (Bump and Friedman, 1986).

The positive effects on the urethra may not only be related to actions on the urethral smooth musculature but also to changes in the urethral mucosa and the vasculature and connective tissue of the lamina propria. Thus, Batra et al. (1986) found that estrogens increased blood perfusion to the urethra of oophorectomized female rabbits. Estrogen treatment may also increase the effect of α-adrenoceptor stimulation both experimentally (Hodgson et al., 1978; Larsson et al., 1984a; Callahan and Creed, 1985), and clinically (Andersson, 1988; Miodrag et al., 1988). Thus, Schreiter et al. (1976) showed in a preliminary investigation in humans that the urethral pressure response to phenylephrine increased after estradiol treatment, a finding confirmed by Beisland et al. (1981). In the rabbit urethra, there was a 3-fold shift to the right of the concentration-response curve for noradrenaline and a more than 2-fold increase of the α-adrenoceptor number (Larsson et al., 1984a).

Progesterone receptors also have been demonstrated in the human urethra (Batra and Iosif, 1987). However, treatment with gestagens seemed to have no affect on urethral pressure parameters (Rud, 1980).

V. Penile Erectile Tissues

Decreased penile vascular resistance with resultant increased penile blood flow is considered a primary hemodynamic event in penile erection. This has focused attention not only on the penile vasculature but also highlighted the central role of corporeal smooth muscle

in the erection process (Adaikan and Karim, 1981; Hedlund and Andersson, 1985a; Andersson et al., 1987a; Saenz de Tejada et al., 1988, 1989c; Krane et al., 1989; Andersson and Holmquist, 1990; Adaikan et al., 1991). The therapeutic success of intracorporeal pharmacotherapy in the treatment of erectile dysfunction (for review, see Juenemann and Alken, 1989) has further underlined this role.

Specimens of corpus cavernosum, corpus spongiosum, helicine arteries, deep penile artery and vein, and circumflex veins have been used in several laboratories to study neurotransmission and the effect of drugs in isolated penile erectile tissues and vasculature (Adaikan and Karim, 1981; Andersson et al., 1983a; Fontaine et al., 1987; Kirkeby et al., 1989a; Saenz de Tejada et al., 1988; Christ et al., 1989; Pickard et al., 1991; Rajfer et al., 1992). One must keep in mind, however, that each of these tissues only gives a piece of information concerning the complex process of penile erection and that in vitro results must be interpreted with caution in terms of physiological and clinical implications.

The restricted availability of human penile erectile tissues is a disadvantage and has led to the use of isolated rabbit cavernosal tissue both as a screening model and for detailed analysis of mechanisms previously demonstrated to exist also in human tissue (Holmquist et al., 1990a,b, 1992a; Broderick et al., 1991). Similar information may be obtained by use of tissues from rat (Dail et al., 1987) and dog (Carati et al., 1985; Kimoto and Ito, 1987) and probably several other species.

A. Anatomy

Details of the innervation and morphology of the human penis can be found in recent reviews (Steers, 1990; Lincoln et al., 1991; de Groat and Booth, 1992; Lue, 1992), and below only a few aspects will be discussed.

The penis consists of three corpora, the paired, dorsally placed corpora cavernosa, and the ventral corpus spongiosum, which surrounds the urethra and forms the glans penis distally. The corpora cavernosa are surrounded by a thick fibrous sheath, the tunica albuginea, and share a perforated septum that allows them to function as a single unit. The tunica albuginea consists of bundles of collagen and elastin fibres and is much thinner around the corpus spongiosum than around the corpora cavernosa.

Cavernosal tissue is sponge-like and composed of a meshwork of interconnected sinusoidal spaces, which are lined by vascular endothelium and separated by trabeculae, containing bundles of smooth muscle in a framework of collagen, elastin, and fibroblasts (Goldstein and Padma-Nathan, 1990). The smooth muscle cells of the corpus cavernosum are connected by gap junctions, which may play an important role during activation of the tissue (Christ et al., 1991a, 1992a; Moreno et al., 1993). A gap junction protein (connexin 43) has been identified between the smooth muscle cells of the human corpus cavernosum (Campos de Carvalho et al., 1993).

The penis is supplied by the terminal branches of the penile artery, which on each side consist of the bulbourethral, dorsal, and cavernous arteries. The cavernous artery (deep penile artery) penetrates the tunica albuginea and gives off the terminal helicine arteries. These are multiple muscular and corkscrew-shaped arteries (150 to 350 μm in diameter), which open directly into the sinusoidal spaces, and act like resistance arteries. Banya et al. (1989) suggested two circulatory routes in the human corpora. One goes from the cavernous artery to capillary networks collected into the venular plexus just beneath the tunica albuginea and is believed to serve as a main circulatory pathway during the flaccid state with the capillaries functioning as nutritional vessels. The other route is through anastomoses from the cavernous artery, via the helicine arteries to the sinusoids, which are then emptied into the postcavernous venules. The postcavernous venules coalesce to form larger emissary veins that pierce the tunica albuginea at an oblique angle. The venous drainage from the pendulous penis is primarily through the deep dorsal vein.

B. Mechanism of Erection

Erection results from a complex interplay between central nervous and local factors; this interaction has been reviewed elsewhere (Lue and Tanagho, 1987; de Groat and Steers, 1988; Krane et al., 1989; Steers, 1990; Brindley, 1991; de Groat and Booth, 1992; Lue, 1992). When the penis is in the flaccid state, there is a dominant sympathetic influence, and the terminal arterioles and sinusoidal smooth muscles are contracted. There is a minimal amount of blood flowing through the sinusoidal spaces and a free outflow of blood from the subtunical venules to the emissary veins. Following sexual stimulation, parasympathetic nervous activity dominates, and the peripheral resistance decreases because of dilation of the cavernosal and helicine arteries. The blood flow into the corpora cavernosa increases without any change in the systemic blood pressure. Relaxation of the trabecular smooth muscle markedly increases the compliance of the sinusoids, causing penile engorgement and erection. The relaxed trabecular muscle will expand and compress the plexus of subtunical venules against the tunica albuginea, reducing venous outflow (the veno-occlusive mechanism) and increasing intracavernous pressure to about 10 to 20 mm Hg below the systolic blood pressure. In a rabbit model, the increase in outflow resistance was estimated to be 100-fold (Saenz de Tejada et al., 1991b).

Detumescence results when the activity in the parasympathetic system decreases and that of the sympathetic nervous system again increases, leading to increased tone in the helicine arteries and contraction of the trabecular smooth muscle. When arterial inflow decreases, the volume of the sinusoids is reduced, the veno-

occlusive mechanism becomes inactivated, and the penis returns to the flaccid state.

C. Electrophysiology

Little information is available concerning electrophysiological characteristics of corporeal smooth muscle cells. It has been suggested that, despite a relatively sparse neuronal innervation, the electrical activity of the human corpus cavernosum in vivo, as revealed by electromyographic studies, is well synchronized (Christ et al., 1992a). Because no action potentials could be detected by electrophysiological investigation of cultured smooth muscle cells from the human corpus cavernosum (Christ et al., 1992c), there may be an important role for a mechanism by which local neural and hormonal stimulation can be rapidly propagated. Some information regarding cultured corporeal smooth muscle cells is available in this respect. Such cells are well coupled with respect to intercellular diffusion of current-carrying ions and of second messengers, such as Ca^{2+} and, maybe, D-myo-inositol 1,4,5-trisphosphate (Christ et al., 1992a).

According to a preliminary report, the resting potential of cultured corporeal smooth muscle cells was found to be 43 ± 4.9 mV (Christ et al., 1992c). Voltage clamp analysis of smooth muscle cells indicated the presence of a Ca^{2+}-sensitive K^+ channel. Single-channel analysis suggested the presence of at least two K^+ channels, a large, predominant maxi-K^+ channel and a smaller, less frequently observed delayed rectifier. Additionally, a presumed chloride channel was demonstrated.

It is obvious that further characterization of the ion channels in corpus cavernosum smooth muscle would be of great interest.

D. Mechanisms of Activation

1. Myogenic activity. When mounted in organ baths, strip preparations of human corpus cavernosum may exhibit spontaneous contractile activity. This is not found in all preparations, and figures of its occurrence vary between approximately a few percent and 100% (Andersson et al., 1983a; Hedlund and Andersson, 1985a; Holmquist et al., 1990a,c; Christ et al., 1990; Kimoto et al., 1990). The variation is most probably due to differences in the experimental approaches and handling of the preparations. The spontaneous activity is not affected by TTX, atropine, or phentolamine, suggesting a myogenic origin. Supporting such a view, removal of extracellular calcium, and addition of calcium antagonists and the K^+-channel opener pinacidil, can abolish this activity (Fovaeus et al., 1987b; Holmquist et al., 1990c). Adaikan (1979) showed that inhibitors of PG synthesis reduced spontaneous activity and decreased resting tone. Christ et al. (1990) confirmed that the spontaneous activity was markedly attenuated by such drugs and suggested that the spontaneous oscillations in tension, at least partly, resulted from the generation and/or presence of a stable cyclooxygenase product.

The physiological significance of spontaneous contractile activity is unknown, but it cannot be excluded that myogenic activity, with or without reinforcement of locally generated PGs, may contribute to the maintenance of tone of cavernous tissue and to the mechanisms maintaining detumescence.

2. Adrenergic mechanisms. Several studies have demonstrated the presence of adrenergic nerves in the cavernosal and helicine arteries as well as in the trabecular smooth muscle (Shirai et al., 1972; Benson et al., 1980; McConnell and Benson, 1982; Gu et al., 1983a). It is generally accepted that, in the detumescent state, penile smooth muscle is kept contracted mainly by release of noradrenaline acting on postjunctional α-adrenoceptors on the cavernous and helicine arteries and on trabecular smooth muscle. The release of noradrenaline seems to be modulated via presynaptic α_2-adrenoceptors (Hedlund et al., 1984; Molderings et al., 1989). Even if contributions of myogenic activity and other contractant factors (e.g., prostanoids, ETs) cannot be excluded, modulation of the adrenergic activity seems to be one of the most important means by which the contractile state of the smooth muscle of the corpus cavernosum and the penile vasculature is influenced.

a. α-ADRENOCEPTORS. It has been shown by several investigators that, in isolated human corpus cavernosum and spongiosum preparations, and in penile arteries and veins, noradrenaline and phenylephrine produce concentration-dependent contractions (Benson et al., 1980; Adaikan and Karim, 1981; Andersson et al., 1983a; Hedlund and Andersson; 1985a; Imagawa et al., 1991; Kimura et al., 1989; Kirkeby et al., 1989a,b; Saenz de Tejada et al., 1989c; Christ et al., 1990, 1991b, 1992b). Several investigators have addressed the question of which α-adrenoceptor subtype mediates the effect in the cavernosal tissue and the penile vasculature. Both phenylephrine, which is selective for α_1-adrenoceptors, and clonidine, which has a preference for α_2-adrenoceptors, contract trabecular tissue. However, clonidine was less potent and had less intrinsic activity than did phenylephrine and noradrenaline (Hedlund and Andersson, 1985a; Kimura et al., 1989; Christ et al., 1990).

In segments of the cavernosal artery, on the other hand, clonidine was the more potent contractile agent (Hedlund and Andersson, 1985a). The α_1-adrenoceptor blocker prazosin, but not rauwolscine and yohimbine which are selective for α_2-adrenoceptors, effectively relaxed noradrenaline-contracted trabecular tissue and inhibited contractions produced by the amine (Hedlund and Andersson, 1985a; Christ et al., 1990). In cavernosal artery segments, prazosin and rauwolscine were about equieffective for relaxation of noradrenaline-induced contractions (Hedlund and Andersson, 1985a). Prazosin was more potent than rauwolscine in inhibiting contractions evoked by electrical stimulation of nerves in trabecular tissue (Hedlund and Andersson, 1985a; Saenz de

Tejada et al., 1989c), but in arterial segments rauwolscine was more potent than prazosin (Hedlund and Andersson, 1985a). There is limited information about the reactivity of the helicine arteries, but they respond to electrical stimulation with contractions that can be blocked by guanethidine; they contract concentration dependently in response to exogenous noradrenaline (Saenz de Tejada, 1992).

These findings suggest that in the human cavernous tissue α_1-adrenoceptors, and in the cavernosal artery, α_2-adrenoceptors, predominate (Hedlund and Andersson, 1985a; Kimura et al., 1989; Saenz de Tejada et al., 1989c; Christ et al., 1990). Also, in circumflex veins (Kirkeby et al., 1989a) and in the deep dorsal penile vein (Fontaine et al., 1987), both α_1- and α_2-adrenoceptor functions can be demonstrated, with a certain predominance of α_1-adrenoceptors in the latter vessel. Both α_{1A}- and α_{1B}-adrenoceptor subtypes seemed to be present in porcine cavernosal smooth muscle (Wagner and Wei, 1992). In human corporeal tissue, three subtypes of α_1-adrenergic receptor in mRNA (α_{1B}, α_{1B}, α_{1C}) were identified. The α_{1A} and α_{1C} receptors were the predomoninant subtypes expressed in this tissue at an mRNA level (Price et al., 1993).

Intracavernosal injection of α-adrenoceptor-active drugs have confirmed the results obtained in vitro. Thus, injection of α-adrenoceptor blockers (phenoxybenzamine, phentolamine, thymoxamine) produced tumescence and erection (Brindley, 1983a,b, 1986; Blum et al., 1985; Buvat et al., 1989), and α-adrenoceptor agonists (metaraminol, noradrenaline) caused detumescence (Brindley, 1984; De Meyer and De Sy, 1986). Brindley (1986) found that intracavernosal injection of the selective a α_2-adrenoceptor blocker, idazoxan, had no affect, supporting the view that the α_1-adrenoceptor is the functionally dominant subtype.

Drugs, such as trazodone and ketanserin have been reported to influence, at least partly, penile erectile tissues by blockade of α-adrenoceptors. Trazodone, a nontricyclic antidepressant, which was reported to cause priapism during treatment for depressive disorders (Andersson et al., 1991d), was shown to have marked α-adrenoceptor-blocking properties (Abber et al., 1987; Azadzoi et al., 1990). Ketanserin, a selective 5-HT receptor blocker, which also blocks α-adrenoceptors in human corpus cavernosum tissue, produced erection following intracavernous injection in man (Adaikan et al., 1991).

In some cases, impotence can be secondary to changes in α-adrenoceptor function. Christ et al. (1990) found, in some age groups, a small but significant difference between cavernous tissue obtained from diabetic and nondiabetic patients with impotence, the diabetic patients having both increased and reduced sensitivity to phenylephrine. In contrast, Creed et al. (1989) found no differences in sensitivity to phenylephrine between cavernous tissue preparations taken from impotent men with diabetes, alcoholism, or Peyronie's disease and men with no obvious condition causing the impotence. Kirkeby et al. (1989a) found no difference in the α-adrenoceptor function of isolated penile circumflex veins between potent and impotent men (venous leakage). In a study of the kinetics of α_1-adrenoceptor-mediated contractions at steady state, Christ et al. (1992b) found age- and pathology-dependent alterations that could result in heightened corporeal tissue tone and may contribute to the pathophysiology of erectile dysfunction in some patients. Whether or not such extrapolations from the in vitro situation really can be made remain to be demonstrated.

b. β-ADRENOCEPTORS. In human penile tissue, the density of β-adrenoceptors was found to be only one-tenth of the density of α-adrenoceptors (Levin and Wein, 1980). Nevertheless, both isoprenaline and salbutamol were shown to relax noradrenaline-contracted isolated human corpus cavernosum and to inhibit spontaneous contractile activity (Adaikan and Karim, 1981; Hedlund and Andersson, 1985a). The relaxations could be blocked by propranolol but not by practolol (β_1) and butoxamine (β_2). It was, therefore, suggested that the β-adrenoceptors in human corpus cavernosum were of neither the β_1 nor β_2 subtype (Adaikan, 1979; Adaikan and Karim, 1981). However, other functional data (Hedlund and Andersson, 1985a) as well as radioligand-binding studies (Dhabuwala et al., 1985) suggest that the β-adrenoceptors of the human corpus cavernosum are of the β_2 type. Whether or not they are "atypical" remains to be settled. In isolated segments of the cavernosal artery, isoprenaline had no contractant or relaxant effect (Hedlund and Andersson, 1985a). When injected intracavernosally, salbutamol caused tumidity, but no erection, and propranolol had no effect (Brindley, 1986).

These findings suggest that the physiological role of β-adrenoceptors in both corpus cavernosum tissue and penile vasculature probably is small.

3. Cholinergic mechanisms. The occurrence of muscarinic receptors in human corpus cavernosum was demonstrated in radioligand-binding studies (Godec and Bates 1984; Traish et al., 1990). Godec and Bates (1984) measured by [^{3}H]quinuclidinyl benzilate binding the amount of muscarinic receptors in corpus cavernosum tissue of 13 impotent men undergoing penile implant surgery. In tissue from three of the patients, no receptors were found, but in the other 10, concentrations ranged from 34 to 136 fmol/mg protein. Traish et al. (1990), also using [^{3}H]quinuclidinyl benzilate, found that it bound to crude human corpus cavernosum tissue membranes and to endothelial cells from the corpus cavernosum with high affinity and limited capacity. There was only one class of binding sites. In corporeal tissue incubated with [^{3}H]choline, transmural electrical field stimulation was shown to cause release of [^{3}H]acetylcholine synthesized within the tissue (Blanco et al., 1988).

Several investigators have demonstrated that carbachol and acetylcholine, although having no effect at basal tension, concentration-dependently relax noradrenaline-contracted corpus cavernosum and spongiosum preparations (Andersson et al., 1983a; Hedlund et al., 1984; Hedlund and Andersson, 1985a; Saenz de Tejada et al., 1988). In both tissues, this relaxant effect was blocked by scopolamine, indicating that it was mediated by muscarinic receptors. In contrast, Adaikan et al. (1983) reported that in corpus cavernosum preparations acetylcholine produced contraction, relaxation, or contraction followed by relaxation. There is no obvious explanation for these differing results.

Saenz de Tejada et al. (1988) reported that destruction of the endothelium eliminates or greatly attenuates relaxation produced by acetylcholine, suggesting that the effect, as in several other vascular preparations (Furchgott, 1990), is mediated by release of a relaxation-mediating factor from the endothelium. In isolated segments of the cavernosal artery contracted by noradrenaline, carbachol induced relaxation only at high concentrations and was clearly less effective than in corporeal tissue (Hedlund and Andersson, 1985a).

It has been suggested that the peripheral nervous control of tumescence is dependent on an interaction between adrenergic and cholinergic nerves (Klinge and Sjöstrand, 1977b; Hedlund and Andersson, 1985a; Saenz de Tejada et al., 1988). Thus, tumescence may be the result of relaxation of erectile smooth muscle caused by cholinergic nerves suppressing excitatory adrenergic neurotransmission. In support of this suggestion, Hedlund et al. (1984), studying the effect of carbachol on electrically induced release of [^{3}H]noradrenaline from adrenergic nerves in corpus spongiosum preparations, found a concentration-related inhibition of the electrically evoked efflux of ^{3}H. Scopolamine, blocking muscarinic receptors, concentration-dependently increased the ^{3}H efflux.

Eckhardt (1863) found in dogs that electrical stimulation of the nervi erigentii produced penile erection, and Nikolsky (1879) described that penile erection induced by stimulation of the pelvic nerves was abolished by atropine. However, this was not confirmed by Henderson and Roepke (1933), who found that atropine had almost no effect but that physostigmine enhanced the penile response to pelvic nerve stimulation. Andersson et al. (1984b) found in dogs that muscarinic receptor blockade with atropine caused no significant decrease in the blood flow response to pelvic nerve stimulation but clearly curtailed the erectile response. A reduced erectile response to neurostimulation after intracavernous injection of atropine was also found by Trigo-Rocha et al. (1993b). However, at the concentration of atropine injected (10^{-2} M), atropine can be assumed to block α-adrenoceptors (Larsson et al., 1984b), which makes it unclear to what extent the effect was mediated via muscarinic receptors. Stief et al. (1989) showed that in monkeys intracavernous acetylcholine produced a triphasic response, including full erection.

In man, it has been suggested that muscarinic transmission plays no significant part in penile erection (Wagner and Brindley, 1980). In agreement with this, Brindley (1986) found that intracorporeal injection of atropine or neostigmine had no effect on human penile erection. On the other hand, [^{3}H]choline accumulation and [^{3}H]acetylcholine synthesis and release were significantly reduced in the corporeal tissue from diabetic patients compared to tissue from the nondiabetic patient. It was suggested that a functional penile neuropathic condition of the cholinergic nerves in the corpus cavernosum of diabetic impotent patients may be responsible for the erectile dysfunction (Blanco et al., 1990).

These findings suggest that parasympathetic activity may contribute to penile tumescence and erection by at least two mechanisms, both of which decrease the effects of noradrenaline. The release of noradrenaline may be inhibited by stimulation of muscarinic receptors on adrenergic nerve terminals. In addition, the postjunctional effects of noradrenaline may be counteracted by muscarinic receptor-mediated release of a relaxant factor from the endothelium (see section V.D.4a).

The significance of increased muscarinic receptor-mediated PGI_2 synthesis (Jeremy et al., 1986) for penile erection is not known, and the role of muscarinic receptor functions for penile erection in humans remains to be settled.

4. Nonadrenergic, noncholinergic mechanisms. According to current concepts, erection follows when the sinusoids and the cavernosal and helicinal arteries dilate with subsequent increase in blood flow to the lacunar spaces of the corpora cavernosa. It is believed that this is achieved partly by a decrease in noradrenaline-mediated tone but also through the release of relaxing NANC transmitter(s) from nerves and from the endothelium. The existence of NANC inhibitory innervation in the rat anococcygeus and bovine retractor penis muscles was first reported by Gillespie (1972) and Klinge and Sjöstrand (1974). The response to electrical stimulation of the nerves of the rat anococcygeus muscle was mimicked by nitrovasodilators, including NO, but the mediator of the response was not established (for review, see Gillespie et al., 1990).

To keep the penis in a flaccid state, it cannot be excluded that contractant factors other than noradrenaline may contribute. The nature and mechanism(s) of action of both relaxation- and contraction-mediating transmitters have not been definitely clarified, although much new information has been obtained (for review, see Andersson and Holmquist, 1990).

a. NITRIC OXIDE. It has been known for more than a decade that acetylcholine and several other agents can release relaxing factors from the vascular endothelium

(Furchgott and Zawadski, 1980; Furchgott, 1984). One of these factors has been identified as NO, synthesized from L-arginine (Palmer et al., 1987; Ignarro et al., 1987; Ignarro, 1990; Moncada et al., 1989, 1992). However, NO may also be released from nerves. There is growing evidence that, during erection, local release of NO or related factors produce relaxation of corpus cavernosum tissue. This tissue is known to relax not only after administration of acetylcholine and other agents releasing NO from the endothelium (Saenz de Tejada et al., 1988; Kimoto et al., 1990, Azadzoi et al., 1992) but also in response to electrical stimulation of nerves. Recent data have shown that both acetylcholine and neuronally mediated relaxation in rabbit and human corpus cavernosum involves release of NO, or an NO-like substance (Ignarro et al., 1990; Holmquist et al., 1991a, 1992a; Knispel et al., 1991, 1992a,b; Kim et al., 1991; Pickard et al., 1991; Rajfer et al., 1992; Bush et al., 1992a,b).

Rat and rabbit corpus cavernosum was shown to display substantial NOS activity, as monitored by the ability to convert [^{3}H]arginine to [^{3}H]citrulline (Burnett et al., 1992; Bush et al., 1992c). The enzyme present in rabbit corpus cavernosum was shown to be a cytosolic, constitutive isoform of NOS, like that found in brain neuronal tissue (Bush et al., 1992c).

The source of the NO produced may be the endothelium and/or the nerves innervating the corpus cavernosum. By immunohistochemistry, NOS has been localized in the rat penis (Burnett et al., 1992; Alm et al., 1993). Burnett et al. (1992), using an antiserum to the constitutive NOS found in rat cerebellum, demonstrated staining of the pelvic plexus and the axonal processes forming the cavernous nerve. The nerve plexus of the adventitia of the deep cavernosal arteries and the neuronal processes in the sinusoids and the periphery of the corpora cavernosa stained prominently. Dorsal penile and cavernosal arteries stained for NOS both in the adventitial and endothelial layers, although endothelial staining was faint in the cavernosal vessels. Immunohistochemistry, using antiserum produced in rabbits against a COOH-terminal fragment (Alm et al., 1993) of the rat cerebellar NOS, confirmed these findings.

The most important source of NO in penile tissue seems to be neuronal, because endothelium-derived NOS is primarily membrane bound, whereas neuronally derived NOS, like that demonstrated in rabbit corpus cavernosum (Bush et al., 1992c), is primarily cytosolic or soluble (Förstermann et al., 1991). Furthermore, the relaxant response of isolated cavernous tissue to electrical stimulation of nerves can be evoked after disruption of the endothelium, whereas responses to acetylcholine, BK, and SP are abolished (Saenz de Tejada et al., 1988; Kimoto et al., 1990; Azadzoi et al., 1992). In anesthetized dogs, intracavernous injection of 3-(3-cholamidopropyl)-dimethylammonio]-1-propane sulfonate to destroy the sinusoidal endothelium, abolished the erectile response to acetylcholine but only partially inhibited the response to electrostimulation (Trigo-Rocha et al., 1993b). NOS can be inhibited by analogues of L-arginine, such as L-NNA, L-NMMA, and N^G-nitro-L-arginine methyl ester. They effectively inhibit relaxation of cavernous tissue caused by electrical field stimulation, acetylcholine, or carbachol (Ignarro et al., 1990; Holmquist et al., 1991a, 1992a; Knispel et al., 1991, 1992a,b; Kim et al., 1991; Pickard et al., 1991; Rajfer et al., 1992; Bush et al., 1992a,b), an effect partly counteracted by L-arginine. L-NNA had little or no effect on isolated human corpus cavernosum when given to preparations at basal tension but increased the contractions elicited by electrical stimulation (Holmquist et al., 1991a, 1992a).

L-NNA also augmented the contractions induced by electrical field stimulation or by noradrenaline (Holmquist et al., 1992a). This suggests that passive stretching of cavernous tissue is not sufficient to induce NO release but that continuous release of NO may occur during active contraction. NO may, therefore, be involved not only in the process of erection but also in the minute to minute control of penile blood flow in the detumescent state. Interestingly, the NO production, but not the ability of the smooth muscle to respond to NO, seems dependent on the oxygen tension (Kim et al., 1992, 1993). Thus, electrically induced relaxations were progressively inhibited as a function of decreasing oxygen tension at partial pressures of <50 mm Hg and markedly attenuated at oxygen tensions measured in the flaccid state.

Sjöstrand et al. (1990) could not find any effect of L-NMMA on electrically induced contractions in human corpus cavernosum preparations. They concluded that neurogenic relaxation in human erectile tissue is not produced by a nitrate material formed from L-arginine. However, L-NMMA, but not L-NNA, is extensively metabolized by endothelial cells to L-citrulline (Hecker et al., 1990), and L-NMMA is 30 to 50 times less potent than L-NNA (Gibson et al., 1990). Furthermore, it has been suggested that isoforms of NOS may differ in their sensitivity to inhibition by L-arginine analogues (Förstermann et al., 1991). Such differences may contribute to the discrepancy in results.

Native NO and vasodilators acting through NO, released enzymatically or nonenzymatically (Feelisch, 1991), such as nitroglycerin, sodium nitroprusside, S-nitroso-N-acetylpenicillamine, and SIN-1, cause concentration-dependent relaxation of rabbit and human corpus cavernosum (Ignarro et al., 1990; Holmquist et al., 1991a, 1992a; Bush et al., 1992a,b; Kirkeby et al., 1993). The effects of NO can be reduced or abolished by oxyhemoglobin, which has a high binding affinity for NO in the extracellular compartment, and by pyrogallol, a potent generator of superoxide anions (Bush et al., 1992a,b; Kirkeby et al., 1993). However, oxyhemoglobin and scavengers of NO are not always effective against relaxation induced by electrical stimulation or against relaxation

induced by agents acting through release of NO (Bush et al., 1992a,b; Kirkeby et al., 1993).

NO and NO-related vasodilators produce relaxation of corpus cavernosum through stimulation of soluble guanylate cyclase, leading to an increase in the tissue levels of cGMP. This was first demonstrated in rabbit corpus cavernosum by Ignarro et al. (1990). They also showed that selective inhibition of cGMP phosphodiesterase enhanced the relaxant effect of electrical stimulation (Ignarro et al., 1990; Bush et al., 1992a,b). These findings have been confirmed by other investigators in both rabbit and human corporeal tissue.

The guanylate cyclase-stimulating effect of NO is sensitive to methylene blue (Martin et al., 1985; Waldman and Murad, 1987). In apparent accordance with this, Ignarro et al. (1990) reported that the relaxation induced by electrical stimulation in rabbit corpus cavernosum was inhibited by methylene blue. This was confirmed by other investigators and also in human tissue (Pickard et al., 1991; Holmquist et al., 1992a; Rajfer et al., 1992). Methylene blue in a low concentration (10^{-5} M) and with a short exposure time (10 minutes), was found to inhibit NO- and sodium nitroprusside-induced relaxation of noradrenaline-induced tension in human corpus cavernosum preparations (Kirkeby et al., 1993). However, neither the relaxation induced by electrical stimulation nor acetylcholine-induced relaxations were significantly affected by methylene blue in this concentration. On the other hand, increasing the methylene blue concentration to 5 $\times 10^{-4}$ to 10^{-4} M and extending the exposure time to 60 to 90 minutes significantly decreased these responses. It cannot be excluded that methylene blue may have more than one mode of action. Thus, it may act by formation of superoxide anion (Wolin et al., 1990; Marczin et al., 1992) in addition to its inhibitory effect on guanylate cyclase.

The role of penile veins in control of penile venous outflow resistance is uncertain, but experimental data have suggested that an active mechanism adds to the passive compression of the outflow channels resulting from cavernous sinusoidal distension (Carati et al., 1988; Aoki et al., 1989). If this mechanism includes active venoconstriction, it would require the presence of agents or mechanisms affecting corpus cavernosum and venous smooth muscle tissue differently. Kirkeby et al. (1993) found that inhibitory responses could be evoked by electrical stimulation in corpus cavernosum, but not in penile veins, and that endothelium-dependent responses to acetylcholine in vein preparations were insensitive to L-NNA and to oxyhemoglobin, in contrast to the findings in corpus cavernosum. Thus, endothelium-derived substances unrelated to the L-arginine/NO pathway may be involved in acetylcholine-induced relaxation in human penile vein preparations.

Although the exact neuroeffector mechanisms are not completely understood, these results suggest that, in the isolated corpus cavernosum, both neurogenic and endothelium-dependent relaxations involving NO or an NO-containing compound can be elicited. The physiological significance of this remains to be fully established, but it is tempting to speculate that NO, or a related compound, acts as the main physiological transmitter mediating relaxation of penile vasculature and corpus cavernosum and that it is essential for normal erection. Indeed, in vivo data seem to support that this is the case. Holmquist et al. (1991c) showed that, in anesthetized rabbits, erections induced by stimulation of the cavernous nerves could be dose-dependently inhibited by intracorporeal injection of L-NNA, inhibiting NOS. This was also shown in the pithed rat, in which L-NNA attenuated the corporeal response to spinal stimulation (Finberg and Vardi, 1991), and in the intact rat, in which intravenous L-NNA in low doses (1 to 5 mg/kg) inhibited erection induced by stimulation of the cavernous nerves (Burnett et al., 1992). In dogs, L-NNA blocked pelvic nerve-stimulated erections, an effect that could be reversed by intracavernous injection of L-arginine, inhibited by methylene blue, and enhanced by a cGMP phosphodiesterase inhibitor (Trigo-Rocha et al., 1993a). In men with erection dysfunction, intracorporeal injection of the NO donor SIN-1 produced erection (Stief et al., 1991a, 1992). Further support for a role of the L-arginine/NO pathway in penile erection was obtained by Steers and Selby (1991), who found that intracavernous injection of methylene blue produced detumescence in a patient with priapism.

Saenz de Tejada et al. (1989b) reported that, in isolated corpus cavernosum from diabetic patients with impotence, both neurogenic and endothelium-dependent relaxation was impaired. This was also found in rabbits in which diabetes was induced by alloxan (Azadzoi and Saenz de Tejada, 1992). Evidence supporting the view that the reduced relaxation in cavernosal tissue from diabetic patients was due to lack of NO production, and not to inability of the smooth muscle to relax, was presented by Pickard et al. (1992). They demonstrated that the NO production, measured as the formation of nitrite in response to electrical stimulation, was reduced in men with diabetic impotence.

Also, hypercholesterolemia was found to impair endothelium-mediated relaxation of rabbit corpus cavernosum smooth muscle (Azadzoi and Saenz de Tejada, 1991). The mechanism of this effect is unknown but did not seem to involve cyclooxygenase products or the the ability of the smooth muscle to react to stimulation by an NO donor (nitroprusside).

