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Genital wart virus infections: nuisance or potentially lethal?

Until quite recently warts were regarded as seemingly benign and of no more than nuisance value; but in the past five years the wart and its infective component the wart virus have assumed greater importance. The term wart virus, or more correctly human papillomavirus (HPV), is used to describe a heterogeneous group of small DNA viruses; of the 24 types, at least four are specific to the urogenital tract.[1] Each type of virus usually produces lesions with distinctive histological and topographical features—for example, HPV 1 causes plantar warts and HPV 6 condyloma acuminatum.

Current concern is focused on the part that human papillomavirus may play in the cause of genital tract cancer, especially in the cervix, and how far the changing pattern of genital cancer and precancer might be related to the doubling in the frequency of clinically obvious genital warts in both sexes in the past eight years.[2] The prevalence of these lesions must be a gross underestimate as most are not reported—and the preclinical or flat warts that occur on the cervix are visible only through the magnified illumination of the colposcope. In many colposcopic studies nearly one third of all cervices have evidence of an associated human papillomavirus lesion.[3] The increase in the frequency of warts coincides with a similar dramatic increase of 60% in the past 15 years in the national prevalence of precancerous cervical lesions, especially in young women.[4] In the age group 25 to 34, for instance, the number of smears taken rose by only 11%, while there was a staggering 117% rise in the numbers of carcinomas in situ. A recent study from Aylesbury reported a nearly fourfold increase in carcinoma in situ in 30-39 year olds over a 15 year period, which made the authors wonder if we are in for "an epidemic of cervical precancer."[5] More ominous is the increase in mortality in the under 35s, which has doubled over the past 10 years.[4] And to add further to the concern recent evidence has suggested that cytological screening may not be detecting the precancer or cancerous lesions until late. The report of Bamford and colleagues from the Margaret Pyke Centre in London on 100 women with proved carcinoma in situ showed that nearly 60 of them had had negative cytological reports four years or more before the lesion was diagnosed—and, even more worrying, 27 had had negative smears only 24 months before diagnosis.[6] This suggests that some of these lesions had developed rapidly and might be evidence for an "infective process." How possible is it that human papillomavirus might be the agent responsible for this and the other developments?

Within the past six months Zur Hausen's group in Germany and workers in Britain have found evidence of certain human papillomavirus types in cervical precancer and cancer. With the techniques of DNA-DNA hybridisation with radiolabelled human papillomavirus probes, HPV 6 has been found in 12 of 19 biopsy specimens of premalignant lesions in a group of London women,[7] and HPV 11 was detected in five out of five similar lesions in Germany.[8] More serious is the finding of HPV 16 genomes in almost two thirds of 18 cervical cancers[9] and of a newer type, HPV 18, in a fifth of them (Zur Hausen, personal communication, 1983). With immunochemical staining with an antibody common to human papillomavirus antigen (both human and animal) the antigen may be detected in 20-40% of precancerous lesions.[10,11] These and other studies were discussed in July at the European Molecular Biology Organisation workshop on human papillomavirus held in Sweden, where it was suggested that the HPV 16 and 18 types represented high risk groups as regards malignant progression, while HPV 6 and 11 represented low risk types. Added to this incriminating data is Baird's serological evidence which showed that 93% of women with cancer of the cervix possessed in their sera an IgG antibody against a group specific papillomavirus antigen.[12] Sixty per cent of women with premalignant lesions had positive sera while none of Baird's adult or child controls possessed the antibody.

All this evidence seems to indicate that there is an association between human papillomavirus and cervical cancer; but the participants at the meeting of the European Molecular Biology Organisation were concerned that it might be indicative only of a casual rather than causal relation. At present the question remains unanswered.

