References and Notes

1. D. H. Hubel and T. N. Wiesel, *J. Neurophysiol.* **28**, 229 (1965); *J. Physiol. London* **160**, 106 (1962); *ibid.* **148**, 574 (1959).
2. D. N. Spinelli and T. W. Barrett, *Exp. Neurol.* **24**, 76 (1969).
3. B. M. Dow and R. Dubner, *J. Neurophysiol.* **34**, 47 (1971); *ibid.* **32**, 773 (1969); R. Dubner and F. J. Brown, *Exp. Neurol.* **20**, 70 (1968).
4. P. Buser and M. Imbert, in *Sensory Communication*, W. A. Rosenblith, Ed. (M.I.T. Press, Cambridge, Mass., 1961), p. 607.
5. V. B. Brooks and S. D. Stoney, *Annu. Rev. Physiol.* **33**, 337 (1971).
6. T. J. Teyler, R. A. Roemer, R. F. Thompson, *Physiol. Behav.* **6**, 375 (1971).
7. J. Schlag and M. Schlag-Rey, *Brain Res.* **22**, 1 (1970); M. Schlag-Rey and D. B. Lindsley, *Physiol. Behav.* **5**, 1033 (1970).
8. A. L. Towe, H. D. Patton, T. T. Kennedy, *Exp. Neurol.* **8**, 220 (1963).
9. T. J. Teyler and J. Biela, *Physiol. Behav.*, in press.

10. We thank C. S. Cory, S. J. Adams, and S. A. Beydler for technical assistance. Supported in part by NIH grant NS 07661, MH 06650, and MH 19314 (to R.F.T.) and postdoctoral fellowship MH 35534 (to T.J.T.).

17 January 1972; revised 28 February 1972

Human Virus Vaccines: Why Monkey Cells?

Petricciani *et al.* (*1*) state that, in regard to the human diploid cell strain WI-38, "reservations" and "theoretical objections" exist "about the use of parenterally administered vaccines made from such cells." Regrettably they do not state what their "reservations" or "theoretical objections" are; and, consequently, such gratuitous, unreferenced pronouncements are pejorative on two counts. First, it could be inferred from the language used, that this opinion is shared by many or all national control authorities and their scientific advisers on human virus vaccines. Human vaccines, prepared in WI-38, currently in use and administered by the parenteral route to more than 1 million people have been licensed in the United Kingdom, France, Yugoslavia, and in the U.S.S.R. (*2*). For this reason and because of other published position statements, such a conclusion is, in my view, unwarranted (*3*). Second, the use of such vague statements as "reservations" and "theoretical objections" without revealing what these are, effectively prevents rebuttal. Whenever these terms are clarified, interested parties should be given an opportunity to reply.

One is forced to conclude that the "reservations" or "theoretical objections" held by Petricciani *et al.* (*1*) have failed to impress a substantial proportion of the scientific community including several major national control authorities. Furthermore, any "reservations" or "theoretical objections" that will be proposed by Petricciani *et al.* are equally applicable to any other cell population including, and especially, the monkey cells developed by Wallace [reference 5 in (*1*)].

To state that tests for oncogenicity of monkey cells are better because such cells can be inoculated into monkeys and that this "allows a latitude of testing that does not exist for human diploid cells" is inaccurate on several counts. First, viable normal human cells, including human diploid cell strains, have been inoculated into man with no evidence of tumorigenicity (*4*, *5*). Since hypothetical vaccines to be grown in the monkey cell substrates developed by Wallace are apparently intended for human parenteral use, do Petricciani *et al.* intend to inoculate these monkey cells into man to demonstrate presence or absence of tumorigenicity? Anything short of that begs the question. Second, despite this type of test, or any other test, the potential tumorigenicity of cells derived from any animal species cannot be ascertained with absolute certainty. Finally, if the Division of Biologics Standards (DBS) now recognizes the necessity for tumorigenicity testing of cell substrates used for human virus vaccine preparation, why are such tests not required for primary monkey kidney, dog, rabbit, duck, and chicken cell substrates? If the system for tumorigenicity testing that they now advocate, and which has been known for decades, has merit, why are studies on this question only now "in progress"?

