died six months later with no further pain and without recurrence of the gynaecomastia, the tamoxifen having been stopped after two months.

Case 2—A 67-year-old smoker was treated with radiotherapy to an inoperable squamous-cell carcinoma of the bronchus. Four months later he complained of painful, bilateral, asymmetrical gynaecomastia and wrist pain. Radiographs of the wrists were suggestive but not diagnostic of hypertrophic pulmonary osteoarthropathy. The breast and wrist pain disappeared within two weeks after starting tamoxifen, which was continued for a further three months. He died seven months later with no further symptoms from gynaecomastia or his wrists.

Case 3—This man, aged 73, had a long history of ischaemic heart disease with biventricular failure. He had received digoxin, spironolactone, and frusemide for several years, and when seen he had painful bilateral gynaecomastia. The digoxin and spironolactone were discontinued with no relief of pain. A biopsy specimen showed normal breast tissue. Analgesics were given for two months, with no relief. Tamoxifen was then begun and produced complete relief of pain within one week. Tamoxifen was stopped after six weeks with no recurrence of pain. The treatment caused no appreciable problems of fluid retention in this patient.

Comment

Tamoxifen produced regression of painless gynaecomastia in one other case of a gonadotrophin-secreting oat-cell carcinoma of the bronchus.[3] In the present three cases tamoxifen produced relief from disablingly painful gynaecomastia and regression of the swelling, which was maintained when tamoxifen was stopped.

Digoxin and spironolactone bind to the oestrogen receptor and stimulate breast proliferation. Discussion continues on whether lung tumours produce oestrogens in addition to gonadotrophins.[4] Nevertheless, in both cases tamoxifen could produce regression of gynaecomastia by blocking the oestrogen receptor. In case 2 the symptoms and signs suggestive of hypertrophic pulmonary osteoarthropathy, which has a known occasional association with gynaecomastia, were also relieved by tamoxifen. It has been suggested that the common link is altered oestrogen metabolism, and, if so, tamoxifen might relieve pain and be of benefit in pulmonary osteoarthropathy. From the three cases reported tamoxifen is certainly of benefit in painful gynaecomastia and deserves further study in treating pulmonary osteoarthropathy.

I am grateful for the advice of Professor M H Lessof.

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Cytomegalovirus infection associated with lower urinary tract symptoms

Three members of a renal unit had a similar complex of urinary tract symptoms. Cytomegalovirus (CMV) was recovered from the urine of all three. Antibody titres against CMV during or shortly after the acute phase were negative, subsequently rising in two.

Case reports

All subjects were men over 30 years of age with no previous urological disorders. No subject's urine contained excess leucocytes, red cells, or protein. Cultures were bacteriologically sterile.

Case 1—This man had urgency and frequency of micturition, mild dysuria, suprapubic pain, nocturia, and the sensation of incomplete voiding. Symptoms developed over two days and lasted three weeks. After the initial illness an intravenous urogram was performed under steroid cover, and symptoms returned. Eight weeks later, alerted by the onset of similar symptoms in colleagues, urine was cultured for viruses and CMV isolated. CMV antibody could not be detected, but four weeks later was present at a dilution of 1/64.

Case 2—This man had an identical illness of similar duration. Four weeks afterwards, when asymptomatic, urine virus culture produced CMV. Antibody could not be detected either initially or one month later.

Case 3—He was on holiday during his colleagues' illnesses, and presented two weeks after returning. After a mild prodrome of malaise, headache, and myalgia he developed symptoms similar to the others, though dysuria was more severe. CMV was isolated from urine during the illness and eight weeks later. CMV antibody titre in the acute phase was less than 1/8, rising to 1/64 after 10 weeks.

All subjects agreed that the most striking feature was the sensation that voiding was incomplete. None had urethral discharge. Apart from the transient prodrome in case 3, no features of "classical" CMV infection were recognised. Coincident with their acute illnesses, the wives of two of the men (cases 2 and 3) had transient dysuria and frequency of micturition. The two young children of one of the men (case 3) had acute, non-suppurative parotitis for three days and malaise, fever, lymphadenopathy, hepatosplenomegaly, and generalised macular rash for five days, respectively. Neither underwent investigation. The subjects could not identify a single infective source, though all routinely handle urine and blood specimens, including those from patients receiving immunosuppressive treatment.

