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manikins, such as Resusci or Recording Resusci Anne, and a torso model, such as Ambu-S or Anatomic Anne. For paediatric training a baby or child manikin, or both, should be provided.

For advanced cardiopulmonary resuscitation doctors and nurses in specialised units require access to adult and neonatal intubation trainers and an arrhythmia generator (with or without torso capability).

The burden of teaching has traditionally fallen on anaesthetists, cardiologists, and accident and emergency specialists. The tasks of organisation, training, cleaning, and maintenance of equipment are time consuming if performed properly and merit the appointment of a designated resuscitation training officer, probably with a nursing or paramedical background. Such a person will unify and improve the quality of training and should be affordable within a health district's budget.

Future developments—The use of a microcomputer and video screen to measure performance and display results graphically is already feasible. There is increasing development of sophisticated simulators using computer technology (San Arena, Koken Resim) but these are too costly for most basic cardiopulmonary resuscitation schemes. Hon describes an ingenious computer operated trainer/tester linked to a video disc.⁷ It requires no supervision and has obvious potential for mass training but is very expensive. The market for advanced cardiopulmonary resuscitation trainers is small but demanding and eager for new training techniques. A potential example of a computerised manikin has been described.⁸

In 1967 Sim I, costing some \$100 000, was built as the ultimate in manikin technology.⁹ The next few years will surely see the introduction of affordable and practical simulators at all levels of life support training.

Epidemiology

Haemolytic-uraemic syndrome: clinical experience of an outbreak in the West Midlands

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Abstract

In 1982-3, 35 children from the West Midlands developed the haemolytic-uraemic syndrome. This was a higher incidence than expected and included an epidemic localised to the Wolverhampton area in July 1983 which comprised 11 cases in two weeks. Twenty three children were treated with dialysis, of whom three died. Six patients developed chronic renal failure, four of them from Wolverhampton. Extrarenal manifestations included neurological sequelae in four, two of whom also developed insulin dependent diabetes mellitus and chronic renal

failure. Cardiomyopathy occurred in one child, who also had chronic renal failure.

The outcome of these 35 patients was not predictable from prognostic criteria derived from previous experience in Britain. This, together with the high prevalence of extrarenal disease and the geographical localisation of the 1983 outbreak, suggested an aetiological agent new to the region. Faeces from 10 patients were examined for verotoxin producing *Escherichia coli*, and positive strains of serotype O157.H7 were found in three patients during the Wolverhampton outbreak.

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Introduction

Since the early descriptions of the haemolytic-uraemic syndrome outbreaks have been reported from several countries but rarely from Britain.^{1,2} The West Midlands regional paediatric nephrology service draws patients from throughout the West Midlands region as well as parts of central Wales, Gloucestershire, and Leicestershire, representing a total population of nearly 8 million. In the 13 years 1968-81, 32 children with the haemolytic-uraemic syndrome had been admitted, six patients being the greatest number in any one year. In 1982 and 1983 the syndrome was

diagnosed in a total of 35 children, 11 presenting in an outbreak localised to the Wolverhampton area in July 1983. Though a good outcome would have been anticipated in younger patients with summer onset, "epidemic" haemolytic-uraemic syndrome after a prodrome of diarrhoea,³ a high proportion of these children developed chronic renal failure. This outbreak was further distinguished by a high frequency of extrarenal manifestations affecting the central nervous system, pancreas, and heart. This paper draws attention to these clinical features, which, though described in North American reports, are anomalous to previous experience in Britain and may suggest a change in the aetiology of the syndrome in this region. We also report the results of a search for verotoxin producing *Escherichia coli* in faecal samples.

Present series

This retrospective review is believed to include all cases of the haemolytic-uraemic syndrome in the region. In all patients the diagnostic criteria of renal impairment, microangiopathic haemolytic anaemia, and thrombocytopenia were met.

In 1982, 13 patients (six girls and seven boys) presented, 10 of them during May to October. Most of these children lived in suburban or rural areas (fig 1). In 1983 there were 22 patients—16 girls and six boys; 11 presented during two weeks in July. Ten of these 11 were resident in the Wolverhampton conurbation, the exception being a frequent visitor there.

