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Nocturia and Reversed Circadian Rhythms

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Nocturia is easily remembered by the patient—it is difficult to forget regular cold nocturnal journeys—and sometimes neglected by the doctor. To neglect a history of nocturia is to ignore a valuable diagnostic clue.

If the normal urine volume were excreted evenly during the twenty-four hours, most people would be woken from sleep at least once to pass urine. It is fortunate that there is a circadian rhythm in renal function, which results in low urine flow at night and maximal urine flow in the forenoon. These circadian variations in urine flow are largely independent of the intake of food and water, and of posture (Lahr, 1889), but the mechanisms which control them are still not known (Mills, 1966). Any change in urine flow may be due to changes in the excretion of water alone, or to changes in the amount of solutes excreted (this may be principally a single solute—as in glycosuria—or may involve many solutes—as in the normal forenoon increase in urine flow). The decrease in urine flow at night is associated with an increase in urine concentration, and a decrease in the amount of solute excreted. The decrease in solute excretion is the principal reason for the increase in urine concentration, because there is an increased reabsorption of water in the renal tubule when the rate of solute excretion falls. It is not necessary to postulate alterations in ADH secretion to explain the nocturnal increase in urine concentration. Whether the circadian variation in solute excretion is the result of changes in glomerular filtration rate (Weeson, 1964) or of changes in tubular function, is still unresolved. When this normal circadian rhythm of urine flow is lost, or reversed, nocturia results.

A disturbance of bladder function may cause nocturia, although normal volumes of urine are being excreted at night. Also, if large amounts of urine are being produced, even a normal circadian rhythm will not prevent nocturia. Therefore, several types of disturbance can cause nocturia:

1. *Disturbances of circadian rhythm.* A normal 24-hour urine volume, but a disturbance of the normal circadian rhythm of urine flow.
2. *Polyuria.* An increased 24-hour urine volume.

3. *Frequency with small urine volumes.* A normal 24-hour urine volume, but an increase in the frequency of micturition due either to a decrease in the amount of urine the bladder will tolerate, or to the presence of chronic retention.

It should be easy to separate these by taking a careful history, but patients are often uncertain about the volume of urine they pass and inaccurate in their assessment of daytime frequency. Measurement of urine volumes and of the frequency of micturition may be required to identify the mechanism responsible for nocturia in some patients.

ABNORMAL CIRCADIAN RHYTHMS

A wide range of conditions has been recorded as being associated with absent or reversed circadian rhythms of urine flow. Inadequate knowledge of patho-

TABLE 1. Conditions Associated with Reversal of the Normal Circadian Rhythm of Urine Flow

1. Associated with salt and water retention	
Congestive heart failure	Brod and Fejfar, 1950
Cirrhosis of the liver	Borst and de Vries, 1950 (and others)
	Jones *et al.*, 1952
Nephrotic syndrome	de Vries *et al.*, 1960
Under-nutrition	McCance, 1946
2. Adrenal disorders	
Cushing's syndrome	Doe *et al.*, 1960
	Pena *et al.*, 1966
Hyperaldosteronism	Lennon *et al.*, 1961
	Bartter *et al.*, 1962
Steroid therapy	Pena *et al.*, 1966
	Thomas *et al.*, 1968
Addison's disease	Levy *et al.*, 1946
3. Reno-vascular disorders	
Renal artery stenosis:	
Anatomical	Wrong, 1964
Functional	Donaldson *et al.*, 1967
	Ginn and Parry, 1964
Malignant hypertension	Berlyne *et al.*, 1965
Essential hypertension	Vagnucci and Weeson, 1964
4. Associated with abnormal wake/sleep rhythm	
Depressive illness	Elithorn *et al.*, 1966
Trans-world travel	Flink and Doe, 1959
5. Others	
Steatorrhoea	Flear *et al.*, 1959
After head injury	Payne and de Wardener, 1958
Transplantation kidney	Berlyne *et al.*, 1968
	Albertson and Peterson, 1968
Anorexia nervosa	Russell and Bruce, 1966

physiology makes a logical classification of these conditions difficult, but they fall into several groups, as shown in Table 1.

