BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 20 MARCH 1976

Herpesvirus and cancer of uterine cervix

Groups of women especially at risk for cancer of the uterine cervix are well recognised: those from broken or multiple marriages,[1-4] the promiscuous[1 4 5] and those who attend venereal disease clinics,[1 6] women who marry young,[1-3] and especially those who become sexually active in early adolescence.[3 7 8] Coitus is the common factor, but it seems that coitus with several partners or at a very young age carries the greatest risk.[9] Least likely to develop cervical cancer are celibate women and those who live in communities where marriage is generally stable and where premarital and extramarital coitus is held to be morally wrong.[4 10] All the evidence points strongly to the venereal hypothesis of cervical cancer advanced by Martin[4] in the mid 1960s.

Around the same time colposcopic and laboratory studies of 14 000 women of all ages and reproductive status led Coppleson and Reid[11] to claim to have identified two periods when there is exceptionally active metaplasia in the cervical epithelium—in early adolescence and during a first pregnancy. They went on to suggest that during these times of dynamic activity the nucleic acid of the dividing epithelial cells is most sensitive to the action of any mutagen in the external environment. The longstanding suspicion on epidemiological grounds that herpes simplex virus type 2 (HSV-2) may be implicated in the creation of mutant cells in the cervical epithelium fits with that hypothesis. The interaction between cell nucleus and virus nucleic acid during the phase of dynamic metaplasia would result in variant epithelial cells. Whether or not these mutant cells, with their malignant potential, ever progress to preinvasive or invasive cancer would presumably depend on the individual woman's immunological defences and on such local factors as oxygen tension, pH, and hormonal changes in the cervical tissues.[12] Many years might pass before the continuing struggle between mutant cells and the environmental factors would be finally resolved one way or the other.

More recently reports from the group working at Emory University,[13-17] along with evidence from other centres,[18 19] have steadily tightened the link between HSV-2 and squamous cancer of the cervix. Naib *et al*[13] found that 15% of women whose cervical smears indicated recent herpes infection had either appreciable epithelial dysplasia or carcinoma-in-situ. Josey *et al*[14] have identified virus-like particles in epithelial cells showing early dysplasia. Kessler *et al*,[19] using a microneutralisation technique, determined the presence of herpesvirus-2 antibodies in 350 women with confirmed squamous cancer of the cervix and compared the results with those from a non-cancerous group of women matched for age, marital status, religion, and residence. There was a significantly higher prevalence of HSV-2 antibody among patients than among controls.

In a prospective study of 1500 Atlanta women Josey[15] has reported that dysplasia, carcinoma-in-situ, and invasive cervical cancer have been five to six times more frequent among women shown on serological grounds to have had HSV-2 infection. Royston and Aurelian[16] found herpes-virus-specific antigens in cells taken from cervical smears of women with carcinoma. Aurelian[17] also found serum antibody to the supposed HSV-2 cancer antigen in 35% of patients with dysplasia, 65% of those with carcinoma-in-situ, and 85% of patients with invasive cancer, compared with an incidence of 12% among matched controls.

Josey[15] has claimed that a good cytologist should be able to spot fresh or recent herpes infection of the cervix. But the problem is to identify with assurance those women who have had, at some time (probably during adolescence), a cervical HSV-2 infection. With steadily increasing evidence of a close link between the virus and cervical cancer the time may not be far off when firm diagnosis of HSV-2 infection warrants the more expensive fluorescent antibody test or even virus culture. Those women with a positive result could be kept under careful surveillance, with frequent colposcopic and smear checks, for they seem to be at considerable risk. Much, of course, will depend on the cost and on the effectiveness with which past infection can be identified.

1 Terris, M, and Oalmann, M C, *Journal of the American Medical Association*, 1960, **174**, 1847.
2 Christopherson, W M, and Parker, J E, *New England Journal of Medicine*, 1965, **273**, 235.
3 Boyd, J T, and Doll, R, *British Journal of Cancer*, 1964, **18**, 419.
4 Martin, C E, *Marital and Coital Factors in Cervical Cancer*. Ann Arbor, Michigan, University Microfilms, 1967.
5 Rojel, J, *Acta Pathologica et Microbiologica Scandinavica*, 1953, supplement no 97.
6 Jones, E G, MacDonald, I, and Breslow, L, *American Journal of Obstetrics and Gynecology*, 1958, **76**, 1.
7 Rotkin, I D, and King, R W, *American Journal of Obstetrics and Gynecology*, 1962, **83**, 720.
8 Singer, A, *British Journal of Obstetrics and Gynaecology*, 1975, **82**, 588.
9 Rotkin, I D, *Cancer Research*, 1967, **27**, 603.
10 Lyon, J L, *et al*, *New England Journal of Medicine*, 1976, **294**, 129.
11 Coppleson, M, and Reid, B, *Preclinical Carcinoma of the Uterine Cervix*. Oxford, Pergamon Press, 1967.
12 Coppleson, M, *British Journal of Hospital Medicine*, 1969, **2**, 961.

