enhances the production of rheumatoid factor in mice injected with lipopolysaccharides, a good model for the induction of this autoantibody.[11] There are also interesting ways in which oestrogens may enhance the pathogenicity of autoantibodies.[12] The interactions between gonadal steroids and the immune system are, however, complicated and may result in enhancement or suppression of different immune responses.[13] In addition, many of the published data ignore the contrasting effects of regular and cyclic exposure to oestrogens.[14] The neuroendocrine system has multiple effects on immune responses, and it is oversimplistic to extrapolate from the experimental results of giving oestrogen to a disease such as rheumatoid arthritis.[15]

Current ideas about the aetiopathogenesis of autoimmune diseases centre on the genetic control of autoantigen presentation to T lymphocytes by specialised cells,[16] and it is here that sex differences seem most likely to operate. The effects of ovarian steroids on gene expression may prove at least as relevant as those on immune responses.[17]

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1 Ahmed SA, Talal N. Sex hormones and autoimmune rheumatic diseases. *Scand J Rheumatol* 1989;**18**:69-76.
2 Hazes JMW, Dijkmans AC, Vandenbroucke JP, De Vries RRP, Cats A. Pregnancy and the risk of developing rheumatoid arthritis. *Arthritis Rheum* 1990;**33**:1770-5.
3 Blank M, Mendlovic S, Fricke H, Mozes E, Talal N, Shoenfeld Y. Sex hormone involvement in the induction of experimental systemic lupus erythematosus by a pathogenic anti-DNA idiotype in naive mice. *J Rheumatol* 1990;**17**:311-7.
4 Schuurs AHWM, Verhuel HAM. Sex hormones and autoimmune disease. *Br J Rheumatol* 1989;**28**(suppl 1):59-61.
5 Vandenbroucke JP, Hazes JMW, Dijkmans BAC, Cats A. Oral contraceptives and the risk of rheumatoid arthritis: the great transatlantic divide? *Br J Rheumatol* 1989;**28**(suppl 1):1-3.
6 Hazes JMW, Dijkmans BAC, Vandenbroucke JP, De Vries RRP, Cats A. Reduction of the risk of rheumatoid arthritis among women who take oral contraceptives. *Arthritis Rheum* 1990;**33**:173-9.
7 Van Zeben D, Hazes JMW, Vandenbroucke JP, Dijkmans BAC, Cats A. Diminished incidence of severe rheumatoid arthritis associated with oral contraceptive use. *Arthritis Rheum* 1990;**33**: 1462-5.
8 Hernandez-Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, *et al*. Exogenous sex hormones and the risk of rheumatoid arthritis. *Arthritis Rheum* 1990;**33**:947-53.
9 Hannaford PC, Kay CR, Hirsch S. Oral contraceptives and rheumatoid arthritis: new data from the Royal College of General Practitioners' oral contraception study. *Ann Rheum Dis* 1990;**49**:744-6.
10 Carette S, Marcoux S, Gingras S. Postmenopausal hormones and the incidence of rheumatoid arthritis. *J Rheumatol* 1989;**16**:911-3.
11 McCruden AB, Stimson WH. Rheumatoid factor induction in the mouse: sex differences and the effect of the sex steroids. *Immunopharmacology* 1990;**19**:33-8.
12 Furukawa F, Lyons MB, Lee LA, Coulter SN, Norris DA. Estradiol enhances binding to cultured human keratinocytes of antibodies specific for SS-A/Ro and SS-B/La. *J Immunol* 1988;**141**: 1480-8.
13 Grossman CJ. Interactions between the gonadal steroids and the immune system. *Science* 1985;**227**:257-61.
14 Erbach GT, Bahr JM. Effect of chronic or cyclic exposure to estradiol on the humoral immune response and the thymus. *Immunopharmacology* 1988;**16**:45-51.
15 Wilder RL, Sternberg EM. Neuroendocrine hormonal factors in rheumatoid arthritis and related conditions. *Curr Opin Rheumatol* 1990;**2**:436-40.
16 Demaine AG. The molecular biology of autoimmune disease. *Immunol Today* 1989;**10**:357-61.
17 Rories C, Spelsberg TC. Ovarian steroid action on gene expression: mechanisms and models. *Annu Rev Physiol* 1989;**51**:653-81.

Adenoma screening and colorectal cancer

The need for screening and polypectomy is unproved

Ever since Morson's seminal paper in 1974[1] clinicians have been left in little doubt by their pathologist colleagues that the vast majority of colorectal cancers arise from adenomas rather than de novo. Yet epidemiological data exists to contradict the inevitability of the adenoma-carcinoma sequence. The question has been brought into focus by a recent King's Fund consensus statement, which, while acknowledging the lack of scientific data on which to base practice makes firm recommendations on treatment and screening.[2]

