

Maybe part of the answer to the riddle of the urethral syndrome lies in some micro-organism as yet undiscovered. After all, *Legionella pneumophila*, *Borrelia burgdorferi*, and *Helicobacter pylori* were unknown pathogens 15 years ago.

The urethral syndrome is common and distressing and causes much unhappiness. It inevitably results in the overuse of antibiotics and proliferation of bacteria resistant to antibiotics. It deserves more thorough investigation than it has received in the past.

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Sex hormones, autoimmune diseases, and immune responses

More implications for research than treatment

Autoimmune diseases are far more common in women than in men. For example, the female to male ratio is 9:1 in systemic lupus erythematosus and 4:1 in rheumatoid arthritis.¹ These observations suggest that sex hormones may help to determine this susceptibility. Though some research findings seem to confirm this suggestion, others are more equivocal; and more recent work suggests a much more complex role for sex hormones in autoimmune diseases.

Some of the most suggestive evidence for the influence of sex hormones relates to rheumatoid arthritis. Thus rheumatoid arthritis begins more commonly in the child-bearing years, and both the onset of disease and exacerbations are associated with the postpartum period. Pregnancy is also associated with spontaneous remissions and may itself reduce the risk of developing rheumatoid arthritis.² Similarly, autoimmune thyroiditis is encountered as a transient postpartum disorder.

There are also interesting animal models of human autoimmune disease whose natural course may be drastically altered by manipulating sex hormone concentrations. NZB x NZW F1 (BW) mice develop progressive and eventually fatal immune complex nephritis and autoantibodies resembling human lupus. Female BW mice, however, succumb to the disease far earlier than male mice. Prepubertal orchidectomy or the administration of oestrogens or progesterone accelerates the renal disease and the resulting mortality in male mice. Conversely, dihydrotestosterone retards progression of disease in female BW mice.¹ Likewise, experimental systemic lupus erythematosus induced in normal mice can be rapidly accelerated by oestrogens and retarded by testosterone.³

The practical implication for clinical medicine is that hormonal manipulation may alter susceptibility to autoimmune disease. There is some evidence that oral contraceptives containing oestrogen provoke exacerbations of systemic lupus erythematosus,⁴ but the influence of oral contraceptives on susceptibility to rheumatoid arthritis has proved more contentious. Some studies have shown a significant reduction in the incidence of the disease in women using oral contraceptives.⁵ For example, among a population

attending a Dutch clinic information on contraceptive practice was obtained from 135 young women with rheumatoid arthritis of recent onset and 378 controls with other rheumatic disorders.⁶ The risk of developing the disease was found to be significantly reduced by past or present use of oral contraceptives, and protection was greater in women aged 31-40 at the onset of symptoms and with a family history of rheumatoid arthritis. Further analysis suggested that protection was confined to patients with severe forms of the disease; the incidence in women who had used the pill before the onset of symptoms was less than half that in women who had never used oral contraceptives.⁷

These findings were not confirmed in a study of different design in the United States.⁸ The incidence of rheumatoid arthritis was determined in a cohort of 121 700 female nurses aged 35-55 who were followed up regularly from 1976 to 1984. Past use of oral contraceptives did not reduce their risk of developing rheumatoid arthritis.

Many factors account for the differing results of such surveys. Some studies have drawn on patients attending clinics and others on normal populations, while methods of collating data and statistical analysis have varied greatly. The chronological order of the reported studies may also have influenced the results as there is some evidence that the incidence of rheumatoid arthritis, particularly its more severe forms, may be declining.^{5,9} The influence of postmenopausal hormone replacement is less controversial: there is no evidence that this treatment affects the incidence of the disease.^{8,10} Thus doctors may reasonably infer that prescribing female sex hormones is unlikely to affect the risks of developing rheumatoid arthritis. These hormones are also unlikely to affect the clinical course of established disease.

How does the female preponderance of autoimmune diseases illuminate the pathogenesis of these disorders? As immunopathological mechanisms are implicated the greater immune responsiveness of women to conventional antigens might be supposed to be responsible for the sex differences.¹ And at first sight this enhanced responsiveness might seem attributable to sex hormones. Certainly, 17 β -oestradiol

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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Adenoma screening and colorectal cancer

The need for screening and polypectomy is unproved

Ever since Morson's seminal paper in 1974¹ 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 States¹⁰⁻¹³ 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