Clinical review

Fortnightly review

Screening for asymptomatic colorectal cancer

Hugh E Mulcahy, Michael J G Farthing, Diarmuid P O'Donoghue

Introduction

Colorectal cancer is one of the most common cancers in Western Europe and the United States with more than 300 000 cases a year. Most tumours evolve from normal mucosa to adenomatous polyp to invasive cancer, and survival is directly related to the extent of the disease at operation (fig 1). This strong relation between tumour stage and survival provides a rationale for intervention at an early pathological or premalignant stage.

Methods

Our research interests in gastrointestinal carcinogenesis, cost-benefit analyses of screening, and gastrointestinal endoscopy were helpful in researching and writing this review. The literature on screening for colorectal cancer is extensive, and we were therefore selective in the papers that we reviewed for this article. Our computerised literature search on a medical database (Ovid-Medline, Ovid Technologies, New York, USA)—which used the keywords "colonic neoplasms *or* rectal neoplasms *or* colorectal neoplasms" *and* "mass screening *or* screening (textword)"—yielded over 1800 matches since 1966. We selected randomised controlled trials when possible, but there are relatively few such studies published on faecal occult blood testing and none on flexible sigmoidoscopy. We also selected well conducted case-control studies, though many of the data are necessarily observational. In addition, we continuously reviewed general medical and gastroenterology journals for the most recent and important articles about screening.

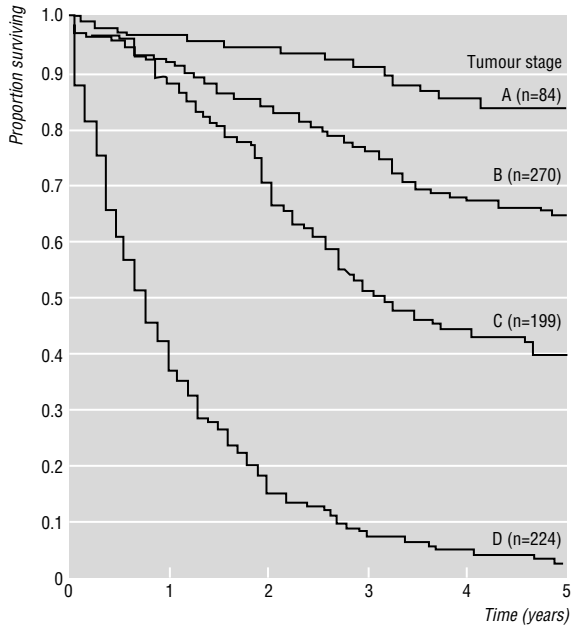

Fig 1 Survival of 777 consecutive patients with colorectal cancer stratified by tumour stage.[1] (Data from St Vincent's Hospital colorectal cancer database)

Summary points

- The strong relation between the stage of colorectal cancer and survival provides a rationale for screening, but present recommendations are controversial
- Regular endoscopic screening is recommended for members of families with adenomatous polyposis and of families with hereditary non-polyposis colorectal cancer
- Subjects with one or two relatives with colorectal cancer should be assessed individually before a decision about colonoscopic screening is made
- Screening populations at average risk of colorectal cancer by faecal occult blood testing and sigmoidoscopy can reduce related mortality, but there are insufficient available data on costs and compliance to advocate a population screening programme at present
- Future population studies should evaluate the acceptability, financial costs, and physical and emotional side effects of screening for colorectal cancer in addition to its effects on related mortality

Screening high risk subjects

Inherited colorectal cancer syndromes

The risk of developing colorectal cancer is closely related to a positive family history (table 1). At the upper end of the risk spectrum lies the dominantly inherited familial adenomatous polyposis syndrome, comprising less than 0.5% of all colorectal cancers. Mutations in the adenomatous polyposis coli (APC)

Digestive Diseases Research Centre, St Bartholomew's and Royal London School of Medicine and Dentistry, London E1

Hugh E Mulcahy, *senior registrar in general medicine and gastroenterology*

Michael J G Farthing, *professor of gastroenterology*

Gastroenterology and Liver Unit, St Vincent's Hospital and University College Dublin, Dublin 4, Republic of Ireland

Diarmuid P O'Donoghue, *consultant physician and gastroenterologist*

Correspondence to: Dr Mulcahy (email: h.e.mulcahy@mds.qmw.ac.uk).

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Table 1 Lifetime risk of developing colorectal cancer (from Lovett[2])

	Risk
More than two first degree relatives affected (suggests dominant pedigree)	1 in 3
Two first degree relatives affected	1 in 6
One first degree relative aged <45 years affected	1 in 10
One first degree and one second degree relative affected	1 in 12
One first degree relative aged >45 years affected	1 in 17
General population	1 in 50

gene are responsible for the familial adenomatous polyposis syndrome (table 2) and result in hundreds or thousands of colorectal adenomas developing during adolescence and adulthood, with an almost certain risk of adenocarcinoma by middle age.

Hereditary non-polyposis colorectal cancer accounts for 5-10% of all colorectal cancers. Whereas familial adenomatous polyposis results from mutation within a single gene, hereditary non-polyposis colorectal cancer results from a dominantly inherited alteration within one of four DNA mismatch repair genes that have been identified to date (table 2), which in turn leads to widespread genomic instability. The clinical hereditary non-polyposis colorectal cancer syndrome is defined by the "Amsterdam criteria," which require the presence of colorectal cancer in at least three family members spanning two generations, with one or more cases diagnosed before the age of 50 years.[3] Tumours tend to occur in the right colon, and subjects with the hereditary non-polyposis colorectal cancer (Lynch type II) syndrome also have an increased incidence of gastrointestinal, urinary tract, and gynaecological malignancies.[4]

Criteria for screening high risk populations

Screening subjects at very high risk (1 in 2 risk) of cancer is the least controversial aspect in the ongoing debate about screening for colorectal cancer. Endoscopic screening is time consuming, expensive, and potentially hazardous but is justified in such subjects because of its sensitivity and specificity for neoplasia. Regular sigmoidoscopy starting in adolescence is indicated for people in families with adenomatous polyposis. Intermittent gastroduodenoscopy with a side or oblique viewing endoscope is also justified in these cases[5] because of the high incidence of upper gastrointestinal malignancy in familial adenomatous polyposis.[6]

The predominance of right sided colorectal cancer in subjects with hereditary non-polyposis colorectal cancer syndrome makes total colonoscopy the endoscopic investigation of choice for such patients, and regular colonoscopy reduces the incidence of cancer in affected families.[7] The average age of such patients when cancer is diagnosed is about 44 years,[4 7] and screening should begin at 25 years or at least five years earlier than the earliest onset of colorectal cancer in the family.[4 8] The optimum screening interval is more contentious: colonoscopy every one to three years is advocated, depending on the presence of neoplasia at initial endoscopy.[4 7-9] However, Vasen *et al* report a high percentage of cancers presenting between screening procedures (interval cancers) and propose biennial or annual screening for known gene carriers.[10] As with subjects with familial adenomatous polyposis syndrome, subjects with the hereditary non-polyposis colorectal cancer syndrome have an increased incidence of extracolonic cancer, and Lynch *et al* are investigating the feasibility of screening for gynaecological malignancies in affected families.[4] Gastroscopy, urinary cytology, and mammography have also been advocated for this group,[7 11] and table 3 shows the recommendations adopted at the 1996 international collaborative group meeting on hereditary non-polyposis colorectal cancer.[12]

A carefully constructed family history is crucial to determine a person's risk of developing colorectal cancer (table 1).[13] However, identifying the point at which the benefits of endoscopic or radiological screening are outweighed by their disadvantages is perhaps the most difficult task for those with an interest in screening high risk populations. Most experts would offer such screening to subjects who have two or more first degree relatives with colorectal cancer,[11 13-15] but what about subjects with only one first degree relative affected? Screening recommendations in these subjects have been based on estimates of risk rather than a documented decrease in mortality from colorectal cancer after intervention. Fuchs *et al* calculated that subjects with an affected family member had a relative risk 1.7 times greater than those with a negative family history[16] and supported recommendations that patients with a positive family history should undergo colonoscopic screening from the age of 40,[14] especially if the affected family member was under 55 years old at diagnosis.[17]

