27 Jakobsen J, Christiansen JS, Kristoffersen I, *et al*. Autonomic and somatosensory nerve function after 2 years of continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes* 1988;**37**:452-5.
28 St Thomas's Diabetic Study Group. Failure of improved glycaemic control to reverse diabetic autonomic neuropathy. *Diabetic Med* 1986;**3**:330-4.
29 Solders G, Wilczek H, Gunnarsson R, Tyden G, Persson A, Groth C-G. Effects of combined pancreatic and renal transplantation on diabetic neuropathy: a two-year follow-up study. *Lancet* 1987;ii:1232-5.
30 Kennedy WR, Navarro X, Goetz FC, Sutherland DER, Najarian JS. Effects of pancreatic transplantation on diabetic neuropathy. *N Engl J Med* 1990;**322**:1031-7.
31 Green A, Jaspan J, Kavin H, Chung S, Schoenberg H. Influence of long-term aldose reductase inhibitor therapy on autonomic dysfunction of urinary bladder, stomach and cardiovascular systems in diabetic patients. *Diabetes Res Clin Pract* 1987;**4**:67-75.
32 Kaiser FE, Korenman SG. Impotence in diabetic men. *Am J Med* 1988;**85**(suppl 5A):147-52.
33 Forsberg L, Höjerback T, Olsson AM, Rosen I. Etiologic aspects of impotence in diabetes. *Scand J Urol Nephrol* 1989;**23**:173-5.
34 Lopes de Faria SRGF, Zanella MT, Andriolo A, Ribeiro AB, Chacra AR. Peripheral dopaminergic blockade for the treatment of diabetic orthostatic hypotension. *Clin Pharmacol Ther* 1988;**44**:670-4.
35 Dejgård A, Hilsted J. No effect of pindolol on postural hypotension in type 1 (insulin-dependent) diabetic patients with autonomic neuropathy. A randomised double-blind controlled study. *Diabetologia* 1988;**31**:281-4.
36 Clouse RE, Lustman PJ. Gastrointestinal symptoms in diabetic patients: lack of association with neuropathy. *Am J Gastroenterol* 1989;**84**:868-72.
37 Clarke BF, Young RJ. Diabetic diarrhoea—a true complication? *Diabetic Med* 1987;**4**:297-8.
38 Janssens J, Peeters TL, Vantrappen G, *et al*. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. *N Engl J Med* 1990;**322**:1028-31.
39 Steel JM. Autonomic neuropathy in pregnancy. *Diabetes Care* 1989;**12**:170-1.
40 MacLeod AF, Smith SA, Sönksen PA, Lowy C. The problem of autonomic neuropathy in diabetic pregnancy. *Diabetic Med* 1990;**7**:80-2.

Detecting bladder cancer

Screening is of doubtful benefit, but all patients with haematuria should be investigated

Screening for bladder cancer was probably the first screening programme for any tumour. In low risk groups dipstick assessment of urine for microscopic haematuria is the main test used in screening for occult lesions of the urinary tract and the finding of blood in the sample has high predictive accuracy.[1] In high risk groups cytological examination of multiple urine samples remains the first line technique for detecting malignant lesions.[2] The sensitivity of cytological tests varies widely, but flow cytometry of urine seems to be the most sensitive method of detecting malignant bladder cells, though this may be because it relies on bladder irrigation samples.[2] Unfortunately, regular widespread sampling is impracticable and the test is expensive.

Studies of screening in the general population (low risk) have shown large variations in the numbers of patients with occult haematuria; in general screening identifies only a few people with occult malignancies. One study found positive dipstick haematuria in 255 out of 10 050 (2·5%) men aged 21-72 years,[3] whereas another found that 132 out of 578 (23%) men aged 60-85 gave positive results.[4] Seventy six of the 255 (30%) patients with positive results in the first study were known to have undergone further urological investigations, and 21 (28%) had urinary tract abnormalities, two of them bladder tumours. Investigations in 87 of the 132 (66%) patients with positive results in the second study showed urological disease in 45 (52%), four of whom had bladder tumours.

The most important issue in any screening programme is whether there is irrefutable evidence that the results of screening tests have prevented or postponed either the onset of the disease or early death due to that disease.[5] Is there, therefore, any benefit in early diagnosis, and can the natural course of bladder cancer be altered by early diagnosis?

In high risk groups, one recent study showed that there was no excess in mortality from bladder cancer in men working in the rubber industry compared with matched controls in the general population.[6] There is, indeed, little evidence to support earlier claims of an improvement in life expectancy in high risk patients in whom transitional cell carcinoma was diagnosed on routine screening.[7] The preliminary conclusion of a recent international meeting in Cincinnati on screening for bladder cancer was that existing data on both high and low risk groups could neither confirm nor refute any positive benefit in life expectancy from early diagnosis (P A Schulte, personal communication). Controlled large scale prospective studies have not been undertaken and are impracticable.

