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# Urinary bladder function and its control in healthy females

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GRIFFITHS, DEREK J., CHRISTOS E. CONSTANTINOU, AND RON VAN MASTRIGT. *Urinary bladder function and its control in healthy females.* Am. J. Physiol. 251 (Regulatory Integrative Comp. Physiol. 20): R225–R230, 1986.—Recordings in eight healthy female volunteers of bladder (detrusor) pressure and flow rate, obtained during bladder filling and during voiding, both through the urethra and through a catheter, demonstrate that a model of bladder function in which the detrusor muscle is considered as completely passive during filling and fully activated during voiding is inadequate. Assessment of the detrusor contraction strength by a new method (described in APPENDIX A) shows that in ideal normal voidings the contraction strength rises to values of 11–24 W/m² and is sustained or rises slightly until the bladder is empty. During unstable detrusor contractions, which even in these healthy women are observed during bladder filling and also during inhibited voidings through the urethra, the contraction is weaker. During voidings through a catheter the detrusor contraction is weak, variable, and fades away before the bladder is empty. An elementary feedback analysis demonstrates that the effect of the micturition reflex governing detrusor behavior differs according to whether or not voiding is taking place. The reflex does not lead to a simple on-off mechanism but to a more complex behavior that is consistent with the observations and that appears to be important for the understanding of pathological obstructed micturition.

urodynamics; detrusor; contraction strength; negative feedback; positive feedback; micturition reflex

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THE FUNCTION of the lower urinary tract is usually divided into two phases: bladder filling and voiding. The standard view of the filling phase is that the bladder muscle (the detrusor) remains relaxed, so that a large volume of urine can be accommodated without much increase in pressure, while the urethral sphincter exerts a tonic contraction that holds the urethra shut. During voiding, however, the urethral sphincter relaxes and the detrusor contracts and empties the bladder to completion (16). On this view there is basically an on-off control system, reflecting the operation of the supraspinal micturition (detrusor-detrusor) reflex (which may, however, be subject to other modulating influences; see Ref. 5 for a recent review). The peaked or bell-shaped form of the ideal normal flow curve and the absence of any measurable residual urine after voiding can indeed be accounted

for by assuming a passive distensible urethra and a detrusor that exerts a contraction of constant strength while the bladder volume decreases to zero (9). In clinical examinations, however, detrusor contractions [detrusor instability or hyperreflexia (18, 19)] are often recorded during bladder filling. Such contractions can cause or exacerbate urinary incontinence; they are common in some neurological diseases and may be provoked by mechanical obstruction of the urethra (24).

During voiding, detrusor contractions that are of less than normal strength or that fade out before the bladder is empty are frequently recorded in the clinic. Such contractions, with residual urine, are found in combination with incomplete relaxation of the urethral sphincter, which can be neurogenic in origin, and with mechanical urethral obstruction (1, 10, 24). In pathological situations, therefore, the on-off hypothesis is certainly inadequate, because states intermediate between ideal filling and ideal voiding are observed (20). It remains possible, however, that normal lower tract function can be adequately described in this simple way.

To discuss detrusor function quantitatively, we have developed a measure of the contraction strength that can be used during both filling and voiding (see APPENDIX A) and have used it to investigate detrusor function in healthy female volunteers. We have performed studies of bladder filling and of voiding through the urethra and through a transurethral catheter. In spite of the unnatural circumstances of such investigations, the results appear to shed light on the working of the lower tract control system.

## MATERIALS AND METHODS

The volunteer subjects consist of eight premenopausal women aged from 28 to 45 yr (median 34 yr), parity zero to three. None had urologic complaints apart from occasional (not recent) urinary tract infections.

At the beginning of the examination the volunteer voided into a DISA flowmeter. Rectal and transurethral catheters (Ch 10) were introduced to measure abdominal and intravesical pressures, and the residual urine was measured. The bladder was filled with physiological saline solution at a medium rate (~20 ml/min) until there was a strong desire to void; the volunteer then voided

again into the flowmeter. After measurement of residual urine the bladder was again filled, and voiding took place as follows. A small balloon on the catheter was inflated and retracted against the bladder neck, the catheter lumen being clamped off. A voluntary detrusor contraction was developed against this total urethral obstruction, and the catheter was then unclamped, so that voiding took place through it. Filling and catheter voiding in this way were usually repeated several times. Intravesical pressure, abdominal pressure, and (during voiding) volume flow rate were recorded on a paper chart and also digitized at a sampling frequency of 1 Hz and stored on disk. Although the circumstances of this examination are clearly artificial, information about the likely artifacts (13, 14) can be drawn from the many similar investigations performed routinely in patients.