Few studies have actually examined the feasibility of screening subjects with a positive family history. Houlston *et al* and Carpenter *et al* provided genetic counselling for relatives of patients with colorectal cancer and offered colonoscopic screening to those with a lifetime risk of 1 in 10 or greater.[11 15] Although neither detected any cancer in subjects whose risk was less than 1 in 2, both reported compliance rates of about 90% and acknowledged the beneficial psychological effect gained from counselling and, no doubt, from a normal

Table 2 Genetic alterations in hereditary and sporadic colorectal cancer

Condition	Gene (location)	Percentage of cases showing mutation
Familial adenomatous polyposis	APC (5q21)	100
Hereditary non-polyposis colorectal cancer	hMLH1 (3p21)	30-70
	hMSH2 (2p21-22)	30-50
	hPMS1 (2q31-33)	<10
	hPMS2 (7p22)	<10
Sporadic colorectal cancer	p53 (17p53)	70
	DCC (18q21)	65
	APC (5q21)	60
	K-*ras* (12p12)	50
	Nm23 (17q21)	25
	Microsatellite instability	15

Table 3 Recommended guidelines for screening subjects with hereditary non-polyposis colorectal cancer syndrome[12]

Cancer site	Screening procedure	Age at initial screen (years)	Interval between screenings (years)
Colorectal	Colonoscopy	20-25	2
Endometrial or ovarian	Gynaecological exam Transvaginal sonography Measurement of serum marker CA-125	30-35	1-2
Stomach*	Gastroscopy	30-35	1-2
Urinary tract*	Sonography Urinary cytology	30-35	1-2

*Only in families at high risk of these cancers.

Table 4 Randomised controlled trials of faecal occult blood testing in populations at average risk

Study	Place of study	No of patients	% Of slides positive	% Of stage A cancers		% Decrease in cancer related mortality in screened group
				Test*	Control	
Kewenter *et al*[22]	Goteborg, Sweden	68 308	4.7†	26	9	NA
Kronborg *et al*[23]	Funen, Denmark	61 933	1.0	22	11	18‡
Mandel *et al*[24]	Minnesota, USA	46 551	9.8†	30§	22	33§
Hardcastle *et al*[25]	Nottingham	150 251	2.1¶	20	11	15‡

*Includes interval cancers and cancers in non-participants as well as screen detected cancers.
†Most slides rehydrated before testing.
‡Biennial screening.
§Annual screening.
¶Percentage positive at initial screen (1.2% of subjects positive during later screening) rounds.
NA=Not available to date.

colonoscopy. If detection of early cancers and polyps was the only positive screening end point, data from small family studies[11 15 18] would tentatively support a policy of regular colonoscopic screening only in subjects with a lifetime risk of 1 in 2. However, the psychological benefits of counselling and screening that accrue to those with an affected first degree relative may be important. Until firm data on efficacy become available, it therefore seems reasonable to select a screening policy for each high risk individual after an analysis of the proband's age, possible side effects of screening, and the needs and anxieties of the subject.

Future of screening high risk subjects

Molecular biologists are rapidly unravelling the mysteries of colorectal carcinogenesis, allowing clinicians a more scientific approach to identifying individual subjects in families with a history of colorectal cancer who are at risk. The discovery that familial adenomatous polyposis and hereditary non-polyposis colorectal cancer syndromes are associated with germ line mutations enables the carrier status of relations to be determined via genetic screening. This will provide reassurance for those without mutations and allow finite endoscopy resources to be focused on family members carrying mutant genes.

Genetic testing may also be valuable before surgery for some familial adenomatous polyposis patients. Vasen *et al* found that the risk of recurrent disease after ileorectal anastomosis was particularly great in patients with mutations after codon 1250 of the APC gene, and they recommended a more radical restorative proctocolectomy for these cases.[19]

Screening populations at average risk

Sporadic disease accounts for over 90% of all cases of colorectal cancer. Age is the most important risk factor for the development of sporadic disease in previously healthy patients, with an approximate doubling in incidence with each decade from the age of 40 to 80. Mutations within oncogenes and tumour suppressor genes play a major, though complex, role in sporadic colorectal carcinogenesis (table 2). About 15% of cases also demonstrate multiple replication errors (microsatellite instability) within the genome.

Population screening for colorectal cancer initially seems an attractive proposition. One person in 50 of the general population will develop colorectal cancer, and effective treatment is available for early tumours. However, single phase screening with colonoscopy is simply too expensive to merit serious consideration for populations at average risk, although some advocate its widespread use.[20] Many questions also remain about the efficacy, acceptability, and cost effectiveness of multiphasic screening starting with faecal occult blood testing or flexible sigmoidoscopy—the cornerstones of contemporary population screening.

Faecal occult blood testing

Traditional faecal occult blood tests detect the peroxidase-like activity of haemoglobin in the stools and rely on the tendency of colorectal cancers to bleed. Sensitivity is limited because many cancers and polyps bleed intermittently, so that blood is unevenly distributed in faeces. Occult blood tests fail to detect 20-50% of cancers and up to 80% of polyps. Specificity is also low and depends on whether patients avoid dietary sources of haemoglobin and myoglobin.[21] Red and white meats, fish, some raw vegetables, and fruits containing peroxidase may yield false positive tests. Sensitivity is increased by rehydrating the slide with a drop of water before testing, but this is at the expense of decreased specificity. A positive test requires further evaluation by colonoscopy or sigmoidoscopy and barium enema.

Four randomised controlled trials are currently examining faecal occult blood testing within average risk populations (table 4).[22-25] Mandel *et al* of the Minnesota group were the first to publish mortality figures and found a 33% reduction in colorectal cancer related mortality (from 0.9% to 0.6%) in patients randomised to annual screening.[24] In an accompanying editorial Winawer stated, "We now have an effective screening method, and I believe we should use it,"[26] yet the Minnesota study raised as many questions about the value of occult blood testing as it answered. The incidence of colorectal cancer was unchanged in the screened population over the 13 year study, and the results were criticised because a high proportion (9.8%) of rehydrated slides were positive. This lack of specificity resulted in almost 40% of annually screened patients undergoing colonoscopy during the study, and it seems reasonable to suggest that the reduction in cancer related mortality arose as much from the large number of colonoscopies performed as it did from occult blood testing per se.[27] Further follow up from the Minnesota study will determine whether mortality decreases after biennial testing.

More recently, Hardcastle *et al* reported the results of the largest occult blood screening programme—over 150 000 subjects followed up for a median of 7.8 years.[25] Various methodological differences are apparent between Hardcastle *et al*'s and Mandel *et al*'s studies. In contrast with the Minnesota trial, subjects in the

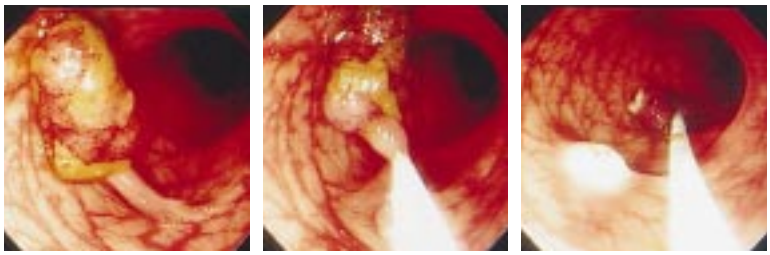

Fig 2 Endoscopic polypectomy: tubulovillous adenoma viewed through colonoscope (left); snare inserted through colonoscope and manoeuvred into position, encircling the stalk (centre); after electrocautery, transection margin is seen in foreground with polyp in background (right)

Nottingham study underwent biennial rather than annual occult blood testing, slides were not rehydrated before testing, and some patients with weakly positive tests underwent immediate retesting to reduce the number of false positive results. This resulted in a test positivity of only 2.1% for initial screening and 1.2% for subsequent rescreening, while only 4% of subjects required colonoscopic or radiological investigation. Overall, there were 60 fewer deaths related to colorectal cancer in the test group compared with the controls, a 15% reduction in colorectal cancer related mortality. Interestingly, the percentage of stage D cancers was almost identical in test and control groups (22% *v* 21%), and the reduction in mortality seems to have been due to a shift from regional (stage C) to local (stage A) disease. A negative aspect in this study was the high rate of interval cancers (28%) compared with screen detected cancers (26%) in the test group. This arose partially because of the relatively low sensitivity of occult blood tests for cancer but also because the authors considered that any cancer arising after a negative test was a potentially "missed" cancer, even if diagnosed more than two years after a negative screen.