As regards WI-38, vaccines produced in these cells have not been found to be tumorigenic in over 1 million individuals parenterally inoculated, nor in nearly 1 million recruits that have received adenovirus vaccine in enteric coated capsules, nor in the several million individuals that have received oral polio vaccine.

Petricciani *et al.* say that "vaccines produced from monkey kidney cell cultures have been overwhelmingly successful" . . . "with no evidence of untoward reactions." There are, however, other factors that should be weighed when the use of monkey kidney cells as a substrate for preparation of human virus vaccines continues:

1) Twenty-three people have died as a result of handling monkeys or their cultured cells (*6*). The most recent incident involving human fatalities (Marburg agent) caused the DBS to halt for several months the licensing of new vaccine lots produced in monkey kidney cells. This incident in which seven individuals died in Germany in 1967 resulted from contact with organs and cell cultures derived from the green monkey and from the tissue culture vessels themselves (*6*).

2) A substantial number (25 to 80 percent) of monkey kidneys processed for vaccine manufacture must be discarded because of extensive contamination with one or more of 20 known viruses.

3) The annual slaughter of monkeys for primary cultures has reached such proportions that several species are endangered (*6*).

4) At least several hundred thousand people in this country have been inoculated with live SV40 found in polio vaccines produced in monkey kidney cells. This virus produces tumors in hamsters and converts normal human cells to cancer cells in vitro.

Petricciani *et al.* justify the expenditure of about a million dollars in contract funds by the DBS to develop monkey diploid cell strains on the basis that "alternatives to WI-38 should be explored." Surely these expenditures and the energies and resources of many scientists should be justified by more than mere unstated "reservations" and "theoretical objections" to a cell substrate now widely used throughout the world for human vaccine preparation. It is noteworthy that when we advocated the use of human diploid cells as an "alternative" to primary monkey kidney (*4*) it was for 10 years unacceptable to the DBS (a U.S. license for the use of attenuated poliomyelitis vaccine produced in WI-38 has just been issued by DBS to Pfizer.)

The work described by Petricciani *et al.* was done under contract to DBS by Lederle Laboratories [reference 5 in (*1*)] and represents one of several examples where DBS engages in activities in which serious conflicts of interest are bound to result. In my view, and in the view of others, no control authority should be in the business of developing products or product components that they themselves will ultimately control. Nor should any control authority be allowed to sit in judgment of products or product components when the choice is between substances developed by that control authority and

those competing with it from other laboratories. Scientists' motivations being what they are (including those at DBS), they cannot help but compromise situations where DBS scientists are asked to choose between two "alternatives," one developed by them and the other by outside scientists. We find just such a situation unfolding now, that is, monkey cell populations developed under contract to DBS, and quite naturally advocated by them, as compared to WI-38 developed by others and for which DBS even 10 years later still has "reservations" and "theoretical objections." It is by just such activities that the credibility gap between DBS and its constituency widens as they abrogate the very confidence on which their control authority rests.

As Petricciani *et al.* quite rightly point out in respect to passaged monkey cells, "further evaluation by other independent investigators will be necessary to increase the level of confidence in the safety of these cells." It is to be hoped that these important studies will be done exhaustively and that the decade of WI-38 vaccine testing required by DBS to increase their level of confidence in WI-38 will be equally applicable to vaccines prepared in DBS-FCL-1 and DBS-FRhL-2.

LEONARD HAYFLICK
Stanford University School of Medicine, Stanford, California

References and Notes

1. J. C. Petricciani, H. E. Hopps, D. E. Lorenz, *Science* **174**, 1025 (1971).
2. S. A. Plotkin, *Amer. J. Epidemiol.* **94**, 303 (1971).
3. D. B. Merchant, Ed., *Nat. Cancer Inst. Monogr.* **29**, 583 (1968); F. T. Perkins, Ed., *Minutes of the First through Seventh Meeting of the Cell Culture Committee of the Permanent Section on Microbiological Standardization, 1963–71* (Medical Research Council Laboratories, Hampstead, London, England, 1971).
4. L. Hayflick and P. S. Moorhead, *Exp. Cell Res.* **25**, 585 (1961).
5. C. M. Southam, A. E. Moore, C. P. Rhoads, *Science* **125**, 158 (1957); L. Hayflick, S. A. Plotkin, T. W. Norton, H. Koprowski, *Amer. J. Hyg.* **75**, 240 (1962).
6. F. T. Perkins and P. N. O'Donoghue, Eds. *Hazards of Handling Simians, Laboratory Animals Handbook No. 4* (Laboratory Animals Ltd., 7 Warwick Court, London, W.C.1, 1969).

