INTRODUCTION

"A vigorous effort to stimulate research directed at a study of the virus origin in human cancer" was urged by the Senate Committee on Appropriations as a specific point in its recommendation of the current increase in funds for the National Cancer Institute's extramural grant program. The Committee recognized that such a program would be a longrange undertaking, and that its success would be heavily dependent upon the training of additional virologists, geneticists, and protein chemists equipped to work on the boundaries between viruses, cancer, and genes. The Committee urged that such a program be most seriously studied, carefully planned, and vigorously executed.

The National Cancer Institute, in seeking advice for the expansion of research in this most important area, requested that the Division of Research Grants employ its customary mechanism of consulting study section members. Accordingly, the Virology and Rickettsiology Study Section sponsored a one-day discussion meeting in which members and ad hoc consultants of five study sections were invited to participate.

Fifteen distinguished scientists spent the day informally exploring the new approaches in virology and other sciences that might lead to a "breakthrough" in human cancer. These panel members were representatives of the fields of virology, biochemistry, pathology, immunology, cellular biology, and biophysics. Noteworthy at the conference was the uncontested agreement that studies on tumor-producing viruses may lead to a major breakthrough in human cancer research. Model animal and virus systems in the form of rather well-known malignant virus tumors of mice, chickens, and rabbits are available as excellent tools for such research. Animal studies imply that viruses may be involved as causative agents of a variety of analogous human cancers, particularly leukemia and breast cancer. With the recent discovery of mouse polyoma, and more recent experimental studies in chicken tumors, these prospects seem even more enhanced.

Four major categories through which tumor-virus research might be advanced were covered in the conference:

1. Basic research on both the virus and host using tissue culture, electron microscopy, and model animal systems with reference to man.
2. Greater emphasis on training of biologists, zoologists, and chemists in those basic medical sciences related to the problem.

3. Improvement of the sources and distribution of living host and viral materials for use in research.

4. Expansion of the research grant mechanism beyond the current project concept to support large-scale interdisciplinary explorations over long periods of time.

This report presents the highlights of the meeting. A more detailed report is being prepared for use by the National Cancer Institute.

HIGHLIGHTS

BASIC RESEARCH

Present leads, which stem largely from a few instances in which viruses have been successfully implicated in certain animal tumor diseases, seem to point principally in the direction of the human counterparts including the leukemias, and mammary cancer, although the recent discovery of mouse polyoma (Drs. Stewart and Eddy) and the more extensive experience in the avian lymphomatoses (Burmester) would seem to widen the implication of viruses as possible causative agents of a variety of human cancers. It is not to be inferred, however, that any of the participants believed that all human cancer was virus caused.

Of the methods and concepts now in general use, the techniques and potential of tissue culture clearly impressed the participants as the most likely to succeed in bringing viruses with cyto-malignant capabilities to light. This is in part due to experience with experimental animal tumor materials which have been found to closely follow species-specific lines of demarkation. Tissue culture opens the way for the use of living cell material derived from human sources and provides a base from which to launch a vigorous, wide spread, accelerated effort to secure additional information, develop new techniques and, hopefully, make new observations. The recent discovery of microscopic neoplastic foci in Rous virus infected chick embryo tissue culture (Bryan and Rubin) is considered a major advance in the detection of virus-induced malignancy. The enhancement of virus proliferation of the presumed mouse mammary tumor agent in tissue culture - as demonstrated by electron microscopy (Moore) - provides another example of a direction that research may take to determine what involvement viruses may have in similar malignant diseases in man.

By the latest techniques of electron microscopy it is now possible to search for viruses directly in tissues of the host, while formerly only those viruses which could be separated from the tissues and effectively purified and concentrated could be studied in this way.

The correlation of viruses which appear in tissue culture preparations with a disease occurring in a whole animal or in man becomes a problem of crucial importance, and, since human beings are not available for direct
experimental proof, the question of passing viruses across species lines - despeciation of the host - becomes a significant problem. In this regard several possible but relatively unexplored areas for research arose from the discussion.

The hamster seems to have a less innate resistance to certain kinds of tissues transplanted from other species, including human, than most experimental animals (Shope). It may be possible to grow and sustain material derived from human sources both cancerous and non-cancerous, more successfully in the hamster than in tissue culture and to adapt and activate viruses that may be lurking in such material.

