millimetre wavelengths, the 3.8-metre United Kingdon Infrared Telescope (UKIRT) atop Mauna Kea, at submillimetre wavelengths, and NASA's Kuiper Airborne Observatory, at far-IR wavelengths.

The resultant radio to optical spectrum (see the figure) shows that the quasar has a flat radio spectrum and becomes transparent at millimetre and shorter wavelengths. It therefore appears that at millimetre and submillimetre wavelengths we are observing the core of the radio emission. This observation makes it all the more worthwhile to develop millimetre-wavelength very-long-baseline interferometry (VLBI), which will allow the angular structure of the core to be determined.

Studies of the variability of quasars at millimetre wavelengths have been rather few until recently. Now, two groups, E. Epstein *et al.* (*Astr. J.* **87**, 499; 1982) and Ennis, Neugebauer and Werner (*Astrophys. J.* **262**, 451; 1982), have published monitoring projects at 3.3 and 1 mm respectively. Unfortunately, new observations only serve further to subvert straightforward interpretation of the observed brightness changes. Sometimes the millimetre variations are correlated with those seen at longer wavelengths, and sometimes they are not. Even when they are connected, the simple models found in the literature do not seem to explain the details of the observations. Moreover, the connection with optical brightness changes is far from clear. Clearly, further observational and theoretical advances are necessary.

Neugebauer and Werner (*Astrophys. J.* **262**, 460; 1982) bears on the radio-quiet QSO problem. They detected no radio-quiet QSOs at 1 mm, so clearly the optical–IR spectrum must cut off at wavelengths substantially shorter than this.

A further curious result is the failure to detect QSOs that have been observed to be weak radio sources, implying that the radio spectrum does not rise steeply from long to short wavelengths as would be the case for a self-absorption cutoff. This behaviour is consistent with Scheuer and Readhead's (*Nature* **277**, 182; 1979) relativistic beaming model, but other observations seem to indicate that this is not the entire explanation.

Fortunately, we can expect further development of millimetre and submillimetre astronomy in the near future. Resurfacing and expansion of the NRAO 36-foot dish (now called the '12-metre' telescope) and the introduction of new millimetre-wave dishes (for example, the upcoming British 15-m dish atop Mauna Kea) should at least partially compensate for the demise of the proposed US 25-m project. Continued advances in submillimetre detectors and the deployment of IR satellites will further assure a place for millimetre and submillimetre astronomy at the forefront of quasar research. □

Vaccine development

Hybrid vaccinia virus for mass hepatitis immunization?

from A.J. Beale

IN this issue of *Nature* (p.490), Smith, Mackett and Moss from the National Institutes of Allergy and Infectious Diseases in Bethesda, Maryland, describe the successful selection of vaccinia virus into which the gene for hepatitis B virus surface antigen has been inserted. The modified virus grows well in cell culture and hepatitis B virus agglutinin (HBsAg) is released into the culture fluid in a form indistinguishable from the native antigen present in the serum of carrier individuals. Even more exciting is their observation that rabbits infected with the hybrid vaccinia virus produce high titres of antibody to the HBsAg, more than those required to provide protection in man. The authors suggest that this type of hybrid vaccinia virus might be ideally suited to mass immunization campaigns in areas of the world where control measures are urgently needed but existing vaccines are too expensive to make or administer. The success of the WHO campaign for the global eradication of smallpox gives added force and credibility to that point of view.

Moss and his colleagues devised a means of introducing foreign DNA into vaccinia virus so that the polypeptide encoded by the new DNA is produced during the growth cycle of the virus. A chimaeric gene consisting of vaccinia virus promoter sequences fused to the coding sequence for the desired foreign protein was flanked by vaccinia virus DNA in a plasmid vector. One such foreign protein used in early experiments was herpes virus thymidine kinase. In order to make vaccinia useful as a general expression vector, plasmids with restriction enzyme sites next to the vaccinia thymidine kinase promoter or another vaccinia promoter engineered in the thymidine kinase gene were constructed. Transfection of vaccinia virus-infected cells with the plasmid allowed recombination to take place. The recombinants containing the foreign protein-coding sequences could be selected by looking for thymidine kinase vaccinia plaques or the presence of herpes virus thymidine kinase.