27 December 1971; revised 16 February 1972

In 1967 a conference on cell cultures for virus vaccine production was held at the National Institutes of Health to review the state of the art so that a basis could be established for future progress.

One of the conclusions of that conference was expressed by the chairman, Donald Merchant, as follows: "A number of lines similar to WI-38 should be developed from human, nonhuman primate and other animal sources so that, as more information is obtained and the need for a wider variety of vaccines is apparent, we will have an ample number and variety of systems with which to work. A number of participants pointed out that we should not have all our eggs in one basket" (*1*).

One year later (1968) there was still no research activity in this area by any groups. The Division of Biologics Standards felt that, on the basis of the discussions and conclusions of the 1967 cell culture conference, it had an obligation to support studies to develop nonhuman diploid cell lines and began two such projects.

In our report (*2*) we were attempting to make available the information that diploid cells from nonhuman primates are now available to those who would study them. The eventual application of these cells depends on the results of a great deal of research by experienced investigators in cell biology and vaccine technology.

JOHN C. PETRICCIANI
HOPE E. HOPPS, DOUGLAS E. LORENZ
Laboratory of Pathology, Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland 20014

References

1. D. B. Merchant, Ed., *Nat. Cancer Inst. Monogr.* **29**, 583 (1968).
2. J. C. Petricciani, H. E. Hopps, D. E. Lorenz, *Science* **174**, 1025 (1971).

12 April 1972

Turbidity of the Atmosphere: Source of Its Background Variation with the Season

In a recent report concerned primarily with the long-term trend in atmospheric turbidity indicated by data from the Mauna Loa Observatory, Ellis and Pueschel (*1*) raised another issue. Considering only "control" days (of atmospheric uniformity in addition to clearness), they found annual cycles in the intensity of solar radiation recorded at the Mauna Loa Observatory between 1958 and 1970. They interpreted these as indicating reduced atmospheric transmissivity during the summer months, "most likely the result of increased worldwide photochemical aerosol formation caused by the oxidation of volatile organic materials of plant origin in the atmosphere . . . or the result of the seasonal variations in general atmospheric circulation, or both." They then concluded: "From the time scales of recovery it can be concluded that such an aerosol is confined, for the most part, to the troposphere."

Dyer and Hicks (*2*) analyzed solar radiation data on "clear" days for the period 1961 through 1965 and found, subsequent to the eruption of Mount Agung, Bali, in 1963, maxima in turbidity moving toward the poles with a period of approximately 1 year. Near the equator the maxima occurred in summer (in agreement with data from Mauna Loa Observatory) but successively later with increasing latitude so that the maxima appeared in winter at mid-latitude stations. They attributed this phenomenon to an annual cycle or equatorial stratospheric dust (presumably from Mount Agung) being fed alternately into each hemisphere.

Three points appear clear: (i) atmospheric turbidity, determined predominantly by the composition of the troposphere, has a pronounced summer maximum (*3*); (ii) measures of stratospheric turbidity, particularly those attributed to volcanic dust, display winter maxima in mid-latitudes (*4, 5*); and (iii) the stratosphere is capable of significant variations in composition on a time scale of 1 year (*6*). What remains unclear is whether the use of solar radiation data on "clear" or "control" days reveals atmospheric turbidity variations reflecting changes in tropospheric composition as postulated by Ellis and Pueschel (*1*) or changes in stratospheric composition as claimed by Dyer and Hicks (*2*).

The available data appear to admit both claims. At Mauna Loa the stratospheric and tropospheric variations are presumably in phase and could produce the single summer maximum observed by Ellis and Pueschel (*1*). Subsequent to the Mount Agung eruption, the stratospheric variations could predominate (on "control" days), producing the single winter maximum in mid-latitudes claimed by Dyer and Hicks (*2*). Prior to the Mount Agung eruption, the two variations could be of comparable magnitude (on "control" days) producing in mid-latitudes either a biannual or an ill-defined seasonal variation as suggested by the analysis of Dyer and Hicks (*2*) for this period.