Formal Discussion of: A Survey of the Tumor Virus Problem from an Epidemiologic Standpoint

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Dr. Rowe has indicated the enormous number and variety of hypotheses that have been and could be developed to link neoplasms to viral agents, and he has suggested some bases that might be used to select the most promising hypotheses for test. In this selection he has been mainly concerned with the problems, "Which viruses?" and "Which cancers?" Beyond specification of the hypothesized cause and effect, there is a 3rd element to be defined if a hypothesis is to be subjected to empiric test. This is the element of time: "When is the supposed cause to be applied?" and "Within what period does the hypothesis predict that the effect will appear?" I would like to devote my discussion to this particular dimension.

Dr. Rowe has mentioned the dissociation between time of maximum virus growth and tumor response in polyoma and has pointed out that it is no longer fashionable to search for virus in tumor tissue. But in turning from the experimental animal to man it is important for us to keep in mind just how remote etiologic factors may be in human cancer. Clinical and pathologic evidence documents the long duration of presymptomatic, precancerous, and equivocal stages of many neoplasms. In addition, there is a great deal of epidemiologic evidence suggestive of the remoteness of etiologic factors. Take, for example, the observation that changes in cancer frequency with time tend to occur in a manner indicating that they affect specific generations, rather than specific time periods. This has been shown for cancer of the buccal cavity, tongue, esophagus, larynx, pharynx, rectum, penis, vagina, and breast (4, 7) and recently for cancer of the lung (11). It suggests that to a considerable extent a person's cancer experience is determined by the generation to which he belongs, rather than by the time in which he is living, at least to the degree that these are separable.

We can interpret these observations in 2 ways. Either the relevant interaction between host and agent occurs at a fairly early stage in the host's life (probably before age 30) and remains effective throughout the rest of his life, or the host's subsequent exposure to etiologic agents is itself determined early in his adult life. In lung cancer, the latter seems the obvious type of explanation, since it is readily understandable that a generation's smoking habits may be determined during early adult life and tend to remain characteristic of the generation throughout its existence. But this may not be the case for all types of cancer; there is, for example, at least one type, leukemia, in which it is known that a single etiologic exposure increases risk for a considerable period thereafter.

The question must at least be considered whether viral agents should be included among the etiologic factors determining this cohort pattern. An epidemiologic study to test an association between virus and cancer will be very different according to whether or not the time specification in the hypothesis is such as to explain the cohort mechanism.

There is one particular case that illustrates the importance of specification of time of action of hypothesized etiologic agents. This is the case of childhood leukemia, one of the neoplasms suggested by Dr. Rowe as a prime suspect for viral etiology. The significance of prenatal and perhaps prezygotic factors in the etiology of this disease is suggested by the high rate of concordance for the disease in monozygous twins. Dr. Levy and I have recently estimated that the concordance rate for affected monozygous sets may be as high as 20% (5). While this observation is open to several interpretations, other known epidemiologic features of the disease, such as its association with Down's syndrome in patients (3, 13) and in sibships (10), and its independent association with maternal age (6), certainly make chromosomal damage one of the most attractive explanatory mechanisms.

Where, then, might viral agents fit into such an hypothesis? There are at least 2 possibilities.

First, the concordance rate for monozygous twins is not 100%, and even if a chromosomal or other prenatal mechanism is a necessary part of the etiology, there may be postnatal factors, including viral and other infections, that determine the onset of the disease in a susceptible child. We should note, however, that in such a model if the concordance is as high as 20% the postnatal stimulating factors must be quite common and the prenatal factors more discriminating in distinguishing susceptible from not susceptible children. It is clear, in addition, that a chromosomal mechanism is not incompatible with the occurrence of discordant monozygous sets, as occur in Down's syndrome (12, 14).

Second, we could postulate viral infections as causal of the chromosomal damage itself, and we would, I suppose, give preferential consideration to those viruses characterized by Dr. Rowe as having the ability to produce chromosomal derangements in infected cells. What, then, would be the time specification in such an hypothesis? In terms of possibilities, as in the selection of the 2 major parties to the relationship, the sky is the limit. But in the logical planning of research it becomes necessary, as Dr. Rowe

has indicated, to select from the possibilities those that seem *a priori* more possible than others.

To my knowledge, there is little work published on the susceptibility of germ cells to viral infection at various stages of development. In recent years, however, a good deal of valuable information has accumulated on the sensitivity of germ cells in different developmental stages to ionizing radiation. During the fetal and neonatal existence of the parents, there are considerable fluctuations in radiosensitivity of the primordial germ cells with, in the female, particular peaks of sensitivity at a time (15 days postcoitus) that in the rat corresponds to the period of greatest mitotic activity and in the immediate postnatal period (1). But, considering this fetal and neonatal period as a whole, as we must for practical epidemiologic purposes, the germ cells must be judged highly radiosensitive. After birth, the radiosensitivity of the oocytes declines rapidly (1), as does that of the testis (2), and it continues to decline as the animal ages (8). A 2nd period of greatly increased sensitivity occurs during the miotic maturation division immediately preceding ovulation, sensitivity increasing by about 10-fold on the day of preestrus in the rat (9). In the absence of direct information, it seems reasonable to postulate that the germ cells may be sensitive to other deleterious and possibly cancerogenic influences during these same periods—at least it would seem reasonable to focus attention here first. There seems little practical possibility of executing empiric epidemiologic tests of hypotheses linking childhood leukemia to viral and other agents acting on the maternal (or paternal) primordial germ cells during fetal existence, but the identification of agents operative during the immediate preovulatory peroid of the ovum that eventually becomes the leukemic child does not seem beyond the bounds of possibility. Past epidemiologic studies of the role of virus diseases in childhood leukemia have been concerned primarily with infections of the child prior to the development of leukemia or, occasionally, during his intrauterine existence. The preovulatory period seems worth a look.

There are many assumptions and speculations in this argument. I have presented it not as a theory of the etiology of leukemia in childhood, but to illustrate the importance of time specification in virus-cancer hypotheses and to indicate that epidemiologic, as well as clinical and experimental, data may be useful in making selections among the infinite variety of time relationships that might be proposed.

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