Saenz de Tejada et al. (1989b) suggested that vasodilators producing endothelium-independent relaxation would be preferable in diabetic patients treated with intracavernosal injections. Whether this prediction is clinically valid remains to be tested. Heaton (1990) found that in vitro synthetic nitrovasodilators effectively re-

laxed human corporeal tissue from impotent men, and it is notable that topical nitroglycerin may have clinically important effects (Claes and Baert, 1989; Heaton et al., 1989; Owen et al., 1989; Meyhoff et al., 1992). The clinical potential of NO donors was shown by Stief et al. (1991a, 1992). They injected SIN-1 intracavernously in men with erectile dysfunction with good clinical results.

b. NEUROPEPTIDES. Several investigators have demonstrated different peptides in nerves of human erectile tissues. Among these peptides are VIP (Polak et al., 1981; Larsen et al., 1981; Willis et al., 1981, 1983; Gu et al., 1983a; Steers et al., 1984), peptide histidine methionine (Yiangou et al., 1985; Kirkeby et al., 1990), SP, somatostatin, NPY (Gu et al., 1983a; Adrian et al., 1984), and CGRP (Stief et al., 1990). The localization of these peptides in penile erectile tissues has led to speculations about their functional roles as inhibitory or excitatory transmitters and/or modulators of neurotransmission.

i. Endothelins. It is well established that release of noradrenaline into the synaptic cleft is involved in returning the erect penis to the flaccid state. However, it is not known whether noradrenaline alone or together with additional factors mediates the constant tone of the penile smooth muscle necessary for maintaining penile flaccidity (Andersson and Holmquist, 1990). There is a possibility that ETs may contribute to this control. ET-1 mRNA was shown to be expressed in cultured endothelial cells from the human corpus cavernosum (Saenz de Tejada et al., 1989a, 1991a), and significant amounts of ET-like activity were measured with radioimmunoassay in the supernatants of endothelial cells in culture (Saenz de Tejada et al., 1991a).

Binding experiments revealed high-affinity, specific, and saturable binding of labeled ETs to corporeal membranes. At least two distinct ET receptors were found to exist, one type with high affinity for ET-1 and -2 and low affinity for ET-3 and another, less abundant, with high affinity for ET-1, -2, and -3 (Saenz de Tejada et al., 1991a). Binding sites for ET-1 were demonstrated by autoradiography in the deep penile artery, the circumflex veins, and throughout the cavernous tissue (Holmquist et al., 1992b). Holmquist et al. (1992b), using a commercially available ET-1 antiserum, did not find any specific immunohistochemical localization of ET-1 in human or rabbit cavernosal tissue. They speculated that in this tissue there were no intracellular stores of ET-1, which did not exclude the possibility that the peptide could be synthesized and released continuously. However, utilizing an ET-1 monoclonal antibody, Saenz de Tejada et al. (1991a) found that ET-like immunoreactivity was localized intensely in the endothelium and, to a lesser degree, in the trabecular smooth muscle from humans.

ET-1 potently induces slowly developing, long-lasting contractions in isolated preparations of both human corpus cavernosum (Saenz de Tejada et al., 1989a; Holmquist et al., 1990b, 1992b,c; Lau et al., 1991), cavernous artery, deep dorsal vein (Lau et al., 1991), and penile circumflex veins (Holmquist et al., 1992b). Similar contractions can be evoked in human corpus cavernosus tissue by ET-2 and -3, although these peptides have a lower potency. Thus, the concentration of ET-3 necessary to initiate contraction in this tissue was 30-fold higher than those of ET-1 and -2 (Saenz de Tejada et al., 1991a).

In the rabbit corpus cavernosum, pretreatment with ET-1 enhanced contractions induced by noradrenaline (Holmquist et al., 1990b). Muscarinic receptor stimulation (carbachol) and VIP effectively counteracted ET-1-induced contractions in both rabbit and human tissue. Likewise, contractions induced in human cavernosal tissue were readily reversed by transmural electrical stimulation, acetylcholine, and sodium nitroprusside (Saenz de Tejada et al., 1991a). This is of particular interest because acetylcholine and VIP, which both may be involved in the mechanisms leading to penile erection (Andersson and Holmquist, 1990), have been localized to the same nerves (Lincoln et al., 1987) and because the L-arginine/NO pathway seems to be of great functional importance for penile erection (see section V.D.4.a).

In corpus cavernosum, the contractions induced by ET-1 were attenuated by the calcium antagonist nimodipine (Holmquist et al., 1990b), whereas in the circumflex veins, the effect of the peptide was independent of influx of extracellular calcium through dihydropyridine-sensitive calcium channels (Holmquist et al., 1992b). In calcium-free medium, on the other hand, contractions induced by ET-1 were greatly reduced, but not abolished, in both corpus cavernosum and circumflex veins. The protein kinase C inhibitor, 1-(5-isoquinolinesulfonyl)-2-methylpiperazine, abolished the contractile component observed in calcium-free medium in the rabbit corpus cavernosum (Holmquist et al., 1990b), and, in addition, ET-1 was shown to induce hydrolysis of phosphoinositides in a concentration-dependent manner (Holmquist et al., 1992c). Whether or not ET-1 also activates phospholipase C in the human corpus cavernosum is not known, but such an action could explain the contraction induced by the peptide in a calcium-free medium.

Available information supports the suggestion that ETs are involved in the control of penile smooth muscle tone.

ii. Neuropeptide Y. Wespes et al., (1988) studied the distribution of NPY-containing nerves in the human penis. They found a concentration of fibres in the inner part of the adventitia close to the media of the arterial and venous vessels and among the intracavernous smooth muscle cells; they speculated that the peptide could act as a neurotransmitter or neuromodulator, especially during detumescence. Adrian et al. (1984) found moderately high concentrations of NPY in the human corpus cavernosum, but nevertheless, they suggested that NPY could be intimately involved in the control of

erection. Of interest is that NPY and VIP were shown to be colocalized in the cavernous tissue and helicine arteries of the monkey (Schmalbruch and Wagner, 1989). Whether or not this is the case in human tissues is not known.

If NPY is a neurotransmitter involved in detumescence, a contractile effect on erectile tissues would be expected. Hedlund and Andersson (1985b) found no effects of NPY in corpus cavernosum or in segments of the cavernosal artery when preparations were studied at basal tension level or contracted by noradrenaline. Electrically induced contractions were not affected. Kirkeby et al. (1990) found that six of eight strips of normal corpus cavernosum did not respond to NPY, and two responded with a contraction approximately 20% of that induced by high K^+. Yajima et al. (1992) did not find any effects of NPY on rabbit corpus cavernosum, nor did the peptide enhance the actions of noradrenaline.

These results do not support the view that NPY is of importance in the control of smooth muscles involved in penile erection.

iii. Arginine vasopressin. Even if it is generally held that AVP is a circulating hormone, AVP-like activity has been demonstrated to be widely distributed in the sympathetic nervous system of mammals (Hanley et al., 1984). This AVP-like activity was demonstrated in both ganglionic neurons and in nerve fibers innervating peripheral tissues.

AVP was found to potently, and in a concentration-dependent way, contract isolated human corpus cavernosum and spongiosum and preparations of the cavernosal artery. AVP could be demonstrated by radioimmunoassay in cavernous tissue in concentrations up to 10 times those circulating in plasma (Andersson et al., 1986a). This suggested that the peptide was either taken up and stored and/or synthesized locally. However, AVP antagonists, in concentrations almost completely suppressing the contractions induced by exogenous AVP, had no effect on electrically induced contractions in corpus cavernosum preparations (Andersson et al., 1986a). This indicates that AVP is not released on electrical stimulation in amounts that can affect the smooth muscle directly and/or influence the response to released noradrenaline.

iv. Somatostatin. Somatostatin-containing nerves have been localized in the male genital tract by immunohistochemistry and are found mainly associated with the smooth muscle of the seminal vesicle and the vas deferens (Gu et al., 1983a). The concentrations of somatostatin in these structures were, however, only slightly higher than those found in corpus cavernosum. Somatostatin had no effects on cavernosal tissue in vitro, except at high concentrations, when contractions were produced. Preparations of the cavernosal artery responded with contraction at 100 times lower concentrations, but the maximum effect was small (Hedlund and Andersson, 1985b). These findings do not suggest that somatostatin has any direct effects on smooth muscle structures of importance for penile erection.

v. Vasoactive intestinal polypeptide and peptide histidine methionine. VIP has been found in high concentrations in the erectile tissue of the human penis (Polak et al., 1981; Shirai et al., 1990). It is present in nerve fibres with nerve endings around cavernous smooth muscle and blood vessels, mainly arteries and arterioles (Polak et al., 1981; Andersson et al., 1983a; Gu et al., 1983a; Willis et al., 1983). Peptide histidine methionine is derived from the same precursor as that of VIP and was shown to be localized to the nerves in close relation to bundles of smooth muscle and around arteries in the corpus cavernosum and in circumflex veins (Yiangou et al., 1985; Kirkeby et al., 1992). A role for these peptides as neurotransmitters and/or neuromodulators has been postulated by several investigators.

VIP has a relaxant action on human erectile tissue (Larsen et al., 1981; Andersson et al., 1983a; Willis et al., 1983; Steers et al., 1984; Hedlund and Andersson, 1985b; Adaikan et al., 1986). In isolated corpus cavernosum strips, the effect on spontaneous (myogenic) contractile activity and on electrically induced contractions was pronounced but not on noradrenaline-contracted preparations (Willis et al., 1981; Hedlund and Andersson, 1985b; Steers et al., 1984; Kirkeby et al., 1992; Pickard et al., 1993). However, VIP was very effective in relaxing preparations of penile circumflex veins precontracted by noradrenaline (Kirkeby et al., 1992), as well as preparations stimulated electrically (F. Holmquist, H. J. Kirkeby, A. Forman, and K.-E. Andersson, unpublished results). VIP antiserum (Adaikan et al., 1986) and α-chymotrypsin (Pickard et al., 1993) reduced or abolished the relaxant effect of exogenous VIP on isolated human corpus cavernosum tissue but had no effect on relaxation induced by electrical stimulation of nerves. The effects on electrically induced contractions in segments of the cavernosal artery were small, as were its relaxant actions on noradrenaline-contracted arterial preparations (Hedlund and Andersson, 1985b).

Kawanishi et al. (1990) found that, in noradrenaline-contracted human corpus cavernosum tissue, the relaxation induced by acetylcholine and VIP together was no greater than that obtained by acetylcholine or VIP given separately. They suggested that the coexistence of acetylcholine and VIP (Lincoln et al., 1987) has no functional significance. On the other hand, in dogs, simultaneous intracavernous injection of VIP and acetylcholine produced a synergistic effect, and it was suggested that the two agents may play a cooperative role in canine penile erection (Takahashi et al., 1992a).

A marked release of VIP during tumescence and erection produced by visual sexual stimulation, by intracavernous injection of papaverine, or by intracavernous infusion of saline has been demonstrated in pilot studies

(Virag et al., 1982; Ottesen et al., 1984). However, Kiely et al. (1987), measuring cavernosal and peripheral VIP concentrations during erection induced by a variety of vasoactive compounds in patients with either predominantly organic or predominantly psychogenic impotence, found no increase in cavernosal VIP concentration. In patients with impotence, Gu et al. (1984) found that VIP-containing nerves were depleted and that the extent of the depletion broadly reflected the severity of erectile dysfunction, irrespective of its etiology. Lincoln et al. (1987) found that five of six diabetic patients with impotence had a marked reduction of VIP-like immunoreactivity in nerves associated with the cavernous smooth muscle. Gu et al. (1984) suggested that VIP was the principal neurotransmitter involved in penile erection and that depletion of the peptide may play a key role in the development of impotence. However, the inability of VIP to produce erection when injected intracavernosally in impotent men (Adaikan et al., 1986; Kiely et al., 1989; Roy et al., 1990) indicates that it cannot be the only, and probably not the main, NANC mediator for relaxation of penile erectile tissues.

Peptide histidine methionine concentration-dependently relaxed corpus cavernosum strips contracted by noradrenaline by only 10%. Corresponding figure for circumflex vein preparations was 90% (Kirkeby et al., 1992). For peptide histidine methionine, as for VIP, a role as neurotransmitter and/or neuromodulator in the nervous control of penile erection cannot be excluded but has to be established.

vi. Calcitonin gene-related peptide. CGRP, a 37-amino acid peptide (Ishida-Yamamoto and Tohyama, 1989), is known to be a potent vasodilator in a variety of human blood vessels, where it is believed to produce an endothelium-dependent relaxation (Hughes et al., 1985; Crossman et al., 1987). The peptide also relaxed the bovine penile artery, mainly by acting directly on the smooth muscle cells (Alaranta et al., 1991). Stief et al. (1990) demonstrated CGRP in nerves of the human corpus cavernosum. However, in vitro, CGRP had little relaxant effects on strips of human corpus cavernosum contracted by noradrenaline or by electrical field stimulation (F. Holmquist and K.-E. Andersson, unpublished results). Whether the peptide has a role in normal penile physiology remains to be established. Even if it does not, this does not exclude that it may be useful for therapeutic purposes (Stief et al., 1991b).

vii. Substance P. Few SP-immunoreactive nerves were found in cavernosal tissue (Andersson et al., 1983a; Gu et al., 1983a). SP was more concentrated in groups of nerve fibres underneath the epithelium of the glans penis (Gu et al., 1983a). In vitro investigations of strips of human corpus cavernosum contracted by noradrenaline showed a transient relaxation by SP, amounting to approximately 30% (Andersson et al., 1983a). In isolated rabbit cavernosal tissue contracted by phenylephrine, SP had a relaxant effect, reaching a maximum of 15% at a concentration of 3×10^{-11} M. The effect was enhanced by indomethacin, reduced by 3-[(3-cholamidopropyl)-dimethylammonio]-1-propane sulfonate to destroy the endothelium, and blocked by L-NMMA (Azadzoi et al., 1992). Strips of human corpus cavernosum showed contractile effects of SP at resting tension, whereas no effects were observed in segments of the cavernosal artery (Andersson et al., 1983a; Hedlund and Andersson, 1985b). The contractant response in isolated human erectile tissue proper is in contrast to the vasodilator effects produced by SP in vivo in the dog (Andersson et al., 1984b). However, the latter action may be explained by SP causing relaxation by releasing NO and relaxation-producing cyclooxygenase products from the endothelium.

It cannot be excluded that SP is involved in the sensory innervation of the penis (Keast and de Groat, 1989, 1992). However, available information does not suggest that the peptide has any direct effects on corpus cavernosum smooth muscle or penile vessels of importance for erection.

c. PROSTANOIDS. The human penis has the ability to synthesize various prostanoids (Roy et al., 1984; Bornman et al., 1986; Jeremy et al., 1986; Roy et al., 1989), and it has been suggested that arachidonatic cascade products may be involved in the control of penile erection. PG dehydrogenase activity has been demonstrated in human corpus cavernosum tissue (Roy et al., 1989), which may be one of the reasons why PGE_1, when given intracavernously, seldom causes prolonged erection and priapism (Juenemann and Alken, 1989).

Luduena and Grigas (1972) showed that PGE_1 in low concentrations relaxed the dog retractor penis muscle, and Klinge and Sjöstrand (1977a) found in various isolated mammalian smooth muscle effectors of penile erection that $PGF_{2\alpha}$ contracted and PGE_1 relaxed the tissues. These findings were confirmed by Adaikan (1979) using human tissue. Hedlund and Andersson (1985c) demonstrated that $PGF_{2\alpha}$, PGI_2, high concentrations of PGE_2, and, most potently among the prostanoids tested, the TXA_2 analogues U46619 and U44069 contracted corpus cavernosum and preparations of the cavernous artery at baseline tension. The contraction-mediating prostanoid receptor in the human corpora is most probably a TXA_2-sensitive receptor, even if the presence of more than one contraction-mediating prostanoid receptor cannot be excluded (Hedlund et al., 1989a,b). Whether or not tone in penile erectile tissues is maintained by stimulation of the TXA_2-sensitive receptor remains to be established. Carbachol completely relaxed $PGF_{2\alpha}$-contracted trabecular preparations, but the arterial segments remained contracted (Hedlund and Andersson, 1985c). Both corpus cavernosum and arterial preparations contracted by $PGF_{2\alpha}$ could be relaxed to baseline by VIP.

Hedlund and Andersson (1985c) found no contractant

action of PGE_1, but the prostanoid effectively relaxed human trabecular tissue and segments of the cavernous artery contracted by noradrenaline and $PGF_{2\alpha}$. Also, PGE_2 at low concentrations was shown to have a certain relaxant action in the corpus cavernosum preparations but was without any obvious effects in noradrenaline-contracted arterial segments. Contributing to a direct smooth muscle effect of PGE_1, the prostanoid has been shown to inhibit release of noradrenaline from penile adrenergic nerves (Porst, 1989; Molderings et al., 1992). This is of particular interest, because such an effect may contribute to PGE_1's relaxant effect on penile erectile tissues when it is injected intracorporeally for treatment of erectile dysfunction (Juenemann and Alken, 1989).

Muscarinic receptor stimulation has been reported to cause synthesis and release of PGI_2 in human penile corpus cavernosum tissue (Jeremy et al., 1986). In isolated preparations of the cavernosal artery, PGI_2 was found to be highly effective as a relaxant agent in both noradrenaline- and $PGF_{2\alpha}$-contracted preparations. However, the findings that PGI_2 caused contraction and had no relaxant action when added to isolated corporeal preparations contracted by noradrenaline and $PGF_{2\alpha}$ (Hedlund and Andersson, 1985c) seems to rule out any major role of this prostanoid in relaxation of cavernous tissue. Supporting this view, intracavernous injection of PGI_2 in pigtailed monkeys did not increase cavernosal arterial blood flow, and there was a large reduction of the cavernosal compliance due to smooth muscle contraction (Bosch et al., 1989). This does not exclude that PGI_2 may serve as a vasodilator in the initial phase of penile erection, as was suggested by Andersson et al. (1984b), based on findings in a dog model. Furthermore, during penile enlargement and blood stasis, PGI_2, synthesized from vascular endothelium as well as from the corporeal sinusoids, may counteract local thrombosis induced by TXA_2 and other endogenous platelet aggregators.

If any of the PGs plays a physiological role in penile erection, PGE_1 seems to have the most appropriate profile of action (Hedlund and Andersson, 1985c).

d. HISTAMINE. Variable responses to histamine have been demonstrated in human cavernosal tissue: contraction, relaxation, or contraction followed by relaxation (Adaikan and Karim, 1977). Stimulation of H_1 receptors by 2-methyl histamine mainly caused contraction, and stimulation of H_2 receptors by 4-methyl histamine produced relaxation. Blockade of H_1 receptors with mepyramine enhanced the relaxant effects, and blockade of H_2 receptors with burimamide enhanced the contractile effects of histamine (Adaikan and Karim, 1977). Further support for the existence of contraction-mediating H_1 receptors and relaxation-mediating H_2 receptors were found in vivo in anesthetized baboons (Adaikan et al., 1991).

Kirkeby et al. (1989b), investigating the effects of histamine on human cavernous tissue and circumflex veins, found no effect of histamine at basal tension but that the amine relaxed both types of preparations when precontracted with noradrenaline. The relaxation was not affected by H_1 (mepyramine) or H_2 (cimetidine) receptor blockade. This apparent discrepancy may be attributed to differences in experimental approach and also to the fact that histamine seems to be able to release NO from the endothelium. The relaxation of noradrenaline-contracted preparations induced by the amine could be partly blocked by L-NNA (K.-E. Andersson and P. Hedlund, unpublished results).

Histamine given intracorporeally has been shown to induce erection (Nahoum et al., 1988; Adaikan et al., 1991). The mechanism of the relaxant effect is unknown but, as indicated before, may be due to stimulation of relaxation-mediating H_2 receptors as well as to release of NO. Histamine, in addition, can interfere with adrenergic function (McGrath and Shepherd, 1976). Because mast cells have been demonstrated in human corpus cavernosum tissue (Sathananthan et al., 1991), and rabbit erectile tissues contain histamine (Pentillo and Vartiainen, 1964), it cannot be ruled out that histamine may have a role in penile erection.

e. ADENOSINE 5′-TRIPHOSPHATE AND ADENOSINE. In the canine penile artery, ATP was found to produce relaxation (Bowman and Gillespie, 1983). Furthermore, ATP was shown to induce a pronounced relaxation of rabbit cavernosal tissue (Broderick et al., 1991; Tong et al., 1992a). The response to ATP was more pronounced than that produced by bethanechol in the same tissue and was independent of the endothelium. It was suggested that ATP is an NANC transmitter in the corpora cavernosa and that purinergic transmission may be an important component involved in the initiation and maintenance of penile erection (Tong et al., 1992a). In line with this, ATP injected intracavernously in dogs was found to produce increases in intracavernous pressure and erection (Takahashi et al., 1992b). This effect, which was unaffected by atropine and hexamethonium, could be obtained without changes in systemic blood pressure.

It is of interest that adenosine also produced full erection when administered intracavernously in dogs (Takahashi et al., 1992c). Whether or not ATP or adenosine are involved in the physiological mechanisms of erection, and if they may be useful alternatives in the treatment of erectile dysfunction in man, remains to be established.

E. Inhibition of Activation Mechanisms

1. Membrane hyperpolarization—potassium channel openers. K^+ channnel openers such as pinacidil, nicorandil, and cromakalim relax various types of smooth muscle cells by opening of ^{86}Rb-permeable K^+ channels and subsequently hyperpolarizing cells. The hyperpolar-

ization will prevent the opening of voltage-dependent calcium channels, but additional mechanisms may be involved in the relaxation (Weston and Abbott, 1987; Cook, 1988; Hamilton and Weston, 1989; Quast and Cook, 1989; Robertson and Steinberg, 1990; Andersson, 1992; Longman and Hamilton, 1992).

In isolated human corpus cavernosum, pinacidil abolished spontaneous contractile activity, effectively relaxed preparations contracted by noradrenaline, and inhibited contractions induced by electrical stimulation of nerves. Pinacidil also depressed contractions induced by low concentrations of K^+ and concentration-dependently increased the efflux of ^{86}Rb from preloaded tissue (Holmquist et al., 1988, 1990c). In isolated corpus cavernosum from rabbit, the effects were similar to those in human tissue. It was also shown that cromakalim was 3 to 4 times more potent than pinacidil and up to 36 times more potent than papaverine (Holmquist et al., 1990c). Furthermore, in rabbit tissue, the effects of pinacidil on contracted preparations and on ^{86}Rb efflux were blocked by glibenclamide, a selective inhibitor of ATP-dependent K^+ channels (F. Holmquist and K.-E. Andersson, unpublished results).

Giraldi and Wagner (1990) showed that pinacidil, in high concentrations ($>10^{-5}$ M), may relax even completely depolarized corpus cavernosum tissue. This effect is most probably not related to pinacidil's K^+ channel-opening action. Intracavernous injection of pinacidil produced tumescence or erection in 16 of 17 monkeys, a result similar to that obtained with papaverine (Giraldi and Wagner, 1990). Although the systemic blood pressure decreased in only one of the five monkeys in which the blood pressure was monitored, the potential risk of systemic side effects should not be disregarded. Lemakalim, nicorandil, and pinacidil all caused erections in a dose-dependent manner when injected intracavernosally in cats (Hellstrom et al., 1992).

Whether or not K^+ channel openers, alone or together with other vasoactive agents, can be used for diagnosis and treatment of erectile dysfunction warrants further investigations.

2. Inhibition of calcium influx—calcium antagonists. Fovaeus et al. (1987b) showed that removal of calcium from the extracellular medium reduced, but did not abolish, contractions of the human corpus cavernosum induced by noradrenaline, suggesting that contractions evoked by α-adrenoceptor stimulation are partly dependent on intracellular calcium. Kimura et al. (1990b) arrived at a similar conclusion. The calcium antagonists verapamil, diltiazem, and nifedipine all depressed the response to noradrenaline but not by more than 50% (Fovaeus et al., 1987b). Diltiazem depressed the contraction induced by $PGF_{2\alpha}$ to a similar extent (Kimura et al., 1990b). In calcium-free medium, the responses to electrical stimulation were rapidly abolished (Fovaeus et al., 1987b). High concentrations of verapamil and diltiazem also completely depressed electrically induced contractions, whereas nifedipine did not. This was also found in isolated rabbit corpus cavernosum preparations (Kerfoot et al., 1992). As expected, the calcium antagonists were able to completely suppress contractions induced by high concentrations of K^+ (Fovaeus et al., 1987b).

Brindley (1986) suggested that intracavernosal injection of verapamil may have a clinical potential for the diagnosis and treatment of impotence. Considering that the effects of verapamil to some extent may be attributable to its α-adrenoceptor-blocking properties, a combination of the two actions may be more useful than calcium channel blockade alone. Christ et al. (1989) found synergistic effects of a combination of papaverine and nifedipine on isolated human erectile tissue and suggested such a drug combination to be particularly effective. This finding supports the view that, for calcium antagonists to be effective for diagnosis and treatment of erectile dysfunction, they should be combined with other drugs.

F. Effects of Sexual Hormones

Many investigations of receptor mechanisms in penile erectile tissue have been performed on tissue from patients undergoing gender reassignment operations after estrogen treatment. Although it has been claimed that hormonal treatment does not qualitatively change responses to drugs and electrical field stimulation (Adaikan and Karim, 1981; Hedlund and Andersson, 1985a), this is open to discussion, because systematic comparisons between tissues from these patient groups and normal subjects have apparently not been performed.

In isolated human corpus cavernosum pretreated with testosterone for 30 minutes, testosterone had no effect on contraction or relaxation (Kimura et al., 1990a). On the other hand, castration enhanced NANC nerve-mediated relaxation in corpus cavernosum tissue from rabbits (Andersson et al., 1992c). Because the response to the NO donor SIN-1 was the same in corpus cavernosum tissue from controls and castrated animals, it may be assumed that the responsiveness of the penile erectile tissue to effects mediated via NO was not changed. Thus, the hormonal changes caused by castration, which include a change in the balance between androgens and estrogens, may stimulate the synthesis and/or release of NO and/or suppress the noradrenaline release from adrenergic nerves. Obviously, hormonal factors may influence the response to electrical field stimulation of nerves in corpus cavernosum tissue, which should be considered in in vitro studies.

VI. Conclusion

In Ruch and Fulton's textbook of medical physiology and biophysics from 1960, Ruch (1960) began his chapter concerning the urinary bladder by stating: "Conflicting concepts, unphysiologic terminology, ignorance of fundamental anatomy and physiology of such structures as

the internal sphincter,' and the intermixture of mechanical, pathologic and neural factors—all contribute to making bladder function a complex subject." Bladder function is still a complex subject, but since Ruch made his statement, much has been done to standardize terminology and to clarify fundamental morphology, physiology, and pharmacology of the urogenital tract. The field of urogenital pharmacology is rapidly expanding, and further investigations of basic mechanisms are needed to create a basis for effective pharmacological treatment of voiding and erectile dysfunctions.

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REFERENCES

ABBER, J. C., LUE, T. F., LUO, J.-A., JUENEMANN, K.-P., AND TANAGHO, E.: Priapism induced by chlorpromazine and trazodone: mechanism of action. J. Urol. **137:** 1039–1042, 1987.

ABDEL-HAKIM, A. M., HASSOUNA, M., RIOUX, F., ST-PIERRE, S., ABDEL-RAHMAN, M., GALEANO, C., AND ELHILALI, M.: Response of urethral smooth muscles to pharmacological agents. II. Noncholinergic, nonadrenergic agonists and antagonists. J. Urol. **130:** 988–991, 1983.

ABDEL-HAKIM, A. M., RIOUX, F., AND ELHILALI, M.: The contractile effect of bombesin on the rat isolated urinary bladder. Eur. J. Pharmacol. **70:** 167–173, 1981.

ABELLI, L., CONTE, B., SOMMA, V., PARLANI, M., GEPETTI, P., AND MAGGI, C. A.: Mechanical irritation induces neurogenic inflammation in the rat urethra. J. Urol. **146:** 1624–1626, 1991.

ABELLI, L., NAPPI, F., PERETTI, F., MAGGI, C. A., MANZINI, S., AND GIACHETTI, A.: Microvascular leakage induced by substance P in rat urinary bladder: involvement of cyclooxygenase metabolites of arachidonic acid. J. Auton. Pharmacol. **12:** 269–276, 1992.

ABELLI, L., SOMMA, V., MAGGI, C. A., REGOLI, D., ASTOLFI, M., PARLANI, M., ROVERO, P., CONTE, B., AND MELI, A.: Effects of tachykinins and selective tachykinin receptor agonists on vascular permeability in the rat lower urinary tract: evidence for the involvement of NK-1 receptors. J. Auton. Pharmacol. **9:** 253–263, 1989.

ABRAMS, P. H., AND FENELEY, R. C. L.: The actions of prostaglandins on the smooth muscle of the human urinary tract in vitro. Br. J. Urol. **47:** 909–915, 1976.

ACEVEDO, C. G., AND CONTRERAS, E.: Possible involvement of adenine nucleotides in the neurotransmission of the mouse urinary bladder. Comp. Biochem. Physiol. **82C:** 357–361, 1985.

ACEVEDO, C. G., AND CONTRERAS, E.: Effect of extracellular calcium and calcium channel antagonists on ATP and field stimulation induced contractions of the mouse urinary bladder. Gen. Pharmacol. **20:** 811–815, 1989.

ACEVEDO, C. G., CONTRERAS, E., ESCALONA, J., LEWIN, J., AND HUIDOBRO-TORO, J. P.: Pharmacological characterization of adenosine A1 and A2 receptors in the bladder: evidence for a modulatory adenosine tone regulating non-adrenergic noncholinergic neurotransmission. Br. J. Pharmacol. **107:** 120–126, 1992.

ACEVEDO, C. G., TAMAYO, L., AND CONTRERAS, E.: Effects of morphine in isolated mouse urinary bladder. Gen. Pharmacol. **17:** 449–452, 1986.

ADAMI, M., BERTACCINI, G., CORUZZI, G., AND POLI, E.: Characterization of cholinoreceptors in the rat urinary bladder by the use of agonists and antagonists of the cholinergic system. J. Auton. Pharmacol. **5:** 197–205, 1985.

ADAIKAN, P. G.: Pharmacology of the human penis. MSc Thesis, University of Singapore, Singapore, pp. 1–213, 1979.

ADAIKAN, P. G., AND KARIM, S. M. M.: Effects of histamine on the human penis muscle in vitro. Eur. J. Pharmacol. **45:** 261–265, 1977.

ADAIKAN, P. G., AND KARIM, S. M. M.: Adrenoceptors in the human penis. J. Auton. Pharmacol. **1:** 199–203, 1981.

ADAIKAN, P. G., KARIM, S. M. M., KOTTEGODA, S. R., AND RATNAM, S. S.: Cholinoreceptors in the corpus cavernosum muscle of the human penis. J. Auton. Pharmacol. **3:** 107–111, 1983.

ADAIKAN, P. G., KOTTEGODA, S. R., AND RATNAM, S. S.: Is vasoactive intestinal polypeptide the principal transmitter involved in human penile erection? J. Urol. **135:** 638–640, 1986.

ADAIKAN, P. G., LAU, L. C., NG, S. C., AND RATNAM, S. S.: Physio-pharmacology of human penile erection - autonomic/nitrergic neurotransmission and receptors of the human corpus cavernosum. Asian Pac. J. Pharmacol. **6:** 213–227, 1991.

ADRIAN, T. E., GU, J., ALLEN, J. M., TATEMOTO, K., POLAK, J. M., AND BLOOM, S. R.: Neuropeptide Y in the human male genital tract. Life Sci. **35:** 2643–2648, 1984.

ALARANTA, S., UUSITALO, H., HAUTAMÄKI, A. M., AND KLINGE, E.: Calcitonin gene-related peptide: immunohistochemical localization in, and effects on, the bovine penile artery. Int. J. Impotence Res. **3:** 49–59, 1991.

ALBERT, D. J., JACOBS, S., AND PERSKY, L.: Bradykinin and urinary tract smooth muscle. Curr. Topics. Surg. Res. **2:** 327–333, 1970.

ALBERTS, P.: Subtype classification of the presynaptic α-adrenoceptors which regulate [^{3}H]-noradrenaline secretion in guinea-pig isolated urethra. Br. J. Pharmacol. **105:** 142–146, 1992.

ALKONDON, M., AND GANGULY, D. K.: Release of prostaglandin E from the isolated urinary bladder of the guinea-pig. Br. J. Pharmacol. **69:** 573–577, 1980.

ALM, P., ALUMETS, J., HÅKANSSON, R., OWMAN, C., SJÖBERG, N.-O., STJERNQUIST, M., AND SUNDLER, F.: Enkephalin-immunoreactive nerve fibres in the feline genito-urinary tract. Histochemistry **72:** 351–355, 1981.

ALM, P., LARSSON, B., EKBLAD, E., SUNDLER, F., AND ANDERSSON, K.-E.: Immunohistochemical localization of peripheral nitric oxide synthase containing nerves using antibodies raised against synthetized C- and N-terminal fragments of a cloned enzyme from rat brain. Acta Physiol. Scand, in press, 1993.

ÅMARK, P., AND NERGÅRDH, A.: Influence of adrenergic agonists and antagonists on urethral pressure, bladder pressure and detrusor hyperactivity in children with myelodysplasia. Acta Paediatr. Scand. **80:** 824–832, 1991.

ÅMARK, P., NERGÅRDH, A., AND KINN, A. C.: The effect of noradrenaline on the contractile response of the urinary bladder. Scand. J. Urol. Nephrol. **20:** 203–207, 1986.

AMBACHE, H., AND ZAR, M. A.: Non-cholinergic transmission by postganglionic motor neurones in the mammalian bladder. J. Physiol. (Lond.) **210:** 761–783, 1970.

ANDERSON, G. F.: Evidence for a prostaglandin link in the purinergic activation of rabbit bladder smooth muscle. J. Pharmacol. Exp. Ther. **220:** 347–352, 1982.