Certainly the proposed carcinogenic potential of human papillomavirus is supported by the part played by papillomaviruses in the production of animal cancers. For example, the Shope papillomavirus induces papillomas to convert to skin carcinomas in domestic rabbits, albeit with the help of a cofactor.[13] Bovine papillomas of the oesophagus and intestine caused by bovine papillomavirus type 4 progress to cancer, again with the aid of a cofactor, bracken.[14] Ultraviolet light seems to be a cofactor in the induction of ocular tumours in cattle exposed to sun and infected by papillomavirus[15] and of tumours of the exposed skin of sheep infected by this virus.[16]

The need for a cofactor for human papillomavirus to exert its malignant potential is supported by the results of recent

studies of the rare skin lesion epidermodysplasia verruciformis, a condition in which papillomas undergo malignant conversion almost exclusively in sites exposed to the sun.[17] In these patients HPV 5 DNA has been found, and recently Lutzner *et al* have found the same HPV type in cancers on skin exposed to the sun in an immunosuppressed recipient of a renal allograft.[18] Again the cofactor seems to be sunlight in association with immunosuppression or depression.

Two other possible cofactors in conjunction with human papillomavirus are the putative aetiological agents in carcinoma of the cervix, infection with herpes simplex virus, and smoking. The evidence supporting an association between herpes simplex virus and cancer of the cervix is extensive,[19] but specific DNA can be found in only a handful of cancers of the cervix,[20] making it difficult to envisage herpes simplex virus as a direct carcinogen. As Zur Hausen has pointed out, however, herpes simplex virus might play a part as a tumour initiator with human papillomavirus acting as a promoter.[21] In a similar way smoking might be acting as either a cofactor or promoter in the presence of human papillomavirus in inducing cervical neoplasia. Trevathan has recently shown in a well controlled study that the relative risk of women developing carcinoma in situ after 12 or more "pack years" of exposure to cigarettes is increased by a factor of nearly 13.[22] Possibly nicotine might have a toxic effect on epithelium, facilitating the entry of human papillomavirus.

What about other genital cancers and human papillomavirus? Premalignant vulvar disease may be becoming more common and may be related to human papillomavirus.[23] Evidence from many centres has also suggested that condyloma acuminatum and vulvar cancer are associated.[24] Indeed, HPV 6 genome has been isolated from a genital verrucous carcinoma[25] and a vulvar carcinoma in situ, and HPV 3 related genome has been found in vulvar cancer.[25] Of more practical importance is the observation that almost a third of 50 young women attending a sexually transmitted disease clinic with simple vulval warts had a premalignant cervical lesion after six months of observation.[26]

What should the gynaecologist and the general practitioner do about this epidemic of wart virus infections? The latter may well be faced with up to 3% of cytological smears showing evidence of infection with human papillomavirus[27] and the former will find that between 60% and 90% of cervical premalignant lesions show histological evidence of human papillomavirus.[28] Cytological smears with human papillomavirus indicate that a potential mutagenic agent exists in the genital tract and that more than usual surveillance is necessary; yearly follow up may be needed. Any abnormal cytological appearance associated with human papillomavirus is an indication for referral for colposcopy. Finding human papillomavirus within premalignant cervical tissue may present a most disturbing picture to the pathologist, whether he is experienced or not. Such confusion has been caused that an editorial in *Acta Cytologica* has recently recommended to clinicians that the finding of human papillomavirus in premalignant lesions "should not modify the clinical approach to these lesions."[29]

We do not know what the malignant potential of the lesions associated with human papillomavirus is. We suspect that for the higher grades of premalignancy it is increased. The lesser grades (for example, mild dysplasia)—which are increasing at an alarming rate[30]—present a real dilemma for clinicians. They are usually found in young women, have a high regression rate, and are universally infected with human papillomavirus. Their management is controversial. It might be argued that, as most are lesions induced by human papillomavirus, an aggressive approach should be adopted—but in practice only a few of these lesions have the aneuploid nuclear DNA distribution or possess abnormal mitotic figures, two morphological features that indicate the likelihood of progression.[31] The gynaecologist does not have ready instant access to such analysis and so is left undecided about treatment. We believe that these lesions should be destroyed—for the following reasons. These young women are at an increased risk for the later development of the higher grades of premalignancy and indeed of cancer of the cervix, especially if the lesion affects a large area of the cervix. The lesions are relatively easy to treat by either laser[32] or electrodiathermy,[33] success rates of 97% being reported. Finally, the anguish engendered in young women faced with regular cytological check ups, sometimes at three monthly intervals, may far outweigh any inconvenience caused by immediate destructive treatment.

