symptoms disappeared and laboratory tests became normal, although corticosteroid treatment was required for one year. There was no renal disease and the test for antibodies to denaturated DNA was positive.

We thank Dr E B Raftery for his help.

[1] Raftery, E B, and Denman, A M, *British Medical Journal*, 1973, **2**, 452.
[2] Harrison, T, Sisca, T S, and Wood, W H, *Postgraduate Medicine*, 1976, **59**, 241.
[3] Peltier, A P, *et al*, *Nouvelle Presse Médicale*, 1974, **3**, 649.

(*Accepted 27 April 1979*)

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Croup associated with parainfluenza type 1 virus: two subpopulations

Croup is a heterogeneous childhood condition of respiratory obstruction invariably affecting the larynx and occasionally the lower airways. It is often associated with virus infection, most commonly parainfluenza (PF) virus types 1 and 3.[1]

Patients, methods, and results

When an adequate history was available one of us (DHK) subdivided patients with croup into two groups according to the prodromal illness. Those in group 1 had croup of sudden onset, either without prodromal coryza or, if present, of less than 24 hours' duration. Those in group 2 had had coryza for 24 hours or longer before the onset of croup. Because PF and mumps viruses are antigenically related we measured the antibodies in sera taken during the acute phase from 24 patients in hospital with croup to detect any differences between croup of sudden or gradual onset. PF1 had been isolated from the nasopharynx of all patients (14 in group 1 and 10 in group 2). Titres of neutralising antibody to PF1, 2, and 3 and mumps viruses were estimated in acute-phase sera[2] before the patient's group was disclosed to the laboratory. The mean age in group 1 was 2·4 years (table) compared with 2·3 in group 2. Group 1 included eight boys and group 2 seven. Sera were taken a mean of 1·4 days after the onset of croup (not coryza) in both groups, but a mean of 1·4 days after the earliest signs in group 1 compared with 4·5 days in group 2. A prodrome was present for a mean of 3·1 days before the onset of croup in group 2.

Neutralising antibodies to one or more of the viruses were present in all the patients in group 1 compared with five in group 2 ($P < 0.01$). Moreover, the geometric mean titre of total antibodies was 31 and 18·1 in groups 1 and 2 respectively. Antibodies to PF3 were present in 11 of the patients in group 1 and four in group 2; there was no appreciable difference in the prevalence of antibodies to the other viruses. The geometric mean titre to PF1 (the infecting virus), however, was 40 in group 1 compared with 10 in group 2. The geometric mean titres to the other viruses were not appreciably different between the groups.

Comment

These serological differences support the division of cases of croup into subpopulations of sudden and gradual onset. The PF1 titres in group 1 were contrary to those expected if these antibodies resulted only from the current infection. An accelerated response resulted from previous infection with either PF1 or one of the other paramyxoviruses. PF3 is the most likely candidate because of its endemicity compared with the biennial appearance of PF1 virus.[1 3] In support of this, 56 out of 115 (49%) PF3 infections in this hospital between 1964 and 1976 occurred in infants aged under 1 year compared with 20 (13%) of 152 PF1 infections.[3] We consider that there may be different pathogenic mechanisms between croup of sudden and gradual onset, the former resulting from prior PF3 infection and a subsequent hypersensitivity reaction to PF1 virus. A relevant observation is that 30% of children with PF3 infections have croup compared with 63% of those with PF1 infections.

Because of different opinions about the efficacy of steroid treatment in croup[4 5] we believe that a double-blind trial based on the historical distinction between subpopulations may be of value, while further laboratory studies should investigate the pathogenesis.

Comparison of patients with PF1 infection and croup of sudden or gradual onset

	Group 1	Group 2
Onset	Sudden	Gradual
Total No of patients	14	10
Mean age (years)	2·4	2·3
Mean No of days sera taken:		
After croup	1·4	1·4
After onset of prodrome	1·4	4·5
No of patients with neutralising antibody to PF1, 2, 3 or mumps	14	5 ($P<0.01$)
GMT of all antibodies	31	18·1
No of patients with neutralising antibody to PF3	11	4
GMT of antibodies to PF1	40	10

PF = Parainfluenza.
GMT = Geometric mean titre.

[1] Buchan, K A, Martin, K W, and Kennedy, D H, *Journal of Hygiene*, 1974, **73**, 143.
[2] Grist, N R, *et al*, *Diagnostic Methods in Clinical Virology*, 3rd edn. Oxford, Blackwell, 1979.
[3] Kennedy, D H, *WHO Yearly Virus Report, 1977 (VIR 78·9)*, *Annex 17*, p 55, Geneva, WHO, 1978.
[4] Eden, A N, Kaufman, A, and Yu, R, *Journal of the American Medical Association*, 1967, **200**, 403.
[5] James, J A, *American Journal of Diseases of Children*, 1969, **117**, 511.

