to a value more characteristic of an elderly patient.[5] Our patient's diet was also deficient in vitamin D. The combination of nutritional deficiency and barbiturate habituation may cause more morbidity in the elderly than is generally recognised.

Although several indices of enzyme induction rely on a single estimation (serum GGT, urinary 24-hour glutaric acid, or 6β-OH-cortisol excretion) they are non-specific and correlate poorly in individual subjects. Antipyrine half life is widely used as an index of drug oxidation but the need for serial blood samples is time consuming and unpleasant for the patient. The use of saliva samples overcomes both problems and provides accurate estimations of half life.[3] The simplicity of sample collection makes it analogous to glucose tolerance tests by finger prick, which can be performed by paramedical staff, and it could have wider clinical application than plasma half life estimations.

[1] Dent, C E, *et al*, *British Medical Journal*, 1970, **4**, 69.
[2] Pierides, A M, *et al*, *British Medical Journal*, 1976, **1**, 190.
[3] Fraser, H S, *et al*, *British Journal of Clinical Pharmacology*, 1976, **3**, 321.
[4] Kolmodin, B, *et al*, *Clinical Pharmacology and Therapeutics*, 1969, **10**, 638.
[5] O'Malley, K, *et al*, *British Medical Journal*, 1971, **3**, 607.

Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12
H S FRASER, MB, MRCP, research registrar
D THOMPSON, MB, MRCP, senior house officer (present address: London Hospital)
CLARE KHAN, BSC, technician

Conception and congenital abnormalities after chemotherapy of acute myelogenous leukaemia in two men

Improvements in cytotoxic chemotherapy for malignant disease have resulted in an increasing number of patients who remain disease-free after stopping chemotherapy. Such patients may wish to have a family and need advice about their fertility and the potential risk to the fetus if conception takes place. We report the cases of two men with acute myelogenous leukaemia (AML) who sired offspring with congenital abnormalities after chemotherapy was stopped.

Case 1

AML was diagnosed in a 17-year-old patient in July 1972. Initially he received seven courses of cytarabine (CA) 50 mg intravenously on days 1-3 followed by daunorubicin (DR) 100 mg intravenously on day 7. Each course was followed by a five-day interval. He was then given thioguanine (TG) 140 mg daily and cyclophosphamide 350 mg weekly by mouth for six weeks, followed by three further courses of DR 90 mg on day 1 and CA 130 mg on days 1-5. In February 1973 he received CA 130 mg for five days. Thereafter he refused further chemotherapy. The bone marrow, however, showed complete remission and he started weekly immunotherapy with BCG and allogeneic AML cells.[1]

In June 1974 his girlfriend gave birth to a full-term boy who had Fallot's tetralogy and syndactyly of the first and second digits of the right foot.

Case 2

A 23-year-old man began treatment for AML in January 1973. Five courses of induction chemotherapy were given. Each consisted of DR 140 mg intravenously on day 1 and CA 200 mg intravenously daily on days 1-5 followed by a 10-day interval. In March complete remission was obtained and he was then given weekly immunotherapy. He also received monthly courses of CA 180 mg intravenously and TG 160 mg by mouth daily for five days, alternating with DR 140 mg intravenously on day 1 and CA 180 mg intravenously daily for five days. Chemotherapy was stopped in March 1974. Since then his remission was maintained with immunotherapy alone.

In February 1975 his wife was delivered of a stillborn anencephalic fetus after eight month's gestation.

Discussion

Cytotoxic drugs may cause failure of both testicular and ovarian function, but fertility often recovers with time.[2,3] Such drugs may be teratogenic when given to the mother in early pregnancy[4] but studies of patients of both sexes who have discontinued treatment with various agents have produced no evidence of an increased incidence of congenital abnormalities in their offspring.[5] There is, however, little information on the effect of agents commonly used to treat AML, such as DR and CA, on reproductive function. These cases illustrate that patients who have received high doses of such drugs for AML may be fertile a few months (seven and three months in our patients) after stopping chemotherapy. They also suggest that the possibility of damage to the germ cells needs to be seriously considered. While there is clearly no proof that the association of the chemotherapy with the congenital abnormalities was more than coincidental, the disturbing fact remains that malformations have occurred in the offspring of the only two patients of ours with AML who have managed to produce children.

Until recently most patients with AML in remission have received some kind of maintenance chemotherapy that probably suppresses gonadal function to some extent. With the increasing use of immunotherapy alone during remission[1] more patients may be seen in whom chemotherapy is stopped and fertility recovers. Only by recording further conceptions by such patients, whatever the outcome, will we be able to obtain a clearer picture of the risks involved and be able to give appropriate advice.

[1] Russell, J A, Chapuis, B, and Powles, R L, *Cancer Immunology and Immunotherapy*, 1976, **1**, 87.
[2] Kumar, B, Biggart, J B, and McEvoy, J, *Lancet*, 1972, **1**, 1212.
[3] Hinkes, E, and Plotkin, D, *Journal of the American Medical Association*, 1973, **223**, 1490.
[4] Sokal, J E, and Lessman, E M, *Journal of the American Medical Association*, 1960, **172**, 1765.
[5] Li, F P, and Jaffe, N, *Lancet*, 1974, **2**, 707.

Department of Medicine, Royal Marsden Hospital, Sutton, Surrey
J A RUSSELL, MRCP, senior registrar
R L POWLES, MRCP, senior lecturer in medicine and honorary consultant physician

Department of Medical Oncology, St Bartholomew's Hospital, London
R T D OLIVER, MD, MRCP, senior scientific officer

Sarcoma after intramuscular iron injection

With the help of the Medical Department of the Office of Population Censuses and Surveys (OPCS) the Committee on Safety of Medicines has carried out a study of drug histories in a series of cases of sarcoma of the buttock. The series comprised all notifications of the diagnosis during about two years (1968 and 1969) and a few cases notified before and after this period. Altogether there were 196 cases, 169 identified from cancer registry entries and 27 from death certificates. Drug histories could be obtained in only 90 cases (46%), apparently because many patients had died since diagnosis and notes had been destroyed or lost. Of the 90 cases intramuscular iron had been given in four. In three of these four cases there was an interval of two years or more between the injections and the diagnosis of sarcoma.

Case histories

Histories are necessarily imprecise because some information, such as numbers of injections into each buttock, was not recorded and could not

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.

Committee on Safety of Medicines, London EC2A 1PP
GILLIAN GREENBERG, MB, BS, senior medical officer

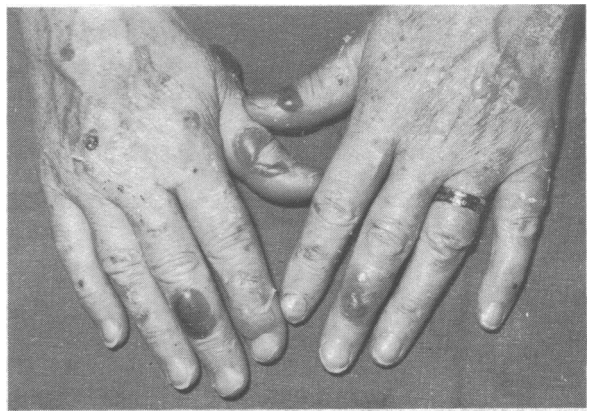
Acquired epidermolysis bullosa due to high-dose frusemide

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.