ANDERSON, G., BARRACO, R. A., NORMILE, H. J., AND ROSEN, T. N.: Evidence for angiotensin II receptors in the urinary bladder of the rabbit. Can. J. Physiol. Pharmacol. **62:** 390–395, 1984.

ANDERSON, G., AND MARKS, B. H.: Spare cholinergic receptors in the urinary bladder. J. Pharmacol. Exp. Ther. **221:** 598–603, 1982.

ANDERSON, G., AND MARKS, B. H.: Beta adrenoceptors in the rabbit bladder detrusor muscle. J. Pharmacol. Exp. Ther. **228:** 283–286, 1984.

ANDERSON, G. F., AND NAVARRO, S. P.: The response of autonomic receptors to castration and testosterone in the urinary bladder of the rabbit. J. Urol. **140:** 885–889, 1988.

ANDERSSON, K.-E.: Clinical relevance of some findings in neuro-anatomy and neurophysiology of the lower urinary tract. Clin. Sci. **70** (Suppl. 14): 21–32, 1986.

ANDERSSON, K.-E.: Current concepts in the treatment of disorders of micturition. Drugs **35:** 477–494, 1988.

ANDERSSON, K.-E.: Neurotransmitters and receptor functions in the human lower urinary tract. *In* Micturition, edited by J. O. Drife, P. Hilton, S. L. Stanton, pp. 29–39, Springer Verlag, Berlin, Heidelberg, New York, 1990a.

ANDERSSON, K.-E.: Autonomic transmission and the unstable bladder. Neurourol. Urodyn. **9:** 555–557, 1990b.

ANDERSSON, K.-E.: Clinical pharmacology of potassium channel openers. Pharmacol. Toxicol. **70:** 244–254, 1992.

ANDERSSON, K.-E., ANDERSSON, P.-O., FOVAEUS, M., HEDLUND, H., MALMGREN, A., AND SJÖGREN, C.: Effects of pinacidil on bladder muscle. Drugs **36** (Suppl. 7): 41–49, 1988a.

ANDERSSON, K.-E., ATTA, M. A., ELBADAWI, A., LARSSON, B., MATTIASSON, A., AND SJÖGREN, C.: Effects of parasympathetic decentralization on some nerve-mediated functions in the feline urinary bladder. Acta Physiol. Scand. **141:** 11–18, 1991a.

ANDERSSON, K.-E., EK, A., AND PERSSON, C. G. A.: Effects of prostaglandins on the isolated human bladder and urethra. Acta Physiol. Scand. **100:** 165–171, 1977.

ANDERSSON, K.-E., EKSTRÖM, B., AND MATTIASSON, A.: Actions of terodiline, its isomers and main metabolite on isolated detrusor muscle from rabbit and man. Pharmacol. Toxicol. **63:** 390–395, 1988b.

ANDERSSON, K.-E., AND FORMAN, A.: Effects of prostaglandins on the smooth muscle of the urinary tract. Acta Pharmacol. Toxicol. **43** (Suppl. II): 90–95, 1978.

ANDERSSON, K.-E., AND FORMAN, A.: Effects of calcium channel blockers on urinary tract smooth muscle. Acta Pharmacol. Toxicol. **58** (Suppl. II): 193–200, 1986.

ANDERSSON, K.-E., FOVAEUS, M., HEDLUND, H., HOLMQUIST, F., AND SUNDLER, F.: Muscarinic receptor stimulation of phosphoinositide hydrolysis in the human urinary bladder (abstract 619). J. Urol. **141:** 324A, 1989.

ANDERSSON, K.-E., FOVAEUS, M., HEDLUND, H., AND LUNDIN, S.: Characterization of immunoreactive arginine vasopressin (AVP) in and effects of AVP on isolated human penile erectile tissue. J. Urol. **137:** 1278–1282, 1986a.

ANDERSSON, K.-E., FOVAEUS, M., MORGAN, E., AND MCLORIE, G.: Comparative effects of five different calcium channel blockers on the atropine resistant contraction in electrically stimulated rabbit urinary bladder. Neurourol. Urodyn. **5:** 579–586, 1986b.

ANDERSSON, K.-E, GARCIA-PASCUAL, A., FORMAN, A., AND TØTTRUP, A.: Non-adrenergic, non-cholinergic nerve mediated relaxation of rabbit urethra is caused by nitric oxide. Acta Physiol. Scand. **141:** 133–134, 21991b.

ANDERSSON, K.-E, GARCIA-PASCUAL, A., PERSSON, K., FORMAN, A., AND TØT-

TRUP, A.: Electrically induced, nerve-mediated relaxation of rabbit urethra involves nitric oxide. J. Urol. **147:** 253–259, 1992a.

ANDERSSON, K.-E., HEDLUND, H., AND FOVAEUS, M.: Interactions between classical neurotransmitters and some neuropeptides in human penile erectile tissues. *In* Neuronal Messengers in Vascular Function, edited by A. Nobin, Ch. Owman, and B. Arneklo-Nobin, pp. 505–524, Elsevier Science Publishers (Biomedical Division), Amsterdam, New York, Oxford, 1987a.

ANDERSSON, K.-E., HEDLUND, H., LARSSON, B., MATTIASSON, A., AND SJÖGREN, C.: Ketanserin interaction with urethral alpha-adrenoceptors. J. Urol. **137:** 534–538, 1987b.

ANDERSSON, K.-E., HEDLUND, H., MATTIASSON, A., SJÖGREN, C., AND SUNDLER, F.: Relaxation of isolated human corpus spongiosum induced by vasoactive intestinal polypeptide, substance P, carbachol and electrical field stimulation. World J. Urol. **1:** 203–208, 1983a.

ANDERSSON, K.-E., HEDLUND, H., AND STAHL, M.: Contractions induced by angiotensin I, angiotensin II and bradykinin in isolated smooth muscle from the human detrusor. Acta Physiol. Scand. **145:** 253–259, 1992b.

ANDERSSON, K.-E., HENRIKSSON, L., AND ULMSTEN, U.: Effects of prostaglandin E_2 applied locally on intravesical and intraurethral pressures in women. Eur. Urol. **4:** 366–369, 1978a.

ANDERSSON, K.-E., AND HOLMQUIST, F.: Mechanisms for contraction and relaxation of human penile smooth muscle. Int. J. Impotence Res. **2:** 209–225, 1990.

ANDERSSON, K.-E., HOLMQUIST, F., AND BØDKER, A.: Castration enhances NANC nerve-mediated relaxation in rabbit isolated corpus cavernosum. Acta Physiol. Scand. **146:** 405–406, 1992c.

ANDERSSON, K.-E., HOLMQUIST, F., FOVAEUS, M., HEDLUND, H., AND SUNDLER, F.: Muscarinic receptor stimulation of phosphoinositide hydrolysis in the human isolated urinary bladder. J. Urol. **146:** 1156–1159, 1991c.

ANDERSSON, K.-E., HOLMQUIST, F., AND WAGNER, G.: Pharmacology of drugs used for treatment of erectile dysfunction and priapism. Int. J. Impotence Res. **3:** 155–172, 1991d.

ANDERSSON, K.-E., HUSTED, S., AND SJÖGREN, C.: Contribution of prostaglandins to the adenosine triphosphate-induced contraction of rabbit urinary bladder. Br. J. Pharmacol. **70:** 443–452, 1980.

ANDERSSON, K.-E., LARSSON, B., AND SJÖGREN, C.: Characterization of the α-adrenoceptors in the female rabbit urethra. Br. J. Pharmacol. **81:** 293–300, 1984a.

ANDERSSON, K.-E., MATTIASSON, A., SJÖGREN, C.: Electrically induced relaxation of the noradrenaline contracted isolated urethra from rabbit and man. J. Urol. **129:** 210–213, 1983b.

ANDERSSON, K.-E., PERSSON, C. G. A., ALM, P., KULLANDER, S., AND ULMSTEN, U.: Effects of acetylcholine, noradrenaline, and prostaglandins on the isolated, perfused human fetal urethra. Acta Physiol. Scand. **104:** 394–401, 1978b.

ANDERSSON, K.-E., AND SJÖGREN, C.: Aspects on the physiology and pharmacology of the bladder and urethra. Prog. Neurobiol. **19:** 71–89, 1982.

ANDERSSON, P.-O., ANDERSSON, K.-E., FAHRENKRUG, J., MATTIASSON, A., SJÖGREN, C., AND UVELIUS, B.: Contents and effects of substance P and vasoactive intestinal polypeptide in the bladder of rats with and without infravesical outflow obstruction. J. Urol. **140:** 168–172, 1988c.

ANDERSSON, P.-O., BLOOM, S. R., MATTIASSON, A., AND UVELIUS B.: Bladder vasodilatation and release of vasoactive intestinal polypeptide from the urinary bladder of the cat in response to pelvic nerve stimulation. J. Urol. **138:** 671–673, 1987c.

ANDERSSON, P.-O., BLOOM, S. R., AND MELLANDER, S.: Hemodynamics of pelvic nerve induced penile erection in the dog: possible mediation by vasoactive intestinal polypeptide. J. Physiol. (Lond.) **350:** 209–224, 1984b.

ANDERSSON, P.-O., SJÖGREN, C., UVNÄS, B., AND UVNÄS-MOBERG, K.: Urinary bladder and urethral responses to pelvic and hypogastric nerve stimulation and their relation to vasoactive intestinal polypeptide in the anaesthetized dog. Acta Physiol. Scand. **138:** 409–416, 1990.

ANDERSSON, S. E.: Effects of intravenous calcitonin gene-related peptide on local blood flow in the cat. Acta Physiol. Scand. **137:** 259–270, 1989.

ANDRIOLE, V. T.: Urinary tract in pregnancy. Urol. Clin. North Am. **2:** 285–287, 1975.

ANGELUCCI, L. G., FALCONIERI ERSPAMER, G., AND NEGRI, L.: Bioassay of vasopressin on the rabbit isolated urinary bladder. J. Pharm. Pharmacol. **26:** 193–196, 1974.

AOKI, H., TAKAGANE, H., MATSUZAKA, J., BANYA, Y., FUJIOKA, T., NAKAYA, S., KUBO, T., AND OHHORI, T.: Quantitative analysis of outflow pathway of corpora cavernosa by pressure flow technique. J. Urol. **141:** 645–650, 1989.

ASMUSSEN, M., AND ULMSTEN, U.: Simultaneous urethro-cystometry with a new technique. Scand. J. Urol. Nephrol. **10:** 7–11, 1976.

AWAD, A. A., BRUCE, G., CARROCAMPI, J. W., LIN, M., AND MARKS, G. S.: Distribution of α- and β-adrenoceptors in human urinary bladder. Br. J. Pharmacol. **50:** 525–529, 1974.

AWAD, S. A., AND DOWNIE, J. W.: The effect of adrenergic drugs and hypogastric nerve stimulation on the canine urethra. A radiologic and urethral pressure study. Invest. Urol. **13:** 298–301, 1976.

AZADZOI, K. M., KIM, N., BROWN, M. L., GOLDSTEIN, I., COHEN, R. A., AND SAENZ DE TEJADA, I.: Endothelium-derived nitric oxide and cyclooxygenase products modulate corpus cavernosum smooth muscle tone. J. Urol. **147:** 220–225, 1992.

AZADZOI, K. M., PAYTON, T., KRANE, R. J., AND GOLDSTEIN, I.: Effects of intracavernosal trazodone hydrochloride: animal and human studies. J. Urol. **144:** 1277–1282, 1990.

AZADZOI, K. M., AND SAENZ DE TEJADA, I.: Hypercholesterolemia impairs endothelium-dependent relaxation of rabbit corpus cavernosum smooth muscle. J. Urol. **146:** 238–240, 1991.

AZADZOI, K. M., AND SAENZ DE TEJADA, I.: Diabetes mellitus impairs neurogenic and endothelium-dependent relaxation of rabbit corpus cavernosum smooth muscle. J. Urol. **148:** 1587–1591, 1992.

AZUMA, H., SUGIMOTO-TOKUSHIMA, M., TANAKA, K., IKENOUE, Y., ITO, S., AND ISHIKAWA, M.: α_1-adrenoceptor antagonist activity of novel pyrimidine derivatives (SHI437 and IK29) in rabbit aorta and trigone of the bladder. Br. J. Pharmacol. **96:** 1000–1006, 1989.

BANYA, Y., USHIKI, T., TAKAGANE, H., AOKI, H., KUBO, T., OHHORI, T., AND IDE, C.: Two circulatory routes within the human corpus cavernosum penis: a scanning electron microscopic study of corrosion casts. J. Urol. **142:** 879–883, 1989.

BAPNA, B. C., RAO, M. S., VAIDYANATHAN, S., CHARY, K. S. N., SWAMY, R. P., AND CHANDRASEKAR, D.: Lowering of maximum urethral closure pressure by phentolamine and by terbutaline. Indian J. Med. Res. **73:** 439–442, 1981.

BATRA, S., AND ANDERSSON, K.-E.: Oestrogen-induced changes in muscarinic receptor density and contractile responses in the female rabbit urinary bladder. Acta Physiol. Scand. **137:** 135–141, 1989.

BATRA, S., BJELLIN, L., SJÖGREN, C., IOSIF, S., AND WIDMARK, E.: Increases in blood flow of the female rabbit urethra following low dose estrogens. J. Urol. **136:** 1360–1362, 1986.

BATRA, S., BIÖRKLUND, A., HEDLUND, H., AND ANDERSSON, K.-E.: Identification and characterization of muscarinic cholinergic receptors in the human urinary bladder and parotid gland. J. Auton. Nerv. Syst. **20:** 129–135, 1987a.

BATRA, S., AND IOSIF, C. S.: Female urethra: a target for oestrogen action. J. Urol. **129:** 418–420, 1983.

BATRA, S., AND IOSIF, C. S.: Progesterone receptors in the female lower urinary tract. J. Urol. **138:** 1301–1304, 1987.

BATRA, S., AND IOSIF, C. S.: Effect of estrogen treatment on the peroxidase activity and estrogen receptors in the female rabbit urogenital tissues. J. Urol. **148:** 935–938, 1992.

BATRA, S., SJÖGREN, C., ANDERSSON, K.-E., AND FOVAEUS, M.: Source of calcium for contraction induced by depolarization and muscarinic receptor stimulation in rabbit urinary bladder. Acta Physiol. Scand. **130:** 545–551, 1987b.

BAUER, F. E., CHRISTOFIDES, N. D., HACKER, G. W., BLANK, M. A., POLAK, J. M., AND BLOOM, S. R.: Distribution of galanin in the genitourinary tract of man and rat. Peptides **7:** 5–10, 1986.

BEISLAND, H. O., FOSSBERG, E., AND SANDER, S.: On incompetent urethral closure mechanism: treatment with estriol and phenylpropanolamine. Scand. J. Urol. Nephrol. **60:** 67–69, 1981.

BENEDITO, S., PRIETO, D., RIVERA, L., COSTA, G., AND GARCÍA-SACRISTÍN, A.: Mechanisms implicated in the histamine response of the sheep ureterovesical junction. J. Urol. **146:** 184–187, 1991.

BENSON, G. S., MCCONNELL, J., LIPSHULTZ, L. J., CORRIERE, J. N., JR., AND WOOD, J. G.: Neuromorphology and neuropharmacology of the human penis. J. Clin. Invest. **65:** 506–513, 1980.

BERGGREN, A., AHLMAN, H., DAHLSTRÖM, A., RUBENSON, A., AND SILLÉN, U.: In vivo effects of substance P on the rat urinary bladder. J. Neural Transm. **74:** 207–217, 1988.

BERGGREN, A., RUBENSON, A., AND SILLÉN, U.: Involvement of opioid mechanisms in peripheral motor control of detrusor muscle. Pharmacol. Toxicol. **71:** 179–184, 1992.

BHAT, M. B., MISHRA, S. K., AND RAVIPRAKASH, V.: Differential susceptibility of cholinergic and non-cholinergic neurogenic responses to calcium channel blockers and low Ca^{2+} medium in rat urinary bladder. Br. J. Pharmacol. **96:** 837–842, 1989.

BISSADA, N. K., AND FINKBEINER, A. E.: Smooth muscle physiology and effect of bladder and urethra muscle length/tension on response to stimulation. Urology **16:** 323–330, 1980.

BLANCO, R., SAENZ DE TEJADA, I., GOLDSTEIN, I., KRANE, R. J., WOTIZ, H. H., AND COHEN, R. A.: Cholinergic neurotransmission in human corpus cavernosum. II. Acetylcholine synthesis. Am. J. Physiol. **254:** H459–H467, 1988.

BLANCO, R., SAENZ DE TEJADA, I., GOLDSTEIN, I., KRANE, R. J., WOTIZ, H. H., AND COHEN, R. A.: Dysfunctional penile cholinergic nerves in diabetic impotent men. J. Urol. **144:** 278–280, 1992.

BLUM, M. D., BAHNSON, R. R., PORTER, T. M., AND CARTER, M. F.: Effect of local alpha-adrenergic blockade on human penile erection. J. Urol. **134:** 479–481, 1985.

BO, X., AND BURNSTOCK, G.: The effects of BAY K 8644 and nifedipine on the responses of rat urinary bladder to electrical field stimulation, β-γ-methylene ATP and acetylcholine. Br. J. Pharmacol. **101:** 494–498, 1990.

BORDA, E., CONTRERAS-ORTIZ, R., GUTNISKI, R., AND GIMENO, M. F.: In vitro effect of acetylcholine and bethanechol on the contractions of the human detrusor muscle. Influence of prostaglandins. Arch. Int. Pharmacodyn. Ther. **259:** 31–39, 1982.

BORNMAN, M. S., FRANZ, R. C., JACOBS, D. J., AND DU PLESSIS, D. J.: Thromboxane B_2 production during erection. Andrologia **18:** 220–223, 1986.

BOSCH, R. J. L. H., BENARD, F., ABOSEIF, S. R., STIEF, C. G., STACKL, W., LUE, T. F., AND TANAGHO, E. A.: Changes in penile hemodynamics after intracavernous injection of prostaglandin E_1 and prostaglandin I_2 in pigtailed monkeys. Int. J. Impotence Res. **1:** 211–221, 1989.

BOWMAN, A., AND GILLESPIE, J. S.: Neurogenic vasodilatation in isolated bovine and canine penile arteries. J. Physiol. (Lond.) **341:** 603–616, 1983.

BRADING, A. F.: Physiology of bladder smooth muscle. *In* The Physiology of the Lower Urinary Tract, edited by M. Torrens and J. F. B. Morrison, pp. 161–191, Springer Verlag, Berlin Heidelberg, 1987.

BRADING, A. F.: Ion channels and control of contractile activity in urinary bladder smooth muscle. Jpn. J. Pharmacol. **58** (Suppl. 2): 120P-127P, 1992.

BRADING, A. F., AND CHEN, H.-I.: High potassium solution induces relaxation in the isolated pig urethra abstract 118P. J. Physiol. (Lond.), 1990.

BRADING, A. F., AND INOUE, R.: Ion channels and excitatory transmission in the smooth muscle of the urinary bladder. Z. Kardiol. **80** (Suppl. 7): 47–53, 1991.

BRADING, A. F., AND MOSTWIN, J. L.: Electrical and mechanical responses of guinea-pig bladder muscle to nerve stimulation. Br. J. Pharmacol. **98:** 1083–1090, 1989.

BRADING, A. F., PAREKH, A., AND TOMITA, T.: Tissue impedance of smooth muscle isolated from guinea-pig. J. Physiol. (Lond.) **417:** 63P, 1989.

BRADING, A. F., AND WILLIAMS, J. H.: Contractile responses of smooth muscle strips from rat and guinea-pig urinary bladder to transmural stimulation: effects of atropine and α,β-methylene-ATP. Br. J. Pharmacol. **99:** 493–498, 1990.

BREDT, D. S., HWANG, P. M., GLATT, C. E., LOWENSTEIN, C., REED, R. R., AND SNYDER, S. H.: Cloned and expressed nitric oxide synthase structurally resembles cytochrome P-450 reductase. Nature (Lond.) **351:** 714–718, 1991.

BRINDLEY, G. S.: Cavernosal alpha-blockade and human penile erection. J. Physiol. (Lond.) **342:** 24, 1983a.

BRINDLEY, G. S.: Cavernosal alpha-blockade: a new technique for investigating and treating erectile impotence. Br. J. Psychiatry **143:** 332–337, 1983b.

BRINDLEY, G. S.: A new treatment for priapism. Lancet **2:** 220–221, 1984.

BRINDLEY, G. S.: Pilot experiments on the actions of drugs injected into the human corpus cavernosum penis. Br. J. Pharmacol. **87:** 495–500, 1986.

BRINDLEY, G. S.: Neurophysiology. *In* Impotence: Diagnosis and Management of Male Erectile Dysfunction, edited by R. S. Kirby, C. Carson, and G. D. Webster, pp. 27–31, Butterworth-Heinemann Ltd, Oxford, 1991.

BRODERICK, G., HYPOLITE, J., AND LEVIN, R. M.: In-vitro contractile response of the rabbit corpus cavernosa to field stimulation and autonomic agonists and antagonists: a qualitative study. Neurourol. Urodyn. **10:** 507–515, 1991.

BROWN, C., BURNSTOCK, G., AND COCKS, T.: Effects of adenosine 5′-triphosphate and beta, gamma-methylene ATP on the rat urinary bladder. Br. J. Pharmacol. **65:** 97–102, 1979.

BROWN, W. W., ZENSER, T. V., AND DAVIS, B. B.: Prostaglandin E_2 production by rabbit urinary bladder. Am. J. Physiol. **239:** F452–F458, 1980.

BULTITUDE, M. J., HILLS, N. H., AND SHUTTLEWORTH, K. E. D.: Clinical and experimental studies on the action of prostaglandins and their synthesis inhibitors on detrusor muscle in vitro and in vivo. Br. J. Urol. **48:** 631–637, 1976.

BUMP, R. C., AND FRIEDMAN, C. I.: Intraluminal urethral pressure measurements in the female baboon: effects of normal manipulation. J. Urol. **136:** 508–511, 1986.

BURCHER, E., AND BUCK, S. H.: Multiple tachykinin binding sites in hamster, rat and guinea-pig urinary bladder. Eur. J. Pharmacol. **128:** 165–177, 1986.

BURCHER, E., BUCK, S. H., LÖVENBERG, W., AND O'DONAHUE, T. L.: Characterization and autoradiographic localization of multiple tachykinin binding sites in gastrointestinal tract and bladder. J. Pharmacol. Exp. Ther. **236:** 819–831, 1986.

BURNETT, A. L., LOWENSTEIN, C. J., BREDT, D. S., CHANG, T. S. K., AND SNYDER, S. H.: Nitric oxide: a physiologic mediator of penile erection. Science (Washington, D. C.) **257:** 401–403, 1992.

BURNSTOCK, G.: Innervation of bladder and bowel. *In* Neurobiology of Incontinence. Ciba Foundation Symposium 151, pp. 2–26, Wiley, Chichester, 1990.

BURNSTOCK, G., COCKS, T., CROWE, R., AND KASAKOV, L.: Purinergic innervation of the guinea-pig urinary bladder. Br. J. Pharmacol. **63:** 125–138, 1978a.

BURNSTOCK, G., COCKS, T., KASAKOV, L., AND WONG, A.: Direct evidence for ATP release from non-adrenergic, non-cholinergic ("purinergic") nerves in the guinea-pig taenia coli and bladder. Eur. J. Pharmacol. **49:** 145–149, 1978b.

BURNSTOCK, G., DUMSDAY, B., AND SMYTHE, A.: Atropine resistant excitation of the urinary bladder: the possibility of transmission via nerves releasing a purine nucleotide. Br. J. Pharmacol. **44:** 451–461, 1972.

BUSH, P. A., ARONSON, W. J., BUGA, G. M., RAJFER, J., AND IGNARRO, L. J.: Nitric oxide is a potent relaxant of human and rabbit corpus cavernosum. J. Urol. **147:** 1650–1655, 1992a.

BUSH, P. A., ARONSON, W. J., RAJFER, J., BUGA, G. M., AND IGNARRO, L. J.: Comparison of nonadrenergic, noncholinergic-and nitric oxide-mediated relaxation of corpus cavernosum. Int. J. Impotence Res. **4:** 85–93, 1992b.

BUSH, P. A., GONZALEZ, N. E., AND IGNARRO, L. J.: Biosynthesis of nitric oxide and citrulline from L-arginine by constitutive nitric oxide synthase present in rabbit corpus cavernosum. Biochem. Biophys. Res. Commun. **186:** 308–314, 1992c.

BUVAT, J., LEMAIRE, A., BUVAT-HERBAUT, M., AND MARCOLIN, G.: Safety of intracavernous injections using an alpha-blocking agent. J. Urol. **141:** 1364–1367, 1989.

CAINE, M.: The place of pharmacologic treatment in benign prostatic hyperplasia. Semin. Urol. **3:** 311–316, 1985.

CAINE, M.: The present role of alpha-adrenergic blockers in the treatment of benign prostatic hyperplasia. J. Urol. **136:** 1–4, 1986.

CALLAHAN, S. M., AND CREED, K. E.: Electrical and mechanical activity of the isolated lower urinary tract of the guinea-pig. Br. J. Pharmacol. **74:** 353–358, 1981.

CALLAHAN, S. M., AND CREED, K. E.: The effects of oestrogen on spontaneous activity and responses to phenylephrine of the mammalian urethra. J. Physiol. (Lond.) **358:** 35–46, 1985.

CALLAHAN, S. M., AND CREED, K. E.: Non-cholinergic neurotransmission and the effects of peptides on the urinary bladder of guinea-pigs and rabbits. J. Physiol. (Lond.) **374:** 103–115, 1986.

CAMPOS DE CARVALHO, A. C., ROY, C., MORENO, A. P., MELMAN, A., HERTZBERG, E. L., CHRIST, G. J., AND SPRAY, D. C.: Gap junctions formed of connexin43 found between smooth muscle cells of human corpus cavernosum. J. Urol., **149:** 1568–1575, 1993.

CARATI, C. J., CREED, K. E., AND KEOGH, E. J.: Vascular changes during erection in the dog. J. Physiol. (Lond.) **400:** 75–88, 1988.

CARATI, C. J., GOLDIE, R. G., WARTON, A., HENRY, P. J., AND KEOGH, E. J.: Pharmacology of the erectile tissue of the canine penis. Pharmacol. Res. Commun. **17:** 951–966, 1985.

CARDOZO, L. D., AND STANTON, S. L.: A comparison between bromocriptine and indomethacin in the treatment of detrusor instability. J. Urol. **123:** 399–401, 1980.

CARDOZO, L. D., STANTON, S. L., ROBINSON, H., AND HOLE, D.: Evaluation of flurbiprofen in detrusor instability. Br. Med. J. [Clin. Res.] **280:** 281–282, 1980.

CARPENTER, F. G.: Atropine resistance and muscarinic receptors in the rat urinary bladder. Br. J. Pharmacol. **59:** 43–49, 1977.

CHALFIN, S. A., AND BRADLEY, W. E.: The etiology of detrusor hyperreflexia in patients with infravesical obstruction. J. Urol. **127:** 938–942, 1982.

CHANCELLOR, M. B., KAPLAN, S. A., AND BLAIVAS, J. G.: The cholinergic and purinergic components of detrusor contractility in a whole rabbit bladder model. J. Urol. **148:** 906–909, 1992.

CHAPPLE, C. R., MILNER, P., MOSS, H. E., AND BURNSTOCK, G.: Loss of sensory neuropeptides in the obstructed human bladder. Br. J. Urol. **70:** 373–381, 1992.

CHEN, H.-I.: Evidence for the presynaptic action of 5-hydroxytryptamine and the involvement of purinergic innervation in the rabbit lower urinary tract. Br. J. Pharmacol. **101:** 212–216, 1990.

CHEN, T. F., DOYLE, P. T., AND FERGUSON, D. R.: Inhibitory role of gamma-amino-butyric acid in the rabbit urinary bladder. Br. J. Urol. **69:** 12–16, 1992.

CHESTER, G. B., AND THORPE, R. H.: The atropine-resistance of the response to intrinsic nerve stimulation of the guinea-pig bladder. Br. J. Pharmacol. **25:** 288–294, 1965.

CHOO, L. K., AND MITCHELSON, F.: The role of prostaglandins in the excitatory innervation of the rat urinary bladder. Prostaglandins **13:** 917–926, 1977.

CHOO, L. K., AND MITCHELSON, F.: The effect of indomethacin and adenosine 5′-triphosphate on the excitatory innervation of the rat urinary bladder. Can. J. Physiol. Pharmacol. **58:** 1042–1048, 1980.

CHRIST, G. J., MAAYANI, S., VALCIC, M., AND MELMAN, A.: Pharmacological studies of human erectile tissue: characteristics of spontaneous contractions and alterations in α-adrenoceptor responsiveness with age and disease in isolated tissues. Br. J. Pharmacol. **101:** 375–381, 1990.

CHRIST, G. J., MORENO, A. P., MELMAN, A., AND SPRAY, D. C.: Gap junction-mediated intercellular diffusion of Ca^{2+} in cultured human corporal smooth muscle. Am. J. Physiol. **263:** C373–C383, 1992a.

CHRIST, G. J., MORENO, A. P., PARKER, M. E., GONDRE, C. M., VALCIC, M., MELMAN, A., AND SPRAY, D. C.: Intercellular communication through gap junctions: a potential role in pharmacomechanical coupling and syncytial tissue contraction in vascular smooth muscle isolated from the human corpus cavernosum. Life Sci. **49:** PL195-PL200, 1991a.

CHRIST, G. J., SCHWARTZ, C. B., STONE, B. A., PARKER, M., JANIS, M., GONDRE, M., VALCIC, M., AND MELMAN, A.: Kinetic characteristics of α_1-adrenergic contractions in human corpus cavernosum smooth muscle. Am. J. Physiol. **263:** H15–H19, 1992b.

CHRIST, G. J., SPRAY, D. C., MELMAN, A., AND BRINK, P.: Electrophysiological studies of ion channels in cultured human corporal smooth muscle cells in culture. Int. J. Impotence Res. **4** (Suppl. 2): A40, 1992c.

CHRIST, G. J., STONE, B., AND MELMAN, A.: Age-dependent alterations in the efficacy of phenylephrine-induced contractions in vascular smooth muscle from the corpus cavernosum of impotent men. Can. J. Physiol. Pharmacol. **69:** 909–913, 1991b.

CHRIST, G. J., VALCIC, M., MAAYANI, S., AND MELMAN, A.: Kinetic studies of contraction in human erectile tissue (HET) and rabbit aortic rings in vitro: modulation by papaverine and the dihydropyridine analog nifedipine. Int. J. Impotence Res. **1:** 1–10, 1989.

CLAES, H., AND BAERT, L.: Transcutaneous nitroglycerin therapy in the treatment of impotence. Urol. Int. **44:** 309–312, 1989.

CLEAN, A., CORSI, M., FENIYUK, W., GAVIRAGHI, G., TOSON, G., TREZISE, D., AND TRIST, D.: Potentiating action of 5-hydroxytryptamine on electrically induced contractions in the mouse urinary bladder. Br. J. Pharmacol. **97:** 564P, 1989.

COHEN, M. L.: Canine, but not rat bladder contracts to serotonin via activation of $5HT_2$ receptors. J. Urol. **143:** 1037–1040, 1990.

CONNOLLY, M. J., ASTRIDGE, P. S., WHITE, E. G., MORLEY, C. A., AND CAMPBELL COWAN, J.: Torsades de pointes complicating treatment with terodiline. Lancet **338:** 344–345, 1991.