Heart failure was among the earliest disorders in which a reversal of the normal pattern of urine flow was observed (Quinke, 1893), but other conditions associated with salt and water retention, e.g. cirrhosis of the liver, and nephrotic syndrome, may also have nocturia as a prominent symptom. In thirteen patients with heart failure, not receiving diuretics, investigated by the author (Fig. 1) a normal rhythm was present in only three. The disturbance in rhythm, when present, was due to an alteration in the rhythm of solute excretion and not to changes such as would have been produced by alterations in the concentration or activity of ADH.

Similar, but more marked, changes were present in four out of six patients with Cushing's syndrome (Fig. 2). In one patient with Cushing's disease due to a pituitary tumour, there was evidence that some of the nocturia was due to reduced ADH activity. Alterations in circadian rhythms have also been

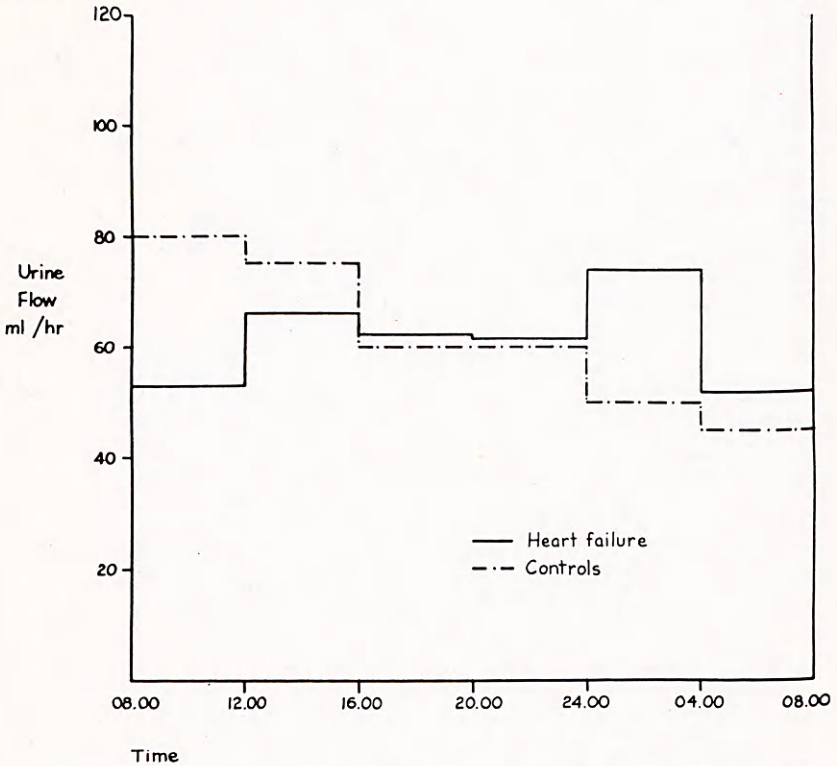

Fig. 1. Circadian rhythm of urine flow in congestive cardiac failure (mean value from thirteen subjects)

reported in patients with primary hyperaldosteronism and in Addison's disease.

The relevance of adrenocortical rhythms to the control of urine excretion rhythms has obviously to be considered. Adrenocortical rhythms are important