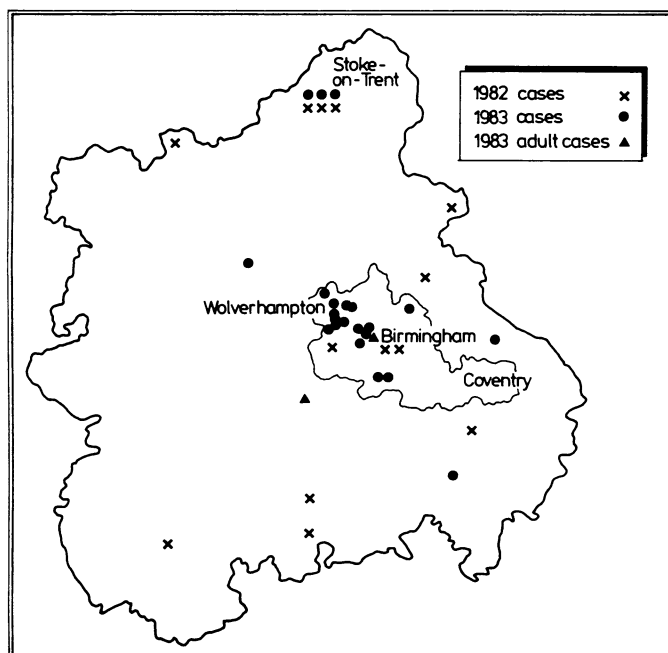


FIG 1—West Midlands region: place of residence of patients.

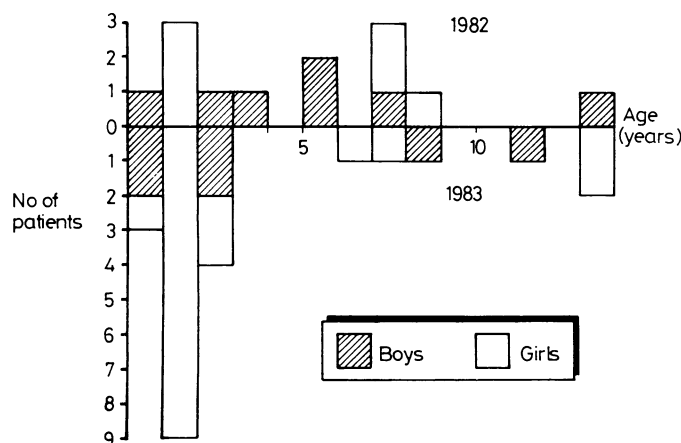


FIG 2—Age of patients at onset of haemolytic-uraemic syndrome.

In the same fortnight two adults from the same urban area (not included in this report) contracted the disease (fig 1). Figure 2 shows the ages of the children at onset, the youngest being 8 months.

Laboratory methods—Haematological and biochemical investigations were performed in the clinical laboratories by standard automated techniques. Faecal specimens were obtained as soon as possible and cultured for *Salmonella*, *Shigella*, and *Campylobacter* spp. Ten faecal specimens were sent to the Central Public Health Laboratory. From each sample 40 *E coli* were examined for verotoxin production⁴ and verotoxin producing strains serotyped according to the internationally accepted scheme.⁵

TABLE I—Prodromal symptoms in 35 children

	No of patients		No of patients
Diarrhoea	35	Jaundice	3
Rectal bleeding	26	Purpura	1
Vomiting	21	Seizure	2
Abdominal pain	6		

Results

Table I lists the prodromal symptoms in all 35 children. Diarrhoea developed from one to 10 days before admission (mean 5.7 days). A 2 year old boy with abdominal pain underwent a laparotomy for suspected peritonitis, which showed extensive serosal inflammation confined to the colon but no perforation. Peritoneal swabs proved sterile and no pathogens were identified in his stools.

Twelve children had seizures, two before admission. There was a close association between seizure and the timing and magnitude of hyponatraemia. All but one of those with seizures had a plasma sodium concentration below 126 mmol(mEq)/l, the exception being a boy with presumed vasculopathy of the central nervous system (case 3; see below), whose sodium concentration remained normal. The lowest recorded plasma sodium concentration in patients with seizures (123.3 mmol/l (SE 1.56)) was significantly lower than those without (129.2 mmol/l (SE 1.35); $t=2.85$; $p<0.01$). Hyponatraemia was typically a feature of rehydration with hypotonic saline. Only 10 patients maintained a plasma sodium concentration above 130 mmol/l throughout their illness.