Virus studies—Freshly voided urine samples were neutralised and inoculated into human embryonic lung monolayer cultures. Isolates were identified by cytopathogenic effect and specific immunofluorescence. Antibody tests were by complement fixation using cytomegalovirus strain AD 169.

Comment

Attempts to identify CMV as an agent in non-specific urethritis have been unsuccessful.[1] Although dysuria may occur during a glandular fever-like illness due to CMV,[2] we know of no other report in which symptoms referable exclusively to the lower urinary tract have been associated with CMV isolation. The incidence of urinary excretion of CMV is high in patients receiving immunosuppressive treatment, and in one of our subjects (case 1) symptoms returned after administration of steroids. Other viruses have been associated with lower urinary tract disorders, including adenoviruses in acute haemorrhagic cystitis[3 4] and *Herpesvirus hominis* type 2 in vulvovaginitis and penile infections.[5]

A fortuitous association between isolation of CMV in all and a rise of antibody titre in two of the three apparently non-immune subjects with identical clinical features is improbable. The unlikely possibility remains that another agent was responsible for the syndrome and reactivation of latent CMV had occurred. If the subjects had not worked in a renal unit their common illness may not have been recognised. This report shows the value of virus studies in patients with lower urinary tract symptoms without bacteriuria.

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Controlled trial of cyclophosphamide in active chronic hepatitis

Although survival in hepatitis-B-negative active chronic hepatitis (ACH) is prolonged by corticosteroid treatment,[1] side effects are common,[1 2] so other effective treatments are needed. Azathioprine may be beneficial when combined with prednisone, although not when given alone.[1] Cyclophosphamide has been reported to induce biochemical remission of ACH[3] and, in combination with prednisone, to produce dramatic histological resolution,[4] but these observations

were uncontrolled. We report on a prospective randomised double-blind trial of cyclophosphamide in ACH, during which serum gonadotrophin concentrations were monitored to assess the degree of gonadal damage.

Patients, methods, and results

Ten patients with histologically proved aggressive hepatitis, a history of liver disease for more than three months, and an aspartate aminotransferase (AST; GOT) concentration greater than 150 IU/l (normal <50 IU/l) entered the trial. None had carried hepatitis virus B, and eight had positive titres of antinuclear factor or smooth muscle antibody, or both. The disease activity was first brought under "control" (AST concentration <100 IU/l) for four weeks with prednisolone, which was then reduced every two weeks by 2 mg/day until "relapse" (AST concentration >150 IU/l). The prednisolone dose was then increased fortnightly by 4 mg/day until control had been regained for four weeks. The patients were then randomly allocated to receive either cyclophosphamide 3 mg/kg in a single morning dose or placebo for 12 weeks, and the prednisolone dose was reduced. After relapse the prednisolone dose was increased, and after four weeks' control the patients were crossed over. Patients were seen fortnightly, when blood counts and gonadotrophin concentrations were estimated and liver function tests carried out. In the single male patient testosterone concentrations and sperm counts were also measured.

Responses of patients who completed trial to addition of cyclophosphamide or placebo to corticosteroid treatment

Case No	Treatment	Prednisolone dose at relapse (mg/day)	No of weeks no prednisolone before relapse	Peak AST during relapse (IU/l)	No of weeks to control
1	Cyclophosphamide	0	14	230	5
	Placebo	0	2	240	2
1	Cyc ophosphamide	0	2	650	4
	Placebo	0	10	180	4
2	Cyclophosphamide	8	0	1225	24
	Placebo	0	2	875	4
3	Placebo	2	0	1600	5
	Cyclophosphamide	0	36	R	R
4	Placebo	0	0	225	2
	Cyclophosphamide	0	0	650	4
5	Placebo	0	2	575	10
	Cyclophosphamide	0	5	550	2
6	Placebo	12	0	190	8
	Cyclophosphamide	0	15	500	14

R = Remains in remission.