Using the digitized data we studied the contraction strength and the outflow resistance as follows. As a measure of the contraction strength we used the variable WF, which is calculated from the urine flow rate, the detrusor pressure [defined as the difference between the intravesical and abdominal pressures (18)], and the volume in the bladder (see APPENDIX A). WF may be considered as a modified form of the mechanical power generated by the contraction per unit of bladder surface area and is approximately constant for constant contraction strength, independent of changes in bladder volume.

The outflow resistance was presented graphically, by plotting the detrusor pressure against the corresponding flow rate throughout micturition (18). This graph also enables recognition of changes of outflow resistance due to urethral sphincter activity (14).

## RESULTS

### Filling Phase

In two volunteers unstable detrusor contractions were recorded during one of the first two bladder fillings (Fig. 1). Two other volunteers with initially stable bladders developed instability after repeated catheter voidings. In the unstable contractions the detrusor pressure was nearly always lower than in the voiding contractions. Even when this was not so, the contraction strength, as expressed by WF, was always lower in the unstable contraction (Fig. 1).

### Voiding Phase

*Free flow curve.* The initial flow rate recordings showed that all the volunteers were able to produce a flow curve of ideal normal form with $\leq$10 ml residual urine (Fig. 1).

*Outflow resistance.* The pressure-flow studies of voiding through the urethra can be divided into two types, eight with $\leq$10 ml residual urine and a flow curve of ideal form (cf. Fig. 1) and the remainder with residual urine of >10 ml and/or an abnormal flow curve (Fig. 2). In the ideal voidings the pressure-flow relation approximated a near-horizontal straight line (Fig. 3), as is expected for a passively distensible outlet. In the nonideal voidings there was usually some sphincter activity, although the grossest abnormalities were due primarily to fluctuations
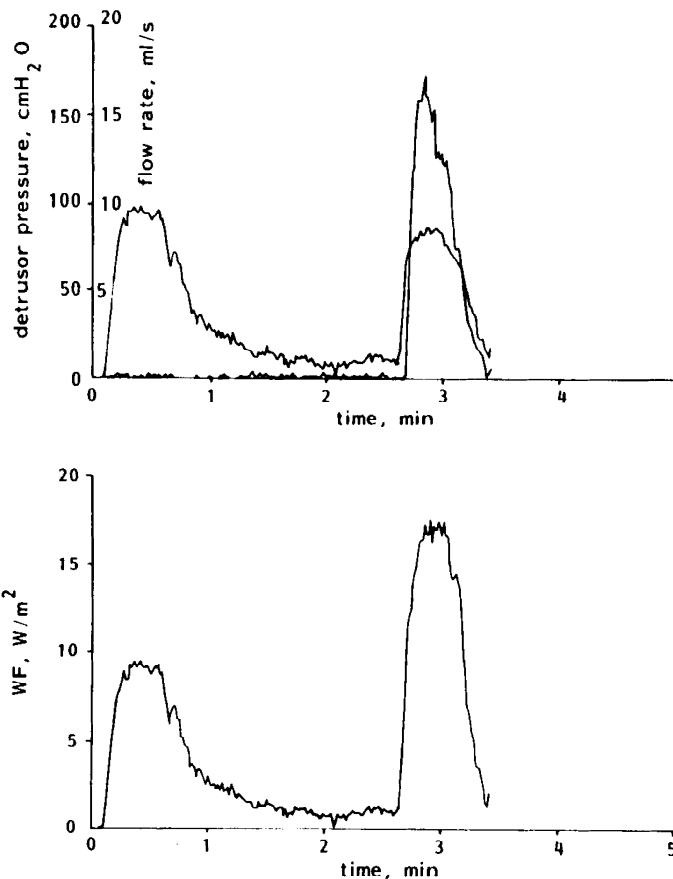