The recloned vaccinia containing the HBsAg-coding sequences were used to vaccinate two rabbits; typical vaccinia lesions were produced and, in addition, high titres of antibodies were seen to last for at least 31 days. These preliminary results hold promise that many other antigens may be expressed in the same way and used as vaccines, either as a means of producing antigens in culture or, more imaginatively, to use them as combination vaccines. Several problems in developing vaccines by new technology may thus be solved. Although rDNA techniques should enable protective antigens to be produced in large quantities, some antigens are poorly expressed or poorly immunogenic when produced in *Escherichia coli*, as is the case with foot-and-mouth disease virus VP1 or HBsAg. Again, the presentation of the immunogen to the host may be below the optimum, and it is commonly thought that a new generation of adjuvants or a deeper understanding of the nature of immunogenicity will be required before it will be easy to elicit the range of immune responses necessary for clinical immunity.

The cost of vaccines, and particularly of their administration, are vital factors in determining the success of an immuniza-

Oncogenic Intelligence

Oncogene, not polymorphism

from Peter Newmark

THE 15 April issue of *Science* contains a retraction of a paper published there two months ago and the subject of this column in *Nature* **301**, 654 (1983). In their paper (*Science* **219**, 853; 1983) R.J. Muschel, G. Khoury, P. Lebowitz, R. Koller and R. Dhar claimed that polymorphism rather than somatic mutation accounted for the single base change that distinguishes the c-*ras*^{H} oncogene of T24 bladder carcinoma cells from that in normal tissue gene banks and accounts for the ability of the former to transform NIH 3T3 cells.

At best their evidence — for the same base change in the c-*ras*^{H} gene of both normal and tumour tissues of an individual with bladder cancer as in T24 cells — was decidedly preliminary. At worst, as they have since discovered, it was all accounted for by contamination. Further tests have convinced them that neither normal nor tumour tissue of their patient had the mutation that characterizes the c-*ras*^{H} oncogene of T24 cells.

Polymorphism remains a possible explanation of the T24 mutation but the attempt by Muschel *et al.* to make that explanation stick should now be counted as a casualty of the fierce competition that abounds between oncogene laboratories. □

Peter Newmark is Deputy Editor of Nature.

0028-0836/83/140476-02$01.00

tion campaign, especially in developing countries. The use of vaccinia as a vehicle might solve both these problems. Hepatitis B vaccine derived from blood is prohibitively expensive but the cost of vaccinia-expressing HBsAg should be little more than regular vaccinia virus; and, moreover, the methods of administration pioneered by the WHO smallpox eradication programme are very cost effective. The bifurcated needle developed by Wyeth Laboratories is easy to use by relatively unqualified vaccinators and the vaccination scar is a clear sign of a previous successful vaccination.

Some difficult problems remain to be solved before this strategy can be adopted. In order to eradicate smallpox, a high proportion of the world population was vaccinated with vaccinia virus and will, if revaccinated, have immunity or partial immunity (Fenner, F. *Prog. med. Virol.* **23**, 1; 1977) which will limit the growth of vaccinia virus and the production and response to HBsAg. The scope of any new campaign based on vaccinia virus will thus be reduced. The immunizing effect of the vaccinia virus vehicle against itself might also limit its usefulness as a general method; even supposing it could be used for hepatitis B immunization for a defined population group, it would not be available for use with another immunogen. To overcome this problem, a series of antigenically distinct, safe attenuated viruses would be required, but that would be by no means easy to supply.

A second major problem is safety. In several Western countries the danger from vaccinia virus immunization was thought too great relative to the risk from smallpox at the time the WHO eradication campaign was launched (Dick, G. *Prog. med. Virol.* **8**, 1; 1966). In the USA and UK, for example, the risk of death from imported smallpox was already extremely low. The great advances in molecular genetics that are now taking place, however, should make it possible to manipulate the virus to avoid these drawbacks, or to produce a series of attenuated viruses colonizing the mucous membranes of the intestinal or respiratory tract. Adenovirus, for example, might be used to induce local immunity at the portal of entry as well as circulating antibody and cell-mediated immunity. □

A.J. Beale is Director of Biological Products at the Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS.

Latent herpes simplex virus

The state of the herpes genome

IN this issue of *Nature* (p.523), Daniel Rock and Nigel Fraser of the Wistar Institute report the successful detection of herpes simplex virus (HSV) DNA in the latently infected central nervous tissue of mice. The new results provide the first step in understanding the nature of the latent virus; it seems that although the whole of the herpes virus genome is present in the latent form, it is qualitatively different from that in virus particles or infected cells.

Since the introduction of animal models to the study of HSV latency and the demonstration that sensory ganglia are the prime source of latent virus[1] the question of the nature of the latent virus has been a fascinating but frustrating one. The assay for latent virus, the detection of infectious virus following culture of explanted neural tissue but not by direct homogenization and assay, implies the presence of the virus genome in a non-infectious form during latency. It can be argued, however, that explant culture is merely a more sensitive assay, allowing the detection of very small numbers of infectious particles resulting from a low-level chronic infection; support for this view comes from the electron microscopic observation of virus particles in the trigeminal ganglia of latently infected rabbits[2].