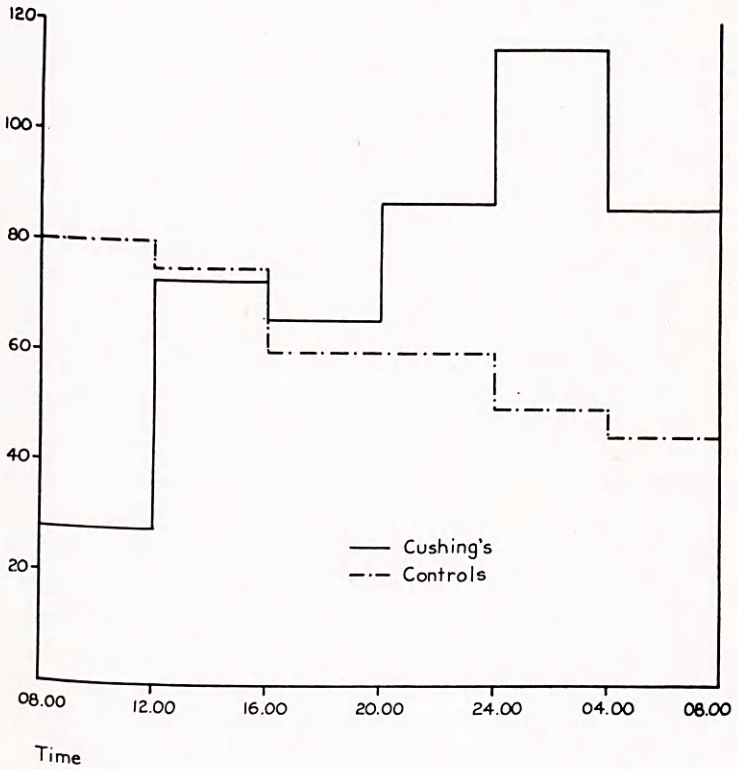

Fig. 2. Circadian rhythm of urine flow in Cushing's syndrome (mean value from six patients)

in the control of the normal rhythm of potassium excretion. There is now strong evidence that they do not control the normal rhythm of sodium excretion (Liddle, 1966) and, as sodium is the principal urinary solute, of urine flow. However, it is possible that disturbances of adrenal rhythmicity may be partly responsible for the disturbed urinary rhythms seen in disease. Loss of the normal rhythm of plasma cortisol has been observed in many of the disorders so far discussed, e.g. heart failure (Knapp *et al.*, 1967), cirrhosis of the liver (Tucci *et al.*, 1966), Cushing's syndrome (Doe *et al.*, 1960). The explanation of the abnormal rhythms associated with these conditions almost certainly involves more complex mechanisms than just disturbed adrenal function and further investigations into this problem are required.

Very severe nocturia has been documented in several patients who have been thought to have abnormal renal vasculature. Berlyne and his colleagues (1965) described two patients with malignant hypertension in whom 'nephrogenic diabetes insipidus', i.e. pitressin resistance, was present at night but not during the day. This was associated with a nocturnal increase in glomerular filtration rate and solute excretion and therefore with marked nocturia. Experiments in which angiotensin was infused during the day reproduced the situation found at night and suggested the possibility of an abnormality in the circadian rhythm of renin level, but this was not supported by measurement of renin levels. This syndrome is still not explained, but the hypotonic nocturnal urine was different from the concentrated urine excreted at night in other disorders discussed, and so any explanation is of doubtful relevance when considering the cause of these other nocturnal diureses. Donaldson *et al.* (1967) and Ginn *et al.* (1964) described patients with a reversed rhythm of solute and water excretion, which became more normal when the patient was kept lying flat. They showed that the erect posture in these patients was associated with distortion of the renal artery; the symptoms decreased after nephroplexy. This is unlikely to be the explanation for nocturia in many patients, although symptoms are often decreased if the patient is supine during the day. As arteriography has not been performed in most of the conditions associated with reversed circadian rhythms this possible mechanism may deserve further consideration in some of these.

In depressive illness nocturia is very common, 37 per cent in one series (Butler, 1968), and many of these patients have a disturbed urine excretion rhythm. There is an association with early morning waking and with diurnal variations in mood. Three of six patients with depressive illness investigated by the author had a nocturnal diuresis due to a marked increase in nocturnal sodium excretion, similar to that observed by Elithorn *et al.* (1966) in a larger group of patients with depressive illness.

In patients with malabsorption (Flear *et al.*, 1959) and in anorexia nervosa (Russell and Bruce, 1966) the nocturnal diuresis is not a solute diuresis but appears to be the result of an inability to excrete water ingested during the day, which is therefore excreted at night. Russell and Bruce showed that in their patients with anorexia nervosa a water diuresis did not occur after a water load given in the morning, although a marked fall in plasma osmolality resulted. They did not report water loading experiments at night but did observe that, as long as the patients were allowed to go to bed, over half of the urine volume was excreted at night. There is inadequate information published to decide whether the nocturnal diuresis in steatorrhoea is due to delay in absorption or to delay in excretion of water. An impaired ability to

excrete a water load is a feature of Addison's disease, but the nocturnal diuresis seen in some patients (de Vries *et al.*, 1960) is at least partly due to an abnormal rhythm of solute excretion, but delay in the excretion of water may contribute to the nocturia.