FIG. 1. Detrusor pressure, flow rate, and contraction strength variable (WF) as functions of time during unstable detrusor contraction followed by voiding through urethra. Flow curve has ideal peaked form.
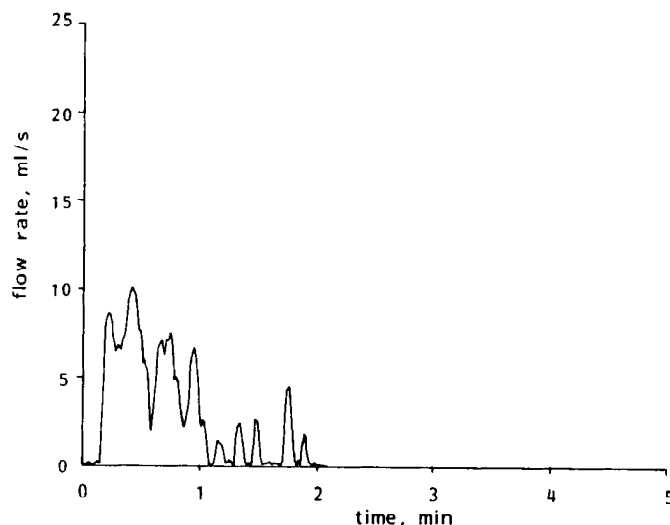


FIG. 2. Flow curve of nonideal form recorded during pressure-flow study of voiding through urethra.

of the detrusor contraction strength (see Fig. 7). For voidings through the catheter the flow curve was plateau shaped (Fig. 4) and the pressure-flow plot showed the steep curving form characteristic of a near-rigid tube (Fig. 5).

*Contraction strength WF.* In the ideal voidings through the urethra, WF rose to values of 11–24 W/m$^2$. Plots of WF vs. bladder volume show that it rose sharply at first
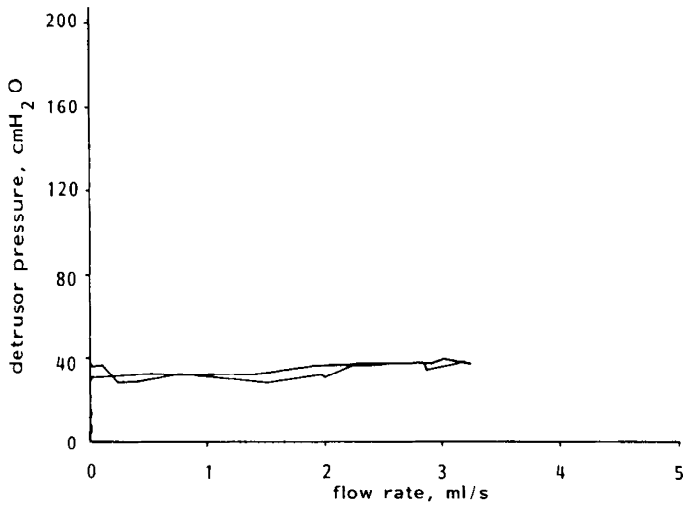
FIG. 3. Pressure-flow plot for ideal voiding through urethra, showing normal form. No flow occurs as long as detrusor pressure is less than a threshold value, here ~30 $cmH_2O$. During flow, detrusor pressure remains nearly constant, just above threshold value.
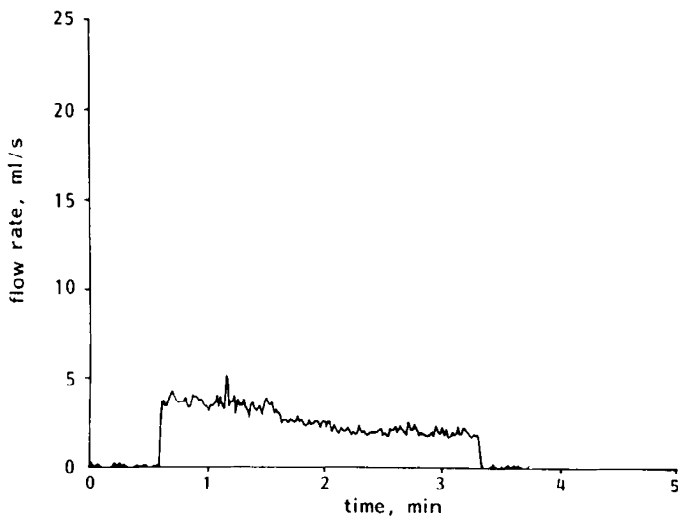


FIG. 6. Contraction strength variable (WF) plotted as function of instantaneous bladder volume, for ideal voiding through urethra. Note that start of voiding is on *right* and end on *left*.