Evidence against a chronic infection or 'dynamic' latency comes from three types of experiment. First, latent infection has been established using temperature-sensitive mutants in tissues whose temperatures are non-permissive for mutant replication[3,4]. Second, antiviral drugs that efficiently suppress virus replication during the acute phase of infection fail to 'cure' animals of established latent infection[5-7]. Third, HSV DNA was detected in latently infected tissue by kinetic hybridization[8], but no virus-specific RNA was found, a result in contrast to that obtained with tissue taken from the acute phase of infection. These observations argue against viral replication being a requirement for maintenance of the latent infection and favour a 'static' model.

Attempts to examine the form of HSV DNA in latently infected tissue have been bedevilled by the small amount of virus DNA present and by the considerable cross-hybridization of HSV DNA sequences with mammalian cell DNA[9-11]. Success has finally come in the new work reported by Rock and Fraser. Virus sequences were detected in DNA from the central nervous system and trigeminal ganglia of mice several months after corneal inoculation of HSV-1. Using virus DNA as a hybridization probe they were able to show that the entire virus genome was present. Of particular interest is that when a DNA fragment composed of the internal repeated sequences was used to probe blots of restricted DNA, the probe detected both internal and terminal repeats in DNA from the acute phase of infection but only internal repeats in DNA from the latent phase. The virus DNA in latently infected mice thus appears to be 'endless'. The data are of course open to several interpretations since 'endless' DNA could result from the formation of circles or long concatamers or from the random integration of linear molecules. Nevertheless, these are the first data that demonstrate that 'latent' HSV DNA molecules are qualitatively different from the molecules found in virus particles or in infected cells.

Rock and Fraser have combined sensitive hybridization techniques with an animal model in which relatively large amounts of viral DNA persist in the latent phase of infection, so further data should soon be forthcoming. It will be particularly interesting to see whether the viral DNA in latently infected animals is present in more than one of the four isomeric forms found in virus particles.

A note of caution should perhaps be sounded about the use of the term 'latent virus DNA'. Much of Rock and Fraser's evidence derives from experiments with DNA from the brain stem of latently infected animals and, while there is considerable evidence that the central nervous system can act as a site of latent HSV, *in vitro* reactivation of virus from the central nervous system is very inefficient by comparison with reactivation from the sensory ganglia[12]. Indeed, Rock and Fraser were unable to reactivate virus from the brain stem of latently infected mice despite the presence of detectable HSV DNA, a result previously reported by Cabrera *et al.*[13]. Thus while the brain stem is a valuable source of material for biochemical studies, it lacks authenticity as a 'latently infected tissue'.

Finally, two lines of evidence suggest that limited viral gene expression occurs in latently infected cells. Galloway *et al.*[14] have detected virus-specific transcripts in neurones from human sensory ganglia by *in situ* hybridization, while Green *et al.*[15] have detected an immediate-early polypeptide of HSV in the sensory neurones of latently infected rabbits by immunofluorescence. Unfortunately, the transcripts detected by Galloway *et al.* are not derived from that part of the HSV genome that encodes the immediate-early polypeptide in question. This problem, like so many in this field, remains to be resolved. □

A.C. Minson is in the Department of Pathology, University of Cambridge, Hills Road, Cambridge CB2 2QQ.

1. Stevens & Cook *Science* **173**, 843 (1971).
2. Baringer & Swaveland *Lab. Invest.* **30**, 230 (1974).
3. Lofgren *et al. Virology* **76**, 440 (1977).
4. McLennan & Darby *J. gen. Virol.* **51**, 223 (1980).
5. Field *et al. Antimicrob. Ag. Chemother.* **15** 554 (1979).
6. Klein *et al. Antimicrob. Ag. Chemother.* **15**, 723 (1979).
7. Blyth *et al. J. gen. Virol.* **48**, 417 (1980).
8. Puga *et al. Virology* **89**, 102 (1978).
9. Maitland *et al. J. gen. Virol.* **55**, 123 (1951).
10. Peden *et al. Cell* **31**, 71 (1982).
11. Puga *et al. Cell* **31**, 81 (1982).
12. Cook & Stevens *J. gen. Virol* **31**, 75 (1976).
13. Cabrera *et al. Nature* **288**, 288 (1980).
14. Galloway *et al. J. Virol.* **41**, 686 (1982).
15. Green *et al. Infect. Immun.* **34**, 987 (1981).

0028-0836/83/140477-01$01.00