Final Statement of the Study Week on Modern Biological Experimentation

Like all scholars, we seek in our daily lives to enrich man's understanding of himself and the world about him. Without opportunities to share our knowledge, to have it inform the human condition, our work would be without significance. Therefore, we are all grateful for the opportunity to share with the Vatican, the Pope and the Church, through the Pontifical Academy of Sciences, the results of our efforts.

Also, for all of us, I express our personal thanks for the gracious hospitality and for the rare privilege of working in this beautiful building. We especially thank the Academy personnel for their kind attention.

Finally, Professor Chagas, each of us counts it a special fortune to have met and worked with you. We admire your knowledge, your wisdom, and your polite way of prodding us. More, we all admire and applaud your vision and hard work in shaping the Pontifical Academy of Sciences to its present unique and critical role. Too often, science and religion stand at odds rather than recognizing their common roots in humanity. Under your leadership, this special place has become a quiet meeting ground.

Because this is a quiet and private meeting ground, it is appropriate that I make one divergence from my charge. The point I will raise should probably have been discussed yesterday during our consideration of questions of ethics and morality. It was in fact Father Wisser's remarks that reminded me of the issue. He described to us the process, within the Church, by which positions

on moral questions are reached. It is self-evident that the ethical quality of the decision process itself is critical to the worldwide perception and evaluation of any final position. With great respect then I would point out a severe difficulty in that process, as it relates to questions of human reproduction. Without full and equal participation of women at every step of the process, the Church's position on these matters will continue to be seen as ethically compromised by me and by millions of others, Roman Catholics and non-Catholics alike.

Dr. Lejeune and I agreed that to summarize the week's proceedings was pointless. It did however appear useful to try, in a non-technical way, to highlight what we have learned about Modern Biological Experimentation. And according to our conversation, I will emphasize the molecular aspects while Dr. Lejeune will emphasize the cellular aspects.

Dan Nathans made the point yesterday that because of recombinant DNA techniques we now approach biological experimentation in a way that was unimaginable before 1974. To recombinant DNA techniques themselves, I would add the methods which allow investigating genetic molecules on extremely small samples as well as techniques for determining nucleotide structure, synthesizing DNA molecules and carrying out specific mutations at will. Together these procedures have had profound effects and one of the most important is that previously distinct disciplines are merging. The phenomenological approach to biological problems is disappearing as we try to understand living systems as expressions of their fundamental genetic programs. We can do this because we are able to manipulate biological systems to yield precise answers to carefully stated questions. John Carbon's report on the chemical structure of functional yeast centromeres is a dramatic example of this. We saw the same principles at work in Beatrice Mintz's experiments with mouse embryo cells, and at yet another level in Dan Nathan's efforts to understand the complex interaction between T-antigen and the SV40 genome. We also learned from Gunter Hammerling how these techniques are helping to sort out the complexities of the histocompatibility system.

The manipulation of biological systems depends on the availability of cloned and characterized genes and cDNAs. Increasingly powerful variations of recombinant DNA techniques, some of which were described by Ron Davis, are leading to the point where essentially any gene of interest will be obtainable. In addition to their use in fundamental investigations of the regulation and modulation of gene expression, some of these genes will supply important therapeutic and industrial proteins. As Michel Revel stressed in his talk about interferon, newly designed bacterial host-vector systems increase the efficiency of eukaryote gene expression thereby bringing closer the realization of commercially feasible methods. Also, recent and continuing redesigns of eukaryotic vector systems are improving experiments aimed at understanding the control of gene expression – an essential step toward understanding development and differentiation.

Major advances in scientific understanding are almost always related to new methods. Certainly, the last decade stands out as a time of remarkable progress because there have been two major

technical innovations. One is recombinant DNA. The other is the development of monoclonal antibodies. As with recombinant DNA, monoclonal antibodies are pleiotropic tools, useful in many kinds of investigations. George Kohler did the amateurs in our group a great service by explaining both advantages and problems associated with their use.

One of the most remarkable insights of the past few years is the growing appreciation of the flexibility of biological systems. Dr. Mintz stressed the flexibility of embryos and embryonic cells. Others talked about the flexibility of genomes themselves. Classical homologous crossing-over is only one of the ways by which genetic information is rearranged. Ron Davis showed us the many ways in which recombination occurs in yeast and how they could be manipulated to alter yeast genes. Ernest Winocour introduced us to the surprisingly high level of non-homologous recombination in mammalian cells and suggested that the reactions are dependent on specific nucleotide sequences. My own report tried to emphasize the surprising plasticity of some mammalian DNA sequences both in contemporary and evolutionary time. The construction of immunoglobulin genes from dispersed DNA segments was reviewed briefly by George Köhler (reminding us that genome flexibility is not only a random process but is specifically used in differentiation). And we had various hints that genome rearrangement is likely to have played a critical role in evolution.

The importance of genome reorganization and exchange in natural processes was dramatically demonstrated by Jeff Schell's description of the intimate relation between the Ti plasmid of *Agrobacterium tumefaciens* and infected plant cells. And this system also suggests a way to exploit natural recombination for the design of desirable plants. While not specifically covered during our meeting, I would point out that the rapidly developing work on the retroviruses of vertebrates also concerns genomic rearrangements and exchanges, and implicates such reactions in the evolution of the viruses and in carcinogenesis itself.

It is worth remembering that one of the fears frequently expressed during the height of the recombinant DNA debates concerned "tinkering" with genomes. It was, some said, "unnatural". Clearly, it is not unnatural but is a fundamental property of genetic systems. Genomes are not fixed – and they evolve in many complex ways besides simple mutation by base pair changes. It is important to remember the inherent changeability of genomes in future, when we confront specific ethical issues in relation to alteration of human genomes. In this brief week, many aspects of modern biological research have been described. The experience of hearing such a diverse program was a highly instructive one and quite different from our normally more specialized meetings. We come away with a sense of the great accomplishments and of high expectation for the future. But a meeting like this also reminds us of our ignorance. In expressing our enthusiasm for the accomplishments of biological research to non-scientists, it is essential that we also state what is unknown. Otherwise we risk serious misunderstanding of our endeavors.

Maxine F. Singer