FIG. 4. Flow curve recorded during voiding through catheter.
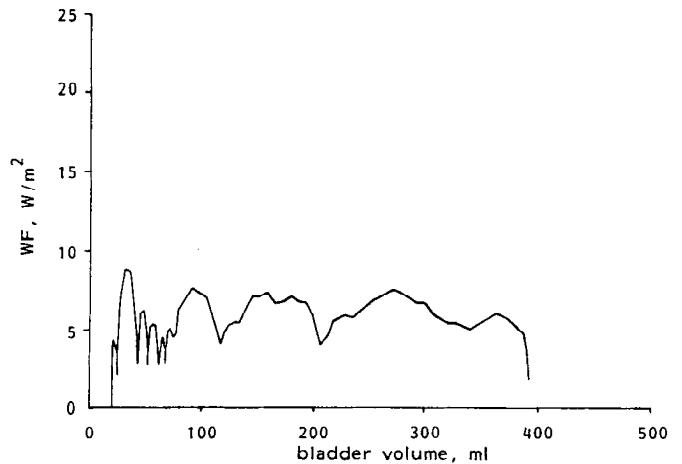


FIG. 7. Contraction strength variable (WF) plotted as function of instantaneous bladder volume for nonideal flow curve shown in Fig. 2.

sustained, and was sometimes very variable (Fig. 7). For voidings through the catheter, WF again reached only low maximum values (range 4–11 $W/m^2$) and always faded to a very low value before the bladder was empty, leaving the bladder to continue draining passively under gravity (Fig. 8). Occasionally, as in Fig. 8, the contraction strength oscillated before finally fading away.

## DISCUSSION

During bladder filling, unstable detrusor contractions were often observed in these healthy volunteers and were variable from one investigation to the next. This is in accord with observations that show that instability can be provoked by the anxiety associated with a urodynamic investigation (13). The observation that in some volunteers instability developed after repeated catheter voidings (i.e., after the detrusor had repeatedly been forced to contract against a totally obstructed urethra) suggests that it can be provoked even by short-term urethral obstruction (3). During unstable contractions the strength of the detrusor contraction was less than during ideal voiding.
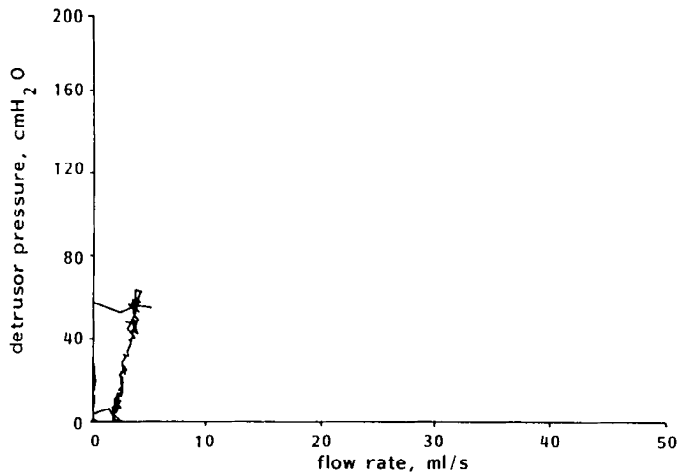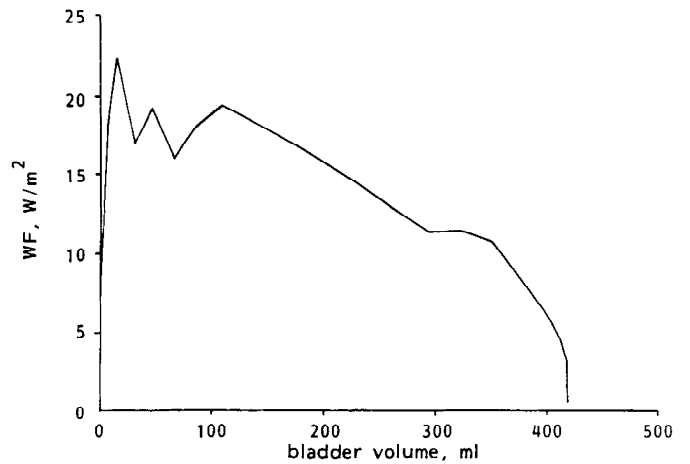