In 1982 an adenovirus was isolated from the faeces of one child. In 1983 *Salmonella typhimurium* was isolated from one of the 22 patients and rotaviruses were found in two other children. Of the 10 faecal samples examined for verotoxin producing *E coli*, positive strains of serotype 0157.H7 were found in three children. One of these children also excreted *S derby*. All three children made full recoveries.

In 24 children the plasma creatinine concentration had returned to normal and proteinuria disappeared within four months of onset. A further two children had marginally raised creatinine concentrations and moderate proteinuria at four months but normal results by one year. Hypertension was not detected in any of these 26 patients with a good outcome during a minimum follow up of one year.

Peritoneal dialysis was undertaken in 23 children. Apart from the one child who died suddenly on the fourth day, all patients who were dialysed for less than 14 days regained normal renal function, whereas six out of 10 patients who were dialysed for 14 to 52 days progressed to chronic renal failure (fig 3). No patient proceeded directly from acute to end stage renal failure.

Death or long term morbidity was confined to nine patients (table II), five of whom were less than 2 years old at onset. Three children died. One of these (case 1) had stable chronic renal failure for seven months but then developed acute renal failure without recurrence of thrombocytopenia or red cell fragmentation. The cause of death in case 6 was aspiration pneumonia secondary to spastic quadriplegia. The cardiorespiratory arrest during dialysis in case 7 was not satisfactorily explained. Necropsy showed extensive renal cortical necrosis and intravascular thrombosis confined to the kidney.

Four children sustained neurological damage. In case 2 a right hemiplegia occurred four days after admission. Computed tomography subsequently showed cortical atrophy in the territory supplied by the left middle cerebral artery. Central nervous system disease was more diffuse in the other children. One patient (case 3) developed seizures three hours after admission without hypertension or electrolyte disturbance. After 11 days of ventilatory support he improved but sustained cortical blindness. Two other patients (cases 6 and 8) developed coma, seizures, and spastic quadriplegia followed within a few days by insulin dependent diabetes mellitus. The second of these, who received neither diazoxide nor dexamethasone, remained insulin

dependent and six months after the original illness was found to have subnormal faecal chymotrypsin activity.

The last patient (case 9) presented with left ventricular failure eight weeks after the onset of the haemolytic-uraemic syndrome, in the absence of electrolyte disturbance or previous hypertension. Antibody to Coxsackie B virus serotypes 1-6 was undetectable. The electrocardiogram showed

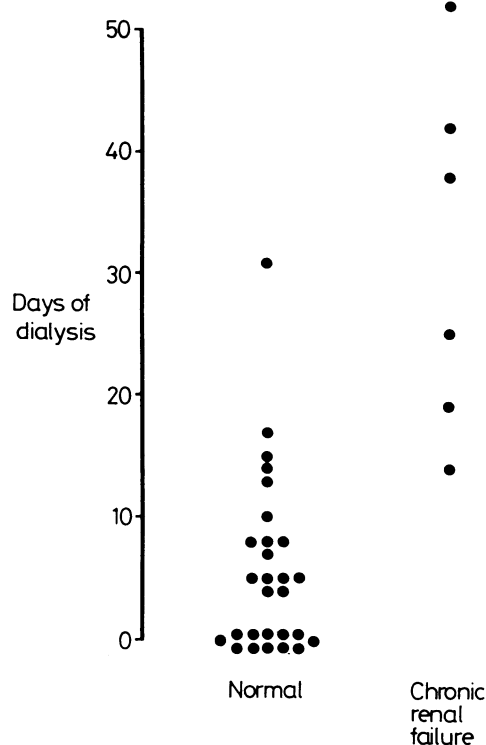


FIG 3—Duration of dialysis and follow up renal function (case 7 excluded).

TABLE II—Details of patients with poor outcome

Case No	Date of onset	Age		Sex	Chronic renal failure	Died	Extrarenal manifestations
		Years	Months				
1	Feb '82	0	11	M	+	+	
2	July '82	1	4	F			Neurological
3	Sept '82	5	5	M			Neurological
4	July '83	1	7	F	+		
5	July '83	2	8	M	+		
6	July '83	8	7	M	+		Neurological; diabetes mellitus
7	July '83	1	11	F		+	Unexplained sudden death
8	July '83	2	4	F	+		Neurological; diabetes mellitus
9	Sept '83	1	10	F	+		Cardiomyopathy

transient and non-specific T wave inversion in leads V4 and V5 with ST elevation in V2 and V3 only, but there were echocardiographic findings of ventricular dilatation and hypocontractility, which supported a diagnosis of cardiomyopathy. Serial studies showed return to normal of the size of the left ventricle but ventricular function, though improved, had not become normal by one year of follow up.