[13] Naib, Z M, Nahmias, A J, and Josey, W E, *Cancer*, 1966, **19**, 1026.
[14] Josey, W E, Nahmias, A J, and Naib, Z M, *American Journal of Obstetrics and Gynecology*, 1968, **101**, 718.
[15] Josey, W E, *Journal of the American Medical Association*, 1975, **234**, 1101.
[16] Royston, I, and Aurelian, L, *Proceedings of the National Academy of Sciences of the United States of America*, 1970, **67**, 204.
[17] Aurelian, L, *Journal of the American Medical Association*, 1975, **234**, 1101.
[18] Kessler, I, *Cancer Research*, 1974, **34**, 1091.
[19] Kessler, I, *et al*, *Journal of the National Cancer Institute*, 1974, **52**, 369.

Radiation dangers and volunteers

The very first requirement in a hospital, said Florence Nightingale, is that it should do the sick no harm. The deficiencies in hygiene and nursing which she identified have been made good, but newer dangers associated with drugs, electricity, and radiation still require vigilance.

Radiation generates hazards of two kinds. When *x* rays and radioactive isotopes are used in investigating or treating individual patients the risks and the benefits can usually be assessed by reference to clinical experience, published recommendations, and (in nuclear medicine) the Medical Research Council Isotope Advisory Panel. Hazards to volunteers present ethical problems of a different kind. In nuclear medicine the irradiation of healthy controls is essential to establish normal values. When new drugs are being tested and metabolic pathways and modes of action are under investigation almost always procedures are necessary in which labelled material is given to normal individuals.

At a meeting held recently under the auspices of the British Radiological Protection Association to examine these issues discussion centred on the definition of a volunteer and on the prescription of acceptable radiation doses. Clearly children and mental defectives cannot give valid consent and, along with pregnant women, should not be used as controls—except perhaps when the radiation doses are very small in relation to the natural background. Whether other patients can be sufficiently informed (even when efforts are made to estimate the risk by comparison with road traffic, cigarette smoking, or occupational hazards) is an open question.

Faced with this problem the most realistic proposals are those made by WHO/IAEA Working Party[1] in 1972 and endorsed, without major alteration, by the British Institute of Radiology in 1975.[2] These suggested that experiments requiring the irradiation of volunteers should be subject to approval at three levels. When the dose is less than 50 millirem (about half of the annual natural radiation background in Britain) to the whole body or 250 millirem to any single organ approval should be given by a hospital committee including at least one medically qualified member, one with wide experience in medical research, and one with expert knowledge of radiation effects. When the radiation dose is larger, up to 0·5 rem (2·5 rem to a single organ), the project should be referred to an external committee of similar composition but made up of people from outside the hospital—possibly on an area or regional basis.

These two categories would include most research projects in nuclear medicine as well as *x*-ray exposures needed for teaching purposes. Investigations requiring volunteers to undergo greater radiation exposure should be undertaken only after approval by a national expert committee, similar to the MRC Isotope Advisory Panel. At present all radioisotope investigations (on patients or volunteers) are subject to approval by this panel; in most instances a hospital ethical committee is also concerned. This procedure has some advantages: it may, for example, be linked with arrangements for the supply of radioisotopes from the Radiochemical Centre. Some hospitals do not have ready access to physicists or radiobiologists with the resources to make accurate estimations of radiation dose; consequently an investigation approved on the basis of local advice might on more expert examination be reclassified because of a higher radiation dose.

There are other problems which no committee can solve. The radiation dose in an isotope investigation can vary by a large factor according to the isotopes used and the nature of the counting equipment. Should experimenters be required or encouraged to use up-to-date apparatus and techniques so as to minimise radiation doses to patients and volunteers? Should the previous radiation exposure (clinical, occupational, and experimental) of potential volunteers influence their selection as control subjects? Should junior colleagues and students ever be used as volunteers?

Fortunately the experimental uses of radiation are, in most places, regulated by a high level of integrity and responsibility. Doses incurred by volunteers are generally so low as to cause no serious concern. Nevertheless, it is right that the matter should be kept under review, particularly since recent legislation on health and safety is likely to produce new regulations and other controlling mechanisms.

[1] Report of a WHO/IAEA consultation on the use of ionising radiation on human beings for medical research and teaching including the use of radioactive materials. Unpublished working document, available in limited numbers from the World Health Organisation, 1211 Geneva, Switzerland.
[2] *British Institute of Radiology Bulletin*, 1975, **1**, (2) 4.

Shoulder-cuff lesions

Experts do not agree on the diagnosis and management of painful lesions of the rotator cuff of the shoulder. Undoubtedly one factor is the complexity of the shoulder mechanism. The act of raising the arm not only requires movement in the sternoclavicular, acromioclavicular, and glenohumeral joints but also entails scapulothoracic rotation. Furthermore, since the shoulder is not a weight-bearing joint and so many tendon lesions are of minor importance, the region is rarely exposed to surgical view. Add to these complexities the fact that most cases settle with time and there may seem to be a convincing case for expectant treatment—and indeed two retrospective studies of painful stiff shoulders[1 2] treated variously by physiotherapy, manipulation under anaesthetic, and steroid injection support this view: all the patients slowly improved irrespective of treatment.

The opposite approach has been presented by Cyriax,[3] who advocates accurate diagnosis of the lesion by applied functional anatomy and distinguishes the management of intracapsular lesions (arthritis) from pericapsular lesions affecting the tendons and subacromial bursa. Localised infiltration with a steroid injection is claimed to relieve symptoms in most cases of both kinds. This view has been supported by Richardson,[4] who divided cases into two simple groups: one termed "tendinitis," in which pain on resisted movement exceeded restriction of movement; and the other "capsulitis," when restriction of movements was the predominant feature. The