The greatly increased risk of secondary leukaemia in patients treated with the nitrosourea lomustine is the major new finding in the present study. Lomustine (CCNU) is known to be leukaemogenic in other cancers²⁴ and was identified as a risk factor in Hodgkin's disease in a smaller case-control study by Nayfield and Cuzick.¹⁴ In our series, however, most patients who developed leukaemia had received this drug (9/17, 53%), and despite the fact that it is used as second or third line treatment in relapsed patients the risk due to lomustine seemed to be independent of treatment quantity. No significant difference was observed when lomustine was given as maintenance treatment compared with its more usual role as a salvage drug, but the number of patients maintained on the drug was too small to allow meaningful conclusions to be drawn.

The reason for the special risk associated with treatment with lomustine is not clear, but it may be related to the way in which the drug is used: it is usually given as chronic low dose treatment to relapsed patients who have already received a considerable amount of other treatment. It is of interest that another study found a high risk of leukaemia in patients given chronic low dose chlorambucil as maintenance treatment.¹¹ Whatever the reason for the particular leukaemogenicity of lomustine in our study, the finding is of interest because of the increasing use of nitrosoureas in high dose salvage regimens. No cases of leukaemia have yet been observed in patients treated in this way in the British National Lymphoma Investigation's studies, but numbers are still small and follow up short.

There are two major implications of this study. Firstly, concern over the occurrence of secondary leukaemia when radiotherapy and chemotherapy are combined is misplaced. Secondly, it is clear that most cases of leukaemia occur in heavily treated patients with multiple relapses of Hodgkin's disease, few of whom would be expected to be cured of their Hodgkin's disease; indeed, many had active lymphoma when their leukaemias were diagnosed. Control of Hodgkin's disease remains the main problem, and there is thus no sound basis for reducing the intensity of treatment to avoid secondary leukaemias. The risks of other second malignancies may be a more serious concern and careful analysis of their occurrence is in progress.

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Ischaemic colitis as a complication of colonoscopy

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Ischaemic colitis complicating colonoscopy is apparently rare. Indeed, a Medline search of reports published in the past 10 years found no such case.

Case report

A woman aged 59 presented in 1985 with dyspepsia and loose motions. She had had Raynaud's phenomenon since a teenager, arthralgia, and a photosensitive facial rash suggestive of systemic lupus erythematosus. Biopsy of the skin lesion had shown discoid lupus erythematosus, and she had been positive for antibodies

to nuclear (1 in 200) and double stranded (1 in 160) DNA on several occasions.

Clinical examination was unremarkable, but rigid sigmoidoscopy showed a 1 cm polyp at 15 cm which histological examination identified as a tubular adenoma. This and another adenomatous polyp at 35 cm were removed by snare diathermy at total colonoscopy. Her abdominal symptoms settled. Follow up colonoscopy was performed after six months (one tiny metaplastic polyp removed by diathermy), one year, and three years; no evidence of recurrent polyps or other abnormality was found.

The five year colonoscopy in January 1990 was apparently not traumatic. Endoscopy lasted only 15 minutes, no procedures were undertaken, and no abnormality was seen. A few hours after colonoscopy she developed colicky lower abdominal pain, vomiting, and watery diarrhoea. After 24 hours she developed fresh, and later dark, rectal bleeding and was admitted to hospital.

On admission she looked pale and unwell but her temperature was normal. Abdominal examination showed lower abdominal tenderness, guarding, and rebound, particularly in the left iliac fossa. She also had an epigastric bruit, but no pulsatile mass was palpable and peripheral pulses were normal.

Investigations showed a haemoglobin concentration of 141 g/l, white cell count $24.4 \times 10^9/l$ (neutrophilia), platelet count $255 \times 10^9/l$, erythrocyte sedimentation rate 33 mm in the first hour, and sodium concentration 129 mmol/l; urea and electrolyte concentrations and amylase activity were normal. Stool microscopy and culture gave negative results. An erect chest radiograph was normal, showing no free subdiaphragmatic gas, but supine abdominal radiography suggested mucosal oedema of the transverse and distal colon. Sigmoidoscopy to 12 cm showed severely inflamed mucosa with contact bleeding, and multiple biopsy specimens were taken, which showed patchy areas of destruction with necrotic debris heavily laden with polymorphs. Intact, fairly normal mucosa was also seen, implying focal destruction. Tests for antibodies to nuclear and double stranded DNA were negative.