Views differ, too, on the cost effectiveness of screening for bladder cancer. Fraser *et al* found that their screening programme added to hospital costs without benefit to the patient.[5] Using a mathematical model, however, Ellwein and Farrow suggested that cytological screening—with its predilection for identifying high grade, aggressive tumours—would be cost effective in patients in their 60s and 70s and would yield a projected increase in life expectancy of three years or more in patients without symptoms who were truly positive for tumours.[8] In terms of increased life expectancy from early diagnosis of tumours, continuing cytological screening in high risk groups is therefore of doubtful benefit. Why, then, do we continue to screen? Certain screening programmes in high risk groups are required by statute.[9] While uncertainty of benefit remains and industrial compensation is at issue careful surveillance should continue in new high risk groups such as people working with plastic mouldings who handle 4,4′ diamino-3,3′ dichlorodiphenylmethane (MBOCA).[10]

Long term screening programmes may serve to alleviate patients' anxieties. Conversely, regular surveillance may promote anxieties.[11] It is too early to know whether regular infusion of agents such as BCG into the bladder is effective in reducing the progression of dysplasia or carcinoma in situ.

The benefit of dipstick screening for haematuria to detect carcinoma of the bladder in the general population also remains unproved. When the patients with positive results are investigated only a few have tumours. Although larger numbers are found to have other urological disorders, probably less than half benefit from early treatment. At present, all sorts of health prevention programmes, including screening, are being promoted by private and government institutions alike—often without good evidence of their value. Furthermore, even those patients found to have microscopic haematuria on screening may not be referred by their general practitioners for further investigations.[3 5]

The overall picture, then, is confused and unsatisfactory. For the present it seems unnecessary to screen the general population at all ages for bladder cancer, even though bladder tumours may occur in patients aged under 40.[3] Yet despite screening being of doubtful benefit it remains imperative to investigate any incidental finding of haematuria by dipstick analysis, particularly in older people, even in those with a trace of blood. Doctors should be aware that haematuria, even in the presence of identifiable disease, may occur intermittently.[4] With the increasing accuracy of ultrasonography and availability of outpatient flexible cystoscopy examination, each patient can be thoroughly investigated for roughly £50. Integrated, single visit haematuria clinics may soon be commonplace.

ROGER PLAIL

Senior Urological Registrar,
St Helier Hospital,
Carshalton,
Surrey SM5 1AA

1 Arm JP, Peile EB, Rainford DJ, Strike PW, Tettmar RE. Significance of dipstick haematuria. 1. Correlation with microscopy of the urine. *Br J Urol* 1986;**58**:211-7.
2 Badalament RA, Hermansen DK, Kimmel M, *et al*. The sensitivity of bladder wash flow cytometry, bladder wash cytology, and voided cytology in the detection of bladder carcinoma. *Cancer* 1987;**60**:1423-7.
3 Ritchie CD, Bevan EA, Collier St J. Importance of occult haematuria found at screening. *Br Med J* 1986;**292**:681-3.
4 Britton JP, Dowell AC, Whelan P. Dipstick haematuria and bladder cancer in men over 60: results of a community study. *Br Med J* 1989;**299**:1010-2.

5 Fraser CG, Smith BC, Peake MJ. Effectiveness of an outpatient urine screening programme. *Clin Chem* 1977;**23**:2216-8.
6 Sorahan T, Parkes HG, Veys CA, Waterhouse JAH, Straughan JK, Nutt A. Mortality in the British rubber industry 1946-85. *Br J Ind Med* 1989;**46**:1-11.
7 Cartwright RA, Gadian T, Garland JB, Bernard SM. The influence of malignant cell cytology screening on the survival of industrial bladder cancer cases. *J Epidemiol Community Health* 1981;**35**:35-8.
8 Ellwein LB, Farrow GM. Urinary cytology screening: the decision facing the asymptomatic patient. *Med Decis Making* 1988;**8**:110-9.
9 Health and Safety Executive. *Control of substances hazardous to health. Approved code of practice. 29. Control of carcinogenic substances.* London: HMSO, 1988.
10 Wallace DMA. Occupational urothelial cancer. *Br J Urol* 1988;**61**:175-82.
11 Jacobs R. A review of the effectiveness of urinary cytology as a screening technique for occupational bladder cancer. *J Soc Occup Med* 1987;**37**:24-6.

Endothelins

Chemical messengers with many functions

Our understanding of the network of chemicals by which cells communicate with each other is becoming ever more detailed. The endothelins are the latest chemical messengers in a long line that began with insulin and thyroxin and has recently included the interleukins and the leukotrienes. Endothelins (like many other similar chemicals) were first recognised in a cell culture supernatant—in this case endothelial cells from the pig aorta.[1] The name endothelin was given to a peptide present in the culture fluid that caused the contraction of vascular strips—and did so with a greater potency than any known mammalian vasoconstrictor.

Information from a library of human recombinant DNA has shown that three distinct genes code for three endothelins.[2] Each of the three endothelins comprises 21 amino acid residues, and endothelin 2 and endothelin 3 differ from endothelin 1 in only two and five positions respectively. Endothelin 1 is derived from a 203 amino acid polypeptide, which is truncated to produce a 38 amino acid intermediate called "big" endothelin 1 before the final cleavage to the 21 amino acid active molecule.[3] So similar are the three endothelins that most antisera raised against one cross react with the other two, and for this reason it has been difficult to distinguish between their various localisations and activities. Nevertheless, they are thought to have different receptors and functions.

