Epidemiological Implications of Animal Leukemia Virus Models for the Human Situation: Formal Discussion

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Understanding how C-type viruses behave in lower species can reasonably be expected to provide useful clues for the human situation. Data concerning birds, cats, and mice have been presented in the 3 preceding papers, each animal model suggesting certain parallels for humans. One cannot help noting, however, that these 3 animal systems are not identical, the most striking difference being the apparent relative lack of horizontal virus transmission in mice as opposed to birds and cats. In extrapolating to humans, therefore, we must be cautious since, just as the murine model does not fully predict the avian and feline situations, none of the 3 may entirely foreshadow the human.

I would comment on 4 aspects of this subject. First, although this segment of the conference bears the title, "Acute Leukemia," the range of diagnoses associated with oncornavirus infection encompasses the entire spectrum of hematopoietic cancers, lymphoid as well as myeloid, lymphomas as well as leukemias. Research on humans with respect to oncornavirus-related cancer etiology should, therefore, not be confined to acute leukemia. By the same token, however, the range of tumor diagnoses to be given primary consideration should not extend much beyond the realm of hematological and lymphoid cancer. As Dr. Gardner (3) has indicated, experimental evidence in animals suggests no direct relationship to tumors of other tissues, with the exception of sarcomas. However, the finding of increased incidence of various nonhematopoietic tumors in mice with heightened virus activity implies perhaps some other viral agent or some associated genetic-host factor which, in turn, will need further study.

The 2nd point is to emphasize the importance of host factors, both genetic and immunological, in all 3 model systems. This is perhaps most clearly seen in the avian model where viral infection and tumorigenesis are determined by a mix of genetic makeup, maternal infection, and maternal immune status. Different combinations of these 3 factors appear to predict quite precisely the extent to which Subgroup A virus will produce lymphoid tumor in young chickens. Dr. Crittenden in his paper (1) refers only briefly to the Subgroup E virus, Rous-associated virus type 0, which apparently is an endogenous virus widespread in flocks but only rarely a cause of tumor in chickens less than 2 years of age. Since 2 years is relatively young for a chicken, I suspect that the experimental emphasis on subgroup A reflects the economic dictates of the poultry world where few, if any, birds are privileged to reach senescence. As an experimental model for the human situation, therefore, where most tumors appear preferentially in old age, it may be that some investigation akin to the California murine study should be attempted in chickens whereby data concerning the viral etiology of tumors in older birds can be assembled. While this is just surmise, conceivably the endogenous Rous-associated virus type 0 may be related more to tumor in old age. In contrast, observations concerning Subgroup A virus seem particularly relevant to human leukemia-lymphoma in children and young adults, emphasizing as they do the familiar hypothesis that 1 major determinant of such human tumors may be the virological, immunological, and genetic status of the patient's mother, particularly as concerns possible viral transmission during pregnancy.

The 3rd point concerns viral transmission itself. Here, as I have indicated, the evidence seems contradictory. For cats and birds, virus spreads easily from animal to animal, not only in the vertical or epigenetic sense of transplacental transmission or passage via eggs but also horizontally after birth through interanimal contact and perhaps especially in young animals. So frequent is this transmission that now in cats, as in chickens earlier, it appears. as Dr. Hardy (5) suggests, that removal of feline leukemia virus-infected cats from contact with cats not yet infected may be an important public health measure for control of feline leukemia-lymphoma. In mice, however, very little horizontal transmission has yet been shown (4-7), and various forms of vertical transmission seem to account for most viral perpetuation in populations. Conceivably, this may not be the true state of affairs. Compared with the bird and cat models, little attention has yet been given to possibilities of horizontal transmission in mice. Given the discrepancy between animal models and the relative importance of extrapolations to man with respect to modes of viral spread, further epidemiological observations in the murine system may well be needed. For the present, however, animal models make no clear prediction for the human situation with respect to horizontal transmission of virus.

For humans, various lines of indirect evidence suggest little, if any, horizontal viral transmission (incidence in family groups, time-space, and now interpersonal contact cluster analyses). Such data, however, may be quite misleading since they lack any backup from laboratory tests and since they are likely to misrepresent grossly or oversimplify crucial matters such as latency and mode of viral spread. Horizontal spread of virus therefore remains a real possibil-
C. W. Heath, Jr.

ity. In this connection it may conceivably be significant that the leukemia patient from whom a candidate C-type virus was recently isolated gave a history of prior contact with another person with leukemia (2). Until the issue of human viral transmission is clearly settled through appropriate combinations of laboratory and epidemiological studies, all human case-contact situations deserve scrutiny, at least with respect to hematopoietic and lymphoid cancers. At the same time, of course, human family studies directed at hypotheses of vertical transmission and genetic influence should not be neglected.

The last point deals with the possible association between lymphoid tumor and paralytic disease as suggested in the California murine studies. To my knowledge, no case histories or epidemiological reports have yet been published suggesting any such associations in the human or in other animals for that matter. In 1971, however, a time-space cluster of 3 cases of amytrophic lateral sclerosis was investigated by the Center for Disease Control, and at that time questions were raised concerning a possible familial relationship between this particular disease and leukemia. The 3 patients were all men (ages 54, 62, and 63), and they all lived in a 1-block area and were diagnosed over a 6-year period. Detailed study of the 3 cases with respect to possible risk factors and to general amytrophic lateral sclerosis incidence in the surrounding region led to the tentative conclusion that the case cluster was merely a coincidental event. One of the 3 men, however, had a brother who died of acute leukemia at age 45. In light of the present murine observations, it seems indicated to review these particular human data and to look for familial and possibly community situations that are similar elsewhere in human populations.

References

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