The evidence for the adenoma-carcinoma sequence seems incontrovertible to pathologists, who daily observe the progression of adenomas to cancer and whose bread and butter includes the staging of colorectal carcinoma. Surgeons, faced with the annual toll of 20 000 deaths from colorectal cancer in Britain[3,4] and overall five year survival figures of less than 40%,[5] are only too glad to perform polypectomies in their attempts to arrest the disease. In support of the orthodox view is the fact that adenomas and carcinomas increase in parallel with age. Except in the rare familial form, cancer of the colon and rectum is a disease of older people, the risk doubling with every decade over 40 years.[3] Adenomas also increase in incidence with age and are common only in countries with a high incidence of large bowel cancer.[6]

Against the inevitability of the adenoma-carcinoma sequence, there are, however, two pieces of evidence. Firstly, necropsy studies of asymptomatic patients show that the prevalence of adenomas in Britain is 34% in 50-60 year olds, rising to 40-60% in those over 75.[7-9] These data are supported by studies in the United States[10-13] and Scandinavia.[14,15] Compare these figures with those of the prevalence of cancer. Necropsy studies find a prevalence of cancers in asymptomatic patients in comparable age groups of 1·6% to 3%,[9,16,17] whereas the actual annual incidence of colorectal cancer in the general population is less than three in 10 000,[4,5] rising to three in 1000 people over 75. Owing to the poor survival rates the prevalence of colorectal cancer in the population is much lower: less than two per 10 000 overall and less than seven per 10 000 aged over 75.[4,5] Thus the epidemiological evidence suggests that most polyps do not give rise to cancers and that when they do most of the cancers do not present a lifetime risk.

The second piece of epidemiological evidence comes from those few studies that have attempted to follow the natural course of polyps. In a retrospective radiological study of 226 symptomatic patients with large adenomas (greater than 1 cm) Stryker *et al* suggested a cumulative risk of a diagnosis of cancer at the site of the index polyp at five years, 10 years, and 20 years of 2·5%, 8%, and 24% respectively.[18] A two year endoscopic follow up of 215 polyps under 5 mm detected in a population screening study showed that of 35 polyps classified as adenomas, 17 grew, 13 remained the same, and five reduced in size. Even those that grew did so slowly, no polyp reaching more than 5 mm in two years.[19] An epidemiological comparison of the prevalences of adenomas and carcinoma in Norway calculated the annual risk of an adenoma converting to a carcinoma to be 0·25% for all adenomas, 3% for adenomas greater than 1 cm, 17% for villous adenomas, and 37% for those villous adenomas showing severe dysplasia.[20]

Can the risk of the development of a malignant adenoma be predicted? Currently there are only three measures—histological characteristics, size, and the degree of dysplasia—that appear to determine the progression of an adenoma to malignancy, but all are fallible. The type of adenoma most likely to transform itself is the villous adenoma, which accounts for only 10% of adenomas occurring in the large bowel; of these, fewer than half will actually become malignant.[21] The size of polyp is important, but again only 46% of polyps more than 2 cm will contain an invasive focus,[21] and those adenomas that will grow to such a size cannot be identified. An increasing degree of dysplasia increases the

likelihood of an adenoma becoming malignant, but in practice this factor is severely weakened by interobserver variation.[22]

The key questions for clinicians still remain unanswered—who should be screened, when should a polyp be removed, and what follow up should be given. The King's Fund consensus panel lacked the data to reach an answer on the natural course of adenomas, and its recommendations were a balance of the available scientific data and the need for clinical application.[2] Thus a primary recommendation required future research efforts to be directed to the natural course of the adenoma, dysplasia, and cancer and the effects of intervention.

The panel also made recommendations—admittedly pragmatic—to aid clinical decision making in patients with symptoms. Thus in symptomatic patients with a polyp the whole large bowel should be examined and polyps greater than 5 mm removed. Follow up is not recommended for patients with a single small tubular rectal adenoma and those aged over 75, but those with a large adenoma or any type of multiple adenomas should undergo colonoscopy every three to five years. This last recommendation has potentially huge implications for the population.

Despite being a routine procedure polypectomy has not been evaluated in a controlled trial and is clinically unproved. Many people may undergo polypectomy to prevent one potential cancer which may not present even a lifetime risk. Colonoscopy and polypectomy carry their own risks of haemorrhage and perforation,[23] including the 1-2% risk of slow perforation or the burnt colon syndrome as a consequence of using hot biopsy forceps on small lesions.[19] There are also the hazards of bowel preparation,[24] the costs of unnecessary procedures (colonoscopies cost £107-250),[25] and above all the costs to the patient in anxiety, discomfort, and time.

Current research techniques have yielded no predictive tools to aid clinicians. The early hopes for tumour markers in high risk or asymptomatic patients have not come to fruition,[26] although molecular genetics may have a potential application. Even molecular genetics, however, cannot provide the definitive answer without epidemiological support. The current trials of faecal occult blood testing[27] and the increasing activity in genetic screening make it even more imperative that a coherent strategy of NHS clinical research is undertaken into the natural course of early disease. This calls for a combination of studies, the most urgent being a randomised controlled trial of polypectomy. We cannot continue to base clinical practice on empirical evidence alone. It is time to overhaul the epidemiological, clinical, and histological evidence and increase our knowledge of the adenoma-carcinoma sequence.