COOK, N. S.: The pharmacology of potassium channels and their therapeutical potential. Trends Pharmacol. Sci. **9:** 21–28, 1988.
COOLSAET, B.: Bladder compliance and detrusor activity during the collection phase. Neurourol. Urodyn. **4:** 263–273, 1985.
CORNISH, K. G., JOYNER, W. L., AND GILMORE, J. P.: Direct evidence for the presence of a different converting enzyme in the hamster cheek pouch. Circ. Res. **44:** 540–544, 1979.
CORSI, M., PIETRA, C., TOSON, G., TRIST, D., TUCCITTO, G., AND ARTIBANI, W.: Pharmacological analysis of 5-hydroxytryptamine effects on electrically stimulated human isolated urinary bladder. Br. J. Pharmacol. **104:** 719–725, 1991.
COWAN, W. D., AND DANIEL, E. E.: Human female bladder and its noncholinergic contractile function. Can. J. Physiol. Pharmacol. **61:** 1236–1246, 1983.
CRAGGS, M. D., RUSHTON, D. N., AND STEPHENSON, J. D.: A putative noncholinergic mechanism in urinary bladder of new but not old world primates. J. Urol. **136:** 1348–1350, 1986.
CRANKSHAW, D.: [Arg^8]vasopressin-induced contractions of rabbit urinary bladder smooth muscle. Eur. J. Pharmacol. **173:** 183–188, 1989.
CREED, K. E.: Membrane properties of smooth muscle membrane of the guinea-pig urinary bladder. Pflugers Arch. **326:** 115–126, 1971a.
CREED, K. E.: Effects of ions and drugs on the smooth muscle cell membrane of the guinea-pig urinary bladder. Pflugers Arch. **326:** 127–141, 1971b.
CREED, K. E., AND CALLAHAN, S. M.: Prostaglandins and neurotransmission at the guinea pig and rabbit urinary bladder. Pflugers Arch. **413:** 299–302, 1989.
CREED, K. E., CARATI, C. J., ADAMSON, G. M., AND CALLAHAN, S. M.: Responses of erectile tissue from impotent men to pharmacological agents. Br. J. Urol. **64:** 180–182, 1989.
CREED, K. E. ISHIKAWA, S., AND ITO, Y.: Electrical and mechanical activity recorded from rabbit urinary bladder in response to nerve stimulation. J. Physiol. (Lond.) **338:** 149–164, 1983.
CREED, K. E., ITO, Y., AND KATSUYAMA, H.: Neurotransmission in the urinary bladder of rabbits and guinea pigs. Am. J. Physiol. **261:** C271–C277, 1991.
CREED, K. E., AND TULLOCH, A. G. S.: The effect of pelvic nerve stimulation and some drugs on the urethra and bladder of the dog. Br. J. Urol. **50:** 398–405, 1978.
CROSSMAN, D., MCEWAN, J., MACDERMOT, J., MACINTYRE, I., AND DOLLERY, C. T.: Human calcitonin gene-related peptide activates adenylate cyclase and releases prostacyclin from human umbilical vein endothelial cells. Br. J. Pharmacol. **92:** 695–701, 1987.
CULLUMBINE, H., MCKEE, W., AND CREASEY, N. H.: The effects of atropine sulphate upon healthy male subjects. Q. J. Exp. Physiol. **30:** 309–319, 1955.
CUSACK, N. J, AND HOURANI, S. M. O.: Some pharmacological and biochemical interactions of the enantiomers of adenylyl 5′-(β,γ-methylene)-diphosphonate with the guinea-pig urinary bladder. Br. J. Pharmacol. **82:** 155–159, 1984.
DAHLÉN, S.-E., AND HEDQVIST, P.: ATP. β,γ-methylene-ATP, and adenosine inhibit non-cholinergic, non-adrenergic transmission in rat urinary bladder. Acta Physiol. Scand. **109:** 137–142, 1980.
D'AGOSTINO, G., KILBINGER, H., CHIARI, M. C., AND GRANA, E.: Presynaptic inhibitorymuscarinic receptors modulating ^{3}H-acetylcholine release in the rat urinary bladder. J. Pharmacol. Exp. Ther. **239:** 522–528, 1986.
DAIL, W. G., MCGUFFEE, L., MINORSKY, N., AND LITTLE, S.: Responses of smooth muscle strips from penile erectile tissue to drugs and transmural nerve stimulation. J. Auton. Pharmacol. **7:** 287–293, 1987.
DANIEL, E. E., COWAN, W., AND DANIEL, V. P.: Structural bases for neural and myogenic control of human detrusor muscle. Can. J. Physiol. Pharmacol. **61:** 1247–1273, 1983.
DAVE, K. C., AND DHATIWALLA, A. S.: Adrenoceptors of the guinea-pig urinary bladder. Br. J. Pharmacol. **58:** 37–41, 1976.
DAWSON, T. M., BREDT, D. S., FOTUHI, M., HWANG, P. M., AND SNYDER, S. H.: Nitric oxide synthase and neuronal NADPH diaphorase are identical in brain and peripheral tissues. Proc. Natl. Acad. Sci. USA **88:** 7797–7801, 1991.
DEAN, D. M., AND DOWNIE, J. W.: Contribution of adrenergic and "purinergic" neurotransmission to contraction in rabbit detrusor. J. Pharmacol. Exp. Ther. **207:** 431–445, 1978a.
DEAN, D. M., AND DOWNIE, J. W.: Interaction of prostaglandins and adenosine-5′-phosphate in the noncholinergic neurotransmission in rabbit detrusor. Prostaglandins **16:** 245–251, 1978b.
DE GROAT, W. C.: The actions of γ-aminobutyric acid and related amino acids on mammalian autonomic ganglia. J. Pharmacol. Exp. Ther. **172:** 384–396, 1970.
DE GROAT, W. C.: Nervous control of the urinary bladder of the cat. Brain. Res. **87:** 201–211, 1975.
DE GROAT, W. C.: Central neural control of the lower urinary tract. *In* Neurobiology of Incontinence. Ciba Foundation Symposium 151, pp. 27–56, Wiley, Chichester, 1990.
DE GROAT, W. C., AND BOOTH, A. M.: Inhibition and facilitation in parasympathetic ganglia of the urinary bladder. Fed. Proc. **39:** 2990–2996, 1980.
DE GROAT, W. C., AND BOOTH, A. M.: Neural control of penile erection. *In* The Autonomic Nervous System, Vol. 6, Chapter 13, Nervous Control of the Urogenital System, edited by C. A. Maggi, pp. 465–513, Harwood Academic Publishers, London, 1992.
DE GROAT, W. C., BOOTH, A. M., AND YOSHIMURA, N.: Neurophysiology of micturition and its modification in animal models of human disease. *In* The Autonomic Nervous System,. Vol. 6, Chapter 8, Nervous Control of the Urogenital System, edited by C. A. Maggi, pp. 227–289, Harwood Academic Publishers, London, 1992.
DE GROAT, W. C., AND KAWATANI, M.: Neural control of the urinary bladder: possible relationship between peptidergic inhibitory mechanisms and detrusor instability. Neurourol. Urodyn. **4:** 285–300, 1985.
DE GROAT, W. C., AND KAWATANI, M.: Enkephalinergic inhibition in parasympathetic ganglia of the urinary bladder of the cat. J. Physiol. (Lond.) **413:** 13–29, 1989.
DE GROAT, W. C., KAWATANI, M., HISAMITSU, T., CHENG, C.-L., MA, C.-P., THOR, K., STEERS, W., AND ROPPOLO, J.: Mechanisms underlying the recovery of urinary bladder function following spinal cord injury. J. Auton. Nerv. Syst. **30:** S71–S78, 1990.
DE GROAT, W. C., KAWATANI, M., HISAMITSU, T., LOWE, I., MORGAN, C., ROPPOLO, J., BOOTH, A. M., NADELHAFT, I., KUO, D., AND THOR, K.: The role of neuropeptides in the sacral autonomic reflex pathways in the cat. J. Auton. Nerv. Syst. **7:** 339–350, 1983.
DE GROAT, W. C., NADELHAFT, I., MILNE, R. J., BOOTH, A. M., MORGAN, C., AND THOR, K.: Organization of the sacral parasympathetic reflex pathways to the urinary bladder and large intestine. J. Auton. Nerv. Syst. **3:** 135–160, 1981.
DE GROAT, W. C., AND SAUM, W. R.: Sympathetic inhibition of the urinary bladder and of pelvic ganglionic transmission in the cat. J. Physiol. (Lond.) **220:** 297–314, 1972.
DE GROAT, W. C., AND STEERS, W. D.: Neuroanatomy and neurophysiology of penile erection. *In* Contemporary Management of Impotence and Infertility, edited by E. A. Tanagho, T. F. Lue, T. F., and R. D. McClure, pp. 3–27, Williams & Wilkins, Baltimore, 1988.
DE GROAT, W. C., AND THEOBALD, R. C.: Reflex activation of sympathetic pathways to vesical smooth muscle and parasympathetic ganglia by electrical stimulation of vesical afferents. J. Physiol. (Lond.) **259:** 223–237, 1976.
DELAERE, K. P. J., DEBRUYNE, F. M. J., AND BOOIJ, L. H. D.: Influence of ketanserin (serotonin antagonist) on bladder and urethral function. Urology **29:** 669–673, 1987.
DELAERE, K. P. J., THOMAS, C. M. G., MOONEN, W. A., AND DEBRUYNE, F. M. J.: The value of intravesical prostaglandin E_2 and $F_{2\alpha}$ in women with abnormalities of bladder emptying. Br. J. Urol. **53:** 306–309, 1981.
DELANCEY, J. O. L.: Functional anatomy of the female lower urinary tract and pelvic floor. *In* Neurobiology of Incontinence, Ciba Foundation Symposium 151, pp. 57–76, Wiley, Chichester, 1990.
DE MEYER, J. M., AND DE SY, W. A.: Intracavernous injection of noradrenaline in interrupt erections during surgical interventions. Eur. Urol. **12:** 169–170, 1986.
DESAI, K. M., SESSA, W. C., AND VANE, J. R.: Involvement of nitric oxide in the reflex relaxation of the stomach to accommodate food or fluid. Nature **351:** 477–479, 1991.
DESMOND, A. D., BULTITUDE, M. I., HILLS, N. H., AND SHUTTLEWORTH, K. E. D.: Clinical experience with intravesical prostaglandin E_2. A prospective study in 36 patients. Br. J. Urol. **52:** 357–366, 1980.
DHABUWALA, C. B., RAMAKRISHNA, V. R., AND AND ERSON, G. F.: Beta adrenergic receptors in human cavernous tissue. J. Urol. **133:** 721–723, 1985.
DHASMANA, K. M., GUPTA, G. P., AND BHARGAVA, K. P.: Analysis of the adrenergic receptors in the urinary tract of dog. Jpn. J. Pharmacol. **20:** 461–466, 1970.
DIEDERICHS, W., SROKA, J., AND GRAFF, J.: Comparison of Bay K8644, nitrendipine and atropine on spontaneous and pelvic-nerve-induced bladder contractions on rat bladder in vivo. Urol Res. **20:** 49–55, 1992.
DION, S., CORCOS, J., CARMEL, M., DRAPEAU, G., AND REGOLI, D.: Substance P and neurokinins as stimulants of the human isolated urinary bladder. Neuropeptides **11:** 83–87, 1988.
DION, S., D'ORLEANS-JUSTE, P., DRAPEAU, G., RHALEB, N. E., ROUISSI, N., TOUSIGNANT, C., AND REGOLI, D.: Characterization of neurokinin receptors in various isolated organs by the use of selective agonists. Life Sci. **41:** 2269–2276, 1987.
DIXON, J., AND GOSLING, J.: Structure and innervation in the human. *In* The Physiology of the Lower Urinary Tract, edited by M. Torrens and J. F. B. Morrison, pp. 3–22, Springer Verlag, Berlin, Heidelberg, 1987.
DIXON, J. S., AND GOSLING, J. A.: Ultrastructure of smooth muscle cells in the urinary system. *In* Ultrastructure of Smooth Muscle, edited by P. M. Motta, pp. 153–169, Kluwer Academic Publishers, Boston, Dordrecht, London, 1990.
DOKITA, S., MORGAN, W. R., WHEELER, M. A., YOSHIDA, M., LATIFPOUR, J., AND WEISS, R. M.: N^G-nitro-L-arginine inhibits non-adrenergic, non-cholinergic relaxation in rabbit urethral smooth muscle. Life Sci. **48:** 2429–2436, 1991.
DONKER, P. J., AND VAN DER SLUIS, C.: Action of β-adrenergic blocking agents on the urethral pressure profile. Urol. Int. **31:** 6–12, 1976.
DOWNIE, J. W., AND DEAN, D. M.: The contribution of cholinergic postganglionic neurotransmission to contractions of rabbit detrusor. J. Pharmacol. Exp. Ther. **203:** 417–425, 1977.
DOWNIE, J. W., DEAN, D. M., CARRO-CIAMPI, G., AND AWAD, S. A.: A difference in sensitivity to alpha-adrenergic agonists exhibited by detrusor and bladder neck of rabbit. Can. J. Physiol. Pharmacol. **53:** 525–530, 1975.
DOWNIE, J. W., AND KARMAZYN, M.: Mechanical trauma to bladder epithelium liberates prostanoids which modulate neurotransmission in rabbit detrusor. J. Pharmacol. Exp. Ther. **230:** 445–449, 1984.
DOWNIE, J. W., AND LARSSON, C.: Prostaglandin involvement in contractions evoked in rabbit detrusor by field stimulation and by adenosine 5′-triphosphate. Can. J. Physiol. Pharmacol. **59:** 253–260, 1981.

DOWNIE, J. W., AND LAUTT, W. W.: Is sympathetic control of the urethra mediated through vasomotor action? Neurourol. Urodyn. **5:** 219–225, 1986.

DOWNIE, J. W., MOOCHALA, S. M., AND BIALIK, G. J.: The role of reflexes in modifying the response to bethanechol chloride: a basis for selectivity of action on the bladder. Neurourol. Urodyn. **2:** 301–309, 1983.

DOWNIE, J. W., AND ROUFFIGNAC, S.: Response of rabbit detrusor to bradykinin. Life Sci. **28:** 603–608, 1981.

DOWNIE, J. W., AND SLACK, B. E.: Sensitivity to indomethacin of tetrodotoxin-resistant contractions of smooth muscle from the base of rabbit bladder. Br. J. Pharmacol. **79:** 334–336, 1983.

DRAY, A., AND METSCH, R.: Morphine and the centrally-mediated inhibition of urinary bladder motility in the rat. Brain Res. **297:** 191–195, 1984.

DUMSDAY, B.: Atropine-resistance of the urinary bladder. J. Pharm. Pharmacol. **23:** 222–225, 1971.

DVEKSLER, G., FRANCHI, A. M., GONZALEZ, E. T., GIMENO, M. A. F., AND GIMENO, A. L.: Electric field stimulation alters the output of prostaglandins from isolated rat urinary bladder preparations. Influences of papaverine and tetradotoxin. Prostaglandins Leukotrienes Essent. Fatty Acids. **36:** 65–68, 1989.

DVEKSLER, G., GIMENO, M. F., AND GIMENO, A. L.: Non-cholinergic inotropic responses evoked by electric field stimulation in the isolated rat urinary bladder. Pharmacol. Res. Commun. **17:** 1109–1119, 1985.

DZAU, V. J: Circulating versus local renin-angiotensin system in cardiovascular homeostasis. Circulation **77** (Suppl. I): 1–4, 1988.

EATON, A. C., AND BATES, C. P.: An in vitro physiological study of normal and unstable human detrusor muscle. Br. J. Urol. **54:** 653–657, 1982.

ECKHARDT, C.: Untersuchungen über die Erection des Penis beim Hunde. Beiträge zur Anatomie und Physiologie **3:** 123–166, 1863.

EDGE, N. D.: A contribution to the innervation of the urinary bladder of the cat. J. Physiol. (Lond.) **127:** 54–68, 1955.

EDVARDSEN, P.: Nervous control of urinary bladder in cats. III. Effects of autonomic blocking agents in the intact animal. Acta Physiol. Scand. **72:** 183–193, 1968.

EDWARDS, G., HENSHAW, M., MILLER, M., AND WESTON, A. H.: Comparison of the effects of several potassium-channel openers on rat bladder and rat portal vein in vitro. Br. J. Pharmacol. **102:** 679–686, 1991.

EDYVANE, K. A., AND MARSHALL, V. R.: Neuropeptides in the human urinary tract. Neurourol. Urodyn. **9:** 346–347, 1990.

EK, A., ALM, P., ANDERSSON, K.-E., AND PERSSON, C. G. A.: Adrenoceptor and cholinoceptor mediated responses of the isolated human urethra. Scand. J. Urol. Nephrol. **11:** 97–102, 1977.

EK, A., ANDERSSON, K.-E., AND ULMSTEN, U.: The effects of norephedrine and bethanechol on the human urethral closure pressure profile. Scand. J. Urol. Nephrol. **12:** 97–104, 1978.

ELBADAWI, A: Comparative neuromorphology in animals. *In* The Physiology of the Lower Urinary Tract, edited by M. Torrens and J. F. B. Morrison, pp. 23–51, Springer Verlag, Berlin, Heidelberg, 1987.

ELBADAWI, A: Anatomy and innervation of the vesicourethral muscular unit of micturition. *In* Clinical Neurourology, edited by R. J. Krane and M. B. Siroky, 2nd ed., pp. 5–23, Little, Brown and Company, Boston, Toronto, London, 1991.

ELLIOTT, R. A., CASTLEDEN, C. M., MIODRAG, A., AND KIRWAN, P.: The direct effects of diethylstilboestrol and nifedipine on the contractile responses of isolated human and rat detrusor muscles. Eur. J. Clin. Pharmacol. **43:** 149–155, 1992a.

ELLIOTT, R. A., CASTLEDEN, C. M., AND MIODRAG, A.: The effect of in vivo oestrogen pretreatment on the contractile response of rat isolated detrusor muscle. Br. J. Pharmacol. **107:** 766–770, 1992b.

ELMÉR, M.: Action of drugs on the innervated and denervated urinary bladder of the rat. Acta Physiol. Scand. **91:** 289–297, 1974a.

ELMÉR, M.: Inhibitory β-adrenoceptors in the urinary bladder of the rat. Life Sci. **15:** 273–280, 1974b.

ERDÖ, S. L., MIONE, M. C., AMENTA, F., AND WOLFF, J. R.: Binding of [^{3}H]-muscimol to $GABA_A$ sites in the guinea-pig urinary bladder: biochemical assay and autoradiography. Br. J. Pharmacol. **96:** 313–318, 1989.

ERSPAMER, V., RONZONI, G., AND FALCONIERI-ERSPAMER, G.: Effects of active peptides on the isolated muscle of the human urinary bladder. Invest. Urol. **18:** 302–304, 1981.

FABER, P., AND HEIDENREICH, J.: Treatment of stress incontinence with estrogen in postmenopausal women. Urol. Int. **32:** 221–223, 1977.

FALCONIERI ERSPAMER, G., NEGRI, L., AND PICCINELLI, D.: The use of preparations of urinary bladder smooth muscle for bioassay of and discrimination between polypeptides. Naunyn Schmiedebergs Arch. Pharmacol. **279:** 61–64, 1973.

FALCONIERI ERSPAMER, G., SEVERINI, C., ERSPAMER, V., MELCHIORRI, P., DELLE FAVE, G., AND NAKAJIMA, T.: Parallel bioassay of 27 bombesin-like peptides on 9 smooth muscle preparations. Structure activity relationships and bombesin receptor subtypes. Regul. Pept. **21:** 1–11, 1988.

FAUSTINI, S., SALVINI, A., PIZZI, P., CONTI, M., MAGISTRETTI, M. J., AND VESCOVINI, R.: Experimental study on the action of diltiazem on detrusor muscle and clinical evaluation in patients with detrusor hyperactivity. Arzneim. Forsch. **39:** 899–903, 1989.

FEELISCH, M.: The biochemical pathways of nitric oxide formation from nitrovasodilators: appropriate choice of exogenous NO donors and aspects of preparation and handling of aqueous NO solutions. J. Cardiovasc. Pharmacol. **17** (Suppl. 3): S25–S33, 1991.

FETISSOF, F., DUBOIS, M. P., ARBEILLE-BRASSART, B., LANSON, Y., BOIVIN, F., AND JOBARD, P.: Endocrine cells in the prostate gland, urothelium and Brenner tumors. Immunohistological and ultrastructural studies. Virchows Arch. B Cell Pathol. **42:** 53–64, 1983.

FINBERG, J. P. M., AND VARDI, Y.: Evidence for a role of EDRF in penile erection. Br. J. Pharmacol. **102:** 82P, 1991.

FINKBEINER, A. E.: In vitro effects of vasoactive intestinal polypeptide on guinea pig urinary bladder. Urology **22:** 275–277, 1983a.

FINKBEINER, A. E.: Effect of extracellular calcium and calcium blocking agents on detrusor contractility: an in vitro study. Neurourol. Urodyn. **2:** 245–257, 1983b.

FINKBEINER, A. E., AND O'DONNELL, P. D.: Responses of detrusor smooth muscle to stretch and relaxation: in vitro study. Urology **36:** 193–198, 1990.

FLORANTE, T., LEYSON, T., MARTIN, B. F., AND SPORER, A.: Baclofen in the treatment of detrusor-sphincter dyssynergia in spinal cord injury patients. J. Urol. **124:** 82–84, 1980.

FONTAINE, J., SCHULMAN, C. C., AND WESPES, E.: Postjunctional alpha-1- and alpha-2-like activity in human isolated deep dorsal vein of the penis. Br. J. Pharmacol. **89:** 493, 1987.

FORMAN, A., ANDERSSON, K.-E., HENRIKSSON, L., RUD, T., AND ULMSTEN, U.: Effects of nifedipine on the smooth muscle of the human urinary tract in vitro and in vivo. Acta Pharmacol Toxicol. **43:** 111–118, 1978.

FÖRSTERMANN, U., SCHMIDT, H. H. H. W., POLLOCK, J. S., SHENG, H., MITCHELL, J. A., WARNER, T. D., NAKANE, M., AND MURAD, F.: Isoforms of nitric oxide synthase. Biochem. Pharmacol. **42:** 1849–1857, 1991.

FOSTER, C. D., FUJII, K., KINGDOM, J., AND BRADING, A. F.: The effect of cromakalim on the smooth muscle of the guinea-pig urinary bladder. Br. J. Pharmacol. **97:** 281–291, 1989a.

FOSTER, C. D., SPEAKMAN, M. J., FUJII, K., AND BRADING, A. F.: The effects of cromakalim on the detrusor muscle of human and pig urinary bladder. Br. J. Urol. **63:** 284–29, 1989b.

FOVAEUS, M., ANDERSSON, K.-E., BATRA, S., MORGAN, E., AND SJÖGREN, C.: Effects of calcium, calcium channel blockers and Bay K8644 on contractions induced by muscarinic receptor stimulation of isolated bladder muscle from rabbit and man. J. Urol. **137:** 798–803, 1987a.

FOVAEUS, M., ANDERSSON, K.-E., AND HEDLUND, H.: Effects of some calcium channel blockers on isolated human penile erectile tissue. J. Urol. **138:** 1267–1272, 1987b.

FOVAEUS, M., ANDERSSON, K.-E., AND HEDLUND, H.: The action of pinacidil in the isolated human bladder. J. Urol. **141:** 637–640, 1989.

FOWLER, C. J., JEWKES, D., MCDONALD, W. I., LYNN, B., AND DE GROAT, W. C.: Intravesical capsaicin for neurogenic bladder dysfunction. Lancet **339:** 1239, 1992.

FREDERICKS, C. M.: Characterization of the rabbit detrusor response to histamine through pharmacologic antagonism. Pharmacology **13:** 5–11, 1975.

FUJII, K.: An electrophysiological investigation of the mechanism of action of BRL 34915 on the guinea-pig bladder. Br. J. Pharmacol. **92:** 750P, 1987.

FUJII, K.: Evidence for adenosine triphosphate as an excitatory transmitter in guinea-pig rabbit and pig urinary bladder. J Physiol. (Lond.). **404:** 39–52, 1988.

FUJII, K., FOSTER, C. D., BRADING, A. F., AND PAREKH, A. B.: Potassium channel blockers and the effects of cromakalim on the smooth muscle of the guinea-pig bladder. Br. J. Pharmacol. **99:** 779–785, 1990.

FURCHGOTT, R. F.: The role of endothelium in the responses of vascular smooth muscle to drugs. Annu. Rev. Pharmacol. Toxicol. **24:** 175–197, 1984.

FURCHGOTT, R. F.: Studies on endothelium-dependent vasodilation and the endothelium-derived relaxing factor. Acta Physiol. Scand. **139:** 257–270, 1990.

FURCHGOTT, R. F., AND ZAWADSKI, J. V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature (Lond.) **288:** 373–376, 1980.

GABELLA, G.: Structure of smooth muscles. *In* Smooth Muscle: An Assessment of Current Knowledge, edited by E. Bülbring, A. F. Brading, A. W. Jones and T. Tomita, pp. 1–46, Arnold, London, 1981.

GABELLA, G., AND UVELIUS, B.: Urinary bladder of rat: fine structure of normal and hypertrophic musculature. Cell Tissue Res. **262:** 67–79, 1990.

GANGULY, D. K., AND VEDASIROMONI, J. R.: Beta-adrenoceptors in urinary bladder. Arch. Int. Pharmacodyn. Ther. **222:** 193–199, 1976.

GANITKEVICH, V. Y., AND ISENBERG, G.: Depolarization-mediated intracellular calcium transients in isolated smooth muscle cells of guinea-pig urinary bladder. J. Physiol. (Lond.) **435:** 187–205, 1991.

GANITKEVICH, V. Y., AND ISENBERG, G.: Contribution of Ca^{2+}-induced Ca^{2+} release to the $[Ca^{2+}]_i$ transients in myocytes from guinea-pig urinary bladder, J. Physiol. (Lond.) **458:** 119–137, 1992.

GARCIA-PASCUAL, A., COSTA, G., GARCIA-SACRISTAN, A., AND ANDERSSON, K.-E.: Calcium dependence of contractile activation of isolated sheep urethra I: responses to electrical stimulation. Pharmacol. Toxicol. **69:** 263–269, 1991a.

GARCIA-PASCUAL, A., COSTA, G., GARCIA-SACRISTAN, A., AND ANDERSSON, K.-E.: Calcium dependence of contractile activation of isolated sheep urethra II: Responses to exogenous noradrenaline. Pharmacol. Toxicol. **69:** 270–275, 1991b.

GARCIA-PASCUAL, A., COSTA, G., GARCIA-SACRISTIAN, A., AND ANDERSSON, K.-E.: Relaxation of sheep urethral muscle induced by electrical stimulation of nerves: involvement of nitric oxide. Acta Physiol. Scand. **141:** 531–539, 1991c.

GARCIA-PASCUAL, A., COSTA, G., ISLA, M., JIMENEZ, E., AND GARCIA-SACRISTIAN, A.: Potassium-induced contraction in the lamb proximal urethra: involve-

ment of norepinephrine and different calcium entry pathways. J. Pharmacol. Exp. Ther. **256:** 127–134, 1991d.

GARCIA-PASCUAL, A., LARSSON, B., AND ANDERSSON, K.-E.: Contractile effects of endothelin-1 and localization of endothelin binding sites in rabbit lower urinary tract smooth muscle. Acta Physiol. Scand. **140:** 545–555, 1990.

GARCIA-PASCUAL, A., PERSSON, K., HOLMQUIST, F., AND ANDERSSON, K.-E.: Endothelin-1-induced phosphoinositide hydrolysis and contraction in isolated rabbit detrusor and urethral smooth muscle. Gen. Pharmacol., **24:** 131–138, 1993.

GHATEI, M. A., GU, J., ALLEN, J. M., POLAK, J. M., AND BLOOM, S. R.: Bombesin-like immunoreactivity in female rat genitourinary tract. Neurosci. Lett. **54:** 13–19, 1985a.

GHATEI, M. A., GU, J., MULDERRY, P. K., BLANK, M. A., ALLEN, J. M., MORRISON, J. F. B., POLAK, J. M., AND BLOOM, S. R.: Calcitonin gene-related peptide in the female rat urinary tract. Peptides **6:** 809–815, 1985b.

GHONEIM, M. A., FRETIN, J. A., GAGNON, D. J., LEBEL, E., VAN LIER, J., ARSENAULT, A., AND SUSSET, J. G.: The influence of vesical distension on the urethral resistance to flow: a possible role for prostaglandins? J. Urol. **116:** 739–743, 1976.

GHONEIM, G. A., REGNIER, C. H., BIANCANI, P., AND SUSSET, J. G.: Effect of diethylstibestrol on bladder contractility in male rat. J. Urol. **129:** 865–868, 1983.

GIBSON, A., MIRZAZADEH, S., HOBBS, A. J., AND MOORE, P. K.: L-N^G-monomethyl arginine and L-N^G-nitro arginine inhibit non-adrenergic, non-cholinergic relaxation of the mouse anococcygeus muscle. Br. J. Pharmacol. **99:** 602–606, 1990.

GILLESPIE, J. S.: The rat anococcygeus muscle and its response to nerve stimulation and to some drugs. Br. J. Pharmacol. **45:** 404–416, 1972.

GILLESPIE, J. S., LIU, X., AND MARTIN, W.: The neurotransmitter of the non-adrenergic, non-cholinergic inhibitory nerves to smooth muscle of the genital system. *In* Nitric Oxide from L-arginine: A Bioregulatory System, edited by S. Moncada and E. A. Higgs, pp. 147–164, Elsevier, Amsterdam, 1990.

GILMORE, N. J., AND VANE, J. R.: Hormones released into the circulation when the urinary bladder of anaesthetized dog is distended. Clin. Sci. **41:** 69–83, 1971.

GIRALDI, A., AND WAGNER, G.: Effects of pinacidil upon penile erectile tissue in vitro and in vivo. Pharmacol. Toxicol. **67:** 235–238, 1990.

GIULIANI, S., SANTICIOLI, P., TRAMONTANA, M., GEPETTI, P., AND MAGGI, C. A.: Peptide N-formyl-methionyl-leucyl-phenylalanine (FMLP) activates capsaicin-sensitive afferents in guinea-pig atria and urinary bladder. Br. J. Pharmacol. **102:** 730–734, 1991.

GLAHN, B. E.: Neurogenic bladder diagnosed pharmacologically on the basis of denervation supersensitivity. Scand J. Urol. Nephrol. **4:** 13–24, 1970.

GODEC, C. J., AND BATES, H.: Cholinergic receptors in corpora cavernosa. Urology **24:** 31–33, 1984.

GODFREY, P. P., MCCLUE, S. J., WHITE, A. M., AND WOOD, A. J.: Subacute and chronic lithium treatment inhibits agonist and sodium fluoride-stimulated inositol phosphate production in rat cortex. J. Neurochem. **52:** 498–506, 1989.

GOLDSTEIN, A. M. B., AND PADMA-NATHAN, H.: The microarchitecture of the intracavernosal smooth muscle and the cavernosal fibrous skeleton. J. Urol. **144:** 1144–1146, 1990.

GOSLING, J. A., GILPIN, S. A. DIXON, J. S., AND GILPIN, C. J.: Decrease in the autonomic innervation of human detrusor muscle in outflow obstruction. J. Urol. **136:** 501–504, 1986.

GOTOH, M., HASSOUNA, M., AND ELHILALI, M.: The mode of action of prostaglandin E_2, $F_{2\alpha}$ and prostacyclin on vesicourethral smooth muscle. J. Urol. **135:** 431–437, 1986a.

GOTOH, M., HASSOUNA, M., MOKHLESS, I., AND ELHILALI, M. M.: Intravesical instillation of a calcium entry blocker and its effect on detrusor contractility: in vitro and in vivo experiments. J. Urol. **135:** 1304–1307, 1986b.

GRANT, T. L., AND ZUZACK, J. S.: Effects of K^+ channel blockers and cromakalim (BRL 34915) on the mechanical activity of guinea pig detrusor smooth muscle. J. Pharmacol. Exp. Ther. **259:** 1158–1164, 1991.

GREGG, R. A., BOYARSKY, S., LABAY, P., AND BAINS LEVIE, B.: Presence of beta-adrenergic receptors in urinary bladder of dog and cat: response to isoproterenol. Arch. Phys. Med. **51:** 88–94, 1970.

GROZDANOVIC, Z., BAUMGARTEN, H. G., AND BRÜNING, G.: Histochemistry of NADPH-diaphorase, a marker for neuronal nitric oxide synthase, in the peripheral autonomic nervous system of the mouse. Neuroscience **48:** 225–235, 1992.

GU, J., POLAK, J. M., LAZARIDES, M., MORGAN, R., PRYOR, J. P., MARANGOS, P. J., BLANK, M. A., AND BLOOM, S. R.: Decrease of vasoactive intestinal polypeptide (VIP) in the penises from impotent men. Lancet **2:** 315–318, 1984.

GU, J., POLAK, J. M., PROBERT, L., ISLAM, K. N., MARANGOS, P. J., MINA, S., ADRIAN, T. E., MCGREGOR, G. P., O'SHAUGHNESSY, D. J., AND BLOOM, S. R.: Peptidergic innervation of the human male genital tract. J. Urol. **130:** 386–391, 1983a.

GU, J., RESTORICK, J. M., BLANK, M. A., HUANG, W. M., POLAK, J. M., BLOOM, S. R., AND MUNDY, A. R.: Vasoactive intestinal polypeptide in the normal and unstable bladder. Br. J. Urol. **55:** 645–647, 1983b.

GYERMEK, L.: Action of 5-hydroxytryptamine on the urinary bladder of the dog. Arch. Int. Pharmacodyn. Ther. **87:** 137–144, 1962.

HACHEN, H. J., AND KRUCKER, V.: Clinical and laboratory assessment of the efficacy of baclofen (Lioresal) on urethral sphincter spasticity in patients with traumatic paraplegia. Eur. Urol. **3:** 237–240, 1977.

HAK, J., GRIFFITHS, D. J., VAN MASTRIGT, R., KOOPAL, B., AND KLÜCK, P.: Quantitative study in vitro of the spontanous contractions of pig detrusor muscle and their frequency-selective inhibition by drugs. Neurourol. Urodyn. **7:** 471–481, 1988.

HALL, J. M., FLOWERS, J. M., AND MORTON, I. K. M.: A pharmacological study of NK_1 and NK_2 tachykinin receptor characteristics in the rat isolated urinary bladder. Br. J. Pharmacol. **107:** 777–784, 1992.

HAMILTON, T. C., AND WESTON, A. H.: Cromakalim and pinacidil: novel drugs which open potassium channels in smooth muscle. Gen. Pharmacol. **20:** 1- 9, 1989.

HANLEY, M. R., BENTON, H. P., LIGHTMAN, S. L., TODD, K., BONE, E. A., FRETTEN, P., PALMER, S., KIRK, C. J., AND MICHELL, R. H.: A vasopressin-like peptide in the mammalian sympathetic nervous system. Nature (Lond.) **309:** 258–261, 1984.

HARRISON, S. C. V., HUNNAM, G. R., FARMAN, P., AND DOYLE, P. T.: Bladder instability and denervation in patients with bladder outflow obstruction. Br. J. Urol. **60:** 519–522, 1987.

