VIRIONS RESEMBLING PAPILLOMAVIRUSES IN HYPERKERATOTIC LESIONS FROM SUN-DAMAGED SKIN

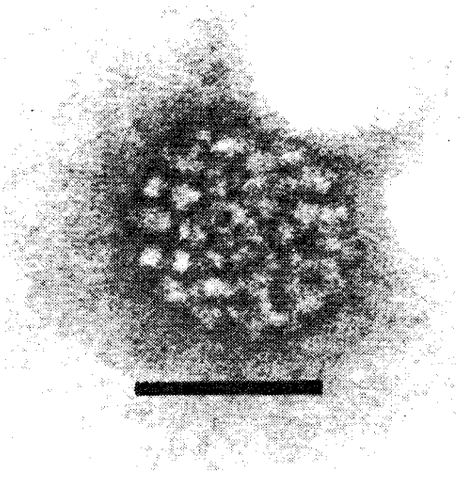
SIR,—Papillomaviruses may be involved in the genesis of certain carcinomas in animals and man. These neoplastic diseases share common features, including derivation from a lesion (not necessarily a papilloma) caused by a papillomavirus and the contribution of host and environmental factors to carcinogenesis. Where adequate molecular studies have been made, the viral genome has been shown to persist in the cells of the carcinoma but the genome is not fully transcribed and no virions are produced. The process has been extensively studied and experimentally reproduced with Shope's papillomavirus in cottontail rabbits and in domestic rabbits.[1] Carcinomas also develop from papillomas in the digestive tracts of cattle that ingest bracken fern[2] and on the sun-exposed skin of patients with epidermodysplasia verruciformis.[3] Human laryngeal and genital lesions caused by papillomaviruses may also transform to carcinomas.[4] In tropical and subtropical Australia carcinomas occur commonly on the faces, ears, and vulvas of sheep and on the eyes of cattle. These carcinomas have usually been attributed to chronic exposure to sunlight, but they are now known to arise from, or be associated with, precursor lesions that contain papillomaviruses.

Carcinomas of human skin, attributed to chronic exposure to sunlight, are common in tropical and subtropical regions. These carcinomas may develop in areas of solar keratosis.[5] The similarity of the sequence of lesions occurring in man and domestic animals in the same environment prompted us to seek papillomaviruses in clinically diagnosed solar keratoses. We report the preliminary examination of such lesions from four patients and the demonstration of virions resembling those of papillomaviruses in one of these.

The lesions were initially stored in 50% glycerol saline at 4°C. They were then homogenised, subjected to differential centrifugation, and examined electron microscopically after negative staining.[6] Virions were detected in the lesions from one patient, a man aged 67 with solar keratoses on his forearms. The virions were unenveloped, about 58 nm in diameter, and resembled those of papillomaviruses (figure). The virions were very sparse and were found only after prolonged search. However, similar particles were again detected when the same preparation was examined on a second occasion.

The virions of papillomaviruses are sometimes very difficult to demonstrate in clinical lesions and indirect methods that detect viral antigens or viral DNA must be used. Although we detected virions in keratoses from only one of four patients, an examination of further keratoses by more sensitive methods would be warranted. It is possible that both actinic radiation and a papillomavirus contribute to some of these lesions.

The possible contribution of the papillomavirus to carcinogenesis also merits attention. Human papillomavirus type 5 produces benign lesions in patients with epidermodysplasia verruciformis. On sun-exposed skin these lesions may transform to carcinomas, and the viral genome has been detected in the cells of these carcinomas.[7] The same virus produces benign skin lesions on immunosuppressed recipients of allografts[8] and these patients are also at risk of cutaneous carcinomas. The involvement of a papillomavirus in even some sun-associated skin cancers would offer new approaches for therapy and prevention.



Virion from hyperkeratotic lesion on patient with solar-damaged skin.

Bar represents 50 nm.

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ASBESTOS AND NON-HODGKIN'S LYMPHOMA

SIR,—Dr Ross and colleagues' paper (Nov. 20, p. 1118) may explain similar findings apparent in other workers potentially exposed to asbestos. Among social security disability claimants from 1959–62 in the U.S., proportionate morbidity ratios were significantly raised for lymphoma and leukaemia among stationary engineers (1·4), mechanics (1·5), and carpenters (1·5).[1] Likewise, an analysis of deaths in 1950 among U.S. males demonstrated significantly increased standardised mortality ratios (SMRs) for lymphopoietic and haematopoietic malignancies, excluding leukaemia (7th revision I.C.D. 200–203, 205), among stationary engineers (1·6), shipbuilders (1·7), and construction workers (1·2).[2]

As Ross et al. point out, few cohort studies of asbestos workers have reported the number of observed and expected deaths due to non-Hodgkin's lymphoma (NHL). However, one cohort study[3]