Until there is a better understanding of the patho-physiology of these rhythms a logical classification is impractical. The clinician considering a patient with this type of nocturia must use an empirical approach, perhaps based on Table 1, and some patients will probably still defy classification.

POLYURIA

An increase in urine volume of more than 2·5 litres will usually produce nocturia, even if the circadian rhythm is normal (Fig. 2). A useful diagnostic classification was suggested by de Wardener (1967) when moderate polyuria, usually associated with azotaemia, is separated from severe polyuria. Diabetes mellitus, the commonest cause of polyuria, does not take a convenient place in this classification. An alternative is to consider whether the polyuria is a solute or a water diuresis (Table 2). If a water diuresis, it may be due to excessive drinking, excessive thirst, abnormal hypothalamic-posterior pituitary

TABLE 2. Causes of Polyuria

A. **Solute diuresis**
   1. Excessive solute in urine, e.g. sugar-diabetes mellitus, sodium-diuretic therapy—following relief of urinary obstruction
   2. Renal failure—a reduced number of nephrons results in an increased solute load for each nephron, and results in an inability to concentrate urine

B. **Water diuresis**
   1. Increased ingestion of water—compulsive water drinking
   2. Increased thirst—hypothalamic damage with disorder of 'thirst' centre
   3. Diabetes insipidus—disorder of hypothalamus or posterior pituitary
   4. Renal resistance to action of ADH
      a. Hereditary nephrogenic diabetes insipidus
      b. Nephrogenic diabetes insipidus associated with other renal tubular disorders, e.g. Fanconi syndrome
      c. Hypercalcaemia and hypercalciuria
      d. Hypokalaemia
      e. Renal damage especially due to chronic pyelonephritis
      f. Sickle-cell anaemia

function, a resistance to the action of ADH on the kidney, or to a combination of these. The differential diagnosis of these conditions is usually straightforward, but the distinction between diabetes insipidus and compulsive water drinking can be difficult (de Wardener, 1961).

INCREASED FREQUENCY OF MICTURITION WITHOUT POLYURIA

Despite the normal amount of urine being passed at night, there will be nocturia when there is a reduced bladder capacity, if micturition is initiated before the bladder is full, e.g. in cystitis, or if there is chronic retention. These situations are common in the elderly and partly account for the high incidence of nocturia in the geriatric population, 64 per cent of persons over sixty-five in a recent survey (Brocklehurst *et al.*, 1968). Nocturia is more likely to result because the circadian rhythm of urine flow is not so marked in the elderly (Elithorn *et al.*, 1966). Measurement of the volume of individual urine collections will arouse suspicion of this type of disorder if the patient's history and the examination have not already done so. A diagnosis is often possible from the clinical evidence but urine culture, radiology and investigation of the lower urinary tract by cystoscopy and urethroscopy may be needed.

The symptom of nocturia may be the result of a pathological process in almost any system of the body. Sometimes the explanation and the diagnosis may be obvious; at other times, a careful consideration of the reason for this symptom may result in the diagnosis of an unsuspected condition.