FIG. 5. Pressure-flow plot for catheter voiding shown in Fig. 4.

and then more gently, until the bladder was very nearly empty (Fig. 6). In the nonideal voidings WF did not attain such high values (range 5–10 $W/m^2$), was less well
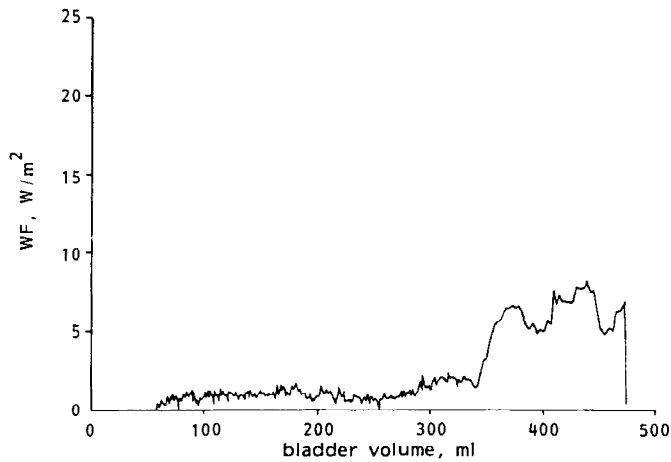
FIG. 8. Contraction strength variable (WF) plotted as function of instantaneous bladder volume for catheter voiding in which oscillation occurred.

All the women were able to produce a micturition of ideal form through the urethra, although not on every occasion. Departures from the ideal may be provoked by anxiety or discomfort associated with the investigation (14). In ideal voidings the strength of the detrusor contraction was well sustained, or even rose slightly, until the bladder was essentially empty. During nonideal voidings through the urethra the detrusor contraction had less than its full strength and was variable. In catheter voidings the detrusor contraction again had less than its full strength and faded prematurely to zero, occasionally with oscillations.

Unstable contractions, nonideal urethral voidings, and catheter voidings are therefore associated with detrusor contraction strengths intermediate between fully on and fully off. They show that the detrusor contraction is not simply switched on and off and suggest that its strength is modulated by a control system.

It is hypothetically possible that the premature fading of the detrusor contraction in catheter voidings is merely a reflection of the unnatural circumstances of such voidings. However, the fact that it was an invariable finding and can be accounted for by the working of the micturition reflex itself suggests a more fundamental significance. As usually envisaged (2, 4), this reflex causes positive feedback of the tension developed in a detrusor contraction. The instability inherent in positive feedback results in an on-off switching mechanism for the voiding detrusor contraction. The operation of this basic parasympathetic mechanism is modulated by inhibitory sympathetic innervation of the detrusor and its ganglia, which normally delays the switching on of the detrusor contraction during bladder filling until a large volume of urine has accumulated (4). Other urethrally based reflexes may be involved but probably play a minor role.

As shown in APPENDIX B, the sign of the feedback produced by the micturition reflex in fact depends on the form of the pressure-flow relation characterizing the outlet resistance. As long as the outlet remains closed the feedback is indeed positive. During voiding through a normal urethra, however, the feedback becomes negative, and this tends to stabilize the detrusor contraction.

During voiding through a catheter the dominant feedback loop may remain positive, destabilizing the contraction, with premature fading of the contraction, residual urine, and perhaps oscillation (6) as possible results. If the urethra is obstructed, the pathological pressure-flow relation resembles that for a catheter (1, 8, 9). Similar fading of the detrusor contraction is often observed and is responsible for failure to empty the bladder completely (1). The altered working of the micturition reflex may thus at least partially account for the occurrence of residual urine in urethral obstruction.