Mortality figures from Kronborg *et al*'s Danish trial[23] are remarkably similar to those of Hardcastle *et al* (see table 4). Kronborg *et al* found that 22% of cancers in the screened group were stage A and that the proportion of incurable tumours was similar in test and control groups. Mortality from colorectal cancer was reduced by 18% in the screened group, again because of a shift from locoregional to local disease. Further follow up of the Minnesota, Nottingham, and Danish study populations will determine whether the incidence of cancer eventually decreases in screened populations secondary to detection and removal of adenomas.

Mortality results from the Swedish study will soon be available and may help clarify the value of population screening with occult blood tests.[22] Interim results showed that 36% of screen detected cancers were confined to the bowel wall compared with 9% of those in controls, and 9% were incurable at diagnosis (25% in controls). This provides further evidence that occult blood testing can detect early colorectal cancers, although the shift to early disease was again diluted by a high proportion of incurable cancers (28%) in non-compliant test subjects and in those presenting with interval cancers.

Flexible sigmoidoscopy

Flexible sigmoidoscopy is both sensitive and specific for distal cancers and polyps while allowing polypectomy (fig 2) and pinch biopsy at the time of initial examination. However, it is also a mildly uncomfortable procedure, entailing a hospital visit and preparatory enema. In addition, 30 to 40% of cancers are beyond reach of a 60 cm sigmoidoscope. Case-control studies show that screening sigmoidoscopy and polypectomy reduces colorectal cancer incidence and mortality due to distal disease in average risk populations.[28-30] Selby *et al* reported that the risk of death from distal colorectal cancer was 60% lower in subjects who had undergone rigid sigmoidoscopy compared with controls,[28] and was 80% lower in subjects over a 10 year period following flexible sigmoidoscopy.[29] These results appear impressive; however, case-control studies have many inherent methodological inadequacies,[31] and well constructed randomised controlled trials are necessary to confirm the efficacy of this form of screening.

The American Cancer Society recommend sigmoidoscopy every three to five years for people with average risk and a negative initial examination.[17] However, Rex *et al* found no cancers or large (>1 cm) or dysplastic polyps in any patient examined a mean of 3.4 years after a normal flexible sigmoidoscopy,[32] suggesting that a longer screening interval is more appropriate. This is supported by data from Aitken *et al* showing that subsequent cancer formation is a rare early event, even in patients who have had polyps removed at initial examination.[30]

Aitken *et al* have extrapolated the data on endoscopic screening and have proposed a single flexible sigmoidoscopy between the ages of 55 and 60 as a potentially effective screening strategy.[33] Their rationale is that the sequence of changes from polyp to cancer is a slow and orderly process taking perhaps 10-25 years to complete. Since colorectal cancer is often diagnosed in the seventh decade, sigmoidoscopy of people in their late 50s would be expected to identify pathologically early distal tumours and precancerous lesions in a proportion of cases. In addition, sigmoidoscopic screening might also indirectly identify a substantial number of proximal neoplasms because large or villiform polyps in the distal large bowel serve as markers of susceptibility for proximal disease.[30] Subsequent colonoscopic screening of this relatively small group of patients (estimated at 3-5%) with important distal adenomas might be expected to identify up to a third of proximal adenomas or cancers.[33]

Aitken *et al* assume a 70% compliance rate within the population for a single sigmoidoscopic screen, and suggest that sigmoidoscopy and polypectomy (with subsequent colonoscopy in a proportion of patients) might prevent 5500 colorectal cancers a year in the United Kingdom. Although it would take almost 200 000 subjects (65 000 of whom would undergo sigmoidoscopy) and 10-15 years to show whether a survival benefit for this form of screening exists,[33] a controlled trial of single flexible sigmoidoscopy might answer important questions relating to endoscopic screening. Indeed, such a multicentre study has started recently, and preliminary data suggest that single sigmoidoscopy is both logistically feasible and acceptable to patients.[34]

Screening costs

The cost of initial occult blood testing and subsequent colonic assessment is largely unknown. The Nottingham group estimate that about 20% of costs might be

recouped by removing polyps that would otherwise progress to symptomatic cancers requiring surgery.[35] Mathematical models have also been constructed to determine screening costs,[13 36 37] and it is estimated that faecal occult blood testing and subsequent colonic evaluation of those with positive results would cost the United States at least $1.2 billion a year at 1991 costs,[36] rising to $2.5bn by the year 2000.[38] Regular sigmoidoscopy starting at 50 years of age is even more expensive than faecal occult blood testing and would increase American screening costs by over $5bn a year.[13]

Although the above figures suggest that population screening would be expensive, they tell us little about the costs in relation to the benefits that might ensue from screening. Preliminary estimates from Britain suggest that a single flexible sigmoidoscopy between 55 and 60 years might be a relatively cost effective screening approach, with an anticipated annual expenditure of £30m or £8500 per cancer death prevented (at 1993 costs).[33]

More recently, Lieberman constructed a comprehensive cost-benefit algorithm which incorporated not only initial screening expenses but also the subsequent cost of treatment, complications, and additional endoscopic follow up of patients who had polyps removed at first endoscopy.[37] With 100% compliance at all stages, different screening regimens were estimated to cost between $225 000 and $280 000 per death prevented, rising to about $350 000 as compliance fell to a more realistic 50%. Compliance and the cost of colonoscopic evaluation were the keys to cost effective screening in Lieberman's study, but all cost-benefit analyses will remain provisional without reliable data about sensitivity, specificity, compliance, and mortality for different forms of screening.

Screening compliance

Lieberman and Hardcastle *et al* have noted that compliance is an important aspect of screening populations at average risk.[37 39] Acceptable initial uptake rates (53-67%) were achieved in all three European trials of faecal occult blood testing, in which subjects were randomly recruited with mailed invitations and reminder letters.[22 23 25] Compliance was somewhat higher (75%) in the Minnesota study,[24] probably because participants were recruited from members of the American Cancer Society and other highly motivated groups. However, uptake rates of under 25% are often observed in uncontrolled trials.[40] Furthermore, in Germany faecal occult blood testing has been offered nationally since 1977, but only 21% of women and 10% of men take advantage of such screening.[41] Satisfactory compliance levels have occasionally been observed for flexible sigmoidoscopic screening programmes, with acceptance rates as high as 70%.[42] In uncontrolled studies of screening sigmoidoscopy, however, levels rarely rise above 30%.[43]

Compliance in average risk populations depends on demographic, behavioural, and educational factors.[44] Many people in the general population are ignorant of the sequence of adenoma to carcinoma, the concept of asymptomatic disease, and the potential benefits of screening. Some non-responders also suppose that they are less susceptible to cancer than others,[45] which is clearly erroneous since the incidence of colorectal cancer in non-responders from the initial Nottingham trial was 0.92 per 1000 person years compared with 0.72 per 1000 in the controls.[39] These issues might be addressed by public health education focusing on the concept of asymptomatic and premalignant disease and the benefits of early detection.[45] Education could also highlight the high incidence and hereditary aspects of colorectal cancer in Western society and the aetiological role of a high fat, low fibre diet in carcinogenesis.

Although compliance is relevant to the success of population screening, it remains questionable as to how far healthcare agencies should go to promote screening to potentially unreceptive populations.[46] Statements such as "Mammography helps your doctor see breast cancer before there is a lump when the cure rates are near 100%"[47] and "Given the overwhelming evidence that (colorectal cancer) screening is effective in detecting and curing this second deadliest cancer"[48] may increase compliance, but they give an inaccurate perception of the efficacy of screening. Public health education might also reasonably include information about the emotional costs of false positive tests, the inappropriate reassurance caused by false negative results, and the possibility of detecting incurable disease. This would allow people to make informed decisions about participating in screening programmes.

