Meetings

Cell Cultures

The Committee on Cell Cultures of the Permanent Section on Microbiological Standardization of the International Association of Microbiological Societies collects, evaluates, and disseminates information on in vitro substrates for virus growth, with particular reference to virus vaccines. At the third annual meeting held on 18 May 1966 in Philadelphia, Pennsylvania, the Committee agreed to the following statement:

There is increasing evidence that primary nonhuman cell cultures have many undesirable properties when used as substrates for preparation of human virus vaccines. The use of serially propagated, human diploid cell strains for this purpose would not only avoid many of these problems but would provide some new advantages.

It is important to consider the supposed distinction between primary cultures and serially propagated, unaltered cell strains. The generally accepted definition of a primary culture is a cell population derived from an animal tissue which is in its first in vitro culture and has not been subcultivated. Once subcultivated, the population is defined as a diploid cell strain. The difference is more apparent than real. Depending on the inoculation density, primary cultures may undergo many cell doublings before being used for vaccine preparation. A primary culture initiated with a few cells will obviously undergo many more cell doublings before becoming a confluent cell sheet than a similar culture initiated, for example, with one-half the total cell capacity of the culture vessel. If primary cultures are acceptable as virus vaccine substrates after many cell doublings, serially passaged cell populations should be equally acceptable. At present, there are no biological parameters that distinguish serially propagated diploid cell strains from primary cultures. Since trypsin has been used for many years in producing primary cultures for use as vaccine substrates, its use in subcultivation cannot be implicated as a procedure that would give rise to unacceptable cell populations.

If the most important reason for accepting primary cultures is because they are "normal," then both primary cultures and diploid cell strains satisfy this criterion. In contrast, initially mixoploid cell populations and cells that have undergone a "spontaneous" or virus-induced transformation in vitro, as evidenced by one or more altered characteristics, are unacceptable as a substrate for use in vaccine preparation.

The present rejection of all cell populations except primary cell cultures for virus vaccine production is, presumably, based on the supposition that cells may acquire abnormal properties when passaged. In cells from man and many other animals, however, the spontaneous acquisition of abnormal properties leading to the establishment of a mixoploid cell line during serial subcultivation is a rare event. It has not yet been reported to occur in the fibroblasts composing a human diploid cell strain.

Primary cultures are often inherently infected, and their use for vaccine production before there has been time for a thorough search for extraneous agents therefore carries an inherent risk. Such risks are no longer theoretical since the simian virus 40 has been shown to be present in some vaccines. On the other hand, a single tissue from a single donor can produce great quantities of a human diploid cell strain, which can be preserved at low temperatures and exhaustively examined for safety prior to use. This makes it possible to provide a uniform, fully characterized stock of seed cells, available for the production of a wide variety of viral vaccines. This concept is similar to the principle of the "seed virus system" in vaccine production in which a seed virus is fully characterized and thereafter used as the starting point for all vaccine production to ensure uniformity. In a similar manner a "seed cell system" is possible with a human diploid cell strain, because adequate tests can be introduced to ensure that the cells used for vaccine production do not differ in any way from the "seed cells" or even from cultures of primary human cells. Thus, from a single, carefully examined cell population, large quantities of a number of vaccines could be produced by several production facilities from a standard cell population derived from one tissue. The use specifically of human cells is obligatory for at least one group of viruses since many of the rhinoviruses either grow poorly or not at all in other-than-human diploid cells. In view of recent evidence for viral hybridization and the role of "helper" viruses, the use of a fully characterized and standard cell substrate that has no demonstrable neoplastic properties and is proven free from extraneous agents becomes even more important. Current practice in which many new cell populations are continuously derived for vaccine production is repeatedly subject to inherent risks for hybridization of latent viral genomes that may be present in primary cells with the vaccine virus.

The Committee on Cell Cultures, therefore, recommends that serially propagated, human diploid cells be considered a satisfactory substrate for the production of human viral vaccines. It recommends further that the following criteria be satisfied before a given strain is adjudged acceptable for use:

1) The strain should be derived from normal human tissue. This should be of fetal origin in order to decrease the possibility of harboring contaminating viruses.

2) The karyotype must not differ significantly from normal standards during the period of active growth.

3) The morphological and biochemical characteristics should be normal, and should not change throughout the period of propagation.

4) The cell population must be free from all extraneous microorganisms.

5) The cells must not induce tumors when inoculated into the cheek pouch of the hamster or in another equally sensitive in vivo test.

6) The cell population must be preserved in sufficient quantity and at a passage level low enough to ensure its supply for reasonable periods of time.

7) The cells must produce a high

yield of human viruses for vaccine production.

8) The cells must be approved by the National Control Authority.

The data obtained in a number of field trials of vaccine produced in one such human diploid cell strain is sufficiently encouraging to warrant continued efforts. Over 200,000 persons have now received vaccines produced in the human diploid cell strain WI-38. Vaccines against poliomyelitis, adenovirus type 4, measles, rubella, and rhinovirus, some administered orally and others parenterally, have produced no known untoward effects.