In spite of the elementary nature of the analysis presented in APPENDIX B, it is clear that with a normal bladder outlet the action of the micturition reflex is fundamentally different outside the period of flow and during flow and that this difference is obscured if there is severe urethral obstruction. These conclusions should be taken into account in any discussion of the micturition reflex, the effect of obstruction, or the origin of residual urine.

## APPENDIX A

### Contraction Strength Variable WF

Of the various methods of assessing the strength of a detrusor contraction during voiding (7, 11, 23), the most appealing is the calculation of the external mechanical power generated (detrusor pressure × flow rate) (1, 23). However, it is dependent on the volume in the bladder and is not constant for a constant contraction strength, falling to zero if the contraction is isovolumetric (flow rate = 0) or the outlet resistance is vanishingly small (detrusor pressure = 0). We have therefore developed a modified form in which these objections are overcome.

The contraction of the detrusor is governed by the Hill equation, which describes the relation between the tension developed and the velocity of shortening of the contracting muscle (12, 15, 21). The equation may be written in terms of the pressure $P_{det}$ developed by the complete bladder (assumed spherical) and the velocity of shortening of the detrusor circumference $v_{det}$ as

$$(P_{det} + a)(v_{det} + b) = 5\,ab \qquad (A1)$$

This form of the equation (22) is convenient because its two adjustable parameters, the isovolumetric detrusor pressure (= $4a$) and the physiological maximum value of the detrusor shortening velocity (= $4b$), are normally roughly independent of the volume in the bladder (8, 11). Thus the left-hand side of Eq. A1 is approximately constant for fixed contraction strength, irrespective of the volume in the bladder, and it also increases with increase of $P_{det}$ and/or $v_{det}$. It is therefore a possible volume-independent measure of contraction strength. To ensure a value of zero when there is no contraction at all, it is appropriate to subtract $ab$ from it. Because $P_{det} \times v_{det}$ is approximately equal to $2\pi \times$ the external mechanical power developed by the detrusor divided by the surface area of the bladder, it is appropriate to divide it by $2\pi$. The resulting measure of detrusor contraction strength is

$$WF = [(P_{det} + a)(v_{det} + b) - ab]/2\pi \qquad (A2)$$

WF may be considered approximately as the mechanical power per unit area of bladder surface developed by the contracting detrusor, modified to allow for the finite power necessary to sustain an isovolumetric contraction or to shorten at high velocity under zero load.

$v_{det}$ is calculated from the equation

$$v_{det} = Q/2[3(V + V_t)/4\pi]^{2/3} \qquad (A3)$$

in which the bladder is treated as a thick-walled sphere having a lumen of volume V (8, 23). Q is the measured volume flow rate of urine, and $V_t$ represents the volume of noncontracting tissue enclosed by the effectively contracting detrusor tissue near the end of bladder emptying. If the bladder is not spherical, then $v_{det}$ represents an average velocity
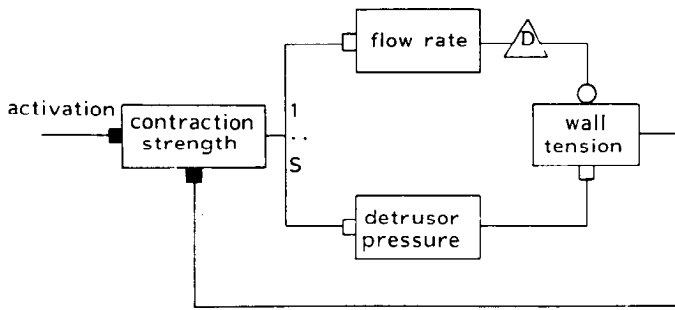
FIG. 9. Feedback via micturition reflex, shown using notation based on Friesen and Block (6). *Squares*, positive (excitatory) inputs or relations; *circles*, negative (inhibitory) inputs or relations; *filled symbols*, nervous inputs; *open symbols*, mathematical or mechanical relations. As long as there is no flow, feedback follows the lower path labeled S; initial activation leads to increase of WF and of detrusor pressure, which is associated with increased detrusor wall tension. Tension receptors in the wall (17) respond with afferent signals that are amplified supraspinally (2) and fed back so as to further increase WF. Overall feedback in this situation is thus positive. In contrast, when flow is occurring through normal urethral outlet, pressure is approximately constant and feedback of changes occurs via upper path labeled 1. Because of negative relation between flow rate and wall tension, overall sign of feedback is negative; because integration is involved, time delay D may be introduced. For catheter voidings or when there is urethral obstruction, however, feedback occurs via 2 paths in ratio S:1; dominant feedback loop may be negative or positive depending on value of S.

of shortening of the detrusor circumference. V is calculated by integrating Q backward from the end of voiding, allowing for any residual urine. In principle, the values of $P_{det}$ used in *Eq. A1* should be delayed by 0.5–0.8 s in order to allow for the time delay in measuring Q, but in this study only slow changes of flow rate and pressure were studied, and correction for the delay was superfluous.

