

transit time has previously been shown,<sup>5</sup> photo-therapy-induced lactose intolerance being implicated as a cause.<sup>6</sup>

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## Management of leukaemic infiltration of the testis

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**SUMMARY** Of 95 boys treated for acute lymphoblastic leukaemia 25 have developed leukaemic infiltration of the testes. In 15 children relapse was apparently confined to the testes, and since treatment 7 of these boys remain in remission. The median duration of remission after testicular relapse was 72 weeks, considerably longer than that reported after other forms of leukaemic relapse.

Now that long haematological remissions occur in children with acute lymphoblastic leukaemia (ALL) greater attention is being paid to extramedullary sites of leukaemic relapse. Prophylactic therapy to the central nervous system has reduced the incidence of meningeal leukaemia, but in boys residual disease in the testis now presents an important obstacle.<sup>1</sup>

The management and prognosis of boys with leukaemic infiltration of the testis may depend on whether the relapse is confined to the testis or associated with previous or concurrent relapse elsewhere. We report our experience with 'isolated' testicular relapse.

#### Patients and treatment

Between December 1970 and June 1976, 95 boys were treated for ALL at our two centres, and leukaemic infiltration of the testis was detected in 25 of them.

15 (17%) had no evidence of leukaemia elsewhere and had had no previous relapses, so the disease was apparently confined to the testes. All had been

treated according to current Medical Research Council UKALL I-V protocols, and 13 of them had features at diagnosis that suggested good prognoses. Two boys, one with a white cell count  $>20 \times 10^9/l$  and one aged over 14 years, were thought to have a poorer outlook (Table). In 13, testicular relapse (TR) was suspected clinically while in 2 it was discovered by routine testicular biopsy at the end of 2 years' treatment. The diagnosis was confirmed by needle biopsy in 9 patients and by wedge biopsy in 6. Testicular disease was diagnosed during 'maintenance' chemotherapy in 3, and between 1 and 24 (mean 7.8) months after stopping treatment in the remaining 12 boys. Both testes were affected in 9 boys and 6 had only unilateral infiltration.

Since 1975, we have used a standard treatment for isolated TR consisting of irradiation to both gonads and cords to a total tumour dose of 2500 rad (given in 10 fractions), and 2 years' intensive chemotherapy usually with the UKALL II 'maintenance' protocol.<sup>2</sup> Three early cases had lower doses of radiotherapy (Case 4 had 1800 rad in 6 fractions, Cases 10 and 11 1500 rad in 5 fractions). No further prophylaxis to the central nervous system was given.

The 10 children with previous or concurrent haematological or meningeal relapse were individually treated and all died of leukaemia (median survival 38 weeks); they will not be described further.

**Treatment results.** All 15 boys with isolated TR showed a clinical response to treatment but 5 suffered

Table Data for 15 boys with leukaemic infiltration of the testes

Case	Prognostic* features at presentation	Extent of TR	Age when TR diagnosed (years)	Time from presentation until TR (weeks)	Time off treatment before TR (weeks)	Remission length since TR (weeks)
1	Good	Bilateral	8	134	21	24†
2	Good	Bilateral	6	122	12	71†
3	Good	Bilateral	5	140	OT	60†
4	Good	Bilateral	10	180	12	>236
5	Good	Bilateral	5	150	32	132
6	Good	Bilateral	9	150	26	>144
7	Good	Bilateral	7	116	OT	54
8	Good	Bilateral	14	104	OT	32
9	Poor	Bilateral	5	134	9	72†
10	Poor	Unilateral	6	152	40	>147
11	Good	Unilateral	12	129	20	>100
12	Good	Unilateral	11	148	36	>91
13	Good	Unilateral	4	121	4	44
14	Good	Unilateral	9	213	96	>30
15	Good	Unilateral	6	73	18	>58

OT = on treatment, TR = testicular relapse.

† Dead.

\*Defined to have poor prognosis if one of the following features is present: WCC >20 × 10<sup>9</sup>/l, aged >13 years, mediastinal mass, doubtful cytology, Negro race.

subsequent haematological relapse between 24 and 132 weeks later, 2 boys had meningeal relapse after 44 and 72 weeks, and one died of subacute sclerosing panencephalitis after 60 weeks.

On 1 May 1979, 7 boys were alive and well without further relapse between 30 and 236 weeks after diagnosis of TR. Four children had died, while the remaining 4 were alive but still receiving treatment for haematological or meningeal relapse, or both (Table). The median duration of remission after treatment of TR was 72 weeks.

Needle biopsy of the testes was repeated in Cases 7 and 8 (Table) 52 weeks after testicular irradiation and no leukaemic infiltration was found, although interstitial fibrosis and loss of tubular epithelium were present.