HASHIMOTO, S., KIGOSHI, S., AND MURAMATSU, I.: Neurogenic responses of urethra isolated from the dog. Eur. J. Pharmacol. **213:** 117–123, 1992.

HASHIMOTO, S., KIGOSHI, S., AND MURAMATSU, I.: Nitric oxide-dependent and -independent neurogenic relaxations of isolated dog urethra. Eur. J. Pharmacol. **231:** 209–214, 1993.

HASSOUNA, M., ABDEL-HAKIM, A., ABDEL-RAHMAN, M., GALEANO, C., AND ELHILALI, M. M.: Response of the urethral smooth muscles to pharmacological agents. I. Cholinergic and adrenergic agonists and antagonists. J. Urol. **129:** 1262–1264, 1983.

HASSOUNA, M., NISHIZAWA, O., MIYAGAWA, I., TOGURI, A., GOTOH, M., AND ELHILALI, M.: Role of calcium ion antagonists on the bladder detrusor muscle: in vitro and in vivo study. J. Urol. **135:** 1327–1331, 1986.

HEATON, J. P. W.: Synthetic nitrovasodilators are effective, in vitro, in relaxing penile tissue from impotent men: the findings and their implications. Can. J. Physiol. Pharmacol. **67:** 78–81, 1990.

HEATON, J. P. W., MORALES, A., OWEN, J., SAUNDERS, F. W., AND FENEMORE, J.: Topical glyceryl trinitrate causes measurable penile arterial dilatation in impotent men. J. Urol. **143:** 729–731, 1989.

HECKER, M., MITCHELL, J. A., HARRIS, H. J., KATSURA, M., THIEMERMANN, C., AND VANE, J. R.: N^G-monomethyl-L-arginine but not N^ω-nitro-L-arginine is metabolized by endothelial cells to L-citrulline. Eur. J. Pharmacol. **183:** 648–649, 1990.

HEDLUND, H., AND ANDERSSON, K.-E.: Comparison of the responses to drugs acting on adrenoceptors and muscarinic receptors in human isolated corpus cavernosum and cavernous artery. J. Auton. Pharmacol. **5:** 81–88, 1985a.

HEDLUND, H., AND ANDERSSON, K.-E.: Effects of some peptides on isolated human penile erectile tissue and cavernous artery. Acta Physiol. Scand. **124:** 413–419, 1985b.

HEDLUND, H., AND ANDERSSON, K.-E.: Contraction and relaxation induced by some prostanoids in isolated human penile erectile tissue and cavernous artery. J. Urol. **134:** 1245–1250, 1985c.

HEDLUND, H., ANDERSSON, K.-E., FOVAEUS, M., HOLMQUIST, F., AND USKI, T.: Characterization of contraction-mediating prostanoid receptors in human penile erectile tissues. J. Urol. **141:** 182–186, 1989a.

HEDLUND, H., ANDERSSON, K.-E., HOLMQUIST, F., AND USKI, T.: Effect of the thromboxane receptor antagonist AH 23848 on human isolated corpus cavernosum. Int. J. Impotence Res. **1:** 19–25, 1989b.

HEDLUND, H., ANDERSSON, K.-E., AND MATTIASSON, A.: Pre- and postjunctional adreno- and muscarinic receptor functions in the isolated human corpus spongiosum urethrae. J. Auton. Pharmacol. **4:** 241–249, 1984.

HEDLUND, H., MATTIASSON, A., AND ANDERSSON, K.-E.: Effects of pinacidil on detrusor instability in men with outlet obstruction. J. Urol. **146:** 1345–1347, 1991.

HELLSTROM, W. J. G., WANG, R., KADOWITZ, P. J., AND DOMER, F. R.: Potassium channel agonists cause penile erection in cats. Int. J. Impotence Res. **4:** 35–43, 1992.

HENDERSON, V. E., AND ROEPKE, M. H.: On the mechanism of erection. Am. J. Physiol. **106:** 441–448, 1933.

HENDERSON, V. E., AND ROEPKE, M. H.: The role of acetylcholine in bladder contractile mechanisms and in parasympathetic ganglia. J. Pharmacol. Exp. Ther. **51:** 97–111, 1934.

HILLS, J., MELDRUM, L., KLARSKOV, P., AND BURNSTOCK, G.: A novel non-adrenergic, non-cholinergic nerve mediated relaxation of the pig bladder neck; an examination of possible neuro-transmitter candidates. Eur. J. Pharmacol. **99:** 287–293, 1984.

HINDMARSH, J. R., GOSLING, P. T., AND DEANE, A. M.: Bladder instability. Is the primary defect in the urethra? Br. J. Urol. **55:** 648–651, 1983.

HINDMARSH, J. R., IDOWU, O. A., YEATES, W. K., AND ZAR, M. A.: Pharmacology of electrically evoked contractions of the human bladder. Br. J. Pharmacol. **61:** 115P, 1977.

HISAYAMA, T., SHINKAI, M., TAKAYANAGI, I., AND TOYODA, T.: Mechanism of action of nicotine in isolated urinary bladder of guinea-pig. Br. J. Pharmacol. **95:** 465–472, 1988.

HISAYAMA, T., SHINKAI, M., TAKAYANAGI, I., AND TOYODA, T.: Mechanism of action of nicotine in isolated urinary bladder of gurinea-pig: involvement of tachykinin(s) released by nicotine in the drug's sympathomimetic effect. Arch. Int. Pharmacodyn. Ther. **301:** 277–284, 1989.

HODGSON, B. J., DUMAS, S., BOLLING, D. R., AND HEESCH, C. M.: Effect of

estrogen on sensitivity of rabbit bladder and urethra to phenylephrine. Invest. Urol. **16:** 67–69, 1978.

HÖKFELT, T., SCHULTZBERG, M., ELDE, R., NILSSON, G., TERENIUS, L., SAID, S., AND GOLDSTEIN, M.: Peptide neurons in peripheral tissues including the urinary tract: immunohistochemical studies. Acta Pharmacol. Toxicol. **43** (Suppl. II): 79–89, 1978.

HOLMQUIST, F., ANDERSSON, K.-E., FOVAEUS, M., AND HEDLUND, H.: K^+-channel openers for relaxation of penile erectile tissue. *In* Proceedings of the International Society for Impotence Research, p. 148, Boston, MA, 1988.

HOLMQUIST, F., ANDERSSON, K.-E., FOVAEUS, M., AND HEDLUND, H.: K^+-channel openers for relaxation of isolated penile erectile tissue from rabbit. J. Urol. **144:** 146–151, 1990a.

HOLMQUIST, F., ANDERSSON, K.-E., AND HEDLUND, H.: Actions of endothelin on isolated corpus cavernosum from rabbit and man. Acta Physiol. Scand. **139:** 113–122, 1990b.

HOLMQUIST, F., ANDERSSON, K.-E., AND HEDLUND, H.: Effects of pinacidil on isolated human corpus cavernosum penis. Acta Physiol. Scand. **138:** 463–469, 1990c.

HOLMQUIST, F., HEDLUND, H., AND ANDERSSON, K.-E.: L-N^G-nitro arginine inhibits non-adrenergic, non-cholinergic relaxation of human isolated corpus cavernosum. Acta Physiol. Scand, **141:** 441–442, 1991a.

HOLMQUIST, F., ANDERSSON, K.-E., AND HEDLUND, H.: Characterization of inhibitory neurotransmission in the isolated copus cavernosum from rabbit and man. J. Physiol. (Lond.) **449:** 295–311, 1992a.

HOLMQUIST, F., KIRKEBY, H. J., LARSSON, B., FORMAN, A., AND ANDERSSON, K.-E.: Functional effects, binding sites and immunolocalization of endothelin-1 in isolated penile tissues from man and rabbit. J. Pharmacol. Exp. Ther. **261:** 795–802, 1992b.

HOLMQUIST, F., LUNDIN, S., LARSSON, B., HEDLUND, H., AND ANDERSSON, K.-E.: Studies on binding sites, contents, and effects of AVP in isolated bladder and urethra from rabbits and humans. Am. J. Physiol. **261:** R865–R874, 1991b.

HOLMQUIST, F., PERSSON, K., GARCIA-PASCUAL, A., AND ANDERSSON, K.-E.: Phospholipase C activation by endothelin-1 and noradrenaline in isolated penile erectile tissue from rabbit. J. Urol. **147:** 1632–1635, 1992c.

HOLMQUIST, F., STIEF, C. G., JONAS, U., AND ANDERSSON, K.-E.: Effects of the nitric oxide synthase inhibitor N^G-nitro-L-arginine on the erectile response to cavernous nerve stimulation in the rabbit. Acta Physiol. Scand. **143:** 299–304, 1991c.

HOLT, S. E., COOPER, M., AND WYLLIE, J. H.: Evidence for purinergic transmission in mouse bladder and for modulation of responses to electrical stimulation by 5-hydroxytryptamine. Eur. J Pharmacol. **116:** 105–111, 1985.

HOLT, S. E., COOPER, M., AND WYLLIE, J. H.: On the nature of the receptor mediating the action of 5-hydroxytryptamine in potentiating responses of the mouse urinary bladder strip to electrical stimulation. Naunyn Schmiedebergs Arch. Pharmacol. **334:** 333–340, 1986.

HOLZER-PETSCHE, U., AND LEMBECK, F.: Systemic capsaicin treatment impairs the micturition reflex in the rat. Br. J. Pharmacol. **83:** 935–941, 1984.

HONDA, K., MIYATA-OSAWA, A., AND TAKENAKA, T.: a_1-Adrenoceptor subtype mediating contraction of the smooth muscle in the lower urinary tract and prostate of rabbits. Naunyn Schmiedebergs Arch. Pharmacol. **330:** 16–21, 1985.

HONDA, K., MOMOSE, N., AND NAKAGAWA, C.: In vitro characterization of α-adrenergic receptor in rabbit detrusor muscle. Jpn. J. Pharmacol. **44:** 345–353, 1987.

HONDA, K., AND NAKAGAWA, C.: Alpha-1 adrenoceptor antagonist effects of the optical isomers of YM-12617 in rabbit lower urinary tract and prostate. J. Pharmacol. Exp. Ther. **239:** 512–516, 1986.

HOPE, B. T., MICHAEL, G. J., KNIGGE, K. M., AND VINCENT, S. R.: Neuronal NADPH diaphorase is a nitric oxide synthase. Proc. Natl. Acad. Sci. USA **88:** 2811–2814, 1991.

HØRBY-PETERSEN, J., SCHMIDT, P. F., MEYHOFF, H. H., FRIMODT-MØLLER, C., AND MATHISEN, F. R.: The effects of a new serotonin receptor antagonist (ketanserin) on lower urinary tract function in patients with prostatism. J. Urol. **133:** 1095–1098, 1985.

HOURANI, S. M. O.: Desensitization of the guinea-pig urinary bladder by the enantiomers of adenylyl 5′-(β,γ-methylene)-diphosphonate and by substance P. Br. J. Pharmacol. **82:** 161–164, 1984.

HOURANI, S. M. O., WELFORD, L. A., AND CUSACK, N. J.: L-AMP-PCP, an ATP receptor agonist in guinea-pig bladder is inactive on taenia coli. Eur. J. Pharmacol. **108:** 197–200, 1985.

HOYLE, C. H. V., AND BURNSTOCK, G.: Atropine-resistant excitatory junction potentials in rabbit bladder are blocked by α,β-methylene ATP. Eur. J. Pharmacol. **114:** 239–240, 1985.

HOYLE, C. H. V., CHAPPLE, C., AND BURNSTOCK, G.: Isolated human bladder: evidence for an adenine dinucleotide acting on P_{2x}-purinoceptors and for purinergic transmission. Eur. J. Pharmacol. **174:** 115–118, 1989.

HUA, X. Y.: Tachykinins and calcitonin gene-related peptide in relation to peripheral functions of capsaicin-sensitive sensory neurons. Acta Physiol. Scand. [Suppl.] **551:** 1–45, 1986.

HUDDART, H., AND BUTLER, D. J.: Field stimulation responses of rat urinary bladder detrusor-muscle. Dependence upon slow calcium channel activity determined by K^+ depolarization and calcium antagonists. Gen. Pharmacol. **17:** 695–703, 1986.

HUGHES, A., THOM, S., MARTIN, G., AND SEVER, P.: Endothelial dependent relaxation of human arteries by peptide hormones. Clin. Sci. [Suppl.] **13:** 88P, 1985.

HUKOVIC, S., RAND, M. J., AND VANOV, S.: Observations on an isolated, innervated preparation of rat urinary bladder. Br. J. Pharmacol. Chemother. **24:** 178–188, 1965.

HULME, E. C., BIRDSALL, N. J. M., AND BUCKLEY, N. J.: Muscarinic receptor subtypes. Annu. Rev. Pharmacol. Toxicol. **30:** 633–673, 1990.

HUSTED, S., ANDERSSON, K.-E., SOMMER, L., AND ØSTERGAARD, J. R.: Anticholinergic and calcium antagonistic effects of terodiline in rabbit urinary bladder. Acta Pharmacol. Toxicol. **46** (Suppl. I): 20–30, 1980a.

HUSTED, S., SJÖGREN, C., AND ANDERSSON, K.-E.: Role of prostaglandins in the responses of rabbit bladder smooth muscle. Arch. Int. Pharmacol. Ther. **246:** 84–97, 1980b.

HUSTED, S., SJÖGREN, C., AND ANDERSSON, K.-E.: Mechanism of the responses to non-cholinergic, non-adrenergic nerve stimulation and to ATP in isolated rabbit urinary bladder: evidence for ADP evoked prostaglandin release. Acta Pharmacol. Toxicol. **47:** 84–92, 1980c.

HUSTED, S., SJÖGREN, C., AND ANDERSSON, K.-E.: Substance P and somatostatin and excitatory neurotransmission in rabbit urinary bladder. Arch Int. Pharmacodyn. Ther. **252:** 72–85, 1981.

HUSTED, S., SJÖGREN, C., AND ANDERSSON, K.-E.: Direct effects of adenosine and adenine nucleotides on isolated human urinary bladder and their influence on electrically induced contractions. J. Urol. **130:** 392–398, 1983.

IACOVOU, J. W., HILL, S. J., BIRMINGHAM, T. A., AND BATES, C. P.: Calcium dependence and inositol phosphate accumulation in human detrusor smooth muscle. Neurourol. Urodyn. **8:** 418–419, 1989.

IACOVOU, J. W., HILL, S. J.,AND BIRMINGHAM, T. A.: Agonist-induced contraction and accumulation of inositol phosphates in the guinea-pig detrusor: evidence that muscarinic and purinergic receptors raise intracellular calcium by different mechanisms. J. Urol. **144:** 775–779, 1990.

IGAWA, Y., MATTIASSON, A., AND ANDERSSON, K.-E.: Functional importance of cholinergic and purinergic neurotransmission for micturition contraction in the normal, un-anaesthetized rat. Br. J. Pharmacol., **109:** 473–479, 1993a.

IGAWA, Y., MATTIASSON, A., AND ANDERSSON, K.-E.: Effects of GABA-receptor stimulation and blockade on micturition in normal rats and rats with bladder outflow obstruction. J. Urol., **150:** 537–542, 1993b.

IGAWA, Y., PERSSON, K., ANDERSSON, K.-E., UVELIUS, B., AND MATTIASSON, A.: Effects of vasoactive intestinal polypeptide on bladder function in conscious rats with and without detrusor instability. J. Urol., **149:** 884–889, 1993c.

IGNARRO, L. J.: Biosynthesis and metabolism of endothelium-derived nitric oxide. Annu. Rev. Pharmacol. Toxicol. **30:** 535–560, 1990.

IGNARRO, L. J., BUGA, G. M., WOOD, K. S., BYRNS, R. E., AND CHAUDHURY, G.: Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc. Natl. Acad. Sci. USA **84:** 9265–9269, 1987.

IGNARRO, L. J., BUSH, P. A., BUGA, G. M., WOOD, K. S., FUKOTO, J. M., AND RAJFER, J.: Nitric oxide and cyclic GMP formation upon electrical field stimulation cause relaxation of corpus cavernosum smooth muscle. Biochem. Biophys. Res. Commun. **170:** 843–850, 1990.

IMAGAWA, A., KIMURA, K., KAWANISHI, Y., AND TAMURA, M.: Effect of moxisylyte hydrochloride on isolated human penile corpus cavernosum. Life Sci. **44:** 619–623, 1991.

INOUE, R., AND BRADING, A. F.: The properties of the ATP-induced depolarization and current in single cells isolated from the guinea-pig urinary bladder. Br. J. Pharmacol. **100:** 619–625, 1990.

INOUE, R., AND BRADING, A. F.: Human, pig and guinea-pig bladder smooth muscle cells generate similar inward currents in response to purinoceptor activation. Br. J. Pharmacol. **103:** 1840–1841, 1991.

IOSIF, C. S.: Effects of protracted administration of estriol on the lower genitourinary tract in postmenopausal women. Arch. Gynecol. Obstet. **251:** 115–120, 1992.

IOSIF, C. S., BATRA, S., EK, A., AND ÅSTEDT, B.: Estrogen receptors in the human female lower urinary tract. Am. J. Obstet. Gynecol. **141:** 817–820, 1981.

IRAVANI, M. M., AND ZAR, M. A.: Evidence for neuropeptide Y (NPY) as the probable non-cholinergic motor transmitter in rat urinary bladder in vitro. J. Physiol. (Lond.) **403:** 61P, 1988.

ISENBERG, G., WENDT-GALLITELLI, M. F., AND GANITKEVICH, V.: Contribution of Ca^{2+}-induced Ca^{2+} release to depolarization-induced Ca^{2+} transients of myocytes from guinea-pig urinary bladder myocytes. Jpn. J. Pharmacol. **58** (Suppl. 2): 81P–86P, 1992.

ISHIDA-YAMAMOTO, A., AND TOHYAMA, M.: Calcitonin gene-related peptide in the nervous tissue. Progr. Neurobiol. **33:** 335–386, 1989.

ITO, Y., AND KIMOTO,Y.: The neural and non-neural mechanisms involved in urethral activity in rabbits. J. Physiol. (Lond.) **367:** 57–72, 1985.

JAMES, M. J., BIRMINGHAM, A. T., AND BATES, C. P.: Relaxation of human isolated detrusor strips in response to electrical field stimulation: a possible role for nitric oxide in the human bladder (abstract 380). J. Urol. **145:** 307A, 1991.

JENSEN, D.: Uninhibited neurogenic bladder treated with prazosin. Scand. J. Urol. Nephrol. **15:** 229–233, 1981.

JEREMY, J. Y., MIKHAILIDIS, D. P., AND DANDONA, P.: The rat urinary bladder produces prostacyclin as well as other prostaglandins. Prostaglandins Leukotrienes Med. **16:** 235–248, 1984.

JEREMY, J. Y., MORGAN, R. J., MIKHAILIDIS, D. P., AND DANDONA, P.: Prostacyclin synthesis by the corpora cavernosa of the human penis: evidence for

muscarinic control and pathological implications. Prostaglandins Leukotrienes Med. **23:** 211–216, 1986.

JEREMY, J. Y., TSANG, V., MIKHAILIDIS, D. P., ROGERS, H., MORGAN, R. J., AND DANDONA, P.: Eicosanoid synthesis by human urinary bladder mucosa: pathological implications. Br. J. Urol. **59:** 36–39, 1987.

JOHNS, A.: The effect of indomethacin and substance P on the guinea pig urinary bladder. Life Sci. **29:** 1803–1809, 1982.

JOHNS, A.: Alpha- and beta-adrenergic and muscarinic cholinergic binding sites in the bladder and urethra of the rabbit. Can. J. Physiol. Pharmacol. **61:** 61–66, 1983.

JOHNS, A., AND PATON, D. M.: Effect of indomethacin on atropine-resistant transmission in rabbit and monkey urinary bladder: evidence for the involvement of prostaglandins in transmission. Prostaglandins **13:** 245–254, 1977.

JUENEMANN, K.-P., AND ALKEN, P.: Pharmacotherapy of erectile dysfunction: a review. Int. J. Impotence Res. **1:** 71–93, 1989.

KALBFLEISCH, R. E., AND DANIEL, E. E.: The role of substance P in the human urinary bladder. Arch. Int. Pharmacodyn. **285:** 238–248, 1987.

KASAKOV, L., AND BURNSTOCK, G.: The use of the slowly degrading analogue α,β-methylene ATP, to produce desensitisation of the P_2-purinoceptor: effect on non-adrenergic, non-cholinergic responses of the guinea-pig urinary bladder. Eur. J. Pharmacol. **86:** 291–294, 1983.

KASAKOV, L. M., AND VLASKOVSKA, M. V.: Profile of prostaglandins generated in the detrusor muscle of rat urinary bladder: effects of adenosine triphosphate and adenosine. Eur. J. Pharmacol. **113:** 431–436, 1985.

KATSURAGI, T., USUNE, S., AND FURUKAWA, T.: Antagonism by nifedipine of contraction and Ca^{2+}-influx evoked by ATP in guinea-pig urinary bladder. Br. J. Pharmacol. **100:** 370–374, 1990.

KAWANISHI, Y., HASHINE, K., KIMURA, K., TAMURA, M., AND IMAGAWA, A.: Interaction of VIP and acetylcholine on the relaxation of human corpus cavernosal tissue. Int. J. Impotence Res. **2** (Suppl. 2): 9, 1990.

KAWATANI, M., LOWE, I. P., BOOTH, A. M., BACKES, M. G., ERDMAN, S. L., AND DE GROAT, W. C.: The presence of leucine-enkephalin in the sacral preganglionic pathway to the urinary bladder of the cat. Neurosci. Lett. **39:** 143–148, 1983.

KEAST, J. R.: A possible neural source of nitric oxide in the rat penis. Neurosci. Lett. **143:** 69–73, 1992.

KEAST, J. R., AND DE GROAT, W. C.: Immunohistochemical characterization of pelvic neurons which project to the bladder, colon, or penis in rats. J. Comp. Neurol. **288:** 387–400, 1989.

KEAST, J. R., AND DE GROAT, W. C.: Segmental distribution and peptide content of primary afferent neurons innervating the urogenital organs and colon of male rats. J. Comp. Neurol. **319:** 615–623, 1992.

KEAST, J. R., KAWATANI, M., AND DE GROAT, W. C.: Sympathetic modulation of cholinergic transmission in cat vesical ganglia is mediated by α_1- and α_2-adrenoceptors. Am. J. Physiol. **258:** R44–R50, 1990.

KERFOOT, W. W., PARK, H. Y., SCHWARTZ, L. B., HAGEN, P.-O., AND CARSON, C. C., III: Comparative efficacy of calcium channel blocker activity on isolated rabbit corpus cavernosum. Int. J. Impotence Res. **4** (Suppl. 1): 1–8, 1992.

KHALAF, I. M., GHONEIM, M. A., AND ELHILALI, M. M.: The effect of exogenous prostaglandins $F_{2\alpha}$ and E_2 and indomethacin on micturition. Br. J. Urol. **53:** 21–28, 1981.

KHALAF, I. M., LEHOUX, J.-G., ELSHAWARBY, L. A., AND ELHILALI, M. M.: Release of prostaglandins into the pelvic venous blood of dogs in response to vesical distension and pelvic nerve stimulation. J. Urol. **17:** 244–247, 1979.

KHALAF, I. M., RIOUX, F., QUIRION, R., AND ELHILALI, M. M.: Intravesical prostaglandin: release and effect of bladder installation on some micturition parameters. Br. J. Urol. **52:** 351–356, 1980.

KHANNA, O. P., BARBIERI, E. J., AND MCMICHAEL, R. F.: Effects of prostaglandins on vesicourethral smooth muscle of rabbit. Therapeutic implications. Urology **12:** 674–681, 1978.

KHANNA, O. P., BARBIERI, E. J., AND MCMICHAEL, R. F.: The effects of adrenergic agonists and antagonists on vesicourethral smooth muscle of rabbits. J. Pharmacol. Exp. Ther. **216:** 95–100, 1981.

KHANNA, O. P., BARBIERI, E. J., MOSS, M., SON, D., AND MCMICHAEL, R. F.: Effects of calcium and verapamil on vesicourethral smooth muscle of rabbits. Urology **21:** 284–290, 1983.

KHANNA, O. P., DE GREGORIO, G. J., SAMPLE, R. G., AND MCMICHAEL, R. F.: Histamine receptors in urethrovesical smooth muscle. Urology **10:** 375–381, 1977.

KIELY, E. A., BLANK, M. A., BLOOM, S. R., AND WILLIAMS G.: Studies on intracavernosal VIP levels during pharmacologically induced penile erections. Br. J. Urol. **59:** 334–339, 1987.

KIELY, E. A., BLOOM, S. R., AND WILLIAMS G.: Penile response to intracavernosal vasoactive intestinal polypeptide alone and in combination with other vasoactive agents. Br. J. Urol. **64:** 191–194, 1989.

KIESSWETTER, H., AND SCHOBER, W: Lioresal in the treatment of neurogenic bladder dysfunction. Urol. Int. **30:** 63–71, 1975.

KIHL, B., JONSSON, O., LUNDSTAM, S., AND PETTERSSON, S.: Effects of vasoactive intestinal polypeptide on the spontaneous phasic activity of rabbit bladder and kidney pelvis preparations in vitro. Acta Physiol. Scand. **123:** 497–499, 1985.

KIM, N., AZADZOI, K. M., GOLDSTEIN, I., AND SAENZ DE TEJADA, I.: A nitric oxide-like factor mediates nonadrenergic-noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. J. Clin. Invest. **88:** 112–118, 1991.

KIM, N., VARDI, Y., PADMA-NATHAN, H., DALEY, J., GOLDSTEIN, I., AND SAENZ DE TEJADA, I.: Oxygen tension regulates erection by modulating nitric oxide production in corpus cavernosum. Int. J. Impotence Res. **4** (Suppl. 2): A3, 1992.

KIM, N., VARDI, Y., PADMA-NATHAN, H., DALEY, J., GOLDSTEIN, I., AND SAENZ DE TEJADA, I.: Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. J. Clin. Invest. **91:** 437–442, 1993.

KIMOTO, Y., AND ITO, Y.: Autonomic innervation of the canine penile artery and vein in relation to neural mechanisms involved in erection. Br. J. Urol. **59:** 463–472, 1987.

KIMOTO, Y., KESSLER, R., AND CONSTANTINOU, C. E.: Endothelium dependent relaxation of human corpus cavernosum by bradykinin. J. Urol. **144:** 1015–1017, 1990.

KIMOTO, Y., NOZAKI, M., AND ITO, Y.: Actions of the alpha-1 adrenoceptor blocker bunazosin on the norepinephrine-induced contraction of smooth muscles in the rabbit proximal urethra. J. Pharmacol. Exp. Ther. **24:** 1017–1022, 1987.

KIMURA, K., HASHINE, K., TAMURA, M., KAWANISHI, Y., AND IMAGAWA, A.: Effect of testosterone on contraction and relaxation of isolated human corpus cavernosum tissue. Int. J. Impotence Res. **2** (Suppl. 1): 53, 1990a.

KIMURA, K., HASHINE, K., TAMURA, M., KAWANISHI, Y., AND IMAGAWA, A.: Alpha receptor and prostaglandin receptor-operated calcium channels in human corpus cavernosum. Int. J. Impotence Res. **2** (Suppl. 1): 17, 1990b.

KIMURA, K., KAWANISHI, Y., TAMURA, M., AND IMAGAWA, A.: Assessment of the alpha-adrenergic receptors in isolated human and canine corpus cavernosum tissue. Int. J. Impotence Res. **1:** 185–189, 1989.

KINDER, R. B., AND MUNDY, A. R.: Atropine blockade of nerve-mediated stimulation of the human detrusor. Br. J. Urol. **57:** 418–421, 1985a.

KINDER, R. B., AND MUNDY, A. R.: Inhibition of spontaneous contractile activity in isolated human detrusor muscle strips by vasoactive intestinal polypeptide. Br. J. Urol. **57:** 20–23, 1985b.

KINDER, R. B., AND MUNDY, A. R.: Pathophysiology of idiopathic detrusor instability and detrusor hyperreflexia. An in vitro study of human detrusor muscle. Br. J. Urol. **60:** 509–515, 1987.

KINDER, R. B., RESTORICK, J. M., AND MUNDY, A. R.: Vasoactive intestinal polypeptide in the hyperreflexic neuropathic bladder. Br. J. Urol. **57:** 289–291, 1985a.

KINDER, R. B., RESTORICK, J. M., AND MUNDY, A. R.: A comparative study of detrusor muscle from normal, idiopathic unstable and hyperreflexic bladder. *In* Proceedings of the 15th Annual Meeting of the International Continence Society, pp. 170–171, London, 1985b.

KIRKEBY, H. J., FAHRENKRUG, J., HOLMQUIST, F., AND OTTESEN, B.: Vasoactive intestinal polypeptide (VIP) and peptide histidine methionine (PHM) in human penile corpus cavernosum tissue and circumflex veins: localization and in vitro effects. Eur. J. Clin. Invest. **22:** 24–30, 1992.

KIRKEBY, H. J., FORMAN, A., SØRENSEN, S., AND ANDERSSON, K.-E.: Alpha-adrenoceptor function in isolated penile circumflex veins from potent and impotent men. J. Urol. **142:** 1369–1371, 1989a.

KIRKEBY, H. J., FORMAN, A., SØRENSEN, S., AND ANDERSSON, K.-E.: Effects of noradrenaline, 5-hydroxytryptamine and histamine on human penile cavernous tissue and circumflex veins. Int. J. Impotence Res. **1:** 181–188, 1989b.

KIRKEBY, H. J., JØRGENSEN, J., AND OTTESEN, B.: Neuropeptide Y (NPY) in human penile corpus cavernosum and circumflex veins. J. Urol. **145:** 605–609, 1990.

KIRKEBY, H. J., SVANE, D., POULSEN, J., TØTTRUP, A., FORMAN, A., AND ANDERSSON, K.-E.: Role of the L-arginine/nitric oxide pathway in relaxation of isolated human penile cavernous tissue and circumflex veins. Acta Physiol. Scand., in press. 1993.

KISHII, K.-I., HISAYAMA, T., AND TAKAYANAGI, I.: Comparison of contractile mechanisms by carbachol and ATP in detrusor strips of rabbit urinary bladder. Jpn. J. Pharmacol. **58:** 219–229, 1992.

KIZAWA, Y., SHINKAI, M., AND TAKAYANAGI, I.: Effects of chronic nicotine treatment on nicotine receptors in the rabbit urinary bladder. Can. J. Physiol. Pharmacol. **68:** 99–103, 1990.

KIZAWA, Y., TAKAYANAGI, I., SHINKAI, M., AND OHNO, Y.: Pharmacological action of nicotine in the isolated urinary bladder from rabbit: special reference to the chronic nicotine treatment. Gen. Pharmacol. **19:** 269–271, 1988.

KLARSKOV, P.: Non-cholinergic, non-adrenergic inhibitory nerve responses of bladder outlet smooth muscle in vitro. Br. J. Urol. **60:** 337–342, 1987a.

KLARSKOV, P.: Enkephalin inhibits presynaptically the contractility of urinary tract smooth muscle. Br. J. Urol. **59:** 31–35, 1987b.

KLARSKOV, P.: Influence of prostaglandins and ketoprofen on contractile response of human and pig detrusor and trigone muscles in vitro. Pharmacol. Toxicol. **61:** 37–41, 1987c.

KLARSKOV, P., GERSTENBERG, T., AND HALD, T.: Vasoactive intestinal polypeptide influence on lower urinary tract smooth muscle from human and pig. J. Urol. **131:** 1000–1004, 1984.

KLARSKOV, P., GERSTENBERG, T., RAMIREZ, D., CHRISTENSEN, P., AND HALD, T.: Prostaglandin type E activity dominates in urinary tract smooth muscle in vitro. J. Urol. **129:** 1071–1074, 1983a.

KLARSKOV, P., GERSTENBERG, T., RAMIREZ, D., AND HALD, T.: Non-cholinergic, non-adrenergic nerve mediated relaxation of trigone, bladder neck and urethral smooth muscle in vitro. J. Urol. **129:** 848–850, 1983b.

KLARSKOV, P., HOLM-BENTZEN, M., NØRGAARD, T., OTTESEN, B., WALTER, S., AND HALD, T.: Vasoactive intestinal polypeptide concentration in human

bladder neck smooth muscle and its influence on urodynamic parameters. Br. J. Urol. **60:** 113–118, 1987.

KLARSKOV, P., AND HØRBY-PETERSEN, J.: Influence of serotonin on lower urinary tract smooth muscle in vitro. Br. J. Urol. **58:** 507–513, 1986.

KLEVMARK, B.: Motility of the urinary bladder in cats during filling at physiological rates. II. Effects of extrinsic bladder denervation on intramural tension and on intravesical pressure patterns. Acta Physiol. Scand. **101:** 176–184, 1977.

KLÖCKNER, U., AND ISENBERG, G.: Action potentials and net membrane currents of isolated smooth muscle cells (urinary bladder of the guinea-pig). Pflügers Arch. **405:** 329–339, 1985a.

KLÖCKNER, U., AND ISENBERG, G.: Calcium currents of cesium loaded isolated smooth muscle cells (urinary bladder of the guinea pig). Pflügers Arch. **405:** 340–348, 1985b.

KLINGE, E., AND SJÖSTRAND, N. O.: Contraction and relaxation of the retractor penis muscle and the penile artery of the bull. Acta Physiol. Scand. [Suppl.] **420:** 1–88, 1974.