Compliance might also be improved by tackling concerns about the specific type of screening offered and its mode of delivery. A proportion of non-responders find the concept of faecal occult blood testing aesthetically unacceptable,[49] while dietary restrictions before screening also adversely affect uptake rates.[50] Strategies to overcome people's distaste for screening could include developing more acceptable, and possibly self administered, tests.[49] Participation rates would also be increased by involving well motivated primary healthcare staff in the delivery process.[51]

Criteria for screening average risk populations

There is much debate about the desirability or need for a colorectal cancer screening programme for the general population. The American Cancer Society recommend an annual digital rectal examination from the age of 40, annual faecal occult blood testing from age 50, and sigmoidoscopy every three to five years from age 50.[17] Faecal occult blood testing is offered in Germany as part of an annual cancer checkup.[52] In contrast, the King's Fund and the Canadian Task Force on the Periodic Health Examination do not currently advocate screening in average risk subjects.[53 54]

What should doctors make of these conflicting messages? It is clear that intensive screening by competent researchers can reduce mortality from colorectal cancer, but it is questionable whether this in itself justifies establishing a national screening programme. Overall, we believe it is premature to implement such a programme until there are reliable data on the acceptability, financial costs, logistics, and the potential physical and emotional side effects of screening. In this context it is useful to review the results of long established breast and cervical cancer screening programmes that have recently been criticised as hugely expensive and largely ineffective.[46 55-57] In one of the largest studies of its kind, Raffle *et al* concluded that "The real lesson from 30 years' cervical screening is that no matter how obvious

the predicted benefit may seem from any screening test, introduction should never take place without adequate prior evaluation of both positive and negative effects in controlled trials."[57]

When applied to colorectal cancer, the overall benefits of conventional screening do not seem particularly obvious. Screening by a single sigmoidoscopy is no more than an attractive concept, while regular sigmoidoscopy or faecal occult blood testing seems excessively expensive at present. In addition, the high rate of false positive faecal occult blood tests would cause substantial distress to many healthy subjects where none would have existed but for screening.

Future of population screening

Current results are encouraging enough to warrant further research into more effective screening regimens for average risk subjects. Increased cost effectiveness and more refined screening strategies may eventually tip the balance in favour of population screening. The cost effectiveness of sigmoidoscopic screening would increase considerably if gastroenterologists were replaced by nurse endoscopists for diagnostic examinations. Large studies have concluded that nurse practitioners can perform flexible sigmoidoscopy as accurately and safely as trained gastroenterologists or colorectal surgeons,[58 59] and patients' pain, bloating, or embarrassment is no greater when examinations are performed by nurses rather than gastroenterologists.[58]

The cost effectiveness of faecal occult blood testing may also improve with the introduction of new tests. Haemoccult II Sensa (SmithKline Diagnostics) is a modification of the Haemoccult II test, while Haemselect (SmithKline Diagnostics) is an immunoassay for human haemoglobin. Both have higher sensitivity than Haemoccult for blood loss in symptomatic[60] and asymptomatic patients,[61 62] and, when used in combination, their specificity is close to that of unrehydrated Haemoccult II.[62] Increased sensitivity without a corresponding loss of specificity might substantially improve the performance of faecal occult blood testing[63] and eventually result in relatively cost effective screening.

Molecular biology may also be used in the future. Genetic mutations are found with relative ease in DNA extracted from tumour tissue, but they can also be detected in DNA recovered from the sputum, urine, pancreatic juice, and faeces of patients with various different malignancies. Sidransky *et al* and Smith Raven *et al* recently isolated K-*ras* mutations in faeces and suggested that genetic analyses might eventually evolve into screening tests for colorectal cancer.[64 65] There are certain advantages in screening for gene alterations rather than occult blood in stool. DNA is extremely stable, whereas blood, especially from the right colon, may be degraded by bacteria and subsequently result in false negative faecal occult blood tests. Mutations are also highly specific for neoplasia, virtually eliminating the problem of false positive results.

The range of somatic mutations that can be detected in faecal DNA[64-66] is too limited to allow practical genetic screening studies at present, and many molecular biological assays are unsuitable for routine clinical use. However, if developments in molecular biology continue to unfold at their current pace the concept of a non-invasive, sensitive, and specific genetic screening test for colorectal cancer may not be as far fetched as it seems.

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1 Davis NC, Newland RC. Terminology and classification of colorectal adenocarcinoma: The Australian clinico-pathological staging system. *Aust N Z J Surg* 1983;53:211-21.
2 Lovett E. Family studies in cancers of the colon and rectum. *Br J Surg* 1976;63:13-8.
3 Vasen HFA, Mecklin JP, Meera Khan P, Lynch HT. The international collaborative group on hereditary non-polyposis colorectal cancer. *Dis Colon Rectum* 1991;34:424-5.
4 Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM, *et al.* Genetics, natural history, tumour spectrum and pathology of hereditary non-polyposis colorectal cancer: an updated review. *Gastroenterology* 1993;104:1535-49.
5 Debinski HS, Spigelman AD, Hatfield A, Williams CB, Phillips RKS. Upper intestinal surveillance in familial adenomatous polyposis. *Eur J Cancer* 1995;31A:1149-53.
6 Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RKS. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989;2:783-5.
7 Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary non-polyposis colorectal cancer. *Gastroenterology* 1995;108:1405-11.
8 Vasen HF, Mecklin JP, Watson P, Utsunomiya J, Bertario L, Lynch P, *et al.* Surveillance in hereditary non-polyposis colorectal cancer: an international cooperative study of 165 families. The international collaborative group on HNPCC. *Dis Colon Rectum* 1993;36:1-4.
9 Green SE, Chapman PD, Burn J, Bishop DT, Varma JS. Clinical impact of colonoscopic screening in first-degree relatives of patients with hereditary non-polyposis colon cancer. *Br J Surg* 1995;82:1338-40.
10 Vasen HF, Nagengast FM, Meera Khan P. Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome). *Lancet* 1995;345:1183-4.
11 Houlston RS, Murday V, Harocopos C, Williams CB, Slack J. Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. *BMJ* 1990;301:366-8.
12 Weber J. Cancer surveillance recommendations adopted for HNPCC. *Lancet* 1996;348:465.
13 Eddy DM. Screening for colorectal cancer. *Ann Intern Med* 1990;113:373-84.
14 Burt RW, Bishop DT, Cannon-Albright L, Samowitz WS, Lee RL, DiSario JA, *et al.* Hereditary aspects of colorectal cancer. *Cancer* 1992;70:1296-9.
15 Carpenter S, Broughton M, Marks CG. A screening clinic for relatives of patients with colorectal cancer in a district general hospital. *Gut* 1995;36:90-2.
16 Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med* 1994;331:1669-74.
17 Levin B, Murphy GP. Revision in American Cancer Society recommendations for the early detection of colorectal cancer. *CA Cancer J Clin* 1992;42:296-9.
18 Luchtefeld MA, Syverson D, Solfelt M, MacKeigan JM, Krystosek R, Waller J, *et al.* Is colonoscopic screening appropriate in asymptomatic patients with a family history of colon cancer? *Dis Colon Rectum* 1991;34:763-8.
19 Vasen HFA, van der Luijt RB, Slors JFM, Buskens E, de Ruiter P, Baeten CGM. Molecular genetic tests as a guide to surgical management of familial adenomatous polyposis. *Lancet* 1996;348:433-5.
20 Bhattacharya I, Sack EM. Screening colonoscopy: the cost of common sense. *Lancet* 1996;347:1774-5.
21 Simon JB. Occult blood screening for colorectal carcinoma: a critical review. *Gastroenterology* 1985;88:820-37.
22 Kewenter J, Brevinge H, Engaras B, Haglind E, Ahren C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. results for 68,308 subjects. *Scand J Gastroenterol* 1994;29:468-73.
23 Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal occult blood test. *Lancet* 1996;348:1467-71.
24 Mandel JS, Bond JH, Church JR, Snover DC, Bradley GM, Schuman LM, *et al.* Reducing mortality from colorectal cancer by screening for faecal occult blood. *N Engl J Med* 1993;328:1365-71.
25 Hardcastle JD, Chamberlain JO, Robinson MHE, Moss SM, Amar SS, Balfour TW, *et al.* Randomised controlled trial of faecal occult blood screening for colorectal cancer. *Lancet* 1996;348:1472-7.
26 Winawer SJ. Colorectal cancer screening comes of age. *N Engl J Med* 1993;328:1416-7.
27 Lang CA, Ransohoff DF. Fecal occult blood screening for colorectal cancer. Is mortality reduced by chance selection for screening colonoscopy? *JAMA* 1994;271:1011-3.
28 Selby JV, Friedman GD, Quesenbery CP, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;326:653-7.
29 Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 1992;84:1572-5.
30 Aitken WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *N Engl J Med* 1992;326:658-62.
31 Shapiro S. Case-control studies of colorectal cancer mortality: Is the case made for screening sigmoidoscopy? *J Natl Cancer Inst* 1992;84:1546-7.