Two boys (Cases 4 and 8) have shown normal pubertal development after testicular irradiation. Two others (Cases 11 and 12) are currently undergoing pubertal changes.

## Discussion

Leukaemic infiltration of the testis is more often being recognised in boys treated for ALL, perhaps because haematological remissions are becoming longer. The incidence of TR has been reported to be between 8 and 16%.<sup>3-5</sup> However, Eden *et al.*<sup>1</sup> found that 30% of boys entered into the Medical Research Council's UKALL trials I to III had developed this complication, not surprisingly a figure close to ours (26%). The incidence of apparently isolated TR was 17% in our patients and 13% in the MRC series.

The prognosis for boys with TR who have had previous or concurrent haematological relapse is poor, 19 of 20 boys having had short further

remissions, or none.<sup>6</sup> These results resemble those for treatment of haematological relapse; Cornbleet and Chessells<sup>7</sup> found median second remission lengths after haematological relapse to be 12 weeks for patients relapsing during treatment and 35 weeks for those relapsing after treatment had ended.

The outlook for boys with isolated TR may be better, particularly if this is diagnosed early and treated adequately with radiotherapy and intensive chemotherapy. In Memphis<sup>6</sup> 1100 to 2400 rad to one or both gonads, and chemotherapy, produced long remissions (37-138 months) in 4 of 5 boys with isolated TR, while, after treating 111 boys with TR (7 of 47 with isolated TR survived) Schaison *et al.*<sup>5</sup> recommended 2400 rad to both gonads, and further chemotherapy for isolated TR. Atkinson *et al.*<sup>8</sup> also recommended 2400 rad to sites of extramedullary leukaemia; this was the dose we used, together with further chemotherapy, for our patients. This treatment had eradicated lymphoblasts from the testes of our 2 boys who had further biopsies 52 weeks after radiotherapy, but it produced the expected damage to spermatogenesis. Thus, boys surviving after this treatment will be infertile, but Leydig cell function appears to be adequate, at least for some years, to permit normal sexual maturation.

The median remission length for our boys treated for isolated TR was 72 weeks, and 7 of our 15 patients are still apparently in complete remission 30 to 236 weeks after diagnosis of TR. This period of follow-up is shorter than for the Memphis series and further relapses are still possible. However, as in the French series,<sup>5</sup> the median remission length of 72 weeks after isolated TR greatly exceeded that reported after haematological relapse,<sup>7,9</sup> so it is possible that radiotherapy and chemotherapy, as

used for our patients, may cure some boys. Diagnosis of residual disease in the testis by routine biopsy before completion of chemotherapy may permit detection of those boys who require this treatment and perhaps improve the overall outlook for boys with leukaemia.

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## Decreased serum tuftsin concentrations in sickle cell disease

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**SUMMARY** The serum concentrations of the phagocytosis-stimulating peptide, tuftsin, were determined by radioimmunoassay in 21 patients with sickle cell disease and in 12 healthy controls. The mean serum tuftsin concentration was significantly lower in patients with haemoglobin SS disease ( $154.3 \pm 35.1$  ng/ml;  $308.6 \pm 70.2$  nmol/l,  $P < 0.01$ ) and in patients with haemoglobin SC and CC disease ( $180.9 \pm 42.7$  ng/ml;  $361.8 \pm 85.4$  nmol/l,  $P < 0.05$ ) than in healthy controls ( $228.7 \pm 46.7$  ng/ml;  $457.4 \pm 93.4$  nmol/l). Tuftsin deficiency is an indicator of splenic hypofunction and may contribute to the increased susceptibility of patients with sickle cell disease to severe infection.

Najjar and his associates described a cytophylic gammaglobulin, leucokinin, that stimulates phagocytosis by polymorphonuclear leucocytes and macrophages. The full biological activity of leucokinin resides in a tetrapeptide (Thr-Lys-Pro-Arg) named tuftsin, which is covalently bound to the heavy chain of the gammaglobulin.<sup>1-2</sup> It is believed that the

spleen is actively involved in either the generation or the release, or both, of the peptide from its carrier heavy chain as serum tuftsin concentrations are very low after elective splenectomy, and in functional asplenia due to infiltrative disease or infarction of that organ.<sup>3-5</sup> Functional asplenia contributes to the increased susceptibility of patients with sickle cell disease (SCD) to severe infections.<sup>6</sup> We have, therefore measured the serum tuftsin concentrations in patients with SCD and compared the values with those found in healthy controls.

#### Patients and methods

21 patients (14 with homozygous SS disease, 5 with haemoglobin SS disease, and 2 with haemoglobin CC disease) and 12 healthy age-matched controls were studied; the patients and controls were aged between 3 and 21 years. The patients were neither infected nor in crisis at the time or during the 6-month period preceding blood collection, and none of them had been transfused in the 6 months before the study. In 7 of the patients with haemoglobin SS disease,