References

Albertson, K. and Peterson, V. P. (1968) *Lancet*, **ii**, 636.
Bartter, F. C., Delea, C. S. and Halberg, F. (1962) *N.Y. Acad. Sci.*, **98**, 788
Berlyne, G. M., Nilwarangkur, S., Janabi, K. and Cooper, M. (1965) *Quart. J. Med.*, **34**, 463.
Berlyne, G. M., Mallick, N. P., Seidat, Y. K., Edwards, E. C., Harris, R. and Orr, W. McN. (1968) *Lancet*, **ii**, 435.
Borst, J. G. G. and de Vries, L. A. (1950) *Lancet*, **ii**, 1.
Brocklehurst, J. C., Dillane, J. B., Griffiths, L. and Fry, J. (1968) *Gerontologia Clinica*, **10**, 242.
Brod, J. and Fejfar, Z. (1950) *Quart. J. Med.*, **43**, 187.
Butler, V. J. (1968) *Modern Medicine*, p. 1029. London: Modern Medicine of GB Ltd.
de Vries, L. A., ten Holt, S. P., Van Daatselaar, J. J., Mulder, A. and Borst, J. G. G. (1960) *Clin. Chim. Acta.*, **5**, 915.
de Wardener, H. E. (1967) *The Kidney*, 3rd ed. London: Churchill.
Doe, R. P., Vennes, J. A. and Flink, E. B. (1960) *J. Clin. Endocr.*, **20**, 253.
Donaldson, I. M. L., Doig, A. and Knight, I. C. S. (1967) *Amer. J. Med.*, **43**, 289.
Elithorn, A., Bridges, P. K., Lobban, M. C. and Tredre, B. E. (1966) *Brit. med. J.*, **ii**, 1620.
Flear, C. T. G., Cooke, W. T. and Quinton, A. (1959) *Clin. Sci.*, **18**, 137.
Flink, E. B. and Doe, R. P. (1959) *Proc. Soc. Exp. Biol. Med.*, **100**, 498.
Ginn, H. E. and Parry, W. L. (1964) *Southern M. J.*, **57**, 739.
Jones, R. A., McDonald, G. O. and Last, J. H. (1952) *J. Clin. Invest.*, **31**, 326.
Knapp, M. S., Keane, P. M. and Wright, J. G. (1967) *Brit. med. J.*, **ii**, 27.
Knapp, M. S. (1967) M.D. Thesis, University of Bristol.
Lahr, H. (1889) *Allg. Z. Psychiat.*, **46**, 286.
Lennon, E. J., Ruetz, P. P. and Engstrom, W. W. (1961) *Amer. J. Med.*, **30**, 475.
Levy, M. S., Power, M. H. and Kepler, E. J. (1946) *J. Clin. Endocr.*, **6**, 607.
Liddle, G. W. (1966) *Arch. Int. Med.*, **117**, 739.
McCance, R. A. (1946) *Medical Research Council Special Series Report No. 275.* London: HMSO.
Mills, J. N. (1966) *Physiol. Rev.*, **46**, 128.
Payne, R. W. and de Wardener, H. E. (1958) *Lancet*, **i**, 1098.
Pena, J. C., Herrera, J., Pencardo, R. M., Rojo, B. and Gual, C. (1966) *Rev. Invest. Clin. (Mexico)*, **18**, 141.
Quinke, H. (1893) *Arch. exp. Path.*, **32**, 211.
Russell, G. F. M. and Bruce, J. T. (1966) *Amer. J. Med.*, **40**, 38.

Thomas, J. P., El Shaboury, A. H. and Coles, G. A. (1968) *Lancet*, **ii**, 777.
Tucci, J. R., Albacete, R. A. and Martin, M. M. (1966) *Gastroenterology*, **50**, 637.
Vagnucci, A. I. and Weeson, L. G. (1964) *J. Clin. Invest.*, **43**, 522.
Weeson, L. G., Jr. (1964) *Medicine*, **43**, 547.
Wrong, O. (1964) 'Hyperaldosteronism and renal ischaemia'. In *Aldosterone*. Eds E. E. Baulieu and P. Rokel. Oxford: Blackwell.

No Fixed Abode

Adam Neale was a wandering Scot. Taking his MD in Edinburgh, he became a Licentiate of the College in 1806. He served with Sir John Moore in the Peninsular War and published his experiences. Returning to a more peaceful life, he settled first in Exeter, but he changed his address so many times that even Munk could not keep track of him for his *Roll*. Some modern Members give the same sort of trouble to the College post room. Neale then decided to take Cheltenham by storm but his method of attracting practice drew storms, not patients. On arrival in 1820 he published a pamphlet, *A letter to a Professor of Medicine in the University of Edinburgh respecting the Nature and properties of the Mineral Waters in Cheltenham*, in which he doubted their efficacy. The established practitioners whose ample living depended on the reputation of the waters were quick to counter-attack with their own pamphlets, ending with a satire entitled *Hints to a Physician in the opening of his Medical Career at Cheltenham*. Routed by the spate of words and lack of patients, Neale returned to Exeter where he applied for the post of physician to the Devon and Exeter Hospital. Again he was heavily defeated, this time by the family influence of the successful candidate, Dr Granger. The long-suffering Munk managed to record Neale's death in Dunkirk twelve years later. Neale managed to put quite a lot into print, as, apart from his chronicle of the Peninsular War and his disastrous pamphlet, he wrote an account of a journey that took him through Germany, Scandinavia, and Poland on to Turkey. He also recorded his researches into epidemic diseases and the effects of ergot on the uterus.