32 Rex DK, Lehman GA, Ulbright TM, Smith JJ, Hawes RH. The yield of second screening flexible sigmoidoscopy in average-risk persons after one negative examination. *Gastroenterology* 1994;106:593-5.
33 Aitken WS, Cuzick J, Northover JMA, Whynes DK. Prevention of colorectal cancer by once-only sigmoidoscopy. *Lancet* 1993;341:736-40.
34 Aitken WS, McIntyre P, Aubrey R, Cuzick J, Edwards R, Northover JMA. Pilot study for a multicentre randomised trial of 'once only' flexible sigmoidoscopy for prevention of bowel cancer. *Gut* 1996;38:A9.
35 Whynes DK, Walker AR, Hardcastle JD. Cost savings in mass population screening for colorectal cancer resulting from the early detection and excision of adenomas. *Health Econ* 1992;1:53-60.
36 Ransohoff DF, Lang CA. Screening for colorectal cancer. *N Engl J Med* 1991;325:37-41.
37 Lieberman DA. Cost-effectiveness model for colon cancer screening. *Gastroenterology* 1995;109:1781-90.
38 Brown ML. Screening for colorectal cancer. *N Engl J Med* 1993; 329:1352-3.
39 Hardcastle JD, Chamberlain J, Sheffield J. Randomised controlled trial of faecal occult blood screening for colorectal carcinoma: results for first 107,349 subjects. *Lancet* 1989;i:1160-4.
40 Bralow SP, Kopel J. Haemoccult screening for colorectal cancer: an impact study in Sarasota, Florida. *J Fla Med Assoc* 1979;66:915-9.
41 Gnauck R. Screening for colon cancer in Germany. *Tumori* 1995;81:30-7.
42 Foley DP, Dunne P, O'Brien M, Crowe J, O'Callaghan TW, Lennon JR. Left-sided colonoscopy as screening procedure for colorectal neoplasia in asymptomatic volunteers. *Gut* 1987;28:A1367.
43 Bejes C, Marvel MK. Attempting the improbable: offering colorectal cancer screening to all appropriate patients. *Fam Pract Res J* 1992;12:83-90.
44 Hart AR, Wicks AC, Mayberry JF. Colorectal cancer screening in asymptomatic populations. *Gut* 1995;36:590-8.
45 MaCrae FA, Hill DJ, St John JB, Ambikapathy A, Garner JF. Predicting colorectal cancer screening behaviour from health beliefs. *Prev Med* 1984;13:115-26.
46 Wright CJ, Barber Mueller C. Screening mammography and public health policy: the need for perspective. *Lancet* 1995;346:29-32.
47 American Cancer Society. *Pamphlet 86-(30mm);No 2077-LE.* Washington, DC: ACS, 1986.
48 Colorectal cancer bill introduced: AGA coordinates coalition. *AGA News* 1995;29:12.
49 Hunter W, Farmer A, Mant D, Verne J, Northover J, Fitzpatrick R. The effect of self-administered faecal occult blood tests on compliance with screening for colorectal cancer: Results of a survey of those invited. *Fam Pract* 1991;8:367-72.
50 Robinson MH, Pye G, Thomas WM, Hardcastle JD, Mangham CM. Haemoccult screening for colorectal cancer: the effect of dietary restriction on compliance. *Eur J Surg Oncol* 1994;20:545-8.
51 Launoy G, Veret JL, Richir B, Reaud JM, Ollivier V, Valla A, *et al.* Involvement of general practitioners in mass screening. Experience of a colorectal cancer mass screening programme in the Calvados region (France). *Eur J Cancer Prevent* 1993;2:229-32.
52 Gnauck R. Cancer related checkup in the Federal Republic Germany. In: *Secondary prevention of colorectal cancer.* Basel: Karger, 1986:143-55.
53 Kings Fund Centre. Cancer of the colon and rectum: the seventh Kings Fund consensus statement. *Br J Surg* 1990;77:1063-5.
54 Canadian Task Force on the Periodic Health Examination. *Canadian guide to clinical preventive health care.* Ottawa: Canada Communication Group, 1994:797-809.
55 Mueller CB. Breast cancer: reporting results with inflationary arithmetic. *Am J Clin Oncol* 1994;17:86-92.
56 Skrabanek P. False premises and false promises of breast cancer screening. *Lancet* 1985;ii:316-9.
57 Raffle AE, Alden B, Mackenzie EFD. Detection rates for abnormal cervical smears: what are we screening for? *Lancet* 1995;345:1469-73.
58 Maule WF. Screening for colorectal cancer by nurse endoscopists. *N Engl J Med* 1994;330:183-7.
59 Marks G, Boggs HW, Castro AF, Gathright JB, Ray JE, Salvati E. Sigmoidoscopic examinations with rigid and flexible fibreoptic sigmoidoscopies in the surgeons office: a comparative study of effectiveness in 1,012 cases. *Dis Colon Rectum* 1979;22:162-8.
60 St John JB, Young GP, Alexeyeff MA, Deacon MC. Evaluation of new occult blood tests for detection of colorectal neoplasia. *Gastroenterology* 1993;104:1661-8.
61 Robinson MHE, Kronoberg O, Williams CB, Bostock K, Rooney PS, Hunt LM, *et al.* Faecal occult blood testing and colonoscopy in the surveillance of subjects at high risk of colorectal neoplasia. *Br J Surg* 1995;82:318-20
62 Allison JE, Tekawa IS, Ransom LJ, Adrian AL. A comparison of fecal occult blood tests for colorectal cancer screening. *N Engl J Med* 1996;334:155-9.
63 Lance P. Faecal occult blood tests: what's new? *Gastroenterology* 1993;104:1852-5.
64 Sidransky D, Tokino T, Hamilton SR, Kinzler KW, Levin B, Frost P, *et al.* Identification of ras oncogene mutations in the stool of patients with curable colorectal tumours. *Science* 1992;256:102-5.
65 Smith Raven J, England J, Talbot IC, Bodmer W. Detection of c-Ki-*ras* mutations in faecal samples from sporadic colorectal cancer patients. *Gut* 1995;36:81-6.
66 Eguchi S, Norihiro K, Komuta K, Kanematsu T. Mutations of the p53 gene in the stool of patients with resectable colorectal cancer. *Cancer* 1996;77:1707-10.

Lesson of the Week

Carotid dissection causing stroke in a child with migraine

V Ganesan, F J Kirkham

The aetiology of stroke in childhood and adolescence often remains obscure. Up to 50% of published cases are said to be idiopathic, but often the search for an underlying cause is not exhaustive. Arterial dissection, usually of the internal carotid artery, is an important cause of stroke in this age group, accounting for 6% of cases in our series of 115 patients (unpublished data). Migrainous infarction, on the other hand, is rare in all ages and should be a diagnosis of exclusion. Unfortunately, in a patient with a history of headache it is often tempting to make this diagnosis. This case shows that other, potentially treatable, disease may be missed as a consequence.

