news and views

Towards an anti-viral vaccine for a human cancer

from M. A. Epstein

WHEN the US National Cancer Institute set up the Special Virus-Leukaemia Program in 1964 (later expanded as the Special Virus Cancer Program) with the explicit objectives of (1) determining whether at least one human cancer is caused by an oncogenic virus, and if so of (2) developing an effective vaccine for the control of such a tumour (Rauscher, Carrese and Baker, *Cancer Res.*, **26**, 1176; 1966), the project was viewed with considerable scepticism by many leading workers in the cancer and virus fields. Looking back at the impressive progress made in tumour virology over the last ten years, the far-sightedness of the whole project is now evident, particularly in relation to the herpesviruses following striking recent advances with vaccines against some oncogenic members of the group.

Herpesviruses are known to cause the ubiquitous Marek's type of malignant lymphoma in chickens (Churchill and Biggs, *Nature*, **215**, 528; 1967; Solomon *et al.*, *Proc. Soc. exp. Biol. Med.* **127**, 173; 1968), an experimental malignant lymphoma in South American sub-human primates (Meléndez *et al.*, *Lab. Animal Care*, **19**, 378; 1969), and the Lucké kidney carcinoma of the leopard frog (Mizell *et al.*, *Science*, **165**, 1134; 1969; Naegele *et al.*, *Proc. natn. Acad. Sci. U.S.A.*, **71**, 830; 1974), and the closeness of the association of Epstein–Barr virus with African Burkitt's lymphoma and nasopharyngeal carcinoma in man is increasingly suggestive of some aetiological relationship (Epstein and Achong, *A. Rev. Microbiol.*, **27**, 413; 1973; Klein in *The Herpesviruses*, edit by A. Kaplan; Academic Press, London and New York, 1973; Henle and Henle, *Cancer Res.*, **33**, 1419; 1973). There is also a more tenuous association between herpes simplex virus type II and carcinoma of the human cervix (reviewed by Rapp and Buss, *Am. J. Path.*, **77**, 85; 1974), but this has been weakened by the failure of biochemical probes to detect the viral genome in tumour biopsy cells (zur Hausen *et al.*, *Int. J. Cancer*, **13**, 657; 1974).

The development in 1969 of live, attenuated herpesvirus vaccines capable of giving chickens almost complete protection against Marek's lymphomas (Churchill *et al.*, *Nature*, **221**, 744; 1969; Okazaki *et al.*, *Avian Dis.*, **14**, 413; 1970) was of great significance both in economic terms and because it provided the first example of a naturally occurring malignant tumour to be controlled in this way. Although the importance of this step forward was widely recognised, its applicability to the ultimate control of those human cancers suspected of having a herpesvirus cause was clearly slight because of the impossibility of administering to man a suspected tumour-inducing virus, however attenuated. Indeed, it is unlikely that even an inactivated virus of this kind would ever be usable as a human vaccine because of the difficulty of proving total inactivation and the possibility that traces of the viral DNA in such a preparation might be capable of bringing about malignant transformation. But further progress with oncogenic animal herpesvirus vaccines is beginning to indicate the ways in which these difficulties could be overcome. Thus, it is now known that chickens can be significantly protected against Marek's lymphomas by vaccines free of virus nucleic acid. Lesnick and Ross (*Br. J. Cancer*, in the press) have reported some success with a vaccine consisting only of soluble viral antigens extracted from Marek's virus-infected tissue culture cells by treatment with nonionic detergent and other workers have used highly purified plasma membranes from similar virus-infected cells as a vaccine, and reduced the mortality from Marek's lymphomas by 94% when the vaccinated chickens were subsequently challenged with virulent virus (Kaaden and Dietzschold, *J. gen. Virol*, **25**, 1; 1974).

Now Laufs and Steinke (this issue of *Nature*, page 71) have moved the problem closer to man by showing that sub-human primates can also be successfully protected against a herpesvirus-induced malignant lymphoma. These workers have used a combination of heat and formaldehyde to inactivate herpesvirus saimiri, which is otherwise carcinogenic in South American primates, and have shown by complement-fixation tests that the inactivated vaccine maintains considerable specific viral antigenicity after these treatments. Forty-two cotton-top marmosets have been immunised with the vaccine in the present experiments, have remained well after this, and have developed high titres of neutralising and complement-fixing antibodies to the virus. So far 22 immunised animals have been challenged with filtered, virulent herpesvirus saimiri in doses many times greater than those needed to induce fatal lymphomas in control animals and at the time of writing all were alive and well between 121 and 293 days after the challenge, whereas inoculated control animals died of malignant lymphoma within 52 days.

It seems reasonable to anticipate that herpesvirus saimiri vaccines free of viral nucleic acid will be developed before long on similar lines to those already being used to protect against Marek's lyphomas in chickens. The possibility this provides of a model system involving animals phylogenetically related to man has important implications for the planning, production, and testing of vaccines against suspected human tumour viruses. In this connection Epstein–Barr virus is not only a leading candidate because of its special association with Burkitt's lymphoma, but also has certain unique advantages. Thus, as has been pointed out elsewhere (Epstein and Achong, *A. Rev. Microbiol.*, **27**, 413; 1973), since Epstein–Barr virus causes infectious mononucleosis the efficacy of any vaccine developed could be tested by its ability to protect those at risk from this disease, and the existence of areas of high endemicity of Burkitt's lymphoma provide populations where the effect of such a vaccine on tumour incidence could be relatively easily tried out. Finally, since Burkitt's lymphoma occurs most frequently around the age of six, vaccination of infants in the months after birth should allow the efficacy of protection against Burkitt's lymphoma to be judged within five to 10 years. It seems that tumour control by an anti-viral vaccine will be the only way of proving whether or not Epstein–Barr virus is a human tumour virus aetiologically related to Burkitt's lymphoma either with or without additional cofactors.