(*Accepted 20 April 1979*)

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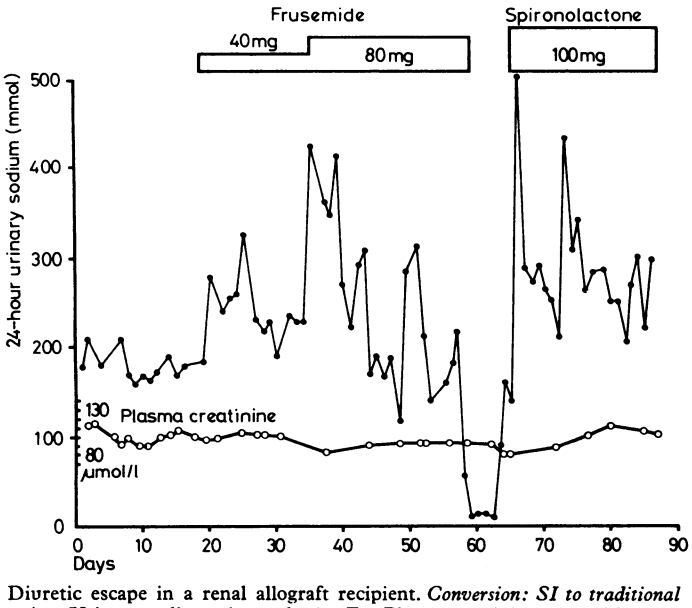
Diuretic escape and rebound oedema in renal allograft recipients

Dependent oedema occurs often in renal allograft recipients, particularly during rejection episodes. Clinicians often prescribe potent diuretics to get rid of the excess salt and water. We have found that patients soon become dependent on the diuretics. We have therefore examined this problem in five patients who received cadaveric renal transplants.

Patients, method, and results

We analysed the records of four patients in whom daily collections of urine were made while frusemide was administered. All showed diuretic escape. We therefore studied an additional patient prospectively. Frusemide was prescribed at 40 mg daily when the patient had clinical oedema. The dosage was increased to 80 mg daily after about two weeks and continued for about four weeks before being abruptly withdrawn. Spironolactone was then introduced after five days and continued for about three weeks. Twenty-four-hour urine collections were made daily. Creatinine, sodium, and potassium concentrations were measured in aliquots by standard methods. Blood (5 ml) was taken for estimations of plasma creatinine and sodium concentrations, the frequency of sampling varying from daily to weekly. Blood pressure, weight, and the presence or absence of oedema were recorded whenever blood was taken. Salt and water intakes were not restricted, and data were recorded for about 90 days. Throughout the study the patient's creatinine clearance was largely stable.

The figure shows the diuretic regimen, 24-hour urinary excretion of sodium, and plasma creatinine concentrations. Before treatment the 24-hour urinary sodium excretion was about 175 mmol (mEq). This increased sharply to a peak of above 300 mmol when frusemide was introduced, the increase lasting for about 10 days and returning to baseline levels at 14 days despite continued administration of frusemide. When the frusemide dosage was increased sodium excretion rose further to peak values above 400 mmol in 24 hours, only to return to baseline levels again after two weeks. The second spurt in sodium excretion probably resulted from oscillations in balance between the diuretic and the patient's salt-retaining mechanism. When frusemide was stopped abruptly urinary sodium excretion fell to below 20 mmol and the patient gained 2 kg overnight. Sodium excretion increased to baseline levels in six days and a further rise was induced by



Diuretic escape in a renal allograft recipient. *Conversion: SI to traditional units*—Urinary sodium: 1 mmol = 1 mEq. Plasma creatinine: 1 μmol/l ≈ 11·3 mg/100 ml.

administering spironolactone. The excretion gradually fell but remained above baseline levels even after two weeks.

Comment

Oedema perpetuated by diuretics has been reported in patients with "idiopathic oedema."[1 2] Our results show that this phenomenon is commoner than generally realised. The pathogenesis of oedema during rejection episodes is multifactorial. The denervated kidney can secrete renin when stimulated.[3] A decreased filtration rate, increased renin secretion in response to renal ischaemia, and the mineralocorticoid activity of the increased dose of steroids will invariably produce oedema if the patient's fluid intake is not curtailed drastically. Frusemide, owing to its potent saliuretic effect, would further enhance secretion of renin, thereby producing the secondary hyperaldosteronism that probably caused the escape from the diuretic action of the drug. Sudden withdrawal of frusemide left the salt-retaining mechanism unopposed, resulting in rebound oedema. Thus patients become dependent on the diuretic and oedema is perpetuated. Prolonged diuretic treatment produces hyperuricaemia for which the unwary might prescribe allopurinol, which would cause severe marrow suppression because it potentiates the action of azathioprine. Furthermore, prolonged diuretic treatment depletes plasma volume and must increase blood viscosity, which may be specially relevant since some renal allograft recipients become erythraemic and risk thromboembolism.[4] Potent diuretics such as frusemide should be used sparingly. Since the maximal increase in urinary sodium excretion was in the first week, every effort must be made to discontinue the diuretic as soon as possible to avoid the counteracting secondary hyperaldosteronism. Frusemide should not be stopped abruptly in patients who have been taking it for some time. Spironolactone may reasonably be prescribed while the patient is being weaned off frusemide, thus avoiding the unpleasant rebound oedema.

