be reliably remembered. Injections of intramuscular iron are usually given into the buttock, using each side alternately.

Case 1—An 18-year-old man with iron-deficiency anaemia received intramuscular Jectofer (iron sorbitol and citric acid complex) in the buttock. The number of injections is unknown but was definitely not more than five. Two years later he developed a fibrosarcoma of the left buttock.

Case 2—A 40-year-old woman was given seven injections of 2 ml Jectofer intramuscularly (injection site not recorded) for anaemia in pregnancy. Four years later she developed a myxoid type of liposarcoma in the right buttock.

Case 3—A 35-year-old woman was given 12 injections of 5 ml iron dextran (Imferon) intramuscularly (injection site not recorded) for anemia in pregnancy. Thirteen years later she developed a rhabdomyosarcoma in the right buttock.

Case 4—A 51-year-old woman received intramuscular injections of iron in the buttock for iron-deficiency anaemia. Several months later a palpable thickening was found at the injection site; biopsy showed this to be a poorly differentiated chondrosarcoma.

Discussion

Only three other cases of a possible association between intramuscular iron and tumour induction in man have been described. Robinson *et al*[1] described a case in which an undifferentiated soft-tissue sarcoma developed at the injection site four years after Imferon had been given into the deltoid of an elderly woman. MacKinnon and Bancewicz[2] described a reticulum-cell sarcoma developing in the buttock of a middle-aged woman six years after starting two courses of intramuscular iron (one of iron sorbitol and citric acid complex, one of iron dextran), and a pleomorphic sarcoma developing in the buttock of a young woman five years after starting two courses of intramuscular iron dextran. Tumour localisation was described by Crowley and Still[3] in a case in which a secondary deposit from a cervical carcinoma localised at the site of an earlier intramuscular injection of iron dextran.

Although there is no proof of a cause-effect relationship in the four cases described here, they are further examples of possible tumour induction by intramuscular iron; however, in case 4 the time between the course of injections and diagnosis of the tumour was unusually short for tumour induction.

It is impossible to estimate risk of developing sarcoma at the injection site of intramuscular iron because the number of patients treated is unknown. A figure for the total sale of suitable iron preparations over the relevant period permits no more than an approximate calculation, since the numbers of doses given to individual patients vary widely.

I am grateful for the help I have received from Dr William Fraser, Mrs Amelia Marrow, Miss Sarah Macaskill, Mr James Scott, Dr Thomas Slattery, Dr William Walker, and other doctors caring for these patients. I thank the staff of the OPCS, particularly Dr Abraham Adelstein, for permission to make use of their data. I also thank Dr Arnold Levene, Professor Sir Eric Scowen, Professor Sir Richard Doll, and my colleagues Dr Edmund Harris and Dr William Inman for help and advice.

[1] Robinson, C E G, Bell, D N, and Sturdy, J H, *British Medical Journal*, 1960, **11**, 648.
[2] MacKinnon, A E, and Bancewicz, J, *British Medical Journal*, 1973, **2**, 277.
[3] Crowley, J D, and Still, W J S, *British Medical Journal*, 1960, **1**, 1411.

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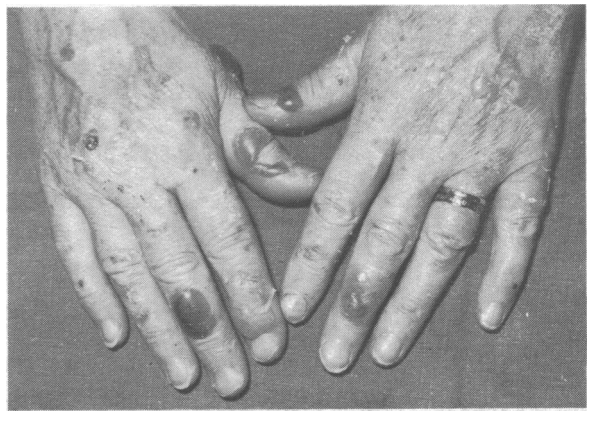
Acquired epidermolysis bullosa due to high-dose frusemide

Frusemide, in high doses, is extensively used to treat oedematous patients with chronic renal failure. We have now seen seven patients who developed epidermolysis bullosa while on such treatment. We are unaware of a previous similar report.

Clinical data

Of the seven patients (five men and two women aged from 17 to 57 years) three had glomerulonephritis; the other diagnoses were pyelonephritis, polycystic disease, secondary amyloidosis, and polyarteritis nodosa. Renal function was seriously impaired in six patients (creatinine clearance 4-10 ml/min), and the remaining patient had refractory oedema associated with the nephrotic syndrome with a creatinine clearance of 62 ml/min.

The dose of frusemide ranged from 0·5 g/day to 2·0 g/day, and most patients had received high-dose frusemide treatment for several months before the skin lesions developed. The shortest duration of treatment was two months and the longest three years. Associated treatment comprised potassium supplements (4 patients), spironolactone (1 patient), warfarin (1 patient), methyldopa (3 patients), aluminium hydroxide (3 patients), prednisolone (1 patient), and thyroxine (1 patient had pre-existing myxoedema). None had received nalidixic acid.



Bullous lesions on hands of patient aged 57 years who had received frusemide 0·5-1·5 g/day for three years.