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of 2722 males employed in an asbestos textile, friction, and packaging products manufacturing facility in Pennsylvania noted 7 deaths due to NHL (7th revision I.C.D. 200 only) versus 3·28 expected. On the death certificates, 3 of the cases were malignant lymphomas and 4 were lymphosarcomas. Their average age at death was 44 years (range 25–56); average duration of plant employment, 14 years (range 1–35); and average time from initial employment until death, 21 years (range 4–39). This last figure was substantially less than that reported by Ross et al. Among females employed in the same plant, no deaths due to lymphoma were observed, but less than 1 such death would have been expected. An earlier study of 68 cases of asbestosis from this same plant identified 5 additional haematapoietic and lymphatic malignancies.[4]

99% of the asbestos used in the Pennsylvania plant was chrysotile[3,4] and 2 of 3 cases of immunoproliferative and lymphoproliferative malignancy reported by Kagan et al.[5] also were exposed to chrysotile asbestos (1 exclusively). Unfortunately, none of six other published cohort studies of workers exposed solely to chrysotile asbestos have reported data for NHL. However, reticulosarcomas have been reported in rats administered chrysotile asbestos either orally or by intratracheal injection with benzopyrene.[6] The plausibility of an asbestos aetiology for NHL is supported by Bignon's[7] finding that thoracic lymph nodes are important points in the clearance pathway of asbestos fibres in both animals and man.

Because of the carcinogenicity of all major types of asbestos, the continually changing criteria for classification of subtypes of NHL, and the few deaths due to NHL in any given cohort, perhaps the investigators who have followed up the thirty-three cohorts of asbestos workers[8] could determine the numbers of observed and expected deaths due to NHL and submit pathologic material from these deaths to a central panel of pathologists for review.

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SIR,—Dr Ross and colleagues have presented an epidemiological study of non-Hodgkin's lymphomas of the gastrointestinal tract in patients exposed to asbestos. Neoplastic lymphoid disorders associated with a prolonged asbestos exposure may not be limited to the gut. We have seen two cases of non-gastrointestinal lymphoproliferative disorder in men after prolonged occupational exposure to asbestos.

Case 1.—A 55-year-old plumber had been working for 30 years at the grinding and installation of asbestos containing pipes. 5 years ago he started complaining of dyspnoea, cough with bloody sputum, and respiratory discomfort. Chest X-ray and lung biopsy pointed to asbestos-induced lung fibrosis. 1 year ago a routine laboratory investigation revealed a peak in the serum gamma-globulin fraction on electrophoresis. Bone marrow examination and immuno-electrophoresis confirmed IgG multiple myeloma. The patient died, after 1 year, of heart failure and pneumonia.

Case 2.—This 50-year-old man had been working for 25 years in building industry, continually exposed to asbestos powders. 15 years ago he was successfully treated for pulmonary tuberculosis. Chest X-rays over the ensuing years revealed a diffuse interstitial fibrosis with coarse nodular pattern, and a "vanishing lung" morphology of the apexes. 1 year ago a routine laboratory investigation revealed a marked leucocytosis (46 000/μl) with 90% mature lymphocytes and many Gumprecht shadows in the blood smear. Bone marrow examination and immunofluorescent techniques for surface immunoglobulins confirmed the diagnosis of B chronic lymphocytic leukaemia. The peripheral blood T-lymphocyte percentage was much reduced (only 15% were positive on the E-rosette test and only 18% reacted to mitogen stimulation).

Ross et al. suggested that asbestos fibres absorbed by the oral and gastrointestinal mucosa might be responsible for prolonged local irritation leading to stimulation of the lymphoid tissue and culminating in lymphoproliferative disease. In our cases the effects of asbestos on immunological control,[1–3] T-lymphocyte numbers, and cell-mediated immunity may be more relevant. Although lymphoproliferative disorders constitute only a small percentage of the malignancies seen in asbestos workers,[4,5] the immunological status of these people should be monitored to detect early signs of immunological alterations.

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CLOUDS OVER GALACTOSAEMIA

SIR,—The meteorological observation referred to in your Dec. 18 editorial was communicated to the Society for Inborn Errors of Metabolism in Cardiff in 1971.[6] At that time I expressed my concern about the long-term prognosis in galactosaemia, based on the Manchester and Los Angeles follow-up studies, and emphasised the repeated finding of raised galactose-l-phosphate (Gal-l-P) levels in the cord blood of homozygously affected babies following pregnancies where galactose had been carefully excluded from the mother's diet. This suggested a significant intrauterine and probably deleterious exposure of the fetus to galactose. You do not mention these findings although you do state that galactose and its metabolites can reach concentrations by mid-gestation which are probably toxic. Neither do you mention the work of Gitzelmann and Hansen on the role of the pyrophosphorylase pathways in homozygously affected patients.

Workers with considerable experience of this disorder who have monitored patients on diet have seldom been able to restore the red cell Gal-l-P levels to normal unless the patient concerned was a double heterozygote for classical galactosaemia and one of the galactosaemia variants—again suggesting a continuous low-grade damage to the developing brain during the first years of life.

Despite my pessimism about the prognosis for galactosaemia I would strongly support a collaborative study which would include a careful retrospective review of all known cases as well as prospective observations of the effect of a carefully controlled dietary regime on newly diagnosed cases.

I think that the damage in this condition occurs largely before birth.[7]

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