Case report

A 15 year old left handed boy fell off his skateboard, sustaining a blow to the right occiput without loss of consciousness. The next day he developed right occipital headache, blurred vision, nausea, and left hemiparesis, which extended to his face. The limb weakness and headache resolved over 24 hours but the facial weakness persisted. He had blurred vision and felt nauseated but did not vomit. Despite bedrest and simple analgesics, his symptoms did not resolve and he was admitted to hospital on the third day with a presumptive diagnosis of hemiplegic migraine. That night, he fell out of bed, hitting his head again. It became clear the following morning that his condition had deteriorated, and he became disorientated, with a recurrence of the left hemiparesis. Power in the hand was Medical Research Council grade 0/5 and in the leg grade 2/5. There were no other clinically relevant findings. He had a history of migraine without aura which had been controlled by pizotifen. Two years earlier he had had one previous episode of headache with a focal deficit (left facial weakness) lasting 16 hours. Magnetic resonance imaging of the brain had shown normal results.

T2 weighted magnetic resonance imaging five days after the onset of symptoms showed extensive high signal and swelling in the region of the right middle cerebral artery, suggestive of infarction. He was unable to tolerate magnetic resonance angiography and was managed conservatively with a working diagnosis of migrainous cerebral infarction. Seventy two hours

See editorial by Blunt and Galton

Arterial dissection should be considered as a cause of juvenile stroke even in cases when the aetiology seems obvious

Neurosciences Unit, Institute of Child Health, Wolfson Centre, London WC1N 2AP
V Ganesan, *research fellow*
F J Kirkham, *senior lecturer*
Correspondence to: Dr Ganesan.

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Fig 1 Contrast study (intra-arterial digital subtraction angiogram) showing tapered irregular narrowing of the right internal carotid artery, suggestive of dissection

later, despite complete resolution of his headache, his hemiparesis had not improved. There was evidence of reduced flow in the right middle cerebral artery on transcranial Doppler ultrasonography. Magnetic resonance angiography at this time showed reduced flow in the right internal carotid artery and absent flow in the distal right middle cerebral artery. Magnetic resonance imaging showed that the previously noted area of high signal on T2 weighted imaging had spread. Intra-arterial digital subtraction angiography showed irregular narrowing of the right internal carotid artery with reduced flow, which, in the absence of any proximal internal carotid artery disease, suggested right internal carotid artery dissection (fig 1).

He was extensively investigated for other risk factors for juvenile stroke. Detailed cardiac, metabolic, and haematological investigations yielded normal results. He was given anticoagulant treatment and improved slowly, requiring prolonged rehabilitation. At the time of writing, he had a residual dense hemiparesis and had not regained any useful function of his hand, although he was able to walk independently. He has had to forgo an apprenticeship in the building trade. Anticoagulant treatment was discontinued after six months.

Discussion

Cervicocephalic arterial dissection is an important cause of stroke in childhood and adolescence.[1] It may occur spontaneously (although there is often a history of trauma, which may be minor)[2] and affect many vessels. In children the anterior circulation is more usually affected.[1] Pain in the ipsilateral head, neck, or eye is typical and there may be Horner's syndrome if the cervical sympathetic chain is affected. There is evidence to suggest that migraine increases the risk of arterial dissection.[3]

A focal neurological deficit may form part of the migrainous aura, but a recent study estimated that the risk of stroke was doubled in those with migraine[4]; this seems to be greatest in young women, especially those taking the contraceptive pill.[5] The International Headache Society emphasises that other causes of stroke should be excluded before migrainous cerebral infarction is firmly diagnosed[6]; a history of migraine in a patient with acute stroke is not sufficient. Unfortunately, this stipulation is often ignored both in published findings and in clinical practice.

Non-atheromatous cerebrovascular disease, including arterial dissection, is common in childhood stroke; imaging the cerebral circulation is important in establishing aetiology. Magnetic resonance imaging and magnetic resonance angiography permit non-invasive imaging of cervicocephalic vessels and are useful in the diagnosis of carotid dissection.[2] An abnormal but non-diagnostic study, as in this case, may prompt the clinician to consider contrast angiography, which remains the gold standard.

Prompt anticoagulant treatment is of confirmed therapeutic benefit in carotid dissection,[2] although its efficacy in the presence of an established infarction is less clear.

From the available published findings, which emphasise the importance of early diagnosis and treatment of carotid dissection, the outcome in this case might well have been improved by earlier anticoagulant treatment. A history of migraine must not preclude prompt and thorough investigation of juvenile stroke.

1 Schievnik WI, Mokri B, Piepgras DG. Spontaneous dissection of the cervicocephalic arteries in childhood and adolescence. *Neurology* 1994;**44**:1607-12.
2 Sturzenegger M. Spontaneous internal carotid artery dissection: early diagnosis and management in 44 patients. *J Neurol* 1995;**242**:231-8.
3 D'Anglejan-Chatillon J, Ribeiro V, Youl BD, Bousser MG. Migraine—a risk factor for dissection of cervical arteries. *Headache* 1989;**29**:560-1.
4 Buring JE, Herbert P, Romero J, Kittross A, Cook N, Manson J, *et al.* Migraine and the subsequent risk of stroke in the physicians' health study. *Arch Neurol* 1995;**52**:129-34.
5 Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, D'Anglejan-Chatillon J, *et al.* Case-control study of migraine and risk of ischaemic stroke in young women. *BMJ* 1995;**310**:830-3.
6 Welch KMA. Relationship of stroke and migraine. *Neurology* 1994;**44**(suppl 7):S33-6.

Grand Round—Queen Elizabeth Medical Centre, Birmingham

Systemic lupus erythematosus

Complicated by lupus nephritis and antiphospholipid antibody syndrome

Queen Elizabeth Medical Centre, Birmingham B15 2TH

BMJ 1997;314:292–5

continued over

Systemic lupus erythematosus is an idiopathic autoimmune disease. Studies based on hospital outpatient populations suggest a prevalence of 20-30/100 000, but recent community based pilot studies suggest that this figure may be as high as 200/100 000.[1] The peak age of presentation in Britain is 30-40 years, with a female:male ratio of 9:1. The clinical course in most patients is one of relapses and remissions. Renal involvement occurs in up to 75% of cases, and its treatment presents a major therapeutic challenge. In addition, a substantial proportion of cases are associated with an antiphospholipid antibody syndrome with recurrent thromboses and fetal loss. We present a case of systemic lupus erythematosus with coexisting glomerulonephritis and an antiphospholipid antibody syndrome.

Case history

In 1991 a previously healthy 21 year old woman presented to her local hospital with a swollen right leg. She smoked 20 cigarettes a day and took the contraceptive pill. Doppler ultrasonography confirmed a deep vein thrombosis in the right leg, and she

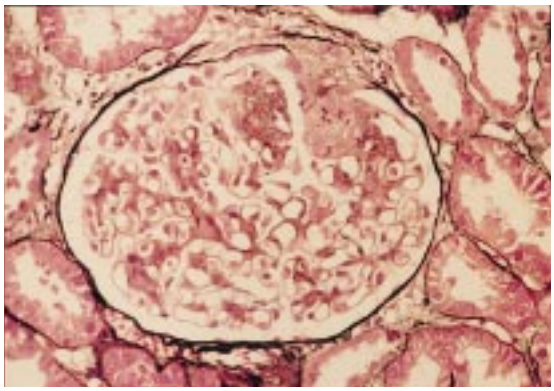

Fig 1 Glomerulus in renal biopsy, showing erratic mesangial expansion and segmental lesion with thrombosis, disruption of capillary loops, and adhesion to Bowman's capsule (haematoxylin and eosin ×300)

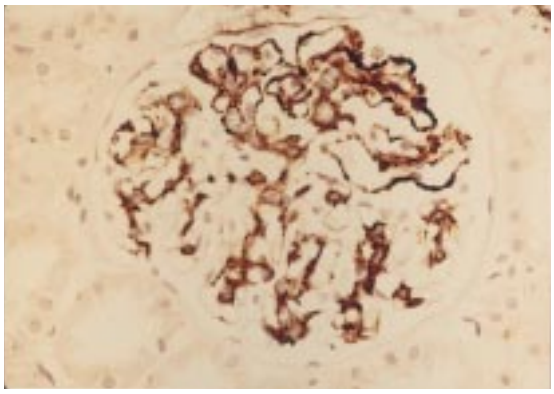

Fig 2 Glomerulus in renal biopsy, stained for complement component C9. There is heavy deposition in mesangium and on the outside of a few capillary loops (×350)

received anticoagulation with warfarin for three months. She stopped taking the contraceptive pill but continued to smoke. In May 1995 she developed a deep vein thrombosis in the left leg and again received anticoagulants for three months. Shortly after this admission she developed a facial rash and arthralgia of the small joints of the hands. There were no other systemic symptoms. On clinical examination the only notable findings were a classic malar facial rash and tenderness and swelling of the small joints of the hand.