As with the interferons and the interleukins the cells from which endothelins were originally derived have proved to be only one of several production sites, and the activity first observed is not necessarily the most important. Cells capable of secreting endothelins may be identified by radioimmunoassay of cell culture supernatant; by immunocytochemical staining; or, most convincingly, by the recognition of specific messenger RNA by in situ hybridisation. With these techniques epithelial cells from the renal and respiratory tracts[4,5] and neurones of the spinal cord[6] have been suggested as sites of endothelin synthesis as well as the vascular endothelial cells in which they were first detected. Receptors for endothelin have been detected in the respiratory tract, and endothelins produce bronchoconstriction when inhaled or injected intravenously.[7,8] They also act as growth promoters and mitogens for various cell types, including Swiss 3T3 fibroblasts,[9] quiescent rat glomerular mesangial cells,[10] and rat vascular smooth muscle cells.[11]

From this welter of information can we say how important the endothelins are? Clearly they play some part in regulating vascular tone. Concentrations of messenger RNA encoding endothelin 1 increase rapidly on exposure to thrombin or adrenalin,[12] both of which are potent stimulators of platelet aggregation. This suggests that endothelins have an important role in haemostasis. Within the lung their bronchoconstrictor activity implies a role in asthma, but endothelin like immunoreactivity has also been localised to pulmonary endocrine cells, especially in the fetal lung,[5] and in non-small cell carcinomas of the lung.[13] It may be that the mitotic function operates in the embryological development of the lung and even that the growth promoting activity plays a part in the aetiology of pulmonary tumours.

Finally, endothelins may contribute to the degree of myocardial damage after coronary thrombosis. One study in rats showed that infusion of monoclonal antibody to endothelin reduced the area of infarction after ligation of the left coronary artery.[14]

T J HAMBLIN

Professor of Immunohaematology,
Royal Victoria Hospital,
Bournemouth BH1 4JG

1 Yanagisawa M, Kurihara H, Kimura S, *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;**332**:411-5.
2 Inoue A, Yanagisawa M, Kimura S, *et al.* The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc Natl Acad Sci USA* 1989;**86**:2863-7.
3 Yanagisawa M, Masaki T. Molecular biology and biochemistry of the endothelins. *Trends in Pharmacological Sciences* 1989;**101**:374-8.
4 Kitamura K, Tanaka T, Kato J, Eto T, Tanaka K. Regional distribution of immunoreactive endothelin in porcine tissues: abundance in inner medulla of kidney. *Biochem Biophys Res Commun* 1989;**161**:348-52.
5 Rozengurt N, Springall DR, Polak JM. Localisation of endothelin-like immunoreactivity in airway epithelium of rats and mice. *J Pathol* 1990;**160**:5-8.
6 Giaid A, Gibson SJ, Ibrahim NBN, *et al.* Endothelin, an endothelium derived peptide is expressed in neurones of the human spinal cord and dorsal root ganglia. *Proc Natl Acad Sci USA* 1989;**86**:7634-8.
7 Power RF, Wharton J, Zhao Y, Bloom SR, Polak JM. Autoradiographic localisation of endothelin-1 binding sites in the cardiovascular and respiratory systems. *J Cardiovasc Pharmacol* 1989;**13**:550-6.
8 Turner NC, Power RF, Polak JM, Bloom SR, Dollery CT. Contraction of rat tracheal smooth muscle by endothelin. *Br J Pharmacol* 1989;**98**:361-6.
9 Takuwa N, Takuwa Y, Yanagisawa M, Yamashita K, Masaki T. A novel vasoactive peptide endothelin stimulates mitogenesis through inositol lipid turnover in Swiss 3T3 fibroblasts. *J Biol Chem* 1989;**264**:7856-61.
10 Simonson MS, Wann S, Mene P, *et al.* Endothelin stimulates phospholipase C, Na^+/H^+ exchange, c-fos expression, and mitogenesis in rat mesangial cells. *J Clin Invest* 1989;**83**:708-12.
11 Komuro I, Kurihara H, Sugiyama T, Takaku F, Yazaki Y. Endothelin stimulates c-fos and c-myc expression and proliferation of vascular smooth muscle cells. *FEBS Lett* 1988;**238**:249-52.
12 Gordon J. Vascular biology: put out to contract. *Nature* 1988;**332**:395-6.
13 Gaid A, Hamid QA, Springall DR, *et al.* Detection of endothelin immunoreactivity and mRNA in pulmonary tumours. *J Pathol* (in press).
14 Watanabe T, Suzuki N, Shimamoto N, Fujino M, Imada A. Endothelin in myocardial infarction. *Nature* 1990;**344**:114.

Correction

Emergency treatment of avulsed teeth

An author's error occurred in this editorial by Mr Barry Scheer (7 July, p 4). The concentration of chlorhexidine in the mouth rinse used to reduce accumulation of plaque should have been 0·2% and not 2% as published.