[1] MacGregor, G A, Tasker, P R W, and De Wardener, H E, *Lancet*, 1975, **1**, 489.
[2] MacGregor, G A, *et al*, *Lancet*, 1979, **1**, 397.
[3] West, T H, Tincotte, J G, and Vander, A, *Journal of Laboratory and Clinical Medicine*, 1969, **73**, 564.
[4] Swales, J D, and Evans, D B, *British Medical Journal*, 1969, **2**, 80.

(*Accepted 2 May 1979*)

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Oral metronidazole in Clostridium difficile colitis

Diarrhoea after antibiotic treatment is common, and certain antibiotics, particularly clindamycin, may cause pseudomembranous colitis. Recent interest has focused on the cytopathic enterotoxin produced by *Clostridium difficile* as causing such conditions,[1] and treatment has therefore aimed at eradicating *Cl difficile*. Vancomycin has been used successfully[2] but is difficult to prepare in oral form. We describe success with oral metronidazole in two cases of clindamycin-induced colitis, in which *Cl difficile* and high titres of neutralisable cytopathic enterotoxin were found in the stool.

Case reports

Case 1—A 28-year-old woman with no past history of gastrointestinal disturbance was admitted for repair of a femoral hernia. Six days before operation she had completed a one-week course of oral clindamycin (250 mg six-hourly) for peridontal infection. Thirty-six hours after uncomplicated herniorrhaphy she became feverish and developed colicky, lower abdominal pain with watery, bloodstained diarrhoea. Sigmoidoscopy showed no obvious pseudomembrane, and histological examination showed patchy, non-specific acute proctitis with intervening normal mucosa. Stool taken at onset was cultured in reinforced clostridial medium with 0·2% paracresol[3] and grew *Cl difficile* (identified by morphological and biochemical criteria[3]) sensitive to metronidazole in vitro. Enterotoxin, measured by its cytopathic effect on HeLa cells in tissue culture and neutralisable by *Cl sordellii* antitoxin (Wellcome Foundation Research Laboratories), was found in the stool in high titre (table). Treatment was started with oral metronidazole 400 mg eight-hourly for five days, reducing to 200 mg eight-hourly for five days.

Effect of metronidazole given for Cl difficile-associated diarrhoea on stool culture and stool toxin titres

No of days of metronidazole treatment	Stool culture for *Cl difficile*	Neutralisable *Cl difficile* toxin titre in stool*
	Case 1	
Pretreatment	Positive	1/2000
Day treatment began	Positive	1/2000
3	Negative	1/500
4	Negative	1/50
10	Negative	Nil
	Case 2	
Pretreatment	Positive	1/1000
6	Negative	1/500
2 days after completion	Negative	Nil
19 days after completion	Negative	Nil

*1 g wet-weight stool extracted in 5 ml physiological saline.

Within 36 hours she had less abdominal pain and fewer bowel actions. After a further 36 hours there was no diarrhoea or abdominal pain, stool culture did not grow *Cl difficile*, and enterotoxin titre was reduced. Sigmoidoscopy showed slightly oedematous patches of mucosa to 18 cm. After completing treatment she remained symptom-free, with no toxin in her stool and negative cultures for *Cl difficile*. Subsequent barium-enema appearances were normal.

Case 2—A 57-year-old woman with no history of bowel disturbance received a five-day course of oral clindamycin (250 mg six-hourly) for paronychia. During treatment she noticed looser but formed stools which progressed over two weeks to watery diarrhoea without blood. She became weak and dehydrated and was admitted to hospital. Sigmoidoscopy showed slightly opaque rectal mucosa but no ulceration, bleeding, or obvious pseudomembrane. Stool culture grew *Cl difficile*, and cytopathic enterotoxin neutralisable with *Cl sordellii* antitoxin was found (table). She began treatment with oral metronidazole (400 mg eight-hourly for 10 days). Rapid symptomatic improvement was seen, and after six days stool culture for *Cl difficile* was negative with a falling titre of neutralisable toxin. After 10 days she was asymptomatic and stool culture remained negative for *Cl difficile* with no neutralisable toxin detectable.

Comment

Cl difficile is thought to be a common aetiological agent in antibiotic-associated diarrhoea[1 2 4] and that treatment should aim to eliminate the organism from the gut. This has been achieved with oral vancomycin,[2] but it is expensive, toxic, and available only in parenteral form, which is diluted for oral use. Successful use of metronidazole to treat diarrhoea after antibiotics has been reported,[5] but without specific bacteriological studies. Although *Cl difficile* is sensitive to metronidazole in vitro, it has been thought to be valueless in practice[2] owing to rapid absorption from the upper gut. Our findings, however,