Clustering of Cancer

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The feline leukemia virus (FeLV) causes cancer in cats and, in some cases, appears to be transmitted from cat to cat much like "ordinary" viruses, with most infected animals immunologically resisting disease, and only the occasional one developing leukemia. Although probably uncommon, the mere existence of this phenomenon in animals makes a similar situation clearly in the realm of possibility for at least some types of human cancer as well.

Attempts to isolate a virus which causes human cancer have not been successful. However, there are a number of candidates such as the Epstein-Barr and herpes genitalis viruses, and biochemical analysis of tumor material has shown evidence of RNA viruses similar to the oncornaviruses of many animal species. This is a very active field and rapid progress can be expected.

Concurrent with a purely laboratory approach, epidemiologic studies are searching for a link between various candidate viruses and cancer. In addition, data are being collected and evaluated on the possibility of person-to-person transmission—"contagion"—of both leukemia and Hodgkin's disease. One goal of these investigations

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is obviously to guide the search to likely tumors for isolation of viruses. Another is to lay the groundwork for future control should an infectious etiology be proven.

"Clusters" of leukemia cases have been reported since the 1930s. However, reports of this phenomenon in Hodgkin's disease are relatively recent. There is no doubt that clusters of cancer cases exist. The question is, "Do they occur more often than would be expected by chance alone?" This question is often evaded, and the position adopted that a particular cluster is so startling that it couldn't possibly be due to chance. Such an attitude is unfortunate and disturbing: unfortunate because on deeper analysis the clusters have invariably been not quite so startling, and disturbing because it reveals an essential lack of seriousness regarding the implications of contagion. Patients with a reportedly "infectious" cancer would certainly be severely ostracized. In fact, a number of patients with Hodgkin's disease have, we suspect, committed suicide rather than risk "infecting" others. It is therefore imperative that all studies be properly evaluated statistically and reported fairly.

The Statistical Evaluation of Clustering

Most human cancers are thought to occur randomly. This, of course, is not true for common infectious diseases which tend to develop in time-space
clusters. To differentiate "real" from chance clusters of cancer cases, however, it is not sufficient to simply observe anomalous clustering; one must test whether such anomalous clustering happens more often than one should expect purely by chance.

The "standard" test of clustering (time-space interaction) is the one proposed by Knox which considers each possible pair of patients and records all those with cancers that occurred within a specified time (T days) and a specified distance (D miles).\textsuperscript{4} One can then evaluate whether the number of observed cluster pairs is greater than would be expected by chance. Of course, data on all cases of cancer occurring in a well-defined area over a set time must be collected in an unbiased manner, without any preknowledge of distribution.

The time-space interaction method has two serious flaws. First, it assumes that patients living close together had direct or at least indirect contact through only a few intermediaries. Second, it presumes that both the latent period of the disease and the time interval between clinical onset and diagnosis are short and relatively constant. This is unlikely in cancer.

Therefore, if the aim in studying clustering is to determine the importance of an infectious process, it is necessary to demonstrate that cases had more contact at a "relevant" time than did controls—not that they lived close together at disease onset. This requires a case-control method of statistical analysis with detailed interviewing of both groups.

To implement the case-control method, all patients with cancer that occurred in a specified area over a period of preferably 10 years or more must be identified and a matched control selected based on age, sex and socioeconomic status. If a very stringent test is wanted, then the controls should be matched within an area of residence smaller than that of the total study. By interviewing both groups or, if dead, their relatives or friends (note that the type of person interviewed should be the same for cases and controls), it can be established whether a pair had "effective" contact which could have resulted in contagion. (This can also include indirect contact through a third party.) A statistical significance level is then determined after analysis of the total number of links between patients, compared to those between controls, and between cases and controls.

\textbf{Hodgkin's Disease}

Two recent reports have studied clusters of Hodgkin's disease using the time-space method. One, by Alderson and Nayak, evaluated 737 patients diagnosed in Manchester, England from 1962-1968.\textsuperscript{5} They found no evidence of clustering using Knox's statistical test, with a variety of space and time differences. Here the investigators were concentrating on the date of diagnosis, with the attendant, very unlikely assumption of a brief latency period.
The other by Kryscio and colleagues examined Hodgkin's disease patients diagnosed in Connecticut from 1940-1969. No evidence of clustering was found.6

Another study by Klinger and Minton on clustering of Hodgkin's disease in Union County, Ohio (1970 population: 23,786) provides an excellent example of pseudo-statistical reporting.7 Five of the 12 cases of Hodgkin's disease diagnosed from 1960-1971 occurred in Darby Township (1970 population: 1212). The authors, it seems, then compared the annual incidence in Darby—34.4 per 100,000—to that in the remainder of the county—2.6 per 100,000—and claimed a statistical significance level (p) of less than 0.05 percent. This is not correct.