The recent study showing an increased rate of early invasive cervical cancer in users of oral contraceptives as compared with intrauterine devices is disturbing as it raises the possibility that an association may exist between the coitally transmitted mutagen, in this case HPV, and the use of sex hormones.[34] Possibly the hormones might stimulate HPV infection and replication in the cervix. Glucocorticosteroids are known to increase the synthesis of mouse mammary tumour virus in cell culture,[35 36] and progesterone and oestradiol benzoate increase the replication of the small DNA tumour virus polyoma in mouse tissue culture.[37] Vulvar warts tend to increase in size during pregnancy, and again this might be a hormonal effect.[38 39] Clearly this relation needs careful and urgent clinical and biological investigation.

Unfortunately, human papillomavirus is probably here to stay for many years, especially if current sexual practices persist. We should not be surprised if both premalignant and malignant genital disease continue to become more common. Only by surveillance, both clinical and cytological of the whole lower genital tract, will this "epidemic" be contained.

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Where's the block?

Twenty five years have now passed since the first implantation of a cardiac pacemaker in man.[1] More than 500 000 patients have had units implanted and no dispute exists about the safety and efficacy of therapeutic pacing for symptomatic bradycardia.

So the recent publication of the quadrennial world survey of cardiac pacing makes depressing reading for British cardiologists and should concern the British public.[2] The proportion of the population fitted with pacemakers in Britain is only one fifth of that in the major developed countries; it is less than half the average in western Europe and only slightly greater than the average in eastern Europe. Only Greece, Spain, and Portugal in western Europe provide a poorer service to the community in terms of pacing, and historically Britain now lags some 14 years behind the United States in rates of implantation.

These data demand both questioning and interpretation. The figures themselves are probably correct. The world survey of cardiac pacing has been carefully built up over many years from international contacts, and many countries (of which Britain was the first) now operate complex interactive computerised data bases which link the pacing centres. The nature of the procedure and the availability of manufacturers' sales figures for cross checking make pacing practice an ideal subject for accurate medical audit.

By nature British medical practice is conservative, and it might be argued that the disparity with other countries is due to their unnecessary implantation of large numbers of pacemakers. If the data are broken down to represent implantation rates for "hard" (syncope) and "soft" (heart failure/cerebral dysfunction) indications the results do not not show much change. For the "hard" indications the British rate is 31% of the United States equivalent, and only Portugal in western Europe has a lower implant rate. The numbers of pacemakers implanted for "soft" indications are three times greater in the United States than in Britain, but these account for only 18% of the overall number in the United States. Nor can variation in the distribution of the population by age and sex account for the differences: Britain has a relatively high proportion of people in the older age groups, in whom heart block is more prevalent.[3]

No relation exists between implant rate and physician fee for service in North America and western Europe, and remarkably there is an inverse relation with the direct cost of a pacemaker. Britain is a prestigious, highly competitive, and cost conscious market for pacemaker manufacturers: for equivalent devices prices in the United States are 300% higher and in Europe 150% higher than in Britain. This is all the more surprising since there is no British owned manufacturer and in theory no external control of buying policy is imposed on British cardiologists. No evidence exists that direct costs influence implant rates in Britain, though the choice of device is subject to intense restriction on regional costs (P Sleight, personal communication). With the reduction in worldwide rate of growth of the pacemaker market Britain seems unlikely to continue to benefit from low prices at the expense of other countries.

If the figures are correct and the problem does not relate to economic factors then the system of medical practice itself must be examined. Cardiology in Britain is highly centralised. The 62 pacing centres on average implant more than 100 generators each year, and 87% have full specialised cardiovascular services—compared with figures in the United States