Ischaemic colitis was diagnosed, and she was treated conservatively with intravenous fluids and analgesia.

Over the next three days her condition improved, although her haemoglobin concentration fell by almost 30 g/l. Because of her history of systemic lupus erythematosus and her epigastric bruit she underwent mesenteric arteriography, which showed no abnormality. On day 5, when her condition was improving, a barium enema gave normal results, reflecting rapid mucosal recovery.

She was discharged the next day: her bleeding had stopped, her condition was stable, and her epigastric bruit had disappeared. She made an uncomplicated recovery, and subsequent sigmoidoscopy and rectal biopsy gave normal results.

Comment

Because of her history of systemic lupus erythematosus we postulate that this patient had had a compromised circulation to the large bowel, which the mechanical effects of colonoscopy reduced to below a critical level. We found no evidence of large vessel disease, but one possibility must be that her small vessel circulation was compromised as a result of her connective tissue disease.

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Screening for carriers of cystic fibrosis among partners of people heterozygous for the disease

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Since the gene for cystic fibrosis was sequenced in 1989¹ there has been much debate on the introduction of screening for carriers in the population.^{2,3} The most common mutation is the deletion of three base pairs (ΔF_{508}) in exon 10 of the transmembrane conductance regulator on cystic fibrosis chromosomes⁴; the 30 or more other mutations identified so far are very rare and thus much less suitable for screening. The frequency of ΔF_{508} in cystic fibrosis chromosomes varies among different populations and ethnic groups. In Switzerland this deletion is present in about 70% of cystic fibrosis chromosomes and the prevalence of carriers (q) is about 1 in 20.

A serious problem with screening for carriers is that it will detect many couples in which only one partner carries ΔF_{508} , but heterozygosity in the other partner cannot be excluded without screening for the increasing number of other, rare mutations. General screening may be acceptable if the risk of having an affected child is less after screening than before. This means that with a prevalence of carriers of 1 in 20 (5%) population screening should be postponed until at least 96% of the mutations can be detected.²

In high risk circumstances, however, such as marriages between a heterozygous relative of a patient with cystic fibrosis and an unrelated partner screening of both partners for ΔF_{508} can help in genetic counselling and prenatal diagnosis. This is shown by the recent results of DNA analysis in a Swiss family affected by cystic fibrosis.

Subjects, methods, and results

After his divorce the father of a patient with cystic fibrosis asked about the risk of having another child with cystic fibrosis as he wanted to marry an unrelated Swiss woman with no family history of cystic fibrosis. The risk before screening ($\frac{1}{4} \times q$) was $\frac{1}{4} \times \frac{1}{20} = \frac{1}{80}$.

If the woman was shown not to be a carrier of ΔF_{508} the risk of having a child with cystic fibrosis ($\frac{1}{4} \times (1-a) \times q$) would be reduced to $\frac{1}{4} \times 0.3 \times \frac{1}{20} = \frac{1}{267}$, where a is the proportion of mutations screened for (0.7 for ΔF_{508}). The risk after screening would therefore be less than that before. The probability of ΔF_{508} not occurring in a partner unrelated to him ($(1-q):(1-aq)$) was 98.4%. Alternatively, if the woman was shown to be a carrier of ΔF_{508} (probability 1.6%) the risk of having an affected child would be $\frac{1}{4}$, but the reliability of prenatal diagnosis of cystic fibrosis in a future pregnancy would be 100%.

After being told of these theoretical results the couple asked for an analysis of DNA. Unfortunately, this showed that both of them were carriers of ΔF_{508} , and they decided to consider prenatal diagnosis.

Comment

We suggest that screening for ΔF_{508} should be offered to partners of people heterozygous for cystic fibrosis in countries in which the prevalence of carriers is about 5% and the prevalence of the deletion on cystic fibrosis chromosomes is about 70%. Under these circumstances the risk of having a child with cystic fibrosis after screening would be less than that before screening for 49 out of 50 couples.

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Correction

Cost analysis of prophylaxis with antibiotics to prevent infected knee arthroplasty

Three authors' errors occurred in this paper by Dr Sten Bengtson and colleagues (1989;299:719-20). In the table the total cost for patients with infection should be Kr 358 166 and not 353 951; in the paragraph before the comment the cost saved with flucloxacillin is Kr 136 617 and with cephalexin is Kr 119 459 and not the other way round as published; and reference 2 was in fact published in the *Journal of Bone and Joint Surgery [Br]* (1984;66:580-2) and not in *Clinical Orthopaedics*.