Discussion

The experience during 1982 and 1983 in the West Midlands contains differences from other reports in Britain,^{1,3} though the incidence of death and chronic renal failure was broadly similar to that described by Trompeter *et al* for 1969-80.³ It is widely accepted that the prognosis is more favourable in younger patients presenting in the summer with a prodrome of diarrhoea—the so called “epidemic” form of the disease⁶—but in the West Midlands cases chronic renal failure was more prevalent in younger patients and was a particular feature of the summer outbreak in Wolverhampton.

The prognostic score index based on age, sex, season, and prodrome derived from experience in south east England³ was applied to our data (fig 4). It predicted a better than 84% probability of a good outcome for each child who developed chronic renal failure and better than 90% for those from Wolverhampton; conversely, eight of the 26 children who recovered were given a less than 50% probability of doing so.

It is unlikely that this inconsistency between two centres in Britain was related to referral practice or treatment, and we consider that the difference in disease pattern was probably related to aetiological factors. A prognostic index which can reliably be applied on admission to hospital is greatly needed in planning a prospective, multicentre, therapeutic trial. The search for such an index in the haemolytic-uraemic syndrome is by no means new, and, though successive attempts^{3,7,8} have employed increasingly intricate statistical methods, each has in turn failed when applied to a different patient population, reflecting the heterogeneity of the condition. Other workers have referred to the duration of anuria as an index of severity, but this can be applied only after a variable period in hospital. In modern times this is paralleled by the number of days of dialysis required, and in this respect our findings accord with those of Trompeter *et al*: that the watershed between good and poor outcomes is at 14 days.³

From the earliest descriptions of the haemolytic-uraemic syndrome extrarenal and, in particular, neurological complications have been recorded,⁹ but more emphasis has been given to this in recent North American than European reports. We confirm the observation of Bale *et al* that the most frequent cerebral disturbance was seizure related to hyponatraemia.¹⁰ Typically this occurred close to the time of admission and in several instances administration of fluid had been inappropriate. In temperate climates finding hyponatraemia in a child with diarrhoea should suggest the possibility of renal impairment and the need to adjust rehydration appropriately. More serious was fixed neurological deficit (as in cases 2 and 3), in which hypertension and hyponatraemia played no part. From our experience both diffuse and focal lesions may occur. The pathogenesis is unknown. Arteriolar microthrombi have been

found in the basal ganglia of some patients at necropsy¹¹ but others have reported cerebral oedema and anoxic changes without thrombus formation.^{10,12}

Insulin dependent diabetes has been described in the haemolytic-uraemic syndrome.^{13,14} Burns *et al* reported haemorrhagic necrosis affecting the pancreatic islets,¹³ whereas Andreoli and Bergstein found the β cells to be preserved.¹⁴ Furthermore, Upadhyaya *et al* detected microthrombi in the pancreatic vasculature of a patient who had died with extensive defects in the central nervous system.¹¹ Finding reduced faecal chymotrypsin activity in the surviving diabetic patient in our series suggests exocrine as well as endocrine disease, which would be compatible with an ischaemic insult. Nevertheless, the hypothesis that microvascular occlusion causes the extrarenal disease in the haemolytic-uraemic syndrome, though attractive, fails to explain the apparent predilection of the syndrome for neurological, pancreatic, and myocardial systems. Tissue injury by free radicals containing oxygen may also have a role in the haemolytic-uraemic syndrome, and the recently reviewed suscepti-

bility of pancreatic β cells and cardiac muscle to free radical attack is therefore of interest.¹⁵

Verotoxin producing *E coli* organisms are known to be associated with acute haemorrhagic colitis and were first implicated in the