To calculate WF we used approximate median values for $a$ and $b$ [25 $cmH_2O$ and 6 mm/s, respectively (11)] that are consistent with the results of Griffiths (7). Tests showed that the value of WF was not very sensitive to changes in these assumed values. Estimates of $V_t$ have ranged from 2 (23) to 50 ml (8). Changes in this value affect WF significantly only at the end of voidings with little residual urine. If too small a value is assumed, WF may fluctuate wildly under these circumstances. The anatomically reasonable value of 10 ml eliminates such artifacts and was used in the calculations.

WF can be used to measure detrusor contraction strength during both voiding and filling. During filling WF is directly proportional to $P_{det}$ (see *Eq. A2*): with the assumed value of $b$, WF (in W/m² or $\mu$W/mm²) is approximately equal to 0.1 $P_{det}$ (in $cmH_2O$). Clearly the quantification of detrusor contraction strength, as proposed here, is a potentially useful technique for evaluating detrusor function during pharmacological therapy.

## APPENDIX B

*Operation of Micturition Reflex*

For a normal urethral outlet in the voiding phase the pressure-flow relation has two distinct branches: a zero-flow branch for detrusor pressures less than a threshold pressure ($P_0$) and a branch with roughly constant pressure, close to $P_0$, for all flow rates greater than zero (Fig. 3). At the start of micturition, while the flow rate is still zero and $P_{det}$ less than $P_0$, activation of the detrusor leads to increase of contraction strength, i.e., to increased pressure and tension, which is fed back positively, further increasing the contraction strength (Fig. 9). This continues until the detrusor pressure reaches $P_0$ and the urethral sphincter opens.

Once flow has started, increase of WF cannot influence the pressure, which is fixed at $P_0$, and therefore results in an increased flow rate, which leads after a time delay to a smaller bladder volume V. The tension T in the wall of the detrusor is given by

$$T = KP_0 [V + V_t]^{2/3} \qquad (B1)$$

In this equation the bladder has again been treated as a thick-walled

sphere of volume V, and $K$ is a numerical constant (8). Because $P_0$ is constant, T increases and decreases monotonically with V. An increase in WF therefore leads, after a delay, to a reduction in T. Feedback of this signal reduces the contraction strength (Fig. 9). The dominant feedback loop thus changes sign, from positive to negative, when flow begins and so may prevent the contraction strength from rising to too high a value or from fading prematurely to too low a value. The delay in the feedback loop can in principle give rise to oscillations (6). They are not, however, visible in normal voiding.

If the outlet is a catheter or the urethra is obstructed, the finite-flow branch of the pressure-flow relation no longer corresponds to a roughly constant pressure but has a nonzero slope $S = dP_{det}/dQ$ (Fig. 5). During an increase in contraction strength causes increases in both pressure and flow rate, in the ratio $S:1$. If $S$ is small, the situation is close to normal. If it is large, however (narrow catheter or severe obstruction), the situation during flow becomes similar to that on the no-flow branch (Fig. 9). The dominant feedback loop becomes positive instead of negative, and therefore destabilization of the detrusor contraction is to be expected, e.g., premature fading and residual urine. (An uncontrolled increase is unlikely because of saturation of the contraction strength.) The negative feedback loop is weakened but still present; it may possibly be related to the oscillations that are occasionally observed (Fig. 8).