The possibility of "despeciating" experimental animals by subduing or impairing the normally active immune mechanism(s) in order to favor viral "infection" or growth was discussed (Moore, Luria, Rubin, Koprowski). In particular, the use of animals rendered "tolerant" to material derived from human sources by the injection of human cytological material during the late embryonic stages of development of the experimental animal would make use of recent advancements in immunology. Whole animal irradiation and extended cortisone treatment are methods which have been in use for rendering animals more physiologically receptive to heterologous transplant material.

Biochemistry with its many new analytical methods is now in a position to contribute substantially through characterizing tumors in those respects in which they differ biochemically from normal tissue. If successful, such methods would make possible identification of the malignant process before it is expressed as a tumor either in tissue culture or in the experimental animal.

TRAINING NEEDS

The major problem in training was conceded to be the shortage of interested people, rather than lack of mechanisms for their training. Although research in tumor-viruses is primarily a biological problem, biologists are in general not well trained in the basic medical sciences essential for pursuit of research in this area.

Just as for several years medical students have received basic science training through special courses tailored to their needs, the students in the basic sciences, especially biologists, should now be given the reciprocal opportunity. Medical school courses designed for this need must likewise take into account the fact that the customary prerequisite courses must be waived in favor of a more direct entry into the subject. In addition, a more restricted or differently oriented selection of subject matter must be provided.

Avenues for remedy of the situation suggested by the participants include emphasis upon the subsidy of graduate and post-doctoral training, particularly in biology, zoology, and chemistry departments, with specific provision for pathology as a graduate subject, and the addition of other basic medical sciences, so that a three-year post-doctoral curriculum of virology, immunology, genetics, biochemistry and pathology can be carefully interrelated.
Research in the many aspects of tumors and viruses should be stimulated in the background thus prepared. All of these would seem possible through research grant and training grant mechanisms now in force, but needing program emphasis.

**RESEARCH MATERIALS**

The availability of specific living viral and host materials needs great improvement.

Perhaps the most obvious immediate need for fostering research on human cancer is that of making human materials available on a demand basis, if possible, for study and for biological starting and source material. This problem arises from two difficulties inherent in human cancer research. The first of these is the lack of an experimental animal - alluded to above - and the necessity to have readily available, in quantity as the demand increases, fresh human tissue, preferably of embryonic origin. Although this problem was not explored fully, it is possible that with encouragement, such material might be made available through Sweden and/or Denmark where legal abortion is practiced on a rather extended scale. (The scheduled airlines might be enlisted for special service in forwarding such material to transshipment centers on short notice.) It should be noted that such material is now in extensive use in Russian laboratories. The possible use of primate material for undertaking extended research on the cancer problem both for human passage studies and for direct experimentation was considered worthy of encouragement.

The second aspect of the problem of availability of human source material is the need for excised tumors which have been carefully examined and for which detailed descriptions and characterizations are available. Suggestions were made favoring a subsidized central service for the collection, holding and supply of human and animal material, and/or a liaison arrangement to attempt to satisfy the requirements between cooperative groups as they develop. It was stressed that without this kind of material there was little expectation that a large scale research effort could get underway or be sustained.

Several governmental laboratories have been especially helpful in making some animal tumor materials available and in rendering service to research laboratories expressing a need for material of known or suspected virus potential. Dr. W. Ray Bryan of the National Institutes of Health and Dr. B. R. Burmester of the U. S. Department of Agriculture have been especially helpful to other investigators in this way. Further encouragement should be given to development of such resources. At present there appears to be no direct way for the extramural grants program to support government laboratories which serve these highly functional purposes, however such laboratories cannot be expected to keep up with increasing demands being made upon them for service functions and also for work upon research problems lying outside the immediate concern of their departments. Such material and the information that accompanies it has become invaluable in training new personnel, developing new techniques, and serving as "model systems" in orienting research workers in the area.
RESEARCH GRANT CONCEPTS

Grant support for research on tumor viruses and their role in human malignancies must go beyond the concept of the individual research grant project, and be modified to fill the needs of a highly interdisciplinary area in which negative results over long periods of time must be patiently accepted. Many discussants feel that the predominantly negative nature of such work should lead to long-term, but part-time, support of research activities in the field, because of the investigators' understandable need for some accompanying diversion into less difficult areas with positive research productivity.

CONCLUSION

Viewed in summary, the problem is one in basic cell biology for which model experimental animal and virus systems, tissue culture, electron microscopy, and other workable tools can now be made available. The critical need is for well trained and interested people to work consistently in this difficult area of research.

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