Investigation results included an erythrocyte sedimentation rate of 38 mm in the first hour, antinuclear antibody titre of 1:1600, anti-double stranded DNA levels of 202 kU/l (normal range 0-75), and hypocomplementaemia (C3, 0.65 g/l (0.75-1.75 g/l), C4, 0.05 g/l (0.14-0.54 g/l)). IgM anticardiolipin antibodies, a subset of antiphospholipid antibodies, were strongly positive at 54 U/l (0-6), and IgG anticardiolipin antibodies were negative. Full blood count, prothrombin time, and partial thromboplastin time were normal. Urine analysis showed blood (+) and protein (+ + +), with the proteinuria quantified as 3.4 g/24 h. Serum concentrations of urea, creatinine, and electrolytes were normal, as were creatinine clearance and an ultrasound scan of the kidneys. These clinical and laboratory features supported a diagnosis of systemic lupus erythematosus with a secondary antiphospholipid antibody syndrome. The initial management was symptomatic with non-steroidal anti-inflammatory drugs.

In December 1995 she was referred to this hospital for further management and underwent a percutaneous renal biopsy. This showed a severe lupus nephritis with focal segmental, necrotising glomerular lesions associated with extracapillary proliferation typical of a vasculitic glomerulonephritis (fig 1). There were also features of a patchy membranous nephropathy and mesangial hypercellularity (fig 2). Oral cyclophosphamide (2 mg/kg/day) and oral prednisolone (60 mg/day) were started, and she was discharged home with weekly outpatient monitoring of disease activity and drug complications. Treatment with warfarin was withheld for one week after the biopsy owing to the risk of bleeding. Six days after the renal biopsy, however, she was re-admitted with a left ileofemoral venous thrombosis (fig 3) and was anticoagulated. There were no further complications, and three months after her renal biopsy she is well, her disease is clinically inactive, and serological markers of disease activity are improving. Treatment with cyclophosphamide has been changed to azathioprine (100 mg/day), and her current dose of prednisolone is 20 mg/day. She will remain on lifelong warfarin.

Comment

Systemic lupus erythematosus and lupus nephritis

The typical malar rash (as seen in this patient), together with a photosensitive, erythematous rash, is the commonest skin manifestation of systemic lupus erythematosus (seen in 60% of cases). She also developed an inflammatory arthritis affecting the small joints of the hands in the same distribution as rheumatoid arthritis. This feature is present in up to 95% of patients. The synovitis of systemic lupus erythematosus, however, does not progress to joint erosions and

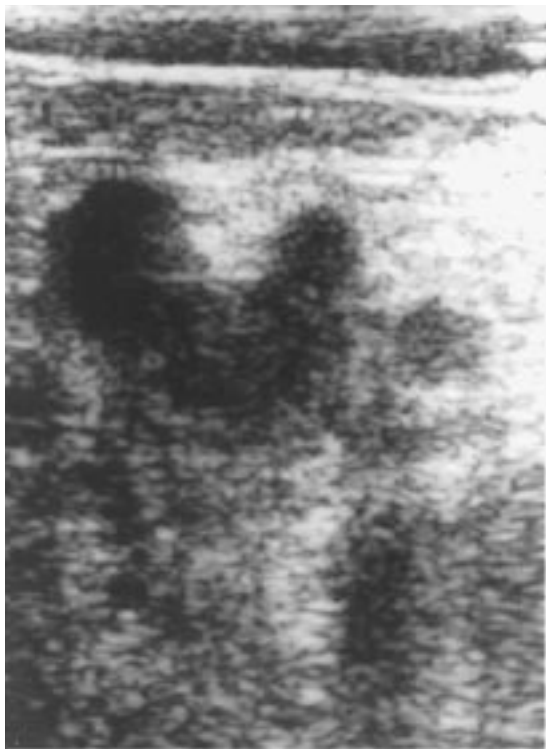

Fig 3 Doppler ultrasonography of left femoral vein showing echogenic thrombus in vessel lumen

Case presented by:
P Cockwell, *clinical research fellow in medicine (nephrology)*
Chairman:
C O S Savage, *senior lecturer in medicine (nephrology)*
Discussion group:
J J T Owen, *professor of anatomy*
R A Thompson, *professor of immunology*
C Gordon, *senior lecturer in rheumatology*
D Adu, *consultant nephrologist*
A J Howie, *senior lecturer in pathology*
M C Sheppard, *professor of medicine*
P M Stewart, *reader in medicine*
W A Littler, *professor of cardiology*
M J S Langman, *professor of medicine*
J Holmes, *consultant haematologist*

Antiphospholipid antibody syndrome

Clinical features
Recurrent thromboembolism (venous or arterial, or both)
Recurrent fetal loss
Livedo reticularis
Thrombocytopenia
Neurological events
Valvar heart disease

Laboratory features
High titre IgG anticardiolipin antibodies
High titre IgM anticardiolipin antibodies
Lupus anticoagulant

rarely causes deformities, although joint subluxation due to ligamentous laxity can occur. Antinuclear antibodies are almost always present. Complement levels and anti-double stranded DNA antibody titres are useful serological markers of disease activity in some patients. This patient's clinical and serological features were consistent with a diagnosis of systemic lupus erythematosus as defined by the classification criteria of the American Rheumatological Association.[2]

Clinically important renal disease occurs in 40-75% of cases of systemic lupus erythematosus, and in up to 25% of all cases this is the presenting feature.[3] Markers of renal involvement include haematuria, cellular casts, and proteinuria, which are interpreted in combination with the glomerular filtration rate. It is notable, however, that despite a normal creatinine clearance this patient had severe glomerulonephritis, indicating that renal histology is the gold standard in guiding the treatment of the renal lesion.

A range of glomerular lesions can be found in lupus nephritis, and typically more than one type of lesion is present.[4] This patient exhibited both segmental lesions of the vasculitic type (fig 1) and generalised glomerular disease with mesangial expansion and evidence of a patchy membranous nephropathy (fig 2). The treatment of patients with lupus nephritis depends on the severity of the renal lesion. Patients with a mesangial proliferative glomerulonephritis or membranous nephropathy usually respond to oral prednisolone, occasionally with the addition of azathioprine as a steroid sparing agent. Patients with a severe proliferative or necrotising glomerulonephritis or with extracapillary proliferation benefit from the addition of cyclophosphamide. A controlled study from the National Institutes of Health in the United States showed that oral prednisolone together with monthly intravenous pulses of cyclophosphamide (0.5-1 g/m^2) for six months, followed by quarterly pulses for a further two years, seemed more effective in reducing exacerbations than monthly pulses of methylprednisolone for six months.[5] This extended cyclophosphamide regimen was also more effective in reducing exacerbations than a six month course of cyclophosphamide. Debate continues about whether this pulse regimen is more effective and less toxic than oral prednisolone and cyclophosphamide with conversion at three to six months from cyclophosphamide to azathioprine. A controlled trial is needed to address this issue, particularly as, in contrast with cyclophosphamide, azathioprine is not gonadotoxic and is considered safe in a pregnant woman with lupus. The incidence of sustained amenorrhoea is as high as 60% in patients older than 25 years treated with cyclophosphamide for two years.[6]

Antiphospholipid antibody syndrome
The box shows the major clinical and laboratory features of the antiphospholipid antibody syndrome. The syndrome is characterised by the association of a range of clinical features with a heterogeneous group of antibodies that are targeted against phospholipids and phospholipid linked antigens and may cause a prothrombotic tendency.[7] Some patients manifest the phenomenon of lupus anticoagulant, which is an abnormality of coagulation, particularly of the intrinsic pathway, which does not correct on the addition of normal serum. The presence of lupus anticoagulant is highly correlated with antiphospholipid antibodies, although, as in this patient, these features can occur separately. The antiphospholipid antibody syndrome is frequently associated with systemic lupus erythematosus and other connective tissue diseases but is also recognised as a primary clinical syndrome.[8] In addition, antiphospholipid antibodies can occur without producing a prothrombotic tendency in various diseases, such as viral infections, malignancies, and end stage renal failure. No consensus definition exists for diagnosing the syndrome, but criteria have been proposed,[9] and our patient with strongly positive IgM anticardiolipin antibodies (more than five times the normal) and recurrent thromboses probably has this syndrome.