Four of the 10 patients did not relapse more than once after prednisolone was withdrawn and therefore did not receive both cyclophosphamide and placebo. Five patients crossed over once and one twice, providing seven pairs of data for comparison. In four pairs placebo preceded and in three followed cyclophosphamide. The table shows the outcome. In four patients the control period was longer after cyclophosphamide treatment, two patients remaining in remission without treatment for over three months, but in two a longer control period followed placebo, and in one there was no difference. There was no significant difference in the severity of the relapse or the establishment of control after the two treatment periods (Wilcoxon rank sign test: $P>0.1$).

Complications—All six patients noticed some hair loss, which was not severe. One developed sterile haemorrhagic cystitis and two mild frequency or dysuria; these resolved on stopping treatment. Three developed leucopenia ($<2.5\times10^9$/l (2500/mm^3)) without clinical consequences. The only male patient receiving cyclophosphamide developed testicular failure. Before treatment the sperm count was low (13.7×10^6/ml, volume 1.4 ml, 75% motile) but plasma concentrations of follicle-stimulating and luteinising hormones were normal. After cyclophosphamide treatment he had complete azoospermia and a persistently raised plasma gonadotrophin concentration, and there was no evidence of gonadal recovery 12 months after stopping treatment. There was no consistent change in gonadotrophin concentrations in the women.

Comment

Although the prognosis is poor without corticosteroids, the course of ACH is variable; thus steroids were withdrawn without relapse in four of the 10 patients. This underlines the importance of an adequate control or placebo period in the trials of treatment and may explain previous reports of apparent success with cyclophosphamide. The number of patients in this trial was small, and a difference between the treatment and placebo periods might emerge with larger numbers. In view of the complications, however, particularly the profound and persistent azoospermia that commonly results from cyclophosphamide treatment,[5] the benefits would have to be striking to justify its use.

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Labetalol in severe tetanus

Curarisation can control the neuromuscular manifestations of severe tetanus, but the problem of periodic cardiovascular stimulation remains. This is an uncommon phenomenon, which may be due to interference with the hypothalamic control of vasomotor activity,[1] and may be accompanied by a rise in circulating catecholamine concentrations.[2 3] Many drugs have been used to control this condition, with variable results. Some of the adrenergic-blocking agents can be given only by mouth, which has caused problems in administration, since gastrointestinal absorption is often impaired. Tachyphylaxis develops to others, and some have a transient effect when given intravenously. Long-term toxicity limits the use of vasodilators such as nitroprusside. Furthermore, each patient's condition varies, with predominance of tachycardia or hypertension, or both. The combined alpha- and beta-adrenergic blocking effect of labetalol[4] and its relative lack of tachyphylaxis may be advantageous. We have shown its efficacy when given by intermittent injection, and now report on its successful administration by continuous infusion over 19 days.

Case report

A 33-year-old man cut his knee playing football. The wound was dressed at the local hospital where he was given a "booster" dose of tetanus toxoid. (There was subsequently some doubt whether he ever had toxoid before.) One week later he developed stiffness of his jaws, and on the eighth day was admitted to the respiratory and intensive care unit of the Royal Victoria Hospital. By then the clinical picture was typical of tetanus, with back pain, stiffness of jaw, tongue-biting, and some difficulty in swallowing. Sedation with diazepam and chlorpromazine eased the symptoms. He was given human tetanus antitoxin, tetanus toxoid, and antibiotics and the wound was thoroughly excised.

Tetanus progressed rapidly, and two days later he had to be curarised to control symptoms. The blood pressure and heart rate were labile and tachycardia and hypertension (systolic >200 mm Hg) were not controlled by heavy sedation. In view of the short history, it seemed likely that control of blood pressure and heart rate would be difficult. An infusion of 1 mg/min labetalol was started and pancuronium was replaced by tubocurarine. He was sedated with buprenorphine and lorazepam given alternately every three hours. This stabilised the cardiovascular symptoms for six days, when the dosage of labetalol had to be increased to 2 mg/min. Tubocurarine was stopped after eight days and again after 12 days of curarisation when it was obvious that he still had persisting signs of tetanus.

On the 19th day of curarisation labetalol and tubocurarine were again withdrawn. After eight hours curarisation was "reversed" with 5 mg neostigmine, preceded by and also mixed with 1.8 mg atropine. Despite this dose of atropine, the heart rate dropped dramatically after the neostigmine and a brief period of asystole occurred. Symptoms of tetanus were minimal, but