Epstein–Barr virus

Infection and tumour induction

from M. A. Epstein

EPSTEIN–BARR (EB) virus, a herpesvirus of man, resembles all other herpesviruses in establishing a persistent carrier state throughout life following initial infection. It has long appeared to infect B lymphocytes exclusively and this specific tropism has been explained by the recent demonstration that the B-lymphocyte C3d receptor CR2 for serum complement also acts as the virus receptor. Infected individuals, however, shed virus into the saliva and the cellular site of viral replication in the epithelium-lined oropharynx has been an enigma. So too has been the oncogenic role of the virus in undifferentiated nasophargeal carcinoma, a tumour whose malignant epithelial cells always carry the viral DNA. The finding of virus receptors on epithelial cells[1] and of a viral transforming gene[2] has now shed the first light on these interrelated problems.

Because only B lymphocytes could be infected experimentally by EB virus it was easy to understand the presence of latent infection readily demonstrable in a percentage of the circulating B cells of infected subjects. For similar reasons, it was assumed that the productive infection responsible for the infectious virions shed into saliva probably arose from infected B cells within the lymphoid tissue of Waldeyer's ring — including tonsils, adenoids, Eustachian cushions and lingual follicles. Hints that epithelial cells might be involved proved difficult to interpret in the absence of a satisfactory mechanism whereby the virus could enter and infect them. But early claims that EB virus replicated in oropharyngeal epithelial cells during primary infection accompanied by infectious mononucleosis were eventually supported and there were also reports that the viral DNA was present in both salivary gland and normal nasopharyngeal epithelial cells. Furthermore, a small proportion of epithelial cells from the human uterine cervix, not usually thought to be associated with EB virus, could apparently be infected after appropriate manipulation *in vitro*.

Striking and unequivocal evidence for EB virus replication in epithelial cells has recently been obtained[3] in the context of the immunological disarray which accompanies the acquired immune deficiency syndrome (AIDS). 'Hairy' leukoplakia of the tongue is a newly described lesion of homosexual males suffering from characteristic immunodepression involving absent or poor responses to antigen skin tests and altered, or frankly inverted, ratios of helper to suppressor T lymphocytes. The patients either have AIDS or are likely to develop it and large numbers of biopsy samples of the tongue lesions have been shown by electron microscopy, specific immunofluorescence tests, and DNA hybridization using EB virus probes in Southern blots, to have EB virus replicating in prickle cells[3]; a papillomavirus was frequently also present, sometimes even in the same cells.

The crucial importance of specific cytotoxic T cells in maintaining the virus-host balance in the life-long EB virus infection has come to be recognized in the past few years. The balance is delicate, and impairment of T-cell surveillance predisposes to virus-induced pathology. It has been demonstrated repeatedly that transplant recipients on immunosuppressive therapy to prevent graft rejection have depressed numbers of cytotoxic T cells and increased amounts of EB virus shed from the mouth; they also have a heightened incidence of EB virus-associated lymphomas. There is thus a clear parallel with certain aspects of AIDS in which cytotoxic lymphocytes are depleted, unusual EB virus production takes place as seen in the epithelial prickle cells of "hairy" leukoplakia[3], and lymphomas carrying EB virus are common. It is of great interest that attacks of falciparum malaria are likewise accompanied by a fall in T-cell numbers and inversion of the ratio of helper to suppressor T cells, since the hyperendemic form of this disease has been recognized for many years as an essential co-factor in the induction of virus-related endemic Burkitt's lymphoma.

Interactions between EB virus and epithelial cells are no longer mysterious. Using two monoclonal antibodies against different epitopes of the complement C3d CR2 EB virus receptor, Young and colleagues[1] show that the receptor molecules are present on the cells of oral and nasopharyngeal squamous epithelia and, in view of the hairy leukoplakia findings, it may be significant that on the tongue the receptors appear to be restricted to the prickle cell layers. All the evidence now supports the view that permissive productive replication of EB virus takes place in oral and pharyngeal epithelial cells, which fits well with the ten-year-old observation that malignant epithelial cells of nasopharyngeal carcinoma, which carry the virus genome, can be readily induced to produce infectious virus both in tissue culture and in nude mice.

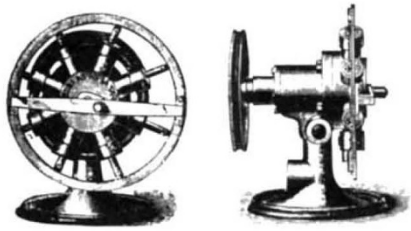
If entry of EB virus into epithelial cells can now at last be understood, what of its role in changing them into cancer cells? As far as nasopharyngeal carcinoma is concerned, nothing has hitherto been clear,

100 years ago

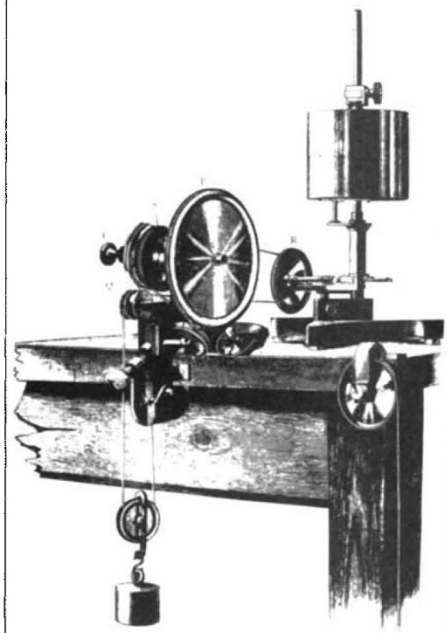
Power in Laboratories

IN connection with the admirable devices for the distribution of driving-power in laboratories, illustrated in *Nature*, vol. xxxiii. p. 248 (shown opposite), the description of a novel and very effective form of water-engine, with which I have been experimenting for several months, will be of interest.

One of these motors is set up in the cellar of our science hall, where it is supplied with aqueduct-pressure of sixty pounds to the square inch, and the power is transmitted from it by means of rubber belting led over



"idle pulleys" to the upper stories of the building, where a small engine-lathe and dynamo are driven. A word will suffice to explain the very simple construction of the motor-system of radial cylinders, with their bases at the centre of the motor, through which runs the driving-shaft. The pistons in these cylinders are single-acting, and the water is admitted to them in succession by the rotary valve which forms part of the main shaft. The pistons, thus, in pressing outward, exert their force against a strong ring, to which is bolted a crossbar which engages the crank of the main shaft. Thus the ring, in turning the shaft, has the vibratory motion of an eccentric, and returns the opposite pistons to the bases of the cylinders, at the same exhausting the water through the interior of the rotary valve.



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