KLINGE, E., AND SJÖSTRAND, N. O.: Comparative studies of some isolated mammalian smooth muscle effectors of penile erection. Acta Physiol. Scand. **100:** 354–367, 1977a.

KLINGE, E., AND SJÖSTRAND, N. O.: Suppression of the excitatory adrenergic neurotransmission; a possible role of cholinergic nerves in the retractor penis muscle. Acta Physiol. Scand. **100:** 368–376, 1977b.

KNISPEL, H. H., GOESSL, C., AND BECKMAN, R.: Basal and acetylcholine-stimulated nitric oxide formation mediates relaxation of rabbit cavernous smooth muscle. J. Urol. **146:** 1429–1433, 1991.

KNISPEL, H. H., GOESSL, C., AND BECKMAN, R.: Nitric oxide mediates relaxation in rabbit and human corpus cavernosum smooth muscle. Urol. Res. **20:** 253–257, 1992a.

KNISPEL, H. H., GOESSL, C., AND BECKMAN, R.: Nitric oxide mediates neurogenic relaxation induced in rabbit cavernous smooth muscle by electric field stimulation. Urology **40:** 471–476, 1992b.

KOLEY, B., KOLEY, J., AND SAKA, J. K.: The effects of nicotine on spontaneous contractions of cat urinary bladder in situ. Br. J. Pharmacol. **83:** 347–355, 1984.

KONDO, M., TANIYAMA, K., AND TANAKA, C.: Histamine H_1-receptors in the guinea-pig urinary bladder. Eur. J Pharmacol **114:** 89–92, 1985.

KOYANAGI, T.: Denervation supersensitivity of the urethra to α-adrenergics in the chronic neurogenic bladder. Urol. Res. **6:** 89–93, 1978.

KOYANAGI, T.: Further observation on the denervation supersensitivity of the urethra in patinets with chronic neurogenic bladders. J. Urol. **122:** 348–351, 1979.

KOYANAGI, T., AND TSUJI, I: Reappraisal of the sympathetic role in the sphincteric urethra. Denervation supersensitivity of the urethra of the chronic neurogenic bladder to α-adrenergic drugs. Invest. Urol. **15:** 267–269, 1978.

KRANE, R. J., GOLDSTEIN, I., AND SAENZ DE TEJADA, I.: Impotence. N. Engl. J. Med. **321:** 1648–1659, 1989.

KRELL, R. D., MCCOY, J. L., AND RIDLEY, P. T.: Pharmacological characterization of the excitatory innervation to the guinea-pig urinary bladder in vitro: evidence for both cholinergic and non-adrenergic-non-cholinergic neurotransmission. Br. J. Pharmacol. **74:** 15–22, 1981.

KRIER, J., THOR, K. B., AND DE GROAT, W. C.: Effects of clonidine on the lumbar sympathetic pathways to the large intestine and urinary bladder of the cat. Eur. J. Pharmacol. **59:** 47–53, 1979.

KUNISAWA, Y., KAWABE, Y., NIJIMA, T., HONDA, K., AND TAKENAKA, T.: A pharmacological study of alpha adrenergic receptor subtypes in smooth muscle of human urinary bladder base and prostatic urethra. J. Urol. **134:** 396–398, 1985.

KURA, H., YOSHINO, M., AND YABU, H.: Blocking action of terodiline on calcium channels in single smooth muscle cells of the guinea pig urinary bladder. J. Pharmacol. Exp. Ther. **261:** 724–729, 1992.

KURIHARA, S.: The effect of procaine on the mechanical and electrical activities of the smooth muscle cells of the guinea-pig urinary bladder. Jpn. J. Physiol. **25:** 775–788, 1975.

KUSUNOKI, M., TANIYAMA, K., AND TANAKA, C.: Neuronal GABA release and GABA inhibition of ACh release in guinea-pig urinary bladder. Am. J. Physiol. **246:** R502–R509, 1984.

LABADIA, A., RIVERA, L., AND GARCIA-SACRISTIAN, A.: Influence of the autonomic nervous system in the horse urinary bladder. Res. Vet. Sci. **44:** 282–285, 1988.

LANGLEY, J. N., AND ANDERSON, H. K.: The innervation of the pelvic and adjoining viscera. Part II. The bladder. J. Physiol (Lond.) **19:** 71–139, 1895.

LANGTRY, H. D., AND MCTAVISH, D.: Terodiline. A review of its pharmacological properties, and therapeutic use in the treatment of urinary incontinence. Drugs **40:** 748–761, 1990.

LAPIDES, J., FRIEND, C. R., AJEMIAN, E. P., AND REUS, W. F.: A new method for diagnosing the neurogenic bladder. Univ. Mich. Med. Bull. **28:** 166–180, 1962.

LARSEN, J. J.: α- and β-adrenoceptors in the detrusor muscle and bladder base of the pig and β-adrenoceptors in the detrusor of man. Br. J. Urol. **65:** 215–222, 1979.

LARSEN, J.-J., OTTOSEN, B., FAHRENKRUG, J., AND FAHRENKRUG, L.: Vasoactive intestinal polypeptide (VIP) in the male genito-urinary tract, concentration and motor effect. Invest. Urol. **19:** 211–213, 1981.

LARSSON, B.: Demonstration of α-adrenoceptors in the rabbit bladder base and urethra with ^{3}H-dihydroergocryptine ligand binding. Acta Pharmacol. Toxicol. **52:** 188–194, 1983.

LARSSON, B., ALM, P., PERSSON, K., AND ANDERSSON, K.-E.: Studies on the localization of some neurotransmitters, nerve markers, and NADPH diaphorase activity in tissues from the pig lower urinary tract. Neurourol. Urodyn. **11:** 444–445, 1992.

LARSSON, B., ANDERSSON, K.-E., AND MATTIASSON, A.: Influence of antimuscarinics on alpha-adrenoceptors in the female rabbit urethra. Acta Physiol. Scand. **120:** 537–542, 1984b.

LARSSON, B., ANDERSSON, K.-E., BATRA, S., MATTIASSON, A., AND SJÖGREN, C.: Effects of estradiol on norepinephrine-induced contraction, alpha-adrenoceptor number and norepinephrine content in the female rabbit urethra. J. Pharmacol. Exp. Ther. **229:** 557–563, 1984a.

LARSSON, B., HÖGESTÄTT, E. D., MATTIASSON, A., AND ANDERSSON, K.-E.: Differential effects of nifedipine, verapamil and diltiazem on noradrenaline-induced contractions, adrenergic transmitter release and alpha-adrenoceptor binding in the female rabbit urethra. Naunyn Schmiedebergs Arch. Pharmacol. **326:** 14–21, 1984c.

LARSSON, C.: Production and effects of prostaglandins in the detrusor from homo, cat, rabbit and rat. Adv. Prostaglandin Thromboxane Res. **8:** 1263–1267, 1980.

LARSSON-BACKSTRÖM, C., ARRHENIUS, E., AND SAGGE, K.: Comparison of the calcium-antagonistic effects of terodiline, nifedipine and verapamil. Acta Pharmacol. Toxicol. **57:** 8–17, 1985.

LATIFPOUR, J., KONDO, S., O'HOLLAREN, B., MORITA, T., AND WEISS, R. M.: Autonomic receptors in the urinary tract: sex and age differences. J. Pharmacol. Exp. Ther. **235:** 661–667, 1990.

LATIFPOUR, J., YOSHIDA, M., AND WEISS, R. M.: Evidence for the presence of regional differences in the calcium antagonist receptors in lower urinary tract smooth muscle. Naunyn Schmiedebergs Arch. Pharmacol. **345:** 679–687, 1992.

LAU, L. C., ADAIKAN, P. G., AND RATNAM, S. S.: Effect of endothelin-1 on the human corpus cavernosum and penile vasculature. Asia Pacific J. Pharmacol. **6:** 287–292, 1991.

LAVAL, K. U., AND LUTZEYER, W.: Effects of beta-adrenergic stimulation and blocking agents on the dynamics of the human bladder outlet. Urol. Int. **33:** 366–369, 1978.

LEANDER, S., HÅKANSSON, R., ROSELL, S., FOLKERS, K., SUNDER, F., AND TORNQUIST, K.: A specific substance P antagonist blocks smooth muscle contractions induced by noncholinergic nonadenergic nerve stimulation. Nature (Lond.) **294:** 467–471, 1981.

LEARMONTH, J. R.: A contribution to the neurophysiology of the urinary bladder in man. Brain **54:** 147–176, 1931.

LECCI, A., GIULIANI, S., PATACCHINI, R., AND MAGGI, C. A.: Evidence against a peripheral role of tachykinins in the initiation of micturition reflex in rats. J. Pharmacol. Exp. Ther. **264:** 1327–1332, 1993.

LEPOR, H., GUP, D., SHAPIRO, E., AND BAUMANN, M.: Muscarinic cholinergic receptors in the normal and neurogenic human bladder. J. Urol. **142:** 869–874, 1989.

LESLIE, C. A., PAVLAKIS, A. J., WHEELER, J. S., SIROKY, M. B., AND KRANE, R. J.: Release of arachidonate cascade products by the rabbit bladder: neurophysiological significance? J. Urol. **132:** 376–379, 1984.

LEVIN, R. M., HAYES, L., ZHAO, Y., AND WEIN, A. J.: Effect of pinacidil on spontaneous and evoked contractile activity. Pharmacology **45:** 1–8, 1992.

LEVIN, R. M. HIGH, J., AND WEIN, A. J.: The effect of short-term obstruction on urinary bladder function in the rabbit. J. Urol. **132:** 789–791, 1984a.

LEVIN, R. M. HIGH, J., AND WEIN, A. J.: Evidence against the presence of spare muscarinic receptors in the rabbit urinary bladder. Neurourol. Urodyn. **2:** 317–322, 1984b.

LEVIN, R. M., JACOBY, R., AND WEIN, A. J.: Effect of adenosine triphosphate on contractility and adenosine triphosphatase activity of rabbit urinary bladder. Mol. Pharmacol. **19:** 525–528, 1981a.

LEVIN, R. M., MALKOWICZ, S. B., JACOBOWITZ, D., AND WEIN, A. J.: Ontogeny of the autonomic innervation and contractile response of the rabbit urinary bladder. J. Pharmacol. Exp. Ther. **219:** 250–257, 1981b.

LEVIN, R. M., RUGGIERI, M. R., VELAGAPUDI, S., GORDON, D., ALTMAN, B., AND WEIN, A. J.: Relevance of spontaneous activity to urinary bladder function: an in vitro and an in vivo study. J. Urol. **136:** 514–521, 1986a.

LEVIN, R. M., RUGGIERI, M. R., AND WEIN, A. J.: Functional effects of the purinergic innervation of the rabbit urinary bladder. J. Pharmacol. Exp. Ther. **236:** 452–457, 1986b.

LEVIN, R. M., RUGGIERI, M. R., AND WEIN, A. J.: Identification of receptor subtypes in the rabbit and human urinary bladder by selective radio-ligand binding. J. Urol. **139:** 844–848, 1988.

LEVIN, R. M., SHOFER, F. S., AND WEIN, A. J.: Cholinergic, adrenergic and purinergic responses of sequential strips of rabbit urinary bladder. J. Pharmacol. Exp. Ther. **212:** 536–540, 1980a.

LEVIN, R. M., SHOFER, F. S., AND WEIN, A. J.: Estrogen-induced alterations in the autonomic responses of the rabbit urinary bladder. J. Pharmacol. Exp. Ther. **215:** 614–618, 1980b.

LEVIN, R. M., AND WEIN, A. J.: Distribution and function of adrenergic receptors in the urinary bladder of the rabbit. Mol. Pharmacol. **16:** 441–448, 1979a.

LEVIN, R. M., AND WEIN, A. J.: Quantitative analysis of alpha and beta adrenergic receptor densities in the lower urinary tract of the dog and the rabbit. Invest. Urol. **17:** 75–77, 1979b.

LEVIN, R. M., AND WEIN, A. J.: Adrenergic alpha-receptors outnumber beta-receptors in human penile corpus cavernosum. Invest. Urol. **18:** 225–226, 1980.
LEVIN, R. M., AND WEIN, A. J.: Effect of vasoactive intestinal polypeptide on the contractility of the rabbit urinary bladder. Urol. Res. **9:** 217–218, 1981.
LEVIN, R. M., ZDERIC, S. A., EWALT, D. H., DUCKETT, J. W., AND WEIN, A. J.: Effects of pregnancy on muscarinic receptor density and function in the rabbit urinary bladder. Pharmacology **43:** 69–77, 1991.
LI, J. H., YASAY, G. D., AND KAU, S. T.: β-Adrenoceptor subtypes in the detrusor of guinea-pig urinary bladder. Pharmacology **44:** 13–18, 1992.
LINCOLN, J., CROWE, R., AND BURNSTOCK, G.: Neuropeptides and impotence. *In* Impotence: Diagnosis and Management of Male Erecetile Dysfunction, edited by R. S. Kirby, C. Carson and G. D. Webster, pp. 27–31, Butterworth-Heinemann Ltd., Oxford, 1991.
LINCOLN, J., CROWE, R., BLACKLEY, P. F., PRYOR, J. P., LUMLEY, J. S. P., AND BURNSTOCK, G.: Changes in the VIPergic, cholinergic and adrenergic innervation of human penile tissue in diabetic and non-diabetic impotent males. J. Urol. **137:** 1053–1959, 1987.
LINDBERG, B. F., NILSSON, L.-G., HEDLUND, H., STAHL, M., AND ANDERSSON, K.-E.: Angiotensin I is converted to angiotensin II by a serine proteinase in isolated smooth muscle from the human detrusor. Submitted for publication, 1993.
LINDSKOG, M., SJÖGREN, C., ANDERSSON, K.-E., AND ULMSTEN, U.: Oestrogen binding sites in nuclear fractions from the rat urogenital tract. Acta Pharmacol. Toxicol. **50:** 238–240, 1982.
LONGHURST, P. A., BELIS, J. A., O'DONNELL, J. P., GALIE, J. R., AND WESTFALL, D. P.: A study of the atropine-resistant component of the neurogenic response of the rabbit urinary bladder. Eur. J. Pharmacol. **99:** 295–302, 1984.
LONGHURST, P. A., KANG, J., WEIN, A. J., AND LEVIN, R. M.: Comparative length-tension relationship of urinary bladder strips from hamsters, rats, guinea-pigs, rabbits and cats. Comp. Biochem. Physiol. **96A:** 221–225, 1990.
LONGMAN, S. D., AND HAMILTON, T. C.: Potassium channel activator drugs: mechanism of action, pharmacological properties, and therapeutic potential. Med. Res. Rev. **12:** 73–148, 1992.
LONGMORE, J., AND HILL, R. G.: Characterization of NK receptors in guinea-pig urinary bladder smooth muscle: use of selective antagonists. Eur. J. Pharmacol. **222:** 167–170, 1992.
LOW, J. A.: Urethral behaviour during the involuntary detrusor contraction. Am. J. Obstet. Gynecol. **128:** 32–42, 1977.
LOW, J. A., ARMSTRONG, J. B., AND MAUGER, G. M.: The unstable urethra in the female. Obstet. Gynecol. **74:** 69–74, 1989.
LOWE, V. C., AND NORONHA-BLOB, L.: Effect of extracellular Ca^{2+} on cholinergic, KCl and phorbol ester-mediated phosphoinositide turnover and guinea pig urinary bladder contraction. Eur. J. Pharmacol. **195:** 273–279, 1991.
LUCCHELLI, A., GRANA, E., AND SANTAGOSTINO-BARBONE, M. G.: Influence of lithium pretreatment and of cooling on the responsiveness of the rat isolated jejunum and urinary bladder to muscarinic agonists. J. Auton. Pharmacol. **12:** 61–72, 1992.
LUDUENA, F. P., AND GRIGAS, E. O.: Effect of some biological substances on the dog retractor penis in vitro. Arch. Int. Pharmacodyn. **196:** 269–274, 1972.
LUE, T. F.: Physiology of erection and pathophysiology of impotence. *In* Campbell's Urology, edited by P. C. Walsh, A. B. Retik, T. A. Stamey, and E. D. Vaughan, Jr., 6th ed., pp. 709–728, W. B. Saunders Company, 1992.
LUE, T., AND TANAGHO, E.: Physiology of erection and pharmacological management of impotence. J. Urol. **137:** 829–836, 1987.
LUHESHI, G., AND ZAR, A.: Purinoceptor desensitization impairs but does not abolish the non-cholinergic motor transmission in rat isolated urinary bladder. Eur. J. Pharmacol. **185:** 203–208, 1990a.
LUHESHI, G. N., AND ZAR, M. A.: Presence of non-cholinergic motor transmission in human isolated bladder. J. Pharm. Pharmacol. **42:** 223–224, 1990b.
LUNDBERG, J. M., HUA, X.-Y., AND FRANCO-CERECEDA, A.: Effects of neuropeptide y (NPY) on mechanical activity and neurotransmission in the heart, vas deferens and urinary bladder of the guinea-pig. Acta Physiol. Scand. **121:** 325–332, 1984.
MACKENZIE, I., AND BURNSTOCK, G.: Neuropeptide action on the guinea-pig bladder; a comparison with the effects of field stimulation and ATP. Eur. J. Pharmacol. **105:** 85–94, 1984.
MAGGI, C. A.: Omega conotoxin and prejunctional modulation of the biphasic response of the rat isolated urinary bladder to single pulse electrical field stimulation. J. Auton. Pharmacol. **11:** 295–304, 1991a.
MAGGI, C. A.: The role of peptides in the regulation of the micturition reflex: an update. Gen. Pharmacol. **22:** 1–24, 1991b.
MAGGI, C. A.: Prostanoids as local modulators of reflex micturition. Pharmacol. Res. **25:** 13–20, 1992.
MAGGI, C. A., ASTOLFI, A., SANTICIOLI, P., TRAMONTANA, M., LEONCINI, G., GEPETTI, P., GIACHETTI, A., AND MELI, A.: Effect of thiorphan on the response of guinea-pig isolated urinary bladder to exogenous and endogenous tachykinins. J. Urol. **144:** 1546–1549, 1990a.
MAGGI, C. A., BARBANTI, C. A., SANTICIOLI, P., BENEFORTI, P., MISURI, D., MELI, A., AND TURINI, D.: Cystometric evidence that capsaicin-sensitive nerves modulate the afferent branch of micturition reflex in humans. J. Urol. **142:** 150–154, 1989a.
MAGGI, C. A., COY, D. H., AND GIULIANI, S.: Effect of [D-Phe6] bombesin (6–13) methylester, a bombesin receptor antagonist, towards bombesin-induced contractions in the guinea-pig and rat isolated urinary bladder. J. Auton. Pharmacol. **12:** 215–222, 1992a.
MAGGI, C. A., EVANGELISTA, S., GRIMALDI, G., SANTICIOLI, P., GIOLITTI, A., AND MELI, A.: Evidence for the involvement of arachidonic acid metabolites in spontaneous and drug-induced contractions of rat urinary bladder. J. Pharmacol. Exp. Ther. **230:** 500–513, 1984a.
MAGGI, C. A., FURIO, M., SANTICIOLI, P., CONTE, B., AND MELI, A.: Spinal and supraspinal components of GABAergic inhibition of the micturition reflex in rats. J. Pharmacol. Exp. Ther. **240:** 998–1005, 1987a.
MAGGI, C. A., GEPETTI, P., SANTICIOLI, P., FRILLI, S., GIULIANI, S., FURIO, M., THEODORSSON, E., FUSCO, B., AND MELI, A.: Tachykinin-like immunoreactivity in the mammalian urinary bladder: correlation with the functions of the capsaicin-sensitive sensory nerves. Neuroscience **26:** 233–242, 1988a.
MAGGI, C. A., GIULIANI, S., CONTE, B., FURIO, M., SANTICIOLI, P., MELI, P., GRAGNANI, L., AND MELI, A.: Prostanoids modulate reflex micturition by acting through capsaicin-sensitive afferents. Eur. J. Pharmacol. **145:** 105–112, 1988b.
MAGGI, C. A., GIULIANI, S., DELBIANCO, E., GEPETTI, S., THODORSSON, E., AND SANTICIOLI, P.: Calcitonin gene-related peptide in the regulation of urinary tract motility. Ann. N. Y. Acad. Sci. **657:** 328–343, 1992b.
MAGGI, C. A., GIULIANI, S., PATACCHINI, R., BARBANTI, G., TURINI, D., AND MELI, A.: Contractile responses of the human urinary bladder, renal pelvis and renal artery to endothelins and sarafotoxin S6b. Gen. Pharmacol. **21:** 247–249, 1990b.
MAGGI, C. A., GIULIANI, S., PATACCHINI, R., SANTICIOLI, P., TURINI, D., BARBANTI, G., AND MELI, A.: Potent contractile activity of endothelin on the human isolated urinary bladder. Br. J. Pharmacol. **96:** 755–757, 1989b.
MAGGI, C. A., GIULIANI, S., PATACCHINI, R., TURINI, D., BARBANTI, G., GIACHETTI, A., AND MELI, A.: Multiple sources of calcium for contraction of the human urinary tract. Br. J. Pharmacol. **98:** 1021–1031, 1989c.
MAGGI, C. A., GIULIANI, S., SANTICIOLI, P., ABELLI, L., AND GIACHETTI, A.: Facilitation of reflex micturition by intravesical administration of [bAla8]-neurokinin A (4–10), a selective NK-2 tachykinin receptor agonist. J. Urol. **145:** 184–187, 1991a.
MAGGI, C. A., GIULIANI, S., SANTICIOLI, P., ALBELLI, L., AND MELI, A.: Viscero-omotor responses to calcitonin gene-related peptide (CGRP) in the lower urinary tract: evidence for a transmitter role in the capsaicin-sensitive nerves of the ureter. Eur. J. Pharmacol **143:** 73–82, 1987b.
MAGGI, C. A., GIULIANI, S., SANTICIOLI, P., ABELLI, L., REGOLI, D., AND MELI, A.: Further studies on the mechanism of the tachykinin-induced activation of micturition reflex in rats: evidence for the involvement of the capsaicin-sensitive bladder mechanoreceptors. Eur. J. Pharmacol. **136:** 189–205, 1987c.
MAGGI, C. A., MANZINI, S., PARLANI, M., CONTE, B., GIULIANI, S., AND MELI, A.: The effect of nifedipine on spontaneous, drug-induced and reflexly-activated contractions of the rat urinary bladder: evidence for the participation of an intracellular calcium store to micturition contraction. Gen. Pharmacol. **19:** 73–81, 1988c.
MAGGI, C. A., AND MELI, A.: Modulation by beta-adrenoceptors of spontaneous contractions of rat urinary bladder. J. Auton. Pharmacol. **2:** 255–260, 1982.
MAGGI, C. A., AND MELI, A.: The role of neuropeptides in the regulation of the micturition reflex. J. Auton. Pharmacol. **6:** 133–162, 1986.
MAGGI, C. A., PARLANI, M., ASTOLFI, M., SANTICIOLI, P., ROVERO, P., ABELLI, L., SOMMA, V., GIULIANI, S., REGOLI, D., PATACCHINI, R., AND MELI, A.: Neurokinin receptors in the rat lower urinary tract. J. Pharmacol. Exp. Ther. **246:** 308–315, 1988d.
MAGGI, C. A., AND PATACCHINI, R.: Tachykinin NK_1 receptor in the guinea-pig isolated proximal urethra: characterization by receptor selective agonists and antagonists. Br. J Pharmacol. **106:** 888–892, 1992.
MAGGI, C. A., PATACCHINI, R., SANTICIOLI, P., GEPETTI, P., CECCONI, R., GIULIANI, S., AND MELI, A.: Multiple mechanisms in the motor responses of the guinea-pig isolated urinary bladder to bradykinin. Br. J. Pharmacol. **98:** 619–629, 1989d.
MAGGI, C. A., PATACCHINI, R., SANTICIOLI, P., AND GIULIANI, S.: Tachykinin antagonists and capsaicin-induced contraction of the rat isolated urinary bladder: evidence for tachykinin-mediated cotransmission. Br. J. Pharmacol. **103:** 1535–1541, 1991b.
MAGGI, C. A., PATACCHINI, R., SANTICIOLI, P., TURINI, D., BARBANTI, G., BENEFORTI, P., ROVERO, P., AND MELI. A.: Further studies on the motor response of the human isolated urinary bladder to tachykinins, capsaicin and electrical field stimulation. Gen. Pharmacol. **20:** 663–669, 1989e.
MAGGI, C. A., SANTICIOLI, P., ABELLI, L., PARLANI, M., CAPASSO, M., CONTE, B., GIULIANI, S., AND MELI, A.: Regional differences in the effects of capsaicin and tachykinins on motor activity and vascular permeability of the rat lower urinary tract. Naunyn Schmiedebergs Arch. Pharmacol. **335:** 636–645, 1987d.
MAGGI, C. A., SANTICIOLI, P., FURIO, M., AND MELI, A.: The effect of cyclooxygenase inhibitors on the low filling rate cystometrogram in urethane anesthetized rats. J. Urol. **134:** 800–803, 1985a.
MAGGI, C. A., SANTICIOLI, P., FURIO, M., AND MELI, A.: Dual effects of clonidine on micturition reflex in urethane anaesthetized rats. J. Pharmacol. Exp. Ther. **235:** 528–536, 1985b.
MAGGI, C. A., SANTICIOLI, P., GIULIANI, S., FURIO, M., CONTE, B., MELI, P., GRAGNANI, L., AND MELI, A.: The effect of baclofen on spinal and supraspinal micturition reflexes in rats. Naunyn Schmiedebergs Arch. Pharmacol. **336:** 197–203, 1987e.
MAGGI, C. A., SANTICIOLI, P., GIULIANI, S., REGOLI, D., AND MELI, A.: Activation of micturition reflex by substance P and substance K: indirect evidence

for the existence of multiple tachykinin receptors in the rat urinary bladder. J. Pharmacol. Exp. Ther. **238:** 259–266, 1986.

MAGGI, C. A., SANTICIOLI, P., GRIMALDI, G., AND MELI, A.: The effect of peripherally administered GABA on spontaneous contractions of the rat urinary bladder in vivo. Gen. Pharmacol. **14:** 455–460, 1983.

MAGGI, C. A., SANTICIOLI, P., AND MELI, A.: $GABA_B$ receptor mediated inhibition of field stimulation induced contractions of detrusor strips from newborn rats. J. Auton. Pharmacol. **4:** 45–51, 1984b.

MAGGI, C. A., SANTICIOLI, P., AND MELI, A.: GABA inhibits excitatory neurotransmission in rat pelvic ganglia. J. Pharm. Pharmacol. **37:** 349–351, 1985c.

MAGGI, C. A., SANTICIOLI, P., AND MELI, A.: Pharmacological evidence for the existence of two components in the twitch response to field stimulation of detrusor strips from the rat urinary bladder. J. Auton. Pharmacol. **5:** 221–230, 1985d.

MAGGI, C. A., SANTICIOLI, P., AND MELI, A.: Sympathetic inhibition of reflex activation of bladder motility during filling at a physiological-like rate in urethane anaesthetized rats. Neurourol. Urodyn. **4:** 37–45, 1985e.

MAGGI, C. A., SANTICIOLI, P., AND MELI, A.: $GABA_A$ and $GABA_B$ receptors in detrusor strips from guinea-pig bladder dome. J. Autonom. Pharmacol. **5:** 55–64, 1985f.

MAGGI, C. A., SANTICIOLI, P., AND MELI, A.: Dual effect of GABA on the contractile activity of the guinea-pig isolated bladder. J. Auton. Pharmacol. **5:** 131–141, 1985g.

MAGGI, C. A., SANTICIOLI, P., AND MELI, A.: Evidence for the involvement of endogenous substance P in the motor effect of capsaicin on the rat urinary bladder. J. Pharm. Pharmacol. **37:** 203–204, 1985h.

MAGGI, C. A., SANTICIOLI, P., PATACCHINI, R., CELLERINI, M., TURINI, D., BARBANTI, G., BENEFORTI, P., ROVERO, P., AND MELI, A.: Contractile response of the human isolated urinary bladder to neurokinins: involvement of NK-2 receptors. Eur. J. Pharmacol. **145:** 335–340, 1988e.

MAGGI, C. A., SANTICIOLI, P., PATACCHINI, R., GEPETTI, P., GIULIANI, S., ASTOLFI, M., BALDI, E., PARLANI, M., THEODORSSON, E., FUSCO, B., AND MELI, A.: Regional differences in the motor response to capsaicin in the guinea-pig urinary bladder: relative role of pre- and postjunctional factors related to neuropeptide-containing sensory nerves. Neuroscience **27:** 675–688, 1988f.

MAGGI, C. A., SANTICIOLI, P., PATACCHINI, R., TURINI, D., BARBANTI, G., BENEFORTI, P., GIULIANI, S., AND MELI, A.: Galanin: a potent modulator of excitatory neurotransmission in the human urinary bladder. Eur. J. Pharmacol. **143:** 135–137, 1987f.

MALKOWICZ, S. B., ATTA, M. A., ELBADAWI, A., WEIN, A., AND LEVIN, R.: The effect of parasympathetic decentralization on the feline urinary bladder. J. Urol. **133:** 521–523, 1985.

MALKOWICZ, S. B., WEIN, A. J., RUGGIERI, M. R., AND LEVIN R.: Comparison of calcium antagonist properties of antispasmodic agents. J. Urol. **138:** 667–670, 1987.

MALMGREN, A., ANDERSSON, K.-E., ANDERSSON, P. O., FOVAEUS, M., AND SJÖGREN, C.: Effects of nifedipine and Bay K8644 on normal and hypertrophied rat detrusor. Neurourol. Urodyn. **7:** 27–35, 1988.

MALMGREN, A., ANDERSSON, K.-E., SJÖGREN, C., AND ANDERSSON, P. O.: Effects of pinacidil and cromakalim (BRL 34915) on bladder function in rats with detrusor instability. J. Urol. **142:** 1134–1138, 1989.

MALMGREN, A., ANDERSSON, K.-E., SJÖGREN, C., AND ANDERSSON, P. O.: Effects of cromakalim (BRL 34915) and pinacidil on normal and hypertrophied rat detrusor in vitro. J. Urol. **143:** 828–834, 1990.

MALMGREN, A., SJÖGREN, C., UVELIUS, B., MATTIASSON, A., ANDERSSON, K.-E., AND ANDERSSON, P. O.: Cystometrical evaluation of bladder instability in rats with infravesical outflow obstruction. J. Urol. **137:** 1291–1294, 1987.

MALMQVIST, U., ARNER, A., AND UVELIUS, B.: Mechanics and Ca^{++}-sensitivity of human detrusor muscle bundles studied in vitro. Acta Physiol. Scand. **143:** 373–380, 1991.

MANNING, D. C., AND SNYDER, S.: ^{3}[H]-Bradykinin binding site localization in guinea pig urinary system. Adv. Exp. Biol. Med. **198:** 563–570, 1986.

MARCZIN, N., RYAN, U. S., AND CATRAVAS, J. D.: Methylene blue inhibits nitrovasodilator- and endothelium-derived relaxing factor-induced cyclic GMP accumulation in cultured pulmonary arterial smooth muscle cells via generation of superoxide anion. J. Pharmacol. Exp. Ther. **263:** 170–179, 1992.

MARTIN, W., VILLANI, G. M., JOTHIANANDAN, D., AND FURCHGOTT, R. F.: Selective blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation by haemoglobin and by methylene blue in the rabbit aorta. J. Pharmacol. Exp. Ther. **232:** 708–716, 1985.

MATSUMURA, S., TAIRA, N., AND HASHIMOTO, K.: The pharmacological behavior of the urinary bladder and its vasculature of the dog. Tohuko J. Exp. Med. **96:** 247–258, 1968.

MATTIASSON, A., ANDERSSON, K.-E., ANDERSSON, P.-O., LARSSON, B., SJÖGREN, C., AND UVELIUS, B.: Nerve-mediated functions in the circular and longitudinal muscle layers of the proximal female rabbit urethra. J. Urol. **143:** 155–160, 1990.

MATTIASSON, A., ANDERSSON, K.-E., ELBADAWI, A., MORGAN, E., AND SJÖGREN, C.: Interaction between adrenergic and cholinergic nerve terminals in the urinary bladder of rabbit, cat and man. J. Urol. **137:** 1017–1019, 1987a.

MATTIASSON, A., ANDERSSON, K.-E., AND SJÖGREN, C.: Adrenoceptors and cholinoceptors controlling noradrenaline release in the urethra of rabbit and man. J. Urol. **131:** 1190–1195, 1984a.

MATTIASSON, A., ANDERSSON, K.-E., AND SJÖGREN, C.: Urethral sensitivity to a-adrenoceptor stimulation and blockade in patients with parasympathetically decentralized lower urinary tract and in healthy volunteers. Neurourol. Urodyn. **3:** 223–233, 1984b.

MATTIASSON, A., ANDERSSON, K.-E., AND SJÖGREN, C.: Adrenergic and non-adrenergic contraction of isolated urethral muscle from rabbit and man. J. Urol. **133:** 298–303, 1985a.

MATTIASSON, A., ANDERSSON, K.-E., AND SJÖGREN, C.: Contractant and relaxant properties of the female rabbit urethral submucosa. J. Urol. **133:** 304–310, 1985b.

MATTIASSON, A., ANDERSSON, K.-E., AND SJÖGREN, C.: Inhibitory α-adrenoceptors on cholinergic axon terminals in the urethra of rabbit and man. Neurourol. Urodyn. **6:** 449–456, 1988.