When the statistical test takes into account that Darby Township was not chosen a priori, the value of "p" is approximately two percent.8 Furthermore, this rate discounts the important fact that Union County was selected because of an initial report of three cases, which if considered would cause the statistical significance to completely disappear. Using the same pseudo-statistical approach, clusters of Hodgkin's disease throughout the United States could be reported every week for three years and still represent no more than chance.

Fortunately, a number of case-control interview studies of clustering have been or are being conducted. The credit for this lies with Vianna and his colleagues in Albany who were the first to realize the need for a control group and the importance of detailed questioning. Working outward from an anomalous situation in which a small number of cases of Hodgkin's disease occurred in friends in an Albany high school, they "linked" 31 of 208 patients diagnosed from 1950-1970. There were nine instances of possible case-case "spread" and 25 possibilities of case-contact-case transmission. Unfortunately, their control group was completely inadequate since it was chosen only for the linked patients rather than for the entire group. In addition, since any patient with Hodgkin's disease has a 20 percent or greater probability of contacting another patient with the disease over a 10-year period by chance alone,9 the findings were not, in fact, especially surprising.

Prompted by this report, Kinlen and his colleagues have recently completed a case-control study in Oxford, England. They identified all 97 patients under the age of 40 with Hodgkin's disease diagnosed from 1962-1971 in the Oxford area. This age restriction is based on the observation that transmission was most likely to occur between young persons. For each patient a matched control was chosen with a non-malignant disease who was admitted to a local hospital during the year the patient was diagnosed. Each person was then interviewed in depth to build up a chronological life history.

The results are currently being eval-
uated in detail. Initial analysis reveals a considerable number of links between patients, but no more so than among controls. For example, 12 pairs of patients went to school together, but the expected number based on the total data was 11.7 (with a standard error of 3.6). Another such investigation is currently under way in Connecticut.

Unfortunately, other interview studies with inadequate or even no control groups continue to be reported. One produced evidence showing that certain schools had a continuing, high incidence of Hodgkin’s disease; another found a high rate of the disease in doctors; and a third, a high rate in schoolteachers. Serious doubt has been thrown on all these results. The school report is suspected of being only a non-random sample of the data required to make such claims. The reported high rate in doctors is flatly contradicted by a much larger and more complete study on the mortality of British doctors. Finally, the apparent excess risk in schoolteachers has been proven an artifact of study design; the teachers had, in fact, a normal risk of Hodgkin’s disease, which appeared high only in relation to their low rate of other diseases. These studies on contagion are of little, if any, scientific value and can only confuse and dismay patients with Hodgkin’s disease.

Leukemia

Are the reported clusters of leukemia cases simply a chance phenomenon? This is still very much an unanswered question.

A good many studies of clusters of childhood leukemia cases have been performed using the time-space interaction method. These efforts have produced either negative findings or such weak positive results that they can, in our opinion, be disregarded. A few studies of this type have used data on place and time of birth—the logic being that childhood leukemia is likely induced in utero. These efforts have also been found to produce essentially negative results.

A good example of how easy it is to produce “irrelevant” clusters is provided by a study by Glass, Hill and Miller in Los Angeles County. When the distribution of cases was allowed to define small areas within Los Angeles, the investigators could find “with truly minimal efforts...in nine areas, leukemia rates...as high or higher than those in Niles, Illinois or Orange, Texas...where the two most renowned leukemia clusters have occurred.” However, when their complete data were analyzed, no evidence whatsoever of clustering was observed. This study implies that small chance clusters continually occur throughout the United States and reports of them must now be considered irrelevant.

The issue of clustering in leukemia remains open not because there are a sufficient number of positive results, but because the phenomenon has only been studied superficially. Although a
plea can be made to conduct at least a few case-control interview studies on clustering in childhood and adult leukemia, none have yet been done.

Conclusions
At the present time there is no solid evidence that any human cancer has the characteristics of a communicable disease. If future rigidly controlled studies produce hard evidence of an infectious component to cancer, very difficult ethical problems in patient care could arise. One major problem will then be to determine whether the patient is infectious before or after diagnosis. Clearly, if he is only infectious preclinically, a not unlikely situation, the patient is no longer any risk to others once his disease is diagnosed. No data are yet available on this most important aspect of the situation which has such serious implications for the patient.

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