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1 Morson BC. Evolution of cancer of the colon and rectum. *Cancer* 1974;**34**:845-9.
2 King's Fund Centre. Cancer of the colon and rectum: the seventh King's Fund consensus statement. *Br J Surg* 1990;**77**:1063-5.
3 Cancer Research Campaign. *Facts on cancer. Mortality in the U.K.* London: Cancer Research Campaign, 1988.
4 Office of Population Censuses and Surveys. *Cancer statistics registrations. Cases of diagnosed cancer registered in England and Wales 1985.* London: HMSO, 1990. (Series MB1 No 18.)
5 Office of Population Censuses and Surveys. *Cancer statistics. Incidence, survival, and mortality in England and Wales.* London: HMSO, 1981. (Studies on medical and population subjects No 43.)
6 Burkitt DP. Epidemiology of cancer of the colon and rectum. *Cancer* 1974;**28**:3-13.
7 Armiski TC, Maclean DW. Incidence and distribution of adenomatous polyps of the colon and rectum based on 1000 autopsy examinations. *Dis Colon Rectum* 1964;**7**:249-61.
8 Clark JC, Collan Y, Eide TJ, *et al.* Prevalence of polyps in an autopsy series from areas with varying incidence of large bowel cancer. *Int J Cancer* 1985;**36**:179-86.
9 Williams AR, Balasooriya BAW, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. *Gut* 1982;**23**:835-42.
10 Atwater JS, Bargen JA. The pathogenesis of intestinal polyps. *Gastroenterology* 1945;**4**:395-408.
11 Chapman I. Adenomatous polyps of the large intestine. Incidence and distribution. *Ann Surg* 1963;**157**:223-6.
12 Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel. An autopsy survey. *Cancer* 1979;**43**:1847-57.
13 Blatt LJ. Polyps of the colon and rectum: incidence and distribution. *Dis Colon Rectum* 1961;**4**: 277-82.
14 Eide TJ, Stalsberg H. Polyps of the large intestine in northern Norway. *Cancer* 1978;**42**:2839-48.
15 Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. *Cancer* 1982;**49**:819-25.
16 Delendi M, Gardivian D, Riboli E, Sasco AJ. Latent colorectal cancer found at necropsy. *Lancet* 1989;ii:1331-2.
17 Stemmermann GN. Cancer of the colon and rectum discovered at autopsy in Hawaiian Japanese. *Cancer* 1966;**19**:1567-72.
18 Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL, *et al.* Natural history of untreated colonic polyps. *Gastroenterology* 1987;**93**:1009-13.
19 Hoff G, Foerster A, Vatn MH, Sauar J, Lorsen S. Epidemiology of polyps in the rectum and colon. Recovery and evaluation of unresected polyps 2 years after detection. *Scand J Gastroenterol* 1986;**21**:853-62.
20 Eide TJ. Risk of colorectal cancer in adenoma bearing individuals within a defined population. *Int J Cancer* 1986;**38**:173-6.
21 Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975;**36**:2251-70.
22 Brown LJR, Smeeton NC, Dixon MF. Assessment of dysplasia in colorectal adenomas; an observer variation and morphometric study. *J Clin Pathol* 1985;**38**:174-9.
23 Ott DJ, Gelfand DW, Yu MC, Munitz A. Colonoscopy and barium enema: a radiologic viewpoint. *South Med J* 1985;**78**:1033-5.
24 Phipps R, Fraser SCA. Faecal peritonitis induced by picolax. *BMJ* 1987;**295**:1027.
25 Walker A, Whynes DK, Chamberlain J. The hospital costs of diagnostic procedures. *J Clin Epidemiol* 1991 (in press).
26 Cooke T, Makin C. The use of tumour markers in clinical practice. *Baillieres Clin Gastroenterol* 1989;**3**:713-26.
27 Hardcastle JD, Chamberlain J, Sheffield J, *et al.* Randomised controlled trial of faecal occult blood screening for colorectal cancer: results for the first 107 349 patients. *Lancet* 1989;i:1160-4.

Forensic use of DNA tests

Courts need ways to assess the reliability of new scientific methods

Heralded as revolutionary, the forensic use of DNA profiling has grown dramatically since the technique was developed in 1985.[1] Because DNA testing has the potential for identifying people with an extremely high degree of certainty—so high that the danger exists that DNA evidence will override any other—it is important to ensure that there is a correspondingly high degree of certainty about the validity and reliability of the tests.

Yet DNA profiling was subjected to only limited scrutiny in the courtroom before 1989, when it received the first serious challenge to its forensic use. In 1989 the judge in a criminal case in the United States, People v Castro, excluded certain DNA evidence because of flawed laboratory techniques.[2] The Castro decision focused attention on the validity and reliability of DNA tests for forensic casework; the need for standards and quality assurance for DNA analysis and interpretation; the importance of allowing the defence access to forensic science resources; and, more generally, the admissibility of novel scientific evidence.

The validity of the molecular and genetic principles underlying DNA analysis is generally accepted. What is in dispute is the application of the technology to forensic samples—especially those taken from the scene of crime, which may have deteriorated, be contaminated, or be very