Tumour virology

Papilloma viruses and cervical tumours

from Lionel Crawford

THE epidemiology of cancer is, in general, not what would be expected for a group of diseases caused by infectious agents but there are some exceptions. Tumours of the uterine cervix and elsewhere in the female genital tract as well as cancer of the penis appear to involve infection. Cervical cancer is strongly correlated with sexual promiscuity both of women and their male partners^{1,2}. Genital warts, which are caused by papilloma viruses, are sexually transmitted and their incidence is also correlated with promiscuity. About half the women with vulvar genital warts examined in one study also had evidence of abnormalities of the cervix³. It was natural, then, for zur Hausen to ask whether papilloma viruses are implicated in the causation of cervical tumours as well as genital warts⁴. The answer seems likely to be yes.

The incidence of genital warts, the incidence of cervical cancer and the mortality from cervical cancer, especially among women under 35 years old, have all increased markedly over the last two decades^{5,6}. If we are to believe the results of surveys which have featured so prominently in the Sunday papers, there has been a substantial increase in sexual activity in this country over the same period, coupled with a decrease in the age of first sexual experience. The increasing mortality from cervical cancer is particularly striking since, together with lung cancer (associated with smoking cigarettes and still rising in women), the overall mortality due to cancer has been falling slowly. This adds urgency to the efforts being made to identify an infectious cause of cervical tumours. Intrinsically, the problem is difficult because any sexually transmitted agent is likely to be more frequently present in promiscuous than celibate or non-promiscuous women, so a simple demonstration of the presence of virus or its traces in tumours is by no means enough. Certainly most women with cancer of the cervix have been exposed to papilloma virus; one study reports antibodies against a papilloma virus group specific antigen in the serum of 93 per cent of cervical cancer patients⁷, and, surprisingly, none in the controls.

It would be much more convincing if evidence of persistent viral DNA could be found in tumours (although this is not required if the mechanism of transformation is postulated to be 'hit and run', as has been suggested for herpes viruses). Repeated efforts to show that herpes simplex type II DNA persists in cervical tumours have produced some positive results

but at best in only a small minority of tumours. Similar studies with papilloma viruses were initially also rather disappointing but the reasons are now clear. Human papilloma viruses (HPVs) comprise a very heterogeneous group with more than 24 different types already isolated. The different types are generally only weakly related by the criterion of nucleic acid hybridization. Thus, in general, it is necessary to probe tumour tissue with the corresponding HPV DNA probe if the presence of a particular type of HPV is to be reliably detected.

Largely as a result of the efforts of zur Hausen and his group in Germany, DNAs from several previously unknown types of HPV have recently been cloned and characterized. Four of the types — HPV 6, 11, 16 and 18 — are commonly associated with various lesions of the genital tract. Types 6 and 11 are associated with genital warts (condylomata acuminata) and with premalignant lesions of the cervix but rarely with carcinomas^{8,9}. Conversely, types 16 and 18 are predominantly associated with tumours. In one study, HPV 16 DNA was detected in over 60 per cent of the cervical tumours examined but less often in condylomata acuminata where it was found in conjunction with the more usual HPV 6 and 11 (ref. 10). In premalignant lesions of the cervix, HPV 16 is most frequently found in association with histologically abnormal mitotic figures, suggesting that the lesions are likely to progress to malignancy¹¹; the same may be true for lesions elsewhere in the genital tract¹². Seven out of eight carcinomas *in situ* of the vulva were recently found to contain HPV 16 (D. McCance, personal communication). HPV 18 is also found predominantly in tumours; zur Hausen's group report its presence in about 25 per cent of cervical tumours and in three out of four cervical tumour cell lines (including HeLa and KB lines which have been passed extensively in culture), but its absence from benign tumours and premalignant lesions¹³.

Clearly the situation is complex but it all adds up to a strong association of HPV with cervical tumours, particularly HPV 16 and 18. The other types, 6 and 11, may be associated with premalignant lesions and could also act as helper viruses for HPV 16 and 18. As with other tumours, there may be several stages between normal cervical cells and the fully malignant carcinoma cells, with different agents involved at different stages. These could be different HPV types or other viruses such as herpes simplex type II, or non-viral agents. Work with papilloma viruses in humans and

animals suggests that ultraviolet or ionizing radiation and chemical carcinogens or promoting agents act in concert with papilloma viruses to produce malignant tumours. Everyone working with HPV and cervical tumours has been careful to emphasize that what has been shown is an association between HPV and cervical tumours with no proof that they actually cause the tumours. The expectation would be that, if they did so, it would be in conjunction with other agents.

The details of HPV structure and replication are in the process of being unravelled and it is already clear that they are very different from simian virus 40 and polyoma virus in their genome size, organization and expression. They are also probably quite different in their mode of transformation and analogies with the smaller papova viruses are likely to be misleading rather than useful. In condylomata acuminata and in premalignant lesions, papilloma virus usually exists in the form of free episomal DNA, whereas HPV 16 and 18 may be integrated into chromosomal DNA in carcinomas (ref. 13 and D. McCance, personal communication). It is not clear what part rearrangement of the viral DNA or integration may play in transformation and whether integration is into specific sites in the cellular DNA. None of these uncertainties detracts from the importance of the now very impressive body of evidence implicating papilloma viruses with cervical and also with penile cancer. If they play an essential part in one or more stages of the malignant process the best prospect yet for intervention and control of these tumours will be on offer. □

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1. Buckley, J.D. *et al.* *Lancet* **ii**, 1010 (1981).
2. Singer, A. *J. Rep. Med.* **28**, 109 (1983).
3. Walker, P.G. *et al.* *Br. J. vener. Dis.* **59**, 327 (1983).
4. zur Hausen, H. *Cancer Res.* **36**, 794 (1976).
5. Roberts, A. *Health Trends* **14**, 41 (1982).
6. Oriel, J.D. *Dermatologic Clinics* **1**, 93 (1983).
7. Baird, P.J. *Lancet* **ii**, 17 (1983).
8. Gissmann, L. *et al.* *Proc. natn. Acad. Sci. U.S.A.* **80**, 560 (1983).
9. McCance, D.J. *et al.* *Br. med. J.* **287**, 784 (1983).
10. Durst, M. *et al.* *Proc. natn. Acad. Sci. U.S.A.* **80**, 3812 (1983).
11. Crum, C.P. *et al.* *New Engl. J. Med.* **310**, 880 (1984).
12. Ikenberg, H. *et al.* *Int. J. Cancer* **32**, 563 (1983).
13. Boshart, M. *et al.* *EMBO J.* **3**, 1151 (1984).

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In the article 'Progress in malignancy' by Miranda Robertson (*Nature* **309**, 512; 1984), the last sentence of the first paragraph should have read 'At the same time, Schwab *et al.*, who originally discovered the *N-myc* gene², report that in neuroblastomas *N-myc* amplification is associated with late stages of tumour progression, and thus may have prognostic implications'.