The antiphospholipid antibody syndrome is a non-inflammatory disorder, and specific immunotherapy does not seem effective in decreasing the prothrombotic tendency. There are no controlled studies to guide anticoagulant regimens, and retrospective studies suggest only a small decrease in the risk of thrombosis with low dose anticoagulation with warfarin (international normalised ratio <3). When the international normalised ratio is maintained at >3, however, these studies suggest that the relative risk of thrombosis is negligible.[10] If treatment is stopped rebound thrombosis tends to occur in the following six months (relative risk 4.55). Our patient developed her last thrombosis five months after warfarin was stopped. In pregnancy aspirin is currently recommended only if the patient has a history of one fetal loss. For two or more fetal losses or recurrent thromboses a regimen of low dose aspirin and subcutaneous heparin is advised.

Discussion

COSS: What do the renal biopsy findings predict about the long term renal prognosis?

AJH: The best predictor of long term renal prognosis is tubular and interstitial damage. In this patient there are lots of tubules and little chronic damage. Assuming, therefore, that the systemic lupus erythematosus remains in remission, her long term renal prognosis should be excellent.

DA: Other adverse prognostic factors in terms of renal survival include black race and impaired renal function at presentation. So one would predict a good long term outcome for this patient.

COSS: Why was the patient not given anticoagulants when she was referred to this hospital?

DA: A renal biopsy was thought to be necessary, and anticoagulation is a contraindication to renal biopsy. We decided, therefore, to start lifelong anticoagulation at the earliest one week after an urgent

biopsy, when the risk of haemorrhage from the biopsy was small. Unfortunately she developed a thrombosis before anticoagulation was started.

MCS: What do we know about the genetics of lupus and whether there are loci that predispose to the development of the disease?

CG: There are associations with several of the major histocompatibility antigens, particularly DR3 and in some communities DR2. Also the concordance of systemic lupus erythematosus in identical twins is 24%. You cannot account for that concordance from major histocompatibility complex associations alone, and inherited complement deficiencies and some complement alleles also predispose; studies of other candidate genes are in progress.

PMS: What are the mechanisms for early fetal loss, and is there any evidence that you can prevent it with aspirin, as obviously warfarin is contraindicated in this situation?

CG: It is suggested that thrombosis of placental vessels leads to retardation of intrauterine growth and poor development of the fetus. Aspirin prevents thrombosis, as does heparin, in patients with recurrent fetal loss, particularly if they have a history of thrombosis and have been taking warfarin before pregnancy. It is a complex situation, but it is clear that anticoagulation does decrease thrombosis and fetal loss during pregnancy in these patients.

WAL: Why are women so susceptible to systemic lupus erythematosus, and does this sex preference tell us anything about the pathogenesis?

RAT: Undoubtedly the female sex hormones have an influence on lymphocyte activity. For example, it is well known that in the mouse model of spontaneous lupus, onset of the disease is earlier in the female mouse, and you can retard it by giving male sex hormones. I am not sure, however, of the precise mechanisms by which sex hormones affect these aspects of lymphocyte function.

MJSL: A simple method might be to use record linkage to examine outcome in women who take oral contraceptives or hormone replacement therapy.

CG: Those studies are being done, and there is a lot of circumstantial evidence that in women who are at risk of lupus or who have lupus who start to take the contraceptive pill the disease flares up. This is particularly so if the pills contain high oestrogen levels.

JH: Is there a role for stem cell rescue in this disease?

DA: It is possible that high dose chemotherapy and autologous stem cell rescue might be a future therapeutic option, but there are real anxieties about the toxicity associated with such an approach. In lupus nephritis the main challenge is not so much achieving remission, which occurs in the large majority of patients, but the long term toxicity of our current treatments.[11] There are increasing problems with the potential for malignancy secondary to immunosuppressant drugs and osteoporosis due to steroids and vascular disease, although it is unclear whether this is due to the lupus, lipid abnormalities, or steroids.

COSS: Have recent advances in immunology contributed to our understanding of the disease?

JJTO: Certainly, gene-knockout mice in particular are providing valuable insights into the mechanisms driving the development of autoimmune diseases. One example is the development of lymphoproliferative disorders in the CTLA-4 knockout animal identifying this molecule as a critical negative regulator of T cell costimulation.

The *BMJ* welcomes grand rounds from other hospitals.

1 Johnson AE, Gordon C, Hobbs FDR, Bacon PA. Undiagnosed systemic lupus erythematosus in the community. *Lancet* 1996;347:367-9.
2 Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus (SLE). *Arthritis Rheum* 1982;25:1271-7.
3 Adu D, Cameron JS. Lupus nephritis. *Clin Rheum Dis* 1982;8:153-82.
4 Pontcelli C, Banfi G. Systemic lupus erythematosus (clinical). In: Cameron S, Davison AM, Grunfeld J-P, Kerr D, Ritz E, eds. *Oxford textbook of clinical nephrology*. Vol 1. Oxford: Oxford University Press, 1992:646-67.
5 Boumpas DT, Austin HA, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, *et al.* Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992;340:741-5.
6 Boumpas DT, Austin HA, Vaughn EM, Yarboro CM, Klippel JH, Balow JE. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med* 1993;119:366-9.
7 D'cruz D, Hughes G. Antibodies, thrombosis and the endothelium. *Br J Rheumatol* 1994;33:2-4.
8 Hughes GRV. The antiphospholipid syndrome—10 years on. *Lancet* 1993;342:341-4.
9 Alarcon Segovia D, Perez Vasquez ME, Villa AR, Drenkard C, Cabiedes J. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. *Semin Arthritis Rheum* 1992;21: 275-86.
10 Immunosuppressive drugs and their complications. *Drug Ther Bull* 1994;32:66-70.
11 Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid antibody syndrome. *N Engl J Med* 1995;332:993-7.

(Accepted 16 October)

ONE HUNDRED YEARS AGO

The condition of the miner today

Comparing the calling of the coal miner today with what it was sixty years ago, it must be acknowledged that it is safer and freer from risk to life and limb, that the conditions of labour are altogether better, and that coal mining, hard and trying as the work undoubtedly is, is not an unhealthy occupation. Running parallel with this improvement in his industrial conditions house accommodation is better, his children receive superior education, and his wages have risen. In the Thirties a miner's wage stood at 11s. a week, in 1872 they had risen to 23s. 4d., whilst in 1892 he received 33s. 3d. Taking the Northumberland miner, his wages per diem in the Thirties was 2s. 10d.; in 1872, 8s.; 1873, 9s.; and in 1892, 6s. 8d., and on an average he would work five days a week. Along with the rise in wages his hours of toil have been shortened from 12 hours a shift to 7 or 8. With more leisure at his command, and the benefits of a larger education, increased wages, and their greater purchasing power, we may say that in the improved social, moral, and financial condition of the coal miner of today we find a fairly accurate reflection of the general industrial prosperity characteristic of the Queen's reign.
(*BMJ* 1897;i:1666.)