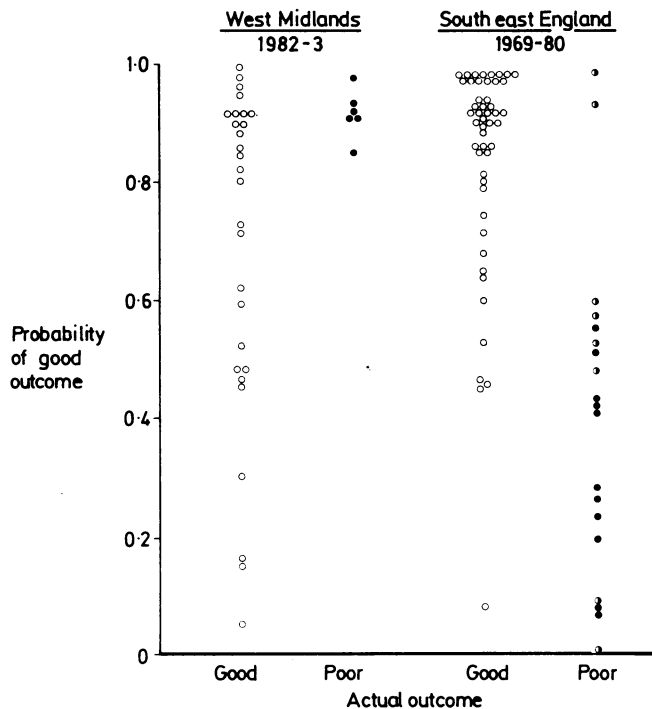


FIG 4—Actual outcome and calculated probability of full recovery. West Midlands patients: ○=Complete recovery; ●=Chronic renal failure. South east England patients: ○=Complete recovery; ●=Residual nephropathy; ●=No recovery of renal function.

pathogenesis of the haemolytic-uraemic syndrome by Karmali *et al* in 1983.¹⁶ In addition to our three patients, verotoxin producing *E coli* have been isolated from patients with the haemolytic-uraemic syndrome in other parts of the British Isles (B Rowe, unpublished data). Moreover, Rose *et al* have shown that plasma incubated with verotoxin is a powerful platelet agonist, whereas verotoxin alone has no aggregatory effect.¹⁷ Though the clinical characteristics of the Wolverhampton outbreak cannot firmly be attributed to verotoxin producing *E coli*, the clinical and pathological data described here raise the possibility of a causal relation between verotoxin producing

E coli and the haemolytic-uraemic syndrome. Karmali *et al* showed that it was necessary to test large numbers of bacterial colonies from each faecal specimen in order to detect verotoxin producing strains of *E coli*.¹⁶ This is a laborious task, but recently developed deoxyribonucleic acid probes which recognise the genome responsible for production of verotoxin allow numerous *E coli* colonies to be easily tested. This new laboratory tool permits large numbers of patients to be investigated with valid statistical analysis, and will facilitate a controlled prospective study of the association between verotoxin and the haemolytic-uraemic syndrome.

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What might be the cause of an apparently fit man in his mid-70s passing little urine during the day and copious amounts at night?

Appropriate tests to eliminate cardiovascular, renal, and endocrine disease are obviously essential but are unlikely to show appreciable abnormality. The effect of drugs, such as alcohol, caffeine, or steroids must also be considered, but the most probable explanation is reversed rhythm of urine output associated with age. Recent studies suggest that the circadian rhythm seen in young people, who normally excrete twice as much urine during the day as during the night, is gradually lost or reversed with advancing years.¹ Most people over the age of 70 produce the greater part of their urine at night, despite attempts to prevent nocturia by avoiding drinking from late afternoon and high nocturnal plasma osmolalities.² Experiments in young people have shown that the excretory rhythms of water, sodium, potassium, and creatinine can be made to vary independently from each other, so that there is unlikely to be a single cause for their breakdown in the elderly. Variations in the patterns of flow probably result from a combination of changes of endogenous circadian rhythms with age, and deterioration of

cardiovascular stretch reflexes which affect the action of salt and water regulating hormones. Changes in physiological responses to posture appear to be important. Tilt tests in apparently healthy, elderly people have shown functional abnormalities similar to those seen in cardiac failure, and a study in chronically catheterised, female geriatric patients has shown that chair, as opposed to bed, nursing during the day may cause increased excretion of urine at night.³ Mild increases in nocturnal urine do not necessarily result in nocturia, which is more often due to insomnia and detrusor instability, often complicated by prostatic disease in men.—M R BLISS, consultant geriatrician, London.

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