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Paleomagnetism: United States–Japan Committee on Scientific Cooperation

Since 1962 geophysicists from the United States and Japan have been engaged in a research program involving rock magnetism, archeomagnetism, paleomagnetism, and geomagnetism of the Pacific area. An organizational meeting for this program was held in Tokyo 4 years ago; a second meeting was held in Berkeley in 1964; and a third meeting, the latest, was held 27–29 October 1966 in Kyoto, Japan. Approximately 13 U.S. scientists and 20 Japanese scientists attended the conference.

The fundamental mechanisms by which rocks become stably magnetized were discussed by the groups from Tokyo University, Pittsburgh University, Massachusetts Institute of Technology, and the University of Colorado. Among the important new results reported was an improved model for the acquisition of thermoremanent magnetization by multidomain grains; a demonstration that the extreme stability of the thermoremanent magnetization in volcanic rocks may be due to the formation in large titanomagnetite grains of single domains of magnetite separated by ilmenite lamellae; an explanation for the irreversible changes on heating of titanomaghemite, and various studies by the Tokyo and Osaka groups of pressure effects on remanent magnetization.

Naoto Kawai (Osaka University) hypothesized that the main dipole component of the geomagnetic field is undergoing an eastward rotation. To the extent that they are coherent, archeomagnetic results from Iceland, England, France, Russia, Japan, and the western United States suggest such an eastward movement. However, it was pointed out that the evidence for this conclusion is somewhat inconclusive because the nondipole field tends to obscure changes in the main dipole. Therefore, more archeomagnetic data from the southern hemisphere and from the central Pacific regions are needed. Paleomagnetic studies of secular variation on a longer time scale made by the U.S. Geological Survey group indicate that the low values of secular variation presently observed in the central Pacific region have persisted for at least 700,000 years. In contrast, the secular variation at midlatitudes in North America and in Alaska has been larger than that expected from the present nondipole field.

One of the main objectives of the program was to determine a radiometric time scale for reversals of the geomagnetic field. This has now been done for the interval back to 4 million years ago. During this time there have been four broad epochs of alternating polarity, as well as four much briefer polarity fluctuations termed events. The fourth event was identified on the basis of new data presented at Kyoto by the U.S. Geological Survey group and the Tokyo–M.I.T.–Colorado group. The two sets of results were complimentary, each group having identified one of the boundaries of the same short polarity event occurring about 3.8 million years ago. Rikitake (Tokyo University) discussed the current state of theoretical studies of geomagnetic reversals.

The focus of much of the paleomagnetic research now being done has shifted to geomagnetic intensity studies. The research reported by groups from Tokyo University, Kyoto University, and the University of California indicate that it is possible to recover information about ancient intensities of the earth's field from some rocks, provided great care is exercised in experimental procedures.

Paleomagnetic results for the Cretaceous and Tertiary from the Pacific Basin were reported by groups from Tohoku University, Tokyo University, Kyoto University, Osaka University, the University of California, and Washington University. Among the generalizations to emerge from these studies are the following: (i) Cretaceous pole positions form a well-defined grouping for each continent, but the groups for different continents are displaced from each other. The implication is that there was little polar wandering during the Cretaceous. (ii) Paleomagnetic results from Japan fall into two distinct groupings, suggesting that the Japan arc was bent during the Late Cretaceous. (iii) The remanent magnetization of sea mounts in the western Pacific, as determined from magnetic anomalies, are consistent with paleomagnetic poles in the Atlantic. S. Uyeda and V. Vacquier interpret this as indicating a northward movement of the Pacific Ocean basin relative to North America and Asia.

In his summary remarks, John Verhoogen (University of California) stated that the U.S.–Japan program had been rewarding not only in terms of scientific advances but also in terms of furthering cooperation and understanding among geophysicists of the two countries. The exchange of postdoctoral and graduate students was an especially successful part of the program. Verhoogen, speaking for all of the American delegates, urged that the channels be kept open for such exchanges in the future, and also that the conferences be continued at 2- or 3-year intervals. Tsuneji Rikitake (Tokyo University) responded that he also felt the exchange of students had been extremely beneficial, and urged continuation of the meetings. These suggestions met with the approval of the entire group.

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Forthcoming Events

February

26. **Psychoanalysis**, 5th annual conf., New York, N.Y. (D. M. Kaplan, 175 W. 12 St., New York 10011)

26–2. International **Anesthesia Research** Soc., 41st congr., Bal Harbour, Fla. (Executive Secretary, 227 Wade Park Manor, Cleveland, Ohio 44106)

27. **Thermoanalysis**, Chemical Inst. of Canada, symp., Toronto, Ont. (H. G. McAdie, Ontario Research Foundation, Toronto, Ont.)