## REFERENCES

1. ABRAMS, P. H., AND D. J. GRIFFITHS. The assessment of prostatic obstruction from urodynamic measurements and from residual urine. *Br. J. Urol.* 51: 129–134, 1979.
2. BRADLEY, W. E. Micturition reflex amplification. *J. Urol.* 101: 403–407, 1969.
3. CONSTANTINOU, C. E. Isometric detrusor contractility as an index of pharmacologic action. *Proc. Annu. Meeting Int. Continence Soc., 13th, Innsbruck, Austria, 1984*, p. 197–199.
4. DE GROAT, W. C. Nervous control of the urinary bladder of the cat. *Brain Res.* 87: 201–211, 1975.
5. DE GROAT, W. C., AND A. M. BOOTH. Autonomic systems to the urinary bladder and sexual organs. In: *Peripheral Neuropathy*, edited by P. J. Dyck, P. K. Thomas, E. H. Lambert, and R. Bunge. Philadelphia, PA: Saunders, 1984, vol. I, p. 285–299.
6. FRIESEN, W. O., AND G. D. BLOCK. What is a biological oscillator? *Am. J. Physiol.* 246 (*Regulatory Integrative Comp. Physiol.* 15): R847–R851, 1984.
7. GRIFFITHS, D. J. Urodynamic assessment of bladder function. *Br. J. Urol.* 49: 29–36, 1977.
8. GRIFFITHS, D. J. *Urodynamics*. Bristol, UK: Hilger, 1980, p. 110–111, 116–120, and 127.
9. GRIFFITHS, D. J. The mechanism of micturition. In: *Scientific Foundations of Urology*, edited by G. D. Chisholm and D. Innes Williams. London: Heinemann, 1982, p. 411–420.
10. GRIFFITHS, D. J. Residual urine, underactive detrusor function, and the nature of detrusor/sphincter dyssynergia. *Neurourol. Urodyn.* 2: 289–294, 1983.
11. GRIFFITHS, D. J., AND R. VAN MASTRIGT. The routine assessment of detrusor contraction strength. *Neurourol. Urodyn.* 4: 77–87, 1985.
12. GRIFFITHS, D. J., R. VAN MASTRIGT, W. A. VAN DUYL, AND B. L. R. A. COOLSAET. Active mechanical properties of the smooth muscle of the urinary bladder. *Med. Biol. Eng. Comput.* 17: 281–290, 1979.
13. GRIFFITHS, D. J., AND R. J. SCHOLTMEIJER. Detrusor instability in children. *Neurourol. Urodyn.* 1: 187–192, 1982.
14. GRIFFITHS, D. J., AND R. J. SCHOLTMEIJER. Detrusor/sphincter dyssynergia in neurologically normal children. *Neurourol. Urodyn.*

2: 27–37, 1983.

15. HILL, A. V. The heat of shortening and the dynamic constants of muscle. *Proc. R. Soc. Lond. B Biol. Sci.* 126: 136–195, 1938.

16. HINMAN, F., JR., AND C. E. COX. Residual urine volume in normal male subjects. *J. Urol.* 97: 641–645, 1967.

17. IGGO, A. Tension receptors in the stomach and urinary bladder. *J. Physiol. Lond.* 128: 593–607, 1955.

18. INTERNATIONAL CONTINENCE SOCIETY. First, second, and third reports on the standardisation of terminology of lower urinary tract function. *J. Urol.* 121: 551–554, 1979.

19. INTERNATIONAL CONTINENCE SOCIETY. Fourth report on the standardisation of terminology of lower urinary tract function. *Br. J. Urol.* 53: 333–335, 1981.

20. MASTRIGT, R. VAN. Determination of the contractility of children's bladders from isometric contractions. *Urol. Int.* 38: 354–362, 1983.

21. MASTRIGT, R. VAN, AND D. J. GRIFFITHS. The contractility of the urinary bladder. *Urol. Int.* 34: 410–420, 1979.

22. MASTRIGT, R. VAN, AND D. J. GRIFFITHS. A clinical comparison of bladder contractility parameters calculated from isometric contractions and pressure-flow studies. *Urology.* In press.

23. SCHAEFER, W. Detrusor as the energy source of micturition. In: *Benign Prostatic Hypertrophy*, edited by F. Hinman, Jr. New York: Springer-Verlag, 1983, p. 470–496.

24. TURNER WARWICK, R. Observations on the function and dysfunction of the sphincter and detrusor mechanisms. *Urol. Clin. North Am.* 6: 13–30, 1979.