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Modern Trends in Human Leukemia IV
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General Summary

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During the last few days we have met for the fourth time here in Wilsede to discuss *Modern Trends in Human Leukemia.* The title itself is rather a misnomer because there are no modern trends in leukemia, a disease which does not change from year to year; our present day civilization probably influences profoundly leukemia's incidence and course but this aspect found no place in our deliberations. It is our approach to understanding the pathogenicity of leukemia, lymphoma, and related diseases which changes, and I will reflect briefly on this.

The clinical papers have been summarized by Dr. Frey and discussed by Dr. M. Feldman. Dr. Frey's statement that "antibody – drug complexes" might be one of the future approaches to chemotherapy of leukemia and related diseases was particularly interesting and reminded me of Albert Coon's early studies on the combination of antitumor antibodies with chemicals, mostly dyes, with the goal of concentrating cytostatic or cytotoxic substances in tumors. This idea did not work then but it brought about the development of the fluorescent antibody techniques. Maybe today the time has come when the combination of more highly specific antibodies, i.e., monoclonal antibodies, with more potent chemotherapeutics would be successful.

During the other sessions of the conference I looked for indications of trends, for those "red threads" which may be a guide for future work. In the virology section the long arguments of the past on the specificity of molecular hybridization and the stringency needed for obtaining significant results have disappeared, and in comparison to past conferences, there were few reports on virus isolations or detection of viral antigens or antibodies in man. The retroviruses supposedly isolated from man, all of which shared genetic information with nonhuman primate viruses, received relatively little attention, but the riddle of these isolations has not been solved nor has the question whether they were all laboratory contaminations been answered. Much more work is needed before further discussion of these agents would be fruitful, but most of these isolates can probably be declassified from their human status, and the significance of the indirect evidence for human retroviruses by demonstration in man of antigens or antibodies which were related or identical to simian viruses is at least questionable. Even so, as I am tempted to announce that "The king is dead", Dr. Gallo is proclaiming "Long live the king" as he presented us with a new candidate for a human leukemia virus, a report which is certain to stimulate a new wave of research in this area.

In contrast, we heard a great deal (perhaps too much and in too much technical detail) about *gag, env, pol, onc, sarc, leuk,* and other genes of animal and particularly avian retroviruses, their characteristic gene products, and their functions. The relevance of these studies of experimental, artificially produced diseases created under laboratory conditions for the natural genesis of leukemia is questionable. Nevertheless, dissection of the genomes of these retroviruses with endonucleases and the cloning of specific parts of the genomes in bacterial plasmids with subsequent evaluation of the function of the various regions of the genes and of the gene products, both in in vitro translation systems and in their normal eukaryotic target cells, may improve our understanding of the basic mechanisms of cell transformation in vitro and possibly also of tumor

induction in vivo by the RNA retroviruses. It is still a major puzzle that similar or identical genomes can induce quite different malignancies, as observed for example in the induction of tumors as different as fibrosarcomas, melanomas, and glioblastomas by a single strain of Rous sarcoma virus, and that the same malignancy can be initiated by different viral genomes. I am sure that the pathogenicity of these diseases will be understood much better during the coming years, although this understanding will be achieved not only by analysis of the genomes down to the last base pair but more by examination of the total process of transformation, i.e., the virus, the route of infection, the type and physiologic state of the infected cells, and the response of the total organism to the emergence of transformed cell clones.

There was relatively little discussion of DNA tumor viruses, except for an overview of the structure of the primate lymphotropic herpesviruses and discussions of the pathogenesis of Epstein – Barr virus (EBV) infections. The pathogenic events leading from primary lymphoproliferative EBV infections to complete recovery with a lifelong carrier state and the development later of monoclonal malignancies or an immediate progression of an acute monucleosis into a malignant fatal lymphoproliferative disease are particularly interesting and deserve intensive study. The report of lytic activity of EBV is important for two reasons: it allows better study in vitro of EBV and it may explain the infection of epithelial cells in vivo. Of importance also is the demonstration of EBV genomes in normal parotic cells which may answer the old question of where EBV multiplies during the long periods of oral excretion.

On reflecting generally on the viral studies I want to repeat a caution sounded often before: We must not ignore the fact that some of our virus models, and I am referring particularly to the avian and murine retroviruses, are highly artificial, using inbred selected animals and laboratory-propagated and perhaps laboratory-created viruses, whose relevance to naturally occurring disease is at least in part questionable, although their value for a basic understanding of cell function and regulation is undisputed. Studies in outbred animal populations, such as cats and cattle, may be more comparable to real life. Particularly intriguing is the situation of "virus-free" cat leukemias in which the virus might have acted as a "hit and run" villain, leaving either only a small part of itself behind or changing only the genes responsible for cell regulatory mechanisms without a need for persistence of any part of the viral genome, a mechanism which has also been considered for the transformation of cells by some DNA viruses, particularly the herpesviruses.

In yesterday's sessions we heard about very exciting developments in cell biology and immunology. The differentiation of the cells of the hematopoietic and the immune systems into many highly specialized cell subpopulations has been analyzed in detail, thus allowing a much finer and detailed analysis of the immune mechanisms which play a role in the emergence of tumors and the defense of the organism against them. Use of monoclonal antibodies has almost revolutionized this field, and it will be most interesting to study not only the physiologic and immunologic functions and antigenic identities of the various cell types but also their susceptibility to exogenous viral infection, to activation of endogenous viral genes, and to chemical or physical carcinogens. The development of cell culture techniques and separation of various cell populations have progressed rapidly and already have improved our understanding of normal differentiation and of regulatory disturbances leading to malignant transformation, although this is another area in which we must remember that isolated cells in vitro may behave quite differently from cells in the intact organism with its multiple cell interactions and regulatory mechanisms, to which we should add Dr. Moore's newly defined "*onc*gene"-mediated "pericrine" controls as well as still unidentified influences. The report of thymic nurse cells within which differentiation of other cells seems to occur is an intriguing observation, the general significance of which needs further exploration. In addition the nude thymusless, the spleenless, and the very special mice lacking both of these organs are now joined by the "beige mouse," a strain which is deficient for natural killer cells and which will permit a further dissection of the immune defenses against tumor development. The new perspective of the various, specific chromosomal aberrations in different diseases should stimulate further research to relate specific chromosomal to specific pathologic changes, and in this respect the studies on the X-linked lymphoproliferative syndrome (Duncan's disease) which is associated with

immunodeficiency, multiclonal lymphoproliferation, and finally lymphoma or lymphosarcoma are particular interesting. Better tools will be needed for a finer analysis of the human genetic material before we can understand the genetic influences on leukemias and lymphomas, as our current methods of chromosomal analysis are at best very crude. Another significant observation was the identification of Ia antigens on various tumor cells and the implication that they have not only immunologic functions but also play some role in differentiation and cell regulation.

In closing, it must be said that we are still far from understanding the pathogenicity of leukemia, lymphoma, and related diseases but that our knowledge has rapidly increased and will continne to do so with the help of modern molecular, virologic, and immunologic techniques developed during the last years. I must, however, remind you that in the clinical arena the battle against leukemia needs a better exchange and co-ordination between clinicians, immunologists, molecular biologists, geneticists, and virologists. Only then can our potential be realized.