MATTIASSON, A., ANDERSSON, K.-E., AND SJÖGREN, C., SUNDIN, T., AND UVELIUS, B.: Supersensitivity to carbachol in the parasympathetically decentralized feline urinary bladder. J. Urol. **131:** 562–565, 1984c.

MATTIASSON, A., EKBLAD, E., SUNDLER, F., AND UVELIUS, B.: Origin and distribution of neuropeptide Y-, vasoactive intestinal polypeptide- and substance P-containing nerve fibers in the urinary bladder of the rat. Cell Tissue Res. **239:** 141–146, 1985c.

MATTIASSON, A., EKSTRÖM, J., LARSSON, B., AND UVELIUS, B.: Changes in the nervous control of the rat urinary bladder induced by outflow obstruction. Neurourol. Urodyn. **6:** 37–45, 1987b.

MCCONNELL, J., AND BENSON, G. S.: Innervation of human penile blood vessels. Neurourol. Urodyn. **1:** 199–210, 1982.

MCGRATH, M. A., AND SHEPHERD, J. T.: Inhibition of adrenergic neurotransmission in canine vascular smooth muscle by histamine: mediation by H_2-receptors. Circ. Res. **39:** 566–573, 1976.

MCGUIRE, E. J.: Reflex urethral instability. Br. J. Urol. **50:** 200–204, 1978.

MCNEILL, D. L., TRAUGH, N. E., JR., VAIDYA, A. M., HUA, H. T., AND PAPKA, R. E.: Origin and distribution of NADPH-diaphorase-positive neurons and fibers innervating the urinary bladder of the rat. Neurosci. Lett. **147:** 33–36, 1992.

MELDRUM, L. A., AND BURNSTOCK, G.: Evidence against VIP or substance P being the transmitter in non-cholinergic excitatory nerves Supplying the guinea-pig bladder. J. Pharm. Pharmacol. **37:** 432–434, 1985.

MEYHOFF, H. H., ROSENKILDE, P., AND BØDKER, A.: Non-invasive management of impotence with trancutaneous nitroglycerin. Br. J. Urol. **69:** 88–90, 1992.

MIKHAILIDIS, D. P., JEREMY, J. Y., AND DANDONA, P.: Urinary bladder prostanoids - their synthesis, function and possible role in the pathogenesis and treatment of disease. J. Urol. **137:** 577–582, 1987.

MIODRAG, A., CASTLEDEN, C. M., AND VALLANCE, T. R.: Sex hormones and the female urinary tract. Drugs **36:** 491–504, 1988.

MIZRAHI, J., DION, S., D'ORLEANS-JUST, P., ESCHER, E., DRAPEAU, G., AND REGOLI, D.: Tachykinin receptors in smooth muscles: a study with agonists (substance P, neurokinin A9) and antagonists. Eur. J. Pharmacol. **118:** 25–36, 1985a.

MIZRAHI, J., DION, S., D'ORLEANS-JUST, P., AND REGOLI, D.: Activities and antagonism of bombesin on urinary smooth muscles. Eur. J. Pharmacol. **111:** 339–346, 1985b.

MOLDERINGS, G. J., GÖTHERT, M., VAN AHLEN, H., AND PORST, H.: Noradrenaline release in human corpus cavernosum and its modulation via presynaptic a_2-adrenoceptors. Fundam. Clin. Pharmacol. **102:** 261–267, 1989.

MOLDERINGS, G. J., VAN AHLEN, H., AND GÖTHERT, M.: Modulation of noradrenaline release in human corpus cavernosum by presynaptic prostaglandin receptors. Int. J. Impotence Res. **4:** 19–26, 1992.

MONCADA, S.: The L-arginine:nitric oxide pathway. The 1991 Ulf von Euler Lecture. Acta Physiol. Scand. **145:** 201–227, 1992.

MONCADA, S., PALMER, R. M. J., AND HIGGS, E. A.: Biosynthesis of nitric oxide from L-arginine. Biochem. Pharmacol. **38:** 1709–1715, 1989.

MONFERINI, E., GIRALDO, E., AND LADINSKY, H.: Characterization of the muscarinic receptor subtypes in the rat urinary bladder. Eur. J. Pharmacol. **147:** 453–458, 1988.

MONTGOMERY, B. S., AND FRY, C. H.: The action potential and net membrane currents in isolated human detrusor smooth muscle cells. J. Urol. **147:** 176–184, 1992.

MONTGOMERY, B. S., THOMAS, P. J., AND FRY, C. H.: The actions of extracellular magnesium on isolated human detrusor muscle function. Br. J. Urol. **70:** 262–268, 1992.

MOORE, K. H., GILPIN, S. A., DIXON, J. S., RICHMOND, D. H., AND SUTHERST, J. R.: Increase in presumptive sensory nerves of the urinary bladder in idiopathic detrusor instability. Br. J. Urol. **70:** 370–372, 1992.

MORENO, A. P., CAMPOS DE CARVALHO, A. C., CHRIST, G., MELMAN, A., AND SPRAY, D. C.: Gap junctions between human corpus cavernosum smooth muscle cells: gating properties and unitary conductance. Am. J. Physiol. **264:** C80–C92, 1993.

MORITA, T., DOHKITA, S., KONDO, S., NISHIMOTO, T., HIRANO, S., AND TSUCHIDA, S.: Cyclic adenosine monophosphate production and contractile response induced by beta-adrenoceptor subtypes in rabbit urinary bladder smooth muscle. Urol. Int. **45:** 10–15, 1990.

MORITA, T., KONDO, S., TSUCHIDA, S., AND WEISS, R. M.: Characterization of functional beta-adrenoceptor subtypes in rabbit urinary bladder smooth muscle. Tohoku J. Exp. Med. **149:** 389–395, 1986.

MORITA, T., LATIFPOUR, J., O'HOLLAREN, B., WHEELER, M. A., AND WEISS, R. M.: Sex differences in function and distribution of a_1- and a_2-adrenoceptors in rabbit urethra. Am. J. Physiol. **252:** F1124–1128, 1987.

MORITA, T., TSUJII, T., AND DOKITA, S.: Regional difference in functional roles of cAMP and cGMP in lower urinary tract smooth muscle contractility. Urol. Int. **49:** 191–195, 1992.

MORRISON, J. F. B., NIMMO, A. J., AND WHITAKER, E. M.: The localization of beta-adrenoceptor subtypes in the rat urinary bladder. J. Physiol. (Lond.) **38:** 29P, 1986.

MOSS, H. E., AND BURNSTOCK, G.: A comparative study of electrical field stimulation of the guinea-pig, ferret and marmoset urinary bladder. Eur. J. Pharmacol. **114:** 311–316, 1985.

MOSTWIN, J. L.: Receptor-operated intracellular calcium stores in the smooth muscle of the guinea-pig bladder. J. Urol. **133:** 900–905, 1985.

MOSTWIN, J. L.: The action potential of guinea pig bladder smooth muscle. J. Urol. **135:** 1299–1303, 1986.

MOSTWIN, J. L.: Electrical membrane events underlying contraction of guinea pig bladder muscle. Neurourol. Urodyn. **6:** 429–437, 1988.

MOSTWIN, J. L.: Electrical properties of bladder smooth muscle. Neurourol. Urodyn. **10:** 87–96, 1991.

MURRAY, K. H. A., AND FENELEY, R. C. L.: Endorphins - a role in lower urinary tract function? The effect of opioid blockade on the detrusor and urethral sphincter mechanisms. Br. J. Urol. **54:** 638–640, 1982.

MUTOH, S., UEDA, S., FUKOMOTO, Y., MACHIDA, J., AND IKEGAMI, K.: Effect of adrenergic and cholinergic drugs on the noradrenergic transmission in bladder neck smooth muscle. J. Urol. **138:** 212–215, 1987.

NAHOUM, C. R. D., HADLER, W. A., AND SANTANA, C. A. R.: *In* Proceedings of the International Society for Impotence Research, p. 43, Boston, MA, 1988.

NAKAHATA, N., ONO, T., AND NAKANISHI, H.: Contribution of prostaglandin E_2 to bradykinin-induced contraction in rabbit detrusor. Jpn. J. Pharmacol. **43:** 351–359, 1987.

NANNINGA, J. B., FROST, F., AND PENN, R.: Effect of intrathecal baclofen on bladder and sphincter function. J. Urol. **142:** 101–105, 1989.

NERGÅRDH, A., AND BORÉUS, L. O.: Autonomic receptor functions in the lower urinary tract of man and cat. Scand. J. Urol. Nephrol. **6:** 32–36, 1972.

NERGÅRDH, A., AND BORÉUS, L. O., AND NAGLO, A. S.: Characterization of the adrenergic beta-receptors in the urinary bladder of man and cat. Acta Pharmacol. Toxicol. **40:** 14–21, 1977.

NERGÅRDH, A., AND KINN, A. C.: Neurotransmission in activation of the contractile response in the human urinary bladder. Scand. J. Urol. Nephrol. **15:** 97–102, 1983.

NESBIT, R. M., LAPIDES, J., VALK, W. W., SUTLER, M., BERRY, R. L., LYONS, R. H., CAMPBELL, K. N., AND MOE, G. K.: The effects of blockade of the autonomic ganglia on the urinary bladder in man. J. Urol. **57:** 242–250, 1947.

NICHOLLS, J., HOURANI, S. M. O., AND KITCHEN, I.: Characterization of P_1-purinoceptors on rat duodenum and urinary bladder. Br. J. Pharmacol. **105:** 639–642, 1992.

NIKOLSKY, W.: Ein Beitrag zur Physiologie der Nervii Erigentes. Arch. Anat. Physiol. (Lpz). Jahrgang **209:** 221, 1879.

NILVEBRANT, L., ANDERSSON, K.-E., AND MATTIASSON, A.: Characterization of the muscarinic cholinoceptors in the human detrusor. J. Urol. **134:** 418–423, 1985.

NILVEBRANT, L., EKSTRÖM, J., AND MALMBERG, L.: Muscarinic receptor density in the rat urinary bladder after denervation, hypertrophy and urinary diversion. Acta Pharmacol. Toxicol. **59:** 306–314, 1986.

NIMMO, A. J., ANDERSSON, P. O., AND MORRISON, J. F. B.: Reactive changes in neurokinin receptor density following selective denervations and outlet obstruction of rat bladder. J. Physiol. (Lond.) **446:** 524P, 1992.

NIMMO, A. J., MORRISON, J. B. F., AND WHITAKER, E. M.: A comparison of the distribution of substance P and calcitonin gene-related peptide receptors in the rat bladder. Q. J. Exp. Physiol. **73:** 789–792, 1988.

NORDLING, J.: Effects of clonidine (Catapresan) on urethral pressure. Invest. Urol. **16:** 289–291, 1979.

NORDLING, J.: Influence of the sympathetic nervous system on lower urinary tract in man. Neurourol. Urodyn. **2:** 3–26, 1983.

NORLÉN, L. J., BLAIVAS, J., GRODIN, W., AND LUNDBERG, J. M.: Contractile effect of substance P on the canine urinary bladder in vivo. Neurourol. Urodyn. **2:** 323–327, 1983.

NORONHA-BLOB, L., LOWE, V. C., HANSON, R. C., AND U'PRICHARD, D. C.: Heterogeneity of muscarinic receptors coupled to phosphoinositide breakdown in guinea pig brain and peripheral tissues. Life Sci. **41:** 967–975, 1987.

NORONHA-BLOB, L., LOWE, V. C., PATTON, A., CANNING, B., COSTELLO, D., AND KINNIER, W. J.: Muscarinic receptors: relationships among phosphoinositide breakdown, adenylate cyclase inhibition, in vitro detrusor muscle contractions and in vivo cystometrogram studies in guinea pig bladder. J. Pharmacol. Exp. Ther. **249:** 843–851, 1989.

NORONHA-BLOB, L., PROSSER, J. C., STURM, B. L., LOWE, V. C., AND ENNA, S. J.: (±)Terodiline: an M_1-selective muscarinic receptor antagonist. In vivo effects at muscarinic receptors mediating urinary bladder contraction, mydriasis and salivary secretion. Eur. J. Pharmacol. **201:** 135–142, 1991.

OHTSUKA, M., MORI, J., TSUJIOKA, K., AND KUMADA, S.: Pharmacological study on sympathetic inhibition of the urinary bladder in dogs. Jpn. J. Pharmacol. **30:** 187–198, 1980.

OKAMURA, T., OKUNISHI, H., AYAJIKI, K., AND TODA, N.: Conversion of angiotensin I to angiotensin II in dog isolated renal artery: role of two different angiotensin II-generating enzymes. J. Cardiovasc. Pharmacol. **15:** 353–359, 1990.

OKUNISHI, H., MIYAZAKI, M., AND TODA, N.: Evidence for a putatively new angiotensin II-generating enzyme in the vascular wall. J. Hypertens. **5:** 155–160, 1984.

OLIVER, J. A., AND SCIACCA, R. R.: Local generation of angiotensin II as a mechanism of regulation of peripheral vascular tone in the rat. J. Clin. Invest. **74:** 1247–1251, 1984.

ØSTERGAARD, J. R., ØSTERGAARD, K., ANDERSSON, K.-E., AND SOMMER, L.: Calcium antagonistic effects of terodiline in rabbit aorta and human uterus. Acta Pharmacol. Toxicol. **46** (Suppl. I): 12–19, 1980.

OTTESEN, B., WAGNER, G., VIRAG, R., AND FAHRENKRUG, J.: Penile erection: possible role for vasoactive intestinal polypeptide as a neurotransmitter. Br. Med. J. [Clin. Res.] **288:** 9–11, 1984.

OWEN, J. A., SAUNDERS, F., HARRIS, C., FENEMORE, J., REID, K., SURRIDGE, D., CONDRA, M., AND MORALES, A.: Topical nitroglycerin: a potential treatment for impotence. J. Urol. **141:** 546–548, 1989.

PALMER, J. H., WORTH, P. H. L., AND EXTON-SMITH, A. N.: Flunarizine: a once-daily therapy for urinary incontinence. Lancet **2:** 279–281, 1981.

PALMER, R. M. J., FERRIGE, A. G., AND MONCADA, S.: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature (Lond.) **327:** 524–526, 1987.

PARIJA, S. C., RAVIPRAKASH, V., AND MISHRA, S. K.: Adenosine- and α,β-methylene ATP-induced differential inhibition of cholinergic and non-cholinergic neurogenic responses in rat urinary bladder. Br. J. Pharmacol. **102:** 396–400, 1991.

PARLANI, M., CONTE, B., MAJMONE, S., MAGGI, C. A., ROVERO, P., AND GIACHETTI, A.: The contractile effect of tachykinins on human prostatic urethra: involvement of NK-2 receptors. J. Urol. **144:** 1543–1545, 1990.

PAVLAKIS, A. J., SIROKY, M. B., LESLIE, C. A., AND KRANE, R. J.: Prostaglandins in lower urinary tract. Neurourol. Urodyn. **2:** 105–116, 1983.

PENTILLO, O., AND VARTIAINEN, A.: Acetylcholine, histamine, 5-hydroxytryptamine and catecholamine contents of mammalian penile erection and urethral tissue. Acta Pharmacol. Toxicol. **21:** 145–151, 1964.

PERLBERG, S., AND CAINE, M.: Adrenergic response of bladder muscle in prostatic obstruction. Urology **20:** 524–537, 1982.

PERSSON, C. G. A.: Inhibitory effect at the bladder-urethral junction. Acta Physiol. Scand. **97:** 139–141, 1976.

PERSSON, C. G. A., AND ANDERSSON, K.-E.: Adrenoceptor and cholinoceptor mediated effects in the isolated urethra of cat and guinea-pig. Clin. Exp. Pharmacol. Physiol. **3:** 415–426, 1976.

PERSSON, K., ALM, P., JOHANSSON, K., LARSSON, B., AND ANDERSSON, K.-E.: Nitric oxide synthase in pig lower urinary tract: immunohistochemistry, NADPH diaphorase histochemistry, and functional effects. Br. J. Pharmacol., in press, 1993.

PERSSON, K., AND ANDERSSON, K.-E.: Nitric oxide and relaxation of pig trigone and urethral smooth muscle. Br. J. Pharmacol. **106:** 416–422, 1992a.

PERSSON, K., AND ANDERSSON, K.-E.: Nerve-mediated relaxation of the rabbit isolated urethra is associated with an increase in the smooth muscle content cGMP. (abstr. 693). Urol. **149:** 386A, 1993.

PERSSON, K., GARCIA-PASCUAL, A., AND ANDERSSON, K-E.: Difference in the actions of calcitonin gene-related peptide on pig detrusor and vesical arterial smooth muscle. Acta Physiol. Scand. **143:** 45–53, 1991a.

PERSSON, K., GARCIA-PASCUAL, A., FORMAN, A., TØTTRUP, A., AND ANDERSSON, K-E.: Nitric oxide and non-adrenergic, non-cholinergic nerve-mediated relaxation of isolated pig and rabbit urethral and pig trigonal smooth muscle. *In* The Biology of Nitric Oxide, I Physiological and Clinical Aspects, edited by S. Moncada, M. A. Marletta, J. B. Hibbs, Jr., and E. A. Higgs, pp. 312–317, Portland Press, London and Chapel Hill, 1991b.

PERSSON, K., IGAWA, Y., MATTIASSON, A., AND ANDERSSON, K.-E.: Effects of inhibition of the L-arginine/nitric oxide pathway in the rat lower urinary tract in vitro and in vivo. Br. J. Pharmacol. **107:** 178–184, 1992.

PERSSON, K., IGAWA, Y., MATTIASSON, A., AND ANDERSSON, K.-E.: Inhibition of the arginine/nitric oxide pathway causes bladder hyperactivity in the rat. Acta Physiol. Scand. **144:** 107–108, 1991c.

PETERSON, J. S., AND NORONHA-BLOB, L.: Effects of selective cholinergic antagonists and α,β-methylene ATP on guinea-pig urinary bladder contractions in vivo following pelvic nerve stimulation. J. Auton. Pharmacol. **9:** 303–313, 1989.

PETERSEN, T., HUSTED, S., AND SIDENIUS, P.: Prazosin treatment of neurological patients with detrusor hyperreflexia and bladder emptying disability. Scand. J. Urol. Nephrol. **23:** 189–194, 1989.

PICKARD, R. S., POWELL, P. H., AND ZAR, M. A.: The effect of inhibitors of nitric oxide biosynthesis and cyclic GMP formation on nerve-evoked relaxation of human cavernosal smooth muscle. Br. J. Pharmacol. **104:** 755–759, 1991.

PICKARD, R. S., POWELL, P. H., AND ZAR, M. A.: Evidence against vasoactive intestinal polypeptide as the relaxant neurotransmitter in human cavernosal smooth muscle. Br. J. Pharmacol. **108:** 497–500, 1993.

PICKARD, R. S., ZAR, M. A., AND POWELL, P. H.: Nerve-evoked nitric oxide production in cavernosal tissue from potent and impotent men. Int. J. Impotence Res. **4** (Suppl. 2): A2, 1992.

POGGESI, L., NICITA, G., CASTELLANI, S., SELLI, C., GALANTI, G., TURINI, D., AND MASOTTI, G.: The role of prostaglandins in the maintenance of the tone of the rabbit urinary bladder. Invest. Urol. **17:** 454–458, 1980.

POIRIER, M., RIFFAUD, J. P., LACOLLE, J. Y., AND DUPONT, CH.: Effects of five alpha-blockers on the hypogastric nerve stimulation of the canine lower urinary tract. J. Urol. **140:** 165–167, 1988.

POLAK, J. M., GU, J., MINA, S., AND BLOOM, S. R.: Vipergic nerves in the penis. Lancet **2:** 217–219, 1981.

POLI, E., CORUZZI, G., AND BERTACCINI, G.: Pre- and postjunctional effects of histamine on the guinea-pig urinary bladder: evidence for heterogeneity in the H_1 population? Agents Actions **23:** 241–243, 1988.

POLI, E., MACALUSO, G., AND POZZOLI, C.: Actions of two novel prostaglandin analogs, SC-29169 and SC-31391, on guinea pig and human isolated urinary bladder. Gen. Pharmacol. **23:** 805–809, 1992a.

POLI, E., MONICA, B., ZAPPIA, L., POZZOLI, C., AND BERTACCINI, G.: Antimuscarinic activity of telenzepine on isolated human urinary bladder: no role for M1-muscarinic receptors. Gen. Pharmacol. **23:** 659–664, 1992b.

PORST, H.: Prostaglandin E_1 bei erektiler Dysfunktion. Urologe **28:** 94–98, 1989.

POTJER, R. M., AND CONSTANTINOU, C. E.: Frequency of spontaneous contractions in longitudinal and transverse bladder strips. Am. J. Physiol. **257:** R781–R787, 1989.

PRICE. D. T., SCHWINN, D. A. KIM, J. H., CARSON, C. C., III, CARON, M. G., AND LEFKOWITZ, R. J.: Alpha, adrenergic receptor subtype mRNA expression in human for press cavernosum (abstr. 287). J. Urol. **149:** 285A, 1993.

QUAST, U., AND COOK, N. S.: Moving together: K^+ channel openers and ATP-sensitive K^+ channels. Trends Pharmacol. Sci. **10:** 431–435, 1989.

RAEZER, D. M., WEIN, A. J., JACOBOWITZ, D., AND CORRIERE, J. N.: Autonomic innervation of the canine urinary bladder. Urology **2:** 211–221, 1973.

RAJFER, J., ARONSON, W. J., BUSH, P. A., DOREY, F. J., AND IGNARRO, L. J.: Nitric oxide as a mediator of relaxation of the corpus cavernosum on response to nonadrenergic, noncholinergic neurotransmission. N. Engl. J. Med. **326:** 90–94, 1992.

RAO, M. S., BAPNA, B. C., SHARMA, P. L., CHARY, K. S. N., AND VAIDYANATHAN, S.: Clinical import of beta-adrenergic activity in the proximal urethra. J. Urol. **124:** 254–255, 1981.

RAZ, S.: Peripheral bladder denervation. *In* Proceedings of the 2nd Joint Meeting of the International Continence Society and the Urodynamic Society, pp. 177–180, Aachen, 1983.

REGOLI, D., DION, S., RHALEB, N. E., DRAPEAU, G., ROUISSI, N., AND D'ORLEANS-JUSTE, P.: Receptors for neurokinins, tachykinins and bombesin: a pharmacological study. Ann. N. Y. Acad. Sci. **547:** 158–173, 1988.

REGOLI, D., DRAPEAU, G., ROVERO, P., DION, S., D'ORLEANS-JUSTE, P., AND BARABÉ, J.: The actions of kinin antagonists on B_1 and B_2 receptor systems. Br. J. Pharmacol. **123:** 61–65, 1986.

RESNICK, N. M., AND YALLLA, S. V.: Detrusor hyperactivity with impaired contractile function: an unrecognized but common cause of incontinence in elderly patients. J. A. M. A. **257:** 3076–3081, 1987.

RESNICK, N. M., YALLLA, S. V., AND LAURINO, R.: The pathophysiology of urinary incontinence among institutionalized elderly persons. N. Engl. J. Med. **320:** 1–7, 1989.

RESTORICK, J. M., AND MUNDY, A. R.: The density of cholinergic and alpha and beta adrenergic receptors in the normal and hyper-reflexic human detrusor. Br. J. Urol. **63:** 32–35, 1989.

RICHARDS, M. H.: Pharmacology and second messenger interaction of cloned muscarinic receptors. Biochem. Pharmacol. **42:** 1645–1653, 1991.

RIVERA, L., HERNÀNDEZ, M., BENEDITO, S., PRIETO, D., AND GARCÍA-SACRISTÀN, A.: Mediation of contraction by cholinergic muscarinic receptors in the ureterovesical junction. J. Auton. Pharmacol. **12:** 175–181, 1992.

ROBERTSON, D. W., AND STEINBERG, M. I.: Potassium channel modulators: scientific applications and therapeutic promise. J. Med. Chem. **33:** 1529–1541, 1990.

ROHNER, T. J., HANNIGAN, J. D., AND SANFORD, E. J.: Altered in vitro adrenergic response of dog detrusor muscle after chronic bladder outlet obstruction. Urology **11:** 357–361, 1978.

ROKAEUS, A.: Galanin: a newly isolated biologically active neuropeptide. Trends Neurosci. **10:** 158–164, 1987.

ROUISSI, N., RHALEB, N. E., NANTEL, F., DION, S., DRAPEAU, G., AND REGOLI, D.: Characterization of bombesin receptors in peripheral contractile organs. Br. J. Pharmacol. **101:** 1141–1147, 1991.

ROY, A. C., ADAIKAN, P. G., SEN, D. K., AND RATNAM, S. S.: Prostaglandin 15-hydroxydehydrogenase activity in human penile corpora cavernosa and its significance in prostaglandin-mediated penile erection. Br. J. Urol. **64:** 180–182, 1989.

ROY, J. B., PETRONE, R. L., AND SAID, S.: A clinical trial of intracavernous vasoactive intestinal peptide to induce penile erection. J. Urol. **143:** 302–304, 1990.

ROY, A. C., TAN, S. M., KOTTEGODA, S. R., AND RATNAM, S. S.: Ability of human corpora cavernosa muscle to generate prostaglandins and thromboxanes in vitro. IRCS Med. Sci. **12:** 608–609, 1984.

RUCH, T. C.: The urinary bladder. *In* Medical Physiology and Biophysics, edited by T. C. Ruch and J. F. Fulton, 18th ed., pp. 955–962, W. B. Saunders Company, Philadelphia and London, 1960.

RUD, T.: The effects of estrogens and gestagens on the urethral pressure profile in urinary continent and stress incontinent women. Acta Obstet. Gynecol. Scand. **59:** 265–270, 1980.

RUD, T., ANDERSSON, K.-E., ASMUSSEN, M., HUNTING, A., AND ULMSTEN, U.: Factors maintaining the intraurethral pressure in women. Invest. Urol. **17:** 343–347, 1980.

RUD, T., ANDERSSON, K.-E., AND ULMSTEN, U.: Effects of nifedipine in women with unstable bladder. Urol. Int. **34:** 421–425, 1979.

RUD, T., ULMSTEN, U., AND ANDERSSON, K.-E.: Initiation of voiding in healthy women and those with stress incontinence. Acta Obstet. Gynecol. Scand. **57:** 457–461, 1978.

RUDY, D. C., AND DOWNIE, J. W.: Evidence for local neural modulation of sympathetic influences on the feline bladder. Neurourol. Urodyn. **7:** 461–470, 1988.

RÜEGG, J. C.: Smooth muscle tone. Physiol. Rev. **51:** 201–248, 1971.

RUGGIERI, M. R., BODE, D. C., LEVIN, R. M., AND WEIN, A. J.: Muscarinic receptor subtypes in human and rabbit bladder. Neurourol. Urodyn. **6:** 119–128, 1987.

RUGGIERI, M. R., WHITMORE, K. E., AND LEVIN, R. M.: Bladder purinergic receptors. J. Urol. **144:** 176–181, 1990.

SABAN, R., KEITH, I. M., NIELSEN, K. T., CHRISTENSEN, M. M., RHODES, P. R., AND BRUSKEWITZ, R. C.: In vitro effects of bladder mucosa and an enkephalinase inhibitor on tachykinin induced contractility of the dog bladder. J. Urol. **147:** 750–755, 1992.

SAENZ DE TEJADA, I.: Mechanisms for the regulation of penile smooth muscle contractility. *In* World Book of Impotence, edited by T. F. Lue, pp. 39–48, Smith-Gordon and Company Limited, London, 1992.

SAENZ DE TEJADA, I., BLANCO, R., GOLDSTEIN, I., AZADZOI, K., DE LAS MORENAS, A., KRANE, R. J., AND COHEN, R. A.: Cholinergic neurotransmission in human corpus cavernosum. I. Responses of isolated tissue. Am. J. Physiol. **254:** H468–472, 1988.

SAENZ DE TEJADA, I., CARSON, M. P., DE LAS MORENAS, A., GOLDSTEIN, I., AND TRAISH, A. M.: Endothelin: localization, synthesis, activity, and receptor types in human penile corpus cavernosum. Am. J. Physiol. **261:** H1078–H1085, 1991a.

SAENZ DE TEJADA, I., CARSON, M. P., TRAISH, A., EASTMAN, E. H., AND GOLDSTEIN, I.: Role of endothelin, a novel vasoconstrictor peptide, in the local control of penile smooth muscle. J. Urol. **141:** 222A, 1989a.

SAENZ DE TEJADA, I., GOLDSTEIN, I., AZADZOI, K., KRANE, R. J., AND COHEN, R. A.: Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. N. Engl. J. Med. **320:** 1025–1030, 1989b.

SAENZ DE TEJADA, I., KIM, N., LAGAN, I., KRANE, R. J., AND GOLDSTEIN, I.: Regulation of adrenergic activity in penile corpus cavernosum. J. Urol. **142:** 1117–1121, 1989c.

SAENZ DE TEJADA, I., MOROUKIAN, P., TESSIER, J., KIM, J. J., GOLDSTEIN, I., AND FROHRIB, D.: Trabecular smooth muscle modulates the capacitor function of the penis. Studies on a rabbit model. Am. J. Physiol. **260:** H1590–H1595, 1991b.

SAENZ DE TEJADA, I., MUELLER, J. D., DE LAS MORENAS, A., MACHADO, M., MORELAND, R. B., KRANE, R. J., WOLFE. H. J., AND TRAISH, A. M.: Endothelin in the urinary bladder. I. Synthesis of endothelin-1 by epithelia, smooth muscle and fibroblasts suggests autocrine and paracrine cellular regulation. J. Urol. **148:** 1290–1298, 1992.

SAEZ, S., AND MARTIN, P. M.: Evidence of estrogen receptors in the trigone area of human urinary bladder. J. Steroid Biochem. **15:** 317–320, 1981.

SAITO, M., GOTOH, M., KATO, K., AND KONDO, A.: Denervation supersensitivity of the rabbit urinary bladder to calcium ion. J. Urol. **142:** 418–421, 1989.

SAITO, M., KONDO, A., GOTOH, M., AND KATO, K.: Age-related changes in the rat detrusor muscle: the contractile response to inorganic ions. J. Urol. **146:** 891–894, 1991.

SAITO, M., KONDO, A., KATO, T., AND MIYAKE, K.: Response of the human urinary bladder to angiotensins: a comparison between neurogenic and control bladders. J. Urol. **149:** 408–411, 1993a.

SAITO, M., LONGHURST, P. A., TAMMELA, T. L. J., WEIN, A., AND LEVIN, R. M.: Effects of partial outlet obstruction of the rat urinary bladder on micturition characteristics, DNA synthesis and the contractile response to field stimulation and pharmacological agents. J. Urol., in press, 1993b.

SALIMI, M., SETEKLEIV, J., AND SKOBBA, T. J.: The sensitivity of adrenergic excitatory and inhibitory receptors in the smooth muscle of the rabbit urinary bladder. Acta Pharmacol. Toxicol. **27:** 213–224, 1969.

SANTICIOLI, P., MAGGI, C. A., AND MELI, A.: The effects of clonidine on electrically-induced contractions of rat detrusor stripe in vitro. J. Auton. Pharmacol. **3:** 161–166, 1983.

SANTICIOLI, P., MAGGI, C. A., AND MELI, A.: $GABA_B$ receptor mediated inhibition of field stimulation-induced contractions of rabbit bladder muscle in vitro. J. Pharm. Pharmacol. **36:** 378–381, 1984.

SANTICIOLI, P., MAGGI, C. A., AND MELI, A.: The postganglionic excitatory innervation of the mouse urinary bladder and its modulation by prejunctional $GABA_B$ receptors. J. Auton. Pharmacol. **6:** 53–66, 1986.

SANTICIOLI, P., TRAMONTANA, M., DEL BIANCO, E., MAGGI, C. A., AND GEPPETTI, P.: $GABA_A$ and $GABA_B$ receptors modulate the K^+-evoked release of sensory CGRP from the guinea pig urinary bladder. Life Sci. **48:** PL69-PL72, 1991.

SATAKE, N., SHIBATA, S., AND VEDA, S.: Phentolamine-induced rhythmic contractions in bladder detrusor muscle of guinea-pig. Br. J. Pharmacol. **83:** 965–971, 1984.

SATHANANTHAN, A. H., ADAIKAN, P. G., LAU, L. C., HO, J., AND RATNAM, S. S.: Fine structure of the human corpus cavernosum. Arch. Androl. **26:** 107–117, 1991.

SATOH, K., SHIMIZU, N., TOHYAMA, M., AND MAEDA, T.: Localization of the micturition reflex center at dorsolateral pontine tegmentum of the rat. Neurosci. Lett. **8:** 27–33, 1978.

SAUM, W. R., AND DE GROAT, W. C.: The actions of 5-hydroxytryptamine on the urinary bladder and on vesical autonomic ganglia in the cat. J. Pharmacol. Exp. Ther. **185:** 70–83, 1973.

SAXENA, P. R., HEILIGERS, J., MYLECHARANE, E. J., AND TIO, R.: Excitatory 5-hydroxytryptamine receptors in the cat urinary bladder are of the M- and HT_2-type. J. Auton. Pharmacol. **5:** 101–107, 1985.

SCHMALBRUCH, H., AND WAGNER, G.: Vasoactive intestinal polypeptide (VIP)- and neropeptide Y (NPY)-containing nerve fibres in the penile cavernous tissue of green monkeys (Cercopithecus aethiops). Cell Tissue Res. **256:** 529–541, 1989.