The lesions were superficial bullae, of up to 3 cm in diameter, situated on the dorsum of the fingers or hands (see figure) and, in two patients, also on the dorsum of the feet. One of these patients had been sunbathing, with her feet exposed, the day before the bullae on her feet appeared. The lesions were itchy but without systemic manifestations. The bullae were superficial, easily ruptured, leaving a raw surface, and filled with clear fluid. Skin biopsy showed a subepidermal blister with very few inflammatory cells in the blister fluid and minimal inflammatory infiltrate in the dermis. The lesions persisted for three to nine weeks and then healed, whether frusemide was continued or not. Some of the patients believed that minor trauma to the hands had predisposed to the development of the bullae. The condition appeared clinically to be an acquired form of epidermolysis bullosa.

Discussion

The only treatment common to all patients was high-dose frusemide, and it seems inescapable that frusemide was the responsible agent. Dermatological complications attributed to frusemide are rare. Ebringer *et al*[1] described a patient who developed a haemorrhagic bullous eruption two months after starting frusemide; the patient had congestive cardiac failure, chronic bronchitis, a high alcohol intake, and he had received erythromycin. Gibson and Blue[2] reported a single patient with erythema multiforme which they believed to be due to six days of treatment with frusemide; the patient had congestive cardiac failure. The blisters in our patients contained no blood nor were there any associated features suggesting erythema multiforme, the blisters having arisen on clinically normal skin. Both Ebringer *et al* and Gibson and Blue note that frusemide is a sulphonamide derivative. Eruptions secondary to the sulphonamides are well recognised, although we are not aware of any reports that they have caused epidermolysis bullosa, except perhaps by precipitating porphyria. Fellner and Katz[3] described a 76-year-old woman with Parkinson's disease, urinary tract infection, and congestive cardiac failure who developed bullous pemphigoid while taking 40 mg frusemide daily and six other medications.

The lesions described in this report resembled those seen in porphyria cutanea tarda in their predilection for developing on parts of the body habitually exposed to light and the observation, in some patients, that minor trauma appeared to be a predisposing event. Porphyrin studies on urine, faeces, and blood were carried out in three of the patients, all with negative results, and we feel that it is unlikely that porphyria was responsible.

The mechanism of blistering is obscure. Although its onset in relation to high-dose frusemide is extremely suggestive, the blistering tendency subsides in weeks or months, irrespective of whether large doses of frusemide are continued or not. It is tempting to speculate that frusemide interferes with tissue metabolism in the region of the dermal-epidermal junction in a manner that depends on light exposure, inducing what is clinically an acquired form of epidermolysis bullosa.

We are grateful to Professor A Goldberg who arranged for the porphyrin studies.

[1] Ebringer, A, Adam, W R, and Parkin, J D, *Medical Journal of Australia*, 1969, **1**, 768.
[2] Gibson, T P, and Blue, P, *Journal of the American Medical Association*, 1970, **212**, 1709.
[3] Fellner, M J, and Katz, J M, *Archives of Dermatology*, 1976, **112**, 75.

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Comparative trial of two enterostomy sealants

Some 5000 colostomies and 930 ileostomies are created yearly,[1] yet no controlled trials have been reported on preparations for maintaining a watertight seal between the enterostomy appliance and the skin around the stoma. The two most important factors are the quality of adhesion and the incidence of skin sensitivity, and with these in mind we have carried out a cross-over trial of two commonly used sealants, Reliaseal and Stomahesive.

Patients, methods, and results

The trial was supervised by GE, who is trained in stoma care. Forty patients (21 women and 19 men) who agreed to the trial were given printed details and their general practitioners informed. They were then divided into two groups: those with established stomas and those in the immediate postoperative period. Half of the patients in each group were allocated at random to Reliaseal and half to Stomahesive, with cross-over at monthly intervals until at least four changes had been completed. Follow-up was from four to nine months. Since adhesion and sensitivity are related to the layer next to the skin no attempt was made to influence the type of appliance worn, although this was noted. Patients recorded in a daily diary the frequency of emptying and changing their appliances, and skin reaction or soreness, and any other comments regarding the appliance. If skin sensitivity was observed the sealant was changed to the other type and a patch test set up against the one that had produced the reaction.

Altogether 35 patients preferred Stomahesive and five Reliaseal (see table). Reasons for preferring Stomahesive included fewer changes, greater security because of better adhesiveness, particularly over the uneven surface of an obese abdomen, greater comfort, and flexibility of size. Reasons for preferring Reliaseal were that it is less bulky and easier to clean off the skin. Skin sensitivity with a positive patch test reaction was recorded in three patients with Stomahesive and eight with Reliaseal.

Comment

Patients in apparently similar clinical conditions vary considerably in their preference for particular enterostomy appliances. For patients with established stomas it is not possible to predict nor profitable to try to influence their individual reactions to a particular appliance. It is important, however, to have objective information on the incidence of skin sensitivity, and in the early postoperative period, when the psychological effect of stoma problems is greatest, the patient should be given the appliance most likely to prove satisfactory.

Preference of patients for one or other sealant

	Stomahesive		Reliaseal	
	Men	Women	Men	Women
Established colostomy	3	8		
Postoperative colostomy	6	2		1
Established ileostomy	1	8	3	
Postoperative ileostomy	5	2	1	
Total	35		5	

The preference for Stomahesive in the early postoperative period (see table) was related mainly to the oedematous stoma at this stage. This requires a larger internal diameter of the seal with a smaller area of contact, which is less important with Stomahesive because of its superior adhesive quality.

We are grateful to the nursing and surgical staff of the University Hospital of Wales for their co-operation, and to the department of dermatology for help with the patch tests. We are indebted to E R Squibb and Sons Ltd for support in setting up the trial.

[1] Office of Population Censuses and Surveys, *Hospital Inpatients for the Year 1967*. London, HMSO, 1970.

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