SCHNEIDER, P., HOPP, H. H., AND ISENBERG, G.: Ca^{2+} influx through ATP-gated channels increments $[Ca^{2+}]i$ and inactivates I_{Ca} in myocytes from guinea-pig urinary bladder. J. Physiol. (Lond.) **440:** 479–496, 1991.

SCHREITER, F., FUCHS, P., AND STOCKAMP, K.: Estrogenic sensitivity of α-receptors in the urethra musculature. Urol. Int. **31:** 13–19, 1976.

SCHÜSSLER, B.: Comparison of the mode of action of prostaglandin E_2 (PGE_2) and sulprostone, a PGE_2-derivative, on the lower urinary tract in healthy women. A urodynamic study. Urol. Res **18:** 349–352, 1990.

SECREST, R. J., AND COHEN, M. L.: Endothelin: differential effects in vascular and non-vascular smooth muscle. Life Sci. **45:** 1365–1372, 1989.

SEKI, N., KARIM, O. M. A., AND MOSTWIN, J. L.: Membrane electrical properties of guinea pig bladder smooth muscle with growth. Neurourol. Urodyn. **11:** 245–252, 1992a.

SEKI, N., KARIM, O. M. A., AND MOSTWIN, J. L.: Change in electrical properties of guinea pig smooth muscle membrane by experimental bladder outflow obstruction. Am. J. Physiol. **262:** F885–F891, 1992b.

SEKI, N., KARIM, O. M. A., AND MOSTWIN, J. L.: The effect of experimental urethral obstruction and its reversal on changes in passive electrical properties of detrusor muscle. J. Urol. **148:** 1957–1961, 1992c.

SEKI, N., KARIM, O. M. A., AND MOSTWIN, J. L.: Efect of pinacidil on the membrane electrical activity of guinea pig detrusor muscle. J. Pharmacol. Exp. Ther. **263:** 816–822, 1992d.

SHAPIRO, E.: Effect of estrogens on the weight and muscarinic cholinergic receptor density of the rabbit bladder and urethra. J. Urol. **135:** 1084–1087, 1986.

SHAPIRO, E., TANG, R., ROSENTHAL, E., AND LEPOR, H.: The binding and functional properties of voltage dependent calcium channel receptors in pediatric normal and myelodysplastic bladders. J. Urol. **146:** 520–523, 1991.

SHARKEY, K. A., WILLIAMS, R. G., SCHULTZBERG, M., AND DOCKRAY, G. J.: Sensory substance P innervation of the urinary bladder. Possible site of action of capsaicin in causing urine retention in rats. Neuroscience **10:** 861–868, 1983.

SHERRINGTON, C. S.: Postural activity of muscle and nerve. Brain **38:** 191–234, 1915.

SHINKAI, M., AND TAKAYANAGI, I.: Characterization of tachykinin receptors in urinary bladder from guinea pig. Jpn. J. Pharmacol. **54:** 241–243, 1990.

SHINKAI, M., TAKAYANAGI, I., AND KATO, T.: Tachykinin receptors of the NK2 type involved in the acetylcholine release by nicotine in guinea-pig bladder. Br. J. Pharmacol. **108:** 759–762, 1993.

SHIRAI, M., MAKI, A., TAKANAMI, M., AND O. K., NAKAMURA, K., YANAIHARA, N., YANAIHARA, C., IGUCHI, K., FUJITA, T., AND IWANAGA, T.: Content and distribution of vasoactive intestinal polypeptide (VIP) in cavernous tissues of human penis. Urology **35:** 360–363, 1990.

SHIRAI, M., SASAKI, K., AND RIKIMARU, A.: Histochemical investigation on the distribution of adrenergic and cholinergic nerves in human penis. Tohoku J. Exp. Med. **107:** 403–404, 1972.

SHIRAKAWA, J., NAKANISHI, T., TANIYAMA, K., KAMIDONO, S., AND TANAKA, C.: Regulation of the substance P-induced contraction via release of acetylcholine and γ-aminobutyric acid in the guinea-pig urinary bladder. Br. J. Pharmacol. **98:** 437–444, 1989.

SIBLEY, G. N. A.: A comparison of spontaneous and nerve-mediated activity in bladder muscle from man, pig and rabbit. J. Physiol. (Lond.) **354:** 431–443, 1984.

SIBLEY, G. N. A.: The physiological response of the detrusor muscle to experimental bladder outflow obstruction in the pig. Br. J. Urol. **60:** 332–336, 1987.

SILLÉN, U., PERSSON, B., AND RUBENSON, A.: Involvement of central GABA receptor in the regulation of the urinary bladder function of anaesthetized rats. Naunyn Schmiedebergs Arch. Pharmacol. **314:** 195–200, 1979.

SJÖGREN, C., AND ANDERSSON, K.-E.: Effects of cholinoceptor blocking drugs, adrenoceptor stimulants, and calcium antagonists on the transmurally-stimulated guinea-pig urinary bladder in vitro and in vivo. Acta Pharmacol. Toxicol. **44:** 228–234, 1979.

SJÖGREN, C., ANDERSSON, K.-E., ANDERSSON, P.-O., MATTIASSON, A., AND UVELIUS, B.: Different effects of neuropeptide Y on electrically induced contractions in the longitudinal and circular smooth muscle layers of the female rabbit urethra. Acta Physiol. Scand. **133:** 177–181, 1988.

SJÖGREN, C., ANDERSSON, K.-E., AND HUSTED, S.: Contractile effects of some polypeptides on the isolated urinary bladder of guinea-pig, rabbit, and rat. Acta Pharmacol. Toxicol. **50:** 175–184, 1982a.

SJÖGREN, C., ANDERSSON, K.-E., HUSTED, S., MATTIASSON, A., AND MØLLER-MADSEN, B.: Atropine resistance of the transmurally stimulated isolated human bladder. J. Urol. **128:** 1368–1371, 1982b.

SJÖGREN, C., ANDERSSON, K.-E., AND MATTIASSON, A.: Effects of vasoactive intestinal polypeptide on isolated urethral and urinary bladder smooth muscle from rabbit and man. J. Urol. **133:** 136–140, 1985.

SJÖSTRAND, N. O., ELDH, J., SAMUELSON, U. E., ALARANTA, S., AND KLINGE, E.: The effects of L-arginine and N^G-monomethyl L-arginine on the inhibitory neurotransmission of the human corpus cavernosum penis. Acta Physiol. Scand. **140:** 297–298, 1990.

SLACK, B., AND DOWNIE, J. W.: Pharmacological analysis of the responses of the feline urethra to autonomic nerve stimulation. J. Auton. Nerv. Syst. **8:** 141–160, 1983.

SNEDDON, P., AND MCLEES, A.: Purinergic and cholinergic contractions in adult and neonatal rabbit bladder. Eur. J. Pharmacol. **214:** 7–12, 1992.

SOARES DE MOURA, R., DEMELLO, R. F., AND D'AGUINAGA, S.: Inhibitory effect of cromakalim in human de tumor muscle is mediated by glibenclamide-sensitive potassium channels. J. Urol. **149:** 1174–1177, 1993.

SOKOL, H. W. S., AND VALTIN, H. (EDS.): The Brattleboro Rat. Ann. N. Y. Acad. Sci. **394:** 1–828, 1982.

SOMOGYI, G. T., AND DE GROAT, W. C.: Modulation of the release of [^{3}H] norepinephrine from the base and body of the rat urinary bladder by endogenous adrenergic and cholinergic mechanisms. J. Pharmacol. Exp. Ther. **255:** 204–210, 1990.

SOMOGYI, G. T., AND DE GROAT, W. C.: Evidence for inhibtory nicotinic and facilitatory muscarinic receptors in cholinergic nerve terminals of the rat urinary bladder. J. Auton. Nerv. Syst. **37:** 89–98, 1992.

SPEAKMAN, M. J., BRADING, A. F., GILPIN, C. J., DIXON, J. S., GILPIN, S. A., AND GOSLING, J. A.: Blader outflow obstruction - a cause of denervation supersensitivity. J. Urol. **138:** 1461–1466, 1987.

SPEAKMAN, M. J., WALMSLEY, D., AND BRADING, A. F.: An in vitro pharmacological study of the human trigone - a site of non-adrenergic, non-cholinergic neurotransmission. Br. J. Urol. **61:** 304–309, 1988.

SPEDDING, M., AND PAOLETTI, R.: III. Classification of calcium channels and the sites of action of drugs modifying channel function. Pharmacol. Rev. **44:** 363–376, 1992.

STEERS, W. D.: Neural control of penile erection. Semin. Urol. 866–79, 1990.

STEERS, W. D.: Physiology of the urinary bladder. *In* Campbell's Urology, edited by P. C. Walsh, A. B. Retik, T. A. Stamey, and E. D. Vaughan, Jr., 6th ed., pp. 142–176, W. B. Saunders Company, Philadelphia, PA, 1992.

STEERS, W. D., HERRELL, S. D., SESCO, D., MEYTHALER, J., AND HAWORTH, C.: Effect of continuous intrathecal baclofen on genitourinary function (abstract 795). J. Urol. **145:** 411A, 1991.

STEERS, W. D., MCCONNELL, J., AND BENSON, G. S.: Anatomical localization and some pharmacological effects of vasoactive intestinal polypeptide in human and monkey corpus cavernosum. J. Urol. **132:** 1048–1093, 1984.

STEERS, W. D., MEYTHALER, J. M., HAWORTH, C., HERRELL, D., AND PARK, T. S.: Effects of acute bolus and chronic continuous intrathecal baclofen on genitourinary dysfunction due to spinal cord pathology. J. Urol. **148:** 1849–1855, 1992.

STEERS, W. D., AND SELBY J. B., JR.: Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. J. Urol **146:** 1361–1363, 1991.

STEIDLE, C. P., COHEN, M. L., AND NEUBAUER, B. L.: Bradykinin-induced contractions of canine prostate and bladder: effect of angiotensin-converting enzyme inhibition. J. Urol. **144:** 390–392, 1990.

STEWART, D. A., TAYLOR, J., GHOSH, S., MACPHEE, G. J. A., ABDULLAH, I., MCLENACHAN, J. M., AND STOTT, D. J.: Terodiline causes polymorphic ventricular tachycardia due to reduced heart rate and prolongation of QT interval. Eur. J. Clin. Pharmacol **42:** 577–580, 1992.

STIEF, C. G., BENARD, F., BOSCH, R. J. L. H., ABOSEIF, S. R., LUE, T., AND TANAGHO, E.: A possible role for calcitonin-gene-related peptide in the regulation of the smooth muscle tone of the bladder and penis. J. Urol. **143:** 392–397, 1990.

STIEF, C. G., BENARD, F., BOSCH, R. J. L. H., ABOSEIF, S. R., NUNES, L., LUE, T., AND TANAGHO, E.: Acetylcholine as a possible neurotransmitter in penile erection. J. Urol. **14:** 1444–1448, 1989.

STIEF, C. G., HOLMQUIST, F., ALLHOFF, E. P., ANDERSSON, K.-E., AND JONAS, U.: Preliminary report on the effect of the nitric oxide (NO) donor SIN-1 on human cavernous tissue in vivo. World J. Urol. **9:** 237–239, 1991a.

STIEF, C. G., HOLMQUIST, F., DJAMILIAN, M., KRAH, H., ANDERSSON, K.-E., AND JONAS, U.: Preliminary results with the nitric oxide donor linsidomine chlorhydrate in the treatment of human erectile dysfunction. J. Urol. **148:** 1437–1440, 1992.

STIEF, C. G., WETTERAUER, U., SCHAEBSDAU, F. H., AND JONAS, U.: Calcitonin-gene-related peptide: a possible role in human penile erection and its therapeutic application in impotent patients. J. Urol. **146:** 1010–1014, 1991b.

SU, H. C., WHARTON, J., POLAK, J. M., MULDERRY, P. K., GHATEI, M. A., GIBSON, S. J., TERENGHI, G., MORRISON, J. F. B., BALLESTA, J., AND BLOOM, S. R.: Calcitonin gene-related peptide immunoreactivity in afferent neurons supplying the urinary tract: combined retrograde tracing and immunohistochemistry. Neuroscience **18:** 727–747, 1986.

SUNDIN, T., AND DAHLSTRÖM, A.: The sympathetic innervation of the urinary bladder and urethra in the normal state and after parasympathetic denervation at the spinal root level. An experimental study in cats. Scand. J. Urol. Nephrol. **7:** 131–149, 1973.

SUNDIN, T., DAHLSTRÖM, A., NORLÉN, L., AND SVEDMYR, N.: The sympathetic innervation and adrenoceptor function of the human lower urinary tract in the normal state and after parasympathetic denervation. Invest. Urol. **14:** 322–328, 1977.

TAIRA, N.: The autonomic pharmacology of the bladder. Annu. Rev. Pharmacol. Toxicol. **12:** 197–208, 1972.

TAKAHASHI, Y., ABOSEIF, S. R., BENARD, F., STIEF, C. G., LUE, T. F., AND TANAGHO, E. A.: Effect of intracavernous simultaneous injection of acetylcholine and vasoactive intestinal polypeptide on canine penile erection. J. Urol. **148:** 446–448, 1992a.

TAKAHASHI, Y., ISHII, N., LUE, T. F., AND TANAGHO, E. A.: Effects of adenosine triphosphate on canine penile erection. Int. J. Impotence Res. **4:** 27–34, 1992b.

TAKAHASHI, Y., ISHII, N., LUE, T. F., AND TANAGHO, E. A.: Effects of adenosine on canine penile erection. J. Urol. **148:** 1323–1325, 1992c.

TAMMELA, T., KONTTURI, M., KÄÄR, K., AND LUKKARINEN, O.: Intravesical prostaglandin E_2 for promoting bladder emptying after surgery for female stress incontinence. Br. J. Urol. **60:** 43–46, 1987.

TANAGHO, E. A., AND MILLER, E. R.: Initiation of voiding. Br. J. Urol. **42:** 175–183, 1970.

TANG, P. C., AND RUCH, T. C.: Non-neurogenic basis of bladder tonus. Am. J. Physiol. **181:** 249–257, 1955.

TANIYAMA, K., KUSUNOKI, M., AND TANAKA, C.: γ-Amino-butyric acid inhibits motility of the isolated guinea-pig urinary bladder. Eur. J. Pharmacol. **89:** 163–166, 1983.

TANIYAMA, K., KUSUNOKI, M., AND TANAKA, C.: Inhibitory histamine H_2-receptor in the guinea-pig urinary bladder. Eur. J. Pharmacol **105:** 113–119, 1984.

TANIYAMA, K., AND TANAKA, C.: GABAergic mechanisms and their functional relevance in the urinary bladder. *In* GABAergic Mechanisms in the Mammalian Periphery, edited by S. L. Erdö and N. G. Bowery, pp. 175–183, Raven Press, New York, 1986.

TAYLOR, M. C., AND BATES, C. P.: A double-blind crossover trial of baclofen - a new treatment for the unstable bladder syndrome. Br. J. Urol. **51:** 504–505, 1979.

THEOBALD, R. J., JR.: The effect of arylazido aminopropionyl ATP on atropine resistant contractions of the cat urinary bladder. Life Sci. **32:** 2479–2484, 1983.

THEOBALD, R. J., JR.: The effect of arylazido aminopropionyl ATP ($ANAPP_3$) on inhibition of pelvic nerve evoked contractions of the cat urinary bladder. Eur. J. Pharmacol. **120:** 351–354, 1986.

THEOBALD, R. J., JR.: Subclasses of purinoceptors in feline bladder. Eur. J. Pharmacol. **229:** 125–130, 1992.

THIBONNIER, M., SNAJDAR, R. M., AND RAPP, J. P.: Characterization of vasopressin receptors of rat urinary bladder and spleen. Am. J. Physiol. **251:** H115–H120, 1986.

THIND, P., LOSE, G., COLSTRUP, H., AND ANDERSSON, K.-E.: The influence of β-adrenoceptor and muscarinic receptor agonist and antagonists on the static urethral closure function in healthy females. Scand. J. Urol. Nephrol. **27:** 31–38, 1993.

THORNBURY, K. D., HOLLYWOOD, M. A., AND MCHALE, N. G.: Mediation by nitric oxide of neurogenic relaxation of the urinary bladder neck muscle in sheep. J. Physiol. (Lond.) **451:** 133–144, 1992.

TODD, J. K., AND MACK, A. J.: A study of human detrusor muscle. Br. J. Urol. **41:** 448–454, 1969.

TONG, Y.-C., BRODERICK, G., HYPOLITE, J., AND LEVIN, R. M.: Correlations of purinergic, cholinergic and adrenergic functions in rabbit corporal cavernosal tissue. Pharmacology **45:** 241–249, 1992a.

TONG, Y.-C., WEIN, A. J., AND LEVIN, R. M.: Effects of pregnancy on adrenergic function in the rabbit urinary bladder. Neurourol. Urodyn. **11:** 525–533, 1992b.

TORRENS, M.: Human physiology. *In* The Physiology of the Lower Urinary Tract, edited by M. Torrens and J. B. F. Morrison, pp. 333–350, Springer Verlag, Berlin, Heidelberg, 1987.

TRAISH, A. M., CARSON, M. P., KIM, N., GOLDSTEIN, I., AND SAENZ DE TEJADA, I.: Characterization of muscarinic acetylcholine receptors in human penile corpus cavernosum: studies on whole tissue and cultured endothelium. J. Urol. **144:** 1036–1040, 1990.

TRAISH, A., MORAN, E., KRANE, R. J., AND SAENZ DE TEJADA, I.: Endothelin in the urinary bladder. II. Characterization of endothelin receptor subtypes. J. Urol. **148:** 1299–1306, 1992.

TRIGO-ROCHA, F., ARONSON, W. J., HOHENFELLNER, M., IGNARRO, L. J., RAJFER, L. J., RAJFER, J., AND LUE, T. F.: Nitric oxide and cyclic guanosine monophosphate: mediators of pelvic nerve-stimulated erection in dogs. Am. J. Physiol. **264:** H419–H422, 1993a.

TRIGO-ROCHA, F., HSU, G. L., DONATUCCI, C. F., AND LUE, T. F.: The role of cyclic adenosine monophosphate, cyclic guanosine monophosphate, endothelium and nonadrenergic, noncholinergic neurotransmission in canine penile erection. J. Urol. **149:** 872–877, 1993b.

TSUJIMOTO, G., TIMMINS, P. V., AND HOFFMAN, B. B.: Alpha adrenergic receptors in the rabbit bladder base smooth muscle: Alpha-1 adrenergic receptors mediated contractile responses. J. Pharmacol. Exp. Ther. **236:** 384–389, 1986.

UEDA, S., SATAKE, N., AND SHIBATA, S.: α_1- and α_2-adrenoceptors in the smooth muscle of isolated urinary bladder and urethra. Eur. J. Pharmacol. **103:** 249–254, 1984.

UEDA, S., YOSHIDA, M., YANO, S., MUTOH, S., IKEGAMI, K., AND SAKANASHI, M.: Comparison of the effects of primary prostaglandins on isolated human urinary bladder. J. Urol. **133:** 114–116, 1985.

ULMSTEN, U., AND ANDERSSON, K.-E.: The effects of emeprone on intravesical and intra-urethral pressures in women with urgency incontinence. Scand. J. Urol. Nephrol. **11:** 103–109, 1977.

URATA, H., HEALY, B., STEWART, R. W., BUMPUS, F. M., AND HUSAIN, A.: Angiotensin II-forming pathways in normal and failing human hearts. Circ. Res. **66:** 883–890, 1990a.

URATA, H., KINOSHITA, A., MISONO, K. S., BUMPUS, F. M., AND HUSAIN, A.: Identification of a highly specific chymase as the major angiotensin II-forming enzyme in the human heart. J. Biol. Chem. **265:** 22348–22357, 1990b.

URNER, F., WEIL, A., AND HERRMAN, W. L.: Estradiol receptors in the urethra and the bladder of the female rabbit. Gynecol. Obstet. Invest. **16:** 307–313, 1983.

URSILLO, R. C.: Electrical activity of the isolated nerve-urinary bladder strip preparation of the rabbit. Am. J. Physiol. **201:** 408–412, 1961a.

URSILLO, R. C.: Investigation of certain aspects of atropine-resistant nerve effects. J. Pharmacol. Exp. Ther. **131:** 231–235, 1961b.

URSILLO, R. C., AND CLARK, B. N: The action of atropine on the urinary bladder of the dog and on an isolated nerve-bladder strip preparation of the rabbit. J. Pharmacol. Exp. Ther. **118:** 338–347, 1956.

UVELIUS, B.: Isometric and isotonic length-tension relations and variations in cell length in longitudinal smooth muscle from rabbit urinary bladder. Acta Physiol. Scand. **97:** 1–12, 1976.

UVELIUS, B.: Influence of smooth muscle length on the force-velocity relation of K^+-contractures in smooth muscle from rabbit urinary bladder. Acta Physiol. Scand. **101:** 270–277, 1977.

UVELIUS, B.: Relation between mechanical and morphological characteristics in urinary bladder smooth muscle. Acta Physiol. Scand. [Suppl.] **483:** 1–51, 1980.

UVELIUS, B., ARNER, A., AND MALMQVIST, U.: Mechanics of human detrusor muscle bundles studied in vitro (abstract 18). Neurourol. Urodyn. **9:** 343–344, 1990a.

UVELIUS, B., AND GABELLA, G.: Relation between cell lengths and force production in urinary bladder smooth muscle. Acta Physiol. Scand. **110:** 357–365, 1980.

UVELIUS, B., LUNDIN, S., AND ANDERSSON, K.-E.: Content and contractile effect of arginine vasopressin in rat urinary bladder. Eur. J. Pharmacol. **182:** 549–554, 1990b.

UVELIUS, B., LUNDIN, S., AND ANDERSSON, K.-E.: Contractile effects and tissue content of arginine vasopressin in the urinary bladder of Brattleboro rats with hereditary diabetes insipidus. Gen. Pharmacol. **23:** 591–594, 1992.

VAIDYANATHAN, S., RAO, M. S., BAPNA, B. C., CHARY, K. S. N., AND PALANISWAMY, R.: Beta-adrenergic activity in human proximal urethra: a study with terbutaline. J. Urol. **124:** 869–871, 1980.

VAIDYANATHAN, S., RAO, M. S., CHARY, K. S. N., SHARMA, P. L., AND DAS, N.: Enhancement of detrusor reflex activity by naloxone in patients with chronic neurogenic bladder dysfunction. J. Urol. **126:** 500–502, 1981a.

VAIDYANATHAN, S., RAO, M. S., CHARY, K. S. N., AND SWAMY, R. P: Clinical import of serotonin activity in the bladder and urethra. J. Urol. **125:** 42–43, 1981b.

VAIDYANATHAN, S., RAO, M. S., MAPA, M. K., BAPNA, B. C., CHARY, K. S. N., AND SWAMY, R. P: Study of intravesical instillation of 15(S) - 15 - methyl prostaglandin F2-alpha in patients with neurogenic bladder dysfunction. J. Urol. **126:** 81–85, 1981c.

VAN ARSDALEN, K., AND WEIN, A. J.: Physiology of micturition and continence. *In* Clinical Neurourology, edited by R. J. Krane and M. B. Siroky, 2nd ed., pp. 25–82, Little, Brown and Company, Boston, Toronto, London, 1991.

VAN CHARLDORP, K. J., DE JONGE, A., THOOLEN, M. J. M. C., AND VAN ZWIETEN, P. A.: Subclassification of muscarinic receptors in the heart, urinary bladder and sympathetic ganglia in the pithed rat. Naunyn Schmiedebergs Arch. Pharmacol. **331:** 301–306, 1985.

VAN DUYL, W. A.: Spontaneous contractions in urinary bladder smooth muscle: preliminary results. Neurourol. Urodyn. **4:** 301–307, 1985.

VAN DUYL, W. A., VAN DER HOEVEN, A. A. M., AND DE BAKKKER, J. V.: Synchronization of spontaneous contraction activity in smooth muscle of urinary bladder. Neurourol. Urodyn. **9:** 547–550, 1990.

VAN GIERSBERGEN, P. L. M., SHATZER, S. A., BURCHNER, E., AND BUCK, S. H.: Comparison of the effects of neuropeptide K and neuropeptide γ with neurokinin A at NK_2 receptors in the hamster urinary bladder. Naunyn Schmiedeberg's Arch. Pharmacol. **345:** 51–56, 1992.

VAN SANDE, M. E., SCHARPE, S. L., NEELS, H. M., AND VAN CAMP, K. O.: Distribution of angiotensin converting enzyme in human tissues. Clin. Chem. Acta **147:** 255–260, 1985.

VIRAG, R., OTTESEN, B., FAHRENKRUG, J., LEVY, C., AND WAGNER, G.: Vasoactive intestinal polypeptide release during penile erection in man. Lancet **2:** 1166, 1982.

WAGNER, G., AND BRINDLEY, G. S.: The effect of atropine, α and β blockers on human penile erection: a controlled pilot study. *In* Vasculogenic Impotence, edited by A. W. Zorgniotti and G. Rossi, pp. 77–81, Thomas, Springfield, 1980.

WAGNER, G., HUSSLEIN, P., AND ENZELSBERGER, H.: Is prostaglandin E_2 really of therapeutic value for postoperative urinary retention: results of a prospective randomized double-blind study. Am. J. Obstet. Gynecol. **151:** 375–379, 1985.

WAGNER, G., AND WEI, M.-Q.: Subclassification of alpha-1-adrenoceptors in porcine smooth muscle of corpus cavernosum. Int. J. Impotence Res. **4** (Suppl. 2): A42, 1992.

WALDMAN, S. A., AND MURAD, F.: 1987. Cyclic Gmp synthesis and function. Pharmacol. Rev. **39:**163–196, 1987.

WATTS, S. W., AND COHEN, M. L.: Effect of bombesin, bradykinin, substance P and CGRP in prostate, bladder body and neck. Peptides **12:** 1057–1062, 1991.
WEAKER, F. J., HERBERT, D. L., AND SHERIDAN, P. J.: Autoradiographic demonstration of binding sites of oestradiol and dihydrotestosterone in the urinary tract of male and female baboons. Urol. Res. **11:** 127–130, 1983.
WEIN, A., AND LEVIN, R. M.: Comparison of adrenergic receptor density in urinary bladder in man, dog and rabbit. Surg. Forum **30:** 576–578, 1979.
WESPES, E., SCHIFFMAN, S., GILLOTEAUX, J., SCHULMAN, C., VIERENDEELS, G., MENU, R., PELLETIER, G., VAUDRY, H., AND VANDERHAEGHEN, J. J.: Study of neuropeptide Y-containing nerve fibers in the human penis. Cell Tissue Res. **254:** 69–74, 1988.
WESTFALL, D. P., FEDAN, J. S., COLBY, J., HOGABOOM, G. K., AND O'DONNELL, J. P.: Evidence for a contribution by purines to the neurogenic response of the guinea-pig urinary bladder. Eur. J. Pharmacol. **87:** 415–422, 1983.
WESTON, A. H., AND ABBOTT, A.: New class of antihypertensive acts by opening K^+ channels. Trends Pharmacol. Sci. **8:** 283–284, 1987.
WHITFIELD, H. N., DOYLE, P. T., MAYO, M. E., AND POOPALASINGHAM, N.: The effect of adrenergic blocking drugs on outflow resistance. Br. J. Urol. **47:** 823–827, 1976.
WIKLUND, N. P., ÖHLÉN, A., WIKLUND, C. U., CEDERQVIST, B., HEDQVIST, P., AND GUSTAFSSON, L. E: Neuromuscular actions of endothelin on smooth, cardiac and skeletal muscle from guinea-pig, rat and rabbit. Acta Physiol. Scand. **137:** 399–407, 1989.
WILLETTE, R. N., SAUERMELCH, C., AND HIEBLE, J. P.: Stimulation of postjunctional adrenoreceptors increase proximal urethral perfusion pressure in the pithed rat. J. Auton. Pharmacol. **1:** 63–70, 1989.
WILLETTE, R. N., SAUERMELCH, C., AND HIEBLE, J. P.: Role of alpha-1 and alpha-2 adrenoceptors in the sympathetic control of the proximal urethra. J. Pharmacol. Exp. Ther. **252:** 706–710, 1990.
WILLIS, E., OTTESEN, B., WAGNER, G., SUNDLER, F., AND FAHRENKRUG, J.: Vasoactive intestinal polypeptide (VIP) as a possible neurotransmitter involved in penile erection. Acta Physiol. Scand. **113:** 545–547, 1981.
WILLIS, E. A., OTTESEN, B., WAGNER, G., SUNDLER, F., AND FAHRENKRUG, J.: Vasoactive intestinal polypeptide (VIP) as a putative neurotransmitter in penile erection. Life Sci. **33:** 383–391, 1983.
WOLIN, M. S., CHERRY, P. D., RODENBURG, J. M., MESSINA, E. J., AND KALEY, G.: Methylene blue inhibits vasodilatation of skeletal muscle arterioles to acetylcholine and nitric oxide via the extracellular generation of superoxide anions. J. Pharmacol. Exp. Ther. **254:** 872–876, 1990.
YABLONSKY, F., RIFFAUD, J. P., LACOLLE, J. Y., AND DAUSSE, J. P.: a_1- and a_2-adrenoceptors in the smooth muscle of male and female rabbit urethra. Eur. J. Pharmacol. **121:** 1–8, 1986.
YAJIMA, M., KOHNO, S., BABA, K., KOMURA, H., HARAGUCHI, C., IWAMOTO, T., AND OSADA, T.: The coexistence of neuropeptide Y and norepinephrine in rabbit corpus cavernosum penis: an in vitro study. Int. J. Impotence Res. **4** (Suppl. 1): 9–12, 1992.
YAMAGUCHI, T., KITADA, S., AND OSADA, Y.: Role of adrenoceptors in the proximal urethral function of female and male rabbits using an in vivo model of isovolumetric pressure generation. Neurourol. Urodyn. **12:** 49–57, 1993.
YIANGOU, Y., CHRISTOFIDES, N. D., GU, J., BLANK, M. A., POLAK, J. M., AND BLOOM, S. R.: Peptide histidine methionine (PHM) and the human male genitalia. Neuropeptides **6:** 133–142, 1985.
YOKOKAWA, K., TOHYAMA, M., SHIOSAKA, S., SHIOTANI, Y., SONODA, T., EMSON, P. C., HILLYARD, C. V., GIRGIS, S., AND MACINTYRE, I.: Distribution of calcitonin gene-related peptide-containing fibers in the urinary bladder of the rat and their origin. Cell. Tissue. Res. **244:** 271–278, 1986.
YOKOYAMA, M., HIWADA, K., KOKUBU, T., TAKAHA, M., AND TAKEUCHI, M.: Angiotensin-converting enzyme in human prostate. Clin. Chim. Acta **100:** 253–258, 1980.
YOKOYAMA, M., TAKADA, Y., IWATA, H., OCHI, K., TAKEUCHI, M., HIWADA, K., AND KOKUBU, T: Correlation between angiotensin-converting enzyme activity and histologic patterns in benign prostatic hypertrophy tissue. J. Urol. **127:** 368–370, 1982.
YOKOYAMA, O., NAGANO, K., KAWAGUCHI, K., AND HISAZUMI, H.: The response of the detrusor muscle to acetylcholine in patients with infravesical obstruction. Urol. Res. **19:** 117–121, 1991.
YOSHIDA, M., LATIFPOUR, J., NISHIMOTO, T., AND WEISS, R. M.: Pharmacological characterization of alpha adrenergic receptors in the young and old female rabbit urethra. J. Pharmacol. Exp. Ther. **257:** 1100–1108, 1991.
YOSHIDA, M., NISHI, K., MACHIDA, J., SAKIYAMA, H., IKEDA, K., AND UEDA, S.: Effects of phorbol ester on lower urinary tract smooth muscles in rabbits. Eur. J. Pharmacol. **222:** 205–211, 1992.
YOUSIF, F. B., BOLGER, G. T., RUZYCKY, A., AND TRIGGLE, D. J.: Ca^{2+} channel antagonist actions in bladder smooth muscle: comparative pharmacologic and ^3H nitrendipine binding studies. Can. J. Physiol. Pharmacol. **63:** 453–462, 1985.
ZAPPIA, L., CARTELLA, A., POTENZONI, D., AND BERTACCINI, G.: Action of pirenzepine on the human urinary bladder in vitro. J. Urol. **136:** 739–742, 1986.
ZAR, M. A., IRAVANI, M. M., AND LUHESHI, G. N.: Effect of nifedipine on the contractile responses of the isolated rat bladder. J. Urol. **143:** 835–839, 1990.
ZDERIC, S. A., HYPOLITE, J., DUCKETT, J. W., SNYDER, H. M., WEIN, A., AND LEVIN, R. M.: Developmental aspects of bladder contractile function: sensitivity to extracellular calcium. Pharmacology **43:** 61–68, 1991.
ZDERIC, S. A., PLZAK, J. E., DUCKETT, J. W., SNYDER, H. M., IIII, WEIN, A., AND LEVIN, R. M.: Effect of pregnancy on rabbit urinary bladder physiology. I. Effects of extracellular calcium. Pharmacology **41:** 124–129, 1990.
ZOUBEK, J., SOMOGYI, G. T., AND DE GROAT, W. C.: A comparison of inhibitory effects of neuropeptide Y on rat urinary bladder, urethra and vas deferens. Am. J. Physiol., in press, 1993.
ZYGMUNT, P. K. E., PERSSON, K., ALM, P., LARSSON, B., AND ANDERSSON, K.-E.: The L-arginine/nitric oxide pathway in the rabbit urethral lamina propria. Acta Physiol. Scand., in press, 1993.